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Stereoselective Synthesis of D- and L-Carbocyclic Nucleosides by Enzymatically Catalyzed Kinetic Resolution

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Abstract: An efficient synthesis of (*S*)- or (*R*)-3-(benzyloxy-methyl)-cyclopent-3-enol was developed by appling an enzyme-catalyzed kinetic-resolution approach. This procedure allowed the syntheses of the enantiomeric building blocks (*S*)- and (*R*)-cyclopentenol with high optical purity (>98% *ee*). In contrast to previous approaches, the key advantage of this procedure is that the resolution is done on the level of enantiomers that only contain one stereogenic center. Owing to this feature, it was possible to chemically convert the enantiomers into each other. By using this route, the starting materials for the syntheses of carbocyclic D- and L-nucleoside analogues were readily accessible. 3′,4′-Unsaturated D- or L-carbocyclic nucleosides were obtained from the condensation of various nucleobases with (*S*)- or (*R*)-cyclopentenol. Functionalization of the double bond in 3′-deoxy-3′,4′-didehydro-*carba*-D-thymidine led to a variety of new nucleoside analogues. By using the *cyclo*Sal approach, their corresponding phosphorylated metabolites were readily accessable. Moreover, a new synthetic route to carbocyclic 2′-deoxy-nucleosides was developed, thereby leading to D- and L-*carba*-dT. D-*Carba*-dT was tested for antiviral activity against multidrug-resistance HIV-1 strain E2-2 and compared to the known antiviral agent d4T, as well as L-*carba*-dT. Whilst L-*carba*-dT was found to be inactive, its D-analogue showed remarkably high activity against the resistant virus and significantly better than that of d4T. However, against the wild-type virus strain NL4/3, d4T was found to be more-active than D-*carba*-dT.

Keywords: antiviral agents · carbocycles · enzyme catalysis · kinetic resolution · nucleotides

Introduction

Over the last few decades, carbocyclic D- and L-nucleosides have attracted much interest owing to their antiviral activity against a large number of viruses.[1] Carbocyclic nucleoside analogues, such as entecavir (**1**), D-[(*E*)-5-(2-bromovinyl)]-2′-deoxy-*carba*-uridine (*carba*-BVdU, **2**), and *carba*-D-thymidine (*carba*-dT, **3**), exhibit interesting biological activity (Figure 1). Purine analogue entecavir has been shown to be an anti-HBV agent, but it also possesses activity against HIV, HSV-1, VZV, and influenza.[2] Morover, it was approved for the therapy of chronic HBV infections by the FDA in 2005. *Carba*-BVdU is antivirally active against HSV and VZV.[3] *Carba*-dT (**3**) has shown high in vitro activity against several different viruses, such as HIV-1, HIV-2, HSV-1, and VV.[4] Furthermore, it blocks DNA synthesis by a unique mechanism that is termed kinetic- or delayed chain termination, which makes *carba*-dT a very promising lead compound for the development of antiviral agents.[5]

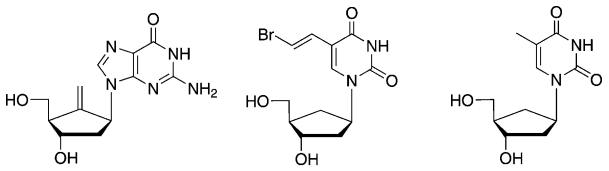

Figure 1. Examples of antivirally active carbocyclic nucleosides.

The advantages of carbocyclic compounds compared to their natural counterparts include their higher metabolic and chemical stability owing to the replaced oxygen atom.[6] In addition, the replacement of the oxygen atom by a methylene group often leads to lower cytotoxicity and increased bioavailability.[7] In many cases, carbocyclic nucleosides show revised biological properties owing to the conformationally changed cyclopentane ring compared to their normal nucleoside analogues.[1a,c,7,8]

The most challenging obstacle to the development of new antivirally active carbocyclic agents is the synthetic approach. Usually, it is necessary to perform a multistep synthesis to introduce the required stereoinformation. There are many synthetic approaches to carbocyclic nucleosides and they can be divided into two groups:[1] The first group is the "linear synthetic strategy", in which the nucleoside is

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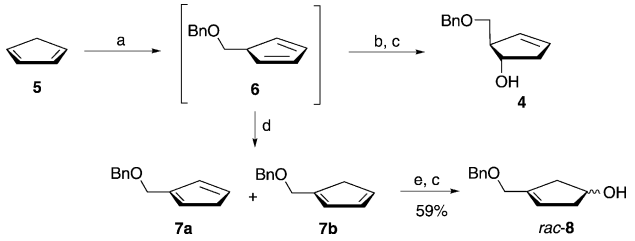
prepared by the initial functionalization of the cyclopentane moiety followed by stepwise construction of the nucleobase. The second approach is the "convergent synthesis", which offers the formation of a variety of nucleoside analogues by the direct coupling of a cyclopentanol derivative and different heterocyclic bases.

Biggadike et al. reported the synthesis of (1*S*,2*R*)-2-(benzyloxymethyl)-cyclopent-3-enol (**4**) starting from cyclopentadiene (**5**), which was first deprotonated with NaH and then alkylated with benzylchloromethylether (BOMCl).[9] The cyclopentadiene derivative was stereoselectively hydroborated by using (−)-di*iso*pinocampheylborane to give (1*S*,2*R*)-2-(benzyloxymethyl)-cyclopent-3-enol. In this reaction, two new stereocenters were created with excellent stereoselectivity. However, the carbocyclic precursor was isolated in low chemical yield and the introduction of two new stereocenters in this molecule at the same time did not allow a general access to carbocyclic D- and L-nucleosides. We developed a convergent synthetic strategy towards carbocyclic 2′-deoxynucleoside analogues with improved chemical yields by using compound **4**; in addition, we showed that symmetric cyclopentadiene intermediate **6** isomerized into two thermodynamically stable cyclopentadienes (**7a** and **7b**) above 0 °C.[10] Subsequently, hydroboration of these two unsymmetrical dienes was achieved by using BH_3·THF. After the hydroboration and alkaline-oxidation steps, only one product, racemic 3-(benzyloxymethyl)-cyclopent-3-enol (**8**), was formed in an overall yield of 59 % starting from cyclopentadiene (Scheme 1).



Scheme 1. a) NaH, BOMCl, THF; b) (−)-diisopinocampheylborane ((−)-(ipc)$_2$BH), THF, −60 °C; c) H_2O_2/NaOH 1:1; d) > 0 °C; e) BH_3·THF, THF.

Furthermore, we demonstrated that racemic cyclopentenol **8** is a good building block for the convergent synthesis of many different racemic carbocyclic D-nucleoside analogues by using a modified Mitsunobu reaction.[11] However, again, this synthetic route is not generally applicable for preparing either carbocyclic D- or L-nucleosides.

The preparation of enantiomerically pure compounds is still challenging. There are various routes for the enantioselective synthesis of new carbocyclic nucleosides, such as the use of natural chiral molecules as starting material or an asymmetric synthetic strategy for the syntheses of optically pure building blocks. In particular, chemoenzymatic methods have become quite popular in organic synthesis over the past few decades.[12]

Herein, we report a stereoselective, chemoenzymatic kinetic resolution of racemic cyclopentenol **8**. Based on this reaction, enantiomerically pure key intermediates (*R*)-**8** or (*S*)-**8** were obtained and used for the preparation of carbocyclic D- or L-3′-deoxy-3′,4′-didehydronucleosides and -nucleotides. Furthermore, a new route to carbocyclic 2′-deoxynucleosides, such as *carba*-dT, is presented; the antiviral activities of these compounds were studied against a multidrug-resistant HIV strain.

Results and Discussion

Kinetic resolution: Our previously reported method, which used *rac*-3-(benzyloxymethyl)-cyclopent-3-enol (**8**), only led to racemic carbocyclic nucleosides.[11] Different approaches were tested for preparing cyclopentenol **8** and their corresponding nucleoside analogues in their optically pure form: The first approach was to convert cyclopentenol **8** into a β,γ-ketone by Swern oxidation and then preparing the enantiomerically pure product by stereoselective reduction. Several reducing reagents, such as the CBS-catalyst, (*R*)-BINAL-H, and diisopinocampheylchloroborane, were tested, but none of them led to the desired enantiomeric cyclopentenol (**8**). Another possibility to obtain chiral alcohol **8** was the stereoselective hydroboration of the two cyclopentadienes (**7a** and **7b**). Diisopinocampheylborane and dilongifolylborane, which were prepared from α-pinene and longifolene, respectively, were used as stereoselective hydroborating reagents.[13] Unfortunately, hydroboration only gave the required product with an enantiomeric excess of ≤81 % and 33 % chemical yield. Next, cyclopentenol **8** was converted into diastereomers by reacting with different chiral acids. We tried to separate the diastereomers by column chromatography on silica gel. Although esterification reactions with (*S*)-mandelic acid, (*R*)-(−)-methoxyphenylacetic acid, and (*S*)-(−)-camphanic acid chloride were successful, the separation of the diastereomers on the preparative scale failed in all three cases.

One further option to achieve the separation of the enantiomers of compound **8** was to perform a kinetic resolution. In this reaction, the two enantiomers show different rates of reaction in the presence of a chiral entity, such as a chiral catalyst or a biocatalyst.[14] In contrast to normal asymmetric reactions, the theoretical maximum yield for kinetic resolutions is 50 %. The parameter that describes the efficiency of an enzyme-catalyzed kinetic resolution is the E value; for a good kinetic resolution, the value should exceed 30.[15]

Finally, we found that an enzyme-catalyzed acylation reaction by using vinyl acetate and triethylamine in the presence of porcine pancreatin was successful. This approach was motivated by a previously reported desymmetrization reaction that led to a different cyclopentene building block for the syntheses of spinosyn A analogues.[16] However, with our substrate, *rac*-3-(benzyloxymethyl)-cyclopent-3-enol (**8**), the rate of the esterification reaction was very low, although the enantiomeric excess of the formed product was high (95 %).

The enantiomeric excesses of the acetylated compound ((*R*)-**9**) and the residual alcoholic enantiomer ((*S*)-**8**) were determined by HPLC by using a CHIRALPAK OD column. The conversion was calculated from the enantiomeric excesses of the substrate and the product.[17]

This promising stereoselectivity led us to optimize the procedure to improve the enantiomeric excess, reaction rate, conversion, and the E value.

First, eight different solvents, that is, acetone, Et_2O, THF, CH_2Cl_2, 1,4-dioxane, toluene, *n*-hexane, and cyclohexane, were used for the kinetic resolution with pancreatin. Acetone, THF, *n*-hexane, and toluene were the best solvents for the esterification reaction with pancreatin. This result correlated well with the study by Secundo et al. regarding the effect on the enantioselectivity of pancreatin in organic solvents.[18] In acetone, the acetylated compound, (*R*)-**9**, was obtained with the highest enantiomeric excess of 95%, but it took 3 days to achieve 38% conversion with 3 mass equivalents of pancreatin annualized to the substrate (**8**). The enantioselectivity (E value) of the kinetic resolution in acetone was quite high ($E=69$, Table 1). The fastest conversions were observed in highly nonpolar solvents: Almost 40% of the substrate was converted into the product within 3 h and the decrease in enantiomeric excess was insignificant. After 3 h, the *ee* value was 94% for the reaction in *n*-hexane with 39% conversion (Table 1). The enantioselectivity of the kinetic resolution was still good ($E=59$). The results of the enzymatic syntheses with pancreatin in different solvents are summarized in Table 1.

Table 1. Kinetic resolution of *rac*-**8** with pancreatin in different solvents.[a]

Solvent	*t* [h]	Conversion [%]	*ee* (*R*)-**9** [%]	*ee* (*S*)-**8** [%]	E
acetone	67	38	95	57	69
THF	48	38	92	56	42
1,4-dioxane	47	36	94	52	54
n-hexane	3	39	94	59	59
toluene	3	40	93	61	51
cyclohexane	3	40	91	61	40

[a] Reagents and conditions: *rac*-**8** (50 mg), pancreatin (150 mg), Et_3N (2 equiv), vinyl acetate (2 equiv), solvent (2 mL), RT.

Besides the solvent, the number of equivalents of the reagents (vinyl acetate and triethylamine) was varied. In these experiments, up to 5 equivalents of these components were tested. The best reaction conditions were achieved with 2 equivalents of both reagents. Less then 2 equivalents of the acyl donor and triethylamine gave lower conversions and reaction rates, whilst using more than 2 equivalents led to a decrease in the enantioselectivity of the acetylated compound ((*R*)-**9**).

In addition to these studies, the effect of the amount of porcine pancreatin on the reaction was examined. Owing to the fact that pancreatin is a mixture of different enzymes, such as lipases, amylases, and proteases, we defined that 1 equivalent of pancreatin correlated to 1 g of enzyme mixture when 1 g of cyclopentenol *rac*-**8** was used. Then, 1, 2, 3, and 5 equivalents of pancreatin were tested. We found that higher amounts of pancreatin not only led to higher reaction rates, but also to a higher selectivity of the reaction.

For studying the temperature dependence of pancreatin, the kinetic resolution was performed at different temperatures, starting at room temperature and rising in 10°C steps up to 60°C (Table 2).

Table 2. Temperature dependence of pancreatin in the kinetic resolution with *rac*-**8**.[a]

T [°C]	*t* [h]	Conversion [%]	*ee* (*R*)-**9** [%]	*ee* (*S*)-**8** [%]	E
RT	28	31	96	43	75
30	20	31	97	44	101
40	24	31	96	44	76
50	28	26	95	33	54
60	28	27	94	34	45

[a] Reagents and conditions: *rac*-**8** (100 mg), pancreatin (300 mg), Et_3N (2 equiv), vinyl acetate (2 equiv), solvent (4 mL).

The optimum temperature of pancreatin as described in the literature is between 30°C and 40°C.[18,19] In our experiments, we observed that the conversion increased at higher temperature. However, after a couple of hours, the enzyme activity and the enantioselectivity of the reactions decreased at 50°C and 60°C, as shown by smaller enantiomeric excesses and slower reaction progress. As expected, the optimal temperature for pancreatin in this reaction was between 30°C and 40°C.

Furthermore, different enzymes, especially lipases, were investigated in the esterification reaction. As mentioned above, porcine pancreatin is a mixture of different enzymes. To determine which enzyme was responsible for the catalysis and to examine if the pure enzyme was a better biocatalyst than porcine pancreatin, different isolated lipases and esterases were used for the kinetic resolution of racemic 3-(benzyloxymethyl)-cyclopent-3-enol (**8**). All of the chemoenzymatic reactions were tested by using 2 equivalents of vinyl acetate and triethylamine in acetone. For comparing the influence of the isolated enzymes on the reaction, the amount of enzyme was calculated from the specific activity of the respective enzyme, so that, in each reaction, 50 enzyme units were used. The results for the kinetic resolution with the isolated esterases were found to be really poor. Even after a couple of days, almost no conversion was observed; thus, no further investigation was done for the esterases. However, the results for the lipases looked to be quite promising. Most of the lipases did work in the kinetic resolution in acetone, but, in general, the results were not as good as for pancreatin. The best results were achieved for the reactions with the enzymes PPL (*porcine pancreas lipase*), HP (*hog pancreas lipase*), PFL (*pseudomonas fluorescens lipase*), CAL (*candida antarctica lipase*), PCC (*candida cylindraca lipase*), and PCL (*pseudomonas cepacia lipase*; Table 3).

Table 3. Kinetic resolution of *rac*-**8** with different lipases.[a]

Enzyme	Amount of enzyme [mg]	*t* [h]	Conversion [%]	*ee* (*R*)-**9** [%]	*ee* (*S*)-**8** [%]	E
pancreatin	150	92	31	94	42	49
PPL	150	92	20	94	23	41
PPL	100	92	13	94	14	37
PPL	0.5	92	4	94	4	34
HP	3.3	73	10	94	10	36
PFL	1.3	73	41	80	56	16
CAL	33.3	73	31	72	33	8
PCC	25	73	8	37	3	2
PCL	1	73	37	70	41	8

[a] Reagents and conditions: *rac*-**8** (15 mg), Et_3N (2 equiv), vinyl acetate (2 equiv), acetone (0.6 mL), RT.

In the reactions with the last four lipases, the enantiomeric excesses of the product were not as high as for the resolutions with pancreatin, PPL, and HP. Because of this result, no further optimization was done for these enzymes. Because PPL was the cheapest enzyme and the selectivity of the chemoenzymatic reaction looked promising, further optimization was performed. By increasing the amount of PPL, it was possible to increase the conversion and reaction rate of the kinetic resolution.

In addition, the effect of the solvent on the kinetic resolution was investigated (Table 4). The highest E value was found with toluene after 47 h (*ee* value of (*R*)-**9**: 91% and 46% conversion).

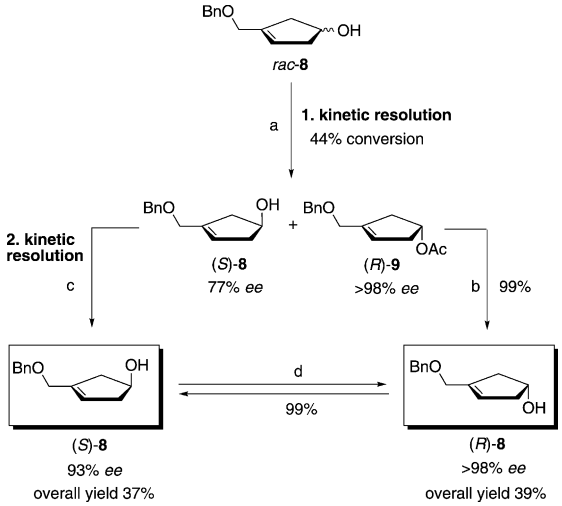
Table 4. Kinetic resolution of *rac*-**8** with PPL in different solvents.[a]

Solvent	*t* [h]	Conversion [%]	*ee* (*R*)-**9** [%]	*ee* (*S*)-**8** [%]	E
acetone	49	15	95	17	46
toluene	47	46	91	78	49
1,4-dioxane	47	16	95	18	47
n-hexane	47	31	85	38	18
cyclohexane	47	16	87	18	20

[a] Reagents and conditions: *rac*-**8** (50 mg), PPL (150 mg), Et_3N (2 equiv), vinyl acetate (2 equiv), solvent (2 mL), RT.

In addition, two other acyl donors were tested. Isopropenyl acetate and *p*-ClPhOAc are two literature-known reagents that have been used in kinetic resolutions and dynamic kinetic resolutions.[20] However, their application showed no advantage over our established procedures with pancreatin and PPL.

In the end, the best results for the kinetic resolution were found when 5 g of the cyclopentenol *rac*-**8**, 5 equivalents of pancreatin, and 2 equivalents of vinyl acetate and triethylamine were used in 170 mL acetone (Scheme 2). After 23 h and 44% conversion, an excellent enantiomeric excess of >98% was obtained for the acetylated compound ((*R*)-**9**). The enantiomeric excess of the remaining (*S*)-cyclopentenol (**8**) was 77%. A further scale-up of reaction to 10 g of *rac*-**8** was easily accomplished and it seems there is no obvious limit to the tolerable scale of the reaction. Compound (*R*)-**9** and the remaining (*S*)-alcohol (**8**) could be easily separated by silica gel column chromatography.

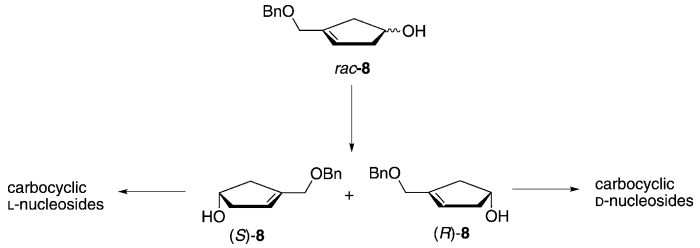


Scheme 2. a) Pancreatin, Et_3N, vinyl acetate, acetone, 23 h; b) NaOH, MeOH; c) pancreatin, Et_3N, vinyl acetate, acetone, 6 h; d) DIAD, PPh_3, benzoic acid, Et_2O.

Product (*R*)-**9** was deacetylated in quantitative yield by using a solution of sodium hydroxide in MeOH, thereby leading to the *R*-configured cyclopentenol (**8**) in an overall yield of 39% starting from *rac*-**8**. The *S*-configured alcohol (**8**), which had an enantiomeric excess of 77%, was generated in its optically pure form by a second kinetic resolution/transesterification reaction with pancreatin. (*S*)-Cyclopentenol (**8**) was isolated in 37% overall yield from *rac*-cyclopentenol. Both enantiomers could be transformed into each other by Mitsunobu inversion in very good yields.[21] Finally, total chemical yields of up to 80% were obtained for either enantiomer. The significant advantage of this procedure is that the resolution is done on the level of a precursor with only one stereogenic center. In the literature, several other enzymatic approaches have been reported that led to the formation of compounds with at least two stereogenic centers such that only diastereomers were obtained that could not be interconverted.[12c] Thus, our approach led directly to compounds that could be used as starting materials for the synthesis of D- and L-carbocyclic nucleoside analogues (Scheme 3). Other advantages of this kinetic resolution by using pancreatin and 3-(benzyloxymethyl)-cyclopent-3-enol (*rac*-**8**) include the low cost of the enzyme and the reagents.

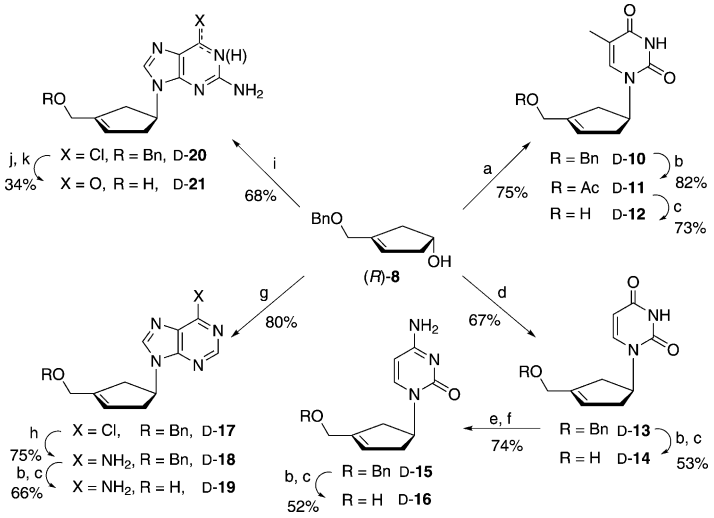
3′-Deoxy-3′,4′-didehydronucleosides and -nucleotides: For the syntheses of carbocyclic 3′-deoxy-3′,4′-didehydro-D-nucleosides, *R*-configured alcohol **8** was used as the starting material and, for the corresponding L-nucleoside analogues, *S*-cyclopentenol **8** was used (Scheme 3).

The introduction of the pyrimidine heterocycles was achieved by using modified Mitsunobu reaction conditions.[22] In addition to the N1-alkylated product, the O2-regioisomer was formed in minor amounts. These mixtures of the N1- and O2-alkylated products were easily separated by column



Scheme 3. Stereoselective access to carbocyclic L- and D-nucleosides from (*S*)-**8** and (*R*)-**8**.

chromatography on silica gel before alkaline cleavage of the benzoyl group. Condensation of *N*3-benzoylthymine and *N*3-benzoyluracil with (*R*)-cyclopentenol (**8**) and subsequent alkaline deprotection led to carbocyclic 5′-*O*-benzylated D-thymidine derivative **10** in 75% yield and its D-uridine analogue (**13**) in 67% yield (Scheme 4). Cleavage of the benzyl

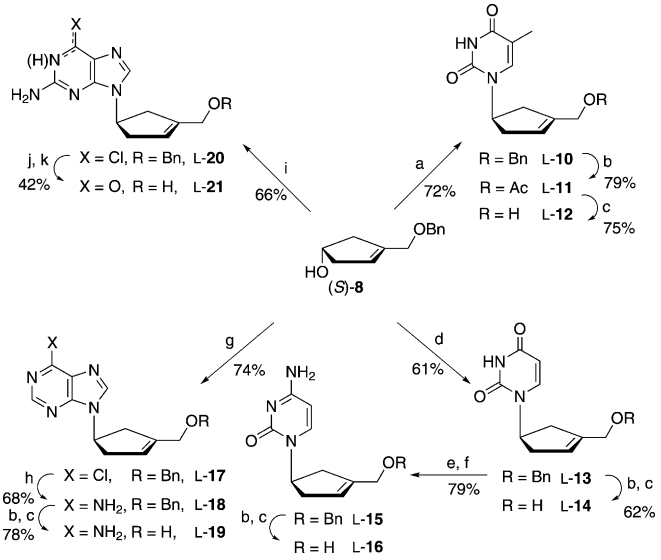


Scheme 4. a) DIAD, PPh_3, *N*3-benzoylthymine, CH_3CN; b) $ZnCl_2$, Ac_2O, AcOH; c) NaOH, MeOH; d) DIAD, PPh_3, *N*3-benzoyluracil, CH_3CN; e) triazole, $POCl_3$, Et_3N, CH_3CN; f) NH_3, CH_3CN; g) DIAD, PPh_3, 6-chloropurine, THF; h) NH_3, MeOH; i) DIAD, PPh_3, 2-amino-6-chloropurine, THF; j) HCOOH k) NH_3, MeOH.

ethers was achieved by $ZnCl_2$ in Ac_2O/AcOH (5:1) and yielded the acetylated D-thymidine analogue (**11**) in 82% yield.[23] Alkaline treatment led to the fully deprotected thymidine (**12**) in 73% yield. Deprotection to the D-uridine derivative (**14**) was achieved in 53% yield without isolating the acetylated intermediate. Transformation into the corresponding D-cytidine analogue (**15**) was achieved by using a method reported by Divakar and Reese.[24] The uridine derivative (**13**) was treated with triazole, phosphoryl chloride, and triethylamine in CH_3CN to afford the triazolide intermediate. This material was then stirred in a mixture of aqueous ammonia in CH_3CN to give compound **15** in 74% yield. After cleavage of the benzyl group, 3′-deoxy-3′,4′-didehydro-*carba*-D-cytidine (**16**) was obtained in 52% yield.

Mitsunobu coupling of precursor (*R*)-**8** with 6-chloropurine in THF led to the formation of the benzyl-protected purine nucleoside (D-**17**) in 80%. Next, nucleoside D-**17** was converted into its adenine-nucleoside analogue (D-**18**) in 75% yield by treatment with ammonia in MeOH; however, in contrast to previous syntheses,[25] the reaction was carried out in a microwave reactor. The fully deprotected D-nucleoside (**19**) was obtained after treatment with $ZnCl_2$ under alkaline conditions. Starting from (*R*)-**8** and 2-amino-6-chloropurine, benzyl-protected D-**20** was formed. Guanine analogue D-**21** was isolated in 34% yield by using formic acid and subsequent treatment with ammonia in MeOH.

Therefore, starting from cyclopentadiene and *R*-configured building block **8**, we were able to prepare various 3′-deoxy-3′,4′-didehydro-*carba*-D-nucleosides by a short chemoenzymatic route in good overall yields. Furthermore, the opposite enantiomer of cyclopentenol, (*S*)-**8**, was used for the preparation of L-nucleoside analogues **10**–**21** with thymine, uracil, cytosine, adenine, and guanine as nucleobases under identical reaction conditions (Scheme 5). Thus, by using this



Scheme 5. a) DIAD, PPh_3, *N*3-benzoylthymine, CH_3CN; b) $ZnCl_2$, Ac_2O, AcOH; c) NaOH, MeOH; d) DIAD, PPh_3, *N*3-benzoyluracil, CH_3CN; e) triazole, $POCl_3$, Et_3N, CH_3CN; f) NH_3, CH_3CN; g) DIAD, PPh_3, 6-chloropurine, THF; h) NH_3, MeOH; i) DIAD, PPh_3, 2-amino-6-chloropurine, THF; j) HCOOH; k) NH_3, MeOH.

route, the preparation of numerous new enantiomerically pure carbocyclic nucleosides was successfully achieved, except for the corresponding D-thymidine analogue (**12**), which has been isolated previously as a byproduct by Béres et al.[4b]

All of the chiral precursors were isolated as oils. Therefore, it was not possible to assign the absolute configuration of these molecules. Because both enantiomers of 3-(benzyloxymethyl)-cyclopent-3-enol (**8**) had not been prepared before, the determination of their optical rotations alone did

not allow for their assignment. To assign the configurations of (*S*)- and (*R*)-cyclopentenol (**8**) and, hence, of all of the other synthesized compounds, 6-chloropurine nucleosides D-**17** and L-**17** were used, which were obtained as crystalline compounds. The assignment of the absolute configuration of these purine derivatives was achieved by using X-ray crystallography (Figure 2 and Figure 3).[26] This result also allowed an assignment of the chirality of acetylated compound (*R*)-**9** and of cyclopentenol (*S*)-**8** that was obtained by kinetic resolution.

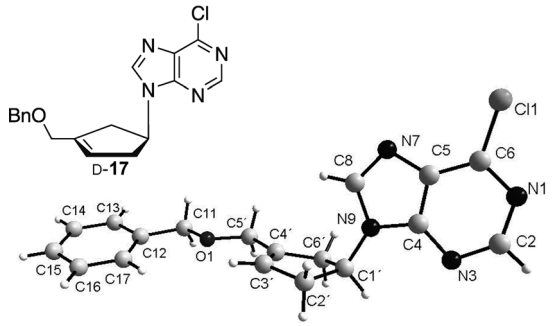


Figure 2. ORTEP of 5′-*O*-benzyl-2′,3′-dideoxy-3′,4′-didehydro-*carba*-D-6-chloro-6-deamino-adenosine (D-**17**).

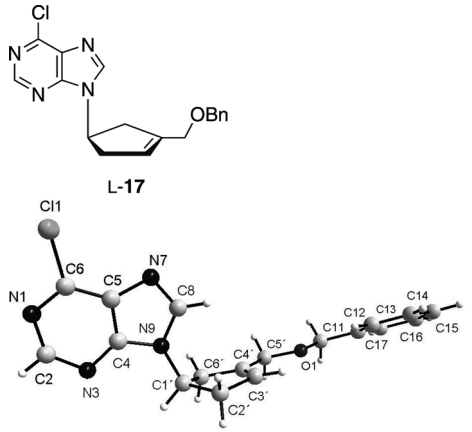
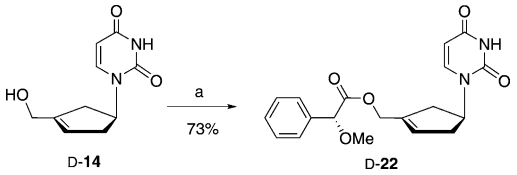


Figure 3. ORTEP of 5′-*O*-benzyl-2′,3′-dideoxy-3′,4′-didehydro-*carba*-L-6-chloro-6-deamino-adenosine (L-**17**).

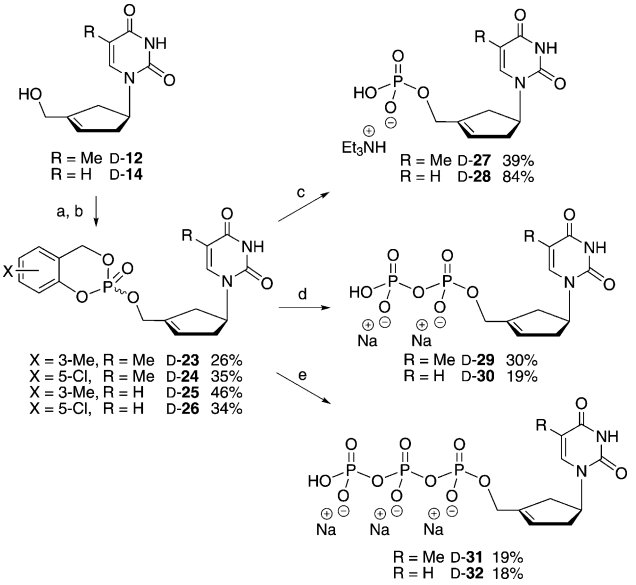
In addition, the optical purity of the prepared carbocyclic nucleoside D-**14** was examined by transformation into its corresponding diastereomers with (*R*)-(−)-methoxyphenylacetic acid (Scheme 6). The diastereomeric ratio of 5′-((2*R*)-methoxy-phenylacetate)-2′,3′-dideoxy-3′,4′-didehydro-*carba*-D-uridine (**22**) and, hence, the enantiomeric excess of D-**14** were determined by ^{1}H NMR spectroscopy. The excellent optical purity of the nucleoside correlates to that of its carbocyclic building block, which showed that all of the synthetic steps in this convergent route were highly stereospecific.

The carbocyclic D-nucleotides were synthesized from *cyclo*Sal nucleotides **23**–**26** as the starting materials.[27] By



Scheme 6. a) (*R*)-(−)-methoxyphenylacetic acid, DCC, DMAP, CH_2Cl_2.

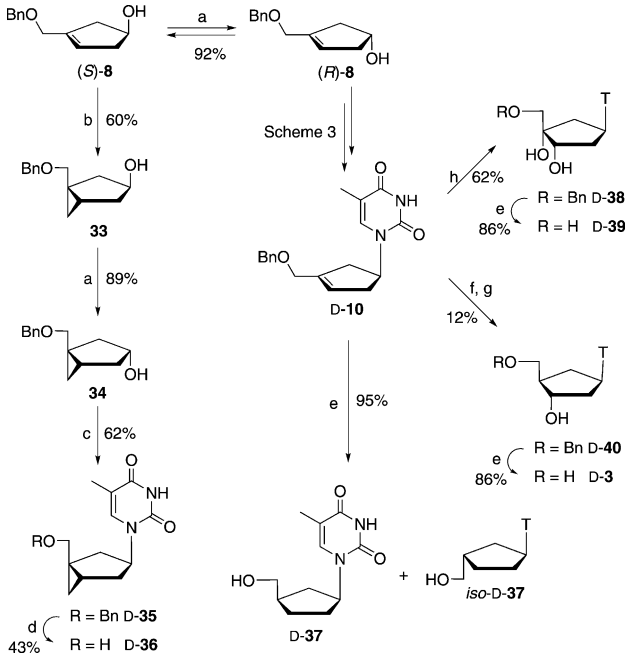
using CH_3CN, water, and triethylamine, D-nucleoside monophosphates **27** and **28** were obtained by hydrolysis of *cyclo*-Sal compounds **23** and **25**. Their corresponding di- and triphosphates (**29**–**32**) were synthesized from *cyclo*Sal-phosphate triesters **24** and **26** by reaction with either phosphate- or pyrophosphate salts as nucleophiles (Scheme 7). In the future, these nucleotides will be used in biological assays with kinases and polymerases, as well as viral enzymes, to evaluate the intracellular metabolic pathway of the carbocyclic nucleosides.



Scheme 7. a) Saligenyl chlorophosphite, DIPEA, CH_3CN; b) oxone in H_2O; c) CH_3CN, H_2O, Et_3N; d) bis(tetra-*n*-butylammonium)hydrogen phosphate, DMF; e) tris(tetra-*n*-butylammonium)hydrogen pyrophosphate, DMF.

Modification of the 3′-deoxy-3′,4′-didehydronucleosides: Furthermore, we established an enantioselective route to various modified carbocyclic nucleoside analogues starting from (*S*)-cyclopentenol (**8**, Scheme 8). In this process, it is possible to functionalize the double bond before or after the introduction of the nucleobase.[11] Cyclopropanation for the synthesis of carbobicyclic thymidine analogue D-**36** was carried out starting from (*S*)-cyclopentenol **8**.

The reaction, using the conditions reported by Furukawa et al., gave the *trans* product (**33**) in 60% yield.[28] The stereochemistry was confirmed by NOE experiments. In the NMR spectra, a strong NOE effect between the H1 atom



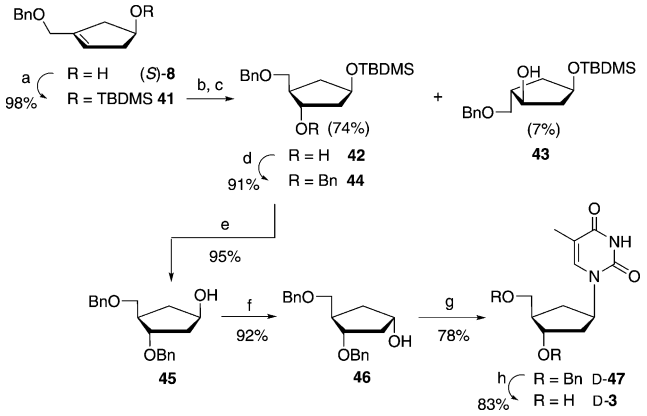
Scheme 8. a) PPh_3, DIAD, benzoic acid, Et_2O; b) CH_2I_2, Et_2Zn, CH_2Cl_2; c) DIAD, PPh_3, *N*3-benzoylthymine, CH_3CN; d) Pd/C, HCOOH; e) Pd/C, H_2, MeOH; f) disiamylborane, THF; g) $NaOH/H_2O_2$; h) NMO, K_2OsO_4, DMF.

and one proton of the cyclopropane group was observed, which confirmed the formation of the *trans* product (**33**). Conversion of the hydroxy group with PPh_3, DIAD, and benzoic acid led to *cis*-cyclopropanated alcohol **34** in 89% yield. In addition, the condensation of *N*3-benzoylthymine and *cis*-**34** was also achieved (Scheme 8). Finally, the benzyl protecting group in nucleoside D-**35** was cleaved by using Pd/C and formic acid to give bicyclic D-thymidine derivative **36** in 43% yield.

(*R*)-Configured alcohol **8** was used as a precursor to 5′-*O*-benzylated D-thymidine analogue **10**. This compound was transferred into the diastereomeric carbocyclic compound 3′-deoxy-2′,3′-didehydro-D-thymidine (**37** and *iso*-**37**, 3:1) in 95% yield by Pd/C-catalyzed hydrogenation and simultaneous debenzylation. The relative stereochemistry was determined by NOE spectroscopy. *cis*-Dihydroxylation was performed with D-**10**, $K_2OsO_4{\cdot}2H_2O$, and *N*-methylmorpholine-*N*-oxide (NMO) in DMF. The electrophilic addition at the cyclopentene moiety led to *cis*-diol D-**38** in 62% yield. Again, debenzylation to afford nucleoside D-**39** was achieved by hydrogenation.

Unfortunately, the hydroboration of thymidine analogue D-**10** with 9-borabicyclo[3.3.1]nonane (9-BBN) failed. Therefore, the nucleoside was treated with disiamylborane. However, from this reaction with *anti*-Markownikow orientation, carbocyclic *carba*-D-dT (**3**) was generated in a poor yield (12%).

***carba*-dT (3)**: Thus, a new synthetic route to *carba*-thymidine D-**3** was elaborated by using (*S*)-cyclopentenol (**8**,



Scheme 9. a) Imidazole, TBDMSCl, DMF; b) disiamylborane, THF; c) $NaOH/H_2O_2$; d) NaH, BnBr, TBAI, THF; e) TBAF, THF; f) DIAD, PPh_3, benzoic acid, Et_2O; g) DIAD, PPh_3, *N*3-benzoylthymine, CH_3CN; h) Pd/C, H_2, MeOH.

Scheme 9) that was obtained by chemoenzymatic kinetic resolution. First, alcohol (*S*)-**8** was protected by using *tert*-butyldimethylsilylchloride (TBDMS-Cl) in 98% yield. Then, the introduction of the additional hydroxy group with disiamylborane afforded diastereomeric cyclopentenols **42** and **43** in a ratio of 11:1 and chemical yields of 74% and 7%, respectively. The correct stereochemistry at the new stereocenters was confirmed by NOE spectroscopy. The two diastereomers were separated by column chromatography on silica gel and *trans*-cyclopentanol was benzylated in 91% yield. Deprotection of the TBDMS group was achieved with tetrabutylammonium fluoride (TBAF), thus yielding compound **45** in 95% yield. The inversion of the configuration at the secondary alcohol was easily carried out by a Mitsunobu inversion in 92% yield. Subsequent coupling of carbocyclic building block **46** and the nucleobase was again accomplished under Mitsunobu conditions in 78% yield by using *N*3-benzoylthymine as the nucleophile. The removal of the benzyl groups for the formation of compound D-**3** was achieved by Pd/C-catalyzed hydrogenation in 83% yield. The overall yield of *carba*-D-dT (**3**) averages 17% over 10 steps starting from cyclopentadiene. With this approach, a few grams of compound D-**3** were synthesized. Furthermore, this synthetic route also allows for the preparation of their corresponding L-nucleosides starting from compound (*R*)-**8**. Consequently, the chemoenzymatic approach reported herein is far more convenient then the previously published synthetic routes to carbocyclic 2′-deoxynucleosides.

Antiviral actvity of *carba*-thymidine (3): *carba*-dT has been studied previously concerning its antiviral potency against HIV. In contrast to a previous report,[4b] we found that *carba*-dT showed promising antiviral activity without increased toxicity.[4a,5] Moreover, studies with the triphosphate of *carba*-dT (*carba*-dTTP) in primer-extension assays by using DNA- or RNA-templates and the viral enzyme reverse transcriptase revealed an interesting mechanism of action. We observed that *carba*-dTTP was incorporated op-

posite the canonical 2′-deoxyadenosine and was further elongated with the following nucleotides but, after several *carba*-dT incorporations, the elongation of the growing DNA strand stopped. This mechanism was entitled a "delayed chain-termination".[5] A growing problem in antiviral chemotherapy is the development of drug-resistant virus strains. This problem has primarily been shown for different antiretroviral-active drugs that are currently being used in combination therapy against HIV/AIDS. Today, multicomponent highly active antiretroviral therapies (HAART) are very effective in decreasing the viral load in HIV-infected patients. However, if resistance develops in such a scenario, multidrug-resistant virus strains may easily emerge. Thus, there is an urgent need for new, effective drugs that target multidrug-resistant viruses. The efficacy of *carba*-dT (**3**) as an RT inhibitor was tested against wildtype HIV-1 (strain NL4/3) and two multidrug-resistant (MDR) HIV-1 clones. The MDR clones, E2-2 and 8ka3, contain a number of well-defined drug-resistant mutations that confer low susceptibility against a number of clinically approved anti-HIV drugs, such as nucleoside analogues and protease inhibitors. As given in the Experimental Section, both MDR viruses exhibit a number of thymidine-analogue mutations (TAMS), thereby conferring resistance to most of the currently licensed nucleo(t)side analogues that are used in clinical practice. Interestingly, D-*carba*-dT (**3**) showed a marked inhibitory effect against the virus replication of both MDR HIV-1 clones. D-*carba*-dT (**3**) inhibited the replication of MDR clone E2-2 in a clearly dose-dependent manner with an IC_{50} value of 0.03 μM (Figure 4). 8ka3 was also potently inhibited, albeit in a less-pronounced manner, with an IC_{50} value of 0.14 μM (not shown). The IC_{50} value for wildtype HIV-1 (NL4/3) was 0.18 μM, which is of the same order of magnitude as the IC_{50} values that were reported previously for different cell-lines and wildtype HIV-1 strains.[5] As expected, the IC_{50} values for MDR HIV-1 clones were lower than the IC_{50} values for wildtype HIV-1 because drug-resistant mutations are commonly associated with a viral-fitness cost (reviewed for RT-inhibitor-resistance mutations).[29] For comparison, the L-configured counterpart and the clinically used antiretroviral drug d4T (Stavudine) were also tested. L-*carba*-dT was entirely inactive in the tested concentration range for all of the tested viruses (E2-2, 8ka3, and NL4/3). d4T inhibited the replication of wildtype HIV-1 (NL4/3) with an IC_{50} value of <0.03 in our experimental setup and MDR clone E2-2, as expected, with a considerably higher IC_{50} value of 0.38 μM, owing to resistance mutations. Notably, none of the tested compounds exerted cellular toxicity in the tested concentration range (Figure 4, bottom). The IC_{50} value for the inhibition of NL4/3 by d4T is considerably lower than the values reported by Rosenblum et al. for different cell-lines and wildtype HIV-1 strains,[30] possibly owing to the relatively long duration of the virus culture of 6 days until readout in our assay. In general, assays with multiple rounds of viral replication give low IC_{50} values.

Although the underlying mechanism that is responsible for overcoming the resistance is still unclear, the strong antiviral activity against multidrug-resistant virus strains makes D-*carba*-dT a promising new compound to combat drug resistance in HIV infection.

Conclusion

Our chemoenzymatic approach offers a convenient route for the preparation of enantiomeric precursors (*S*)-**8** and (*R*)-**8** in high optical purity. Owing to the fact that, by using this procedure, only one stereocenter in this building block is created, it is an excellent key intermediate that allows direct access to either carbocyclic D- or L-2′,3′-dideoxy-3′,4′-didehydronucleosides. Moreover, various functionalization reactions lead to a series of new enantiomerically pure carbocyclic nucleoside and -nucleotide analogues. Furthermore, the general applicability of this carbocyclic precursor was also demonstrated by its use in a new synthetic route to carbocyclic 2′-deoxynucleosides. Finally, we demonstrated that D-*carba*-dT (**3**) exerts strong antiviral activity against multidrug-resistant virus strains, including multiple classical thymidine-analogue mutations, which makes it an attractive compound for thereapeutic approaches that aim to combat drug resistance in HIV.

Experimental Section

General: All experiments that involved water-sensitive compounds were conducted under rigorously dry conditions and under a nitrogen atmosphere. CH_2Cl_2, pyridine, and CH_3CN were distilled from CaH_2 and stored over molecular sieves. Et_2O and THF were distilled from sodium or potassium with benzophenone and stored over molecular sieves. Petroleum ether, EtOAc, CH_2Cl_2, and MeOH that were employed in column chromatography were distilled before use. Column chromatography on silica gel was performed by using silica gel 60, (230–400 mesh, Merck). Reversed-phase column chromatography was performed on reverse-phase silica gel with distilled water as the eluent at RT in a glass column. Ion-exchange chromatography was performed on Dowex (50WX8, 100–200 mesh, ion-exchange resin) in a glass column. Some separations were performed on a chromatotron by using glass plates that were coated with silica gel (60 PF_{254}, layer thickness 1 mm) that contained a fluorescent indicator. Analytical TLC was performed on precoated aluminium plates 60F254 (Merck) with a 0.2 mm layer of silica gel that contained a fluorescence indicator; the compounds were visualized with a spray reagent (4-methoxybenzaldehyde (0.5 mL), EtOH (9 mL), conc. H_2SO_4 (0.5 mL), and glacial AcOH (0.1 mL)) by heating with a heat gun. UV/Vis detection was performed at $\lambda_{max}=254$ nm. Pancreatin from porcine pancreas (CAS 8049–47–6, EC 232–468–9) and all of the isolated enzymes (CAS 9001–62–1, EC 232–619–9) were purchased from Sigma–Aldrich. ^{1}H NMR spectroscopy was either recorded on a Bruker AMX 400 at 400 MHz, on a Bruker DMX 500 at 500 MHz, or on a Bruker AV 400 at 400 MHz with residual solvent peaks used as the internal standard. ^{13}C NMR spectra were either recorded on a Bruker AMX 400 at 101 MHz, a Bruker AV 400 at 101 MHz, or on a DMX 500 at 126 MHz with residual solvent peaks used as the internal standard. All ^{1}H and ^{13}C NMR chemical shifts (δ) are quoted in parts per million (ppm). The spectra were recorded at RT and all ^{13}C NMR spectra were recorded in proton-decoupled mode. MS was either performed on a VG Analytical VG/70–250 F spectrometer (FAB, matrix: *m*-nitrobenzyl alcohol), a VG Analytical VG/70–250S spectrometer (double focused), or on a Finnigan ThermoQuest MAT 95XL (HRMS ESI). Optical rotations were measured on a P8000 polarimeter (A. Kruss Optonic GmbH) at

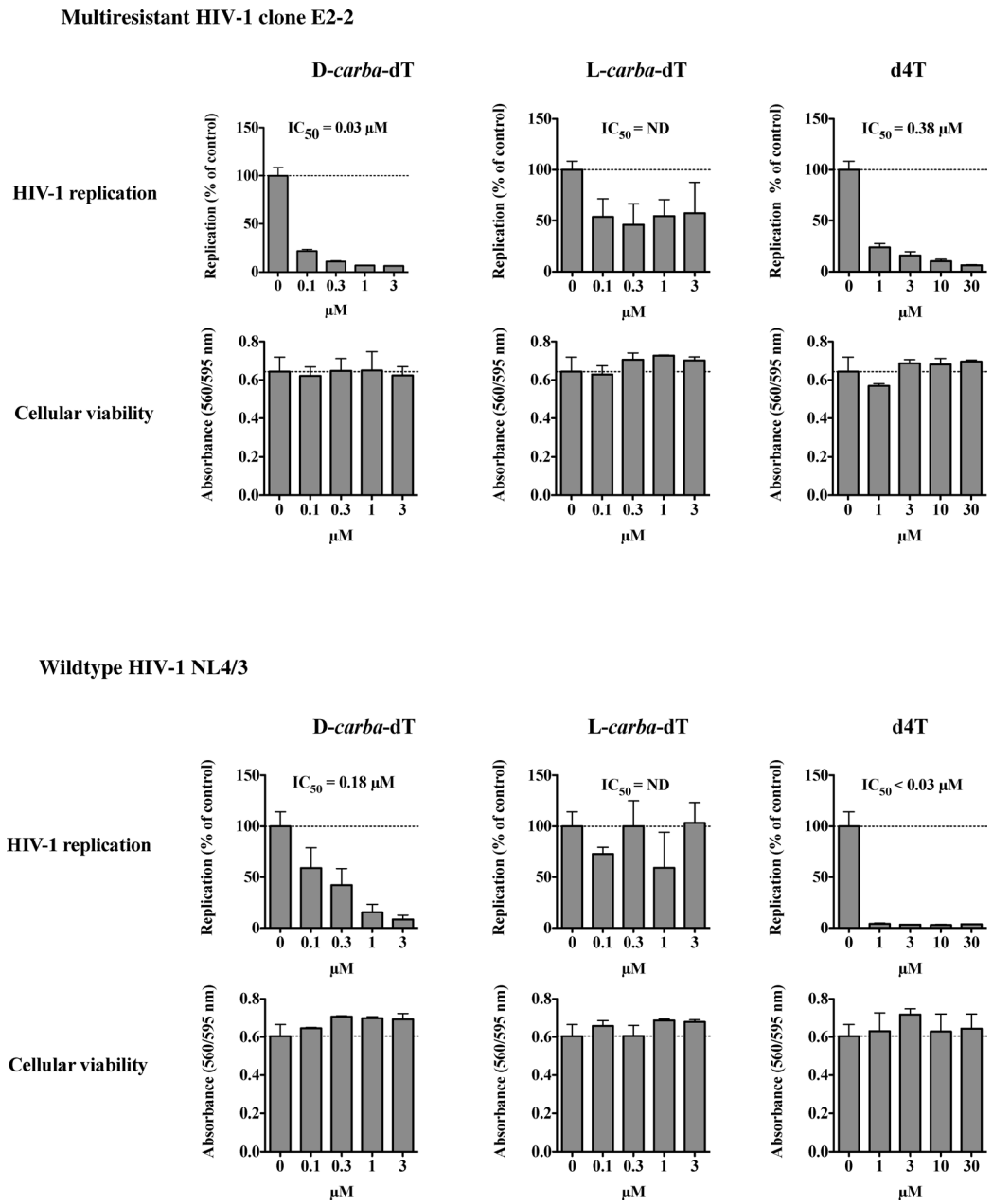


Figure 4. Antiretroviral activity and toxicity of D-*carba*-dT, L-*carba*-dT, and d4T. Top: Percentage of virus replication compared with replication under solvent-control (DMSO) cultures, which was arbitrarily set to 100% and shown as a dotted line. Bottom: AlamarBlue assays, which indicate cell viability from the same cultures. The dotted line indicates the absorbance in DMSO cultures. Mean values of two independent infections are shown. Error bars represent the standard deviation.

589 nm. IR spectra were recorded with a ThermoNicolet Avatar 370 FTIR spectrometer. For the X-ray crystal-structure analysis, data collection was performed on a Bruker Smart APEX CCD area-detector diffractometer. Analytical HPLC was carried out on a Merck-Hitachi D-7000 HPLC system that consisted of a Merck-Hitachi L-7100 pump, an autosampler, and a diode-array detector L-7455. The column used was a CHIRALPAK OD (CS-Chromatographie Service GmbH, Langerwehe, Germany; 250 mm × 4.6 mm) with cellulose tris(3,5-dimethylphenylcarbamate) coated on 100 µm silica gel (method 1: *n*-hexane/2-propanol (95:5, 0–30 min), *n*-hexane/2-propanol (60:40, 30–35 min), *n*-hexane/2-propanol (95:5, 30–40 min), flow rate: 1 mL min^{-1}, UV/Vis detection was performed at λ_{max} = 210 nm; method 2: *n*-hexane/2-propanol (98:2, 0–15 min), *n*-hexane/2-propanol (60:40, 15–20 min), *n*-hexane/2-propanol (98:2, 20–25 min), flow rate: 1 mL min^{-1}, UV/Vis detection was performed at λ_{max} = 210 nm).

Compounds *rac*-**8**, D-**36**, and D-**39** were synthesized according to a literature procedure.[11] Hydroboration with disiamylborane (D-**10**) for the preparation of compound D-**3** was carried out in a similar manner to a previously reported synthesis with 9-BBN.[11]

Kinetic resolution of *rac*-3-(benzyloxymethyl)-cyclopent-3-enol (*rac*-8): Optimal conditions: A suspension of racemic 3-(benzyloxymethyl)-cyclopent-3-enol (*rac*-**8**, 5.00 g, 24.5 mmol), pancreatin (25 g), vinyl acetate (4.54 mL, 49.0 mmol), and Et_3N (6.79 mL, 49.0 mmol) in acetone (170 mL) was stirred at room temperature. After 23 h, the mixture was filtered through celite and the filtrate was concentrated under reduced pressure. The crude product was analyzed by HPLC and then purified by

column chromatography on silica gel (petroleum ether/EtOAc, 4:1→2:1) to afford acetylated compound (*R*)-**9** (2.01 g, 8.16 mmol, 33%, >98% *ee*) as a yellow oil after 44% conversion. $[\alpha]_{589}^{25}=-15.4°$ ($c=0.5$, $CHCl_3$); R_f (petroleum ether/EtOAc, 2:1)=0.86; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 7.38–7.27 (m, 5H; aromatic C*H*), 5.66–5.61 (m, 1H; H4), 5.42–5.36 (m, 1H; H1), 4.52–4.49 (m, 2H; benzyl CH_2), 4.07 (s, 2H; OCH_2), 2.84–2.73 (m, 2H; H2a, H5a), 2.46–2.37 (m, 2H; H2b, H5b), 2.03 ppm (s, 3H; Ac CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=171.2$ (C_q Ac), 139.2 (C3), 138.3 (aromatic C_q), 128.5 (aromatic *C*H), 127.9 (aromatic *C*H), 127.8 (aromatic *C*H), 125.0 (C4), 74.6 (C1), 72.3 (benzyl CH_2), 68.6 (OCH_2), 40.2 (C2), 39.7 (C5), 21.5 ppm (Ac CH_3); IR (film): $\tilde{\nu}=2856$, 1732, 1454, 1362, 1241, 2072, 1026, 736, 697, 606 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{15}H_{18}O_3$: 247.1334 $[M+H]^+$; found: 247.1333.

Alcohol (*S*)-**8** (2.81 g, 13.8 mmol, 56%, 77% *ee*) was used in a second kinetic resolution to increase the enantiomeric excess of compound (*S*)-**8**. The reaction was done under the same conditions as described above, but with only 1.5 equiv of pancreatin. In this reaction, alcohol (*S*)-**8** (1.86 g, 9.11 mmol, 37%, 93% *ee*) was obtained after 6 h. $[\alpha]_D^{25}=+20.0°$ ($c=0.25$, CH_2Cl_2/MeOH 1:1). The spectroscopic data for alcohol (*S*)-**8** were identical to those described for *rac*-**8**.

Conditions for different enzymes: A suspension of racemic 3-(benzyloxymethyl)-cyclopent-3-enol *rac*-**8** (15 mg, 0.073 mmol), vinyl acetate (14 μL, 0.15 mmol), Et_3N (20 μL, 0.15 mmol), and the respective enzyme in acetone or toluene (2 mL) was stirred at room temperature. After different time intervals, samples were taken, filtered through celite, and the filtrate was concentrated under reduced pressure. The crude product was analyzed by HPLC.

(*R*)-3-(Benzyloxymethyl)-cyclopent-3-en-1-ol ((*R*)-8): For the deacetylation reaction, (*R*)-**9** (0.878 g, 4.30 mmol) was stirred in NaOH (2.5 M in MeOH, 25 mL) for 2 h at room temperature. After neutralization with aqueous HCl (1 M), MeOH was evaporated and the aqueous layer was extracted with Et_2O (3×25 mL). The combined organic fractions were dried with Na_2SO_4 and the solvent was removed under reduced pressure. Alcohol (*R*)-**8** (4.26 mmol, 99%, 96% *ee*) was obtained as a yellow oil. $[\alpha]_{589}^{25}=-19.4°$ ($c=1.0$, $CHCl_3$). The spectroscopic data were identical to those described for *rac*-**8**.

General procedure for the inversion of the stereochemistry of the hydroxy group: Diisopropylazodicarboxylate (DIAD, 2 equiv) was slowly added to a suspension of PPh_3 (2 equiv) in Et_2O at 0°C under a nitrogen atmosphere and stirred for 0.5 h. This yellow suspension was added to a solution of the alcohol (1 equiv) and benzoic acid (2 equiv) in Et_2O at 0°C. The reaction mixture was stirred at room temperature until complete conversion was observed by TLC analysis; the mixture was then filtered and concentrated. The residue was treated with a solution of NaOH (1% in MeOH) and stirred overnight. After neutralization with HCl (1 M), the solvent was evaporated and the crude product was purified.

(*R*)-3-(Benzyloxymethyl)-cyclopent-3-en-1-ol ((*R*)-8): The Mitsunobu-inversion reaction was carried out according to the general procedure (see above) with (*S*)-3-(benzyloxymethyl)-cyclopent-3-enol ((*S*)-**8**, 1.00 g, 4.90 mmol), benzoic acid (1.20 g, 9.80 mmol) in Et_2O (30 mL), and DIAD (1.92 mL, 9.80 mmol), PPh_3 (2.57 g, 9.80 mmol) in Et_2O (30 mL). The reaction mixture was stirred for 16 h and was treated with a solution of NaOH (1% in MeOH, 25 mL). The crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc, 2:1) to yield compound (*R*)-**8** (995 mg, 4.87 mmol, 99%) as a yellow syrup. The spectroscopic data were identical to those described for *rac*-**8**.

General procedure for the coupling of *N*3-protected pyrimidines to cyclopentenol: DIAD (2.8 equiv) was slowly added to a suspension of PPh_3 (3 equiv) in CH_3CN at 0°C under a nitrogen atmosphere and the mixture was stirred for 0.5 h. This preformed complex was slowly added to a solution of *N*3-protected pyrimidine (2 equiv) and cyclopentenol (1 equiv) in CH_3CN at −50°C. The reaction mixture was stirred at −40°C for 2 h before being slowly warmed to room temperature and stirred until complete conversion was observed by TLC. The solvent was removed and the residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 1:2) to remove the triphenylphosphine oxide. The benzoyl-protected nucleoside was treated with a solution of NaOH (1% in MeOH) and the mixture was stirred overnight at room temperature. After neutralization with aqueous HCl (1 M), the solvent was evaporated and the crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc, 2:1).

5′-*O*-Benzyl-3′-deoxy-3′,4′-didehydro-*carba*-D-thymidine (D-10): The reaction was carried out according to the general coupling procedure (see above) with a solution of (*R*)-3-(benzyloxymethyl)-cyclopent-3-enol ((*R*)-**8**, 500 mg, 2.45 mmol) and *N*3-benzoyl-protected thymine (1.13 g, 4.90 mmol) in CH_3CN (45 mL) and a preformed complex of PPh_3 (1.95 g, 7.45 mmol) and DIAD (1.35 mL, 6.86 mmol) in CH_3CN (30 mL). The reaction mixture was stirred for 36 h and, after purification, benzylated nucleoside D-**17** (573 mg, 1.84 mmol, 75%) was obtained as a yellow oil. $[\alpha]_{589}^{25}=+28.3°$ ($c=1.0$, $CHCl_3$); R_f (petroleum ether/EtOAc, 1:2)=0.37; ^{1}H NMR (500 MHz, C_6D_6): $\delta=9.84$ (br s, 1H; N*H*), 7.28–7.03 (m, 5H; aromatic C*H*), 6.44 (d, $^4J=1.1$ Hz, 1H; H6), 5.28–5.25 (m, 1H; H3′), 5.12–5.11 (m, 1H; H1′), 4.26 (s, 2H; benzyl CH_2), 3.73–3.63 (m, 2H; H5′), 2.41–2.30 (m, 2H; H6′a, H2′a), 1.96–1.92 (m, 1H; H2′b), 1.91–1.88 (m, 1H; H6′b), 1.65 ppm (d, $^4J=1.0$ Hz, 3H; thymine CH_3); ^{13}C NMR (101 MHz, C_6D_6): $\delta=162.3$ (C4), 151.5 (C2), 138.5 (aromatic C_q), 136.3 (C6), 128.9 (aromatic *C*H), 128.7 (aromatic *C*H), 128.3 (aromatic *C*H), 125.3 (C3′), 124.8 (C4′) 111.5 (C5), 72.8 (benzyl CH_2), 68.6 (C5′), 53.6 (C1′), 39.4 (C2′), 39.3 (C6′), 12.9 ppm (thymine CH_3); IR (film): $\tilde{\nu}=3854$, 3450, 2081, 1666, 1459, 1383, 1203, 1093, 1028, 699 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{18}H_{20}N_2O_3$: 313.1552 $[M+H]^+$; found: 313.1541.

5′-*O*-Benzyl-3′-deoxy-3′,4′-didehydro-*carba*-L-thymidine (L-17): The reaction was carried out according to the general coupling procedure (see above) with a solution of (*S*)-3-(benzyloxymethyl)-cyclopent-3-enol (*S*)-**8** (214 mg, 0.685 mmol) and *N*3-benzoyl-protected thymine (539 mg, 2.06 mmol) in CH_3CN (15 mL) and a preformed complex of PPh_3 (539 mg, 2.06 mmol) and DIAD (0.380 mL, 1.92 mmol) in CH_3CN (20 mL). The reaction mixture was stirred for 36 h and, after purification, benzylated nucleoside L-**17** (154 mg, 0.493 mmol, 72%) was obtained as a yellow syrup. $[\alpha]_{589}^{25}=-25.9°$ ($c=1.0$, $CHCl_3$). The spectroscopic data were identical to those described for D-**17**.

5′-*O*-Benzyl-2′,3′-dideoxy-3′,4′-didehydro-*carba*-D-uridine (D-13): The reaction was carried out according to the general coupling procedure (see above) with a solution of (*R*)-3-(benzyloxymethyl)-cyclopent-3-enol (*R*)-**8** (482 mg, 2.36 mmol) and *N*3-benzoyl-protected uracil (1.02 g, 4.72 mmol) in CH_3CN (50 mL) and a preformed complex of PPh_3 (1.86 g, 7.08 mmol) and DIAD (1.30 mL, 6.61 mmol) in CH_3CN (35 mL). The reaction mixture was stirred for 24 h and, after purification, benzylated nucleoside D-**13** (473 mg, 1.59 mmol, 67%) was obtained as a yellow oil. $[\alpha]_{589}^{25}=+21.5°$ ($c=1.0$, $CHCl_3$); R_f (petroleum ether/EtOAc, 1:2)=0.20; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.95$ (br s, 1H; N*H*), 7.30–7.18 (m, 5H; aromatic C*H*), 7.09 (d, $^3J=8.2$ Hz, 1H; H6), 5.65–5.63 (m, 1H; H3′), 5.59 (d, $^3J=7.9$ Hz, 1H; H5), 5.29–5.24 (m, 1H; H1′), 4.44 (s, 2H; benzyl CH_2), 4.06–3.95 (m, 2H; H5′) 2.91–2.81 (m, 2H; H2′a, H6′a), 2.34–2.28 ppm (m, 2H; H2′b, H6′b); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=163.1$ (C4), 150.8 (C2), 140.9 (C5), 140.6 (C4′), 138.1 (aromatic C_q), 128.6 (aromatic *C*H), 128.0 (aromatic *C*H), 127.8 (aromatic *C*H), 125.4 (C3′), 103.2 (C6), 72.9 (benzyl CH_2), 68.4 (C5′), 53.4 (C1′), 40.0 (C2′), 39.8 ppm (C6′); IR (film): $\tilde{\nu}=3032$, 2853, 1672, 1463, 1370, 1263, 1074, 820, 696, 552, 417 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{17}H_{18}N_2O_3$: 299.1396 $[M+H]^+$; found: 299.1384.

5′-*O*-Benzyl-2′,3′-dideoxy-3′,4′-didehydro-*carba*-L-uridine (L-13): The reaction was carried out according to the general coupling procedure (see above) with a solution of (*S*)-3-(benzyloxymethyl)-cyclopent-3-enol (*S*)-**13** (425 mg, 2.08 mmol) and *N*3-benzoyl-protected uracil (740 mg, 4.16 mmol) in CH_3CN (50 mL) and a preformed complex of PPh_3 (1.64 g, 6.24 mmol) and DIAD (1.03 mL, 5.83 mmol) in CH_3CN (35 mL). The reaction mixture was stirred for 24 h and, after purification, benzylated nucleoside L-**13** (376 mg, 1.26 mmol, 61%) was obtained as a yellow solid. $[\alpha]_{589}^{25}=-18.9°$ ($c=1.0$, $CHCl_3$). The spectroscopic data were identical to those described for D-**13**.

5′-*O*-Benzyl-2′,3′-dideoxy-3′,4′-didehydro-*carba*-D-cyctidine (D-15): Phosphoryl chloride (0.078 mL, 0.86 mmol) and Et_3N (0.53 mL, 3.8 mmol) were added dropwise to a solution of 1,2,4-triazole (0.266 g, 3.85 mmol) in CH_3CN (5 mL) under a nitrogen atmosphere at 0°C and the mixture

was stirred for 0.5 h at the same temperature. To the resulting product was slowly added a solution of benzyl-protected uridine derivative D-**13** (85.0 mg, 0.285 mmol) in CH_3CN (3 mL) and the reaction mixture was stirred for 2 days at room temperature. The solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc (5 mL) and a saturated aqueous solution of sodium hydrogen carbonate (3×5 mL). The organic layer was washed with a saturated aqueous solution of sodium chloride (3×5 mL) and the combined aqueous layer was extracted with EtOAc (5 mL). The combined organic fractions were dried with Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The residue was dissolved in CH_3CN (5 mL) and treated with a solution of aqueous ammonia (25%, 3 mL). The reaction mixture was stirred for 7 days. The solvent was evaporated and the residue was partitioned between CH_2Cl_2 (5 mL) and water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (4×5 mL) and the organic layer was washed with a saturated aqueous solution of sodium chloride (2×5 mL). The combined organic fractions were dried with Na_2SO_4 and the solvent was evaporated. The crude product was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 9:1) to yield compound D-**15** (62.8 mg, 0.211 mmol, 74%) as a yellow solid. $[\alpha]_{589}^{25}=-15.6°$ ($c=1.0$, $CHCl_3$); m.p. 137 °C; R_f (CH_2Cl_2/MeOH, 9:1) = 0.64; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 7.38–7.28 (m, 5H; aromatic C*H*), 7.23 (d, $^3J=7.3$ Hz, 1H; H6), 5.77 (d, $^3J=7.3$ Hz, 1H; H5), 5.73–5.68 (m, 1H; H3′), 5.49–5.41 (m, 1H; H1′), 4.52 (s, 2H; benzyl CH_2), 4.10–4.03 (m, 2H; H5′), 2.99–2.85 (m, 2H; H2′a, H6′a), 2.42–2.34 ppm (m, 2H; H2′b, H6′b); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=$165.3 (C2), 156.4 (C4), 141.9 (C6), 140.4 (C4′), 138.2 (aromatic C_q), 128.6 (aromatic *C*H), 127.8 (aromatic *C*H), 127.8 (aromatic *C*H), 125.6 (C3′), 95.3 (C5), 72.7 (benzyl CH_2), 68.5 (C5′), 54.0 (C1′), 40.3 (C2′/C6′), 40.1 ppm (C2′/C6′); IR (film): $\tilde{\nu}=$3344, 1920, 2852, 1618, 1524, 1483, 1398, 1279, 1070, 906, 786, 726, 598 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{17}H_{19}N_3O_2$: 298.1556 $[M+H]^+$; found: 298.1554.

5′-*O*-Benzyl-2′,3′-dideoxy-3′,4′-didehydro-*carba*-L-cytidine (L-15): The reaction was carried out as described for compound D-**15** with a solution of benzyl-protected uridine derivative L-**13** (150 mg, 0.503 mmol) in CH_3CN (5 mL) and a mixture of 1,2,4-triazole (0.931 g, 6.78 mmol), phosphoryl chloride (0.140 mL, 1.51 mmol) and Et_3N (0.940 mL, 6.80 mmol) in CH_3CN (12 mL). The reaction mixture was stirred for 2 days. The residue was dissolved in CH_3CN (5 mL) and treated with aqueous ammonia (25%, 4 mL). The mixture was stirred for 7 days at room temperature. After column chromatography on silica gel (CH_2Cl_2/MeOH, 9:1), compound L-**15** (118 mg, 0.397 mmol, 79%) was isolated as a yellow solid. $[\alpha]_{589}^{25}=+14.4°$($c$=1.0, $CHCl_3$). The spectroscopic data were identical to those described for D-**15**.

General procedures for the debenzylation reaction: Procedure 1: Benzyl-protected nucleoside (1 equiv), was dissolved in Ac_2O/AcOH (5:1) and the solution was added to a solution of freshly melted $ZnCl_2$ (5 equiv) in Ac_2O/AcOH (5:1). The mixture was stirred at room temperature until complete conversion was observed by TLC. The reaction was stopped by the addition of water and the mixture was extracted with CH_2Cl_2. The combined organic layers were neutralized with a saturated aqueous solution of sodium hydrogen carbonate, dried with Na_2SO_4, and the solvent was evaporated. Procedure 2: The residue was treated with a solution of NaOH (1% in MeOH) at room temperature until complete conversion was observed by TLC. The reaction mixture was neutralized with HCl (1 M), MeOH was evaporated, and, after lyophilization, the crude product was purified by column chromatography on silica gel.

5′-*O*-Acetyl-3′-deoxy-3′,4′-didehydro-*carba*-D-thymidine (D-11): A solution of benzylated nucleoside D-**10** (307 mg, 0.983 mmol) in Ac_2O/AcOH (5:1, 5 mL) was deprotected according to general debenzylation procedure 1 (see above) with a solution of $ZnCl_2$ (670 mg, 4.92 mmol) in Ac_2O/AcOH (5:1, 5 mL). The mixture was stirred for 12 h and purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 20:1) to obtain D-(212 mg, 0.802 mmol, 82%) as a colorless solid. $[\alpha]_{589}^{25}=+17.2°$ ($c=1.0$, $CHCl_3$); m.p. 137 °C; R_f (CH_2Cl_2/MeOH, 20:1) = 0.37; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=$9.17 (br s, 1H; N*H*), 6.97 (d, $^4J=1.0$ Hz, 1H; H6), 5.78–5.73 (m, 1H; H3′), 5.44–5.37 (m, 1H; H1′), 4.71–4.62 (m, 2H; H5′), 3.01–2.87 (m, 2H; H2a′, H6a′), 2.46–2.34 (m, 2H; H2b′, H6b′), 2.09 (s, 3H; Ac CH_3), 1.91 ppm (d, $^4J=1.0$ Hz, 3H; thymine CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=$170.8 (Ac C_q), 163.9 (C4), 151.0 (C2), 138.2 (C4′), 136.4 (C6), 126.7 (C3′), 111.9 (C5), 62.5 (C5′), 52.9 (C1′), 39.8 (C2′/C6′), 39.6 (C2′/C6′), 20.9 (Ac CH_3), 12.7 ppm (thymine CH_3); IR (film): $\tilde{\nu}=$ 3171, 3044, 2925, 2854, 1739, 1681, 1469, 1387, 1270, 1228, 1118, 1027, 870, 667 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{13}H_{16}N_2O_4$: 265.1188 $[M+H]^+$; found: 265.1186.

5′-*O*-Acetyl-3′-deoxy-3′,4′-didehydro-*carba*-L-thymidine (L-11): A solution of benzylated nucleoside L-**10** (147 mg, 0.470 mmol) in Ac_2O/AcOH (5:1, 1.5 mL) was deprotected according to general debenzylation procedure 1 (see above) with a solution of $ZnCl_2$ (320 mg, 2.35 mmol) in Ac_2O/AcOH (5:1, 3 mL). The mixture was stirred for 23 h purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 20:1) to obtain nucleoside L-**11** (83.7 mg, 0.371 mmol, 79%) as a colorless solid. $[\alpha]_{589}^{25}=-16.8°$ ($c=1.0$, $CHCl_3$). The spectroscopic data were identical to those described for D-**11**.

3′-Deoxy-3′,4′-didehydro-*carba*-D-thymidine (D-12): Acetylated nucleoside D-**11** (75.7 mg, 0.286 mmol) was treated with a solution of NaOH (1% in MeOH, 10 mL) at room temperature until complete conversion was observed by TLC analysis. The reaction mixture was neutralized with HCl (1 M), MeOH was evaporated, and, after lyophilization, the crude product was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 15:1) to yield carbocyclic nucleoside D-**12** (46.5 mg, 0.209 mmol, 73%) as a colorless solid. $[\alpha]_{589}^{25}=+24.1°$ ($c=0.5$, MeOH); m.p. 137 °C; R_f (CH_2Cl_2/MeOH, 9:1) = 0.42; ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta=$11.20 (br s, 1H; N*H*), 7.14 (d, $^4J=1.3$ Hz, 1H; H6), 5.46–5.42 (m, 1H; H3′), 4.98–4.88 (m, 1H; H1′), 4.06 (s, 2H; H5′), 3.17 (d, $^3J=4.1$ Hz, 1H; OH′), 2.48–2.42 (m, 1H; H2′a), 2.42–2.31 (m, 1H; H6′a), 2.30–2.20 (m, 1H; H2′b), 1.76 (d, $^4J=1.3$ Hz, 3H; thymine CH_3), 1.71–1.59 ppm (m, 1H; H6′b); ^{13}C NMR (101 MHz, [D$_6$]DMSO): $\delta=$163.9 (C4), 153.1 (C4′), 150.9 (C2), 137.1 (C6), 121.2 (C6′), 109.1 (C5), 60.4 (C1′), 59.9 (C5′), 30.9 (C3′), 30.3 (C2′), 12.2 ppm (thymine CH_3); IR (film): $\tilde{\nu}=$3448, 2252, 2126, 1676, 1054, 1027, 1008, 824, 762, 627 cm^{-1}; UV/Vis (CH_3CN): $\lambda_{max}=$ 271 nm; HRMS (FAB): *m/z* calcd for $C_{11}H_{14}N_2O_3$: 223.1083 $[M+H]^+$; found: 223.1100.

3′-Dideoxy-3′,4′-didehydro-*carba*-L-thymidine (L-12): Acetylated nucleoside L-**11** (51.1 mg, 0.286 mmol) was treated with a solution of NaOH (1% in MeOH, 10 mL) at room temperature until complete conversion was observed. The reaction mixture was neutralized with HCl (1 M), the MeOH was evaporated off and after lyophilization the crude product was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 15:1) to yield the carbocyclic nucleoside L-**12** (32.3 mg, 0.145 mmol, 75%) as a colorless solid. $[\alpha]_{589}^{25}=-22.4°$ ($c=0.7$, MeOH). The spectroscopic data were identical to those described for D-**12**.

2′,3′-Dideoxy-3′,4′-didehydro-*carba*-D-uridine (D-14): A solution of benzylated nucleoside D-**13** (157 mg, 0.526 mmol) in Ac_2O/AcOH (5:1, 4 mL) was deprotected according to general debenzylation procedure 2 (see above) with a solution of $ZnCl_2$ (541 mg, 3.97 mmol) in Ac_2O/AcOH (5:1, 4 mL). The mixture was stirred for 18 h at room temperature and the obtained intermediate was treated with a solution of NaOH (1% in MeOH). After column chromatography on silica gel (CH_2Cl_2/MeOH, 15:1), debenzylated nucleoside D-**14** (58.1 mg, 0.279 mmol, 53%) was obtained as a colorless solid. $[\alpha]_{589}^{25}=+20.2°$ ($c=0.58$, MeOH); R_f (CH_2Cl_2/MeOH, 15:1) = 0.48; ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta=$11.25 (s, 1H; N*H*), 7.41 (d, $^3J=8.0$ Hz, 1H; H6), 5.85–5.83 (m, 1H; H3′), 5.58 (d, $^3J=$ 8.0 Hz, 1H; H5), 5.16–5.08 (m, 1H; H1′), 4.34 (s, 2H; H5′), 2.87–2.76 (m, 2H; H2′a, H6′a), 2.46–2.42 ppm (m, 2H; H2′b, H6′b); ^{13}C NMR (101 MHz, [D$_6$]DMSO): $\delta=$163.3 (C4), 150.8 (C2), 145.7 (C4′), 142.0 (C6), 128.7 (C3′), 109.3 (C5), 53.6 (C1′), 43.0 (C5′), 38.4 (C6′) 38.4 ppm (C2′); IR (film): $\tilde{\nu}=$3433, 3006, 2819, 1686, 1460, 1379, 1272, 1055, 1008, 760 cm^{-1}; UV/Vis (CH_3CN): $\lambda_{max}=$263, 213 nm; HRMS (FAB): *m/z* calcd for $C_{10}H_{12}N_2O_3$: 209.0926 $[M+H]^+$; found: 209.0925.

2′,3′-Dideoxy-3′,4′-didehydro-*carba*-L-uridine (L-14): A solution of benzylated nucleoside L-**13** (131 mg, 0.439 mmol) in Ac_2O/AcOH (5:1, 3 mL) was deprotected according to general debenzylation procedure 2 (see above) with a solution of $ZnCl_2$ (500 mg, 3.70 mmol) in Ac_2O/AcOH (5:1, 8 mL). The mixture was stirred for 13 h at room temperature and the obtained intermediate was treated with a solution of NaOH (1% in MeOH). After column chromatography on silica gel (CH_2Cl_2/MeOH,

15:1), debenzylated nucleoside L-**14** (60.6 mg, 0.291 mmol, 62%) was obtained as a colorless solid. $[\alpha]_{589}^{25} = -19.5°$ ($c = 0.14$, MeOH). The spectroscopic data were identical to those described for D-**14**.

2′,3′-Dideoxy-3′,4′-didehydro-*carba*-D-cytidine (D-16): A solution of benzylated nucleoside D-**15** (53.1 mg, 0.179 mmol) in Ac_2O/AcOH (5:1, 1 mL) was deprotected according to general debenzylation procedure 2 (see above) with a solution of $ZnCl_2$ (122 mg, 0.893 mmol) in Ac_2O/AcOH (5:1, 4 mL). The mixture was stirred for 24 h at room temperature and the obtained intermediate was treated with a solution of NaOH (1% in MeOH). After column chromatography on silica gel (CH_2Cl_2/MeOH, 5:1), debenzylated nucleoside D-**16** (27.6 mg, 0.093 mmol, 52%) was obtained as a colorless solid. $[\alpha]_{589}^{25} = +8.4°$ ($c = 0.28$, MeOH); R_f (CH_2Cl_2/MeOH, 5:1) = 0.14; ^{1}H NMR (400 MHz, CD_3OD): $\delta = 7.55$ (d, $^3J = 7.3$ Hz, 1H; H6), 5.95 (d, $^3J = 7.1$ Hz, 1H; H5), 5.70–5.64 (m, 1H; H3′), 5.40–5.31 (m, 1H; H1′), 4.20–4.10 (m, 2H; H5′), 2.97–2.83 (m, 2H; H2′a, H6′a), 2.51–2.41 ppm (m, 2H; H2′b, H6′b); ^{13}C NMR (101 MHz, CD_3OD): $\delta = 166.9$ (C2), 159.1 (C4), 144.5 (C6), 143.9 (C4′), 96.9 (C5), 61.4 (C5′), 56.4 (C1′), 40.2 (C2′/C6′), 40.1 ppm (C2′/C6′); IR (film): $\tilde{\nu} = 3342$, 1635, 1568, 1498, 1450, 1013, 787 cm^{-1}; UV/Vis (CH_3CN): $\lambda_{max} = 271$ nm; HRMS (FAB): *m/z* calcd for $C_{10}H_{13}N_3O_2$: 208.1086 $[M+H]^+$; found: 208.1091.

2′,3′-Dideoxy-3′,4′-didehydro-*carba*-L-cytidine (L-16): A solution of benzylated nucleoside L-**15** (82.1 mg, 0.276 mmol) in Ac_2O/AcOH (5:1, 1.5 mL) was deprotected according to general debenzylation procedure 2 (see above) with a solution of $ZnCl_2$ (282 mg, 2.07 mmol) in Ac_2O/AcOH (5:1, 3 mL). The mixture was stirred for 35 h at room temperature and the obtained intermediate was treated with a solution of NaOH (1% in MeOH). After column chromatography on silica gel (CH_2Cl_2/MeOH, 5:1), debenzylated nucleoside L-**16** (22.1 mg, 0.107 mmol, 39%) was obtained as a colorless solid. $[\alpha]_{589}^{25} = -9.5°$ (c=0.21, $CHCl_3$). The spectroscopic data were identical to those described for D-**16**.

General procedure for the coupling of chloropurine to cyclopentenol: To a suspension of PPh_3 (3 equiv) in THF was slowly added DIAD (2.8 equiv) at 0°C under a nitrogen atmosphere and the mixture was stirred for 0.5 h. The preformed complex was slowly added to a solution of 6-chloropurine or 2-amino-6-chloropurine (1.5 equiv) and cyclopentenol (1 equiv) in THF at −50°C. The mixture was stirred at −40°C for 2 h, slowly warmed to room temperature, and stirred until complete conversion was observed by TLC. The solvent was evaporated and the crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc, 2:1→1:2).

5′-*O*-Benzyl-2′,3′-dideoxy-3′,4′-didehydro-*carba*-D-6-chloro-6-deamino-adenosine (D-17): The reaction was carried out according to the general coupling procedure (see above) with a solution of compound (*R*)-**8** (400 mg, 1.96 mmol) and 6-chloropurine (454 mg, 2.94 mmol) in THF (35 mL) and a preformed complex of PPh_3 (1.54 g, 5.87 mmol) and DIAD (1.08 mL, 5.48 mmol) in THF (30 mL). The mixture was stirred for 3 days and, after purification, benzylated nucleoside D-**17** (536 mg, 1.57 mmol, 80%) was obtained as a crystalline, colorless solid. $[\alpha]_{589}^{25} = +19.5°$ ($c = 1.0$, $CHCl_3$); m.p. 67°C; R_f (petroleum ether/EtOAc, 1:2) = 0.41; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.53$ (s, 1H; H2), 7.97 (s, 1H; H8), 7.37–7.27 (m, 5H; aromatic C*H*), 5.84–5.80 (m, 1H; H3′), 5.43–5.36 (m, 1H; H1′), 4.55 (s, 2H; benzyl CH_2), 4.18 (s, 2H; H5′), 3.14–3.02 (m, 2H; H2′a, H6′a), 2.77–2.67 ppm (m, 2H; H2′b, H6′b); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 161.2$ (C6), 152.0 (C2), 151.8 (C4), 140.4 (C8), 138.1 (aromatic C_q), 128.6 (aromatic *C*H), 127.8 (aromatic *C*H), 125.1 (C3′), 72.8 (benzyl CH_2), 68.4 (C5′), 53.7 (C1′), 40.7 (C6′), 40.3 ppm (C2′); IR (film): $\tilde{\nu} = 2953$, 2854, 1471, 1252, 1067, 892, 832, 773, 669 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{18}H_{17}ClN_4O$: 341.1169 $[M+H]^+$; found: 341.1182.

5′-*O*-Benzyl-2′,3′-dideoxy-3′,4′-didehydro-*carba*-L-6-chloro-6-deamino-adenosine (L-17): The reaction was carried out according to the general coupling procedure (see above) with a solution of compound (*S*)-**8** (200 mg, 1.47 mmol) and 6-chloropurine (277 mg, 1.47 mmol) in THF (12 mL) and a preformed complex of PPh_3 (700 mg, 2.34 mmol) and DIAD (0.540 mL, 2.74 mmol) in THF (10 mL). The mixture was stirred for 3 days and, after purification, benzylated nucleoside L-**17** (246 mg, 0.722 mmol, 74%) was obtained as a crystalline, colorless solid. $[\alpha]_{589}^{25} = -18.3°$ ($c = 1.0$, $CHCl_3$). The spectroscopic data were identical to those described for D-**17**.

5′-*O*-Benzyl-2′,3′-dideoxy-3′,4′-didehydro-*carba*-D-adenosine (D-18): Chloropurine derivative D-**17** (180 mg, 0.528 mmol) was dissolved in a solution of ammonia (7 M in MeOH, 6.5 mL) and the mixture was stirred for 55 min at 100°C in a microwave reactor. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 20:1→15:1) to yield compound D-**18** (127 mg, 0.396 mmol, 75%) as a colorless solid. $[\alpha]_{589}^{25} = +29.8°$ ($c = 1.0$, $CHCl_3$); m.p. 129°C; R_f (CH_2Cl_2/MeOH, 9:1) = 0.25; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.35$ (s, 1H; H2), 7.86 (s, 1H; H8), 7.39–7.28 (m, 5H; aromatic C*H*), 6.25 (br s, 2H; NH_2), 5.84–5.77 (m, 1H; H3′), 5.40–5.30 (m, 1H; H1′), 4.54 (s, 2H; benzyl CH_2), 4.15–4.10 (m, 2H; H5′), 3.12–2.99 (m, 2H; H2′a, H6′a), 2.77–2.65 ppm (m, 2H; H2′b, H6′b); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 155.8$ (C6), 152.8 (C2), 149.8 (C4), 140.3 (C4′), 138.5 (C8), 138.1 (aromatic C_q), 128.5 (aromatic *C*H), 127.8 (aromatic *C*H), 127.7 (aromatic *C*H), 125.1 (C3′), 119.7 (C5), 72.7 (benzyl CH_2), 68.4 (C5′), 53.3 (C1′), 40.6 (C6′), 40.3 ppm (C2′); IR (film): $\tilde{\nu} = 2904$, 1673, 1597, 1569, 1417, 1303, 1121, 796, 730, 656 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{18}H_{19}N_5O$: 322.1668 $[M+H]^+$; found: 322.1671.

5′-*O*-Benzyl-2′,3′-dideoxy-3′,4′-didehydro-*carba*-L-adenosine (L-18): The reaction was carried out as described for compound D-**18** with chloropurine-derivative L-**17** (201 mg, 0.590 mmol). The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 20:1→15:1) to yield compound L-**18** (129 mg, 0.401 mmol, 68%) as a colorless solid. $[\alpha]_{589}^{25} = -26.6°$ ($c = 1.0$, $CHCl_3$). The spectroscopic data were identical to those described for D-**18**.

2′,3′-Dideoxy-3′,4′-didehydro-*carba*-D-adenosine (D-19): A solution of benzylated nucleoside D-**18** (103 mg, 0.320 mmol) in Ac_2O/AcOH (5:1, 1 mL) was deprotected according to general debenzylation procedure 62 (see above) with a solution of $ZnCl_2$ (136 mg, 1.60 mmol) in Ac_2O/AcOH (5:1, 2 mL). The mixture was stirred for 30 h at room temperature and the obtained intermediate was treated with a solution of NaOH (1% in MeOH). After column chromatography on silica gel (CH_2Cl_2/MeOH, 9:1), nucleoside D-**19** (73.9 mg, 0.269 mmol, 66%) was obtained as a colorless solid. $[\alpha]_{589}^{25} = +28.7°$ ($c = 0.23$, DMSO); m.p. 212°C; R_f (CH_2Cl_2/MeOH, 9:1) = 0.18; ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 8.13$ (s, 1H; H2), 8.09 (s, 1H; H8), 5.65–5.60 (m, 1H; H3′), 5.26–5.16 (m, 1H; H1′), 4.07–4.01 (m, 2H; H5′), 2.94–2.79 (m, 2H; H2′a, H6′a), 2.73–2.63 ppm (m, 2H; H2′b, H6′b); ^{13}C NMR (126 MHz, [D$_6$]DMSO): $\delta = 156.1$ (C6), 152.4 (C2), 149.5 (C4), 144.0 (C4′), 139.1 (C8), 121.7 (C3′), 59.9 (C5′), 53.7 (C1′), 39.3 (C6′), 39.1 ppm (C2′); IR (film): $\tilde{\nu} = 3093$, 2923, 2850, 1675, 1600, 1569, 1307, 1074, 795, 731, 696, 545 cm^{-1}; UV/Vis (CH_3CN): $\lambda_{max} = 261$, 210 nm; HRMS (FAB): *m/z* calcd for $C_{11}H_{13}N_5O$: 232.1198 $[M+H]^+$; found: 232.1208.

2′,3′-Dideoxy-3′,4′-didehydro-*carba*-L-adenosine (L-19): A solution of benzylated nucleoside L-**18** (86.2 mg, 0.268 mmol) in Ac_2O/AcOH (5:1, 1 mL) was deprotected according to general debenzylation procedure 2 (see above) with a solution of $ZnCl_2$ (184 mg, 1.34 mmol) in Ac_2O/AcOH (5:1, 3 mL). The mixture was stirred for 30 h at room temperature and the obtained intermediate was treated with a solution of NaOH (1% in MeOH). After column chromatography on silica gel (CH_2Cl_2/MeOH, 9:1), debenzylated nucleoside L-**19** (48.3 mg, 0.209 mmol, 78%) was obtained as a colorless solid. $[\alpha]_{589}^{25} = -25.8°$ ($c = 0.19$, DMSO). The spectroscopic data were identical to those described for D-**19**.

5′-*O*-Benzyl-2′,3′-dideoxy-3′,4′-didehydro-*carba*-D-2-amino-6-chloro-6-deamino-adenosine (D-20): The reaction was carried out according to the general coupling procedure (see above) with a solution of (*R*)-**8** (400 mg, 1.96 mmol) and 2-amino-6-chloropurine (498 mg, 2.94 mmol) in THF (25 mL) and a preformed complex of PPh_3 (1.54 g, 5.87 mmol) and DIAD (1.08 mL, 5.48 mmol) in THF (30 mL). The mixture was stirred for 5 days and, after purification, benzylated nucleoside D-**20** (474 mg, 1.33 mmol, 68%) was obtained as a yellow syrup. $[\alpha]_{589}^{25} = +9.6°$ ($c = 1.0$, $CHCl_3$); R_f (petroleum ether/EtOAc, 1:2) = 0.17; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.81$ (s, 1H; H8), 7.38–7.28 (m, 5H; aromatic C*H*), 5.84–5.77 (m, 1H; H3′), 5.21 (br s, 3H; H1′, NH_2), 4.54 (s, 2H; benzyl CH_2), 4.16–4.10 (m, 2H; H5′), 3.08–2.96 (m, 2H; H2′a, H6′a), 2.74–2.63 ppm (m, 2H; H2′b, H6′b); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 159.0$ (C2), 153.6 (C6),

151.3 (C4), 140.6 (C8), 140.3 (C4′), 138.1 (aromatic C_q), 128.6 (aromatic *C*H), 127.9 (aromatic *C*H), 127.8 (aromatic *C*H), 125.1 (C3′), 124.4 (C5), 72.7 (benzyl CH_2), 68.4 (C5′), 53.4 (C1′), 40.4 (C6′), 40.0 ppm (C2′); IR (film): $\tilde{\nu}$ = 3318, 3199, 2854, 1607, 1559, 1455, 1403, 1229, 1070, 905, 731, 697 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{18}H_{18}ClN_5O$: 356.1278 $[M+H]^+$; found: 356.1276.

5′-*O*-Benzyl-2′,3′-dideoxy-3′,4′-didehydro-*carba*-L-2-amino-6-chloro-6-deamino-adenosine (L-20): The reaction was carried out according to the general coupling procedure (see above) with a solution of (*S*)-**8** (400 mg, 1.96 mmol) and 2-amino-6-chloropurine (498 mg, 2.94 mmol) in THF (25 mL) and a preformed complex of PPh_3 (1.54 g, 5.87 mmol) and DIAD (1.08 mL, 5.48 mmol) in THF (30 mL). The mixture was stirred for 5 days and, after purification, benzylated nucleoside L-**20** (460 mg, 1.29 mmol, 66%) was obtained as a yellow syrup. $[\alpha]_{589}^{25} = -10.4°$ (c = 1.0, $CHCl_3$). The spectroscopic data were identical to those described for D-**20**.

2′,3′-Dideoxy-3′,4′-didehydro-*carba*-D-guanosine (D-21): To compound D-**20** (179 mg, 0.502 mmol) was added formic acid (10 mL) and the mixture was stirred at 80 °C for 5 h. The solvent was evaporated and the residue was dissolved in ammonia (25% in MeOH, 10 mL) and the mixture was stirred for 12 h at room temperature. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 9:1→1:1) to yield compound D-**21** (42.3 mg, 0.171 mmol, 34%) as a colorless solid. $[\alpha]_{589}^{25} = +23.8°$ (c = 0.6, DMSO); R_f (CH_2Cl_2/MeOH, 1:1) = 0.67; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.10 (br s, 1H; N*H*), 7.61 (s, 1H; H8), 6.63 (br s, 2H; NH_2), 5.62–5.58 (m, 1H; H3′), 5.01–4.93 (m, 1H; H1′), 4.04–4.00 (m, 2H; H5′), 2.87–2.75 (m, 2H; H2a′, H6a′), 2.59–2.53 ppm (m, 2H; H2b′, H6b′); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 154.3 (C6), 151.0 (C4), 143.9 (C4′), 134.8 (C8), 121.4 (C3′), 116.7 (C5), 59.7 (C5′), 52.7 (C1′), 39.8 (C6′), 39.6 ppm (C2′); IR (film): $\tilde{\nu}$ = 3115, 1689, 1605, 1534, 1371, 1183, 1023, 779, 696, 641 cm^{-1}; UV/Vis (MeOH): λ_{max} = 270, 252 nm; HRMS (FAB): *m/z* calcd for $C_{18}H_{18}ClN_5O$: 248.1148 $[M+H]^+$; found: 248.1156.

2′,3′-Dideoxy-3′,4′-didehydro-*carba*-L-guanosine (L-21): The reaction was carried out as described for compound D-**21** with compound L-**20** (57.4 mg, 0.161 mmol) and formic acid (3 mL). After column chromatography on silica gel, compound L-**21** (16.7 mg, 67.8 μmol, 42%) was afforded as a colorless solid. $[\alpha]_{589}^{25} = -16.9°$ (c = 0.3, DMSO). The spectroscopic data were identical to those described for D-**21**.

5′-((2*R*)-Methoxyphenylacetate)-2′,3′-dideoxy-3′,4′-didehydro-*carba*-D-uridine (D-22): Carbocyclic nucleoside D-**14** (0.10 g, 0.48 mmol), (*R*)-(−)-methoxyphenylacetic acid (0.80 g, 0.53 mmol), and *N*,*N*′-dicyclohexylcarbodiimide (DCC, 0.11 g, 0.53 mmol) were dissolved in CH_2Cl_2 (12 mL). 4-Dimethylaminopyridine (DMAP, 6 mg, 0.05 mmol) was added and the reaction mixture was stirred for 48 h at room temperature. After filtration, the solution was washed with saturated aqueous solutions of sodium hydrogen carbonate (2×10 mL) and ammonium chloride (2×10 mL). The organic fraction was dried with Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified on a chromatotron (EtOAc) to yield compound D-**22** (0.12 g, 0.35 mmol, 73%) as a colorless oil and as a mixture of two diastereomers in a ratio of 1.00:0.03. R_f (CH_2Cl_2/MeOH, 9:1) = 0.67; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.85 (br s, 1H; N*H*), 8.80 (br s, 1H; N*H*), 7.37–7.30 (m, 2×5H; 2×aromatic C*H*), 7.01 (d, ^3J = 7.5 Hz, 1H; H6), 6.90 (d, ^3J = 7.5 Hz, 1H; H6), 5.64–5.62 (m, 1H; H5), 5.60–5.57 (m, 1H; H5), 5.56–5.53 (m, 1H; H3′), 5.53–5.49 (m, 1H; H3′), 5.35–5.31 (m, 1H; H1′), 5.25–5.19 (m, 1H; H1′), 4.73–4.60 (m, 2×3H; 2×C*H*, 2×H5′), 3.34 (s, 3H; CH_3), 3.34 (s, 3H; CH_3), 2.98–2.92 (m, 2H; H2a′, H6a′), 2.87–2.79 (m, 1H; H2a′/H6a′), 2.71–2.64 (m, 1H; H2a′/H6a′), 2.41–2.33 (m, 2H; H2b′, H6b′), 2.27–2.22 (m, 1H; H2b′/H6b′), 2.04–2.00 ppm (m, 1H; H2b′/H6b′); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.5 (C=O), 170.2 (C=O), 163.2 (C4), 163.2 (C4), 150.8 (C2), 150.7 (C2), 140.7 (C6), 140.5 (C6), 137.8 (C4′), 137.7 (C4′), 137.8 (aromatic C_q), 129.2 (aromatic *C*H), 129.1 (aromatic *C*H), 128.9 (aromatic *C*H), 128.9 (aromatic *C*H), 127.4 (aromatic *C*H), 127.3 (aromatic *C*H), 127.1 (C3′), 127.1 (C3′), 103.4 (C5), 103.3 (C5), 82.7 (*C*H), 82.6 (*C*H), 62.8 (C5′), 62.8 (C5′), 57.5 (*C*H$_3$), 57.4 (*C*H$_3$), 52.9 (C1′), 52.9 (C1′), 39.7 (C2′), 39.7 (C2′), 39.6 (C6′), 39.6 ppm (C6′); IR (film): $\tilde{\nu}$ = 3055, 2928, 2852, 1456, 1374, 1267, 1170, 1101, 807, 732, 679 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{19}H_{20}N_2O_5$: 357.1451 $[M+H]^+$; found: 357.1456.

General procedure for the synthesis of 3-methyl- and 5-chloro-substituted *cyclo*Sal nucleotides: The carbocyclic nucleosides (1 equiv) were dissolved in CH_3CN, and the solution was cooled to −20 °C. Then, diisopropylethylamine (DIPEA, 2 equiv) and a solution of either 3-methyl-saligenyl chlorophosphite or 5-chloro-saligenyl chlorophosphite (2 equiv) in anhydrous CH_3CN were added. The mixture was warmed to room temperature and stirred for 2 h at this temperature. Subsequently, a solution of oxone (4 equiv) in cold water was added at −10 °C. Cooling was removed and stirring was continued for an additional 15 min. The mixture was directly extracted with EtOAc (2×5 mL) and cold water (2×5 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The resulting solid was purified on a chromatotron.

3-Methyl-*cyclo*Sal-3′-deoxy-3′,4′-didehydro-*carba*-D-thymidine monophosphate (D-23): Following the general procedure for the synthesis of *cyclo*Sal-nucleotides (see above), compound D-**12** (70 mg, 0.31 mmol), 3-methyl-saligenyl chlorophosphite (0.13 g, 0.63 mmol), DIPEA (0.11 mL, 0.63 mmol), oxone (0.78 g, 1.3 mmol), and CH_3CN (7 mL) were used. The crude product was purified on a chromatotron (EtOAc) to yield compound D-**23** (28 mg, 0.070 mmol, 22%) as a colorless foam. R_f (CH_2Cl_2/MeOH, 9:1) = 0.62; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.95 (br s, 2×1H; 2×N*H*), 7.19–7.17 (m, 2×1H; 2×H4″), 7.08–6.96 (m, 2×2H; 2×H6, 2×H5″), 6.94–6.90 (m, 2×1H; 2×H6″), 5.88–5.85 (m, 1H; H3′), 5.85–5.81 (m, 1H; H3′), 5.43–5.24 (m, 2×3H; 2×H1′, 2×H7″), 4.84–4.70 (m, 2×2H; 2×H5′), 2.99–2.86 (m, 2×2H; 2×H2a′, 2×H6a′), 2.48–2.41 (m, 2×2H; 2×H2b′, 2×H6b′), 2.28 (s, 3H; Ar−CH_3) 2.27 (s, 3H; Ar−CH_3), 1.88 ppm (d, ^4J = 1.4 Hz, 2×3H; 2×thymine CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.6 (2×C4), 150.7 (2×C2), 148.6 (2×C2″), 137.7 (d, ^3J(C,P) = 2.5 Hz, C4′), 137.7 (d, ^3J(C,P) = 2.5 Hz, C4′), 136.4 (C4″), 136.4 (C4″), 131.2 (2×C6), 128.4 (C3′), 128.1 (C3′), 127.9 (C3″), 127.8 (C3″), 123.9 (C5″), 123.9 (C5″), 122.8 (C6″), 122.8 (C6″), 120.5 (C1″), 120.5 (C1″), 111.9 (C5), 111.8 (C5), 68.7 (d, ^2J(C,P) = 7.4 Hz, C7″), 68.6 (d, ^2J(C,P) = 7.4 Hz, C7″), 66.3 (d, ^2J(C,P) = 4.8 Hz, C5′), 66.2 (d, ^2J(C,P) = 4.8 Hz, C5′), 52.8 (C1′), 52.6 (C1′), 39.5 (C2′), 39.4 (C2′), 39.2 (C6′), 39.1 (C6′), 15.3 (2×Ar−*C*H$_3$), 12.5 (thymine *C*H$_3$), 12.4 ppm (thymine *C*H$_3$); ^{31}P NMR (162 MHz, $CDCl_3$): δ = −8.43 (s), −8.65 ppm (s) (2 diastereomers in a ratio of 1.0:0.9); IR (film): $\tilde{\nu}$ = 3043, 2925, 1672, 1469, 1294, 1267, 1188, 988, 935, 771, 727, 647 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{19}H_{21}N_2O_6P$: 405.1216 $[M+H]^+$; found: 405.1209.

5-Chloro-*cyclo*Sal-3′-deoxy-3′,4′-didehydro-*carba*-D-thymidine monophosphate (D-24): Following the general procedure for the synthesis of *cyclo*Sal-nucleotides (see above), compound D-**12** (0.19 g, 0.85 mmol), 5-chloro-saligenyl chlorophosphite (0.38 g, 1.7 mmol), DIPEA (0.29 mL, 1.7 mmol), oxone (2.1 g, 3.4 mmol), and CH_3CN (7 mL) were used. The crude product was purified on a chromatotron (EtOAc) to yield compound D-**24** (0.13 g, 0.30 mmol, 35%) as a colorless foam. R_f (CH_2Cl_2/MeOH, 9:1) = 0.44; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (br s, 2×1H; 2×N*H*), 7.32–7.30 (m, 1H; H4″), 7.30–7.28 (m, 1H; H4″), 7.11–7.09 (m, 2×1H; 2×H6″), 7.04–6.98 (m, 2×2H; 2×H3″, 2×H6), 5.89–5.87 (m, 2×1H; 2×H3′), 5.41–5.31 (m, 2×3H; 2×H1′, 2×H7″), 4.87–4.70 (m, 2×2H; 2×H5′), 3.01–2.89 (m, 2×2H; 2×H2a′, 2×H6a′), 2.50–2.45 (m, 2×2H; 2×H2b′, 2×H6b′), 1.90 ppm (d, ^4J = 3.0 Hz, 2×3H; 2×thymine CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.5 (C4), 163.5 (C4), 150.9 (C2), 150.8 (C2), 148.7 (C2″), 148.6 (C2″), 137.5 (C4′), 137.4 (C4′), 136.5 (2×C6), 130.0 (2×C4″), 128.8 (C3′), 128.5 (C3′), 125.4 (2×C6″), 129.6 (C1″), 129.5 (C1″), 122.8 (C5″), 122.7 (C5″), 120.1 (d, ^3J(C,P) = 2.4 Hz, C3″), 119.9 (d, ^3J(C,P) = 2.4 Hz, C3″), 119.5 (2×C5), 68.0 (d, ^2J(C,P) = 7.0 Hz, C7″), 67.9 (d, ^2J(C,P) = 7.2 Hz, C7″), 66.6 (d, ^2J(C,P) = 2.6 Hz, C5′), 66.5 (d, ^2J(C,P) = 2.6 Hz, C5′), 52.9 (C1′), 52.8 (C1′), 39.5 (C2′), 39.4 (C2′), 39.2 (C6′), 39.2 (*C6′*), 12.5 (thymine *C*H$_3$), 12.5 ppm (thymine *C*H$_3$); ^{31}P NMR (162 MHz, $CDCl_3$): δ = −9.63 (s), −9.86 ppm (s) (2 diastereomers in a ratio of 1.0:0.9); IR (film): $\tilde{\nu}$ = 3055, 1670, 1479, 1265, 1186, 988, 934, 861, 815, 718, 613 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{18}H_{18}ClN_2O_6P$: 425.0659 $[M+H]^+$; found: 425.0659.

3-Methyl-*cyclo*Sal-2′,3′-dideoxy-3′,4′-didehydro*carba*-D-uridine monophosphate (D-25): Following the general procedure for the synthesis of

*cyclo*Sal-nucleotides (see above), compound D-**14** (0.10 g, 0.48 mmol), 3-methyl-saligenyl chlorophosphite (0.20 g, 0.96 mmol), DIPEA (0.16 mL, 0.96 mmol), oxone (1.2 g, 1.9 mmol), and CH_3CN (12 mL) were used. The crude product was purified on a chromatotron (EtOAc) to yield compound D-**25** (87 mg, 0.22 mmol, 46%) as a colorless foam. R_f (CH_2Cl_2/MeOH, 9:1) = 0.34; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (br s, 2×1H; 2×N*H*), 7.23–7.18 (m, 2×1H; 2×H4″), 7.20 (d, ^3J = 8.1 Hz, 1H; H6), 7.14 (d, ^3J = 8.1 Hz, 1H; H6), 7.06–7.03 (m, 2×1H; 2×H5″), 6.96–6.90 (m, 2×1H; 2×H6″), 5.89–5.86 (m, 1H; H3′), 5.86–5.83 (m, 1H; H3′), 5.70–5.66 (m, 2×1H; 2×H5), 5.41–5.30 (m, 2×3H; 2×H1′, 2×H7″), 4.85–4.71 (m, 2×2H; 2×H5′), 3.03–2.86 (m, 2×2H; 2×H2a′, 2×H6a′), 2.48–2.42 (m, 2×2H; 2×H2b′, 2×H6b′), 2.29 ppm (s, 2×3H; 2×Ar−C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.7 (C4), 162.6 (C4), 151.8 (C2), 151.8 (C2), 148.8 (2×C2″), 140.7 (C6), 140.6 (C6), 137.8 (C4′), 137.8 (C4′), 131.3 (2×C4″), 129.6 (C3″), 129.4 (C3″), 128.3 (C3′), 128.0 (C3′), 124.0 (C5″), 124.0 (C5″), 122.9 (C6″), 122.9 (C6″), 121.6 (C1″), 121.5 (C1″), 103.2 (C5), 103.2 (C5), 68.7 (d, ^2J(C,P) = 6.7 Hz, C7″), 68.6 (d, ^2J(C,P) = 6.7 Hz, C7″), 66.1 (d, ^2J(C,P) = 4.3 Hz, C5′), 66.0 (d, ^2J(C,P) = 4.3 Hz, C5′), 53.2 (C1′), 53.1 (C1′), 39.7 (C2′), 39.6 (C2′), 39.3 (C6′), 39.2 (C6′), 15.0 ppm (2×Ar−*C*H$_3$); ^{31}P NMR (162 MHz, $CDCl_3$): δ = −8.47 (s), −8.60 ppm (s) (2 diastereomers in a ratio of 1.0:0.8); IR (film): $\tilde{\nu}$ = 3052, 2925, 1673, 1459, 1266, 1188, 987, 933, 809, 767, 647 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{18}H_{19}N_2O_6P$: 391.1059 $[M+H]^+$; found: 391.1071.

5-Chloro-*cyclo*Sal-2′,3′-dideoxy-3′,4′-didehydro-*carba*-D-uridine monophosphate (D-26): Following the general procedure for the synthesis of *cyclo*Sal-nucleotides (see above), compound D-**14** (0.30 g, 1.4 mmol), 5-chloro-saligenyl chlorophosphite (0.64 g, 2.9 mmol), DIPEA (0.49 mL, 2.9 mmol), oxone (3.5 g, 5.8 mmol), and CH_3CN (14 mL) were used. The crude product was purified on a chromatotron (CH_2Cl_2, MeOH gradient 0–5%) to yield compound D-**26** (0.20 g, 0.49 mmol, 34%) as a colorless foam. R_f (CH_2Cl_2/MeOH, 9:1) = 0.36; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (br s, 2×1H; 2×N*H*), 7.32–7.31 (m, 1H; H4″), 7.30–7.28 (m, 1H; H4″), 7.21 (d, ^3J = 8.1 Hz, 1H; H6), 7.18 (d, ^3J = 8.1 Hz, 1H; H6), 7.11–7.09 (m, 2×1H; 2×H6″), 7.01 (d, ^3J = 3.8 Hz, 1H; H3″), 6.99 (d, ^3J = 3.8 Hz, 1H; H3″), 5.88–5.86 (m, 2×1H; 2×H3′), 5.73–5.72 (m, 1H; H5), 5.71–5.69 (m, 1H; H5), 5.42–5.30 (m, 2×3H; 2×H1′, 2×H7″), 4.86–4.70 (m, 2×2H; 2×H5′), 3.03–2.91 (m, 2×2H; 2×H2a′, 2×H6a′), 2.49–2.44 ppm (m, 2×2H; 2×H2b′, 2×H6b′); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.7 (C4), 162.6 (C4), 150.4 (C2), 150.4 (C2), 148.6 (C2″), 148.5 (C2″), 140.8 (C6), 140.7 (C6), 137.6 (C4′), 137.5 (C4′), 130.0 (2×C4″), 128.6 (C3′), 128.4 (C3′), 127.1 (C1″), 127.1 (C1″), 125.4 (2×C6″), 122.8 (C5″), 122.7 (C5″), 120.1 (d, ^3J(C,P) = 2.4 Hz, C3″), 120.0 (d, ^3J(C,P) = 2.4 Hz, C3″), 103.3 (C5), 103.2 (C5), 68.0 (d, ^2J(C,P) = 7.2 Hz, C7″), 67.9 (d, ^2J(C,P) = 7.2 Hz, C7″), 66.5 (d, ^2J(C,P) = 4.3 Hz, C5′), 66.4 (d, ^2J(C,P) = 4.3 Hz, C5′), 53.3 (C1′), 53.2 (C1′), 39.5 (C2′), 39.5 (C2′), 39.3 (C6′), 39.3 ppm (C6′); ^{31}P NMR (162 MHz, $CDCl_3$): δ = −9.61 (s), −9.77 ppm (s) (2 diastereomers in a ratio of 1.0:0.9); IR (film): $\tilde{\nu}$ = 3055, 1672, 1480, 1265, 1185, 987, 934, 860, 807, 716, 613 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{17}H_{16}ClN_2O_6P$: 411.0513 $[M+H]^+$; found: 411.0500.

3′-Deoxy-3′,4′-didehydro-*carba*-D-thymidine monophosphate (D-27): *cyclo*Sal-nucleotide D-**23** (18 mg, 0.045 mmol) was dissolved in CH_3CN (1 mL) and water (330 μL). To this solution was slowly added Et_3N (20 drops) and the mixture was stirred at room temperature until complete hydrolysis of the triester was observed by TLC. The reaction mixture was diluted with water (5 mL) and CH_3CN (5 mL) and the solution was lyophilized. The crude product was purified by column chromatography on RP-C18-silica gel (water). The obtained triethylammonium salt was transferred into the sodium salt by using ion-exchange resin (Dowex 50X8). After lyophilization, compound D-**27** (7 mg, 0.2 mmol 39%) was obtained as a colorless solid. R_f (2-propanol/1 M aqueous ammonium acetate, 2:1) = 0.37; ^{1}H NMR (400 MHz, D_2O): δ = 7.40 (d, ^4J = 0.8 Hz, 1H; H6), 5.80–5.76 (m, 1H; H3′), 5.27–5.21 (m, 1H; H1′), 4.42 (d, ^2J = 8.0 Hz, 2H; H5′), 3.21–3.16 (m, 6H; HN(C*H*$_2$CH$_3$)$_3$), 2.97–2.88 (m, 2H; H2a′, H6a′), 2.50–2.45 (m, 2H; H2b′, H6b′), 1.85 (d, ^4J = 0.8 Hz, 3H; thymine C*H*$_3$), 1.28–1.24 ppm (m, 9H; HN(CH$_2$C*H*$_3$)$_3$); ^{13}C NMR (126 MHz, D_2O): δ = 166.6 (C4), 152.1 (C2), 139.4 (C6), 139.3 (C4′), 125.3 (C3′), 111.5 (C5), 63.4 (C5′), 54.2 (C1′), 46.7 (HN(*C*H$_2$CH$_3$)$_3$), 38.6 (C2′), 38.6 (C6′), 11.4 (thymine *C*H$_3$), 8.2 ppm (HN(CH$_2$*C*H$_3$)$_3$); ^{31}P NMR (162 MHz, D_2O): δ = 1.34 ppm; MS (ESI$^-$): *m/z* calcd for $C_{11}H_{14}N_2O_6P^-$: 301.0 $[M]^-$; found: 301.0.

2′,3′-Dideoxy-3′,4′-didehydro-*carba*-D-uridine monophosphate (D-28): *cyclo*Sal-nucleotide D-**25** (60 mg, 0.12 mmol) was dissolved in CH_3CN (6 mL) and water (1 mL). To this solution was slowly added Et_3N (35 drops) and the mixture was stirred at room temperature until complete hydrolysis of the triester was observed by TLC. The reaction mixture was diluted with water (10 mL) and CH_3CN (10 mL) and the solution was lyophilized. The crude product was purified by column chromatography on RP-C18-silica gel (water). The obtained triethylammonium salt was transferred into the sodium salt by using ion-exchange resin (Dowex 50X8). After lyophilization, compound D-**28** (49 mg, 0.12 mmol 84%) was obtained as a colorless solid. R_f (2-propanol/1 M aqueous ammonium acetate, 2:1) = 0.45; ^{1}H NMR (400 MHz, D_2O): δ = 7.58 (d, ^3J = 8.0 Hz, 1H; H6), 5.85–5.73 (m, 2H; H3′, H5), 5.24–5.18 (m, 1H; H1′), 4.47 (d, ^2J = 7.5 Hz, 2H; H5′), 3.25–3.09 (m, 6H; HN(C*H*$_2$CH$_3$)$_3$), 2.97–2.91 (m, 2H; H2a′, H6a′), 2.49–2.45 (m, 2H; H2b′, H6b′), 1.32–1.18 ppm (m, 9H; HN(CH$_2$C*H*$_3$)$_3$); ^{13}C NMR (126 MHz, D_2O): δ = 166.4 (C4), 152.1 (C2), 144.1 (C6), 139.0 (C4′), 125.6 (C3′), 102.1 (C5), 63.6 (C5′), 54.7 (C1′), 46.6 (HN(*C*H$_2$CH$_3$)$_3$), 38.6 (C2′), 38.5 (C6′) 8.2 ppm (HN(CH$_2$*C*H$_3$)$_3$); ^{31}P NMR (162 MHz, D_2O): δ = 0.39 ppm; MS (ESI$^-$): *m/z* calcd for $C_{10}H_{12}N_2O_6P^-$: 287.0 $[M]^-$; found: 287.0.

General procedure for the synthesis of nucleoside di- and triphosphates: Freshly prepared bis(tetra-*n*-butylammonium)hydrogen phosphate (1.5 equiv) or tris(tetra-*n*-butylammonium)hydrogen pyrophosphate (1.5 equiv) was dried in vacuo for 3 h and further dried for 2 h in anhydrous DMF over activated molecular sieves (4 Å). This solution was added dropwise to a solution of the *cyclo*Sal nucleotide (1 equiv) in DMF. After stirring at room temperature, the solvent was removed under reduced pressure and the residue was extracted twice each with EtOAc and water. The combined aqueous layer was dried by lyophilization. Then, the crude product was converted into its corresponding sodium salt by using ion-exchange resin (Dowex). After lyophilization, the crude product was purified by column chromatography on RP-18 silica gel in a glass column (water).

3′-Deoxy-3′,4′-didehydro-*carba*-D-thymidine diphosphate (D-29): Bis(-tetra-*n*-butylammonium)hydrogen phosphate (48 mg, 0.14 mmol) and compound D-**24** (40 mg, 0.094 mmol) were stirred in DMF (5 mL) for 16 h at room temperature. Nucleoside diphosphate D-**29** (12 mg, 0.028 mmol, 30%) was obtained as a colorless solid. R_f (2-propanol/1 M aqueous ammonium acetate, 2:1) = 0.15; ^{1}H NMR (400 MHz, D_2O): δ = 7.43 (d, ^4J = 1.0 Hz, 1H; H6), 5.82–5.79 (m, 1H; H3′), 5.30–5.24 (m, 1H; H1′), 4.55 (d, ^2J = 7.0 Hz, 2H; H5′), 3.00–2.95 (m, 2H; H2a′, H6a′), 2.53–2.45 (m, 2H; H2b′, H6b′), 1.87 ppm (d, ^4J = 0.8 Hz, 3H; thymine C*H*$_3$); ^{13}C NMR (101 MHz, D_2O): δ = 166.7 (C4), 152.2 (C2), 139.5 (C6), 139.4 (C4′), 125.3 (C3′), 111.6 (C5), 64.1 (C5′), 54.3 (C1′), 38.8 (C2′), 38.7 (C6′), 11.5 ppm (thymine *C*H$_3$); ^{31}P NMR (162 MHz, D_2O): δ = −10.3 (d, ^2J = 22.0 Hz, 1P; P-β), −6.65 ppm (d, ^2J = 21.8 Hz, 1P; P-α); HRMS (ESI$^-$): *m/z* calcd for $C_{11}H_{15}N_2O_9P_2^-$: 381.0258 $[M]^-$; found: 381.0257.

2′,3′-Dideoxy-3′,4′-didehydro-*carba*-D-uridine diphosphate (D-30): Bis(-tetra-*n*-butylammonium)hydrogen phosphate (0.11 g, 0.33 mmol) and compound D-**26** (90 mg, 0.22 mmol) were stirred in DMF (5 mL) for 16 h at room temperature. Nucleoside diphosphate D-**30** (15 mg, 0.041 mmol, 19%) was obtained as a colorless solid. R_f (2-propanol/1 M aqueous ammonium acetate, 2:1) = 0.11; ^{1}H NMR (400 MHz, D_2O): δ = 7.60 (d, ^3J = 8.0 Hz, 1H; H6), 5.82–5.79 (m, 2H; H3′, H5), 5.26–5.20 (m, 1H; H1′), 4.55 (d, ^3J = 3.9 Hz, 2H; H5′), 2.99–2.93 (m, 2H; H2a′, H6a′), 2.53–2.46 ppm (m, 2H; H2b′, H6b′); ^{13}C NMR (101 MHz, D_2O): δ = 166.5 (C4), 152.2 (C2), 144.2 (C6), 138.6 (C4′), 126.3 (C3′), 102.2 (C5), 64.8 (C5′), 54.8 (C1′), 38.8 (C2′), 38.6 ppm (C6′); ^{31}P NMR (162 MHz, D_2O): δ = −10.7 ppm (br s, 2 P; P-α, P-β); HRMS (ESI$^-$): *m/z* calcd for $C_{10}H_{13}N_2O_9P_2^-$: 367.0113 $[M]^-$; found: 367.0093.

3′-Deoxy-3′,4′-didehydro-*carba*-D-thymidine triphosphate (D-31): Tris-(tetra-*n*-butylammonium)hydrogen pyrophosphate (0.18 g, 0.12 mmol) and compound D-**24** (50 mg, 0.12 mmol) were stirred in DMF (5 mL) for 16 h at room temperature. Nucleoside diphosphate D-**31** (12 mg, 0.023 mmol, 19%) was obtained as a colorless solid. R_f (2-propanol/1 M aqueous ammonium acetate, 2:1) = 0.18; ^{1}H NMR (400 MHz, D_2O): δ =

7.41 (d, ^4J = 1.1 Hz, 1H; H6), 5.84–5.80 (m, 1H; H3′), 5.29–5.23 (m, 1H; H1′), 4.58 (d, ^2J = 7.8 Hz, 2H; H5′), 2.99–2.92 (m, 2H; H2a′, H6a′), 2.52–2.45 (m, 2H; H2b′, H6b′), 1.85 ppm (d, ^4J = 0.9 Hz, 3H; thymine CH_3); ^{13}C NMR (101 MHz, D_2O): δ = 166.5 (C4), 152.2 (C2), 139.7 (C6), 138.2 (C4′), 125.8 (C3′), 111.6 (C5), 64.6 (C5′), 54.2 (C1′), 38.6 (C2′), 38.6 (C6′), 11.4 ppm (thymine CH_3); ^{31}P NMR (162 MHz, D_2O): δ = −22.9 (dd, ^2J = 19.8 Hz, ^2J = 19.8 Hz, 1P; P-β), −10.9 (d, ^2J = 19.7 Hz, 1P; P-α), −9.8 ppm (d, ^2J = 19.7 Hz, 1P; P-γ); HRMS (ESI$^-$): *m/z* calcd for $C_{11}H_{16}N_2O_{12}P_3^-$: 460.9933 $[M]^-$; found: 460.9909.

2′,3′-Dideoxy-3′,4′-didehydro-*carba*-D-uridine triphosphate (D-32): Tris-(tetra-*n*-butylammonium)hydrogen pyrophosphate (0.22 g, 0.33 mmol) and compound D-**26** (90 mg, 0.22 mmol) were stirred in DMF (5 mL) for 16 h at room temperature. Nucleoside diphosphate D-**32** (20 mg, 0.039 mmol, 18%) was obtained as a colorless solid. R_f (2-propanol/1 M aqueous ammonium acetate, 2:1) = 0.00; ^{1}H NMR (400 MHz, D_2O): δ = 7.63 (d, ^3J = 8.0 Hz, 1H; H6), 5.85–5.83 (m, 2H; H3′, H5), 5.29–5.23 (m, 1H; H1′), 4.59 (d, ^2J = 7.9 Hz, 2H; H5′), 3.02–2.96 (m, 2H; H2a′, H6a′), 2.55–2.48 ppm (m, 2H; H2b′, H6b′); ^{13}C NMR (101 MHz, D_2O): δ = 166.5 (C4), 152.2 (C2), 144.2 (C6), 138.8 (C4′), 125.8 (C3′), 102.2 (C5), 64.6 (C5′), 54.7 (C1′), 38.8 (C2′), 38.6 ppm (C6′); ^{31}P NMR (162 MHz, D_2O): δ = −22.9 (dd, ^2J = 19.5 Hz, ^2J = 19.5 Hz, 1P; P-β), −10.9 (d, ^2J = 19.8 Hz, 1P; P-α), −9.9 ppm (d, ^2J = 19.7 Hz, 1P; P-γ); HRMS (ESI$^-$): *m/z* calcd for $C_{10}H_{14}N_2O_{12}P_3^-$: 446.9765 $[M]^-$; found: 446.9772.

(1*S*,3*R*,4*R*)-*trans*-3-(Benzyloxymethyl)-bicyclo[3.1.0]hexanol (33): A solution of Et_2Zn (1 M in toluene, 1.63 mL, 1.80 mmol) was added dropwise to a solution of cyclopentenol (*S*)-**8** (330 mg, 1.62 mmol) in CH_2Cl_2 (10 mL) at −10 °C and the mixture was stirred for 15 min. To this mixture was rapidly added a solution of diiodomethane (145 μL, 1.80 mmol) in CH_2Cl_2 (5 mL). After 15 min, Et_2Zn (1 M in toluene, 1.63 mL, 1.80 mmol) was added dropwise. A solution of diiodmethane (145 μL, 1.80 mmol) in CH_2Cl_2 (5 mL) was added rapidly and the mixture was stirred at 0 °C overnight. After quenching with a saturated aqueous solution of NH_4Cl (15 mL), the mixture was stirred at room temperature overnight. The aqueous layer was washed with EtOAc (3×10 mL) and the organic phase was washed with a saturated aqueous solution of NH_4Cl (10 mL), dried with Na_2SO_4, and the solvent was removed under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether/EtOAc, 2:1) afforded compound **33** (213 mg, 0.976 mmol, 60%) as a colorless oil. $[\alpha]_{589}^{25}$ = −14.5° (*c* = 1.0, $CHCl_3$). The spectroscopic data were identical to those previously reported for the racemic hexanol.[11]

(1*R*,3*R*,4*R*)-*cis*-3-(Benzyloxymethyl)-bicyclo[3.1.0]hexanol (34): The Mitsunobu-inversion reaction was carried out according to the general procedure (see above) with a solution of compound **33** (213 mg, 0.976 mmol) and benzoic acid (328 mg, 3.13 mmol) in Et_2O (20 mL) and a preformed complex of DIAD (575 μL, 2.92 mmol) and PPh_3 (820 mg, 3.13 mmol) in Et_2O (30 mL). The reaction mixture was stirred for 16 h and was treated with NaOH (1% in MeOH, 25 mL). The crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc, 2:1) to yield compound **34** (190 mg, 0.870 mmol, 89%) as a colorless oil. $[\alpha]_{589}^{25}$ = +15.9° (*c* = 1.0, $CHCl_3$). The spectroscopic data were identical to those previously reported for the racemic hexanol.[11]

(1*S*,3*R*,4*R*)-5′-*O*-Benzyl-3′-deoxy-3′,4′-methano-*carba*-D-thymidine (35): The reaction was carried out according to the general coupling procedure (see above) with a solution of compound **34** (200 mg, 0.916 mmol) and *N*3-benzoyl-protected thymine (412 mg, 1.83 mmol) in CH_3CN (20 mL) and a preformed complex of PPh_3 (0.721 g, 2.75 mmol) and DIAD (0.505 mL, 2.57 mmol) in CH_3CN (30 mL. The mixture was stirred for 48 h and, after purification, benzylated nucleoside **35** (162 mg, 0.495 mmol, 54%) was obtained as a yellow oil. $[\alpha]_{589}^{25}$ = +17.2° (*c* = 1.0, $CHCl_3$). The spectroscopic data were identical to those previously reported for the racemich nucleoside.[11]

(1*S*,3*R*,4*R*)-3′-Deoxy-3′,4′-methano-*carba*-D-thymidine (36): Benzylated nucleoside **35** (106 mg, 0.335 mmol) was dissolved in MeOH (4 mL) and formic acid (3 mL) and Pd/C (5 mg) were added. The mixture was stirred for 24 h under a hydrogen atmosphere (balloon) at 50 °C. The reaction mixture was filtered through celite and washed with MeOH. The filtrate was concentrated and the crude product was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 9:1) to yield nucleoside **36** (26 mg, 0.10 mmol, 48%) as a colorless solid. $[\alpha]_{589}^{25}$ = +7.8°(*c* = 1.0, MeOH). The spectroscopic data were identical to that previously reported for the racemich nucleoside.[11]

3′-Deoxy-*carba*-D-thymidine (D-37 and *iso*-D-37): Benzylated nucleoside D-**10** (109 mg, 0.671 mmol) was dissolved in MeOH (4 mL) and Pd/C (5 mg) was added. The mixture was stirred for 2 days under a hydrogen atmosphere at room temperature. The reaction mixture was filtered through celite and washed with MeOH. The filtrate was concentrated and the crude product was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 9:1) to yield nucleosides D-**37** and *iso*-D-**37** (74 mg, 0.33 mmol, 95%) as a colorless solid and as a mixture of two diastereomers in a ratio of 3:1. R_f (CH_2Cl_2/MeOH, 15:1) = 0.12; ^{1}H NMR (400 MHz, CD_3OH): δ = 7.51 (d, ^4J = 0.8 Hz, 1H; H6-A), 7.47 (d, ^4J = 0.8 Hz, 1H; H6-B), 4.91–4.80 (m, 2H; H1′-A, H1′-B), 3.59–3.55 (m, 2H; H5′-A), 3.48 (dd, ^2J = 6.7 Hz, ^3J = 3.8 Hz, 2H; H5′-B), 2.47–2.35 (m, 1H; H4′-B), 2.26–1.96 (m, 5H; H4′-A, H6′a-A, H2′a-A, H3′a-B, H2′a-B), 1.92–1.88 (m, 6H; thymine C*H*3A, thymine C*H*3-B), 1.87–1.74 (m, 5H; H3′a-A, H2′b-A, H3′b-B, H2′b-B, H6′a-B), 1.70–1.61 (m, 1H; H3′b-A), 1.55–1.46 (m, 1H; H6′b-A), 1.44–1.34 ppm (m, 1H; H6′b-B); ^{13}C NMR (101 MHz, CD_3OH): δ = 166.4 (C4-A/B), 153.1 (C2-A/B), 139.7 (C6-B), 139.6 (C6-A), 111.5 (C5-A/B), 66.7 (C5′-B), 66.6 (C5′-A), 58.0 (C1′-A), 57.7 (C1′-B), 41.5 (C4′-B), 41.2 (C4′-A), 35.2 (C6′-A), 34.4 (C6′-B), 32.2 (C2′-B), 30.6 (C2′-A), 28.6 (C3′-A), 27.5 (C3′-B), 12.3 ppm (thymine CH_3-A/B); IR (film): $\tilde{\nu}$ = 3174, 2949, 1656, 1472, 1395, 1269, 1222, 1124, 1056, 589, 420 cm^{-1}; UV/Vis (MeOH): λ_{max} = 269, 218 nm; HRMS (FAB): *m/z* calcd for $C_{11}H_{16}N_2O_3$: 225.1239 $[M+H]^+$; found: 225.1237.

(*S*)-3-(Benzyloxymethyl)-1-*tert*-butyldimethylsilyloxycyclopent-3-enol (41): Alcohol (*S*)-**8** (2.44 g, 11.9 mmol) was dissolved in DMF (35 mL) under a nitrogen atmosphere. Afterwards, imidazole (2.11 g, 31.0 mmol) and *tert*-butyldimethylsilylchloride (2.52 g, 16.7 mmol) were added at room temperature and the reaction mixture was stirred for 24 h. The solvent was evaporated and the residue was partitioned between CH_2Cl_2 (50 mL) and water (40 mL). The organic layer was washed with water (2×30 mL) and dried with Na_2SO_4. The crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc, 4:1) to yield compound **41** (3.72 g, 11.7 mmol, 98%) as a colorless oil. $[\alpha]_{589}^{25}$ = +1.6° (*c* = 1.0, $CHCl_3$); R_f (petroleum ether/EtOAc, 4:1) = 0.93; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 5H; aromatic C*H*), 5.60–5.57 (m, 1H; H4), 4.60–4.54 (m, 1H; H1), 4.49 (d, ^3J = 4.4 Hz, 2H; benzyl CH_2), 4.09–4.01 (m, 2H; OCH_2), 2.67–2.58 (m, 2H; H2a, H5a), 2.35–2.26 (m, 2H; H2b, H5b), 0.89 (s, 9H; TBDMS *t*Bu), 0.06 ppm (s, 6H; 2×TBDMS CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.3 (aromatic C_q), 128.6 (aromatic *C*H), 128.0 (aromatic *C*H), 127.8 (aromatic *C*H), 125.4 (C4), 73.0 (C3), 72.1 (benzyl *C*H$_2$), 69.2 (O*C*H$_2$), 43.3 (C2/C5), 42.9 (C2/C5), 26.2 (TBDMS *C*(CH$_3$)$_3$), −4.5 (TBDMS *C*H$_3$), −4.5 ppm (TBDMS *C*H$_3$); IR (film): $\tilde{\nu}$ = 2928, 2854, 1361, 1252, 1194, 1067, 892, 832, 773, 733, 696 cm^{-1}; MS (FAB): *m/z* calcd for $C_{19}H_{30}O_2Si$: 319.2 $[M+H]^+$; found: 319.2.

(1*S*,2*R*,4*R*)-2-(Benzyloxymethyl)-4-*tert*-butyldimethylsilyloxycyclopentanol (42): Under a nitrogen atmosphere, BH_3·S(CH$_3$)$_2$ (450 μL, 4.73 mmol) was added to 2-methyl-2-butene (985 μL, 9.30 mmol) at 0 °C and the solution was stirred 12 h at room temperature to form disiamylborane. Cyclopentene **41** (603 mg, 1.89 mmol) was dissolved in THF (15 mL) and the previously prepared disiamylborane was added dropwise at 0 °C. The solution was stirred at this temperature for 2 days. The reaction mixture was quenched with NaOH (1.7 mL, 3 M) followed by H_2O_2 (1.7 mL, 30%) at 0 °C and the mixture was stirred overnight. After filtration, the phases were separated and the aqueous layer was washed with EtOAc (4×20 mL). The combined organic fractions were dried with Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 4:1→3:1) to yield compound **42** (467 mg, 1.39 mmol, 74%) as a pale yellow oil. $[\alpha]_{589}^{25}$ = +5.0° (*c* = 1.0, $CHCl_3$); R_f (petroleum ether/EtOAc, 4:1) = 0.27; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 5H; aromatic C*H*), 4.53 (s, 2H; benzyl CH_2), 4.38–4.31 (m, 1H; H1), 4.25–4.17 (dd, ^3J = 13.6 Hz, ^3J = 7.0 Hz, 1H; H4) 3.58 (dd, ^2J = 8.8 Hz, ^3J = 5.3 Hz, 1H; OCH_2a), 3.45 (d, ^2J = 9.0 Hz, ^3J = 8.8 Hz, 1H; OCH_2b), 2.28 (br s, 1H; O*H*), 2.15–2.08 (m, 1H; H3a), 2.07–2.00 (m, 1H; H2), 1.95–1.88 (m, 1H; H5a), 1.80–1.73 (m, 1H; H5b), 1.28–1.18 (m, 1H; H3b), 0.86 (s, 9H;

TBDMS $C(CH_3)_3$), 0.03 (s, 3H; TBDMS CH_3), 0.02 ppm (s, 3H; TBDMS CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 138.4 (aromatic C_q), 128.6 (aromatic *C*H), 127.8 (aromatic *C*H), 127.8 (aromatic *C*H), 76.4 (C4), 74.4 (OCH_2), 73.4 (benzyl CH_2), 71.6 (C1), 46.5 (C2), 44.1 (C5), 37.6 (C3), 26.0 (TBDMS $C(CH_3)_3$), −4.7 ppm (2×TBDMS CH_3); IR (film): $\tilde{\nu}$ = 3406, 2954, 2928, 2855, 1471, 1361, 1252, 1096, 1044, 844, 774, 735, 697 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{19}H_{32}O_3Si$: 337.2199 $[M+H]^+$; found: 337.2200.

(1*R*,3*S*,4*R*)-3-Benzyloxy-4-(benzyloxymethyl)-1-*tert*-butyldimethylsilyloxycyclopentanol (44): Alcohol **42** (100 mg, 0.297 mmol) was added dropwise to a suspension of NaH (8.6 mg, 0.39 mmol) in THF (8 mL) at 0 °C under a nitrogen atmosphere. After 1 h, benzyl bromide (46.0 µL, 0.386 mmol) and tetrabutylammonium iodide (TBAI, 0.5 mg, 0.001 mmol) were added at room temperature and the mixture was stirred overnight. The reaction was stopped by the addition of water and the mixture was stirred for a further 1 hour. The aqueous layer was extracted with EtOAc (15 mL) and the combined organic fractions were dried with Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 4:1) to obtain compound **44** (116 mg, 0.271 mmol, 91 %) as a colorless oil. $[\alpha]_{589}^{25}$ = +3.7° (*c* = 1.0, $CHCl_3$); R_f (petroleum ether/EtOAc, 4:1) = 0.80; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.27 (m, 10H; aromatic C*H*), 4.53–4.47 (m, 4H; 2×benzyl CH_2), 4.41–4.33 (m, 1H; H1), 3.93–3.86 (m, 1H; H3), 3.52 (dd, ^2J = 9.1 Hz, ^3J = 7.6 Hz, 1H; OCH_2a), 3.42 (dd, ^2J = 9.1 Hz, ^3J = 6.6 Hz, 1H; OCH_2b), 2.36–2.26 (m, 1H; H4), 2.14–2.10 (m, 1H; H5a), 1.97–1.89 (m, 1H; H2a), 1.88–1.79 (m, 1H; H2b), 1.39–1.30 (m, 1H; H5b), 0.86 (s, 9H; TBDMS *t*Bu), 0.03 ppm (s, 6H; 2×TBDMS CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.0 (aromatic C_q), 138.8 (aromatic C_q), 128.6 (aromatic *C*H),128.5 (aromatic *C*H),128.4 (aromatic *C*H),127.9 (aromatic *C*H), 127.8 (aromatic *C*H), 127.7 (aromatic *C*H), 127.6 (aromatic *C*H), 127.5 (aromatic *C*H), 81.7 (C3), 73.4 (OCH_2), 73.2 (benzyl CH_2), 72.6 (C1), 71.3 (benzyl CH_2), 44.6 (C4), 42.1 (C5), 37.9 (C2), 26.0 (TBDMS $C(CH_3)_3$), −4.6 (TBDMS CH_3), −4.7 ppm (TBDMS CH_3); IR (film): $\tilde{\nu}$ = 2927, 2856, 1454, 1251, 1090, 1068, 775, 692, 603, 547 cm^{-1}; MS (EI): *m/z* calcd for $C_{26}H_{38}O_3Si$: 426 $[M]$; found: 426.

(1*R*,3*S*,4*R*)-3-Benzyloxy-4-(benzyloxymethyl)-cylopentanol (45): A solution of compound **44** (0.952 g, 2.23 mmol) in THF (10 mL) was slowly treated with TBAF (5.6 mL, 5.6 mmol, 1 M in THF) under a nitrogen atmosphere at room temperature and the mixture was stirred for 8 h. The solvent was evaporated and the crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc, 1:2) to yield compound **45** (633 mg, 2.12 mmol, 95 %) as a colorless oil. $[\alpha]_{589}^{25}$ = +36.9° (*c* = 1.0, $CHCl_3$); R_f (petroleum ether/EtOAc, 2:1) = 0.18; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 10H; aromatic C*H*), 4.53 (s, 2H; benzyl CH_2), 4.50 (d, ^2J = 11.7 Hz, 1H; benzyl CH_2), 4.45 (d, ^2J = 11.7 Hz, 1H; benzyl CH_2), 4.35–4.29 (m, 1H; H1), 4.12–4.06 (m, 1H; H3), 3.55 (dd, ^2J = 9.0 Hz, ^3J = 3.9 Hz, 1H; OCH_2a), 3.50 (dd, ^2J = 9.0 Hz, ^3J = 4.3 Hz, 1H; OCH_2b), 2.40 (br s, 1H; OH), 2.37–2.25 (m, 2H; H4, H5a), 2.11–2.04 (m, 1H; H2a), 1.90–1.83 (m, 1H; H2b), 1.55–1.48 ppm (m, 1H; H5b); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.8 (aromatic C_q), 138.0 (aromatic C_q), 128.6 (aromatic *C*H), 128.5 (aromatic *C*H), 127.9 (aromatic *C*H), 127.9 (aromatic *C*H), 127.8 (aromatic *C*H), 127.7 (aromatic *C*H), 82.1 (C1), 73.5 (benzyl CH_2), 72.5 (OCH_2), 72.4 (C3), 71.6 (benzyl CH_2), 44.7 (C4), 42.8 (C2), 37.5 ppm (C5); IR (film): $\tilde{\nu}$ = 3395, 2857, 1453, 1348, 1204, 1062, 1027, 733, 695, 607 cm^{-1}; MS (FAB): *m/z* calcd for $C_{20}H_{24}O_3$: 313.1 $[M+H]^+$; found: 313.1.

(1*S*,3*S*,4*R*)-3-Benzyloxy-4-(benzyloxymethyl)-cyclopentanol (46): The Mitsunobu-inversion reaction was carried out according to the general procedure (see above) with a solution of compound **45** (587 mg, 1.88 mmol) and benzoic acid (459 mg, 3.76 mmol) in Et_2O (35 mL) and a preformed complex of DIAD (728 µL, 3.76 mmol) and PPh_3 (1.10 g, 4.18 mmol) in Et_2O (60 mL). The reaction mixture was stirred for 16 h and treated with NaOH (1 % in MeOH, 25 mL). The crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc, 2:1→1:2) to yield compound **46** (601 mg, 1.92 mmol, 92 %) as a colorless oil. $[\alpha]_{589}^{25}$ = +19.9° (*c* = 1.0, $CHCl_3$); R_f (petroleum ether/EtOAc, 1:2) = 0.47; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 10H; aromatic C*H*), 4.58–4.45 (m, 4H; 2×benzyl CH_2), 4.31–4.26 (m, 1H; H1), 4.00–3.95 (m, 1H; H3), 3.41 (dd, ^2J = 9.4 Hz, ^3J = 5.6 Hz, 1H; OCH_2a), 3.26 (dd, ^2J = 9.1 Hz, ^3J = 7.6 Hz, 1H; OCH_2b), 2.71–2.61 (m, 1H; H4), 2.10–1.97 (m, 2H; H2a, H5a), 1.88–1.80 (m, 1H; H2b), 1.55 ppm (ddd, ^2J = 13.6 Hz, ^3J = 7.9 Hz, ^3J = 5.6 Hz, 1H; H5b); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.1 (aromatic C_q), 138.2 (aromatic C_q), 128.9 (aromatic *C*H), 128.8 (aromatic *C*H), 128.2 (aromatic *C*H), 128.1 (aromatic *C*H), 82.4 (C1), 74.1 (benzyl CH_2), 73.70 (benzyl CH_2), 72.8 (C3), 71.5 (OCH_2), 44.9 (C4), 40.8 (C2), 37.8 ppm (C5); IR (film): $\tilde{\nu}$ = 3410, 2857, 1497, 1453, 1358, 1205, 1065, 1027, 733, 696, 607, 456 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{20}H_{24}O_3$: 313.1804 $[M+H]^+$; found: 313.1799.

3′,5′-Di-*O*-benzyl-*carba*-D-thymidine (D-47): The reaction was carried out according to the general coupling procedure (see above) with a solution of compound **46** (321 mg, 1.03 mmol) and *N*3-benzoyl-protected thymine (621 mg, 2.70 mmol) in CH_3CN (35 mL) and a preformed complex of PPh_3 (1.06 g, 4.05 mmol) and DIAD (744 µL, 3.78 mmol) in CH_3CN (30 mL). The mixture was stirred for 2 days and, after purification, benzylated nucleoside D-**47** (422 mg, 0.804 mmol, 78 %) was obtained as a colorless syrup. $[\alpha]_{589}^{25}$ = +13.6° (*c* = 1.0, $CHCl_3$); R_f (petroleum ether/EtOAc, 1:2) = 0.48; ^{1}H NMR (400 MHz, CD_3OD): δ = 8.53 (br s, 1H; N*H*), 7.40–7.27 (m, 10H; aromatic C*H*), 7.09 (d, ^4J = 1.3 Hz, 1H; H6), 5.19–5.08 (m, 1H; H1′), 4.56–4.43 (m, 4H; 2×benzyl CH_2), 4.02–3.97 (m, 1H; H3′), 3.59 (dd, ^2J = 9.3 Hz, ^3J = 4.5 Hz, 1H; H5′a), 3.54 (dd, ^2J = 9.4 Hz, ^3J = 4.6 Hz, 1H; H5′b), 2.44–2.29 (m, 2H; H4′, H6′a), 2.23–2.15 (m, 1H; H2′a), 2.01–1.92 (m, 1H; H2′b), 1.78 (d, ^4J = 1.3 Hz, 1H; thymine CH_3), 1.67–1.58 ppm (m, 1H; H6′b); ^{13}C NMR (101 MHz, CD_3OD): δ = 164.1 (C4), 151.24 (C2), 138.3 (aromatic C_q), 138.2 (aromatic C_q), 137.2 (C6), 128.5 (aromatic *C*H), 128.4 (aromatic *C*H), 127.8 (aromatic *C*H), 127.6 (aromatic *C*H), 127.6 (aromatic *C*H), 110.8 (C5), 80.5 (C3′), 73.3 (C5′), 71.6 (benzyl CH_2), 71.0 (benzyl CH_2), 54.9 (C1′), 44.6 (C4′), 36.7 (C2′), 32.1 (C6′), 12.4 ppm (thymine CH_3); IR (film): $\tilde{\nu}$ = 2858, 1672, 1553, 1362, 1270, 1066, 1027, 908, 729, 696, 646, 595, 421 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{25}H_{28}N_2O_4$: 421.2127 $[M+H]^+$; found: 421.2121.

***carba*-D-Thymidine (D-3)**: Benzylated nucleoside D-**47** (282 mg, 0.671 mmol) was dissolved in MeOH (7 mL) and Pd/C (5 mg) was added. The mixture was stirred for 2 days under a hydrogen atmosphere at room temperature. The mixture was filtered through celite and washed with MeOH. The filtrate was concentrated and the crude product was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 9:1→6:1) to yield nucleoside D-**3** (134 mg, 0.556 mmol, 83 %) as a colorless solid. $[\alpha]_{589}^{25}$ = +5.9°(*c* = 1.0, MeOH); R_f (CH_2Cl_2/MeOH, 9:1) = 0.21; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, ^4J = 1.0 Hz, 1H; H6), 5.12–5.01 (m, 1H; H1′), 4.22–4.14 (m, 1H; H3′), 3.69 (dd, ^2J = 10.9 Hz, ^3J = 5.3 Hz, 1H; H5′a), 3.63 (dd, ^2J = 10.9 Hz, ^3J = 6.1 Hz, 1H; H5′b), 2.24 (ddd, ^2J = 12.7 Hz, ^3J = 7.5 Hz, ^3J = 7.5 Hz, 1H; H6′a), 2.15–2.02 (m, 2H; H4′, H2′a), 2.02–1.93 (m, 1H; H2′b), 1.89 (d, ^4J = 1.0 Hz, 1H; thymine CH_3), 1.64–1.54 ppm (m, 1H; H6′b); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.4 (C2), 152.9 (C4), 111.5 (C5), 73.7 (C3′), 64.3 (C5′), 55.9 (C1′), 50.3 (C4′), 40.0 (C2′), 33.4 (C6′), 12.3 ppm (thymine CH_3); IR (film): $\tilde{\nu}$ = 3383, 2910, 2496, 1669, 1625, 1470, 1264, 1029, 761, 589, 426 cm^{-1}; UV/Vis (MeOH): λ_{max} = 272, 211 nm; HRMS (FAB): *m/z* calcd for $C_{11}H_{16}N_2O_4$: 241.1188 $[M+H]^+$; found: 241.1192.

Antiviral testing: For the in vitro infection assays, roughly 1×10^7 LuSIV cells[31] (a CEMx174-derived cell-line) were resuspended in the culture medium (500 µL) without the presence of any additional drugs and the medium was incubated at 37 °C for 3 h in the presence of X4 tropic HIV-1 viral stocks that corresponded to p24 NL4/3 (14 ng). After infection, the cells were washed twice with PBS, seeded into 24 well plates at a density of 1×10^6 cells ml^{-1}, and cultivated in the presence of specific antiviral compounds or DMSO as a solvent control. At day 3 post-infection, the culture medium was replaced and the cells cultures were divided. At day 6 post-infection, the p24-levels in the supernatant were determined by an enzyme-linked immunosorbent assay (Innogenetics NV). Cellular viability was tested in parallel by using AlamarBlue (AbD Serotec). LuSIV cells were maintained in an RPMI solution (Invitrogen) that contained 10 % FCS (Biochrom AG), penicillin (100 units mL^{-1}), and streptomycin (100 mg mL^{-1}, Invitrogen). The HIV-1 isolate NL4/3 was obtained from the NIH AIDS Research and Reference Reagent Program.

MDR HIV-1 strains E2–2 and 8ka3 were a kind gift from Dr. Hauke Walter (University Erlangen-Nürnberg). IC_{50} values were calculated by fitting the data to a dose-response curve with the software Graphpad Prism 5. MDR HIV-1 strains were constructed as described by Walter and Schmidt);[32] they contained the following known drug-resistant mutations: E2–2: L10I, K20I, I54 V, A71V, T74S, V82F, L90M, K65R, *D67N*, T69N, V75I, K103N, V108I, Q151M, M184V, *K219E*; 8ka3: L10F, V11I, I13V, K20I, M36I, K43T, I54 V, A71T, G73S, V82C, I84 V, L89V, L90M, *M41L*, *D67N*, T69N, *K70R*, V75M, K101E, V108I, Y181C, M184V, G190A, *L210W*, *T215Y*, *K219E*. Classical thymidine analogue mutations (TAMs) are italicized.

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Drug Resistance

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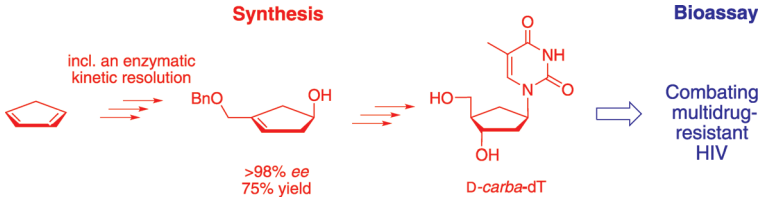
Stereoselective Synthesis of D- and L-Carbocyclic Nucleosides by Enzymatically Catalyzed Kinetic Resolution



Fighting chance: Various carbocyclic D- and L-nucleosides were synthesized from cyclopentadiene by enzyme-catalyzed kinetic resolution with high optical purity. In contrast to its L-analogue, D-*carba*-dT was antivirally active against multidrug-resistant HI-viruses.