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Synthesis and Antiviral Evaluation of Carbocyclic 3′-Azidothymidine (AZT) Analogues and Their *cyclo*Sal-Phosphate Triesters

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Carbocyclic analogues of the *anti*-HIV dideoxynucleoside 3′-azido-3′-deoxythymidine AZT (**1**) were synthesized. Starting from the enantiomerically pure carbocyclic 2′-deoxythymidine **2**, four different carbocyclic AZT analogues **2**,**4**–**6** were prepared. Moreover, the nucleoside analogues were converted into their membrane-permeable *cyclo*Sal-phosphate triesters. All compounds were tested in vitro for their *anti*-HIV activity in human T-lymphocytes (CEM/0).

Introduction

Nucleoside analogues have attracted considerable interest due to their wide range of biological activity.[1] Several structural modifications were applied to both the heterocyclic base and the sugar moiety.[2] Due to this modified structure, these compounds are widely used as antiviral or antitumor drugs in chemotherapy.[3] Since the discovery of AZT **1** as the first nucleoside drug for the treatment of AIDS,[4] considerable efforts have been made to develop new nucleoside analogues that would be more active but less toxic inhibitors of the HIV reverse transcriptase (RT).[5] In order to act as polymerase inhibitors or DNA chain termination agents the nucleoside analogues need to be activated to their 5′-triphosphates by a specific intracellular phosphorylation cascade.[6] However, due to the structural differences compared to natural nucleosides, this metabolisation is often inefficient and therefore only a reduced biological activity is observed.[7]

The intracellular fate of the majority of nucleoside analogues has not been studied in detail. Often these compounds are tested exclusively as nucleosides and if found inactive, they are discarded. For many nucleoside analogues the rate-limiting step of activation is the first phosphorylation to the corresponding 5′-monophosphate due to the high substrate specificity of the nucleoside kinases.[8,9] Consequently, the biological activity of nucleoside analogues may be increased in these cases by applying a nucleotide delivery system (pronucleotide), e.g. the *cyclo*Sal-approach.[10,11] Carbocyclic nucleosides like carbocyclic 2′-deoxythymidine **2** (*carba*-dT) in that the D-ribose moiety is replaced by a cyclopentane system are stable towards hydrolysis by phosphorylases. Therefore they display an enhanced biostability.[12]

Here we report the synthesis of 3′-modified carbocyclic nucleosides **3**–**7** that are structurally related to AZT **1** and their antiviral activity against HIV (Figure 1).

Furthermore, nucleoside analogues **2**,**3**,**5**–**7** were transferred into their *cyclo*Sal phosphates **8**–**12** to bypass the first intracellular phosphorylation step.

Results and Discussion

Recently we reported on a new convergent strategy for the synthesis of carbocyclic nucleosides which allows the preparation of the nucleoside analogues in gram quantities.[13] Thus, as starting material enantiomerically pure *carba*-dT **2** was used for the synthesis of the carbocyclic nucleoside analogues **3**–**7**.

For the synthesis of *carba*-AZT **3** the enantiomerically pure starting material *carba*-dT **2** was selectively protected at the 5′-position with the trityl group to give **13** in 92% yield (Scheme 1). Then a cyclisation under Mitsunobu condition[14] led to the 2,3′-anhydro derivative **14** (90%), which is a useful intermediate for substitutions at the 3′-position. Opening of the aza-enol-ether in **14** with sodium azide in DMF gave the protected *carba*-AZT **15** in 87% yield which was subsequently detritylated with trifluoroacetic acid[15] in CH_2Cl_2/MeOH (7:3) leading to *carba*-AZT **3** in 66% overall yield.[16]

Recently, Décout and co-workers have shown, that 2-(trimethylsilyl)ethanethiol is an interesting reagent for introducing sulfur into nucleosides by formation of stable 2-(trimethylsilyl)ethyl sulfides.[17] These alkyl sulfides undergo cleavage with cyanogen bromide in a modified von Braun reaction[18] to selectively form thiocyanates.[17] The thioether **16** was formed by treatment of the anhydro derivative

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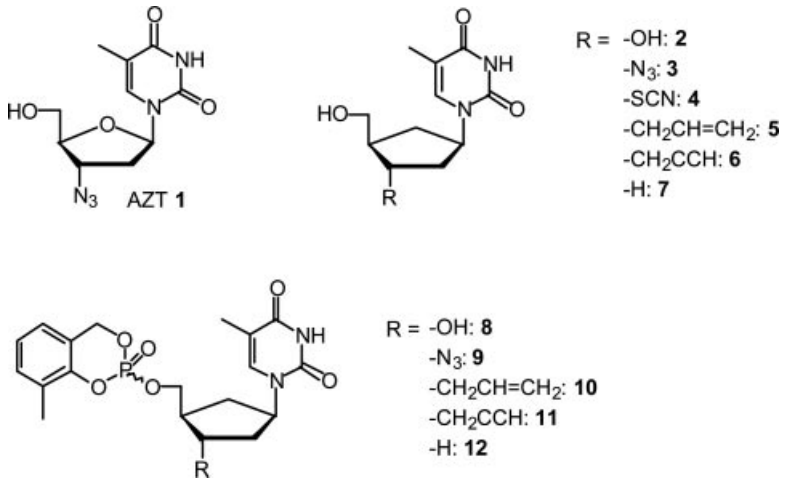
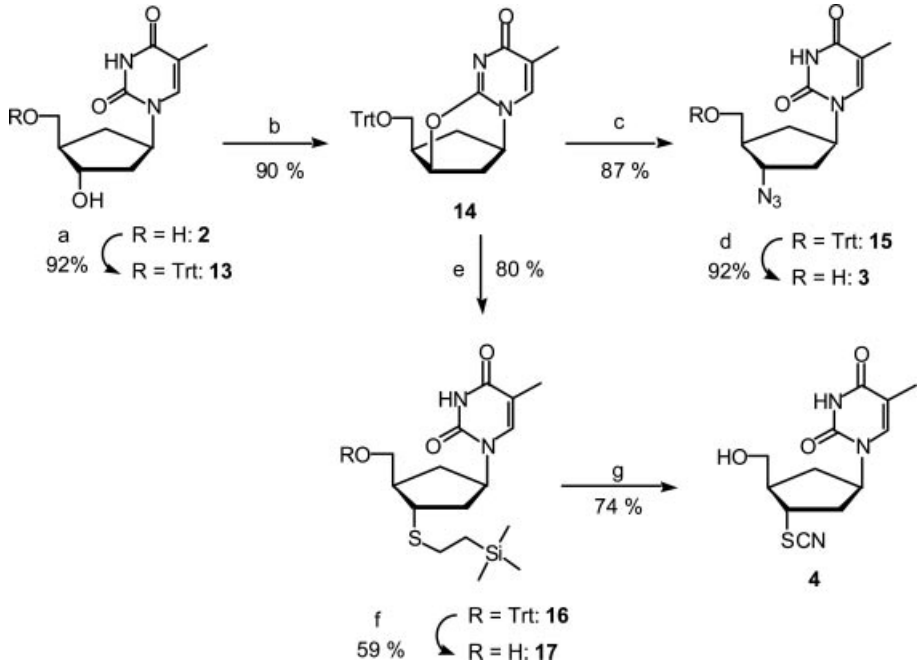


Figure 1. Carbocyclic nucleoside analogues and their corresponding *cyclo*Sal-phosphates.

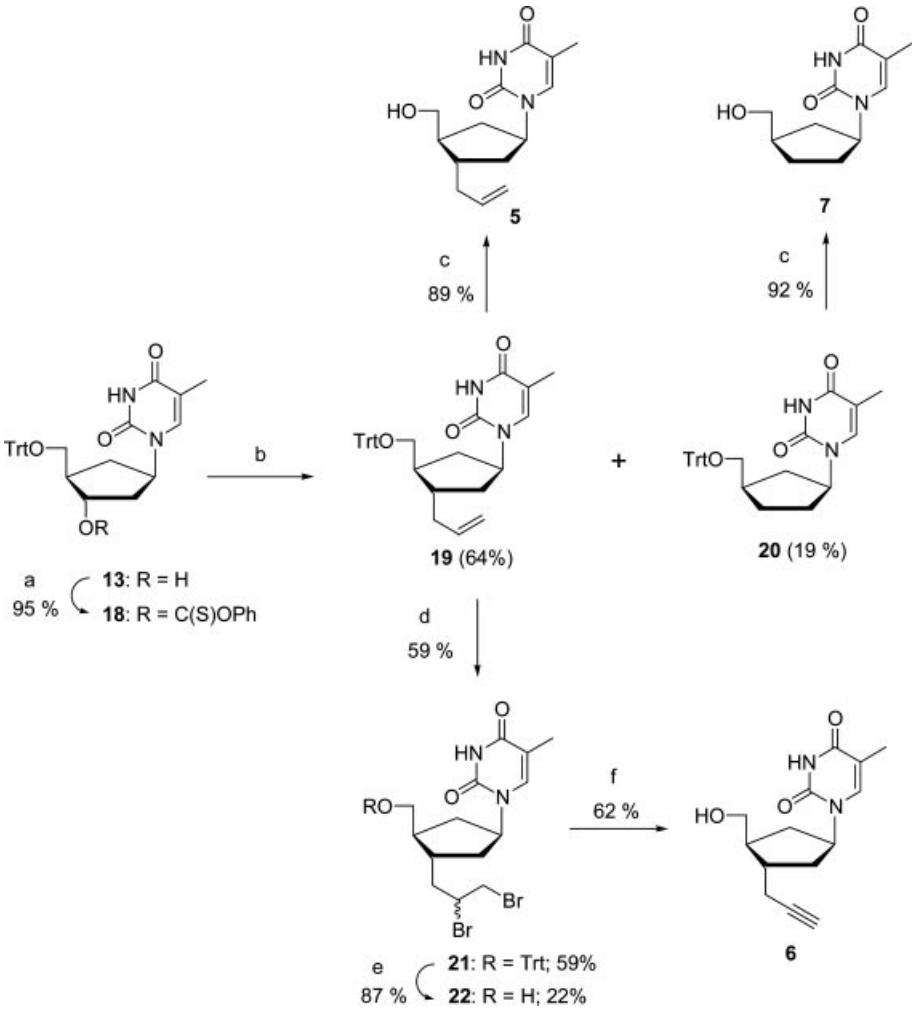


Scheme 1. (a) TrtCl, pyridine, 90 °C, 3 h (b) $P(Ph)_3$, DIAD, MeCN, 0 °C, 12 h (c) NaN_3, DMF, 140 °C, 12 h, (d) TFA, CH_2Cl_2/MeOH, room temp., 10 h, (e) 2-(trimethylsilyl)ethanethiol, NaH, DMF, 90 °C, 2 h (f) HCOOH, Et_2O, room temp. 12 h (g) BrCN, MeOH, room temp. 18 h.

14 with sodium 2-(trimethylsilyl)ethanethiolate, which was prepared *in situ* by reaction of the corresponding thiol with sodium hydride in DMF (Scheme 1). After heating the mixture for 2 h at 90 °C, the mixed sulfide **16** was isolated in 80% yield. After detritylation with formic acid in diethyl ether[19] (59%), the sulfide **17** was subjected to cyanogen bromide cleavage in methanol at room temperature. Selectively one nucleoside was formed, which was characterized as the thiocyanate **4** (74% yield).

The reaction sequence for the synthesis of the carbocyclic 3′-allyl and 3′-propargyl derivatives **5** and **6** was based upon the published work on the natural 2′-deoxyribose system by Chu and co-workers[20a] as well as Fiandor and Tam.[20b] The formation of the new C–C bond at the 3′-position has been achieved by using an organotin-mediated diastereoselective free-radical coupling reaction.[21]

The synthesis of the carbocyclic nucleosides **5** and **6** started with the activation of the 3′-hydroxy group in the protected *carba*-dT derivative **13** by reaction with phenoxythiocarbonyl chloride (PTC-Cl).[22] The resulting thiocarbonate **18** was isolated in 95% yield (Scheme 2). For the coupling reaction, the thiocarbonate **18** and azobis(isobutyronitrile) (AIBN) was heated with excess allyltributylstannane in oxygen-free toluene. After heating for 24 h at 80 °C a considerable amount of starting material **18** was still observed by TLC analysis. Therefore, a second portion of AIBN was added and the mixture was stirred for further 24 h. After work-up, *carba*-3′-allyl-5′-trityl-dT **19** was iso-

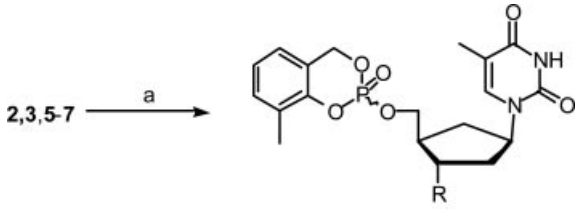


Scheme 2. (a) PTC-Cl, pyridine, CH_2Cl_2, room temp. 12 h (b) nBu$_3$Sn-allyl, AIBN, toluene, 80 °C, 48 h (c) TFA, CH_2Cl_2/MeOH, room temp., 12 h, (d) Br_2, CCl_4, –10 °C, 1 h (e) TFA, CH_2Cl_2/MeOH, room temp., 12 h (f) KOH, EtOH/H_2O, reflux, 20 h.

lated in 64% yield as one single diastereoisomer. Obviously, the different preferred conformations of carbocyclic nucleosides and their natural counterparts did not effect the selectivity of the free-radical reaction. The stereochemistry at C-3′ was confirmed by NOE experiments. As a by-product, the protected *carba*-2′,3′-dideoxythymidine **20** was isolated in 19% yield. Both carbocyclic nucleosides were detritylated (TFA in CH_2Cl_2/MeOH) to give *carba*-3′-allyl-dT **5** and *carba*-ddT **7**[23] with 50% and 15% over all yield, respectively.

The synthesis of *carba*-3′-propargyl-dT **6** started with the reaction of the allyl compound **19** with bromine in CCl_4[24] leading to a mixture of the two diastereomers of dibromide **21** (Scheme 2). Interestingly, the trityl protection group was not stable under the reaction conditions and as a by-product the detritylated dibromide **22** was isolated in 22% yield. After deprotection of the tritylated compound **21** with TFA in CH_2Cl_2/MeOH (87%), the combined brominated derivatives **22** were heated under reflux with excess potassium hydroxide[20b,24] in H_2O/EtOH for 20 h, leading to the target compound *carba*-3′-propargyl-dT **6** in 62% yield.

The described synthetic approaches towards carbocyclic analogues of AZT open the possibility to study the bioactivity of these compounds as well as the corresponding nucleotides after conversion into the *cyclo*Sal-phosphate tri-



R = -OH : **8** (85 %)
R = -N_3 : **9** (85 %)
R = allyl-dT : **10** (65 %)
R = propargyl : **11** (69 %)
R = H : **12** (78 %)

Scheme 3. (a) 3-methyl-cyclosaligenylphosphorchloridate, pyridine, –40 °C, 2 h.

esters.[11] It has been shown before, that *cyclo*Sal-phosphate triesters release the nucleotides and the masking group selectively by a controlled, chemically induced tandem reaction.[25] Often an improvement in the biological activity has been observed.[26] Finally, the phosphate triesters **8**–**12** were easily obtained by reaction of 3-methyl-cyclosaligenylphosphorchloridate[27] with the appropriate carbocyclic nucleoside analogue in dry pyridine at –40 °C in good yields (Scheme 3).

Biological Activity

Nucleosides **2**–**7** and triesters **8**–**12** were evaluated for their antiviral potential against HIV replication (Table 1; AZT and d4T are given for comparison). In agreement to a report by Béres et al.,[16] *carba*-AZT **3** and *carba*-ddT **7** showed no protection against HIV-1 in the CEM/0 system (183 μM and >250 μM, respectively). Nevertheless, by applying the *cyclo*Sal-pronucleotide concept, *cyclo*Sal-*carba*-AZTMP **9** proved to be sixfold more active compared to the nucleoside analogue **3** (30 μM). However and in contrast to the reported data from Béres,[16] *carba*-dT **2** was found to be equipotent (EC_{50} 0.5 μM) as the approved thymidine analogue 2′,3′-dideoxy-2′,3′-didehydrothymidine (d4T) against HIV without increasing cytotoxicity. However, both compounds were inactive in the thymidine-kinase deficient cell line (CEM/TK$^-$). Surprisingly, the attachment of the *cyclo*Sal moiety (**8**) to *carba*-dT **2** did not improve the antiviral activity in these cells. This result points to a different mechanism of activation for this nucleoside analogue. The 3′-thiocyanato derivative **4** proved to be inactive against both HIV strains (>250 μM) and showed no cytotoxicity (>250 μM). Except for *carba*-dT **2**, aliphatic substitutions in **5** and **6** led to weak *anti*-HIV activity (48.3 μM and >10 μM, respectively). Unfortunately, the 3′-propargyl compound **6** was also the most cytotoxic with a CC_{50} value of 17.4 μM for some unknown reasons. Again, the *cyclo*Sal modification (**10**, Table 1) in the allyl-substituted compound **5** led to a fivefold improvement in antiviral activity. More interestingly, *cyclo*Sal-triester **10** derived from 3′-allyl-*carba*-dT **5** retained all antiviral activity observed in the wild-type CEM cells in thymidine-kinase (TK) deficient CEM cells while nucleoside **5** was entirely inactive (EC_{50} > 250). Thus, the antiviral activity is clearly independent on the presence of the enzyme and on the other hand this suggests that thymidine-kinase is responsible for the activation of nucleoside analogue **5**. Although the antiviral potency found is not spectacular, this clearly shows that thymidine-kinase is also able to metabolise certain carbocyclic nucleoside analogues.

Conclusion

In summary, the synthesis of 3′-modified carbocyclic analogues of AZT **1** was achieved. Moreover, the conversion of the nucleoside analogues **2**, **3** and **5**–**7** into their *cyclo*Sal-phosphate triesters is reported. All new compounds were tested *in vitro* for their biological activity in HIV-1- and HIV-2-infected wild-type human T-lymphocyte (CEM/0) cells. Most of the nucleoside analogues were entirely inactive against HIV. However, the *cyclo*Sal derivatives showed better antiviral potency particularly in the case of triester **10**. Interestingly, the activity of triester **10** was entirely retained in the TK-deficient cell line.

Experimental Section

General Remarks: All experiments involving water-sensitive compounds were conducted under totally dry conditions (nitrogen atmosphere) using standard syringe, cannula and septa apparatus. Solvents: benzene, Et_2O and THF were distilled from sodium or potassium benzophenone and stored over molecular sieves. CH_2Cl_2, pyridine and CH_3CN were distilled from CaH_2 and stored over molecular sieves. Ethyl acetate, CH_2Cl_2, and MeOH employed in chromatography were distilled before used. Chromatography: Chromatotron (Harrison Research 7924), silica gel 60_{Pf} (Merck, "gipshaltig" = containing $CaSO_4$). UV detection at 254 nm. TLC: analytical thin-layer chromatography was performed on Merck pre-

Table 1. Antiviral evaluation of the inhibitory effect on HIV-1 and HIV-2-replication of carbocyclic nucleosides 2–6 and *cyclo*Sal-compounds 8–11 in CEM/0 cells and in thymidine kinase-deficient CEM/TK$^-$ cells.

Compound (R)	EC_{50} [μM][a] CEM/0		CC_{50} [μM][b] CEM/TK$^-$	
	HIV-1	HIV-2	HIV-2	
2 (OH)	0.5 ± 0.14	0.4 ± 0.0	> 250	63 ± 5.5
3 (N_3)	183 ± 115	107 ± 125	> 250	> 250
4 (SCN)	> 250	> 250	> 250	> 250
5 (allyl)	48 ± 20	75 ± 66	> 250	138 ± 12
6 (propargyl)	> 10	> 10	> 10	17 ± 3.5
7 (H)	> 250	> 250	> 250	> 250
8 (OH)	0.65 ± 0.07	0.7 ± 0.14	> 250	77 ± 22
9 (N_3)	30 ± 20	32 ± 25	> 50	135 ± 40
10 (allyl)	11.7 ± 7.6	16.7 ± 12.6	10 ± 0.0	61 ± 1.1
11 (propargyl)	> 10	> 10	> 10	21 ± 0.9
12 (H)	> 50	> 50	> 50	> 250
d4T	0.37 ± 0.24	0.35 ± 0.09	25 ± 2.5	≥ 250
AZT, **1**	0.006 ± 0.002	0.005 ± 0.003	>100	>100

[a] 50% Effective concentration. [b] 50% Cytotoxic concentration.

coated aluminium plates 60 F_{254} with a 0.2-mm layer of silica gel containing a fluorescence indicator; sugar-containing compounds were visualized with the sugar spray reagent (0.5 mL of 4-methoxybenzaldehyde, 9 mL of ethanol, 0.5 mL of concentrated sulfuric acid, and 0.1 mL of glacial acectic acid) by heating with a fan. NMR spectra were recorded using (^{1}H NMR) Bruker AC 250 at 250 MHz, Bruker WM 400 at 400 MHz, Bruker AMX 400 at 400 MHz or Bruker DMX 500 at 500 MHz; (^{13}C NMR) Bruker WM 400 at 101 MHz, Bruker AMX 400 at 101 MHz or Bruker DMX 500 at 123 MHz (calibration was done in both cases with the solvent); (^{31}P NMR) Bruker AMX 400 at 162 MHz or Bruker DMX 500 at 202 MHz (H_3PO_4 as external standard). All ^{1}H and ^{13}C NMR chemical shifts (δ) are quoted in parts per million (ppm) downfield from tetramethylsilane, $(CD_3)(CD_2H)SO$ being set at δ_H 2.49 as a reference. ^{31}P NMR chemical shifts are quoted in ppm using H_3PO_4 as external reference. The spectra were recorded at room temperature, and all ^{13}C and ^{31}P NMR were recorded in proton-decoupled mode. Mass spectra were obtained with a VG Analytical VG/70–250 F spectrometer (FAB, matrix was *m*-nitrobenzyl alcohol). Analytical HPLC was performed on a Merck–Hitachi system with LiChroCART 250-3 containing LiChrospher 100-3 RP-18 (5 μm). Standard gradient: 5–100% CH_3CN in water in 20 min, then 10 min. 5% CH_3CN in water, flow: 0.5 mL/min. Optical rotations were measured on a Perkin–Elmer Polarimeter 241 and a Jasco DIP-370 digital polarimeter at 589 nm. IR spectra were recorded using a ThermoNicolet Avatar 370 FT-IR.

6′-Carba-2′-deoxy-5′-*O*-tritylthymidine (13): To a stirred solution of *carba*-dT **2** (1.10 g, 4.58 mmol) in dry pyridine (30 mL) was slowly added triphenylmethyl chloride (1.81 g, 6.49 mmol) at room temperature. The mixture was stirred for 3 h at 90 °C. After evaporation of the solvent, the residue was partitioned between water (100 mL) and CH_2Cl_2 (100 mL). The aqueous layer was extracted again with CH_2Cl_2 (2 × 50 mL) and the combined organic phases were dried with Na_2SO_4. The crude product was purified on silica gel (CH_2Cl_2/MeOH, 20:1) to yield **13** (1.87 g, 85%) as a colourless foam. $[\alpha]_D^{20}$ = –4.8 (*c* = 0.62, CH_3CN); R_f (TLC) = 0.65 (CH_2Cl_2/MeOH, 9:1). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.20 (br. s, 1 H, N*H*), 7.46 (d, 1 H, *J* = 1.0 Hz, H-6), 7.40–7.25 (m, 15 H, CH arom.), 4.98–4.90 (m, 1 H, H-1′), 4.81 (d, 1 H, *J* = 5.0 Hz, 3′-O*H*), 3.98–3.92 (m, 1 H, H-3′), 3.17 (dd, 1 H, *J* = 9.0 Hz, 5.6 Hz, H-5′a), 2.96 (dd, 1 H, *J* = 9.0 Hz, 7.4 Hz, H-5′b), 2.21–2.16 (m, 1 H, H-6′a), 2.12–2.16 (m, 1 H, H-4′), 1.93 (ddd, 1 H, *J* = 13.4 Hz, 9.0 Hz, 7.4 Hz, H-2′b), 1.73 (d, 3 H, *J* = 1.0 Hz, H-7), 1.44–1.36 (m, 1 H, H-6′b) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 164.1 (C-4), 151.3 (C-2), 144.3 (Cq arom.), 138.2 (C-6), 128.9, 128.3, 127.3 (CH arom.), 109.5 (C-5), 86.2 (Cq Trt.), 71.9 (C-3′), 65.5 (C-5′), 53.4 (C-1′), 47.4 (C-4′), 39.2 (C-2′), 33.7 (C-6′), 12.4 (C-7) ppm. IR (KBr): $\tilde{\nu}$ = 3435, 3955, 2925, 1685, 1475, 1450, 1275, 1070, 750, 705, 630 cm^{-1}. HRMS-FAB: *m*/*z* calcd. for $C_{30}H_{30}N_2O_4$ [M + H]: 483.2283; found: 483.2268.

2,3′-Anhydro-6′-carba-2′-deoxy-5′-*O*-tritylthymine (14): To a stirred suspension of triphenylphosphane (980 mg, 3.73 mmol) in dry CH_3CN (15 mL) was slowly added DIAD (730 μL, 3.73 mmol) at 0 °C under a nitrogen atmosphere. The yellow solution was stirred for 0.5 h at 0 °C and then added to a solution of the tritylated nucleoside **13** (900 mg, 1.87 mmol) in dry CH_3CN (10 mL) at 0 °C in a nitrogen atmosphere. The mixture was warmed to room temperature and stirred overnight at that temperature. The solvent was evaporated off and the crude was purified on silica gel (CH_2Cl_2/MeOH, 9:1) to yield the title compound **14** (770 mg, 87%) as a colourless foam. $[\alpha]_D^{20}$ = +26.6 (*c* = 0.21, CH_3CN) R_f (TLC) = 0.31 (CH_2Cl_2/MeOH, 9:1). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.40–7.25 (m, 16 H, C*H* arom., H-6), 5.17–5.14 (m, 1 H, H-3′), 4.39–4.35 (m, 1 H, H-1′), 3.18 (dd, 1 H, *J* = 9.3 Hz, 9.0 Hz, H-5′a), 2.98 (dd, 1 H, *J* = 9.3 Hz, 6.5 Hz, H-5′b), 2.59–2.51 (m, 1 H, H-4′), 2.26–2.21 (m, 1 H, H-2′a), 2.16–2.06 (m, 2 H, H-2′b, H-6′a), 1.74 (d, 3 H, *J* = 1.0 Hz, H-7), 1.50 (ddd, 1 H, *J* = 14.0 Hz, 4.9 Hz, 2.5 Hz, H-6′b) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 171.3 (C-4), 153.9 (C-2), 144.0 (*C*q arom.), 137.9 (C-6), 128.6, 128.2, 127.3 (*C*H arom.), 116.8 (C-5), 86.5 (*C*q Trt.), 80.7 (C-3′), 62.5 (C-5′), 60.5 (C-1′), 43.5 (C-4′), 35.5 (C-2′), 33.3 (C-6′), 13.5 (C-7) ppm. IR (KBr): $\tilde{\nu}$ = 3430, 3060, 2920, 1660, 1630, 1510, 1480, 1450, 1310, 1270, 1210, 1140, 1070, 1030, 970, 870, 770, 700, 630 cm^{-1}. HRMS-FAB: *m*/*z* calcd. for $C_{30}H_{28}N_2O_3$ [M + H]: 465.2178; found: 465.2157.

3′-Azido-6′-carba-2′,3′-dideoxy-5′-*O*-tritylthymidine (15): Compound **14** (300 mg, 0.646 mmol) was dissolved in dry DMF (3.0 mL) under a nitrogen atmosphere and sodium azide (420 mg, 6.46 mmol) was added. The mixture was stirred for 12 h at 140 °C. After removal of the solvent the residue was treated with CH_2Cl_2 (50 mL) and the organic layer was washed with water (3 × 20 mL), dried with Na_2SO_4 and concentrated. The crude was purified on silica gel (hexanes/EtOAc, 2:1) to yield **15** (260 mg, 79%) as a colourless foam. $[\alpha]_D^{20}$ = +2.3 (*c* = 0.58, $CHCl_3$); R_f (TLC) = 0.43 (CH_2Cl_2/MeOH, 30:1). ^{1}H NMR (400 MHz, C_6D_6): δ = 9.80–9.40 (br. m, 1 H, N*H*), 7.55–7.48 (m, 6 H, C*H* arom.), 7.20–7.12 (m, 6 H, C*H* arom.), 7.09–7.02 (m, 3 H, C*H* arom.), 6.02 (s, 1 H, H-6), 4.42–4.33 (m, 1 H, H-1′), 3.61 (dd, 1 H, *J* = 13.4 Hz, 6.7 Hz, H-3′), 3.14 (dd, 1 H, *J* = 9.4 Hz, 5.3 Hz, H-5′a), 3.07 (dd, 1 H, *J* = 9.4 Hz, 5.3 Hz, H-5′b), 1.83–1.76 (m, 1 H, H-4′), 1.69 (s, 3 H, H-7), 1.68–1.65 (m, 1 H, H-6′a), 1.58–1.50 (m, 2 H, 2 × H-2′), 1.33 (ddd, 1 H, *J* = 12.7 Hz, 10.3 Hz, 10.3 Hz, H-6′b) ppm. ^{13}C NMR (101 MHz, C_6D_6): δ = 162.2 (C-4), 149.4 (C-2), 143.0 (*C*q arom.), 135.6 (C-6), 127.6, 126.9, 126.8 (*C*H arom.), 109.2 (C-5), 85.8 (*C*q Trt.), 62.5 (C-5′), 60.9 (C-3′), 53.9 (C-1′), 43.9 (C-4′), 34.3 (C-2′), 31.3 (C-6′), 12.8 (C-7) ppm. IR (KBr): $\tilde{\nu}$ = 3180, 3060, 2920, 2100 (-N$_3$), 1690, 1470, 1450, 1370, 1265, 1070, 1030, 898, 760, 700, 630 cm^{-1}. HRMS-FAB: *m*/*z* calcd. for $C_{30}H_{29}N_5O_3$ [M + H]: 508.2349; found: 508.2361.

3′-Azido-6′-carba-2′,3′-dideoxythymidine (*carba*-AZT) (3): A solution of compound **15** (250 mg, 0.49 mmol) in CH_2Cl_2/MeOH (7:3 v/v, 10 mL) was treated slowly with TFA (100 μL) and stirred at room temperature for 10 h, until complete conversion by TLC was observed. The solvent was evaporated off and the residue was purified on a Chromatotron (CH_2Cl_2/MeOH gradient 0–10%) to yield **3** (105 mg, 81%) as a colourless foam. After lyophilization (CH_3CN/H_2O, 1:1) compound **3** was obtained as a colourless cotton. $[\alpha]_D^{20}$ = +10.0 (*c* = 0.61, CH_3CN) ref.[16] $[\alpha]_D^{20}$ = +16.0 (*c* = 0.98, acetone); R_f (TLC) = 0.39 (CH_2Cl_2/MeOH, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.98 (br. s, 1 H, N*H*), 7.10 (q, 1 H, *J* = 1.2 Hz, H-6), 4.90–4.80 (m, 1 H, H-1′), 3.84 (dd, 1 H, *J* = 10.5 Hz, 4.5 Hz, H-5′a), 3.75 (dd, 1 H, *J* = 10.5 Hz, 4.8 Hz, H-5′b), 2.33–2.22 (m, 2 H, H-2′a, H-6′a), 2.21–2.08 (m, 2 H, H-2′b, H-4′), 1.93 (d, 3 H, *J* = 1.2 Hz, H-7), 1.88–1.80 (m, 1 H, H-6′b) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.1 (C-4), 151.3 (C-2), 138.4 (C-6), 111.7 (C-5), 63.5 (C-5′), 62.7 (C-3′), 56.7 (C-1′), 46.8 (C-4′), 36.8 (C-2′), 32.0 (C-6′), 13.0 (C-7) ppm. IR (KBr): $\tilde{\nu}$ = 3430, 3040, 2100 (-N$_3$), 1690, 1470, 1370, 1270, 1130, 1050, 780, 570, 420 cm^{-1}. HRMS-FAB: *m*/*z* calcd. for $C_{11}H_{15}N_5O_3$ [M + H]: 266.1253; found: 266.1275.

6′-Carba-2′,3′-dideoxy-3′-[2-(trimethylsilyl)ethyl]thio-5′-*O*-tritylthymidine (16): To a stirred suspension of sodium hydride (37.0 mg, 0.77 mmol, 50% in oil) in dry DMF (2.0 mL) was slowly added a solution of 2-(trimethylsilyl)ethanethiol (112 μL, 0.70 mmol) in dry DMF (2.0 mL). The clear solution was stirred for 15 min under a

nitrogen atmosphere, and then the 2,3′-anhydronucleoside **14** (300 mg, 0.65 mmol) was added in one portion. After being heated at 90 °C for 2 h the DMF was evaporated off. The residue was dissolved in CH_2Cl_2 (50 mL), washed with aqueous NaH_2PO_4 (10%, 20 mL), water (2×20 mL), dried with Na_2SO_4 and concentrated. The crude was purified by chromatography on silica gel (hexanes/EtOAc, 1:2) to yield the title compound **16** (310 mg, 80%) as a colourless foam. $[\alpha]_D^{20}$ = +13.4 (*c* = 0.59, CH_3CN); R_f (TLC) = 0.61 (hexanes/EtOAc, 1:2). ^{1}H NMR (500 MHz, [D$_6$]benzene): δ = 9.19 (s, 1 H, N*H*), 7.59 (d, 6 H, *J* = 7.2 Hz, C*H* arom.), 7.22–7.17 (m, 6 H, C*H* arom.), 7.10–7.06 (m, 3 H, C*H* arom.), 6.25 (q, 1 H, *J* = 1.0 Hz, H-6), 4.80–4.70 (m, 1 H, H-1′), 3.40 (dd, 1 H, *J* = 9.1 Hz, 4.8 Hz, H-5′a), 3.28 (dd, 1 H, *J* = 9.1 Hz, 6.3 Hz, H-5′b), 3.10 (ddd, 1 H, *J* = 7.8 Hz, 7.8 Hz, 5.9 Hz, H-3′), 2.54–2.50 (m, 1 H, S–C*H*$_2$-), 2.09–2.03 (m, 1 H, H-4′), 2.02–1.97 (m, 1 H, H-6′a), 1.94–1.88 (m, 2 H, H-2′a, H-2′b), 1.73 (d, 3 H, *J* = 1.0 Hz, H-7), 1.53 (ddd, 1 H, *J* = 12.8 Hz, 10.2 Hz, 10.2 Hz, H-6′b), 0.90–0.85 (m, 2 H, -C*H*$_2$–Si), 0.00 [s, 9 H, Si(C*H*$_3$)$_3$] ppm. ^{13}C NMR (101 MHz, [D$_6$]benzene): δ = 164.5 (C-4), 152.5 (C-2), 146.3 (*C*q arom.), 138.6 (C-6), 130.8, 129.9, 129.3 (*C*H arom.), 112.1 (C-5), 84.6 (*C*q Trt.), 66.9 (C-5′), 57.8 (C-1′), 47.4 (C-4′), 45.8 (C-3′), 40.0 (C-2′), 36.2 (C-6′), 29.2 (S–*C*H$_2$–), 19.2 (*C*H$_2$–Si), 14.3 (C-7), 0.0 [Si(*C*H$_3$)$_3$] ppm. IR (neat): $\tilde{\nu}$ = 3175, 3060, 2950, 1685, 1470, 1450, 1270, 1070, 860, 740, 700 cm^{-1}. HRMS-FAB: *m*/*z* calcd. for $C_{35}H_{42}N_2O_3SSi$ [M + H]: 599.2764; found: 599.2758.

6′-Carba-2′,3′-dideoxy-3′-[2-(trimethylsilyl)ethyl]thiothymidine (17): A solution of compound **16** (200 mg, 0.33 mmol) in Et_2O (2 mL) was treated with formic acid (1.0 mL) and stirred at room temperature for 12 h, until complete conversion by TLC was observed. The solvent was evaporated off and the residue was purified on a Chromatotron (CH_2Cl_2/MeOH gradient 0–10%) to yield **17** (68.9 mg, 59%) as a colourless foam. $[\alpha]_D^{20}$ = +41 (*c* = 0.18, CH_3CN); R_f (TLC) = 0.17 (hexanes/EtOAc, 1:2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.18 (br. s, 1 H, N*H*), 7.09 (q, 1 H, *J* = 1.2 Hz, H-6), 5.00–4.91 (m, 1 H, H-1′), 3.80 (dd, 1 H, *J* = 10.0 Hz, 4.2 Hz, H-5′a), 3.75 (dd, 1 H, *J* = 10.0 Hz, 5.0 Hz, H-5′b), 3.20 (ddd, 1 H, *J* = 8.1 Hz, 8.1 Hz, 5.8 Hz, H-3′), 2.59–2.55 (m, 2 H, S–C*H*$_2$), 2.29–2.21 (m, 2 H, H-2′a, H-6′a), 2.10–2.14 (m, 1 H, H-2′b), 2.10–2.02 (m, 1 H, H-4′), 1.91 (d, 3 H, *J* = 1.2 Hz, H-7), 1.75 (ddd, 1 H, *J* = 12.6 Hz, 10.0 Hz, 10.0 Hz, H-6′b), 0.89–0.78 (m, 2 H, C*H*$_2$–Si), 0.00 [s, 9 H, Si(C*H*$_3$)$_3$] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.3 (C-4), 152.0 (C-2), 139.3 (C-6), 65.9 (C-5′), 57.7 (C-1′), 48.2 (C-4′), 45.6 (C-3′), 40.6 (C-2′), 34.9 (C-6′), 29.2 (S–C*H*$_2$), 19.1 (C*H*$_2$–Si), 14.3 (C-7), 0.0 [Si(C*H*$_3$)$_3$] ppm. IR (neat): $\tilde{\nu}$ = 3440, 1650, 1470, 1420, 1250, 1050, 590 cm^{-1}. HRMS-FAB: *m*/*z* calcd. for $C_{16}H_{28}N_2O_3SSi$ [M + H]: 357.1668; found: 357.1667.

6′-Carba-2′,3′-dideoxy-3′-thiocyanatothymidine (4): To a solution of compound **17** (60.0 mg, 0.17 mmol) in methanol (1.5 mL) was added BrCN (178 mg, 1.70 mmol) in one portion. After being stirred for 18 h at room temperature, the mixture was treated with aqueous phosphate buffer (0.5 M, pH 7.0, 4 mL) and stirred for further 30 min at room temperature, then water (10 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic fractions were dried with Na_2SO_4, concentrated and the crude material was purified by chromatography on a chromatotron (CH_2Cl_2/MeOH gradient 0–10%) to yield **4** (36.2 mg, 75%) as a colourless foam. After lyophilization (CH_3CN/H_2O, 1:1) compound **4** was obtained as a colourless cotton. $[\alpha]_D^{20}$ = +25.0 (*c* = 0.52, CH_3CN); R_f (TLC) = 0.43 (CH_2Cl_2/MeOH, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.90 (br. s, 1 H, N*H*), 7.03 (q, 1 H, *J* = 1.2 Hz, H-6), 4.78–4.69 (m, 1 H, H-1′), 3.86 (dd, 1 H, *J* = 11.0 Hz, 4.0 Hz, H-5′a), 3.81 (d, 1 H, *J* = 7.5 Hz, H-3′), 3.76 (dd, 1 H, *J* = 11.0 Hz, 3.6 Hz, H-5′b), 2.52 (ddd, 1 H, *J* = 14.5 Hz, 8.1 Hz, 6.6 Hz, H-2′a), 2.32 (ddd, 1 H, *J* = 14.5 Hz, 9.3 Hz, 7.3 Hz, H-2′b), 2.28–2.17 (m, 2 H, H-4′, H-6′a), 2.07 (ddd, 1 H, *J* = 11.7 Hz, 9.3 Hz, 9.3 Hz, H-6′b), 1.87 (d, 3 H, *J* = 1.2 Hz, H-7) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.2 (C-4), 151.1 (C-2), 139.0 (C-6), 111.8 (C-5), 111.4 (S–CN), 61.8 (C-5′), 57.7 (C-1′), 47.8 (C-4′), 46.4 (C-3′), 38.8 (C-2′), 32.7 (C-6′), 12.9 (C-7) ppm. IR (KBr): $\tilde{\nu}$ = 3430, 3050, 2930, 2150, 1690, 1470, 1380, 1270, 1220, 1130, 1050, 780, 590 cm^{-1}. HRMS-FAB: *m*/*z* calcd. for $C_{12}H_{15}N_3O_3S$ [M + H]: 282.0912; found: 282.0890.

6′-Carba-2′-deoxy-3′-*O*-phenoxythiocarbonyl-5′-*O*-tritylthymidine (18): Compound **13** (1.80 g, 3.73 mmol) was dissolved in CH_2Cl_2 (10 mL) at 0 °C under a nitrogen atmosphere, then pyridine (1.5 mL) was added. This solution was treated slowly with phenoxythiocarbonyl chloride (PTC-Cl, 1.30 g, 1.00 mL, 7.40 mmol) at 0 °C, then the mixture was warmed to room temperature and stirred at this temperature for 12 h. The solvents were evaporated off and the residue was dissolved in EtOAc (50 mL). The organic phase was washed with water (3×50 mL), dried with Na_2SO_4 and concentrated. The crude material was purified by chromatography on silica gel (hexanes/EtOAc, 1:2) to yield compound **18** (2.17 g, 95%) as a colourless foam. $[\alpha]_D^{20}$ = +2.5 (*c* = 0.57, $CHCl_3$); R_f (TLC) = 0.36 (hexanes/EtOAc, 1:2). ^{1}H NMR (400 MHz, C_6D_6): δ = 9.42–9.30 (br. s, 1 H, N*H*), 7.55–7.50 (m, 6 H, C*H* arom.), 7.18–7.10 (m, 6 H, C*H* arom.), 7.08–7.00 (m, 8 H, C*H* arom.), 6.19 (q, 1 H, *J* = 1.0 Hz, H-6), 5.68 (ddd, 1 H, *J* = 6.5 Hz, 4.3 Hz, 3.9 Hz, H-3′), 4.86–4.76 (m, 1 H, H-1′), 3.32 (dd, 1 H, *J* = 9.1 Hz, 5.3 Hz, H-5′a), 3.15 (dd, 1 H, *J* = 9.1 Hz, 5.8 Hz, H-5′b), 2.37–2.29 (m, 1 H, H-4′), 2.00–1.90 (m, 2 H, 2×H-2′), 1.78–1.70 (m, 1 H, H-6′), 1.66 (d, 3 H, *J* = 1.0 Hz, H-7), 1.29–1.25 (m, 1 H, H-6′b) ppm. ^{13}C NMR (101 MHz, C_6D_6): δ = 195.3 (*C*=S), 164.2 (C-4), 157.3 (*C*q phenol) 151.2 (C-2), 144.7 (*C*q arom.), 136.4 (C-6), 130.1, 129.4, 128.1, 127.89, 127.7, 122.6 (*C*H arom.), 109.4 (C-5), 86.1 (C-3′), 84.9 (*C*q Trt.), 64.8 (C-5′), 55.1 (C-1′), 44.5 (C-4′), 36.7 (C-2′), 32.5 (C-6′), 12.9 (C-7) ppm. IR (KBr): $\tilde{\nu}$ = 3435, 3060, 2930, 1690, 1490, 1450, 1370, 1280, 1200, 1070, 1000, 900, 770, 705, 630 cm^{-1}. HRMS-FAB: *m*/*z* calcd. for $C_{37}H_{34}N_2O_5S$ [M + H]: 619.2267; found: 619.2299.

3′-Allyl-6′-carba-2′,3′-dideoxy-5′-*O*-tritylthymidine (19): A mixture of **18** (2.10 g, 3.39 mmol) allyltributyltin (5.60 g, 17.0 mmol) and AIBN (180 mg, 1.10 mmol) in dry and degassed toluene (15 mL) was heated to 80 °C for 24 h. A second portion of AIBN was added (180 mg, 1.10 mmol) and the mixture was stirred at 80 °C for further 24 h. The solvent was evaporated in vacuo, and the residue was purified on silica gel (hexanes/EtOAc, 2:3) to yield compound **19** (1.10 g, 64%) as the major fraction as a colourless foam. $[\alpha]_D^{20}$ = +2.2 (*c* = 0.97, CH_3CN); R_f (TLC) = 0.45 (hexanes/EtOAc, 1:2). ^{1}H NMR (400 MHz, C_6D_6): δ = 9.90 (br. s, 1 H, N*H*), 7.65–7.60 (m, 6 H, C*H* arom.), 7.25–7.15 (m, 9 H, C*H* arom.), 6.45 (q, 1 H, *J* = 1.0 Hz, H-6), 5.69–5.59 (m, 1 H, C*H*=CH$_2$), 5.05–5.00 (m, 2 H, CH=C*H*$_2$), 4.99–4.90 (m, 1 H, H-1′), 3.28 (dd, 1 H, *J* = 9.0 Hz, 5.0 Hz, H-5′a), 3.08 (dd, 1 H, *J* = 9.0 Hz, 6.6 Hz, H-5′b), 2.14–2.02 (m, 2 H, C*H*$_2$–CH=), 1.82 (d, 3 H, *J* = 1.0 Hz, H-7), 1.78–1.70 (m, 2 H, H-4′, H-6′a), 1.69–1.62 (m, 2 H, H-3′, H-2′a), 1.45–1.32 (m, 2 H, H-2′b, H-6′b) ppm. ^{13}CNMR (101 MHz, C_6D_6): δ = 164.3 (C-4), 151.9 (C-2), 145.0 (*C*q arom.), 137.3 (C-6), 136.2 (*C*H=CH$_2$), 128.0, 127.6, 127.5 (*C*H arom.), 116.5 (CH=*C*H$_2$), 111.0 (C-5), 84.8 (*C*q Trt.), 66.1 (C-5′), 54.4 (C-1′), 44.4 (C-4′), 39.9 (*C*H$_2$–CH=), 39.7 (C-3′), 36.5 (C-2′), 36.1 (C-6′), 13.0 (C-7) ppm. IR (KBr): $\tilde{\nu}$ = 3430, 3180, 3060, 2920, 1685, 1490, 1470, 1450, 1270, 1070, 760, 750, 700, 630 cm^{-1}. HRMS-FAB: *m*/*z* calcd. for $C_{33}H_{34}N_2O_3$ [M + H]: 507.2648; found: 507.2650. As a side product, the deoxygenated compound **20** (294 mg, 19%) was isolated as a colourless foam. $[\alpha]_D^{20}$ = –130.1 (*c* = 0.95, $CHCl_3$); R_f

(TLC) = 0.36 (hexanes/EtOAc, 1:2). ^{1}H NMR (400 MHz, C_6D_6): δ = 9.95–9.85 (m, 1 H, N*H*), 7.55–7.50 (m, 6 H, C*H* arom.), 7.20–7.10 (m, 6 H, C*H* arom.), 7.06–7.00 (m, 3 H, C*H* arom.), 6.26 (q, 1 H, *J* = 1.0 Hz, H-6), 4.80–4.70 (m, 1 H, H-1′), 3.03 (dd, 1 H, *J* = 8.8 Hz, 6.0 Hz, H-5′a), 2.97 (dd, 1 H, *J* = 8.8 Hz, 6.6 Hz, H-5′b), 1.94–1.80 (m, 2 H, H-4′, H-6′a), 1.68 (d, 3 H, *J* = 1.0 Hz, H-7), 1.60–1.52 (m, 1 H, H-2′a), 1.44–1.35 (m, 1 H, H-3′a), 1.33–1.20 (m, 2 H, H-2′b, H-3′b), 1.00–0.90 (m, 1 H, H-6′b) ppm. ^{13}C NMR (101 MHz, C_6D_6): δ = 164.3 (C-4), 152.0 (C-2), 145.0 (*C*q arom.), 136.1 (C-6), 128.1, 127.9, 127.6 (*C*H arom.), 111.0 (C-5), 84.5 (*C*q Trt.), 67.6 (C-5′), 56.0 (C-1′), 38.3 (C-4′), 35.4 (C-2′), 29.9 (C-6′), 27.4 (C-3′), 13.0 (C-7) ppm. IR (KBr): $\tilde{\nu}$ = 3440, 3060, 2950, 2920, 1685, 1470, 1450, 138, 1270, 1070, 760, 700 cm^{-1}. HRMS-FAB: *m*/*z* calcd. for $C_{30}H_{30}N_2O_3$ [M + H]: 467.2335; found: 467.2333.

3′-Allyl-6′-carba-2′,3′-dideoxythymidine (*carba*-3′-allyl-dT) (5): A solution of compound **19** (180 mg, 0.35 mmol) in CH_2Cl_2/MeOH (7:3 v/v, 10 mL) was treated slowly with TFA (100 μL) and stirred at room temperature for 12 h, until complete conversion by TLC was observed. The solvent was evaporated off and the residue was purified on a Chromatotron (CH_2Cl_2/MeOH gradient 0–10%) to yield **5** (65.0 mg, 69%) as a colourless foam. After lyophilization (CH_3CN/H_2O, 1:1) compound **5** was obtained as a colourless cotton. $[\alpha]_D^{20}$ = +14.4 (*c* = 0.42, CH_3CN); R_f (TLC) = 0.41 (CH_2Cl_2/MeOH, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.85 (br. s, 1 H, N*H*), 7.15 (q, 1 H, *J* = 1.0 Hz, H-6), 5.81–5.70 (m, 1 H, C*H*=CH_2), 5.09–5.00 (m, 2 H, CH=CH_2), 4.95–4.88 (m, 1 H, H-1′), 3.78–3.63 (m, 2 H, 5′-CH_2), 2.33–2.20 (m, 2 H, CH_2–CH, H-6′a), 2.09–1.99 (m, 2 H, H-3′, H-2′a), 1.92 (d, 3 H, *J* = 1.0 Hz, H-7), 1.88–1.80 (m, 2 H, H-4′, H-2′b), 1.70–1.60 (m, 1 H, H-6′b) ppm; –^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.0 (C-4), 152.3 (C-2), 137.5 (C-6), 136.9 (*C*H=CH_2), 117.0 (CH=*C*H_2), 111.1 (C-5), 64.9 (C-5′), 55.1 (C-1′), 46.0 (C-4′), 39.7 (C-2′), 39.1 (C-3′), 36.7 (*C*H_2–CH=), 35.2 (C-6′), 13.0 (C-7) ppm. IR (KBr): $\tilde{\nu}$ = 3430, 3060, 2920, 1680, 1470, 1695, 1270, 1220, 1045, 910, 590, 490 cm^{-1}. HRMS-FAB: *m*/*z* calcd. for $C_{14}H_{20}N_2O_3$ [M + H]: 265.1552; found: 265.1548.

6′-Carba-2′,3′-dideoxythymidine (*carba*-ddT) (7): A solution of compound **20** (300 mg, 0.643 mmol) in CH_2Cl_2/MeOH (7:3 v/v, 10 mL) was treated slowly with TFA (200 μL) and stirred at room temperature for 10 h, until complete conversion by TLC was observed. The solvent was evaporated off and the residue was purified on a Chromatotron (CH_2Cl_2/MeOH gradient 0–10%) to yield **7** (132 mg, 92%) as a colourless foam. After lyophilization (CH_3CN/H_2O, 1:1) compound **7** was obtained as a colourless cotton. $[\alpha]_D^{20}$ = –9.5 (*c* = 0.72, CH_3CN) ref.[23] 13 (*c* = 1.0, EtOH); R_f (TLC) = 0.29 (CH_2Cl_2/MeOH, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.75 (br. s, 1 H, N*H*), 7.11 (q, 1 H, *J* = 1.0 Hz, H-6), 4.95–4.85 (m, 1 H, H-1′), 3.67 (d, 2 H, *J* = 5.0 Hz, 5′-CH_2), 2.31–2.16 (m, 2 H, H-4′, H-6′a), 2.14–2.05 (m, 1 H, H-2′a), 1.93 (d, 3 H, *J* = 1.0 Hz, H-7), 1.89–1.81 (m, 1 H, H-3′a), 1.77–1.61 (m, 2 H, H-2′b, H-3′b), 1.55–1.45 (m, 1 H, H-6′b) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.3 (C-4), 152.2 (C-2), 137.3 (C-6), 111.4 (C-5), 66.6 (C-5′), 56.8 (C-1′), 39.9 (C-4′), 34.5 (C-2′), 30.6 (C-2′), 26.9 (C-3′), 13.0 (C-7) ppm. IR (KBr): $\tilde{\nu}$ = 3470, 3160, 3030, 2950, 1680, 1470, 1420, 1400, 1375, 1270, 1125, 1055, 1015, 590, 425 cm^{-1}. HRMS-FAB: *m*/*z* calcd. for $C_{11}H_{16}N_2O_3$ [M + H]: 225.1239; found: 225.1239.

6′-Carba-3′-(2,3-dibrompropyl)-2′,3′-dideoxy-5′-*O*-tritylthymidine (21): A solution of compound **19** (400 mg, 0.790 mmol) in CCl_4 (5.0 mL) was treated with bromine (126 mg, 0.788 mmol, dissolved in 1.0 mL CCl_4) at –10 °C over a period of 45 min. The solution was stirred for further 30 min at that temperature, then the solvent was evaporated in vacuo. The residue was purified by chromatography on a chromatotron (CH_2Cl_2/MeOH gradient 0–10%) to yield compound **21** (310 mg, 59%) as a mixture of two inseparable isomers as a colourless foam. R_f (TLC) = 0.43 (hexanes/EtOAc, 1:2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.25 (br. s, 2 H, 2×N*H*), 7.45–7.40 (m, 12 H, C*H* arom.), 7.35–7.28 (m, 12 H, C*H* arom.), 7.25–20 (m, 6 H, C*H* arom.), 7.06 (q, 1 H, *J* = 1.2 Hz, H-6), 7.01 (q, 1 H, *J* = 1.2 Hz, H-6), 5.06–4.94 (m, 2 H, 2×H-1′), 4.05 (dddd, 1 H, *J* = 10.7 Hz, 9.9 Hz, 4.0 Hz, 3.0 Hz, C*H*Br), 4.98 (dddd, 1 H, *J* = 9.5 Hz, 9.5 Hz, 4.0 Hz, 3.3 Hz, C*H*Br), 3.85 (dd, 1 H, *J* = 10.2 Hz, 4.0 Hz, C*H*HBr), 3.75 (dd, 1 H, *J* = 10.2 Hz, 4.0 Hz, C*H*HBr), 3.54 (dd, 1 H, *J* = 12.8 Hz, 9.6 Hz, CH*H*Br), 3.52 (d, 1 H, *J* = 12.8 Hz, 9.6 Hz, CH*H*Br), 3.23 (dd, 1 H, *J* = 9.6 Hz, 5.0 Hz, H-5′a), 3.21–3.16 (m, 3 H, H-5′b, 5′-CH_2), 2.50–2.40 (m, 1 H, H-3′), 2.37–2.28 (m, 5 H, H-3′, 2×CH_2–CHBr–), 2.05–1.95 (m, 4 H, 2×H-2′a, 2×H-6′a), 1.91 (d, 3 H, *J* = 1.2 Hz, H-7), 1.88 (d, 3 H, *J* = 1.2 Hz, H-7), 1.87–1.84 (m, 2 H, 2×H-4′), 1.80–1.70 (m, 2 H, 2×H-2′b), 1.65–1.58 (m, 2 H, 2×H-6′b) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.7 (C-6), 151.2 (C-2), 144.3 (*C*q arom.), 144.3 (*C*q arom.), 136.8 (C-6), 136.7 (C-6), 129.1, 129.1, 128.3, 128.3, 127.6, 127.5 (*C*H arom.), 84.3 (*C*q Trt.), 65.9 (C-5′), 64.5 (C-5′), 54.7 (C-1′), 54.3 (C-1′), 52.3 (*C*HBr), 51.7 (*C*HBr), 45.2 (C-4′), 44.9 (C-4′), 43.1 (*C*H_2–CHBr), 38.4 (C-3′), 38.0 (*C*H_2Br), 37.0 (*C*H_2Br), 37.0 (C-2′) 36.3 (C-2′), 36.2 (C-6′), 36.1 (C-6′), 13.1 (C-7), 13.1 (C-7) ppm.

6′-Carba-3′-(2,3-dibrompropyl)-2′,3′-dideoxythymidine (22): A solution of compound **21** (300 mg, 0.450 mmol) in CH_2Cl_2/MeOH (7:3 v/v, 10 mL) was treated slowly with TFA (200 μL) and stirred at room temperature for 12 h, until complete conversion by TLC was observed. The solvent was evaporated off and the residue was purified on a Chromatotron (CH_2Cl_2/MeOH gradient 0–15%) to yield **22** (170 mg, 89%) as an inseparable mixture of two isomers as a colourless foam. R_f (TLC) = 0.33 (CH_2Cl_2/MeOH, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.45 (br. s, 2 H, 2×N*H*), 7.17–7.14 (m, 2 H, 2×H-6), 5.05–4.88 (m, 2 H, 2×H-1′), 4.23 (dddd, 1 H, *J* = 9.3 Hz, 9.3 Hz, 4.0 Hz, 4.0 Hz, C*H*Br), 4.06 (dddd, 1 H, *J* = 10.5 Hz, 9.7 Hz, 4.1 Hz, 2.8 Hz, C*H*Br), 3.86 (dd, 1 H, *J* = 10.3 Hz, 4.1 Hz, C*H*HBr), 3.85 (dd, 1 H, *J* = 10.4 Hz, 4.3 Hz, C*H*HBr), 3.77–3.67 (m, 4 H, 2×5′-CH_2), 3.61 (dd, 1 H, *J* = 10.3 Hz, 3.2 Hz, CH*H*Br), 3.59 (dd, 1 H, *J* = 10.3 Hz, 4.0 Hz, CH*H*Br), 2.40–2.30 (m, 3 H, CH_2–CHBr, H-3′), 2.28–2.15 (m, 4 H, H-3′, CH_2–CHBr, H-2′a), 2.12–2.00 (m, 3 H, H-2′a, 2×H-6′a), 1.91 (d, 3 H, *J* = 1.0 Hz, H-7), 1.90 (d, 3 H, *J* = 1.0 Hz, H-7), 1.88–1.75 (m, 4 H, 2×H-4′, 2×H-2′b), 1.73–1.60 (m, 2 H, 2×H6′b) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.3 (C-4), 164.3 (C-4), 151.6 (C-2), 137.5 (C-6), 137.3 (C-6), 111.7 (C-5), 111.5 (C-5), 64.0 (C-5′), 62.1 (C-5′), 55.4 (C-1′), 54.9 (C-1′), 52.3 (*C*HBr), 51.9 (*C*HBr), 46.7 (C-4′), 46.2 (C-4′), 43.1 (*C*H_2–CHBr), 42.0 (*C*H_2–CHBr), 38.4 (C-3′), 38.0 (*C*H_2Br), 37.6 (C-3′), 37.0 (*C*H_2Br), 36.3 (C-2′), 35.3 (C-2′), 34.8 (C-6′), 33.6 (C-6′), 13.1 (C-7), 13.0 (C-7) ppm.

6′-Carba-2′,3′-dideoxy-3′-propargylthymidine (*carba*-3′-propargyl-dT) (6): Compound **22** (165 mg, 0.39 mmol) was dissolved in ethanol (5.0 mL) and treated with aqueous KOH solution (435 mg, 7.75 mmol, in 10 mL). The mixture was refluxed for 20 h, cooled to room temperature and concentrated in vacuo to half of the volume. After neutralization with aqueous HCl (2 M) a colourless precipitate was formed. The aqueous phase was extracted with CH_2Cl_2 (3×10 mL) and the combined organic fractions were dried with Na_2SO_4 and concentrated. The crude material was purified by chromatography on a chromatotron (CH_2Cl_2/MeOH gradient 0–10%) to yield compound **6** (63.0 mg, 62%) as a colourless foam. After lyophyllization (CH_3CN/H_2O, 1:1) the nucleoside **6** was obtained as a colourless cotton. $[\alpha]_D^{20}$ = +4.7 (*c* = 0.45, CH_3CN); R_f (TLC) = 0.27 (CH_2Cl_2/MeOH, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (br. s, 1 H, N*H*), 7.12 (q, 1 H, *J* = 1.2 Hz, H-6), 5.03–4.94

(m, 1 H, H-1′), 3.76 (d, 1 H, J = 5.0 Hz, H-5′a), 3.74 (d, 1 H, J = 5.0 Hz, H-5′b), 2.37 (ddd, 1 H, J = 16.6 Hz, 6.0 Hz, 2.5 Hz, C*H*H–C), 2.30 (ddd, 1 H, J = 16.6 Hz, 6.0 Hz, 2.5 Hz, CH*H*–C), 2.26–2.20 (m, 2 H, H-3′, H-6′a), 2.10–2.00 (m, 2 H, H-4′, H-2′a), 1.99 (dd, 1 H, J = 2.5 Hz, 2.5 Hz, C*H* alkyne), 1.98–1.93 (m, 1 H, H-2′b), 1.93 (d, 3 H, J = 1.2 Hz, H-7), 1.73–1.63 (m, 1 H, H-6′b) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.3 (C-4), 151.3 (C-2), 137.3 (C-6), 111.4 (C-5), 82.7 (*C*q alkyne), 70.2 (*C*H alkyne), 64.5 (C-5′), 55.1 (C-1′), 45.4 (C-4′), 38.7 (C-3′), 36.7 (C-2′), 35.2 (C-6′), 23.7 (*C*H$_2$–C), 13.0 (C-7) ppm. IR (KBr): $\tilde{\nu}$ = 3430, 3300, 3040, 2925, 1685, 1470, 1430, 1395, 1370, 1270, 1130, 1040, 630, 590, 490, 420 cm^{-1}. HRMS-FAB: *m*/*z* calcd. for $C_{14}H_{18}N_2O_3$ [M + H]: 263.1396; found: 263.1408.

Synthesis of the *cyclo*Sal-phosphate triesters: General Procedure

The nucleoside is dissolved in dry pyridine and 5 pieces of activated molecular sieves (3 Å) are added. The mixture is cooled to –40 °C under a nitrogen atmosphere and the 3-methyl-*cyclo*Sal-phosphorchloridate (1.23 M in toluene) is added dropwise over a period of 2 hrs. Stirring is continued for an additional 0.5 hrs at –40 °C. The reaction is warmed to room temperature and the pyridine is evaporated off. The crude is purified by chromatography on a chromatotron (CH_2Cl_2/MeOH gradient 0–10%) to yield the *cyclo*Sal-phosphate triesters as colourless foams. After lyophilization (CH_3CN/H_2O, 1:1) the products are obtained as colourless cottons.

3-Methyl-*cyclo*Saligenyl-(3′-azido-6′-carba-2′,3′-dideoxythymidinyl)monophosphate (3-Me-*cyclo*Sal-*carba*-AZTMP) (9): The reaction has been carried out according to the described general procedure with nucleoside **3** (50.0 mg, 0.19 mmol), pyridine (500 μL) and 3-methyl-*cyclo*Sal-phosphorchloridate (330 μL). Yield: 72.0 mg, (85%) as a mixture of two diastereomers. R_f (TLC) = 0.62 (CH_2Cl_2/MeOH, 9:1) ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.70 (br. s, 2 H, 2×N*H*), 7.19–7.16 (m, 2 H, 2×H-6 arom.), 7.05–7.01 (m, 2 H, 2×H-4 arom.), 6.97 (q, 1 H, J = 1.0 Hz, H-6), 6.95 (q, 1 H, J = 1.0 Hz, H-6), 6.94–6.90 (m, 2 H, 2×H-5 arom.), 5.42–5.30 (m, 4 H, 2×C*H*$_2$ benzyl), 4.85–4.77 (m, 2 H, 2×H-1′), 4.26 (ddd, 1 H, J = 10.8 Hz, 6.8 Hz, 4.6 Hz, H-5′a), 4.22–4.19 (m, 2 H, 5′-C*H*$_2$), 4.17 (ddd, 1 H, J = 10.8 Hz, 7.7 Hz, 5.2 Hz, H-5′b), 4.12–4.09 (m, 2 H 2×H-3′), 2.23 (s, 6 H, 2×3-C*H*$_3$), 2.22–2.11 (m, 6 H, 2×H-4′; 2×H-6′a, 2×H-2′a), 2.10–2.04 (m, 2 H, 2×H-2′b), 1.85 (d, 6 H, J = 1.0 Hz, 2×H-7), 1.74–1.68 (m, 2 H, 2×H-6′b) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.9 (C-4), 151.0 (C-2), 150.9 (C-2), 148.9 (C-2 arom.), 137.9 (C-6), 137.9 (C-6), 131.8 (C-6 arom.), 128.4 (C-1 arom.), 128.3 (C-1 arom.), 124.5 (C-4 arom.), 124.5 (C-4 arom.), 123.3 (C-5 arom.), 122.4 (C-3 arom.), 69.2 (d, J = 6.5 Hz, *C*H$_2$ benzyl), 69.2 (d, J = 6.5 Hz, *C*H$_2$ benzyl), 68.8 (d, J = 6.0 Hz, C-5′), 68.7 (d, J = 5.6 Hz, C-5′), 62.0 (C-3′), 62.0 (C-3′), 56.0 (C-1′), 56.0 (C-1′), 36.5 (C-2′), 36.4 (C-2′), 32.1 (C-6′), 32.0 (C-6′), 15.8 (3-*C*H$_3$), 12.9 (C-7) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –8.7, –8.8 ppm; UV: λ_{max} = 262.8 nm (CH_3CN); IR (KBr): $\tilde{\nu}$ = 3440, 3180, 3050, 2950, 2105, 1690, 1470, 1270, 1295, 1190, 1020, 940, 870, 820, 770, 650, 495, 415 cm^{-1}. HRMS-FAB: *m*/*z* calcd. for $C_{19}H_{22}N_5O_6P$ [M + H]: 448.1386; found: 448.1397. HPLC: t_R = 13.05, 13.20 min.

3-Methyl-*cyclo*Saligenyl-(3′-allyl-6′-carba-2′,3′-dideoxythymidinyl)monophosphate (3-Me-*cyclo*Sal-*carba*-3′-allyl-dTMP) (10): The reaction has been carried out according to the described general procedure with nucleoside **5** (50.0 mg, 0.19 mmol), pyridine (500 μL) and 3-methyl-*cyclo*Sal-phosphorchloridate (330 μL). Yield: 55.0 mg, (65%) as a mixture of two diastereomers. R_f (TLC) = 0.57 (CH_2Cl_2/MeOH, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (br. s, 2 H, 2×N*H*), 7.20–7.15 (m, 2 H, 2×H-6 arom.), 7.05–7.00 (m, 3 H, 2×H-4 arom., H-6), 6.99 (q, 1 H, J = 1.0 Hz, H-6), 6.94–6.90 (m, 2 H, 2×H-5 arom.), 5.77–5.62 (m, 2 H, 2×C*H*=CH$_2$), 5.42–5.25 (m, 4 H, 2×C*H*$_2$ benzyl), 5.07–4.99 (m, 4 H, 2×CH=C*H*$_2$), 4.96–4.87 (m, 2 H, 2×H-1′), 4.31–4.21 (m, 2 H, 2×H-5′a), 4.20–4.11 (m, 2 H, 2×H-5′b), 2.28 (s, 3 H, 3-C*H*$_3$), 2.27 (s, 3 H, 3-C*H*$_3$), 2.26–2.20 (m, 4 H, 2×H-6′a, 2×C*H*$_2$–CH=), 2.10–1.98 (m, 4 H, 2×H-4′, 2×H-3′), 1.91 (d, 3 H, J = 1.0 Hz, H-7), 1.91 (d, 3 H, J = 1.0 Hz, H-7), 1.88–1.81 (m, 4 H, 2×2′-C*H*$_2$), 1,65–1.55 (m, 2 H, 2×H-6′b) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.7 (C-4), 151.2 (C-2), 146.8 (C-2 arom), 136.8 (C-6), 136.2 (*C*H=CH$_2$), 136.1 (*C*H=CH$_2$), 131.7 (C-6 arom.), 128.6 (C-1 arom.), 124.4 (C-4 arom.), 123.3 (C-5 arom.), 122.7 (C-3 arom.), 117.5 (CH=*C*H$_2$), 117.5 (CH=*C*H$_2$), 111.6 (C-5), 70.7 (d, J = 6.0 Hz, 5′-*C*H$_2$), 70.6 (d, J = 5.5 Hz, 5′-*C*H$_2$), 69.0 (d, J = 6.6 Hz, *C*H$_2$ benzyl), 54.6 (C-1′), 54.6 (C-1′), 44.1 (d, J = 2.5 Hz, H-4′), 44.0 (d, J = 2.5 Hz, H-4′), 39.5 (*C*H$_2$–CH=), 39.5 (*C*H$_2$–CH=), 39.0 (C-3′), 36.2 (C-2′), 36.2 (C-2′), 35.4 (C-6′), 35.3 (C-6′), 15.8 (3-*C*H$_3$), 15.8 (3-*C*H$_3$), 13.0 (C-7) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –8.3, –8.4 ppm; UV: λ_{max} = 263.9 nm (MeCN). IR (KBr): $\tilde{\nu}$ = 3440, 3180, 3060, 2950, 1685, 1470, 1395, 1300, 1190, 1020, 940, 780 cm^{-1}. HRMS-FAB: *m*/*z* calcd. for $C_{22}H_{27}N_2O_6P$ [M + H]: 447.1685; found: 447.1691. HPLC: t_R = 13.96, 14.17 min.

3-Methyl-*cyclo*Saligenyl-(6′-carba-2′,3′-dideoxy-3′-propargylthymidinyl)monophosphate (3-Me-*cyclo*Sal-*carba*-3′-propargyl-dTMP) (11): The reaction has been carried out according to the described general procedure with nucleoside **6** (40.0 mg, 0.152 mmol), pyridine (400 μL) and 3-methyl-*cyclo*Sal-phosphorchloridate (260 μL). Yield: 46.0 mg, (69%) as a mixture of two diastereomers. R_f (TLC) = 0.56 (CH_2Cl_2/MeOH, 9:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.31 (m, 2 H, 2×N*H*), 7.20–7.15 (m, 2 H, 2×H-6 arom.), 7.05–7.00 (m, 2 H, 2×H-4 arom.), 7.00 (q, 1 H, J = 1.0 Hz, H-6), 6.99 (q, 1 H, J = 1.0 Hz, H-6), 6.94–6.90 (m, 2 H, 2×H-5 arom.), 5.43–5.25 (m, 4 H, 2×C*H*$_2$ benzyl), 4.99–4.90 (m, 2 H, 2×H-1′), 4.34–4.19 (m, 4 H, 2×5′-C*H*$_2$), 2.40–2.30 (m, 4 H, 2×C*H*$_2$–C), 2.28 (s, 6 H, 2×3-C*H*$_3$), 2.26–2.15 (m, 6 H, 2×H-3′, 2×H-4′, 2×H-6′a), 2.09–2.00 (m, 2 H, 2×H-2′a), 1.96 (dd, 1 H, J = 2.5 Hz, 2.5 Hz, C*H* alkyne), 1.95 (dd, 1 H, J = 2.5 Hz, 2.5 Hz, C*H* alkyne), 1.95–1.92 (m, 2 H, 2×H-2′b), 1.92 (d, 6 H, J = 1.0 Hz, 2×H-7), 1.70–1.60 (m, 2 H, 2×H-6′b) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.7 (C-4), 151.0 (C-2), 145.4 (C-2 arom.), 136.9 (C-6), 131.7 (C-6 arom.), 129.1 (C-1 arom.), 124.4 (C-4 arom.), 123.3 (C-5 arom.), 121.0 (d, J = 2.0 Hz, C-3 arom.), 120.9 (d, J = 2.4 Hz, C-3 arom.), 111.7 (C-5), 81.8 (*C*q alkyne), 81.8 (*C*q alkyne), 70.7 (*C*H alkyne), 70.7 (*C*H alkyne), 70.3 (d, J = 6.0 Hz, C-5′), 70.1 (d, J = 6.0 Hz, C-5′), 69.1 (d, J = 6.8 Hz, *C*H$_2$ benzyl), 54.8 (C-1′), 43.44 (C-4′), 43.4 (C-4′), 38.3 (C-3′), 38.2 (C-3′), 36.0 (C-2′) 36.0 (C-2′), 35.0 (C-6′), 35.2 (C-6′), 23.5 (*C*H$_2$–C), 23.4 (*C*H$_2$–C), 15.8 (3-*C*H$_3$), 13.0 (C-7) ppm. ^{31}PNMR (162 MHz, $CDCl_3$): δ = –8.3, –8.4 ppm; UV: λ_{max} = 264.5 nm (MeCN). IR (KBr): $\tilde{\nu}$ = 3440, 3245, 3050, 2950, 1685, 1470, 1370, 1300, 1190, 1020, 940, 870, 820, 780, 650, 590, 480, 420 cm^{-1}. HRMS-FAB: *m*/*z* calcd. for $C_{22}H_{25}N_2O_6P$ [M + H]: 445.1529; found: 445.1523. HPLC: t_R = 13.21, 13.35 min.

3-Methyl-*cyclo*Saligenyl-(6′-carba-2′,3′-dideoxythymidinyl)monophosphate (3-Me-*cyclo*Sal-*carba*-ddTMP) (12): The reaction has been carried out according to the described general procedure with nucleoside **7** (45.0 mg, 0.20 mmol), pyridine (500 μL) and 3-methyl-*cyclo*Sal-phosphorchloridate (350 μL). Yield: 63.0 mg, (78%) as a mixture of two diastereomers. R_f (TLC) = 0.54 (CH_2Cl_2/MeOH, 9:1) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (br. s, 2 H, 2×N*H*), 7.19–7.15 (m, 2 H, 2×H-6 arom.), 7.05–7.00 (m, 4 H, 2×H-6, 2×H-4 arom.), 6.94–6.98 (m, 2 H, 2×H-5 arom.), 5.41–5.25 (m, 4 H, 2×C*H*$_2$ benzyl), 4.93–4.84 (m, 2 H, 2×H-1′), 4.25–4.12 (m, 4 H, 2×5′-C*H*$_2$), 2.46–2.35 (m, 2 H, 2×H-4′), 2.29 (s, 3 H, 3-C*H*$_3$),

2.27 (s, 3 H, 3-CH_3), 2.26–2.17 (m, 2 H, 2×H-6′a), 2.13–2.04 (m, 2 H, 2×H-2′a), 1.92 (d, 3 H, J = 1.2 Hz, H-7), 1.91 (d, 3 H, J = 1.2 Hz, H-7), 1.90–1.81 (m, 2 H, 2×H-3′a), 1.75–1.60 (m, 4 H, 2×H-2′b, 2×H-3′b), 1.50–1.40 (m, 2 H, 2×H-6′b) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.7 (C-4), 151.3 (C-2), 146.6 (C-2 arom.), 136.8 (C-6), 136.8 (C-6), 131.7 (C-6 arom.), 128.3 (d, J = 8.0 Hz, C-1 arom.), 124.3 (C-4 arom.), 123.3 (C-5 arom.), 120.9 (C-3 arom.), 111.6 (C-5), 71.9 (d, J = 6.0 Hz, CH_2 benzyl), 71.8 (d, J = 6.0 Hz, CH_2 benzyl), 69.0 (d, J = 6.7 Hz, C-5′), 56.3 (C-1′), 38.1 (d, J = 6.6 Hz, C-4′), 38.0 (d, J = 8.1 Hz, C-4′), 34.5 (C-2′), 34.4 (C-2′), 30.2 (C-6′), 30.1 (C-6′), 26.6 (C-3′), 26.5 (C-3′), 15.8 (3-CH_3), 13.0 (C-7) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –8.2, –8.3 ppm; UV: λ_{max} = 263.1 nm (CH_3CN). IR (KBr): $\tilde{\nu}$ = 3440, 3180, 3050, 2955, 1685, 1470, 1370, 1300, 1190, 1020, 940, 870, 820, 780, 490 cm^{-1}. HRMS-FAB: *m/z* calcd. for $C_{19}H_{23}N_2O_6P$ [M + H]: 407.1372; found: 407.1371. HPLC: t_R = 11.25, 12.48 min.

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