DOI: 10.1002/ejoc.201001473

Synthesis of 2′,3′-Modified Carbocyclic L-Nucleoside Analogues

Sönke Jessel[a] and Chris Meier*[a]

Keywords: Medicinal chemistry / Antiviral agents / Nucleosides / Nucleoside analogues / Carbocycles / Hydroboration / Stereoselective synthesis

New divergent approaches to 2′,3′-modified carbocyclic L-nucleoside analogues starting from enantiomerically pure (1*R*,2*S*)- or (1*S*,2*R*)-2-(benzyloxymethyl)cyclopent-3-enol are described. In the key step, stereochemically pure cyclopentanols were condensed with *N*3-protected thymine through a modified Mitsunobu protocol. Moreover, several routes to different cyclopentanol derivatives, to prepare carbocyclic L-2′,3′-didehydro-2′,3′-dideoxynucleosides (L-d4N), L-2′,3′-dideoxynucleosides (L-ddN), and L-ribonucleosides are reported.

Introduction

The application of nucleoside analogues in antiviral therapy has developed into an important option over the last three decades. There are a variety of nucleoside analogues, displaying several modifications relative to their natural counterparts both/either in the nucleobase and/or in the sugar moiety. Thanks to these changes in nucleoside structure, new antiviral and antitumor active compounds have been identified.[1] As well as analogues of the D-configured natural nucleosides there is the important class of L-nucleosides, the mirror images of the natural ones. L-Nucleoside analogues are of particular interest because in recent years there has been an increasing number of L-nucleosides showing antiviral activity.[2] Particularly in the case of the treatment of hepatitis B, the FDA has approved the drugs lamivudine (**1**, Figure 1)[3] and telbivudine (**2**),[4] whereas other candidates such as clevudine (L-FMAU, **3**)[5] and emtricitabine (FTC, **4**)[6] are currently undergoing phase III trials.

The glycosidic bond in a carbocyclic nucleoside in which the furanose oxygen atom has been replaced by a methylene unit is stable towards hydrolysis by phosphorylases.[1,7] This class of enzymes cleaves glycosidic bonds in naturally occurring nucleosides. Consequently, carbocyclic nucleosides display enhanced biostability.

Because of their unusual ring puckering, carbocyclic nucleosides often display structure–activity relationships (SARs) different from those of their natural nucleoside counterparts and can therefore potentially have new biological properties. Additionally, carbocyclic nucleosides are known for their low cytotoxicities.[8] Because of the interesting biological properties of carbocyclic nucleosides, we became interested in developing new strategies for syntheses of carbocyclic L-nucleoside analogues with the aim of preparing new potential nucleoside analogue drugs. However, carbocyclic nucleosides are synthetically the most challenging class of nucleoside analogues, requiring multi-step syntheses to form the necessary stereogenic centers. Different synthetic strategies have been applied.[1] The two principle approaches are the linear and the convergent approach. The linear synthesis starts from a cyclopentylamine, which is converted into the nucleoside by construction of the heterocycle in a stepwise manner. In a convergent synthesis strategy an activated cyclopentane derivative is condensed with an aromatic heterocycle to form one of a variety of carbocyclic nucleoside analogues.

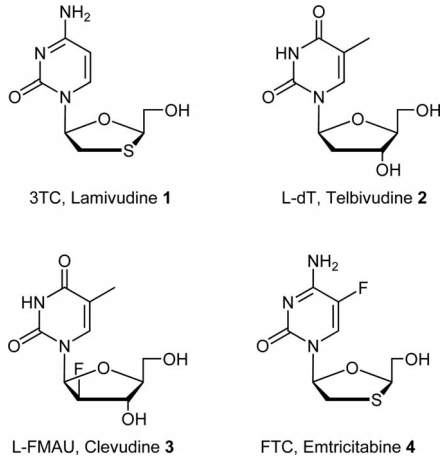
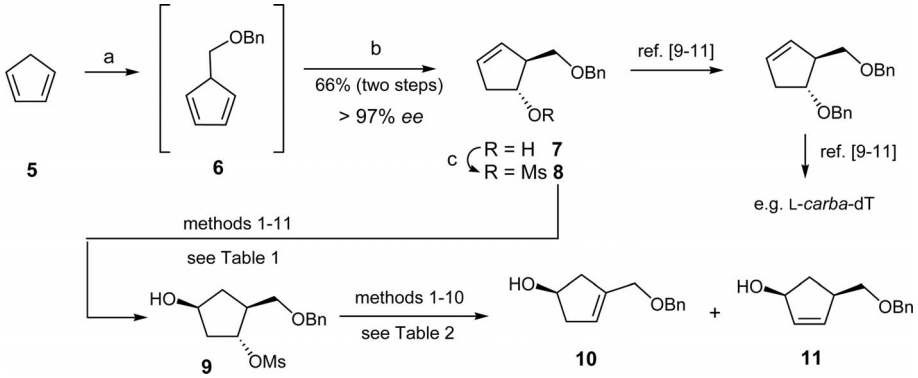


Figure 1. L-Nucleoside analogues in antiviral therapy.

We recently reported on a convergent strategy for the syntheses of carbocyclic nucleoside analogues, starting from the enantiomerically pure cyclopentenol derivative **7** (Scheme 1).[9] Several modifications could be accomplished through different methods of hydroboration at the double bond to prepare carbocyclic α-, *iso*-, or 3′-*epi*-nucleos-

[a] Organic Chemistry, Department of Chemistry, Faculty of Sciences, University of Hamburg,
Martin-Luther-King-Platz 6, 20146 Hamburg, Germany
Fax: +49-40-428-38-2893
E-mail: chris.meier@chemie.uni-hamburg.de



Scheme 1. *Reagents and conditions:* a) NaH, THF, 0 °C, 0.5 h, benzyl chloromethyl ether, DMF, –60 °C, 2 h, b) (+)-$(ipc)_2BH$, THF, –60 °C, 1 h, then room temp. 16 h, NaOH (3 N), H_2O_2 (30%), 0 °C, 12 h, c) Et_3N, MsCl, THF, 3 h.

ides.[10] For the introduction of the nucleobase, a modified Mitsunobu reaction, starting from cyclopentanol derivatives and *N*3-protected pyrimidine nucleobases, was successfully used.[11] Here we report on a complementary convergent route based on the key intermediate **11** (Scheme 1), efficiently prepared from the cyclopentenol **7**. This route gives access to various 2′,3′-modified carbocyclic nucleoside analogues that cannot be prepared by the previously reported routes.

Results and Discussion

The aim was to generate the cyclopentenol **11** through direct elimination of a suitable leaving group from the cyclopentanol **9**, which can be synthesized from the enantiomerically pure starting material (1*R*,2*S*)-2-(benzyloxymethyl)cyclopent-3-enol (**7**).[9,12] The optical purity of the cyclopentanol **8** was determined by HPLC on a chiral stationary phase [cellulose tris(3,5-dimethylphenyl carbamate)]. Treatment of the cyclopentenol **7** with methanesulfonyl chloride and NEt_3 led quantitatively to the mesylated cyclopentene **8**. The mesyl group played two significant roles for the next reactions. On the one hand it served as a protecting group during the hydroboration step; on the other hand it later acted as a leaving group as described above. As expected, the hydroboration of **8** with 9-BBN formed the chiral cyclopentanol **9** consistently with the previously observed regioselectivity.[9,10] Unfortunately, the oxidative alkaline workup resulted in the formation of multiple side products. Some of the side products were identified as the elimination products **6**, **10**, and **11**. Obviously the reaction conditions (standard workup procedure $NaOH/H_2O_2$) are too harsh for the base-labile mesyl group. Nevertheless, the desired product **9** was also obtained in 31% yield (Entry 1, Table 1).

For comparison, in the hydroboration of compound **6** (step b, Scheme 1) the elimination side reaction played no significant role because only a hydroxy group was present instead of the much better mesylate leaving group.

Milder workup conditions therefore had to be used to guarantee the integrity of the cyclopentanol **9**. Firstly, the concentration of the NaOH solution was reduced from 3 N to 0.05 N and the reaction time was then varied. In all attempts, however, the alkaline environment led to uncontrollable side reactions, and so was unsuitable for improvement of the yield of the cyclopentenol **9**. As a consequence, the hydroboration and its workup required pH-neutral to even acidic reaction conditions to prevent side reactions of the mesylated cyclopentenol **9**. Only a few alternatives to the standard procedure not involving the use of sodium hydroxide had been reported (Entries 2–11, Table 1).

Table 1. Hydroboration of the cyclopentene **8** with different oxidative agents.[a]

	Oxidizing agent	Equiv.	Temp. [°C]	Yield **9** [%]
1	$NaOH/H_2O_2$	3	0	31
2	sodium perborate	3	0	61
3	sodium perborate	3	r.t.	55
4	sodium percarbonate	3	0	61
5	sodium percarbonate	3	r.t.	56
6	potassium peroxodisulfate	3	0	45
7	potassium peroxomonosulfate	3	0	43
8	oxone	3	0	77
9	oxone	3	r.t.	68
10	oxone	6	0	76
11	trimethylamine *N*-oxide (TMANO)	3	0	–

[a] *Reagents and conditions:* 9-BBN, cyclopentene **8**, THF, 12 h, oxidizing agent (see Scheme 1).

These strategies involved sodium or potassium peroxo salts to oxidize the carbon–boron bond. The use of sodium perborate[13] and percarbonate[14] nearly doubled the yield relative to the $NaOH/H_2O_2$ procedure. At room temperature the cyclopentenol **9** was obtained in about 56% yield (Entries 3 and 5) whereas at 0 °C compound **9** was formed in 61% yield (Entries 2 and 4). Potassium peroxomono- and disulfate led to yields of about 43–45%.

The best results were achieved with the mixed peroxo salt oxone.[15] Depending on the temperature, the cyclopentanol **9** was obtained in up to 77% yield (Entry 8). A further attempt with use of trimethylamine *N*-oxide (TMANO)[16] failed completely (Entry 11, Table 1). Under the optimized reaction conditions with oxone (3 equiv.) at 0 °C, no elimination products were found.

The cyclopentanol **9** was used as the starting material for a controlled elimination. The challenge was to overcome

the thermodynamically preferred formation of the Saytzeff product **10** and to form the unfavored Hofmann product **11** instead. Treatment with sodium hydroxide in CH_3CN led to poor yields of the desired cyclopentenol **11** (Entry 1, Table 2). The ratio of compounds **10** to **11** in the first approach was 66:34. The following reactions were conducted in aprotic polar solvents in the presence of a sterically hindered base. Generally, a sterically more hindered non-nucleophilic base favors the formation of the Hofmann product. Polar and aprotic solvents amplify this effect. Use of the strong, non-nucleophilic base diazabicyclo[5.4.0]undec-7-ene (DBU) in CH_3CN led to a ratio of 52:48 (**10/11**), which is a slight improvement with respect to the formation of the desired cyclopentenol **11** (Entry 2). With the more polar solvents DMSO and DMF the ratio was found to be identical (57:43, Entries 5 and 8). Interestingly, the use of 1,4-diazabicyclo[2.2.2]octane (DABCO) led to the mixture of the two cycloalkenes in almost identical amounts independently of the solvent used, although the cyclopentene **11** is slightly favored in all cases (Entries 3, 6, and9).

Table 2. Elimination reaction of the cyclopentanol **9** in the presence of different bases and solvents.[a]

Entry	Base	Solvent	Ratio of **10/11**[b]	Yield **11** [%][c]
1	NaOH	CH_3CN	66:34	33
2	DBU	CH_3CN	52:48	42
3	DABCO	CH_3CN	41:59	46
4	KO*t*Bu	CH_3CN	27:73	64
5	DBU	DMSO	57:43	38
6	DABCO	DMSO	36:64	46
7	KO*t*Bu	DMSO	11:89	78
8	DBU	DMF	56:44	40
9	DABCO	DMF	48:52	52
10	KO*t*Bu	DMF	1:99	82

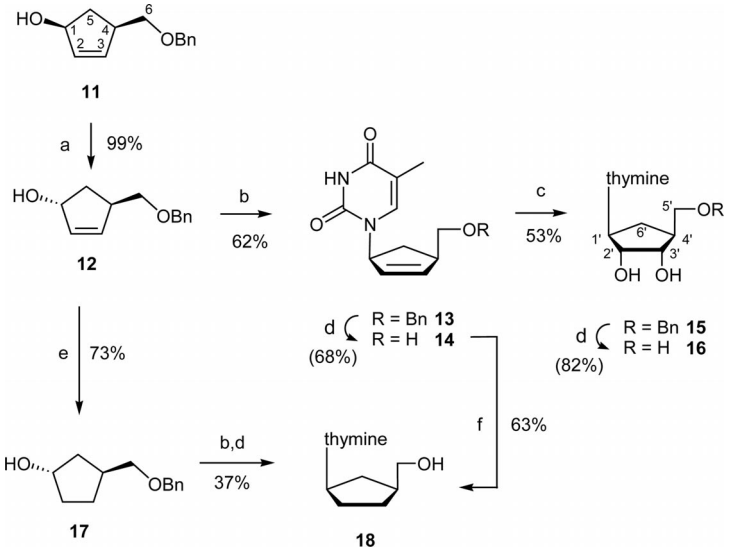
[a] *Reagents and conditions*: cyclopentanol **9**, base, reflux (see Scheme 1). [b] Determined by ^1H NMR. [c] Isolated yield.

In contrast, even better ratios were observed with use of the sterically demanding base potassium *tert*-butoxide. Compound **11** was obtained selectively, and the highest chemical yield (82% yield) was obtained with *t*BuOK in DMF at reflux for 30 min (Entry 10, Table 2).

The two products **10** and **11** are enantiomerically pure cyclopentenols that can both be used as important key intermediates for syntheses of carbocyclic nucleoside analogues. In the case of the cyclopentenol **10** we recently reported an efficient convergent synthetic strategy for the synthesis of carbocyclic 3′,4′-didehydro-3′-deoxynucleoside analogues and their modifications.[7]

Inversion of configuration at the carbon atom bearing the hydroxy function in the cyclopentenol **11** with the aid of a Mitsunobu reaction led to the diastereomer **12** (Scheme 2). Both cyclopentenols **11** and **12** are excellent precursors for the formation of carbocyclic L-2′,3′-didehydro-2′,3′-dideoxynucleoside analogues.[11,17] The introduction of the heterocycle was achieved by use of a modified Mitsunobu protocol. *N*3-Protected thymine was condensed with the cyclopentenol **12**, which led to the benzyl-protected carbocyclic L-d4T **13** in 62% yield. In addition to the formation of the *N*1-alkylated product **13**, the O^2-alkylated product was observed as well. Separation of the two products was easily achieved by silica gel chromatography. The *N*1-alkylation of carbocyclic L-d4T **13** was confirmed by HMBC NMR experiments. Deprotection with $ZnCl_2$ in $AcOH/Ac_2O$ (1:2) gave the nucleoside analogue **14** in 68% yield.[18] The double bond in the d4-nucleoside analogue **13**, as well as in the cyclopentenol **11**, is a suitable starting point for the synthesis of further carbocyclic nucleoside derivatives.

The L-carbocyclic ddT **18** was formed in 63% yield by Pd/C-catalyzed hydrogenation of the double bond in **13**. Under these conditions the debenzylation of the 5′-OH



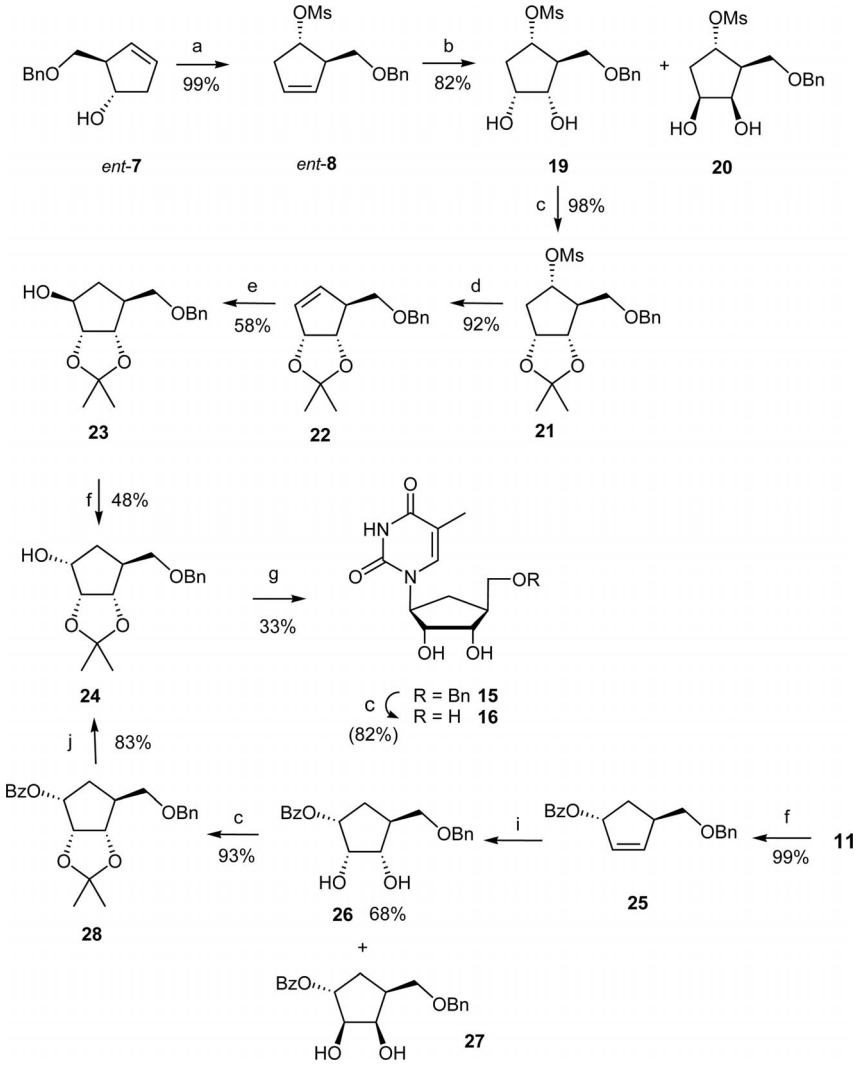
Scheme 2. *Reagents and conditions:* a) PPh_3, DIAD, benzoic acid, Et_2O, 0 °C to room temp., 12 h, b) PPh_3, DIAD, *N*3-benzoylthymine, CH_3CN, –40 °C to room temp., 16 h, c) AD-mix α, *t*BuOH/H_2O, 1:2, 0 °C, 12 h, d) $ZnCl_2$, Ac_2O/AcOH, 2:1, 5 h, e) *p*TsNHNH$_2$, H_2O, 1,4-dioxane, f) Pd/C, H_2, EtOH, 16 h.

group also occurred. In the case of bromovinyl uracil, however, this procedure led to problems. Thus, to ensure a highly flexible convergent route, a second strategy was applied for the synthesis of such L-carbocyclic dideoxynucleosides. The cyclopentenol **12** was treated with *p*-toluenesulfonyl hydrazine to give the protected cyclopentanol **17** in 73% yield.[19] As before, the cyclopentanol **17** was coupled to *N*3-benzoylthymine by the Mitsunobu protocol described above. After cleavage of the benzyl group, the carbocyclic L-ddT **18** was obtained in two steps in 37% yield. Consequently, depending on the requirements of the heterocyclic moiety, this method is complementary to the hydrogenation pathway. Both pathways led to L-*carba*-ddT (**18**) in overall yields of 39% and 27%, respectively (Scheme 2).

The protected L-*carba*-d4T **13** was converted into the corresponding carbocyclic ribonucleoside **15** by literature methods.[20] The 2′- and 3′-hydroxy functions were introduced at the double bond by Sharpless' *cis*-dihydroxylation with AD-mix α. This reaction was carried out from the starting protected L-*carba*-d4T **13** in H_2O/*t*BuOH (2:1) and gave the protected L-*carba*-ribothymidine **15** in 53% yield. Deprotection by hydrogenolysis in the presence of Pd/C proceeded in 82% yield. As before, a second strategy was developed to ensure access to a variety of 2′,3′-modified carbocyclic L-nucleosides.

From the enantiomer of **7** [(1*S*,2*R*)-2-(benzyloxymethyl)-cyclopent-3-enol (*ent*-**7**, Scheme 3)],[9,10,12] the mesylated cyclopentenol *ent*-**8** was obtained as starting material for subsequent *cis*-dihydroxylation studies.

Firstly, *cis*-dihydroxylation of the cyclopentene *ent*-**8** with $KMnO_4$ led to the formation of the two isomers **19** and **20** in moderate yields (48%) and in a 4:1 ratio. These diastereomers could be separated by column chromatography and the major product was found to be the desired diol



Scheme 3. *Reagents and conditions:* a) MsCl, Et_3N, THF, 1 h, b) AD-mix β, *t*BuOH/H_2O (1:2), 0 °C, 12 h, c) 2,2-dimethoxypropane, *p*-toluenesulfonic acid, acetone, 3 h, d) KO*t*Bu, DMF, 30 min, 100 °C, e) 9-BBN, THF, room temp., 12 h, NaOH (3 N), H_2O_2 (30%), 0 °C, f) PPh_3, DIAD, benzoic acid, Et_2O, 0 °C to room temp., 12 h, g) PPh_3, DIAD, *N*3-benzoylthymine, CH_3CN, –40 °C to room temp., 16 h, h) Pd/C, H_2, EtOH, 16 h, i) AD-mix α, *t*BuOH/H_2O (1:2), 0 °C, 12 h, j) NaOH (1%) in MeOH, 6 h.

19. The absolute stereochemistry was confirmed by NOE spectroscopy. Only a slight improvement was obtained when a mixture of K_2OsO_4 and a co-oxidant was used.

The yields increased to 51–62%. However, very long reaction times of up to 7 d were also necessary. Finally, ligand-accelerated variations of osmium-tetroxide-mediated *cis*-dihydroxylations with Sharpless' AD-mixes led to excellent ratios in favor of **19** in 63–82% yields (Table 3). Although AD-mix α only gave a ratio of 3:1 the yield could be improved to 68% by use of additional $K_2OsO_4{\cdot}2H_2O$ and methanesulfonamide (Entry 3, Table 3).

Table 3. *cis*-Dihydroxylation of *ent*-**8**.

Entry		Methanesulfonamide [equiv.]	$K_2OsO_4{\cdot}2H_2O$ [equiv.]	Ratio of **19**/**20**	Yield **19** [%]
1	AD-mix α	–	–	3:1	63
2	AD-mix α	1.0	–	3:1	67
3	AD-mix α	1.0	5	3:1	68
4	AD-mix β	–	–	11:1	73
5	AD-mix β	1.0	–	11:1	82
6	AD-mix β	1.0	5	11:1	81

Moreover, the cyclopentanediol **19** could easily be prepared from the cyclopentane *ent*-**8** by oxidation of the double bond with AD-mix β in 82% yield with an excellent ratio of 11:1 in favor of compound **19**. Protection of the *cis*-diol function in 98% yield was achieved with 2,2-dimethoxypropane catalyzed by *p*-toluenesulfonic acid in acetone. As before, compound **21** was treated with *t*BuOK in DMF to generate the protected cyclopentenediol **22** in 92% yield. This material was subsequently treated with 9-BBN to introduce a hydroxy group in the 1′-position of the desired carbocyclic ribonucleoside analogue.

As before, even in this cyclopentane derivative **22** the hydroboration led almost regiospecifically to the formation of the cyclopentanol **23**. Under standard Mitsunobu inversion conditions the cyclopentanol **24** was prepared in an unexpectedly low 48% yield. The reason for the considerably lower chemical yields in relation to previous Mitsunobu reactions could be steric interactions caused by the C-2 substituent. Compound **24** was used as starting material for the coupling with heterocyclic bases.

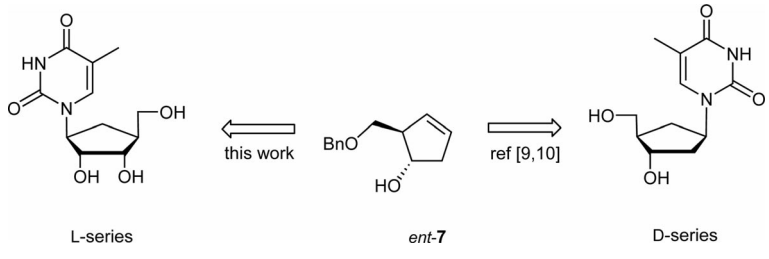
To confirm the absolute configuration of the cyclopentanol **24** an alternative route starting from the enantiomerically pure cyclopentenol **11** was used (Scheme 3). Mitsunobu inversion led quantitatively to the benzoyl-protected cyclopentenol **25**. By the same experimental protocols, the *cis*-dihydroxylation was performed with regioselectivities similar to those observed for the cyclopentene **19**. The protected carbocyclic L-α-ribofuranose **26** was obtained in 68% yield. The best ratios and yields could be achieved with AD-mix α in a 4:1 ratio for **26** and **27**. After protection of the *cis*-diol functionality, compound **28** was debenzoylated to form the cyclopentanol **24** in 83% yield. The ^1H NMR spectra of compounds **24** obtained by the two routes were identical, which confirmed the relative and absolute configurations (Scheme 3).

The precursor **24** was coupled with *N*3-benzoylthymine to form the protected L-*carba*-ribothymidine **15** in 33% yield. Again, the Mitsunobu reaction led to poor yields, most probably due to the sterically hindered C-1 position. For purposes of comparison, both approaches were leading to **15** in approximately the same yields. Although route A (Scheme 2) is even shorter for the synthesis of **15**, the cyclopentane derivatives **19** or **26** from route B (Scheme 3) can additionally be considered excellent precursors for further modifications in the 2′- and/or 3′-positions.

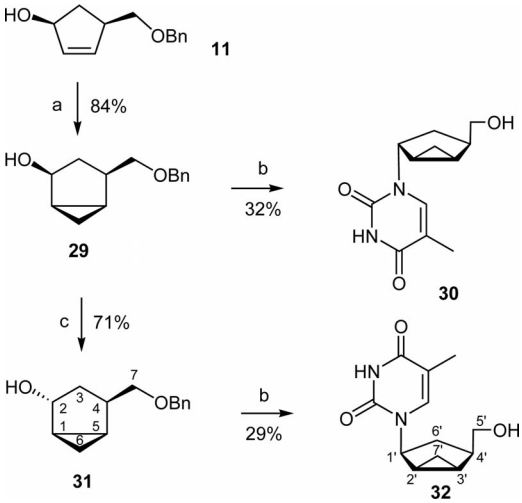
It is worth mentioning that compound *ent*-**7** offers the possibility to access either the D- or the L-series of carbocyclic nucleosides (Scheme 4). The enantiomerically pure cyclopentenol *ent*-**7** could be used for the synthesis of carbocyclic 2′-deoxy-D-nucleoside analogues[9] as well as for the synthesis of carbocyclic L-ribonucleoside analogues as shown in Scheme 3.

Another class of 2′,3′-modified carbocyclic nucleoside analogues could be generated by the synthesis of bicyclic nucleoside analogues such as **30** or **32** (Scheme 5). This class of nucleosides might have interesting biological activities due to a conformational lock in the carbocyclic moiety. It is known that similar bicyclic nucleoside derivatives are locked in either the *northern* or the *southern* conformation and might therefore show interesting biological activity.[21] From the starting cyclopentenol **11**, cyclopropanation by the Simmons–Smith reaction under Furukawa conditions led to the cyclopropanated nucleoside analogues **30** or **32**.[22]

Cyclopropanation of the cyclopentenol **11** led exclusively to the bicyclic alcohol **29** in 84% yield. The hydroxy group directs the incoming carbenoid to the olefinic bond from the upper face. After Mitsunobu coupling and cleavage of the 5′-*O*-benzyl group the nucleoside analogue **30** was synthesized in 32% yield. Inversion of configuration at the hydroxylated position in the bicyclic alcohol **29** led to the alcohol **31** (71% yield), which could be used for the synthe-



Scheme 4. Different synthetic approaches to gain access to the L- or the D-series with the same enantiomerically pure precursor.



Scheme 5. *Reagents and conditions:* a) Et_2Zn, CH_2I_2, CH_2Cl_2, 10 °C, b) PPh_3, DIAD, *N*3-benzoyl thymine, CH_3CN, –40 °C to room temp., 16 h, c) PPh_3, DIAD, benzoic acid, Et_2O, 0 °C to room temp., 12 h, d) Pd/C, H_2, EtOH, 16 h.

sis of a bicyclic nucleoside analogue in the same manner. L-*carba*-2′,3′-*endo*-Methylene-β-thymidine (**32**) was obtained in 29% yield. Interestingly, use of the benzyl-protected carbocyclic d4T **13** as starting material for the synthesis of **32** gave no reaction.

Conclusions

The reported convergent synthetic approaches are short and efficient routes to enantiomerically pure carbocyclic L-nucleoside analogues. Both the cyclopentenol **11** and compound **12** are excellent key intermediates for further modifications to synthesize a variety of 2′,3′-modified carbocyclic nucleoside derivatives. The described routes offer access to the synthesis of L- or D-carbocyclic nucleoside analogues. This is an important aspect, leading to high flexibility in syntheses based on one enantiomerically pure starting material such as **7**.

Experimental Section

General: All experiments involving water-sensitive compounds were conducted under rigorously dry conditions (N_2) with use of standard syringe, cannula, and septa apparatus. Solvents: 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. EtOAc, CH_2Cl_2, and CH_3OH employed in chromatography were distilled before use. Chromatography: Chromatotron (Harrison Research 7924), silica gel 60_{Pf} (Merck, "gipshaltig", that is containing $CaSO_4$). UV detection at 254 nm. TLC: analytical TLC was performed on Merck precoated aluminium plates ($60\ F_{254}$) with a 0.2 mm layer of silica gel containing a fluorescence indicator; compounds were visualized with a spray reagent [4-methoxybenzaldehyde (0.5 mL), EtOH (9 mL), concd. H_2SO_4 (0.5 mL), glacial AcOH (0.1 mL)] by heating with a drying fan. NMR spectra were recorded with a Bruker AMX 400 instrument either at 400 MHz (^{1}H NMR) or at 101 MHz (^{13}C NMR) (calibration was done in both cases with the solvent). All ^{1}H and ^{13}C NMR chemical shifts (δ) are quoted in parts per million (ppm) downfield from tetramethylsilane, with $(CD_3)(CD_2H)SO$ being set at δ_H = 2.49 ppm as a reference. The spectra were recorded at room temp. and all ^{13}C NMR spectra 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), a VG Analytical VG/70-250S spectrometer (double focused) or with a Finnigan ThermoQuest MAT 95XL (electron spray ionization – high resolution). Optical rotations were measured with a P8000 polarimeter (A. Kruss Optonic GmbH) at 589 nm. IR spectra were recorded with a ThermoNicolet Avatar 370 FT-IR spectrometer.

(1*R*,2*S*)-2-(Benzyloxymethyl)cyclopent-3-enol (7): Freshly distilled cyclopentadiene (**5**, 5.0 mL, 60 mmol) was slowly added at 0 °C under nitrogen to a suspension of NaH (1.20 g, 50.0 mmol) in THF (50 mL). The slightly pink solution was stirred for 1 h at 0 °C and added dropwise to a vigorously stirred solution of benzyl chloromethyl ether (8.4 mL, 60 mmol) in anhyd. DMF (20 mL). The reaction mixture was poured into ice-cold hexane (200 mL) and water (100 mL). After phase separation the organic layer was washed with ice-cold water (2×100 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The temperature was kept below –10 °C. The yellowish oil was dissolved in THF (50 mL) and cooled to –78 °C. A suspension of (+)-diisopinocampheylborane (14.3 g, 50.0 mmol) in THF (50 mL) [prepared from (–)-α-pinene] was added dropwise. After the solution had been stirred for 1 h at –60 °C the reaction mixture was slowly warmed to 0 °C and stirred at this temperature for 16 h. Half of the solvent was removed under reduced pressure and was replaced by Et_2O. Aq. NaOH (3 N, 18 mL) was added at 0 °C, followed by H_2O_2 (30%, 18 mL). The reaction mixture was stirred for 4 h at 0 °C. After phase separation the aqueous layer was washed with EtOAc (3×30 mL), the combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (hexane/EtOAc 3:1) to yield **7** (6.74 g, 33.0 mmol, 66%) as a colorless oil. $[\alpha]_D^{20}$ = –87.4 (*c* = 0.91, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.20 (m, 5 H, C*H* arom.), 5.69 (ddd, ^3J = 6.2 Hz, ^3J = 4.2 Hz, ^4J = 2.1 Hz, 1 H, 3-H), 5.59 (ddd, ^3J = 6.2 Hz, ^3J = 4.1 Hz, ^4J = 2.2 Hz, 1 H, 4-H), 4.47 (s, 2 H, CH_2Ph), 4.25 (ddd, ^3J = 7.0 Hz, ^3J = 4.3 Hz, ^3J = 4.3 Hz, 1 H, 1-H), 3.38 (dd, ^2J = 9.3 Hz, ^3J = 5.7 Hz, 1 H, 6a-H), 3.26 (dd, ^2J = 9.3 Hz, ^3J = 7.3 Hz, 1 H, 6b-H), 3.04–2.97 (m, 1 H, 2-H), 2.67–2.61 (m, 1 H, 5a-H), 2.26–2.20 (m, 1 H, 5b-H), 1.66 (br s, 1 H, O*H*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.7 (*C*H arom.), 130.5 (C-3), 129.7 (C-4), 128.9, 128.1, 128.0 (*C*H arom.), 76.8 (C-1), 73.7 (*C*H_2Ph), 72.6 (C-6), 55.6 (C-2), 41.4 (C-5) ppm. IR (film): $\tilde{\nu}$ = 3373, 3087, 3060, 3031, 2858, 1701, 1495, 1453, 1361, 1312, 1274, 1205, 1099, 1028, 951, 736, 613 cm^{-1}. HRMS-FAB: *m*/*z* calcd. for $C_{13}H_{16}O_2$ [M + H]: 205.1229; found 205.1225.

(1*R*,2*S*)-2-(Benzyloxymethyl)cyclopent-3-enyl Methanesulfonate (8): The alcohol **7** (3.01 g, 14.7 mmol) was dissolved in THF (25 mL). Triethylamine (2.27 mL, 16.2 mmol) and methanesulfonyl chloride (1.27 mL, 16.2 mmol) were added dropwise at 0 °C. The reaction mixture was stirred for 30 min at this temperature and the reaction was stopped by addition of crushed ice. After separation of the phases the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (hexane/EtOAc 4:1) to yield **8** (4.15 g, 14.7 mmol, 100%) as a colorless oil. $[\alpha]_D^{20}$ = –60 (*c* = 4.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 5 H, C*H* arom.), 5.77 (ddd, ^3J = 4.2 Hz, ^3J = 2.1 Hz, ^4J = 6.2 Hz, 1 H, 3-H), 5.63 (ddd, ^3J = 4.4 Hz, ^3J = 2.2 Hz, ^4J = 6.2 Hz, 1 H, 4-H), 5.18 (dt, ^3J = 7.0 Hz, ^3J = 2.8 Hz, 1 H, 1-H), 4.53 (s, 2 H, CH_2Ph), 3.57 (dd, ^2J = 9.4 Hz, ^3J = 4.9 Hz, 1 H, 6a-H), 3.32 (dd, ^2J = 9.4 Hz, ^3J = 7.7 Hz, 1 H, 6b-H), 3.20–3.12 (m, 1 H, 2-H), 2.96 (s, 3 H, CH_3), 2.95–2.86 (m, 1 H, 5a-H), 2.67–2.59 (m, 1 H, 5b-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.2, 138.9 (C_q arom.), 130.8 (C-3), 130.1 (C-4), 128.8, 128.2, 128.0 (*C*H arom.), 81.1 (C-1), 72.9 (C benzyl), 71.3 (C-6), 51.1 (C-2), 39.4 (C-5), 37.9 (*C*H_3) ppm. IR (film): $\tilde{\nu}$ = 3029, 2936, 1717, 1454, 1416, 1355, 1174, 1093, 1027, 962, 862, 749, 701 cm^{-1}. MS-FAB: *m*/*z* calcd. for $C_{14}H_{18}O_4S$ [M + H]: 283.4; found 283.1.

(1*R*,2*S*,4*S*)-2-(Benzyloxymethyl)-4-hydroxycyclopentyl Methanesulfonate (9): A solution of 9-BBN in THF (0.5 M, 8.7 mL) was added dropwise at 0 °C under nitrogen to **8** (613 mg, 2.17 mmol) in THF (10 mL). The reaction mixture was allowed to warm slowly to room temp. and stirred overnight. The reaction mixture was cooled to 0 °C, treated with a solution of oxone (4.00 g) in water (50 mL), and stirred for 6 h. The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried (Na_2SO_4). The solvents were removed under reduced pressure. The residue was purified by silica gel chromatography (hexane/EtOAc 1:2) to yield **9** (502 mg, 1.67 mmol, 77%) as a colorless oil. $[\alpha]_D^{20}$ = –34.4 (*c* = 1.22, $CHCl_3$). R_f (TLC) = 0.38 (hexane/EtOAc 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 5 H, C*H* arom.), 5.15 (dt, ^3J = 6.7 Hz, ^3J = 4.1 Hz, 1 H, 4-H), 4.57 (q, ^3J = 11.7 Hz, 2 H, CH_2 benzyl), 4.36 (ddd, ^3J = 8.8 Hz, ^3J = 5.9 Hz, ^3J = 3.2 Hz, 1 H, 1-H), 3.70 (dd, ^2J = 9.2 Hz, ^3J = 3.8 Hz, 1 H, 6a-H), 3.50 (dd, ^2J = 9.2 Hz, ^3J = 5.1 Hz, 1 H, 6b-H), 2.93 (s, 3 H, CH_3), 2.50 (tt, ^3J = 8.4 Hz, ^3J = 4.2 Hz, 1 H, 2-H), 2.32 (ddd, ^2J = 14.0 Hz, ^3J = 10.4 Hz, ^3J = 5.8 Hz, 1 H, 5a-H), 2.26–2.20 (m, 1 H, 5b-H), 2.08 (ddd, ^2J = 14.3 Hz, ^3J = 7.8 Hz, ^3J = 4.1 Hz, 1 H, 3a-H), 1.59–1.53 (m, 1 H, 3b-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 128.6, 128.1, 128.0 (*C*H arom.), 84.9 (C-4), 73.6 (*C*H_2 benzyl), 71.5 (C-1), 70.8 (O*C*H_2), 44.6 (C-2), 43.4 (C-5), 38.0 (*C*H_3), 36.8 (C-3) ppm. IR (film): $\tilde{\nu}$ = 3408, 3029, 2936, 1717, 1454, 1414, 1351, 1174, 1093, 1027, 962, 917, 861, 749, 700, 531 cm^{-1}. MS-ESI$^+$: *m*/*z* calcd. for $C_{14}H_{20}O_5S$ [M + H]: 323.1; found 322.7.

(1*S*,4*R*)-4-(Benzyloxymethyl)cyclopent-2-enol (11): The alcohol **9** (461 mg, 1.54 mmol) was dissolved in DMF (5 mL). KO*t*Bu (346 mg, 308 mmol) was added and the reaction mixture was heated at reflux for 1 h. The mixture was allowed to cool to room temp. and water (10 mL) was added. After phase separation the aqueous phase was washed with water (2 × 5 mL). The combined organic phases were dried (Na_2SO_4) and the solvents were removed under reduced pressure. The crude product was purified by chromatography with a chromatotron (hexane/EtOAc 4:1) to yield **11** (258 mg, 1.26 mmol, 82%) and the isomer **10** as colorless oils. $[\alpha]_D^{20}$ = 6.8 (*c* = 0.88, $CHCl_3$). R_f (TLC) = 0.59 (hexane/EtOAc 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.26 (m, 5 H, C*H* arom.), 5.96 (dt, ^3J = 5.3 Hz, ^3J = 2.0 Hz, 1 H, 2-H), 5.83 (dd, ^3J = 5.6 Hz, ^3J = 2.5 Hz, 1 H, 3-H), 4.62 (dt, ^3J = ^3J = 7.0 Hz, 1.7 Hz, 2 H, 1-H), 4.54 (d, ^3J = 3.0 Hz, 2 H, CH_2Ph), 3.46 (dd, ^3J = 3.7 Hz, ^3J = 1.6 Hz, 2 H, 6-H), 2.85 (m, 1 H, 4-H), 2.32 (ddd, ^2J = 14.0 Hz, ^3J = 8.6 Hz, ^3J = 7.1 Hz, 1 H, 5a-H), 1.58 (dt, ^2J = 14.0 Hz, ^3J = 1.9 Hz, 1 H, 5b-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.6 (*C*H arom.) 135.1 (C-2), 135.0 (C-3), 128.5, 127.8 (*C*H arom.), 75.8 (C-1), 73.4 (*C*H_2Ph), 71.3 (C-6), 44.6 (C-4), 37.3 (C-5) ppm. IR (film): $\tilde{\nu}$ = 3406, 3059, 3030, 2856, 1496, 1453, 1362, 1254, 1205, 1178, 1090, 1027, 937, 738, 698 cm^{-1}. HRMS-FAB: *m*/*z* calcd. for $C_{13}H_{16}O_2$ [M + H]: 205.1223; found 205.1227.

(*R*)-3-(Benzyloxymethyl)cyclopent-3-enol (10): R_f (TLC) = 0.32 (hexane/EtOAc 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.30 (m, 5 H, C*H* arom.), 5.64–5.59 (m, 1 H, 4-H), 4.55–4.49 (m, 1 H, 1-H), 4.48 (s, 2 H, CH_2Ph), 4.06 (s, 2 H, 6-H), 2.75–2.65 (m, 2 H, 2a-H, 5a-H), 2.36–2.27 (m, 2 H, 2b-H, 5b-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.5 (*C* arom.$_q$), 138.9 (C-3), 128.8, 128.2, 128.0 (*C*H arom.), 125.4 (C-4), 74.1 (C-6), 73.0 (C-1), 69.2 (C benzyl), 43.8 (C-2), 43.1 (C-5) ppm. IR (film): $\tilde{\nu}$ = 3395, 3031, 2922, 2920, 2849, 1497, 1454, 1198, 1169, 946, 698 cm^{-1}. HRMS-FAB: *m*/*z* calcd. for $C_{13}H_{16}O_2$ [M + H]: 205.1229; found 205.1223.

(1*R*,4*R*)-4-(Benzyloxymethyl)cyclopent-2-enol (12): DIAD (250 μL, 1.28 mmol) was slowly added at 0 °C under nitrogen to a suspension of PPh_3 (336 mg, 1.28 mmol) in Et_2O (6 mL) and the suspension was stirred for 0.5 h. This preformed complex was slowly added at 0 °C to a suspension of benzoic acid (156 mg, 1.28 mmol) and the alcohol **11** (131 mg, 642 μmol) in Et_2O (10 mL). The reaction mixture was allowed to warm slowly to room temp. and stirred overnight. The solvent was removed and methanolic NaOH solution (1%, 10 mL) was added. The reaction mixture was stirred at room temp. for an additional 6 h. The solution was neutralized by addition of HCl (1 M) and then concentrated. The residue was purified on silica gel (hexane/EtOAc 1:1) to yield **12** (130 mg, 636 μmol, 99%) as a colorless syrup. $[\alpha]_D^{20}$ = +64.4 (*c* = 0.39, $CHCl_3$). R_f (TLC) = 0.64 (hexane/EtOAc 1:4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 5 H, C*H* arom.), 6.00 (dd, ^3J = 5.6 Hz, ^3J = 1.5 Hz, 1 H, 2-H), 5.90 (dt, ^3J = 5.5 Hz, ^3J = 2.1 Hz, 1 H, 3-H), 4.82 (dq, ^3J = 7.4 Hz, ^3J = 2.6 Hz, 1 H, 1-H), 4.51 (s, 2 H, CH_2Ph), 3.36 (dq, ^3J = 8.9 Hz, ^3J = 6.7 Hz, 2 H, 6-H), 3.20 (m, 1 H, 4-H), 1.92 (ddd, ^3J = 10.9 Hz, ^3J = 7.5 Hz, ^3J = 4.0 Hz, 2 H, 5-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.4 (*C*H arom.) 137.0 (C-2), 134.3 (C-3), 128.4, 127.6 (*C*H arom.), 77.1 (C-1), 74.0 (C-6), 73.1 (*C*H_2Ph), 44.9 (C-4), 37.5 (C-5) ppm. IR (film): $\tilde{\nu}$ = 3407, 3059, 2856, 1496, 1363, 1254, 1205, 1178, 1091, 1027, 937, 798, 738, 695 cm^{-1}. HRMS-FAB: *m*/*z* calcd. for $C_{13}H_{16}O_2$ [M + H]: 205.1223; found 205.1232.

Coupling of Thymine to Alcohols. General Procedure: Diisopropyl azodicarboxylate (DIAD, 2.8 equiv.) was added slowly to a suspension of Ph_3P (3 equiv.) in CH_3CN (11 mL), and the solution was stirred for 0.5 h at 0 °C. This preformed complex was slowly added at –40 °C under nitrogen to a suspension of the protected thymine (2 equiv.) and the corresponding alcohol (1 equiv.) in CH_3CN (6.0 mL). The reaction mixture was allowed to warm slowly to room temp. and stirred overnight. The solvent was removed from the reaction mixture, a solution of NaOH in MeOH (1%, 15 mL) was added, and the mixture was stirred overnight at room temp. The solution was neutralized by addition of HCl (1 M) and then concentrated. The crude product was purified on silica gel (hexane/EtOAc 1:2) to yield the protected carbocyclic nucleoside as a colorless syrup.

5′-*O*-Benzyl-2′,3′-didehydro-3′-deoxy-*carba*-β-L-thymidine (13): The reaction was carried out by the General Coupling Procedure with PPh_3 (504 mg, 1.92 mmol) in CH_3CN (6 mL), DIAD (350 μL, 1.79 mmol), *N*3-benzoylthymine (300 mg, 1.30 mmol), the cyclopentenol **12** (131 mg, 640 μmol) in CH_3CN (10 mL), and NaOH in MeOH (1%, 10 mL). The crude product was purified on silica gel (hexane/EtOAc 1:2) to yield **13** (154 mg, 490 μmol, 78%) as a colorless syrup. R_f (TLC) = 0.33 (hexane/EtOAc 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 5 H, Bn arom.), 7.19 (d, ^4J = 0.8 Hz, 1 H, 6-H), 6.10 (ddd, ^3J = 5.3, 2.0, 2.0 Hz, 1 H, 2′-H), 5.73 (m, 1 H, 1′-H), 5.62 (ddd, ^3J = 4.6, 2.0, 2.0 Hz, 1 H, 3′-H), 4.52 (m, 2 H, CH_2Ph), 3.59 (dd, ^2J = 9.2 Hz ^3J = 4.3 Hz, 1 H, 5′a-H), 3.47 (dd, ^2J = 9.2 Hz, ^3J = 4.6 Hz, 1 H, 5′b-H), 3.03–2.97 (m,

1 H, 4′-H), 2.69 (ddd, ^2J = 14.1 Hz, ^3J = 9.1, 9.1 Hz, 1 H, 6′a-H), 1.67 (d, ^4J = 0.8 Hz, 3 H, 7-H), 1.51 (ddd, ^2J = 14.0 Hz, ^3J = 6.0, 6.0 Hz, 1 H, 6′b-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.4 (C-4), 151.6 (C-2), 139.8 (C-2′), 138.4 (C arom.$_q$), 137.9 (C-6), 130.3 (C-3′), 128.9, 128.3, 128.1 (*C*H arom.), 111.2 (C-5), 73.8 (CH_2Ph), 72.6 (C-5′), 61.1 (C-1′), 45.8 (C-4′), 33.7 (C-6′), 12.6 (C-7) ppm. MS-ESI$^+$: *m*/*z* calcd. for $C_{18}H_{20}N_2O_3$ [M + Na]: 325.1; found 324.6.

2′,3′-Didehydro-3′-deoxy-*carba*-β-L-thymidine (L-*carba*-d4T, 14): Freshly melted $ZnCl_2$ (327 mg, 2.40 mmol) was added to a solution of the *carba*-β-L-thymidine **13** (75.0 mg, 240 μmol) in acetic anhydride/acetic acid (2:1, 0.5 mL). The reaction mixture was stirred for 4 h at room temp. The reaction was stopped by addition of water (2 mL) and the mixture was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic phases were dried (Na_2SO_4) and solvents were removed under reduced pressure. The residue was purified by chromatography with a chromatotron (CH_2Cl_2/MeOH gradient 0–5%). After lyophilization (CH_3CN/water) the debenzylated nucleoside **14** (36.2 mg, 163 μmol, 68%) was obtained as a colorless foam. R_f (TLC) = 0.16 (CH_2Cl_2/CH_3OH 9:1). ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 7.51 (d, ^4J = 0.8 Hz, 1 H, 6-H), 6.22 (ddd, ^3J = 5.4, 2.0, 2.0 Hz, 1 H, 2′-H), 5.80 (ddd, ^3J = 4.6, 2.0, 2.0 Hz, 1 H, 3′-H), 5.61–5.56 (m, 1 H, 1′-H), 3.70 (dd, ^2J = 11.0 Hz, ^3J = 5.4 Hz, 1 H, 5′a-H), 3.64 (dd, ^2J = 11.0 Hz, ^3J = 5.4 Hz, 1 H, 5′b-H), 3.04–2.96 (m, 1 H, 4′-H), 2.72 (ddd, ^2J = 14.0 Hz, ^3J = 8.7, 8.7 Hz, 1 H, 6′a-H), 1.89 (d, ^4J = 0.8 Hz, 3 H, 7-H), 1.45 (ddd, ^2J = 14.0 Hz, ^3J = 6.3, 6.3 Hz, 1 H, 6′b-H) ppm. ^{13}C NMR (101 MHz, [D$_6$]-DMSO): δ = 167.2 (C-4), 154.0 (C-2), 140.0 (C-2′), 139.5 (C-6), 129.8 (C-3′), 110.8 (C-5), 64.3 (C-5′), 62.4 (C-1′), 47.1 (C-4′), 33.4 (C-6′), 11.7 (C-7) ppm. IR (film): $\tilde{\nu}$ = 3419, 3057, 2934, 1683, 1470, 1291, 1042 cm^{-1}. UV: λ_{max} = 266 nm (CH_3CN). HRMS-ESI$^+$: *m*/*z* calcd. for $C_{11}H_{14}N_2O_3$ [M + Na]: 245.0902; found 245.0883.

Debenzylation. General Procedure: A mixture of the appropriate benzyl ether and Pd/C in EtOH was stirred under H_2 at room temp. until complete conversion was observed by TLC. The mixture was centrifuged. The solution was concentrated and the residue was purified by chromatography with a chromatotron (CH_2Cl_2/MeOH gradient) to yield the carbocyclic nucleoside after lyophilization (CH_3CN/H_2O, 1:1) as a colorless foam.

2′,3′-Dideoxy-*carba*-β-L-thymidine (L-*carba*-DdT, 18): The protected nucleoside **13** (116 mg, 372 μmol) was reduced and deprotected by the General Debenzylation Procedure. The crude product was purified by chromatography with a chromatotron (CH_2Cl_2/MeOH gradient 0–5%). After lyophilization (CH_3CN/water) the debenzylated nucleoside **18** (52.5 mg, 234 μmol, 63%) was obtained as a colorless foam. $[\alpha]_D^{20}$ = +16.0 (*c* = 1.12, $CHCl_3$). R_f (TLC) = 0.30 (CH_2Cl_2/CH_3OH 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.75 (br s, 1 H, N*H*), 7.10 (d, ^4J = 1.0 Hz, 1 H, 6-H), 4.95–4.86 (m, 1 H, 1′-H), 3.68 (d, ^3J = 5.0 Hz, 2 H, 5′-H), 2.31–2.16 (m, 2 H, 4′-H, 6′a-H), 2.14–2.05 (m, 1 H, 2′-Ha), 1.92 (d, ^4J = 1.0 Hz, 3 H, 7-H), 1.89–1.81 (m, 1 H, 3′a-H), 1.76–1.60 (m, 2 H, 2′b-H, 3′b-H), 1.55–1.45 (m, 1 H, 6′b-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.1 (C-4), 152.4 (C-2), 137.3 (C-6), 111.3 (C-5), 66.6 (C-5′), 56.6 (C-1′), 40.1 (C-4′), 34.5 (C-6′), 30.4 (C-2′), 26.9 (C-3′), 12.9 (C-7) ppm. IR (film): $\tilde{\nu}$ = 3466, 3160, 3032, 2953, 1682, 1471, 1420, 1398, 1374, 1270, 1124, 1055, 1015, 593, 425 cm^{-1}. UV: λ_{max} = 272 nm (CH_3CN). HRMS-FAB: *m*/*z* calcd. for $C_{11}H_{16}N_2O_3$ [M + H]: 225.1239; found 227.1237.

5′-*O*-Benzyl-L-*carba*-ribothymidine (15): 5′-*O*-Benzyl-2′,3′-didehydro-3′-deoxy-*carba*-β-L-thymidine (30 mg, 96 μmol) was dissolved in *tert*-butyl alcohol/water (2:1, 3 mL). The solution was cooled to 0 °C and AD-Mix α (140 mg) was added. The reaction mixture was stirred for 48 h at 0 °C. The reaction was stopped by addition of saturated solution of $NaHSO_3$ (2 mL). After phase separation the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were combined and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude product was purified by chromatography with a chromatotron (CH_2Cl_2/MeOH gradient 0–5%) to yield **19** (17.7 mg, 51 μmol, 53%) as a colorless oil. $[\alpha]_D^{20}$ = –4.0 (*c* = 0.12; MeOH). R_f (TLC) = 0.11 (hexane/EtOAc 1:2). ^{1}H NMR (400 MHz, CD_3OD): δ = 7.72 (d, ^4J = 0.9 Hz, 1 H, 6-H), 7.39–7.25 (m, 5 H, Bn arom.), 5.09–5.01 (m, 1 H, 1′-H), 4.58 (d, ^2J = 11.8 Hz, 1 H, PhCH_2-a), 4.53 (d, ^2J = 11.8 Hz, 1 H, PhCH_2-b), 4.19–4.13 (m, 2 H, 2′-H, 3′-H), 3.79 (dd, ^2J = 9.3 Hz, ^3J = 6.9 Hz, 1 H, 5′a-H), 3.59 (dd, ^2J = 9.3 Hz, ^3J = 6.2 Hz, 1 H, 5′b-H), 2.26–2.11 (m, 2 H, 4′-H, 6′a-H), 1.86 (d, ^4J = 0.9 Hz, 3 H, CH_3), 1.81–1.71 (m, 1 H, 6′b-H) ppm. ^{13}C NMR (101 MHz, CD_3OD): δ = 166.6 (C-4), 153.7 (C-2), 142.9 (C-6), 139.8 (C arom.$_q$), 129.4, 128.9, 128.7 (C arom.), 109.7 (C-5), 74.2 (Ph*C*H$_2$), 73.0 (C-2′), 72.9 (C-3′), 70.8 (C-5′), 55.9 (C-1′), 40.9 (C-4′), 32.5 (C-6′), 12.4 (*C*H$_3$) ppm. UV: λ_{max} = 271 nm (CH_3CN). MS-FAB: *m*/*z* calcd. for $C_{18}H_{22}N_2O_5$ [M + H]: 347.4; found 347.5.

L-*carba*-Ribothymidine (16): The protected nucleoside **15** (20.6 mg, 59.6 μmol) was deprotected by the General Debenzylation Procedure. The crude product was purified by chromatography with a chromatotron (CH_2Cl_2/MeOH gradient 0–10%). After lyophilization (CH_3CN/water) the debenzylated nucleoside **16** (12.5 mg, 48.8 μmol, 82%) was obtained as a colorless foam. $[\alpha]_D^{20}$ = –6.5 (*c* = 0.1, H_2O). R_f (TLC) = 0.21 (CH_2Cl_2/CH_3OH 9:1). ^{1}H NMR (400 MHz, D_2O): δ = 7.74 (d, ^4J = 1.0 Hz, 1 H, 6-H), 5.08–5.01 (m, 1 H, 1′-H), 4.33–4.26 (m, 2 H, 2′-H, 3′-H), 3.86 (dd, ^2J = 11.0 Hz, ^3J = 6.9 Hz, 1 H, 5′a-H), 3.59 (dd, ^2J = 11.0 Hz, ^3J = 5.9 Hz, 1 H, 5′b-H), 2.28–2.17 (m, 2 H, 4′-H, 6′a-H), 1.91 (d, ^4J = 1.0 Hz, 3 H, CH_3), 1.86–1.77 (m, 1 H, 6′b-H) ppm. ^{13}C NMR (101 MHz, D_2O): δ = 166.5 (C-4), 153.0 (C-2), 142.0 (C-6), 109.8 (C-5), 71.5 (C-2′), 71.4 (C-3′), 60.8 (C-5′), 55.0 (C-1′), 40.7 (C-4′), 30.1 (C-6′), 11.5 (*C*H$_3$) ppm. UV: λ_{max} = 271 nm (CH_3CN). HRMS-FAB: *m*/*z* calcd. for $C_{11}H_{16}N_2O_5$ [M + H]: 257.2625; found 257.2629.

(1*S*,3*S*)-3-(Benzyloxymethyl)cyclopentanol (17): The cyclopent-2-enol **12** (102 mg, 500 μmol) and 4-methylbenzenesulfonyl hydrazide (466 mg, 2.50 mmol) were dissolved in dioxane (6 mL) and the mixture was heated at reflux. A solution of sodium acetate (410 mg, 5.00 mmol) in water (3 mL) was added dropwise over a period of 4 h. The reaction mixture was allowed to cool to room temp., added to water (10 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel (hexane/EtOAc 1:1) to afford **17** (75 mg, 365 μmol, 73%) as a colorless oil. R_f (TLC) = 0.54 (hexane/EtOAc 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 5H, C*H* arom.), 5.47–5.40 (m, 1 H, 1-H),4.53–4.47 (m, 2 H, CH_2Ph), 3.39–3.33 (m, 2 H, 6-H), 2.57–2.47 (m, 1 H, 4-H), 2.21–1.88 (m, 4H, 2-H, 3a-H, 5a-H), 1.65–1.48 (m, 2 H, 3b-H, 5b-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.4 (*C*H arom.) 128.4, 128.2, 127.6 (*C*H arom.), 77.1 (C-1), 74.5 (C-6), 72.9 (*C*H$_2$Ph), 44.4 (C-4), 37.5 (C-5), 32.1 (C-2), 27.4 (C-3) ppm. IR (film): $\tilde{\nu}$ = 3360, 3030, 2934, 2857, 1496, 1453, 1363, 1338, 1203, 1164, 1094, 1071, 1026, 951, 814, 735, 696, 603, 557, 459 cm^{-1}. MS-FAB: *m*/*z* calcd. for $C_{13}H_{18}O_2$ [M + H]: 207.2; found 207.0.

2′,3′-Dideoxy-*carba*-β-L-thymidine (L-*carba*-DdT, 18): The reaction was carried out by the General Coupling Procedure with PPh_3 (385 mg, 1.47 mmol) in CH_3CN (6 mL), DIAD (270 μL, 1.32 mmol), *N*3-benzoylthymine (225 mg, 980 mmol), the cyclo-

pentanol **17** (101 mg, 490 μmol) in CH_3CN (10 mL), and NaOH in MeOH (1%, 10 mL). The residue was directly debenzylated by the General Debenzylation Procedure. The crude product was purified by chromatography with a chromatotron (CH_2Cl_2/MeOH gradient 0–5%). After lyophilization (CH_3CN/water) the debenzylated nucleoside **18** (40.7 mg, 181 μmol, 37%) was obtained as a colorless foam. Its spectroscopic data were identical to those described above.

(1*S*,2*S*,3*S*,4*R*)-2-(Benzyloxymethyl)-3,4-dihydroxycyclopentyl Methanesulfonate (19): The methanesulfonate **18** (71.0 mg, 250 μmol) was dissolved in *tert*-butyl alcohol/water (2:1, 3 mL). The solution was cooled to 0 °C and AD-mix β was added. The reaction mixture was stirred for 12 h at 0 °C. The reaction was stopped by addition of saturated $NaHSO_3$ solution (2 mL). After phase separation the aqueous layer was extracted with EtOAc (2 × 5 mL). The organic layers were combined and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel (hexane/EtOAc 1:2) to afford **19** (82%) as a colorless oil. R_f (TLC) = 0.50 (hexane/EtOAc 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 5H, Bn arom.), 4.91–4.85 (m, 1 H, 1-H), 4.56–4.50 (m, 2 H, PhCH_2), 4.09–4.05 (m, 1 H, 4-H), 3.86 (dd, ^3J = 8.3, 4.4 Hz, 1 H, 3-H), 3.70 (dd, ^3J = 9.3, 4.9 Hz, 1 H, 6a-H), 3.67 (dd, ^3J = 9.3, 5.5 Hz, 1 H, 6b-H), 2.93 (s, 3 H, -CH_3), 2.53–2.47 (m, 1 H, 2-H), 2.31 (ddd, ^2J = 15.3, ^3J = 8.1, 5.2 Hz, 1 H, 5a-H), 2.09 (ddd, ^2J = 15.3, ^3J = 3.0, 3.0 Hz, 1 H, 5b-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.7 (C arom.$_q$), 128.5, 127.9, 127.8 (C arom.), 80.1 (C-1), 74.7 (C-3), 73.5 (Ph*C*H$_2$), 71.5 (C-4), 68.5 (C-6), 50.5 (C-2), 38.3 (C-5), 38.2 (-*C*H$_3$) ppm. IR (film): $\tilde{\nu}$ = 3412, 2939, 1716, 1333, 1281, 1168, 1149, 1042, 932, 869, 818, 716, 520, 482, 426 cm^{-1}. MS-FAB: *m*/*z* calcd. for $C_{14}H_{20}O_6S$ [M + H]: 317.4; found 317.1.

(1*S*,2*S*,3*S*,4*R*)-2-(Benzyloxymethyl)-3,4-(isopropylidenedioxy)-cyclopentyl Methanesulfonate (21): *p*-Toluenesulfonic acid (40 mg, 232 μmol) was added to a solution of the alcohol **19** (1.70 g, 5.37 mmol) and 2,2-dimethoxypropane (3.30 mL, 37.7 mmol) in acetone (30 mL). The reaction mixture was stirred for 4 h at room temp., the solvent was removed under reduced pressure, and the crude product was purified by chromatography on silica gel (hexane/EtOAc 1:1) to afford **21** (1.88 g, 5.26 mmol, 98%) as a colorless oil. R_f (TLC) = 0.73 (hexane/EtOAc 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H, Bn arom.), 5.04 (ddd, ^3J = 5.8, 2.9 Hz, 1 H, 1-H), 4.69 (ddd, ^3J = 5.9, ^3J = 1.8, ^3J = 1.8 Hz, 1 H, 4-H), 4.54 (dd, ^3J = 6.0, ^3J = 1.9 Hz, 1 H, 3-H), 4.50–4.46 (m, 2 H, PhCH_2), 3.57 (dd, ^2J = 9.5 Hz, ^3J = 4.1 Hz, 1 H, 6a-H), 3.49 (dd, ^2J = 9.5 Hz, ^3J = 4.9 Hz, 1 H, 6b-H), 2.98 (s, 3 H, CH_3), 2.68–2.63 (m, 1 H, 2-H), 2.34 (dd, ^2J = 15.3 Hz, ^3J = 5.9, ^3J = 5.9 Hz, 1 H, 5a-H), 2.30–2.24 (m, 1 H, 5b-H), 1.50 (s, 3 H, CH_3 isoprop.), 1.29 (s, 3 H, CH_3 isoprop.) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.7 (C arom.$_q$), 128.5, 127.9, 127.6 (C arom.), 111.3 (C2 isoprop.), 84.8 (C-1), 82.8 (C-3), 80.2 (C-4), 73.5 (Ph*C*H$_2$), 68.8 (C-6), 52.6 (C-2), 39.3 (C-5), 38.7 (*C*H$_3$), 26.8 (*C*H$_3$ isoprop.), 24.4 (*C*H$_3$ isoprop.) ppm. IR (film): $\tilde{\nu}$ = 3355, 3029, 2937, 1718, 1338, 1272, 1209, 1171, 1098, 1073, 1027, 1004, 966, 942, 871, 835, 794, 741, 697, 533, 520, 451 cm^{-1}. MS-FAB: *m*/*z* calcd. for $C_{17}H_{26}O_6S$ [M + H]: 357.4; found 357.0.

(1*S*,2*R*,5S)-5-(Benzyloxymethyl)-1,2-(isopropylidenedioxy)cyclopent-3-ene (22): The reaction was carried out as described for **11**, with methanesulfonate **21** (356 mg, 1.00 mmol) in DMF (15 mL) and KO*t*Bu (224 mg, 2.00 mmol). The residue was purified by chromatography on silica gel (hexane/EtOAc 3:2) to afford **22** (240 mg, 920 μmol, 92%) as a colorless oil. R_f (TLC) = 0.92 (hexane/EtOAc 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H, Bn arom.), 5.86 (m, 1 H, 4-H), 5.78 (m, 1 H, 3-H), 5.16–5.13 (m, 1 H, 2-H), 4.57–4.53 (m, 1 H, 1-H), 4.52 (s, 2 H, PhCH_2), 3.50 (dd, ^2J = 9.3 Hz, ^3J = 5.3 Hz, 1 H, 6a-H), 3.37 (dd, ^2J = 9.2 Hz, ^3J = 6.6 Hz, 1 H, 6b-H), 3.07–3.03 (m, 1 H, 5-H), 1.41 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.3 (C arom.$_q$), 134.0 (C-4), 132.7 (C-3), 128.4, 127.6, 127.5 (C arom.), 110.0 (C2 isoprop.), 85.0 (C-2), 81.4 (C-1), 73.1 (Ph*C*H$_2$), 71.1 (C-6), 52.6 (C-5), 27.4 (*C*H$_3$ isoprop.), 25.6 (*C*H$_3$ isoprop.) ppm. IR (film): $\tilde{\nu}$ = 3062, 2985, 2929, 2856, 1721, 1453, 1369, 1314, 1270, 1246, 1206, 1176, 1158, 1098, 1044, 907, 865, 737, 713, 697, 647, 607, 513 cm^{-1}. MS-FAB: *m*/*z* calcd. for $C_{16}H_{20}O_3$ [M + H]: 261.3; found 261.1.

(1*S*,2*R*,3*S*,4S)-4-(Benzyloxymethyl)-2,3-(isopropylidenedioxy)-cyclopentanol (23): The reaction was carried out as described for **9**, with the cyclopent-3-ene derivative **22** (335 mg, 1.28 mmol) and a solution of 9-BBN in THF (0.5 M, 5.2 mL). The crude product was purified by chromatography on silica gel (hexane/EtOAc 1:1) to afford **23** (206 mg, 724 μmol, 58%) as a colorless oil. $[\alpha]_D^{20}$ = –9.4 (*c* = 0.43, $CHCl_3$). R_f (TLC) = 0.62 (hexane/EtOAc 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H, Bn arom.), 4.60–4.56 (m, 1 H, 2-H), 4.56–4.54 (m, 2 H, PhCH_2), 4.43–4.39 (m, 1 H, 3-H), 4.10–4.06 (m, 1 H, 1-H), 3.62 (dd, ^2J = 9.2 Hz, ^3J = 3.5 Hz, 1 H, 6a-H), 3.48 (dd, ^2J = 9.2 Hz, ^3J = 3.3 Hz, 1 H, 6b-H), 2.44 (ddd, ^2J = 14.5 Hz, ^3J = 9.4, ^3J = 5.4 Hz, 1 H, 5a-H), 2.39–2.32 (m, 1 H, 4-H), 1.58–1.52 (m, 1 H, 5b-Hb), 1.41 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.4 (C arom.$_q$), 128.6, 128.2, 128.0 (C arom.), 111.6 (C2 isoprop.), 88.4 (C-3), 84.3 (C-2), (C-4), 76.8 (C-1), 73.2 (Ph*C*H$_2$), 72.2 (C-6), 46.0 (C-4), 35.7 (C-5), 26.7 (*C*H$_3$ isoprop.), 24.1 (*C*H$_3$ isoprop.) ppm. IR (film): $\tilde{\nu}$ = 3368, 2921, 2852, 1564, 1425, 1370, 1337, 1207, 1159, 1042, 925, 867, 717, 698, 649, 460, 410 cm^{-1}. MS-FAB: *m*/*z* calcd. for $C_{16}H_{22}O_4$ [M + H]: 279.4; found 279.0.

(1*R*,2*R*,3*S*,4S)-4-(Benzyloxymethyl)-2,3-(isopropylidenedioxy)-cyclopentanol (24): DIAD (45.0 μL, 230 μmol) was slowly added at 0 °C under nitrogen to a suspension of PPh_3 (60.0 mg, 230 μmol) in Et_2O (3 mL) and the suspension was stirred for 0.5 h. This preformed complex was added slowly at 0 °C to a suspension of benzoic acid (28.0 mg, 230 μmol) and the alcohol **23** (32.0 mg, 115 μmol) in Et_2O (3 mL). The reaction mixture was allowed to warm slowly to room temp. and stirred overnight. The solvent was removed and methanolic NaOH solution (1%, 3 mL) was added. The reaction mixture was stirred for an additional 6 h at room temp. The solution was neutralized by addition of HCl (1 M) and then concentrated. The residue was purified on silica gel (hexane/EtOAc 1:1) to yield **24** (15.3 mg, 55.2 μmol, 48%) as a colorless syrup. $[\alpha]_D^{20}$ = +30.0 (*c* = 0.24, $CHCl_3$). R_f (TLC) = 0.47 (hexane/EtOAc 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H, Bn arom.), 4.74–4.69 (m, 1 H, 3-H), 4.58 (d, 1 H, ^2J = 12.2 Hz, PhCH_2-a), 4.52 (d, 1 H, ^2J = 12.2 Hz, PhCH_2-b), 4.38 (dd, ^3J = 5.5, 1.1 Hz, 1 H, 2-H), 4.14–4.10 (m, 1 H, 1-H), 3.73 (dd, ^2J = 9.2 Hz, ^3J = 7.4 Hz, 1 H, 6a-H), 3.48 (dd, ^2J = 9.2 Hz, ^3J = 6.9 Hz, 1 H, 6b-H), 2.62–2.52 (m, 1 H, 4-H), 1.72–1.66 (m, 2 H, 5-H), 1.39 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.6 (C arom.$_q$), 128.3, 127.6, 127.5 (C arom.), 110.1 (C2 isoprop.), 86.7 (C-2), 79.9 (C-3), 75.6 (C-1), 73.1 (Ph*C*H$_2$), 69.5 (C-6), 41.3 (C-4), 34.5 (C-5), 26.0 (*C*H$_3$ isoprop.), 23.9 (*C*H$_3$ isoprop.) ppm. IR (film): $\tilde{\nu}$ = 3436, 2986, 2930, 2859, 1454, 1371, 1267, 1250, 1207, 1164, 1134, 1090, 1060, 1016, 989, 954, 881, 865, 812, 735, 697, 601, 576, 516, 478, 445 cm^{-1}. MS-FAB: *m*/*z* calcd. for $C_{16}H_{22}O_4$ [M + H]: 279.4; found 279.1.

5′-*O*-Benzyl-L-*carba*-ribothymdine (15): The reaction was carried out by the General Coupling Procedure with PPh_3 (57.0 mg,

216 μmol) in CH_3CN (3 mL), DIAD (40.0 μmol, 201 μmol), *N*3-benzoylthymine (33.1 mg, 143 μmol), the cyclopentanol **24** (20.0 mg, 71.9 μmol) in CH_3CN (3 mL), and NaOH in MeOH (1%, 3 mL). The crude product was purified by chromatography on silica gel (hexane/EtOAc 1:2) to yield **15** (8.2 mg, 24 μmol, 33%) as a colorless oil. Its spectroscopic data were identical to those described above.

(1*R*,4*R*)-4-(Benzyloxymethyl)cyclopent-2-enyl Benzoate (25): DIAD (250 μL, 1.28 mmol) was slowly added at 0 °C under nitrogen to a suspension of PPh_3 (336 mg, 1.28 mmol) in anhyd. Et_2O (6 mL) and the suspension was stirred for 0.5 h. This preformed complex was added slowly at 0 °C to a suspension of benzoic acid (156 mg, 1.28 mmol) and the alcohol **11** (130 mg, 642 μmol) in Et_2O (10 mL). The reaction mixture was allowed to warm slowly to room temp. and stirred overnight. The solvent was removed and the residue was purified on silica gel (hexane/EtOAc 1:1) to yield **25** (129 mg, 634 μmol, 99%) as a colorless syrup. $[\alpha]_D^{20}$ = +128 (*c* = 1.0, $CHCl_3$). R_f (TLC) = 0.44 (hexane/EtOAc 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03–8.02 (m, 2 H, 12-H, 8-H), 7.56–7.53 (m, 1 H, 10-H), 7.46–7.41 (m, 2 H, 9-H, 11-H), 7.38–7.34 (m, 5 H, C*H* arom.), 6.16 (dd, ^3J = 5.6 Hz, ^3J = 1.4 Hz, 1 H, 3-H), 6.01 (ddd, ^3J = 5.5 Hz, ^3J = 2.1 Hz, ^4J = 2.1 Hz, 1 H, 2-H), 5.97–5.96 (m, 1 H, 1-H), 4.54 (s, 2 H, CH_2Ph), 3.43 (dd, ^3J = 6.6 Hz, ^3J = 2.4 Hz, 2 H, 13-H), 3.30–3.24 (m, 1 H, 4-H), 2.16–2.13 (m, 2 H, 5-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.5 (C-6), 139.5 (C-3), 132.8 (C-10), 130.5 (C-2), 129.6 (C-8, C-12), 128.4 (C-9, C11), 128. (*C*H arom.), 127.6 (*C*H arom.), 80.5 (1), 73.7 (C-13), 73.2 (C-14), 45.2 (C-4), 34.1 (C-5) ppm. IR (film): $\tilde{\nu}$ = 3063, 3032, 2855, 1712, 1452, 1315, 1269, 1107, 1070, 1026, 748, 712 cm^{-1}. HRMS-FAB: *m*/*z* calcd. for $C_{13}H_{16}O_2$ [M + H]: 309.1485; found 309.1479.

(1*R*,2*S*,3*S*,4*S*)-4-(Benzyloxymethyl)-2,3-dihydroxycyclopentyl Benzoate (26): Benzoate **25** (77.0 mg, 250 μmol) was dissolved in *tert*-butyl alcohol/water (2:1, 3 mL). The solution was cooled to 0 °C and AD-mix α was added. The reaction mixture was stirred for 12 h at 0 °C and the reaction was stopped by addition of saturated $NaHSO_3$ solution (2 mL). After phase separation the aqueous layer was extracted with EtOAc (2 × 5 mL). The organic layers were combined and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel (hexane/EtOAc 1:2) to afford **26** (66.0 mg, 193 μmol, 68%) as a colorless oil. R_f (TLC) = 0.62 (CH_2Cl_2/CH_3OH 19:1). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.01–7.96 (m, 2 H, Bz arom.), 7.69–7.63 (m, 1 H, Bz arom.), 7.57–7.50 (m, 2 H, Bz arom.), 7.37–7.27 (m, 5H, Bn arom.), 5.13–5.07 (m, 1 H, 1-H), 5.05 (d, ^3J = 6.4 Hz, 1 H, O*H*), 4.67 (d, ^3J = 6.4 Hz, 1 H, O*H*), 4.53–4.43 (m, 2 H, PhCH_2), 4.11–4.07 (m, 1 H, 2-H), 3.97–3.94 (m, 1 H, 3-H), 3.63 (dd, ^3J = 7.2 Hz, ^2J = 9.1 Hz, 1 H, 6a-H), 3.56 (dd, ^3J = 7.2 Hz, ^2J = 9.1 Hz, 1 H, 6b-H), 2.41–2.34 (m, 1 H, 5a-H), 1.66–1.59 (m, 1 H, 5b-H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 166.2 (C-Bz$_q$), 139.1 (C arom.$_q$), 133.6, 129.5, 129.1, 128.5, 128.3 127.9, 127.8 (C arom.), 80.1 (C-1), 78.2 (C-3), 72.4 (Ph*C*H$_2$), 72.1 (C-2), 70.3 (C-6), 32.1 (C-5) ppm. MS-FAB: *m*/*z* calcd. for $C_{20}H_{22}O_5$ [M + H]: 343.4; found 343.1.

(1*R*,2*R*,3*S*,4S)-4-(Benzyloxymethyl)-2,3-(isopropylidenedioxy)-cyclopentyl Benzoate (28): The reaction was carried out as described for **21**, with benzoate **26** (40.0 mg, 117 μmol), 2,2-dimethoxypropane (72 μL, 585 μmol) in acetone (5 mL), and *p*-toluenesulfonic acid (1.0 mg, 6.0 μmol). The crude product was purified by chromatography on silica gel (hexane/EtOAc 1:1) to afford **28** (42 mg, 109 μmol, 93%) as a colorless oil. R_f (TLC) = 0.95 (hexane/EtOAc 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (dd, ^4J = 1.2 Hz, ^3J = 8.3 Hz, 2 H, Bz-a), 7.56 (ddd, ^4J = 1.3 Hz, ^3J = 7.4 Hz, ^3J = 7.4 Hz, 1 H, Bz-c), 7.46–7.40 (m, 2 H, Bz-b), 7.39–7.27 (m, 5 H, Bn arom.), 5.27–5.24 (m, 1 H, 1-H), 4.81–4.77 (m, 1 H, 3-H), 4.54–4.51 (m, 1 H, 2-H), 4.51 (d, ^2J = 12.1 Hz, 1 H, PhCH_2-a), 4.46 (d, ^2J = 12.1 Hz, 1 H, PhCH_2-b), 3.73 (dd, ^2J = 9.0 Hz, ^3J = 7.6 Hz, 1 H, 6a-H), 3.45 (dd, ^2J = 9.0 Hz, ^3J = 6.8 Hz, 1 H, 6b-H), 2.55–2.44 (m, 1 H, 4-H), 1.95–1.87 (m, 1 H, 5a-H), 1.80 (ddd, ^2J = 9.1 Hz, ^3J = 9.0, ^3J = 6.8 Hz, 1 H, 5b-H), 1.37 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.0 (C-Bz$_q$), 138.9 (C arom.$_q$), 133.5 (C-Bz-c), 130.0 (C-Bz-a), 128.8, 128.1, 128.0 (C arom., C-Bz-b), 111.1 (C2 isoprop.), 85.2 (C-2), 80.3 (C-3), 79.0 (C-1), 73.8 (Ph*C*H$_2$), 69.8 (C-6), 42.7 (C-4), 32.4 (C-5), 26.4 (*C*H$_3$ isoprop.), 24.3 (*C*H$_3$ isoprop.) ppm. MS-FAB: *m*/*z* calcd. for $C_{23}H_{26}O_5$ [M + H]: 383.5; found 383.5.

(1*R*,2*R*,3*S*,4S)-4-(Benzyloxymethyl)-2,3-(isopropylidenedioxy)-cyclopentanol (24): Benzoate **23** (40.0 mg, 105 μmol) was dissolved in methanolic NaOH solution (1%, 5 mL) and the mixture was stirred at room temp. for 6 h. The reaction mixture was neutralized with HCl (1 M) and extracted with EtOAc (3 × 5 mL). The organic layers were combined and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude product was purified by chromatography with a chromatotron (hexane/EtOAc 10:1) to yield the alcohol **24** (25.5 mg, 91.6 μmol, 87%) as a colorless oil. Its spectroscopic data were identical to those described above.

(1*R*,2*S*,4*R*,5*R*)-4-(Benzyloxymethyl)bicyclo[3.1.0]hexan-2-ol (29): The cyclopentenol **11** (450 mg, 2.20 mmol) was dissolved in CH_2Cl_2 (12 mL) under nitrogen and the mixture was cooled to –10 °C. A solution of diethylzinc in hexane (1 M, 2.4 mL) was added dropwise. After the mixture had stirred for 15 min at this temperature a solution of diiodomethane (1.30 mg, 4.84 mmol) in anhyd. CH_2Cl_2 (6 mL) was added, followed by diethylzinc in hexane (1 M, 2.4 mL). The reaction mixture was stirred overnight at 0 °C and added to a saturated solution of ammonium chloride (15 mL). Stirring was continued overnight at room temp. The aqueous layer was extracted with EtOAc (4 × 10 mL), the combined organic layers were dried (Na_2SO_4), and solvents were removed under reduced pressure. The crude product was purified by chromatography with a chromatotron (hexane/EtOAc 2:1) to yield the alcohol **29** (408 mg,1.85 mmol, 84%) as a colorless oil. $[\alpha]_D^{20}$ = –23.0 (*c* = 0.79, $CHCl_3$). R_f (TLC) = 0.52 (hexane/EtOAc 1:1, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.26 (m, 5 H, Bn arom.), 4.58–4.50 (m, 3 H, 2-H, Ph-CH_2), 3.42 (dd, ^2J = 7.9, ^3J = 6.3 Hz, 1 H, 7a-H), 3.39 (dd, ^2J = 7.9, ^3J = 5.3 Hz, 1 H, 7b-H), 2.54–2.43 (m, 1 H, 4-H), 1.95 (ddd, ^2J = 13.3 Hz, ^3J = 7.7, 7.7 Hz, 1 H, 3a-H), 1.57–1.50 (m, 1 H, 1-H), 1.47–1.40 (m, 1 H, 5-H), 0.76 (ddd, ^2J = 13.3 Hz, ^3J = 10.9, 8.8 Hz, 1 H, 3b-H), 0.63–0.58 (m, 1 H, 6a-H), 0.37–0.29 (m, 1 H, 6b-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.7 (C arom.$_q$), 128.3, 127.4, 127.4 (C arom.), 74.3 (C-2), 73.1 (C-7), 73.0 (*C*H$_2$-Bn), 37.5 (C-4), 34.3 (C-3), 24.3 (C-1), 18.7 (C-5), 4.5 (C-6) ppm. IR (film): $\tilde{\nu}$ = 3355, 3065, 3030, 3005, 2866, 2286, 1717, 1496, 1467, 1452, 1412, 1363, 1336, 1315, 1273, 1205, 1176, 1093, 1072, 1025, 819, 737, 713, 697, 651, 605, 552, 478 cm^{-1}. MS-FAB: *m*/*z* calcd. for $C_{14}H_{18}O_2$ [M + H]: 219.3; found 219.0.

L-*carba*-2′,3′-*endo*-Methylene-α-thymidine (30): The reaction was carried out by the General Coupling Procedure with PPh_3 (230 mg, 870 μmol) in CH_3CN (4 mL), DIAD (160 μL, 815 μL), the cyclopentanol **29** (63.4 mg, 291 μmol) in CH_3CN (6 mL), and NaOH in MeOH (1%, 6 mL). The residue was directly debenzylated by the General Debenzylation Procedure. The crude product was purified by chromatography with a chromatotron (CH_2Cl_2/MeOH gradient 0–5%). After lyophilization (CH_3CN/water) the debenzylated nucleoside **30** (22.0 mg, 93.0 μmol, 32%) was obtained as a colorless

foam. $[\alpha]_D^{20}$ = –8.0 (c = 0.39, $CHCl_3$). R_f (TLC) = 0.31 (CH_2Cl_2/CH_3OH 9:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.94 (brs, 1 H, NH), 7.28 (d, ^4J = 1.0 Hz, 1 H, 6-H), 5.00–4.96 (m, 1 H, 1′-H), 3.65 (dd, ^2J = 10.4, ^3J = 5.9 Hz, 1 H, 5′a-H), 3.59 (dd, ^4J = 10.4, ^3J = 7.5 Hz, 1 H, 5′b-H), 2.63–2.53 (m, 1 H, 4′-H), 1.93 (d, ^4J = 1.0 Hz, 3 H, CH_3), 1.85–1.78 (m, 1 H, 3′-H), 1.71–1.64 (m, 1 H, 6′a-H), 1.44–1.35 (m, 2 H, 2′-H, 6′b-H), 0.69–0.62 (m, 1 H, 7′a-H), 0.44–0.38 (m, 1 H, 7′b-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.7 (C-4), 150.9 (C-2), 137.0 (C-6), 110.5 (C-5), 65.1 (C-5′), 57.3 (C-1′), 40.5 (C-4′), 32.2 (C-6′), 20.5 (C-3′), 20.4 (C-2′), 12.7 (CH_3), 4.8 (C-7′) ppm. UV: λ_{max} = 271 nm (CH_3CN). HRMS-FAB: m/z calcd. for $C_{12}H_{16}N_2O_3$ [M + H]: 237.2744; found 237.2753.

(1*R*,2*R*,4*R*,5*R*)-4-(Benzyloxymethyl)bicyclo[3.1.0]hexan-2-ol (31): DIAD (320 μL, 1.63 mmol) was slowly added at 0 °C under nitrogen to a suspension of PPh_3 (427 mg, 1.63 mmol) in anhyd. Et_2O (6 mL) and the suspension was stirred for 0.5 h. This preformed complex was slowly added at 0 °C to a suspension of benzoic acid (200 mg, 1.63) and the alcohol **29** (178 mg, 816 μmol) in anhyd. Et_2O (10 mL). The reaction mixture was allowed to warm slowly to room temp. and stirred overnight. The solvent was removed and methanolic NaOH solution (1%, 10 mL) was added. The reaction mixture was stirred for an additional 6 h at room temp. The solution was neutralized by addition of HCl (1 M) and then concentrated. The residue was purified on silica gel (hexane/EtOAc 1:1) to yield **31** (127 mg, 583 μmol, 71%) as a colorless syrup. $[\alpha]_D^{20}$ = –21.0 (c = 0.81, $CHCl_3$). R_f (TLC) = 0.50 (hexane/EtOAc 1:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H, Bn arom.), 4.54 (s, 2 H, PhCH_2), 4.24–4.21 (m, 1 H, 2-H), 3.44 (dd, ^2J = 9.1, ^3J = 7.8 Hz, 1 H, 7a-H), 3.40 (dd, ^2J = 9.1, ^3J = 6.4 Hz, 1 H, 7b-H), 2.82–2.73 (m, 1 H, 4-H), 1.68–1.61 (m, 1 H, 3a-H), 1.57–1.52 (m, 1 H, 5-H), 1.44–1.39 (m, 1 H, 1-H), 1.03 (ddd, ^2J = 15.1, ^3J = 11.0, 5.0 Hz, 1 H, 3b-H), 0.43–0.37 (m, 1 H, 6a-H), 0.15–0.09 (m, 1 H, 6b-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.7 (C arom.$_q$), 128.3, 127.4, 127.4 (C arom.), 74.3 (C-2), 73.1 (C-7), 73.0 (CH_2-Bn), 37.5 (C-4), 34.3 (C-3), 24.3 (C-1), 18.7 (C-5), 4.5 (C-6) ppm. IR (film): $\tilde{\nu}$ = 3355, 3065, 3032, 3002, 2903, 1716, 1495, 1452, 1388, 1351, 1315, 1272, 1177, 1109, 1095, 1070, 1025, 989, 960, 937, 835, 816, 734, 712, 698, 650, 600, 530, 440 cm^{-1}. MS-FAB: m/z calcd. for $C_{14}H_{18}O_2$ [M + H]: 219.3; found 219.1.

L-*carba*-2′,3′-*endo*-Methylene-β-thymidine (32): The reaction was carried out by the General Coupling Procedure with PPh_3 (230 mg, 870 μmol) in CH_3CN (4 mL), DIAD (160 μL, 815 μL), *N*3-benzoylthymine (134 mg, 582 μmol), the cyclopentanol **31** (63.6 mg, 291 μmol) in CH_3CN (6 mL), and NaOH in MeOH (1%, 6 mL). The residue was directly debenzylated by the General Debenzylation Procedure. The crude product was purified by chromatography with a chromatotron (CH_2Cl_2/MeOH gradient 0–5%). After lyophilization (CH_3CN/water) the debenzylated nucleoside **32** (19.8 mg, 84.5 μmol, 29%) was obtained as a colorless foam. $[\alpha]_D^{20}$ = –7.5 (c = 0.31, H_2O). R_f (TLC) = 0.28 (CH_2Cl_2/CH_3OH 9:1). ^1H NMR (400 MHz, D_2O): δ = 7.92 (d, ^4J = 1.0 Hz, 1 H, 6-H), 4.90 (ddd, ^3J = 10.5, 7.2, 3.7 Hz, 1 H, 1′-H), 3.60 (dd, ^2J = 10.8, ^3J = 6.3 Hz, 1 H, 5′a-H), 3.54 (dd, ^2J = 10.8 Hz, ^3J = 7.8 Hz, 1 H, 5′b-H), 2.59–2.48 (m, 1 H, 4-H′), 2.13 (ddd, ^2J = 14.6 Hz, ^3J = 6.6, 6.6 Hz, 1 H, 6′a-H), 1.91 (d, ^4J = 1.0 Hz, 3 H, CH_3), 1.64–1.55 (m, 1 H, 3′-H), 0.88–0.77 (m, 2 H, 6′b-H, 7′a-H), 0.73–0.67 (m, 1 H, 7′b-H) ppm. ^{13}C NMR (101 MHz, D_2O): δ = 166.5 (C-4), 152.7 (C-2), 139.5 (C-6), 109.6 (C-5), 63.4 (C-5′), 58.2 (C-1′), 38.8 (C-4′), 26.5 (C-6′), 16.8 (C-3′), 16.4 (C-2′), 11.1 (CH_3), 2.0 (C-7′) ppm. HRMS-FAB: m/z calcd. for $C_{12}H_{16}N_2O_3$ [M + H]: 237.2744; found 237.2746. UV: λ_{max} = 271 nm (CH_3CN).

[1] a) L. Agrofoglio, E. Suhas, A. Farese, R. Condom, S. R. Challand, R. A. Earl, R. Guedj, *Tetrahedron* **1994**, *50*, 10611–10670; b) E. De Clercq, *J. Med. Chem.* **1995**, *38*, 2491; c) J. Balzarini, *Pharm. World Sci.* **1994**, *16*, 113–126; d) E. De Clercq, *Nat. Rev. Drug Discovery* **2002**, *1*, 13–25; P. Herdewijn, J. Balzarini, E. De Clercq, in: *Advances in Antiviral Drug Design* (Ed.: E. De Clercq), JAI Press Inc., Greenwich (Connecticut), London (England), **1993**, vol. 1, pp. 233–318.

[2] a) G. Gumina, Y. Chong, H. Choo, G.-Y. Song, C. K. Chu, *Curr. Top. Med. Chem. (Hilversum, Neth.)* **2002**, *2*, 1065–1086; b) G. Gumina, G. Y. Song, C. K. Chu, *FEMS Microbiol. Lett.* **2001**, *202*, 9–15; c) C. Mathe, G. Gosselin, *Antiviral Res.* **2006**, *71*, 276–281; d) M. L. Bryant, E. G. Bridges, L. Placidi, A. Faraj, A.-G. Loi, C. Pierra, D. Dukhan, G. Gosselin, J.-L. Imbach, B. Hernandez, A. Juodawlkis, B. Tennant, B. Korba, P. Cote, E. Cretton-Scott, R. F. Schinazi, J.-P. Sommadossi, *Nucleosides Nucleotides Nucleic Acids* **2001**, *20*, 597–607; e) M. L. Bryant, E. G. Bridges, L. Placidi, A. Faraj, A.-G. Loi, C. Pierra, D. Dukhan, G. Gosselin, J.-L. Imbach, B. Hernandez, A. Juodawlkis, B. Tennant, B. Korba, P. Cote, P. Marion, E. Cretton-Scott, R. F. Schinazi, J.-P. Sommadossi, *Antimicrob. Agents Chemother.* **2001**, *45*, 229–235; f) E. Matthes, A. Funk, I. Krahn, K. Gaertner, M. von Janta-Lipinski, L. Lin, H. Will, H. Sirma, *Antimicrob. Agents Chemother.* **2007**, *51*, 2523–2530; g) P. Wang, J. H. Hong, J. S. Cooperwood, C. K. Chu, *Antiviral Res.* **1998**, *40*, 19–44.

[3] a) C. M. Hunt, N. A. Brown, M. Rubin, *Adv. Exp. Med. Biol.* **1999**, *458*, 11–21; b) E. Jaeckel, M. P. Manns, *Intervirology* **1997**, *40*, 322–336; c) B. Jarvis, D. Faulds, *Drugs* **1999**, *58*, 101–141; d) C. M. Perry, D. Faulds, *Drugs* **1997**, *53*, 657–680; J. A. V. Coates, N. Cammack, H. J. Jenkinson, I. M. Mutton, B. A. Pearson, R. Storer, J. M. Cameron, C. R. Penn, *Antimicrob. Agents Chemother.* **1992**, *36*, 202–205; e) P. A. Furman, M. Davis, D. C. Liotta, M. Paff, L. W. Frick, D. J. Nelson, R. E. Dornsife, J. A. Wurster, L. J. Wilson, J. A. Fyfe, J. V. Tuttle, W. H. Miller, L. Condreay, D. R. Averett, R. F. Schinazi, G. R. Painter, *Antimicrob. Agents Chemother.* **1992**, *36*, 2686–2692; f) H. Soudeyns, X. J. Yao, Q. Gao, B. Belleau, J. L. Kraus, B. Nghe Nguyen, B. Spira, M. A. Wainberg, *Antimicrob. Agents Chemother.* **1991**, *35*, 1386–1390.

[4] a) B. Han Steven-Huy, *Expert Opin. Invest. Drugs* **2005**, *14*, 511–519; b) K. Nash, *Adv. Ther.* **2009**, *26*, 155–169; c) R. Jones, M. Nelson, *Int. J. Clin. Pract.* **2006**, *60*, 1295–1299; d) J. Keam Susan, *Drugs* **2007**, *67*, 1917–1929; e) S. J. Matthews, *Clin. Ther.* **2007**, *29*, 2635–2653; f) L. A. Sorbera, J. Castaner, R. M. Castaner, M. Bayes, *Drugs Future* **2003**, *28*, 870–879.

[5] a) Y. Chong, C. K. Chu, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3459–3462; b) G. Q. Yao, S. H. Liu, E. Chou, M. Kukhanova, C. K. Chu, Y. C. Cheng, *Biochem. Pharmacol.* **1996**, *51*, 941–947; c) C.-K. Hui, K. K. Lau George, *Expert Opin. Invest. Drugs* **2005**, *14*, 1277–1284; d) E. Korba Brent, A. Furman Phillip, J. Otto Michael, *Expert Rev. Anti-Infect. Ther.* **2006**, *4*, 549–561; e) G. R. Painter, L. C. Trost, M. R. Blum, G. M. Szczech, P. A. Furman, *Front. Viral Hepatitis* **2003**, 281–300; f) C. K. Chu, J. H. Hong, Y. Choi, J. Du, K. Lee, B. K. Chun, F. D. Boudinot, S. F. Peek, B. E. Korba, B. C. Tennant, Y.-C. Cheng, *Drugs Future* **1998**, *23*, 821–826.

[6] a) L. M. Bang, L. J. Scott, *Drugs* **2003**, *63*, 2413–2424; b) D. D. Richman, *Antiviral Ther.* **2001**, *6*, 83–88.

[7] a) A. D. Borthwick, K. Biggadike, *Tetrahedron* **1992**, *48*, 571–623; b) V. E. Marquez, *Adv. Antiviral Drug Des.* **1996**, *2*, 89–146; c) M. T. Crimmins, *Tetrahedron* **1998**, *54*, 9229–9272.

[8] a) R. C. Cookson, P. J. Dudfield, R. F. Newton, P. Ravenscroft, D. I. C. Scopes, J. M. Cameron, *Eur. J. Med. Chem.* **1985**, *20*, 375–377; b) J. H. Cho, D. L. Bernard, R. W. Sidwell, E. R. Kern, C. K. Chu, *J. Med. Chem.* **2006**, *49*, 1140–1148; c) H.-J. Kim, A. Sharon, C. Bal, J. Wang, M. Allu, Z. Huang, M. G. Murray, L. Bassit, R. F. Schinazi, B. Korba, C. K. Chu, *J. Med.*

Chem. **2009**, *52*, 206–213; d) H. Zhang, R. F. Schinazi, C. K. Chu, *Bioorg. Med. Chem.* **2006**, *14*, 8314–8322.
[9] O. R. Ludek, C. Meier, *Synthesis* **2003**, 2101–2109.
[10] O. R. Ludek, T. Kraemer, J. Balzarini, C. Meier, *Synthesis* **2006**, 1313–1324.
[11] S. Jessel, C. Meier, *Nucleic Acids Symp., Ser.* **2008**, 615–616.
[12] K. Biggadike, A. D. Borthwick, D. Evans, A. M. Exall, B. E. Kirk, S. M. Roberts, L. Stephenson, P. Youds, *J. Chem. Soc. Perkin Trans. 1* **1988**, 549–554.
[13] G. W. Kabalka, T. M. Shoup, N. M. Goudgaon, *J. Org. Chem.* **1989**, *54*, 5930–5933.
[14] G. W. Kabalka, P. P. Wadgaonkar, T. M. Shoup, *Organometallics* **1990**, *9*, 1316–1320.
[15] D. H. B. Ripin, W. Cai, S. J. Brenek, *Tetrahedron Lett.* **2000**, *41*, 5817–5819.
[16] G. W. Kabalka, H. C. Hedgecock Jr., *J. Org. Chem.* **1975**, *40*, 1776–1779.
[17] L. F. Tietze, C. Stadler, N. Boehnke, G. Brasche, A. Grube, *Synlett* **2007**, 485–487.
[18] G. Yang, X. Ding, F. Kong, *Tetrahedron Lett.* **1997**, *38*, 6725–6728.
[19] M.-Y. Chang, C.-H. Lin, A.-Y. Lee, H.-M. Tai, N.-C. Chang, *J. Chin. Chem. Soc.* **1999**, *46*, 205–210.
[20] H. Becker, K. B. Sharpless, *Angew. Chem.* ***1996****, 108*, 447; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 448–451.
[21] a) J. B. Rodriguez, V. E. Marquez, M. C. Nicklaus, H. Mitsuya, J. J. Barchi Jr., *J. Med. Chem.* **1994**, *37*, 3389–3399; b) A. Ezzitouni, V. E. Marquez, *J. Chem. Soc., Perkin Trans. 1* **1997**, 1073–1078; c) A. Ezzitouni, P. Russ, V. E. Marquez, *J. Org. Chem.* **1997**, *62*, 4870–4873; d) V. E. Marquez, A. Ezzitouni, P. Russ, M. A. Siddiqui, H. Ford Jr., R. J. Feldman, H. Mitsuya, C. George, Barchi, J. Joseph, *J. Am. Chem. Soc.* **1998**, *120*, 2780–2789.
[22] a) J. Furukawa, N. Kawabata, J. Nishimura, *Tetrahedron Lett.* **1968**, *9*, 3495–3498; b) J. Furukawa, N. Kawabata, J. Nishimura, *Tetrahedron* **1968**, *24*, 53–58.

Received: October 29, 2010
Published Online: February 7, 2011

