New Convergent Synthesis of Carbocyclic Nucleoside Analogues

Olaf R. Ludek, Chris Meier*

Institut für Organische Chemie, Universität Hamburg, Martin-Luther-King-Platz 6, 20146 Hamburg, Germany
Fax +49(40)428382495; E-mail: chris.meier@chemie.uni-hamburg.de

Received 8 July 2003

Abstract: Two convergent approaches towards the synthesis of carbocyclic nucleoside analogs will be described. Both approaches start from the stereochemically pure cyclopentenol **8** that has been prepared enantioselectively from an alkylated cyclopentadiene. Using these approaches, carbocyclic analogues of dT, FdU and BVdU have been prepared. Moreover, the conversion into the *cyclo*Sal-pronucleotide and the corresponding nucleotide will be presented for one example.

Keywords: carbocyclic nucleosides, stereoselective synthesis, Mitsunobu reaction, *cyclo*Sal-pronucleotides, nucleotides

Recently carbocyclic nucleosides have been the focus of much attention in the development of new antitumor and antiviral therapeutic agents.[1] The bioactivity of the naturally occurring carbocyclic nucleosides (–)-aristeromycin (**1**)[2] and (–)-neplanocin A (**2**),[3] led to an interest in this class of compounds, resulting in the generation of a diverse range of antiviral carbocyclic nucleosides[4] such as Carbovir (**3**),[5] Abacavir (Ziagen™, **4**),[6] Lobucavir (**5**),[7] and more recently BMS-200475 (**6**).[8] Beside carbocyclic purine analogs, an example of a bioactive pyrimidine analog is *carba*-BVdU (**7**) that showed anti-HSV-1 activity (Figure 1).[9,10]

Carbocyclic nucleosides, in which the D-ribose moiety of the nucleoside is replaced by a cyclopentane system, are stable towards hydrolysis by phosphorylases and consequently display enhanced biostability.[11] In addition, the replacement of the oxygen of furanose by a methylene group results also in reduced toxicity of the carbocyclic nucleosides.[12]

Carbocyclic nucleosides are synthetically the most challenging class of nucleosides, requiring multi-step and often elaborate syntheses to introduce the necessary stereochemistry. Different synthetic approaches have been reviewed.[1a]

In our search for a convenient convergent synthesis towards carbocyclic 2′-deoxynucleoside analogues, we decided to start with (1*S*,2*R*)-2-benzyloxymethylcyclopent-3-enol (**8**) which has been described by Biggadike et al.[13] The preparation of the enol **8** starts from cyclopentadiene (**9**) that was first deprotonated (NaH) and alkylated using benzylchloromethylether to give cyclopentadiene **10** (Scheme 1).

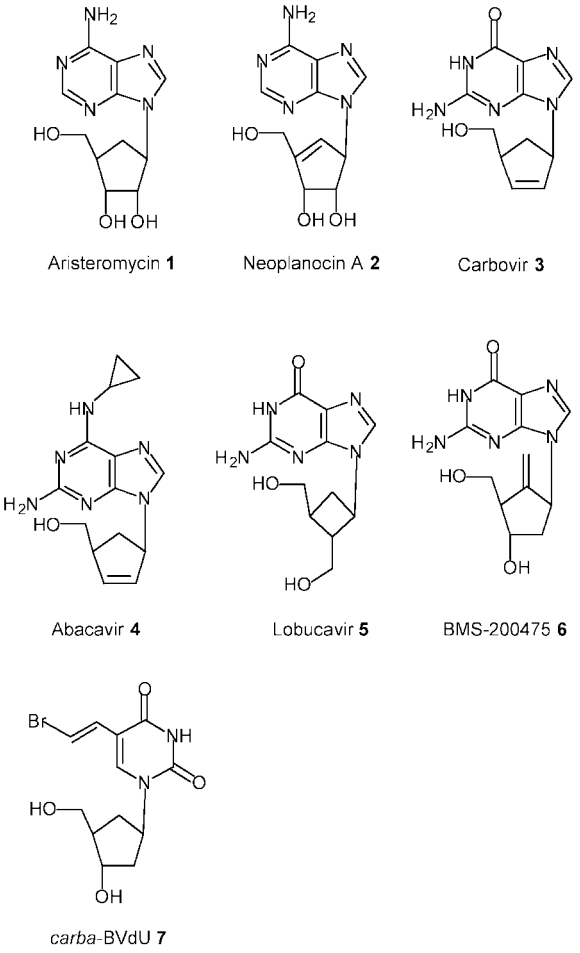
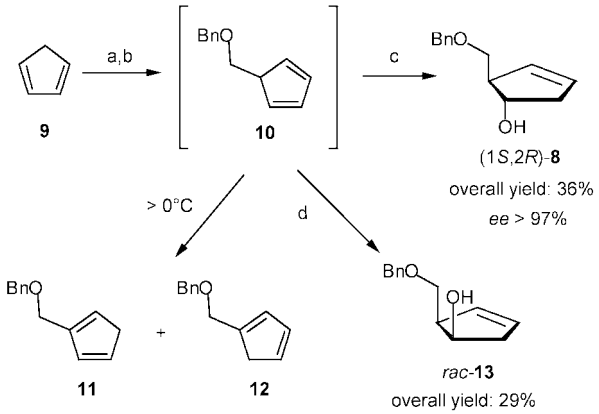


Figure 1

Detailed experiments showed that intermediate **10** isomerizes to yield two thermodynamically more stable cyclopentadiene derivatives **11** and **12** at temperatures above 0 °C. Moreover, higher temperatures and concentrated solutions favor the formation of Diels–Alder products. Therefore, diluted solutions and temperatures between –60 °C and 0 °C were used in the alkylation reaction. Consequently, the following stereoselective hydroboration has also to be carried out at temperatures below 0 °C and intermediate **10** was immediately converted into the chiral, non-racemic cyclopentenol **8** using (–)-diisopinocampheylborane. The chemical yield was 36% (four steps), the relative configuration was proven by NOE-spectroscopy and the optical purity of the cyclopentenol **8** was > 96%ee (chiral GC on a modified cyclodextrine column or ^{31}P NMR after transformation into diastereomers using the Anderson–Shapiro reagent).[14]

SYNTHESIS 2003, No. 13, pp 2101–2109
Advanced online publication: 10.09.2003
DOI: 10.1055/s-2003-41455; Art ID: E09503ss.pdf



Scheme 1 Reagents and Conditions: (a) NaH, THF, 0 °C, 0.5 h (b) Benzylchloromethylether, THF, –60 °C, 2 h (c) $(ipc)_2BH$, THF, –60 °C, 1 h, then 0 °C, 16 h, 3 N NaOH, 30% H_2O_2, 0 °C, 12 h (d) BH_3, THF, –60 °C, 1 h, then 0 °C, 16 h, 3 N NaOH, 30% H_2O_2, 0 °C, 12 h.

From model reactions with cyclopentadiene it became apparent that the hydroboration has to be performed in a very concentrated solution in order to increase the chemical yields. Therefore, the solvent THF was nearly completely evaporated in high vacuum at –10 °C after alkylation. Interestingly, attempts to prepare the racemic mixture of **10** using the borane·THF adduct were unsuccessful. However, the racemic mixture of the corresponding stereoisomer **13** with *cis*-configuration of the two substituents was formed instead (Scheme 1). A possible explanation of this unexpected result may be a complexation of the borane to the oxygen atom of the benzyloxy side chain of **10** and thus the borane can only add to the double bond from that side without stereospecificity (substrate directed reaction). However, compound **13** offers new perspectives as a starting material in the synthesis of carbocyclic nucleoside analogs after separation into its enantiomers, e.g. for the synthesis of *carba*-nucleosides with deoxy-*xylo*-configuration (results not shown).

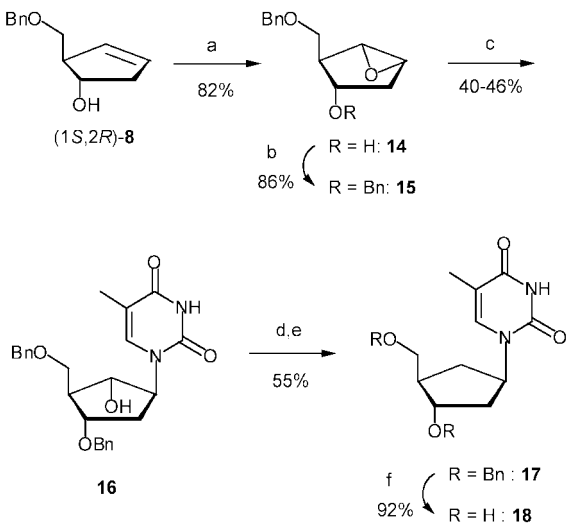
Then, cyclopentenol **8** was converted into epoxide **14** by *t*-butylhydroperoxide in the presence of $Mo(CO)_6$ which led to a stereoselective introduction of the epoxide from the *si*,*re*-face.[15] After benzylation (NaH, benzylbromide and tetrabutylammonium iodide), epoxide **15** was regioselectively opened with the sodium or lithium salt of thymine with introduction of the heterocycle at the C1′-position leading to the carbocyclic thymidine derivative **16** (Scheme 2).[16]

No difference in the chemical yield (40% and 42%, respectively) was found for the two salts, which have been formed from thymine in the presence of sodium or lithium hydride. Alternatively, the epoxide activation was carried out by the addition of triethylaluminium in THF and ultrasonification at room temperature.[17] After two days, 46% of the target thymidine analog **16** had formed. The correct stereochemistry at C1′ was proven by NOE-spectroscopy. It was unequivocally shown that only the desired N1-product and no N3-coupling product formed (HMBC-NMR). Subsequently, a Barton–McCombie deoxygen-

Biographical Sketches

Olaf R. Ludek was born in 1973 in Hamburg, Germany. He received his diploma degree in chemistry at the University of Hamburg (2001) and is currently working on his PhD thesis at the University of Hamburg under the guidance of Prof. Dr. Chris Meier.

Chris Meier was born in 1962 in Berlin, Germany. He studied Chemistry at the University of Marburg-Lahn, where he received his diploma degree in 1987 and his PhD degree in 1989 with Prof. G. Boche. During that time he became interested in bioorganic chemistry. During his postdoctoral studies at the Pasteur-Institute in Paris, France he got involved in the chemistry of nucleosides, oligonucleotides, and prodrugs. In 1991 he returned to the University of Frankfurt-Main and finished his habilitation in 1996. In 1994 he received the Adolf-Messer-Award for interdisciplinary research. In 1997 he became Associate Professor of Organic Chemistry at the University of Würzburg and 1999 he moved to the University of Hamburg as a Full Professor of Organic Chemistry. His research interests are pronucleotide design for antiviral nucleoside analogues, stereoselective synthesis of carbocyclic nucleoside analogues, antisense oligonucleotides, DNA-damage induced by arylamine carcinogens, and new syntheses of activated sugar-nucleotides.



Scheme 2 Reagents and Conditions: (a) $Mo(CO)_6$, *t*-BuOOH, benzene, 80 °C, 3 h (b) NaH, BnBr, TBAI, THF, r.t. 12 h (c) Thymine, LiH, DMF, 140 °C, 3 d or NaH, DMF, 140 °C, 3 d or Et_3Al, THF, r.t., ultrasound, 12 h (d) PTC-Cl, pyridine, DMAP, r.t, 16 h (e) AIBN, Bu_3SnH, toluene, 3.5 h (f) $FeCl_3$, CH_2Cl_2, 0 °C, 2 h

ation using phenoxythiocarbonyl chloride[18] and tri-*n*-butylstannane gave protected *carba*-dT **17** in 72% yield. Finally, both benzyl protecting groups were cleaved by treatment of **17** with $FeCl_3$[15,19] in CH_2Cl_2 at 0 °C to give *carba*-dT **18** in 92% yield (Scheme 2). Starting from *carba*-dT **18**, further modifications in the cyclopentane ring are possible, e.g. elimination to *carba*-d4T, deoxygenation to *carba*-ddT and substitution of the 3′-hydroxyl group.

Alternatively, key intermediate **8** was fully protected by benzylation to yield cyclopentene **19** with *trans*-configuration of the two substituents in 92% yield. Then, compound **19** was reacted with a variety of hydroboration agents[20] (Table 1).

The reaction using 9-BBN led to the formation of only two of the four possible products. Only cyclopentenols **20** were obtained in 91% yield. The ratio of **20β**:**20α** was 85:15 in favor of the *R*-configured **20β** at C1′ after oxidative work-up. Although the yield was slightly lower (90%), the use of dicyclohexylborane gave also predominately product **20β** (75:25 ratio). Interestingly, the chiral (–)-diisopinocampheylborane gave no reaction at all, while the (+)-enantiomer led for the first time to the formation of the *trans*,*trans*-regioisomer **21α** in 42% yield. Moreover, a diastereomeric mixture of the C1′-alcohol **20α**/**β** was isolated after oxymercuration[21] with $Hg[OC(O)CF_3]_2$ in 74% yield (Table 1). Interestingly, none of the reagents led to the formation of the *cis*,*trans*-isomer **21β**.

Table 1 Reaction of Cyclopentene 19 with Different Hydroxylation Agents

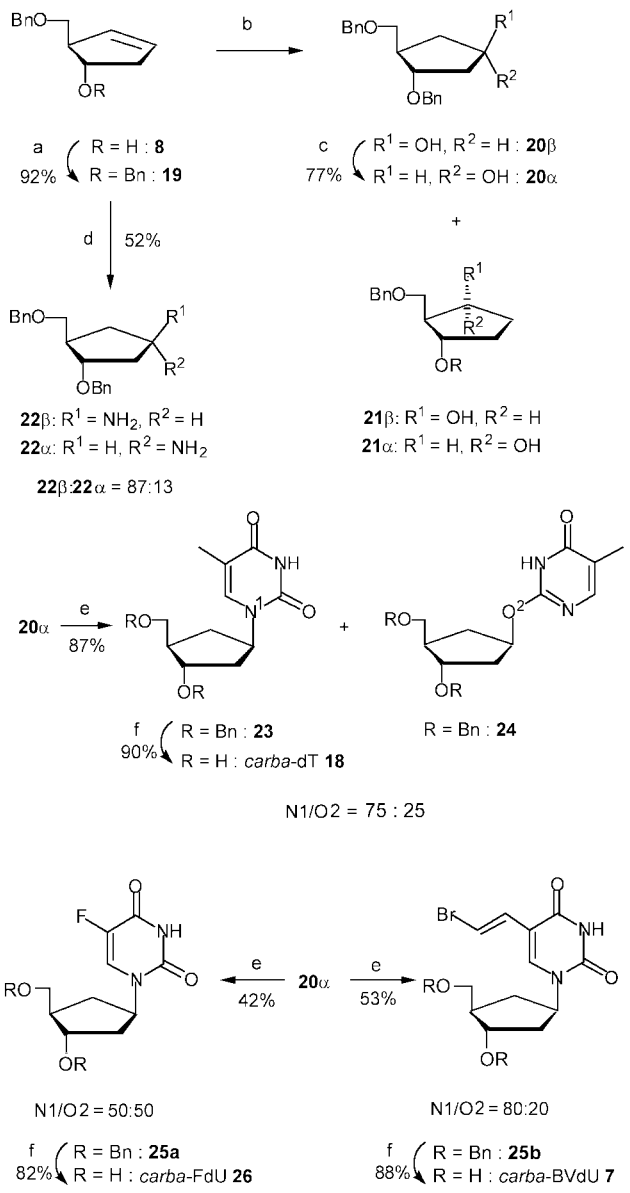
Method	Hydroxylation Agent	Products	Yield[a]	Product Distribution[b]
a	9-BBN, H_2O_2–NaOH	**20α** + **20β**	91%	**20β**: 85%; **20α**: 15%
b	(–)-$(ipc)_2BH$, H_2O_2–NaOH	—	—	—
c	(+)-$(ipc)_2BH$, H_2O_2–NaOH	**21α**	42%	**21α**: 100%
d	$(C_6H_{11})_2BH$, H_2O_2–NaOH	**20α** + **20β**	90%	**20β**: 75%; **20α**: 25%
e	$Hg(F_3CC(O)O)_2$, H_2O	**20α** + **20β**	74%	**20β**: 50%; **20α**: 50%

[a] Yield of all isolated products.
[b] Determined after chromatography.

Besides the oxidative cleavage of the trialkylborane intermediate, an amino group was selectively introduced. Therefore, the trialkylborane resulted from the 9-BBN reaction with **19** was treated with hydroxylaminesulfonate[22] and the C1′ amino derivative **22** was isolated in a β:α-ratio of 87:13. This intermediate allows the linear synthesis of the heterocyclic ring according to literature procedures (Scheme 3).

However, direct substitution of the hydroxyl group in **20β** would lead to α-configured nucleoside analogs. Thus, Mitsunobu-inversion using triphenylphosphine, DIAD, and benzoic acid[23] followed by deprotection with NaOH in methanol led to diastereomer **20α** in 77% yield. A subsequent Mitsunobu-reaction with PPh_3, DIAD and N3-benzoylthymine[24,25] in THF at –78 °C to room temperature led to the known formation of two regioisomers. Although both products showed complete inversion of configuration at the C1′-atom, the bond is formed via the N1-atom in **23** or via the O2-atom of thymine in **24** in 87% yield. The product ratio was 27:73 (**23**:**24**), respectively. A second attempt using Vilsmeyer's reagent [DMF/$(COCl)_2$] in THF for activating the hydroxyl group and subsequent substitution by deprotonated N3-benzoylthymine.[26]followed by deprotection with NaOH/MeOH led again to the same mixture of regioisomers. However, the ratio was 68:32 (**23**:**24**). The best N1/O2 ratio was achieved by using the Mitsunobu protocol and MeCN as solvent. Here, the ratio was found to be 75:25 (**23**:**24**). Separation of both products was easily achieved by chromatography on silica gel. Finally, the regioisomer **23** was debenzylated by BCl_3 treatment in CH_2Cl_2 to give **18** in 90% yield (Scheme 3).

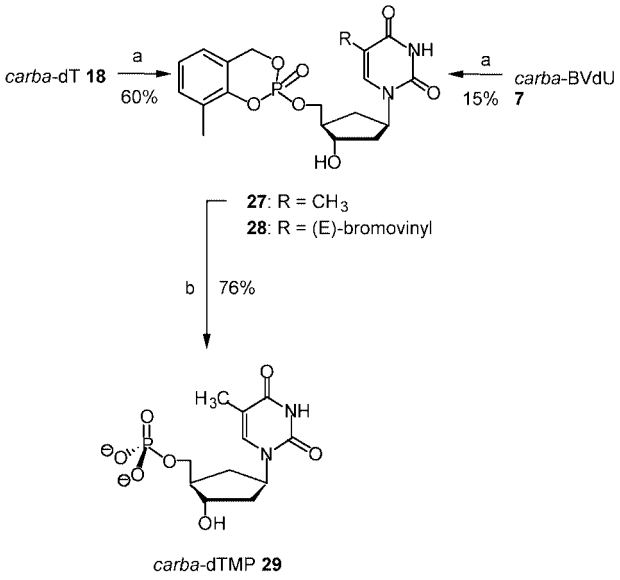
According to the last procedure, further *carba*-nucleoside analogues have been prepared. Introduction of the benzoylated 5-fluorouracil or 5-[(*E*)-bromovinyl]uracil led to the formation of the carbocyclic analogs of the antitumor active nucleoside analog 5-fluorouridine (5-FdU) and of the anti-Herpes active nucleoside 5-[(*E*)-bromovinyl]uridine (BVdU), *carba*-FdU **26** and *carba*-BVdU **7**, respectively. The N1/O^2-ratios were 50:50 in the case of *carba*-FdU **26** and 80:20 for *carba*-BVdU **7** and the yields were found to be 42% and 53% (Scheme 3). The N1/O2-ratio was determined from the ^1H NMR spectra from the unpurified reaction mixtures. Only the N1-product was isolated and used for further reactions.



Scheme 3 Reagents and Conditions: (a) NaH, BnBr, TBAI, THF, r.t. 12 h (b) 9-BBN, THF, r.t, 12 h, 3N NaOH, 30% H_2O_2, 0 °C, 12 h (d) 9-BBN, THF, r.t, 12 h, hydroxylamine-*O*-sulfonic acid, THF, 70 °C, 3 h (e) PPh_3, DIAD, N^3-benzoylpyrimidine, MeCN, –40 °C to r.t, 16 h (f) BCl_3, CH_2Cl_2, 5 h, –78 °C, MeOH, –25 °C to r.t., 12 h

The described synthetic approaches towards carbocyclic nucleoside analogs opens the possibility to study the bioactivity of these nucleoside analogous as well as the corresponding nucleotides after conversion into their membrane-permeable *cyclo*Sal-phosphate triesters.[27]The synthetic access for the conversions of *carba*-dT **18** and *carba*-BVdU **7** into the *cyclo*Sal-triesters **27** and **28**, respectively, are summarized in Scheme 4. *Cyclo*Sal-triesters were obtained in 60% and 15% yield.

It has been shown that *cyclo*Sal-triesters of active antiviral nucleoside analogs are cleaved intracellularly to deliver the corresponding nucleotides efficiently.[28,29] Often an



Scheme 4 Reagents and Conditions: (a) 3-methyl-cyclosaligenyl-chlorophosphane, *i*-Pr_2EtN, MeCN–DMF, 2:1, –40 °C to 0 °C, 2 h, *t*-BuOOH, –40 °C to r.t. 2 h (b) Et_3N, H_2O, MeCN, r.t. 18 h

improvement in the biological activity has been observed.[30–32]Moreover, the *cyclo*Sal-triesters of the carbocyclic nucleoside analogues can be used for the chemical synthesis of nucleotides (Scheme 4).[33] As an example, *carba*-dTMP was prepared from the corresponding *cyclo*Sal-triester in 76% yield by chemical hydrolysis (Scheme 4). The nucleotides will be used for studies concerning their substrate properties on thymidylate kinase (TMP-K),[33,34]an essential enzyme in the activation of nucleotides into the ultimate bioactive triphosphates.[35] Work on this is currently in progress in our laboratories.

All experiments involving water-sensitive compounds were conducted under scrupulously dry conditions (nitrogen atmosphere) using standard syringe, cannula, and septa apparatus. Solvents: benzene, Et_2O, and THF were distilled from sodium or potassium benzophenone and stored over molecular sieves. CH_2Cl_2 and MeCN were distilled from CaH_2 and stored over molecular sieves. EtOAc, CH_2Cl_2, hexane, and MeOH employed in chromatography were distilled before used. *i*-Pr_2EtN was distilled from sodium prior to use. 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 [4-methoxybenzaldehyde (0.5 mL), EtOH (9 mL), concd H_2SO_4 (0.5 mL), and HOAc (0.1 mL)] by heating with a fan or a hot plate. NMR spectra were recorded using (^{1}H NMR) Bruker AC 250 at 250 MHz, Bruker WM 400 at 400 MHz, Bruker AMX 400 at 400 MHz or Bruker DMX 500 at 500 MHz; (^{13}C NMR) Bruker WM 400 at 101 MHz, Bruker AMX 400 at 101 MHz or Bruker DMX 500 at 123 MHz (Calibration was done in both cases with the solvent), (^{31}P NMR) Bruker AMX 400 at 162 MHz or Bruker DMX 500 at 202 MHz (H_3PO_4 as external standard). All ^{1}H and ^{13}C NMR chemical shifts (δ) are quoted in ppm downfield from TMS, $(CD_3)(CD_2H)SO$ was referenced to δ_H 2.49 as a. ^{31}P NMR chemical shifts are quoted in ppm using H_3PO_4 as external reference. The spectra were recorded at r.t.,

and all ^{13}C and ^{31}P NMR were recorded in proton-decoupled mode. Mass spectra were obtained with a VG Analytical VG/70-250 F spectrometer (FAB, matrix was *m*-nitrobenzylalcohol).

(1*S*,2*R*)-2-Benzyloxymethylcyclopent-3-enol (8)

To a suspension of NaH (2.40 g, 0.10 mol) in anhyd THF (50 mL) at 0 °C, was added freshly distilled cyclopentadiene (**9**) (10 mL, 0.11 mol) under nitrogen. The slightly pink solution was stirred for 1 h at 0 °C and then added dropwise to a solution of benzylchloromethylether (14 mL, 0.10 mol) in anhyd THF (50 mL) at –60 °C. The reaction mixture was stirred for 2 h at –40 °C and the solvent was evaporated under reduced pressure. The residue, **10** was cooled to –60 °C and a suspension of (–)-diisopinocampheylborane [28.7 g, 0.10 mol, prepared from (+)-α-pinene] in THF (100 mL) was added dropwise. The solution was stirred for 1 h at–60 °C, slowly warmed to 0 °C and stirred at this temperature for a further 16 h. Half of the THF was evaporated, the temperature was kept below 5 °C, and Et_2O (50 mL) and 3 M aq NaOH (35 mL) solution was added. The temperature was kept below 10 °C and an aq H_2O_2 solution (30%, 35 mL) was added. The mixture was stirred overnight at 0 °C. The formed solid was removed by filtration and washed with Et_2O. After phase separation the aq layer was washed with Et_2O (3 × 50 mL), the combined organic fractions were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (hexane–EtOAc, 2:1) yielding **8** (8.20 g, 40%) as a slightly yellow oil.

The spectroscopic data were identical with those reported.[13]

(1*S*,2*R*,3*S*,5*R*)-2-benzyloxymethyl-6-oxabicyclo[3.1.0]hexan-3-ol (14)

$Mo(CO)_6$ (434 mg, 1.60 mmol) was added to alcohol **8** (2.80 g, 13.7 mmol) in anhyd benzene (100 mL) and the mixture was heated to reflux under nitrogen. Then, *t*-butylhydroperoxide (5.60 mL, 28.0 mmol, 5 M in decane) was added dropwise and the reaction mixture was stirred for a further 3 h under reflux. An ice-cold 20% aq solution of sodium sulfite (50 mL) was added at r.t. After 1 h the layers were separated, the aq phase was extracted with EtOAc (3 × 20 mL), the combined organic phases were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude material was purified on silica gel (hexane–EtOAc, 1:1) yielding **14** (2.50 g, 82%) as a slightly yellow oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 5 H, C*H*-arom.), 4.49 (s, 2 H, CH_2-benzyl), 3.93–3.87 (m, 1 H, H-3), 3.66–3.64 (m, 1 H, H-5), 3.63–3.61 (m, 1 H, H-1), 3.45 (dd, 1 H, *J* = 9.5, 5.5 Hz, OC*H*H), 3.39 (dd, 1 H, *J* = 9.5 Hz, 6.5 Hz, OCH*H*), 2.52 (dd, 1 H, *J* = 6.5, 5.5 Hz, H-2), 2.25 (d, 1 H, *J* = 12.0 Hz, OH), 2.09–2.05 (m, 2 H, H-5).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.42, 128.89, 128.24, 127.93 (*C*-arom.), 73.75 (*C*H_2-benzyl), 73.43 (C-3), 68.98 (O*C*H_2), 60.12 (C-5), 58.35 (C-1), 50.36 (C-2), 37.64 (C-4).

HRMS-FAB: *m*/*z* calcd for $C_{13}H_{16}O_3$ (M + H): 221.1178; found: 221.1201.

(1*S*,2*R*,3*S*,5*R*)-3-Benzyloxy-2-benzyloxymethyl-6-oxabicyclo [3.1.0]hexane (15)

Alcohol **14** (2.40 g, 11.0 mmol) was added dropwise to a stirred suspension of NaH (520 mg, 13.0 mmol) in THF (40 mL) at 0 °C under nitrogen. After 1 h at r.t., benzyl bromide (1.65 mL, 14.0 mmol) and tetrabutylammonium iodide (TBAI, 50 mg) were added. The reaction mixture was kept overnight at r.t. Crushed ice was added, the mixture was stirred for 0.5 h, poured into EtOAc (100 mL), washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified on silica gel (hexane–EtOAc, 1:1) to yield **15** (3.07 g, 86%) as a light-yellow oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.26 (m, 10 H, C*H*-arom.), 4.48–4.45 (m, 4 H, 2 × CH_2-benzyl), 3.91–3.87 (m, 1 H, H-3), 3.55–3.53 (m, 1 H, H-5), 3.46 (d, 1 H, *J* = 2.8 Hz, H-1), 3.42 (dd, 1 H, *J* = 9.4 Hz, 5.8 Hz, OC*H*H), 3.39 (dd, 1 H, *J* = 9.4 Hz, 5.8 Hz, OCH*H*), 2.61 (dd, 1 H, *J* = 5.8 Hz, 5.8 Hz, H-2), 2.18–2.13 (m, 1 H, H-4a), 2.04 (ddd, 1 H, *J* = 15.3 Hz, 2.6 Hz, 1.6 Hz, H-4b).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.63, 138.44 (*C*q-arom.), 128.82, 128.73, 128.22, 128.16, 127.93, 127.86 (*C*-arom.), 81.54 (C-3), 73.67, 71.33 (2 × *C*H_2-benzyl), 69.72 (O*C*H_2), 60.14 (C-1), 58.45 (C-5), 47.92 (C-2), 35.25 (C-4).

HRMS-FAB: *m*/*z* calcd for $C_{20}H_{22}O_3$ (M + H): 311.1647; found: 311.1664.

1-(3′,5′-Di-*O*-benzyl-2′-deoxy-6′-hydroxy-6′-*carba*-β-D-ribofuranosyl)thymine (16)

A 1 M solution of triethylaluminum in hexane (12.8 mL, 12.8 mmol) was slowly added to a suspension of thymidine (1.61 g, 12.8 mmol) in THF (60 mL) at r.t. After 1 h at r.t., the epoxide **15** (2.00 g, 6.40 mmol) was added and the mixture was placed in an ultrasound bath for 48 h at r.t. After quenching with glacial HOAc (2 mL) and dilution with water (200 mL), the mixture was extracted with EtOAc (3 × 75 mL). The combined organic extracts were washed with a sat. aq $NaHCO_3$ solution (100 mL) and concentrated under reduced pressure. Purification of the residue was accomplished by chromatography on silica gel (CH_2Cl_2–MeOH, 20:1) to yield **16** (1.28 g, 46%) as a light yellow oil.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.22 (br s, 1 H, NH), 7.60 (q, 1 H, *J* = 1.0 Hz, H-6), 7.36–7.26 (m, 10 H, C*H*-arom.), 5.28 (d, 1 H, *J* = 4.5 Hz, 6′-OH), 4.86–4.79 (m, 1 H, H-1′), 4.58–4.48 (m, 4 H, 2 × CH_2-benzyl), 3.95–3.90 (m, 2 H, H-3′, H-6′), 3.53 (dd, 1 H, *J* = 9.4 Hz, 6.9 Hz, H-5′a), 3.46 (dd, 1 H, *J* = 9.4 Hz, 6.1 Hz, H-5′b), 2.11–2.01 (m, 3 H, H-4′, H-2′a, H-2′b), 1.80 (d, 3 H, *J* = 1.0 Hz, H-7).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 164.13 (C-4), 150.52 (C-2), 138.82, 138.58 (*C*q-arom.), 138.01 (C-6), 128.74, 128.62, 128.55, 128.35, 128.02, 127.84 (*C*-arom.), 109.63 (C-5), 77.30 (C-1′), 73.35, 72.45 (*C*-benzyl), 70.24 (C-5′), 53.89 (C-3′), 44.33 (C-4′), 35.93 (C-2′), 32.46 (C-6′), 12.37 (C-7).

HRMS-FAB: *m*/*z* calcd for $C_{25}H_{28}N_2O_5$ (M + H): 437.2076; found: 437.2094.

1-(3′,5′-Di-*O*-benzyl-2′-deoxy-6′-*carba*-β-D-ribofuranosyl)thymine (17)

Alcohol **16** (0.75 g, 1.72 mmol) was dissolved in anhyd MeCN (23 mL) and portions of DMAP (420 mg, 3.44 mmol) and phenoxythiocarbonylchloride (PTC–Cl) (384 mg, 2.23 mmol) were added under nitrogen at r.t. After stirring for 16 h at r.t., the solvent was evaporated under reduced pressure and the residue was partitioned between water (50 mL) and EtOAc (100 mL). The organic phase was washed with a 1 M aq HCl solution, water, sat. $NaHCO_3$ solution and brine, dried (Na_2SO_4), and concentrated. The crude material of the thiocarbonate was sufficiently pure to be used directly in the following reduction.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.96 (br s, 1 H, NH), 7.40–7.27 (m, 10 H, C*H*-arom.), 7.16–7.11 (m, 2 H, C*H*-arom.), 7.09 (q, 1 H, *J* = 1.2 Hz, H-6), 6.83–6.75 (m, 3 H, C*H*-arom.), 5.15–5.08 (m, 1 H, H-1′), 4.53 [d, 1 H, *J* = 12.0 Hz, C*H*H-benzyl (5′)], 4.52 (d, 1 H, *J* = 10.4 Hz, H-5′a), 4.49 [d, 1 H, *J* = 10.4 Hz, C*H*H-benzyl (3′)], 4.49 [d, 1 H, *J* = 10.4 Hz, CH*H*-benzyl (3′)], 4.45 [d, 1 H, *J* = 12.0 Hz, CH*H*-benzyl (5′)], 4.08–3.97 (m, 2 H, H-3′, H-6′), 3.59 (dd, 1 H, *J* = 9.2 Hz, 4.3 Hz, H-5′a), 3.53 (dd, 1 H, *J* = 9.2 Hz, 4.6 Hz, H-5′b), 2.40–2.30 (m, 2 H, H-4′, H-2′a), 1.95 (ddd, 1 H, *J* = 13.2 Hz, 10.2 Hz, 6.4 Hz, H-2′b), 1.78 (d, 3 H, *J* = 1.2 Hz, H-7).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.32 (*C*=S), 164.64 (C-4), 156.91 (*C*q-arom.), 151.34 (C-2), 138.24, 138.13 (*C*q-arom.),

135.56 (C-6), 130.12, 129.98, 128.73, 128.65, 128.34, 127.97, 127.75, 127.68, 127.34, 127.10, 121.21, 115.34 (*C*-arom.), 110.23 (C-5), 77.67 (C-1′), 74.02, 73.87 (*C*-benzyl), 68.34 (C-5′), 58.31 (C-6′), 55.65 (C-3′), 44.23 (C-4′), 28.54 (C-2′), 15.88 (C-7).

The thiocarbonate was dissolved in anhyd toluene (35 mL), AIBN (55.0 mg, 0.33 mmol) and *n*-Bu_3SnH (750 mg, 2.60 mmol) were added. The solution was degassed with oxygen-free N_2 for 15 min and then heated to 75 °C for 3.5 h. The solvent was evaporated under reduced pressure and the residue was purified on silica gel (hexane–EtOAc, 1:2) yielding **17** (398 mg, 55% over both steps) as a colorless syrup.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.20 (br s, 1 H, NH), 7.54 (q, 1 H, *J* = 1.2 Hz, H-6), 7.36–7.26 (m, 10 H, C*H*-arom.), 4.97–4.88 (m, 1 H, H-1′), 4.53–4.43 (m, 4 H, 2 × CH_2-benzyl), 3.90–3.85 (m, 1 H, H-3′), 3.50 (dd, 1 H, *J* = 9.4 Hz, 6.9 Hz, H-5′a), 3.45 (dd, 1 H, *J* = 9.4 Hz, 6.1 Hz, H-5′b), 2.38–2.30 (m, 1 H, H-4′), 2.22–2.12 (m, 1 H, H-6′a), 2.06–2.00 (m, 2 H, H2′a, H2′b), 1.79 (d, 3 H, *J* = 1.2 Hz, H-7), 1.50–1.42 (m, 1 H, H-6′b).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 164.24 (C-4), 150.62 (C-2), 138.86, 138.57 (*C*q-arom.), 137.97 (C-6), 128.63, 128.55, 128.48, 128.25, 127.95, 127.76 (*C*-arom.), 109.47 (C-5), 80.07 (C-1′), 72.44, 71.94 (*C*-benzyl), 70.16 (C-5′), 53.89 (C-3′), 44.33 (C-4′), 35.93 (C-2′), 32.46 (C-6′), 12.37 (C-7).

HRMS-FAB: *m*/*z* calcd for $C_{25}H_{28}N_2O_4$ (M + H): 421.2127; found: 421.2146.

rac-2-Benzyloxymethylcyclopent-3-enol (13)

The reaction was carried out as described for cyclopentene **8** with NaH (240 mg, 10 mmol) in THF (10 mL), cyclopentadiene (1.00 mL, 12.0 mmol), benzylchloromethylether (1.40 mL, 10.0 mmol) in THF (5 mL), 1 M borane·THF complex (3.0 mL, 3.00 mmol), aq 3 M NaOH (3.5 mL), H_2O_2 (30%; 3.5 mL). The residue was purified on silica gel (hexane–EtOAc 2:1) to yield **13** (633 mg, 31%) as a light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40–7.33 (m, 5 H, C*H*-arom.), 5.71 (ddd, 1 H, *J* = 6.0 Hz, 4.7 Hz, 2.4 Hz, H-3), 5.56 (ddd, 1 H, *J* = 6.0 Hz, 4.2 Hz, 1.9 Hz, H-4), 4.54–4.49 (m, 1 H, H-1), 4.46 (s, 2 H, CH_2-benzyl), 3.64–3.59 (m, 2 H, OCH_2), 2.94–2.86 (m, 1 H, H-2), 2.62–2.55 (m, 1 H, H-5a), 2.32–2.25 (m, 1 H, H-5b), 2.11 (br s, 1 H, 1-OH).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.72 (*C*q-arom.), 130.71 (C-3), 129.72 (C-4), 128.94, 128.23, 127.49 (*C*-arom.), 73.34 (C-1), 69.63 (*C*-benzyl), 65.75 (OCH_2), 50.12 (C-2), 42.45 (C-5).

HRMS-FAB: *m*/*z* calcd for $C_{13}H_{16}O_2$ (M + H): 205.1229; found: 205.1224.

(1*S*,2*R*)-1-Benzyloxy-2-benzyloxymethylcyclopent-3-ene (19)

The reaction has been carried out as described for hexane **15** with NaH (1.60 g, 0.04 mol) in THF (100 mL), alcohol **8** (6.00 g, 30 mmol), benzyl bromide (4.5 mL, 40 mmol) and TBAI (120 mg). The residue was purified on silica gel (hexane–EtOAc, 10:1) to yield **19** (7.00 g, 92%) as a light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.22 (m, 10 H, C*H*-arom.), 5.75 (ddd, 1 H, *J* = 6.5 Hz, 4.3 Hz, 2.0 Hz, H-3), 5.65 (ddd, 1 H, *J* = 6.1 Hz, 4.2 Hz, 2.1 Hz, H-4), 4.56–4.51 (m, 4 H, CH_2-benzyl), 4.08 (ddd, 1 H, *J* = 6.9 Hz, 3.4 Hz, 3.3 Hz, H-1), 3.45 (dd, 1 H, *J* = 9,3 Hz, 5.7 Hz, OC*H*H), 3.33 (dd, 1 H, *J* = 9.3 Hz, 5.3 Hz, OCH*H*), 3.10–3.03 (m, 1 H, H-2), 2.68 (dddd, 1 H, *J* = 17.2 Hz, 6.5 Hz, 4.5 Hz, 2.0 Hz, H-5a), 2.46–2.37 (m, 1 H, H-5b).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.18, 138.93 (*C*q-arom.), 130.45 (C-3), 130.29 (C-4), 128.83, 128.76, 128.72, 128.21, 128.14, 128.05, 127.98, 127.93 (*C*H-arom.), 81.83 (C-1), 73.48, 72.06 (*C*-benzyl), 71,18 (O-*C*H_2), 53.37 (C-2), 39.50 (C-5).

HRMS-FAB: *m*/*z* calcd for $C_{20}H_{22}O_2$ (M + H): 295.1698; found: 295.1711.

(1*R*,3*S*,4*R*)-3-Benzyloxy-4-benzyloxymethylcylopentan-1-ol (20)

A 0.5 M solution of 9-BBN in THF (88 mL, 44 mmol) was added dropwise to a solution of **19** (6.50 g, 22.0 mmol) in anhyd THF (10 mL) at 0 °C under nitrogen. The reaction was slowly warmed to r.t. overnight. The reaction was cooled to 0 °C and treated sequentially with EtOH (7 mL), 3 N NaOH solution (20 mL), and H_2O_2 (33%, 20 mL). The resulting mixture was stirred at r.t. overnight. The resulting residue was filtered and washed with EtOAc (200 mL). To this suspension, water was added (150 mL) and after separation of the phases, the aq layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to dryness. The crude product was purified on silica gel (hexane–EtOAc, 1:1 to yield **20β** and the epimer **20α** as light yellow oils.

Cyclopentanol 20β

Yield: 5.42 g (79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 10 H, C*H*-arom.), 4.52 (s, 2 H, CH_2-benzyl), 4.49 (d, 1 H, *J* = 11.8 Hz, C*H*H-benzyl), 4.44 (d, 1 H, *J* = 11.8 Hz, CH*H*-benzyl), 4.33–4.28 (m, 1 H, H-1), 4.07 (ddd, 1 H, *J* = 6.6 Hz, 6.6 Hz, 4.1 Hz, H-3), 3.53 (dd, 1 H, *J* = 9.0 Hz, 4.2 Hz, OC*H*H), 3.49 (d, 1 H, *J* = 9.0 Hz, 4.3 Hz, OCH*H*), 2.35–2.25 (m, 2 H, H-4, H-5a), 2.05 (dddd, 1 H, *J* = 13.5 Hz, 6.7 Hz, 3.5 Hz, 1.7 Hz, H-2a), 1.89–1.82 (m, 1 H, H-2b), 1.52–1.46 (m, 1 H, H-5b).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.07, 138.23 (*C*q-arom.), 128.90, 128.86, 128.78, 128.21, 128.19, 128.10 (*C*H-arom.), 82.36 (C-1), 74.08, 73.70 (2 × *C*H_2-benzyl), 72.80 (C-3), 71.51 (OCH_2), 44.94 (C-4), 40.82 (C-2), 37.76 (C-5).

HRMS-FAB: *m*/*z* calcd for $C_{20}H_{24}O_3$ (M + H): 313.1804; found: 313.1808.

Cyclopentanol 20α

Yield: 0.82 g (12%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 10 H, C*H*-arom.), 4.56–4.48 (m, 4 H, 2 × CH_2-benzyl), 4.31–4.26 (m, 1 H, H-1), 4.01–3.97 (m, 1 H, H-3), 3.43 (dd, 1 H, *J* = 9.4 Hz, 5.6 Hz, OC*H*H), 3.28 (dd, 1 H, *J* = 9.4 Hz, 7.5 Hz, OCH*H*), 2.72–2.68 (m, 1 H, H-4), 2.11–2.00 (m, 2 H, H-2a, H-5a), 1.86 (ddd, 1 H, *J* = 14.2 Hz, 5.2 Hz, 5.2 Hz, H-2b), 1.57 (ddd, 1 H, *J* = 13.9 Hz, 7.6 Hz, 5.2 Hz, H-5b).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.67, 138.46 (*C*q-arom.), 128.83, 128.76, 128.70, 128.56, 128.34, 127.89 (*C*H-arom.), 78.34 (C-1), 73.67, 73.23 (2 × *C*H_2-benzyl), 72.34 (C-3), 71.41 (OCH_2), 45.67 (C-4), 41.32 (C-2), 36.34 (C-5).

HRMS-FAB: *m*/*z* calcd for $C_{20}H_{24}O_3$ (M + H), 313.1804; found: 313.1824.

(1*R*,3*S*,4*R*)-3-Benzyloxy-4-benzyloxymethylcylopentanamine (22)

A 0.5 M solution of 9-BBN in THF (4 mL, 2.00 mmol) was slowly added to cyclopentene **19** (294 mg, 1.00 mmol) at 0 °C under nitrogen. The mixture was stirred overnight at r.t. To this mixture hydroxylamine-*O*-sulfonic acid (680 mg, 6.00 mmol) in THF (2 mL) was added dropwise. The mixture was heated to reflux for 3 h, cooled to r.t., and the medium was acidified by addition of hydrochloric acid (2 M, 10 mL). After extraction with Et_2O (3 × 10 mL), the pH value of the aq layer was changed to pH 11 by addition of a 3 M solution of NaOH and extracted again with Et_2O (3 × 10 mL). The combined organic extracts were dried and concentrated under reduced pressure. The crude material was purified on a chromatotron (CH_2Cl_2–MeOH, gradient 0→20%) to yield **22** (149 mg, 52%) as a 87:13 mixture of **22**β:**22**α as a light yellow oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.38–7.26 (m, 10 H, C*H*-arom.), 4.55 (s, 2 H, CH_2-benzyl), 4.50 (d, 1 H, *J* = 12.0 Hz, C*H*H-benzyl), 4.46 (d, 1 H, *J* = 12.0 Hz, CH*H*-benzyl), 3.87–3.80 (m, 1 H, H-3), 3.47 (dd, 1 H, *J* = 9.6 Hz, 5.7 Hz, OC*H*H), 3.40–3.33 (m, 3 H, OCH*H*, H-1), 2.28–2.21 (m, 1 H, H-4), 2.11–2.03 (m, 1 H, H-5a), 1.95 (ddd, 1 H, *J* = 13.9 Hz, 6.0 Hz, 5.2 Hz, H-2a), 1.54 (ddd, 1 H, *J* = 13.9 Hz, 7.2 Hz, 5.2 Hz, H-2b), 1.09–1.00 (m, 1 H, H-5b).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 138.88, 138.15 (*C*q-arom.), 128.92, 128.79, 128.72, 128.41, 128.33, 127.95 (*C*H-arom.), 74.22, 73.86 (2 × *C*H_2-benzyl), 71.65 (C-3), 70.40 (OCH_2), 53.36 (C-1), 47.56 (C-4), 41.43 (C-2), 35.23 (C-5).

HRMS-FAB: *m*/*z* calcd for $C_{20}H_{25}NO_2$ (M + H): 312.1964; found: 312.1975.

(1*R*,2*S*,3*S*)-2-Benzyloxymethyl-3-benzyloxycyclopentan-1-ol (21α)

To cyclopentene **19** (100 mg, 0.34 mmol) at 0 °C under nitrogen, a suspension of (+)-di-isopinocampheylborane (115 mg, 0.40 mmol) in THF (400 μL) was added dropwise. The reaction was stirred for 16 h at 4 °C. The reaction was cooled to 0 °C and treated sequentially with 3 N NaOH solution (150 μL) and H_2O_2 (33%; 150 μL) while stirring. The mixture was stirred for 12 h at r.t. The residue was filtered of and washed with EtOAc (2 mL). The mixture was evaporated to dryness and the crude product was purified on silica gel (hexane–EtOAc 1:1) to yield **21α** (44.6 mg, 42%) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.20 (m, 10 H, C*H*-arom.), 4.55–4.40 (m, 4 H, 2 × CH_2-benzyl), 4.02–3.96 (m, 1 H, H-1), 3.74–3.69 (m, 1 H, H-3), 3.59 (dd, 1 H, *J* = 9.1 Hz, 5.6 Hz, OC*H*H), 3.44 (dd, 1 H, *J* = 9.1 Hz, 7.9 Hz, OCH*H*), 2.29–2.22 (m, 1 H, H-2), 1.95–1.75 (m, 4 H, 4-CH_2, 5-CH_2).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.91, 138.61, 128.85, 128.79, 128.10, 128.05, 128.00, 127.97 (*C*-arom.), 81.20 (C-3), 76.16 (C-1), 73.71, 71.55 (2 × *C*H_2-benzyl), 71.18 (O-*C*H_2), 54.48 (C-2), 32.39 (C-4), 29.41 (C-5).

HRMS-FAB: *m*/*z* calcd for $C_{20}H_{24}O_3$ (M + H): 313.1804; found: 313.1826.

(1*S*,3*S*,4*R*)-3-Benzyloxy-4-benzyloxymethylcylopentan-1-ol (20α)

To a suspension of PPh_3 (6.82 g, 26.0 mmol) in anhyd Et_2O (100 mL) at 0 °C under nitrogen was slowly added DIAD (5.05 mL, 26.0 mmol) and the suspension was stirred for 0.5 h. This preformed complex was slowly added to a suspension of benzoic acid (3.18 g, 26 mmol) and alcohol **20β** (4.10 g, 13 mmol) in anhyd Et_2O (60 mL) at 0 °C under nitrogen. The reaction was slowly warmed to r.t. and stirred overnight. The solid was removed by filtration and washed with Et_2O. The solvent was removed and NaOH solution in MeOH (1%, 100 mL) was added. Stirring was continued overnight at r.t. The solution was neutralized by addition of 1M HCl and then concentrated. The crude material was purified on silica gel (hexane–EtOAc, 1:2) to yield the title alcohol **20α** (3.70 g, 91%) as a colorless oil.

The spectroscopic data were identical to those described above.

Coupling of the Pyrimidines to the Cyclopentanol 20α; General Procedure

To a suspension of PPh_3 (787 mg, 3 mmol) in anhyd MeCN (11 mL), DIAD (585 L, 2.8 mmol) was added slowly and the solution was stirred for 0.5 h at 0 °C. This preformed complex was slowly added to a suspension of the protected nucleobases (2 mmol) and the alcohol **20α** (312 mg, 1 mmol) in anhyd MeCN (6 mL) at –40 °C under nitrogen. The reaction was slowly warmed to r.t. and stirred overnight. The solvent was removed from the reaction mixture and a NaOH solution in MeOH (1%, 15 mL) was added and stirred overnight at r.t. The solution was neutralized by addition of 1M HCl and then concentrated. The crude was chromatographed on silica gel (hexane–EtOAc, 1:2) to yield the *N*-1 alkylated compounds **23**, **25a**, and **25b** as colorless syrups.

1-(3′,5′-Di-*O*-benzyl-2′-deoxy-6′-*carba*-β-D-ribofuranosyl)thymine (23)

Yield: 260 mg (62%).

The spectroscopic data were identical to those described above.

1-(3′,5′-Di-*O*-benzyl-2′-deoxy-6′-*carba*-β-D-ribofuranosyl)-5-[(*E*)-bromovinyl]uracil (25b)

Yield: 98 mg (53%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.60 (s, 1 H, NH), 8.03 (s, 1 H, H-6), 7.45–7.38 (m, 10 H, C*H*-arom.), 7.35 (d, 1 H, *J* = 13.5 Hz, H-8), 6.93 (d, 1 H, *J* = 13.5 Hz, H-7), 5.05–4.97 (m, 1 H, H-1′), 4.63–4.54 (m, 4 H, 2 × CH_2-benzyl), 3.59 (dd, 1 H, *J* = 9.4 Hz, 7.0 Hz, H-5′a), 3.54 (dd, 1 H, *J* = 9.4 Hz, 6.1 Hz, H-5′b), 2.54–2.38 (m, 1 H, H-4′), 2.30–2.23 (m, 1 H, H-6′a), 2.15–2.05 (m, 2 H, H-2′a, H-2′b), 1.62–1.53 (m, 1 H, H-6′b).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 161.96 (C-4), 150.23 (C-2), 141.57 (C-6), 138.85, 138.32 (*C*q-arom.), 130.27 (C-7), 128.63, 128.56, 128.21, 127.87, 127.77, 127.69 (*C*H-arom.), 109.98 (C-5), 106.59 (C-8), 79.87 (C-1′), 72.43, 71.86 (*C*-benzyl), 70.20 (C-5′), 54.64 (C-3′), 44.34 (C-4′), 36.01 (C-2′), 32.70 (C-6′).

HRMS-FAB: *m*/*z* calcd for $C_{26}H_{27}BrN_2O_4$ (M + H): 511.1232 and 513.1212; found: 511.1249 and 513.1237.

1-(3′,5′-Di-*O*-benzyl-2′-deoxy-6′-*carba*-β-D-ribofuranosyl)-5-fluorouracil (25a)

Yield: 182 mg (42%)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.80–11.70 (br s, 1 H, NH), 7.87 (d, 1 H, *J* = 3.6 Hz, H-6), 7.41–7.30 (m, 10 H, C*H*-arom.), 5.00–4.90 (m, 1 H, H-1′), 4.56–4.46 (m, 4 H, 2 × CH_2-benzyl), 3.97–3.85 (m, 1 H, H-3′), 3.52 (dd, 1 H, *J* = 9.6 Hz, 6.9 Hz, H-5′a), 3.44 (dd, 1 H, *J* = 9.6 Hz, 6.1 Hz, H-5′b), 2.40–2.30 (m, 1 H, H-4′), 2.22–2.13 (m, 1 H, H-6′a), 2.06–1.95 (m, 2 H, H-2′a, H-2′b), 1.52–1.44 (m, 1 H, H-6′b).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 156.52 (d, *J* = 27 Hz, C-4), 148.64 (C-2), 140.05 (d, *J* = 230 Hz, C-5), 138.95, 138.06 (*C*q-arom.), 128.79, 128.66, 128.34, 127.64, 127.24, 127.11 (*C*H-arom.), 125.25 (d, *J* = 32 Hz, C-6), 79.89 (C-1′), 72.88, 72,42 (*C*-benzyl), 70.53 (C-5′), 54.66 (C-3′), 43.97 (C-4′), 37.32 (C-2′), 32.38 (C-6′).

HRMS-FAB: *m*/*z* calcd for $C_{24}H_{25}FN_2O_4$ (M + H): 425.1877; found: 425.1898.

Debenzylation; General Procedure

BCl_3 (7.2 mL, 1 M in CH_2Cl_2) was added slowly to a stirred solution of the benzylated *carba*-nucleosides (250 mg) in anhyd CH_2Cl_2 (28 mL) at –78 °C. The reaction mixture was stirred for 5 h at –78 °C. The reaction mixture was warmed to –25 °C and MeOH (14 mL) was added dropwise. The mixture was allowed to warm to r.t. and stirred overnight. The solvent was removed and the residue was concentrated three times with MeOH (10 mL). The crude product was purified by chromatography on a Chromatotron (CH_2Cl_2–MeOH gradient 5∅20%) to yield the *carba*-nucleosides (140 mg, 95%) as white solids. After lyophilization (CH_3CN–water), the debenzylated nucleoside analogs were obtained as colorless solids.

1-(2′-Deoxy-6′-*carba*-β-D-ribofuranosyl)thymine (*carba*-dT) 18

Yield: 130 mg (90%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.20 (s, 1 H, NH), 7.57 (q, 1 H, *J* = 1.0 Hz, H-6), 5.02–4.96 (m, 1 H, H-1′), 4.73 (d, 1 H, *J* = 4.5

Hz, 3′-OH), 4.61 (t, 1 H, *J* = 5.2 Hz, 5′-OH), 4.03–3.98 (m, 1 H, H-3′), 3.53 (ddd, 1 H, *J* = 10.6 Hz, 5.5 Hz, 5.2 Hz, H-5′a), 3.43 (ddd, 1 H, *J* = 10.6 Hz, 5.7 Hz, 5.2 Hz, H-5′b), 2.11–2.04 (m, 1 H, H-6′a), 1.99–1.89 (m, 2 H, H-4′, H-2′a), 1.82 (d, 3 H, *J* = 1.0 Hz, H-7), 1.82–1.74 (m, 1 H, H-2′b), 1.45–1.37 (m, 1 H, H-6′b).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 164.08 (C-4), 151.35 (C-2), 138.06 (C-6), 109.44 (C-5), 71.72 (C-1′), 63.01 (C-5′), 53.58 (C-3′), 49.33 (C-4′), 36.35 (C-2′), 32.70 (C-6′), 12.43 (C-7).

HRMS-FAB: *m*/*z* calcd for $C_{11}H_{16}N_2O_4$ (M + H): 241.1188; found: 241.1195

1-(2′-Deoxy-6′-*carba*-β-D-ribofuranosyl)-5-[(*E*)-bromovinyl] uracil (*carba*-BVdU) (7)
Yield: 42 mg (88%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.50 (br s, 1 H, NH), 7.92 (s, 1 H, H-6), 7.26 (d, 1 H, *J* = 13.5 Hz, H-8), 6.90 (d, 1 H, *J* = 13.5 Hz, H-7), 5.00–4.90 (m, 1 H, H-1′), 4.72 (d, 1 H, *J* = 4.6 Hz, 3′-OH), 4.60 (t, 1 H, *J* = 5.2 Hz, 5′-OH), 4.01–3.95 (m, 1 H, H-5′a), 3.43–3.38 (m, 1 H, H-5′b), 2.13–2.06 (m, 1 H, H-6′a), 1.97–1.87 (m, 2 H, H-4′, H-2′a), 1.83–1.76 (m, 1 H, H-2′b), 1.42–1.35 (m, 1 H, H-6′b).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 164.68 (C-4), 151.02 (C-2), 141.70 (C-7), 130.36 (C-8), 109.23 (C-5), 106.48 (C-6), 71.56 (C-1′), 63.11 (C-5′), 54.35 (C-3′), 49.34 (C-4′), 38.35 (C-2′), 33.00 (C-6′).

HRMS-FAB: *m*/*z* calcd for $C_{12}H_{15}BrN_2O_4$ (M + H): 331.0293 and 333.0273; found: 331.0314 and 333.0310.

1-(2′-Deoxy-6′-*carba*-β-D-ribofuranosyl)-5-fluorouracil (*carba*-FdU) (26)
Yield: 86 mg (82%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.82–11.75 (br s, 1 H, NH), 7.90 (d, 1 H, *J* = 4.0 Hz, H-6), 5.01–4.94 (m, 1 H, H-1′), 3.95–3.86 (m, 1 H, H-3′), 3.60 (dd, 1 H, *J* = 9.8 Hz, 7.0 Hz, H-5′a), 3.48 (dd, 1 H, *J* = 9.8 Hz, 6.0 Hz, H-5′b), 2.43–2.35 (m, 1 H, H-4′), 2.28–2.20 (m, 1 H, H-6′a), 2.02–1.91 (m, 2 H, H-2′a, H-2′b), 1.54–1.48 (m, 1 H, H-6′b).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 156.88 (d, *J* = 28 Hz, C-4), 148.54 (C-2), 140.12 (d, *J* = 230 Hz, C-5),), 126.02 (d, *J* = 32 Hz, C-6), 79.72 (C-1′), 71.11 (C-5′), 54.43 (C-3′), 44.03 (C-4′), 36.87 (C-2′), 33.21 (C-6′).

HRMS-FAB: *m*/*z* calcd for $C_{10}H_{13}FN_2O_4$ (M + H): 245.0938; found: 245.0954.

Preparation of the *cyclo*Sal-phosphate Triesters of the *carba*-Nucleosides
The reaction has been performed as previously described by our laboratories.[27,28] However, instead of CH_3CN, a mixture of CH_3CN and DMF (2:1) was used. The reactions have been carried out at –40 °C. *Cyclo*Sal-triesters **27** and **28** were obtained as colorless foams.

3-Methyl-*cyclo*saligenyl-5′-*O*-[1-(2′-deoxy-6′-*carba*-β-D-ribofuranosyl)thymidinyl]-phosphate (3-Me-*cyclo*Sal-*carba*-dT) (27)
Yield: 107 mg (60%).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.20 (br s, 2 H, 2 × NH), 7.51 (q, 1 H, *J* = 1.2 Hz, H-6), 7.49 (q, 1 H, *J* = 1.2 Hz, H-6), 7.28–7.23 (m, 2 H, C*H*-arom.), 7.11–7.06 (m, 4 H, C*H*-arom.), 5.52–5.40 (m, 4 H, 2 × CH_2-benzyl), 5.00–4.85 (m, 4 H, 2 × H-1′, 2 × 3′-O*H*), 4.27 (ddd, 2 H, *J* = 10.1, 6.4, 6.4 Hz, H-5′a), 4.22 (ddd, 2 H, *J* = 10.1, 6.6, 6,6 Hz, H-5′b), 4.12 (ddd, 2 H, *J* = 10.2, 7.4, 7.4 Hz, H-5′a), 4.06 (ddd, 2 H, *J* = 10.2, 7.2, 7.2 Hz, H-5′b), 4.00–4.95 (m, 2 H, 2 × H-3′), 2.24 (s, 6 H, 2 × CH_3-arom.), 2.13–1.93 (m, 6 H, 2 × H-2′a, 2 × H-4′, 2 × H-6′a), 1.82–1.74 (m, 8 H, 2 × H-2′b, 2 × H-7), 1.42–1.30 (m, 2 H, 2 × H-6′b).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 164.06 (C-4), 151.49 (C-2), 148.11 (C-2arom.), 138.21 (C-6), 131.18 (C-4arom.), 127.54 (C-3arom.), 124.22 (C-5arom.), 123.93 (C-6arom.), 121.46 (d, *J* = 3.5 Hz, C-1arom.), 109.50 (C-5), 71.09 (C-1′), 69.46 (d, *J* = 7.0 Hz, *C*H$_2$-benzyl), 68.74 (d, *J* = 3.8 Hz, C-5′), 53.35 (C-3′), 47.28 (C-4′), 38.62 (C-2′), 32.41 (C-6′), 15.30 (*C*H$_3$-arom.), 12.41 (C-7).

^{31}P NMR (202 MHz, DMSO-d_6): δ = –6.52, –6.64

HRMS-FAB: *m*/*z* calcd for $C_{19}H_{23}N_2O_7P$ (M + H): 423.1321; found: 423.1331.

3-Methyl-*cyclo*saligenyl-5′-*O*-[1-(2′-deoxy-6′-*carba*-β-D-ribofuranosyl)-5-*(E)*-bromovinyl]uracilyl)-phosphate (3-Me-*cyclo*Sal-*carba*-BVdU) (28)
Yield: 12 mg (15%).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.48 (br s, 2 H, 2 × NH), 7.96 (s, 1 H, H-6), 7.83 (s, 1 H, H-6), 7.28 (d, 1 H, *J* = 13.5 Hz, H-8), 7.26 (d, 1 H, *J* = 13.5 Hz, H-8), 7.24–7.20 (m, 2 H, C*H*-arom.), 7.10–7.04 (m, 4 H, C*H*-arom.), 6.85 (d, 1 H, *J* = 13.5 Hz, H-7), 6.81 (d, 1 H, *J* = 13.5 Hz, H-7), 5.49–5.38 (m, 4 H, 2 × CH_2-benzyl), 5.02–4.90 (m, 4 H, 2 × H-1′, 2 × 3′-OH), 4.29 (ddd, 2 H, *J* = 9.8, 6.2, 6.2 Hz, H-5′a), 4.24 (ddd, 2 H, *J* = 9.8, 6.6, 6,6 Hz, H-5′b), 4.11 (ddd, 2 H, *J* = 10.1, 7.2, 7.2, H-5′a), 4.04 (ddd, 2 H, *J* = 10.1, 7.2, 7.2 Hz, H-5′b), 4.02–4.96 (m, 2 H, 2 × H-3′), 2.25 (s, 6 H, 2 × CH_3-arom.), 2.15–1.91 (m, 6 H, 2 × H-2′a, 2 × H-4′, 2 × H-6′a), 1.82–1.77 (m, 2 H, 2 × H-2′b), 1.45–1.35 (m, 2 H, 2 × H-6′b).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 164.20 (C-4), 151.34 (C-2), 149.24 (C-2arom.), 142.55 (C-7), 132.63 (C-4arom.), 130.36 (C-8), 127.22 (C-3arom.), 123.97 (C-5arom.), 123.12 (C-6arom.), 121.22 (d, *J* = 3.5 Hz, C-1arom.), 109.44 (C-5), 106.35 (C-6), 72.35 (C-1′), 70.62 (d, *J* = 7.0 Hz, *C*H$_2$-benzyl), 67.47 (d, *J* = 3.8 Hz, C-5′), 54.25 (C-3′), 49.35 (C-4′), 38.33 (C-2′), 32.25 (C-6′), 15.36 (*C*H$_3$-arom.).

^{31}P NMR (202 MHz, DMSO-d_6): δ = –6.79, –6.92.

HRMS-FAB: *m*/*z* calcd for $C_{20}H_{22}BrN_2O_7P$ (M + H): 513.0426; found: 513.0441.

5′-*O*-[1-(2′-Deoxy-6′-*carba*-β-D-ribofuranosyl)thymidinyl] monophosphate (*carba*-dTMP) (29)
Triester **28** (25.0 mg, 0.06 mmol) was dissolved in MeCN (3 mL) and water (500 μL). To this solution Et_3N (10 drops) was slowly added and the mixture was stirred at r.t. until complete hydrolysis of the triester was observed by TLC. The reaction mixture was diluted with water (5 mL) and MeCN (5 mL) and the solution was lyophilized. The crude product was purified by chromatography on RP-C18-silica gel (Merck). The obtained triethylammonium salt was transferred into the sodium salt by ion-exchange (Dowex 50X8, sodium form). After lyophilization the product **29** (16.6 mg, 76%) was obtained as a colorless solid.

^{1}H NMR (400 MHz, D_2O): δ = 7.46 (q, 1 H, *J* = 1.2 Hz, H-6), 5.05–4.99 (m, 1 H, H-1′), 4.67–4.60 (m, 1 H, H-3′), 4.31 (ddd, 1 H, *J* = 21.2 Hz, 10.6 Hz, 4.3 Hz, H-5′a), 4.15 (ddd, 1 H, *J* = 11.0 Hz, 10.6 Hz, 1.8 Hz, H-5′b), 2.27–2.17 (m, 4 H, H-4′, 2 × H-2′; H-6′a), 1.88 (d, 3 H, *J* = 1.2 Hz, H-7), 1.58–1.50 (m, 1 H, H-6′b).

^{13}C NMR (101 MHz, D_2O): δ = 164.12 (C-4), 151.37 (C-2), 141.26 (C-6), 109.88 (C-5), 80.89 (C-1′), 70.35 (d, *J* = 6.2 Hz, C-5′), 54.91 (C-3′), 42.23 (d, *J* = 4.5 Hz, C-4′), 34.86 (C-2′), 29.23 (C-6′), 11.74 (C-7).

^{31}P NMR (202 MHz, D_2O): δ = 2.21.

MS (ESI$^+$): *m*/*z* calcd for $C_{11}H_{15}N_2O_7PNa_2$: 364.04; found 365.21.

References

(1) (a) Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611. (b) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571. (c) Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745.
(2) Shealy, Y. F.; Clayton, J. D. *J. Pharm. Sci.* **1973**, *62*, 858.
(3) Yaginuma, S.; Muto, N.; Tsujino, M.; Sudate, Y.; Hayashi, M.; Otani, M. *J. Antibiot.* **1981**, *34*, 359.
(4) Marquez, V. E. In *Advances in Antiviral Drug Design*, 2; De Clercq, E., Ed.; JAI Press: Greenwich, **1996**, 89.
(5) Vince, R.; Hua, M. *J. Med. Chem.* **1990**, *33*, 17.
(6) (a) Daluge, S. M.; Martin, M. T.; Sickles, B. R.; Livingston, D. A. *Nucleosides, Nucleotides Nucleic Acids* **2000**, *19*, 297. (b) Crimmins, M. T.; King, B. W. *J. Org. Chem.* **1996**, *61*, 4192. (c) Kimberlain, D. W.; Coen, D. M.; Biron, K. K.; Cohen, J. I.; Lamb, R. A.; Mckinlay, M.; Emini, E. A.; Whitley, R. J. *Antiviral Res.* **1995**, *26*, 369.
(7) Norbeck, D. W.; Kern, E.; Hayashi, S.; Rosenbrook, W.; Sham, H.; Herrin, T.; Plattner, J. J.; Erickson, J.; Clement, J.; Swanson, R.; Shipkowitz, N.; Hardy, D.; Marsh, K.; Arnett, G.; Shannon, W.; Broder, S.; Mitsuya, H. *J. Med. Chem.* **1990**, *33*, 1281.
(8) Bisacchi, G. S.; Chao, S. T.; Bachard, C.; Daris, J. P.; Innaimo, S.; Jacobs, G. A.; Kocy, O.; Lapointe, P.; Martel, A.; Merchant, Z.; Slusarchyk, W. A.; Sundeen, J. E.; Young, M. G.; Colonno, R.; Zahler, R. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 127.
(9) Balzarini, J.; Baumgartner, H.; Bodenteich, M.; De Clercq, E.; Griengl, H. *Nucleosides Nucleotides* **1989**, *8*, 855.
(10) Wyatt, P. G.; Anslow, A. S.; Coomber, B. A.; Cousins, R. P. C.; Evans, D. N.; Gilbert, V. S.; Humber, D. C.; Paternoster, I. L.; Sollis, S. L.; Tapolczay, D. J.; Weingarten, G. G. *Nucleosides Nucleotides* **1995**, *14*, 2039.
(11) Bricaud, H.; Herdewijn, P.; De Clercq, E. *Biochem. Pharmacol.* **1983**, 3583.
(12) Cookson, R.; Dudfield, P.; Newton, R.; Ravenscroft, P.; Scopes, D.; Cameron, J. *Eur. J. Med. Chem. Chim. Ther.* **1985**, *20*, 375.
(13) Biggadike, K.; Borthwick, A. D.; Evans, D.; Exall, A. M.; Kirk, B. E.; Roberts, S. M.; Stephenson, L.; Youds, P. *Chem. Soc., Perkin Trans. 1* **1988**, 549.
(14) (a) Parker, D. *Chem. Rev.* **1991**, *91*, 1441. (b) Anderson, R. C.; Shapiro, M. J. *J. Org. Chem.* **1984**, *49*, 1304.
(15) Gathergood, N.; Knudsen, K. R.; Jørgensen, K. A. *J. Org. Chem.* **2001**, *66*, 1014.
(16) (a) Baumgartner, H.; Marschner, C.; Pucher, R.; Griengl, H. *Tetrahedron Lett.* **1991**, *32*, 611. (b) Bisacchi, G. S.; Chao, S. T.; Bachard, C.; Daris, J. P.; Innaimo, S.; Jacobs, G. A.; Kocy, O.; Lapointe, P.; Martel, A.; Merchant, Z.; Slusarchyk, W. A.; Sundeen, J. E.; Young, M. G.; Colonno, R.; Zahler, R. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 127.
(17) (a) Overman, L. E.; Sugai, S. *J. Org. Chem.* **1985**, *50*, 4154. (b) Kapeller, H.; Baumgartner, H.; Marschner, C.; Pucher, R.; Griengl, H. *Monatsh. Chem.* **1997**, *128*, 953.
(18) Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059.
(19) Rodebaugh, R.; Debenham, J. S.; Fraser-Reid, B. *Tetrahedron Lett.* **1996**, *37*, 5477.
(20) (a) Brown, H. C. *Organic Syntheses via Boranes*; Wiley: New York, **1974**. (b) Brown, H. C.; Jadhav, P. K.; Mandal, A. K. *Tetrahedron* **1981**, *37*, 3547. (c) Brown, H. C.; Ayyangar, N. R.; Zweifel, G. *J. Org. Chem.* **1964**, *86*, 397. (d) Brown, H. C.; Knights, E. F.; Scouten, C. G. *J. Am. Chem. Soc.* **1974**, *96*, 7765.
(21) (a) Larock, R. C. *Solvomercuration/Demercuration Reactions in Organic, Synthesis*; Springer-Verlag: Berlin, **Heidelberg**, 1986, 443. (b) Larock, R. C. *Angew. Chem.* **1978**, *90*, 28.
(22) (a) Brown, H. C.; Heydkamp, W. R.; Breuer, E.; Murphy, W. S. *J. Am. Chem. Soc.* **1964**, *86*, 3565. (b) Rathke, M. W.; Inoue, N.; Varma, K. R.; Brown, H. C. *J. Am. Chem. Soc.* **1966**, *88*, 2870.
(23) Mitsunobu, O. *Synthesis* **1981**, 1.
(24) Cruickshank, K. A.; Jiricny, J.; Reese, C. B. *Tetrahedron Lett.* **1984**, *25*, 681.
(25) (a) Jenny, T. F.; Horlacher, J.; Previsani, N.; Benner, S. A. *Helv. Chim. Acta* **1992**, *75*, 1944. (b) Bonnal, C.; Chavis, C.; Lucas, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1401.
(26) (a) Barrett, A. G. M.; Braddock, D. C.; James, R. A.; Procopiou, P. A. *Chem. Commun.* **1997**, 433. (b) Barrett, A. G. M.; Braddock, D. C.; James, R. A.; Koike, N.; Procopiou, P. A. *J. Org. Chem.* **1998**, *63*, 6273.
(27) Meier, C. *Mini-Rev. Med. Chem.* **2002**, *2*, 219.
(28) Meier, C.; Lorey, M.; De Clercq, E.; Balzarini, J. *J. Med. Chem.* **1998**, *41*, 1417.
(29) Balzarini, J.; Aquaro, S.; Knispel, T.; Rampazzo, C.; Bianchi, V.; Perno, C.-F.; De Clercq, E.; Meier, C. *Mol. Pharmacol.* **2000**, *58*, 928.
(30) Meier, C.; Knispel, T.; Marquez, V. E.; Siddiqui, M. A.; De Clercq, E.; Balzarini, J. *J. Med. Chem.* **1999**, *42*, 1615.
(31) Balzarini, J.; Haller-Meier, F.; De Clercq, E.; Meier, C. *Antiviral Chem. Chemother.* **2002**, *12*, 301.
(32) (a) Meier, C.; Lomp, A.; Meerbach, A.; Wutzler, P. *J. Med. Chem.* **2002**, *45*, 5157. (b) Meier, C.; Habel, L.; Haller-Meier, F.; Lomp, A.; Herderich, M.; Klöcking, R.; Meerbach, A.; Wutzler, P. *Antiviral Chem. Chemother.* **1998**, *9*, 389.
(33) Ostermann, N.; Segura-Pena, D.; Meier, C.; Veit, T.; Monnerjahn, C.; Konrad, M.; Lavie, A. *Biochemistry* **2003**, *42*, 2568.
(34) Konrad M., Lavie A.; Mini-Rev. Med. Chem.; **2003**, in press
(35) Balzarini, J. *J. Pharm. World Sci.* **1994**, *16*, 113.