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Influence of the *N*3-Protection Group on *N*1- vs. O^2-Alkylation in the Mitsunobu Reaction[‡]

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The influence of the *N*3-protection group of thymine on the regioselectivity of the *N*1- vs. O^2-alkylation under Mitsunobu conditions is described. A series of *N*3-protected thymine derivatives **8a–f** was prepared and coupled to cyclopentanol as model compound for carbocyclic nucleoside precursors. Finally, the *N*3-BOM group was selected to improve our previously reported synthetic strategy to carbocyclic thymidine (*carba*-dT). Moreover, the 2,6-dimethyl-Bz group led exclusively to the O^2-analogue of *carba*-dT.

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Introduction

Analogues of naturally occurring nucleosides have attracted considerable interest as antiviral and antitumor agents.[2] A major drawback of this class of compounds is often their low conversion into the ultimate bioactive nucleoside monophosphates (nucleotides) and their hydrolytic and enzymatic instability of the glycosidic bond leading to a rapid degradation of the nucleosides. To overcome these limitations, several modifications have been made to the structure of nucleosides, including the replacement of the furanose oxygen atom by a methylene unit.[3] However, the removal of the aminal oxygen atom abolishes the anomeric and gauche effects, responsible for forcing the furane system into two distinct conformations.[4] Since the conformation of the five-membered ring is believed to play a critical role in modulating biological activity, the behaviour of nucleosides with a cyclopentane moiety sometimes differs significantly from that of their natural counterparts.[5] Nevertheless, carbocyclic nucleoside analogues like carbovir (**1**)[6] and the structurally related abacavir (**2**)[7] (Ziagen™) were found to be potent inhibitors of HIV reverse transcriptase. Moreover, the guanine derivative entecavir (**3**)[8] (Baraclude™) was approved by the FDA in early 2005 for the treatment of chronic HBV infections. Beside carbocyclic purine analogues, *carba*-BVdU (**4**) is an example of a bioactive pyrimidine analogue that showed significant *anti*-HSV-1 activity (Figure 1).[9]

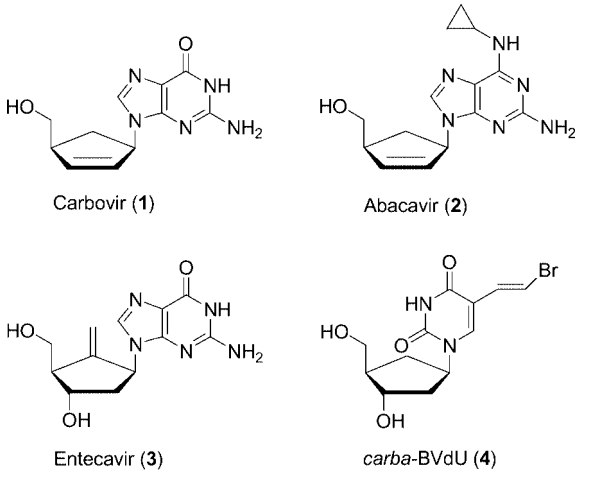

Figure 1. Examples of antivirally active and approved carbocyclic nucleosides.

Carbocyclic nucleosides are synthetically the most challenging class of nucleosides, requiring multi-step syntheses to introduce the required multiple stereogenic centers. A number of strategies, which can be classified into two categories, have been used to obtain enantiomerically pure carbocyclic nucleosides.[10] The linear approach involves an initial synthesis of a functionalized cyclopentylamine. Then the heterocyclic base is built in a step-wise manner. The second strategy is the convergent approach. Here, the appropriate heterocycle is coupled directly to a functionalized carbocyclic moiety, leading to a variety of carbocyclic nucleosides starting from one common cyclopentane precursor.

Recently, we published a new convergent route to carbocyclic nucleoside analogues, starting from enantiomerically pure (1*S*,2*R*)-2-(benzyloxymethyl)cyclopent-3-enol (**5**).[11,12]

[‡] Synthesis of Carbocyclic Pyrimidine Nucleosides, III. Part II: Ref.[1]

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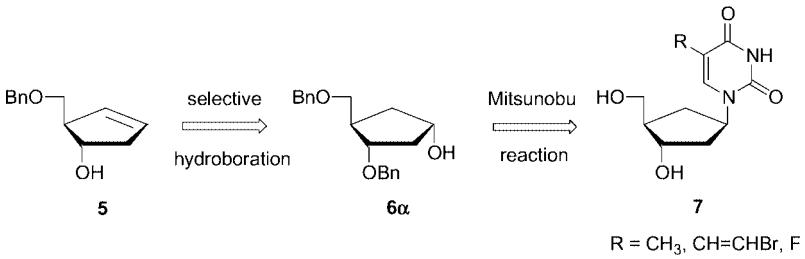


Figure 2. Convergent synthesis of carbocyclic nucleosides starting from a chiral cyclopentanol.

After a stereoselective hydroboration as the key step, the resulting chiral cyclopentanol **6α** is condensed with an *N*3-protected pyrimidine nucleobase to yield the carbocylic nucleoside **7** by a modified Mitsunobu protocol (Figure 2).

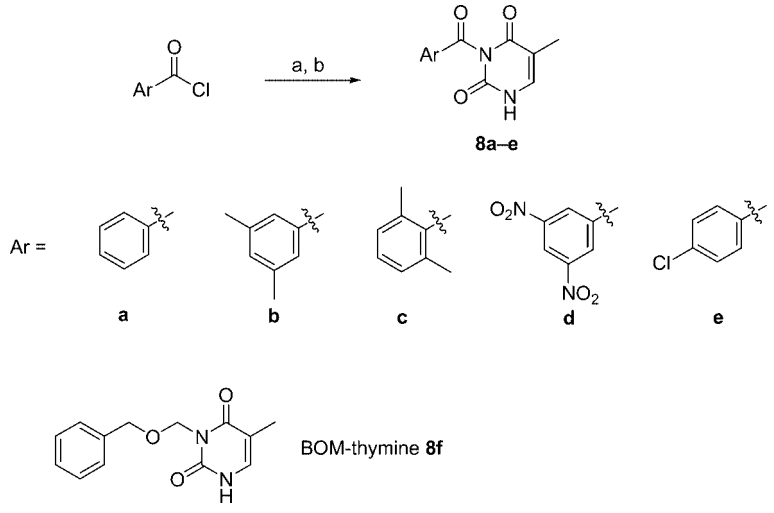
This strategy can also be used for the synthesis of carbocyclic α-, *iso*- and 3′-*epi*-nucleosides.[13] However, the nucleobases often react as ambident nucleophiles, leading to mixtures of isomers (*N*1- and O^2-regioisomers for pyrimidines).[14] In order to maximize reaction yields, to control the regioselective coupling and to minimize purification efforts, reaction conditions leading predominantly to one isomer are highly desirable. In this context we have studied the effect of the alcohol on the coupling to the heterocycle as well as solvent effects. The first study led to a method to predict the regioselectivity for a given alcohol[1] and the second study proved that CH_3CN or DMF are the most suitable solvents to be used in order to furnish predominantly the *N*1-isomer.[15] From previous reactions it became clear that the substituent in the 5-position of the protected nucleobase has a major effect on the outcome of the Mitsunobu coupling.[11,16] The 5-substituent obviously has an influence on the relative nucleophilicity of both alkylation centers. Most probably this can be explained by differences in the electronic structure and differences in the solvation cages.[17]

Here, we report on the effect of different *N*3-protecting groups on the regioselectivity of the coupling of the heterocycle to the alcohol.

Results and Discussion

For the Mitsunobu coupling reaction the *N*3-position of the pyrimidine base has to be protected. Usually the *N*-benzoyl group is used for this purpose.[18] However, due to the results obtained with different 5-substituents, we decided to investigate the influence of different protecting groups in the 3-position of the nucleobase on the product ratio in more detail. Therefore, differently substituted *N*-benzoyl groups were attached to the *N*3-position of thymine (**8a**–**e**). Additionally, we blocked the *N*3-position by alkylation with a benzyloxymethyl (BOM) group (**8f**) (Scheme 1).

These reactions were carried out, according to the procedure for the benzoylation of pyrimidines as described by Cruickshank et al.[18] The intermediately formed *N*1,*N*3-dibenzoylated compounds were not isolated. After evaporation of the solvent, the crude products were purified by silica gel column chromatography (CH_2Cl_2/MeOH, 20:1), leading to a selective methanolysis at the *N*1-position. Ex-



Scheme 1. Synthesis of different *N*3-benzoylthymine derivatives **8**. (a) Thymine, pyridine, CH_3CN, room temp., 2 d; (b) chromatography on silica gel (CH_2Cl_2/MeOH, 20:1).

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cept for (3,5-dinitrobenzoyl)thymine **8d**, the yields of the benzoylated thymine derivatives **8a**–**e** are good to excellent (Table 1).

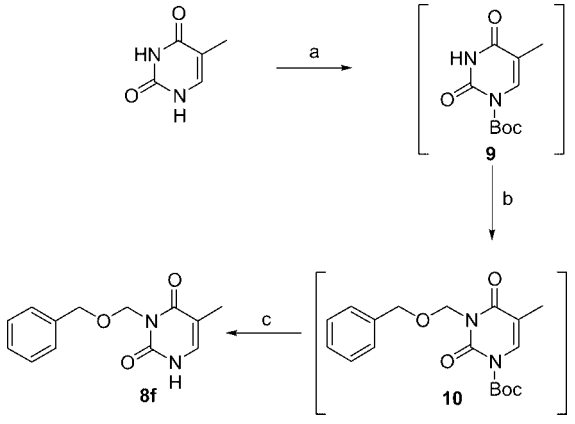
Table 1. Selective acylation on *N*3 of thymine with benzoyl chlorides.

Bz-thymine	Protection group	Yield [%]
8a	benzoyl	80
8b	3,5-dimethylbenzoyl	69
8c	2,6-dimethylbenzoyl	72
8d	3,5-dinitrobenzoyl	25
8e	4-chlorobenzoyl	95

The low yield of the 3,5-dinitro derivative **8d** (Entry 4) is due to the high instability of this compound. When purified on silica gel, not only the *N*1-protecting group was cleaved but also a partial loss of the second benzoyl group was observed. This observation was confirmed by a stability test of compound **8d** in CH_2Cl_2/MeOH (20:1). After stirring for 20 min, TLC showed a noticeable amount of thymine and methyl 3,5-dinitrobenzoate.

In addition to the *N*-acylated compounds **8a**–**e**, one *N*3-alkylated thymine derivative (**8f**) was prepared. Since our reported strategy for carbocyclic nucleoside synthesis involves the cleavage of benzyl ethers by hydrogenolysis in the final step,[11–13,19] a protection group was attached, which can be cleaved at the same time by catalytic hydrogenation. Unfortunately, a benzyl group at the *N*3-atom of an uracil derivative is extremely stable. Therefore, the benzyloxymethyl (BOM) group was used,[20] that degrades to the nucleobase in a tandem reaction after hydrogenolysis of the benzyl ether and spontaneous elimination of formaldehyde.

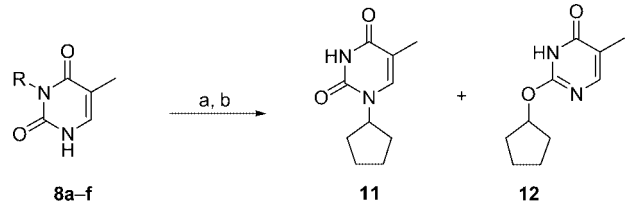
The synthesis of *N*3-BOM-thymine (**8f**) was first described by Schmitt and Caperelli in poor chemical yields.[21] To improve the yield, we applied the three-step one-pot strategy developed by Jaime-Figeroa et al. for the synthesis of *N*3-alkylated pyrimidines (Scheme 2).[22]



Scheme 2. Synthesis of *N*3-(benzyloxymethyl)thymine. (a) Di-*tert*-butyl dicarbonate, DMAP, CH_3CN, room temp., 4 h; (b) NaH, BOM-Cl, DMF, room temp., 1 h; (c) K_2CO_3, MeOH, room temp., 2 h.

Thus, thymine was selectively protected by the Boc group at the *N*1-atom by reaction with di-*tert*-butyl dicarbonate (Boc_2O) in acetonitrile with DMAP as a catalyst. *N*1-Protected thymine **9** was not isolated and the crude mixture was subsequently treated with sodium hydride in DMF and alkylated by slow addition of benzyl chloromethyl ether (BOM-Cl). In the last step the Boc group was cleaved by stirring a mixture of **10** in methanol with potassium carbonate as base. *N*3-(Benzyloxymethyl)thymine (**8f**) (BOM-T) was obtained in an overall yield of 64%.

Compounds **8a**–**f** were then subjected to the coupling reaction under modified Mitsunobu conditions in THF with cyclopentanol as a model for the chiral cyclopentanols used in carbocyclic nucleoside synthesis. The reaction with (3,5-dinitrobenzoyl)thymine **8d** was performed in CH_3CN for solubility reasons (Scheme 3).



Scheme 3. Coupling of the *N*3-protected thymine with cyclopentanol. (a) PPh_3, DIAD, cyclopentanol, THF, –40 °C to room temp., 16 h; (b) 1% NaOH in MeOH, room temp., 12 h.

Both isomers **11** and **12** were isolated and the product ratio was determined by ^{1}H NMR spectroscopy using the integration of the 1′-H protons. The yields and obtained product ratios of the couplings are summarized in Table 2.

Table 2. Alkylation of *N*3-protected thymines with cyclopentanol.

	Pyrimidine	Solvent	Yield [%][a]	*N*1/O^2 ratio [%][b]
1	**8a**	THF	92	66:34
2	**8b**	THF	89	60:40
3	**8c**	THF	85	0:100
4	**8d**	CH_3CN	59	96:4
5	**8e**	THF	88	65:35
6	**8f**	THF	94	80:20

[a] Yield of both isolated products. [b] Determined by ^{1}H NMR spectroscopy.

As already seen in the case of 5-substituted pyrimidine nucleobases, the product ratio of the coupling reaction can also be strongly influenced by the protecting group in the 3-position of the heterocycle. For example the 3,5-dinitrobenzoyl group (**8d**) led almost exclusively to the formation of the *N*1-isomer while the 2,6-dimethylbenzoyl group (**8c**) led highly selectively to the O^2-product. Unfortunately, the yield of the coupling reaction with **8d** is considerably lower than with the other derivatives. However, *N*3-benzyloxymethyl (BOM) protected thymine **8f** is a good alternative, leading to high overall yields and an improved *N*1-selectivity. Benzoylated derivatives **8b** and **8e** gave regioselectivities comparable to prototype **8a**. A surprising effect can be seen from the two dimethylated Bz groups. While 2,6-dimethylbenzoyl-protected thymine led exclusively to O^2-alkylation, the 3,5-dimethylbenzoyl counterpart showed a strong preference for the *N*1-product. Although the reason for this detrimental effect remains unclear, this offers

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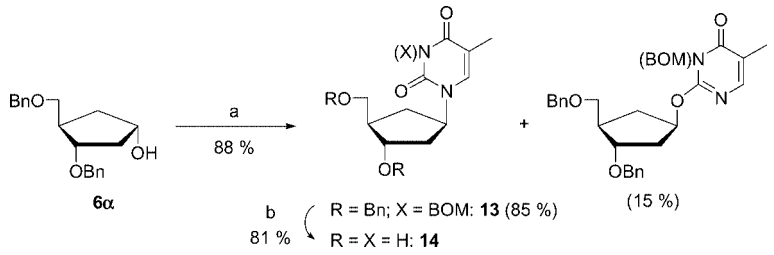

Scheme 4. Application of the *N*3-BOM method to the synthesis of *carba*-dT. (a) PPh_3, DIAD, *N*3-(benzyloxymethyl)thymine (**8f**), CH_3CN, –40 °C to room temp., 16 h.

an elegant and selective access to the O^2-analogues of carbocyclic pyrimidine nucleosides.

To verify and use the above observations, enantiomerically pure (1*S*,3*S*,4*R*)-3-(benzyloxy)-4-(benzyloxymethyl)-cyclopentanol (**6α**), a precursor for carbocyclic 2′-deoxynucleoside analogues, was condensed to *N*3-(benzyloxymethyl)thymine (**8f**) in CH_3CN according to our modified Mitsunobu protocol (Scheme 4).

The products were isolated as a mixture of $N1/O^2$-isomers in a 85:15 ratio The ratio is noticeably better than the ratio observed when *N*-Bz-thymine was used (66:34 in THF). Consequently, *N*3-BOM-thymine should be used as nucleophile, when alkylation at the *N*1-position of thymine is wanted. The fully blocked intermediate **13** was deprotected in one step by hydrogenolysis in ethanol leading to enantiomerically pure *carba*-dT (**14**), a useful starting material for 3′-modified carbocyclic nucleosides.[12] The second important result from our study is that by using (2,6-dimethylbenzoyl)thymine O^2-analogues of carbocyclic pyrimidine nucleosides are exclusively available. Thus, with the help of the protecting group the reaction can be fine-tuned to yield the *N*1- or the O^2-analogues.

Experimental Section

General: All experiments involving water-sensitive compounds were conducted under scrupulously dry conditions (nitrogen) using standard syringe, cannula and septum techniques. Solvents: THF was distilled from sodium or potassium/benzophenone and stored over molecular sieves. Dichloromethane and CH_3CN were distilled from CaH_2 and stored over molecular sieves. Ethyl acetate, dichloromethane, and methanol employed in chromatography were distilled before used. Chromatography: Chromatotron (Harrison Research 7924), silica gel 60_{Pf} (Merck, "gipshaltig"). UV detection at 254 nm. TLC: analytical thin layer chromatography was performed on Merck precoated 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 acetic acid) by heating with a fan or a hot plate. NMR spectra were recorded using Bruker WM 400 at 400 MHz or Bruker AMX 400 at 400 MHz (^{1}H NMR); Bruker WM 400 at 101 MHz or Bruker AMX 400 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, $(CD_3)(CD_2H)SO$ being set at δ_H = 2.49 ppm as a reference. The spectra were recorded at room temperature, 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, *m*-nitrobenzyl alcohol as matrix).

General Procedure for the Benzoylation of Thymine: A stirred suspension of thymine (1.0 equiv.) in CH_3CN and pyridine (4.5 equiv.) was slowly treated with benzoyl chloride (2.1 equiv.) at 0 °C under nitrogen and stirred at room temperature for 2 d. Methanol was added to the mixture (0.1 mL/mmol of benzoyl chloride) and stirring was continued at room temperature for 1 h. Volatiles were evaporated in vacuo and the crude was reconcentrated three times from toluene. The residue was purified on silica gel (CH_2Cl_2/MeOH, 20:1) to yield the *N*3-benzoylated thymine derivatives **8b**–**e** as colourless solids.

***N*3-(3,5-Dimethylbenzoyl)thymine (8b):** The reaction was carried out according to the described general procedure with thymine (1.00 g, 7.93 mmol) in anhydrous CH_3CN (12 mL), pyridine (4.0 mL), 3,5-dimethylbenzoyl chloride (2.90 g, 17.4 mmol) and MeOH (1.5 mL). Yield: 1.40 g (69%); m.p. 250–252 °C; R_f (TLC) = 0.30 (CH_2Cl_2/MeOH, 30:1). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.35 (br. s, 1 H, N*H*); 7.57 (s, 2 H, C*H*-arom.-*o*); 7.55 (q, ^4J = 1.0 Hz, 1 H, 6-H); 7.43 (s, 1 H, C*H*-arom.-*p*); 2.38 (s, 6 H, 3,5-CH_3); 1.85 (d, ^4J = 1.0 Hz, 3 H, 7-H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 170.6 (Ph–CO); 163.3 (C-4); 150.3 (C-2); 139.2 (6-C); 139.0 (C-1 arom.); 137.1 (C-4 arom.); 131.9 (C-3 arom.); 128.1 (C-2 arom.); 108.2 (C-5); 20.9 (3-*C*H$_3$); 12.1 (C-7) ppm. IR (KBr): $\tilde{\nu}$ = 3215, 3170, 2960, 2925, 1740, 1715, 1650, 1485, 1410, 1380, 1300, 1220, 1180, 1160, 1045, 860, 805, 780, 750, 725, 675, 575, 480 cm^{-1}. MS-FAB: *m*/*z* calcd. for $C_{14}H_{15}N_2O_3$ [M + H]$^+$ 259.1; found 259.2.

***N*3-(2,6-Dimethylbenzoyl)thymine (8c):** The reaction was carried out according to the described general procedure with thymine (750 mg, 5.95 mmol) in anhydrous CH_3CN (10 mL), pyridine (3.0 mL), 2,6-dimethylbenzoyl chloride (2.20 g, 13.0 mmol) and MeOH (1.0 mL). Yield: 1.11 g (72%); m.p. 183–185 °C; R_f (TLC) = 0.29 (CH_2Cl_2/MeOH, 30:1). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.60 (br. s, 1 H, N*H*); 8.22 (q, ^4J = 1.0 Hz, 1 H, 6-H); 7.24 (t, ^3J = 7.5 Hz, 1 H, C*H*-arom.-*p*); 7.09 (d, ^3J = 7.5 Hz, 2 H, C*H*-arom.-*m*); 2.17 (s, 6 H, 2-CH_3); 1.94 (d, ^4J = 1.0 Hz, 3 H, 7-H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 169.5 (Ph–CO); 164.1 (C-4); 148.6 (C-2); 137.3 (C-1 arom.); 133.1 (C-6); 132.8 (C-2 arom.); 129.1 (C-4 arom.); 127.6 (C-3 arom.); 113.7 (C-5); 19.2 (2,6-*C*H$_3$); 12.5 (C-7) ppm. IR (KBr): $\tilde{\nu}$ = 3435, 3040, 2840, 1740, 1680, 1460, 1420, 1385, 1345, 1270, 1205, 1105, 1080, 945, 890, 785, 760, 625, 585, 540, 430 cm^{-1}. MS-FAB: *m*/*z* calcd. for $C_{14}H_{15}N_2O_3$ [M + H]$^+$ 259.1; found 259.2.

***N*3-(3,5-Dinitrobenzoyl)thymine (8d):** The reaction was carried out according to the described general procedure with thymine (1.00 g, 7.93 mmol) in anhydrous CH_3CN (12 mL), pyridine (4.0 mL), 3,5-dinitrobenzoyl chloride (4.00 g, 17.4 mmol) and MeOH (1.5 mL).

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Yield: 650 mg (25%); R_f (TLC) = 0.32 (CH_2Cl_2/MeOH, 30:1). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.40 (br. s, 1 H, N*H*); 8.99 (s, 1 H, C*H*-arom.); 8.91 (s, 2 H, C*H*-arom.); 7.54 (q, ^4J = 1.2 Hz, 1 H, 6-H); 1.78 (d, ^4J = 1.2 Hz, 3 H, 7-H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 168.7 (Ph–CO); 164.0 (C-4); 150.3 (C-2); 149.4 (C-3 arom.); 139.6 (C-6); 134.5 (C-1 arom.); 129.7 (C-2 arom.); 124.3 (C-4 arom.); 108.5 (C-5); 12.1 (C-7) ppm.

***N*3-(4-Chlorobenzoyl)thymine (8e):** The reaction was carried out according to the described general procedure with thymine (2.00 g, 15.8 mmol) in anhydrous CH_3CN (20 mL), pyridine (8.0 mL), 4-chlorobenzoyl chloride (6.08 g, 34.8 mmol) and MeOH (3.5 mL). Yield: 3.99 g (95%); m.p. 198–200 °C; R_f (TLC) = 0.35 (CH_2Cl_2/MeOH, 30:1). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.28 (br. s, 1 H, N*H*); 7.96 (d, ^3J = 7.5 Hz, 2 H, C*H*-arom.); 7.65 (d, ^3J = 7.5 Hz, 2 H, C*H*-arom.); 7.54 (q, ^4J = 1.0 Hz, 1 H, 6-H); 1.83 (d, ^4J = 1.0 Hz, 3 H, 7-H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 169.8 (Ph–*C*O); 163.9 (C-4); 150.2 (C-2); 140.8 (C-4 arom.); 139.2 (C-6); 132.4 (C-2 arom., C-6 arom.); 130.6 (C-1 arom.); 129.9 (C-3 arom., C-5 arom.); 108.3 (C-5); 12.0 (C-7) ppm. IR (KBr): $\tilde{\nu}$ = 3250, 3090, 1750, 1710, 1670, 1590, 1490, 1415, 1400, 1255, 1210, 1090, 970, 850, 835, 770, 480 cm^{-1}. MS-FAB: *m*/*z* calcd. for $C_{12}H_{10}ClN_2O_3$ [M + H]$^+$ 265.038; found 265.038.

***N*3-(Benzyloxymethyl)thymine (8f):** To a suspension of thymine (2.50 g, 19.8 mmol) and DMAP (25.0 mg) in anhydrous CH_3CN (100 mL) was added di-*tert*-butyl dicarbonate (Boc_2O, 4.50 g, 20.6 mmol) at 0 °C under nitrogen. The mixture was warmed to room temperature and stirred for 4 h, until conversion was complete according to TLC. The solvent was evaporated under reduced pressure and the residue was dissolved in DMF (100 mL) and cooled to 0 °C. Sodium hydride (1.15 g, 24.0 mmol, 50% in oil) was added in portions and the mixture was stirred at 0 °C under nitrogen for 0.5 h. For the alkylation, benzyl chloromethyl ether (BOM-Cl, 3.3 mL, 24 mmol) was added at 0 °C. The mixture was slowly warmed to room temperature, stirred for 1 h and poured into ice-cold water (200 mL). The aqueous phase was extracted with EtOAc (3 × 100 mL) and the combined organic phases were dried with Na_2SO_4 and concentrated. The crude mixture was dissolved in methanol (200 mL) and K_2CO_3 (1.00 g, 7.24 mmol) was added. After stirring at room temperature for 2 h, the reaction was complete according to TLC. The solvent was evaporated in vacuo and the residue was dissolved in CH_2Cl_2 (200 mL) and washed with satd. aqueous NH_4Cl solution. The organic phase was dried with Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 20:1) to yield the title compound **8f** (3.10 g, 64%) as a colourless solid; m.p. 127 °C; R_f (TLC) = 0.35 (CH_2Cl_2/MeOH, 30:1). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.25 (br. s, 1 H, N*H*); 7.45–7.35 (m, 6 H, C*H*-arom., 6-H); 5.52 (s, 2 H, O–CH_2–N); 4.70 (s, 2 H, CH_2-benzyl); 1.88 (d, ^4J = 1.2 Hz, 3 H, 7-H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 164.2 (C-4); 151.8 (C-2); 138.5 (C$_q$ arom.); 137.5 (C-6); 128.5, 127.8, 127.7 (*C*H-arom.); 107.7 (C-5); 71.3 (O–*C*H$_2$–N); 69.8 (*C*H$_2$-benzyl); 12.7 (C-7) ppm. IR (KBr): $\tilde{\nu}$ = 3220, 3175, 3060, 2930, 1725, 1650, 1585, 1500, 1450, 1380, 1230, 1130, 1110, 1080, 950, 805, 770, 730, 710, 695, 560, 470, 430 cm^{-1}. MS-FAB: *m*/*z* calcd. for $C_{13}H_{15}N_2O_3$ [M + H]$^+$ 247.1; found 247.2.

General Procedure for the Coupling of *N*3-Protected Pyrimidines to Cyclopentanols: To a suspension of triphenylphosphane (787 mg, 3.00 mmol) in dry solvent (THF or CH_3CN, 11 mL), diisopropyl azodicarboxylate (DIAD, 545 µL, 2.80 mmol) was added slowly and the solution was stirred at 0 °C for 0.5 h. This preformed complex was slowly added to a suspension of the protected thymine **8a**–**f** (2.2 mmol) and cyclopentanol (312 mg, 1.00 mmol) in dry solvent (THF or CH_3CN, 6.0 mL) at –40 °C under nitrogen. The reaction mixture was slowly warmed to room temperature and stirred overnight. The solvent was removed from the reaction mixture and an NaOH solution in MeOH (1%, 15 mL) was added and the mixture stirred at room temperature overnight. The solution was neutralized by addition of 1 M HCl and then concentrated. The crude product was purified on silica gel (hexanes/EtOAc, 1:2) to yield the product as a mixture of *N*1- (**11**) and O^2-isomers (**12**) as a colourless syrup. For **8f** the deprotection step was omitted.

Cyclopentylthymine 11: R_f (TLC) = 0.25 (hexanes/EtOAc, 1:2). ^{1}HNMR (400 MHz, [D$_6$]DMSO): δ = 11.20 (br. s, 1 H, N*H*); 7.56 (q, ^4J = 1.2 Hz, 1 H, 6-H); 4.80–4.72 (m, 1 H, 1′-H); 2.00–1.90 (m, 2 H, 2′a-H, 5′a-H); 1.82 (d, ^4J = 1.2 Hz, 3 H, 7-H); 1.80–1.55 (m, 6 H, 2′b-H-, 5′b-H-, 3′-CH_2, 4′-CH_2) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 164.2 (C-4); 152.3 (C-2); 137.4 (C-6); 111.2 (C-5); 56.0 (C-1′); 32.9 (C-2′, C-5′); 25.3 (C-3′, C-4′); 12.8 (C-7) ppm. IR (KBr): $\tilde{\nu}$ = 3175, 3040, 2960, 2875, 1690, 1475, 1415, 1370, 1370, 1320, 1270, 1120, 920, 585, 425 cm^{-1}. HRMS-FAB: *m*/*z* calcd. for $C_{10}H_{15}N_2O_2$ [M + H]$^+$ 195.1134; found 195.1131.

***O*^{2}-Cyclopentylthymine (12):** R_f (TLC) = 0.35 (hexanes/EtOAc, 1:2). ^{1}HNMR (400 MHz, [D$_6$]DMSO): δ = 12.10 (br. s, 1 H, N*H*); 7.60 (q, ^4J = 1.0 Hz, 1 H, 6-H); 5.38–5.30 (m, 1 H, 1′-H); 2.00–1.90 (m, 2 H, 2′a-H, 5′a-H); 1.88 (d, ^4J = 1.0 Hz, 3 H, 7-H); 1.80–1.55 (m, 6 H, 2′b-H, 5′b-H, 3′-CH_2, 4′-CH_2) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 164.2 (C-4); 157.1 (C-2); 151.4 (C-6); 118.4 (C-5); 80.1 (C-1′); 33.7 (C-2′, C-5′); 24.9 (C-3′, C-4′); 12.9 (C-7) ppm. IR (KBr): $\tilde{\nu}$ = 2960, 1650, 1580, 1500, 1380, 1330, 1160, 1040, 955, 920, 770, 750, 590 cm^{-1}. HRMS-FAB: *m*/*z* calcd. for $C_{10}H_{15}N_2O_2$ [M + H]$^+$ 195.1134; found 195.1128.

1-(6′-Carba-2′-deoxy-β-D-*erythro*-pentofuranosyl)thymine (*carba*-dT) (14): The reaction was carried out according to the general procedure with triphenylphosphane (787 mg, 3.00 mmol) in anhydrous CH_3CN (11 mL), DIAD (545 µL, 2.80 mmol), cyclopentanol **6α** (312 mg, 1.00 mmol) and *N*3-BOM-thymine (**8f**) (542 mg, 2.20 mmol) in anhydrous CH_3CN (6.0 mL). After removal of the solvent, the crude mixture was purified on silica gel (hexanes/EtOAc, 1:1) to yield the protected carbocyclic nucleoside **13** (405 mg, 75%) as a light yellow syrup; R_f (TLC) = 0.66 (hexanes/EtOAc, 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.20 (m, 15 H, C*H*-arom.); 6.97 (q, ^4J = 1.0 Hz, 1 H, 6-H); 5.43 (s, 2 H, O–CH_2–N); 5.13–5.05 (m, 1 H, 1′-H); 4.64 (s, 2 H, CH_2-benzyl); 4.48–4.38 (m, 4 H, CH_2-benzyl, CH_2-benzyl-C); 3.95–3.90 (m, 1 H, 3′-H); 3.52 (dd, ^3J = 9.2 Hz, 4.3 Hz, 1 H, 5′a-H); 3.47 (dd, ^3J = 9.2 Hz, 4.7 Hz, 1 H, 5′b-H); 2.36–2.30 (m, 1 H, 4′-H); 2.27–2.20 (m, 1 H, 6′a-H); 2.13–2.08 (m, 1 H, 2′a-H); 1.89–1.80 (m, 1 H, 2′b-H); 1.73 (d, ^4J = 1.0 Hz, 3 H, 7-H); 1.57–1.52 (m, 1 H, 6′b-H) ppm. The benzylated nucleoside **13** was subsequently dissolved in EtOH (25 mL) and Pd/C (10%, 50 mg) was added. This mixture was stirred under hydrogen at room temperature until complete conversion was observed by TLC. The reaction mixture was filtered through Celite and washed with MeOH. The filtrate was concentrated and the residue was purified by chromatography on a chromatotron (CH_2Cl_2/MeOH gradient 0–20%) to yield the carbocyclic nucleoside **14** (145 mg, 81%) as colourless foam. After lyophilization (CH_3CN/H_2O, 1:1) the target compound **14** was obtained as colourless solid; R_f (TLC) = 0.12 (CH_2Cl_2/MeOH, 9:1); $[\alpha]_D^{20}$ = +7.5 (c = 0.37, H_2O) {ref.[5] $[\alpha]_D^{20}$ = +8.9 (c = 1.0, methanol)}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.20 (s, 1 H, N*H*); 7.57 (q, ^4J = 1.0 Hz, 1 H, 6-H); 5.02–4.96 (m, 1 H, 1′-H); 4.73 (d, ^3J = 4.5 Hz, 1 H, 3′-O*H*); 4.61 (t, ^3J = 5.2 Hz, 1 H, 5′-O*H*); 4.03–3.98 (m, 1 H, 3′-H); 3.53 (ddd, 1 H, ^2J = 10.6 Hz, ^3J = 5.5 Hz, 5.2 Hz, 1 H, 5′a-H); 3.43 (ddd, ^2J = 10.6 Hz, ^3J = 5.7 Hz, 5.2 Hz, 1 H, 5′b-H); 2.11–

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2.04 (m, 1 H, H-6′a-H); 1.99–1.89 (m, 2 H, 4′-H, 2′a-H); 1.82 (d, ^4J = 1.0 Hz, 3 H, 7-H); 1.82–1.74 (m, 1 H, 2′b-H); 1.45–1.37 (m, 1 H, 6′b-H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 164.1 (C-4); 151.3 (C-2); 138.1 (C-6); 109.4 (C-5); 71.7 (C-3′); 63.0 (C-5′); 53.6 (C-1′); 49.3 (C-4′); 36.3 (C-2′); 32.7 (C-6′); 12.4 (C-7) ppm. IR (KBr): $\tilde{\nu}$ = 3425, 3025, 1680, 1475, 1420, 1390, 1290, 1265, 1050 cm^{-1}. HRMS-FAB: *m/z* calcd. for $C_{11}H_{17}N_2O_4$ $[M + H]^+$ 241.1188; found 241.1195.

[1] O. R. Ludek, C. Meier, *Synlett*, in press.

[2] For selected reviews, see: a) E. De Clercq, *Ann. N. Y. Acad. Sci.* **1994**, 438–456; b) V. Nair, T. S. Jahnke, *Antimicrob. Agents Chemother.* **1995**, *39*, 1017–1029; c) L. J. Wilson, M. W. Hager, Y. A. El-Kattan, D. C. Liotta, *Synthesis* **1995**, 1465–1479; d) S. Pan, N. M. Amankulor, K. Zhao, *Tetrahedron* **1998**, *54*, 6587–6604; e) C. K. Chu, *Nucleic Acids Symp. Ser.* **1996**, *35*, 1–22.

[3] a) V. E. Marquez, in: *"Advances in antiviral drug design"* (Ed.: E. De Clercq), JAI Press, Greenwich **1996**, vol. *2*, p. 89–146; L. A. Agrofoglio, S. R. Challand, *Acyclic, Carbocyclic and L-Nucleosides*, Kluwer Academic Publishers, Dordrecht, Boston, London, **1998**.

[4] V. E. Marquez, A. Ezzitouni, P. Russ, M. A. Siddiqui, H. Ford, R. J. Feldman, H. Mitsuja, C. George, J. J. Barchi, *J. Am. Chem. Soc.* **1998**, *120*, 2780–2789.

[5] J. Béres, G. Sági, I. Tömösközi, L. Gruber, E. Baitz-Gács, L. Ötvos, E. De Clercq, *J. Med. Chem.* **1990**, *33*, 1353–1360.

[6] R. Vince, M. Hua, *J. Med. Chem.* **1990**, *33*, 17–21.

[7] S. M. Daluge, M. T. Martin, B. R. Sickles, D. A. Livingston, *Nucleosides, Nucleotides Nucleic Acids* **2000**, *19*, 297–327.

[8] G. S. Bisacchi, S. T. Chao, C. Bachard, J. P. Daris, S. Innaimo, G. A. Jacobs, O. Kocy, P. Lapointe, A. Martel, Z. Merchant, W. A. Slusarchyk, J. E. Sundeen, M. G. Young, R. Colonno, R. Zahler, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 127–130.

[9] a) J. Balzarini, H. Baumgartner, M. Bodenteich, E. De Clercq, H. Griengl, *J. Med. Chem.* **1989**, *32*, 1861–1865; b) P. G. Wyatt, A. S. Anslow, B. A. Coomber, R. P. C. Cousins, D. N. Evans, V. S. Gilbert, D. C. Humber, I. L. Paternoster, S. L. Sollis, D. J. Tapolczay, G. G. Weingarten, *Nucleosides Nucleotides* **1995**, *14*, 2039–2049.

[10] a) A. D. Borthwick, K. Biggadike, *Tetrahedron* **1992**, *48*, 571–623; b) L. Agrofoglio, E. Suhas, A. Farese, R. Condom, S. R. Challand, R. A. Earl, R. Guedj, *Tetrahedron* **1994**, *50*, 10611–10670; c) M. T. Crimmins, *Tetrahedron* **1998**, *54*, 9229–9272.

[11] O. R. Ludek, C. Meier, *Synthesis* **2003**, *13*, 2101–2109.

[12] O. R. Ludek, J. Balzarini, C. Meier, *Eur. J. Org. Chem.*, in press.

[13] O. R. Ludek, J. Balzarini, T. Krämer, C. Meier, *Synthesis*, in press.

[14] a) T. F. Jenny, N. Previsani, S. A. Benner, *Tetrahedron Lett.* **1991**, *32*, 7029–7032; b) T. F. Jenny, J. Horlacher, N. Previsani, S. A. Benner, *Helv. Chim. Acta* **1992**, *75*, 1944–1954; c) C. Bonnal, C. Chavis, M. Lucas, *J. Chem. Soc., Perkin Trans. 1* **1994**, 1401–1410; d) M. J. Pérez-Pérez, J. Rozenski, R. Busson, P. Herdewijn, *J. Org. Chem.* **1995**, *60*, 1531–1537; e) A. D. Borthwick, A. J. Crame, A. M. Exall, G. G. Weingarten, M. Mahmoudian, *Tetrahedron Lett.* **1995**, *36*, 6929–6932; f) L. Schmitt, C. A. Caperelli, *Nucleosides Nucleotides* **1997**, *16*, 2165–2192; g) H. Choo, Y. Chong, C. K. Chu, *Org. Lett.* **2001**, *3*, 1471–1473.

[15] O. R. Ludek, C. Meier, *Synlett*, in press.

[16] Y. Chong, G. Gumina, C. K. Chu, *Tetrahedron: Asymmetry* **2000**, *11*, 4853–4875.

[17] C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed., VCH Verlagsgesellschaft GmbH, Weinheim, **1988**.

[18] K. A. Cruickshank, J. Jiricny, C. B. Reese, *Tetrahedron Lett.* **1984**, *25*, 681–684.

[19] O. R. Ludek, C. Meier, *Nucleosides, Nucleotides Nucleic Acids* **2003**, *22*, 683–685.

[20] S. Hanessian, *Trends Synth. Carbohydr. Chem., ACS Symp. Ser.* **1989**, *386*, 64–85.

[21] L. Schmitt, C. A. Caperelli, *Nucleosides Nucleotides* **1997**, *16*, 2165–2192.

[22] S. Jaime-Figeroa, A. Zanilpa, A. Guzman, D. J. Morgans, Jr., *Synth. Commun.* **2001**, *31*, 3739–3746.

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