NEW AND EFFICIENT SYNTHESIS OF RACEMIC CYCLOPENT-3-EN-1-YL NUCLEOSIDE ANALOGUES AND THEIR DERIVATIVES

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Dedicated to Professor Antonín Holý on the occasion of his 70th birthday in recognition of his outstanding contributions to the area of nucleosides and nucleic acid chemistry.

A new, efficient synthesis of racemic cyclopent-3-en-1-yl nucleoside analogues has been developed starting from cyclopentadiene. The key step is the regioselective hydroboration of an intermediately formed mixture of *two* alkylated cyclopentadienes to give *one* cyclopentenol. The remaining double bond was further functionalized by hydroboration, epoxidation, *cis*-hydroxylation and cyclopropanation.

Keywords: Nucleosides; Carbocyclic nucleosides; Cyclopentanes; Cyclopropanation; Hydroboration; Pyrimidines; Antivirals.

Nucleoside analogues have attracted considerable interest due to their important biological activity[1]. Various structural modifications were introduced in both the heterocyclic base and the sugar moiety[2]. In carbocyclic nucleosides the furanose oxygen is replaced by a methylene unit. Such compounds are stable to hydrolysis by phosphorylases that cleave the glycosidic bond in conventional nucleosides. Consequently, carbocyclic nucleosides display enhanced biostability[3]. The removal of the ring oxygen eliminates the anomeric and gauche effects, responsible for forcing the furan 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]. Recently, carbocyclic purine analogues such as carbovir **1** [6] and the structurally related abacavir **2** [7] (Ziagen) were found to be potent inhibitors of HIV reverse

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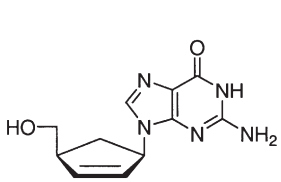
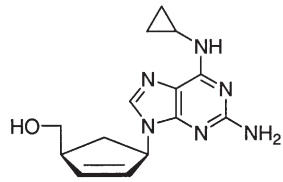
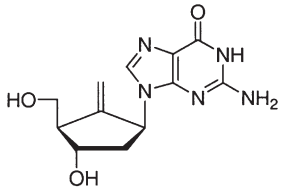
transcriptase. Moreover, entecavir **3** [8] (Baraclude) was approved by FDA in 2005 for the treatment of chronic HBV infections. Examples of bioactive pyrimidine analogues are carba-BVdU **4** that showed significant anti-HSV-1 activity[9] and carba-dT **5** which proved active against HIV-1 and HIV-2 (Chart 1)[10,11].



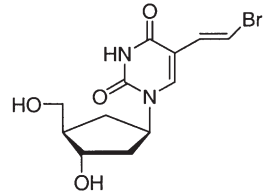
Carbovir (**1**)



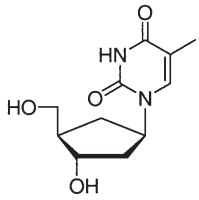
Abacavir (**2**)



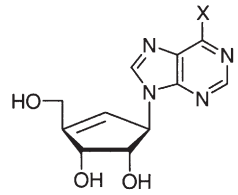
Entecavir (**3**)



carba-BVdU (**4**)

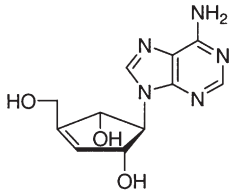


carba-dT (**5**)

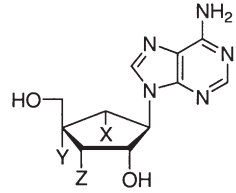


Neplanocin A: X = NH_2

Neplanocin D: X = OH



Neplanocin F



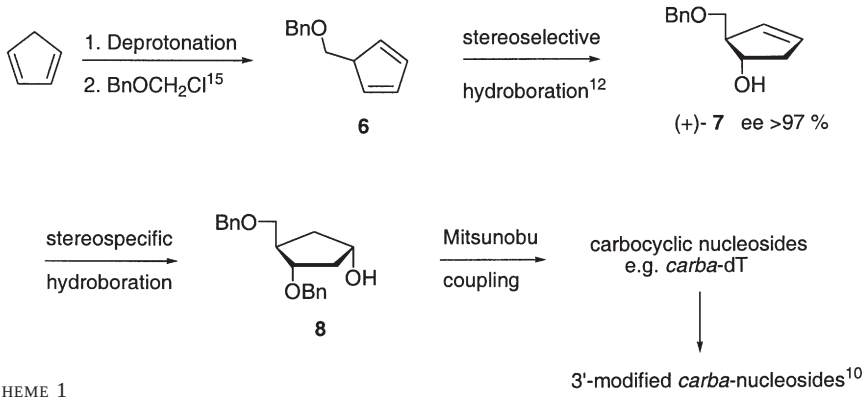
Neplanocin B: X = OH; Y = Z = O

Neplanocin C: Z = OH; X = Y = O

CHART 1

A number of syntheses grouped into two general categories have been designed for the preparation of carbocyclic nucleosides: the linear and the convergent approach. The former approach involves the synthesis of a functionalized cyclopentylamine and then a stepwise formation of the heterocyclic base while in the latter case the intact heterocycle is coupled to a functionalized carbocyclic moiety leading to a variety of carbocyclic nucleosides starting from one common cyclopentane precursor.

Recently we published a new procedure for the preparation of carbocyclic thymidine analogues starting from an alkylated cyclopentadiene **6** [13]. In two hydroboration reactions, one enantioselective reaction leading to (1*S*,2*R*)-2-[(benzyloxy)methyl]cyclopent-3-en-1-ol (**7**)[12] and one stereospecific step leading to cyclopentanol **8**, the required stereogenic centers were introduced[10,13–17]. Condensation of compound **8** with *N*3-protected pyrimidine nucleobases using a modified Mitsunobu protocol resulted in carbocyclic nucleosides like carba-dT **5**. In addition we have shown that 3′-modified carba-nucleosides like carba-AZT are accessible (Scheme 1)[10].



SCHEME 1

Here, we report on a route that offers even more synthetic possibilities as before.

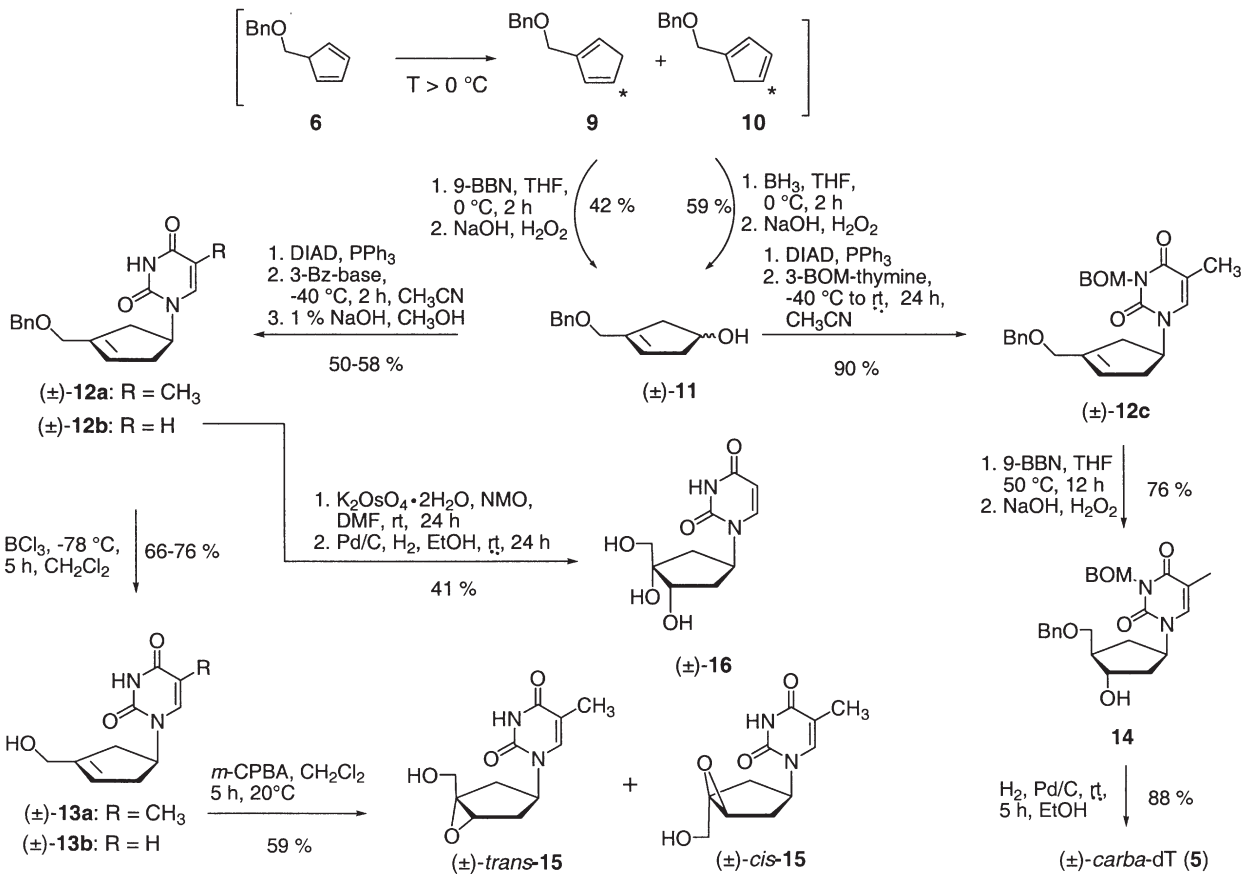
RESULTS AND DISCUSSION

In our previous method, cyclopentadiene was deprotonated and alkylated with (benzyloxy)methyl chloride to give cyclopentadiene **6** which was then stereoselectively hydroborated with (–)-diisopinocampheylborane. Although this reaction created two new stereogenic centers in one step with excellent enantiomeric excess (>97% ee) the chemical yield was only about 55% [12].

The reason was that the intermediately formed diene **6** undergoes isomerization into *two* thermodynamically more stable cyclopentadienes **9** and **10** (Scheme 2). However, a closer look on these two isomerization products brought us to the idea that hydroboration of the mixture should lead eventually to only *one* product because the hydroboration proceeds always at the termini of a diene system due to inhomogeneous electron density distribution (orbital-controlled reaction)[18]. Two positions in **9**, **10** are equivalent (marked with an asterisk in Scheme 3) and the others are sterically less accessible. In a first attempt, the diene mixture was treated with 9-BBN as a sterically demanding hydroboration reagent. Interestingly, the characterization of the reaction product confirms our initial idea that only compound **11** is formed in 42% yield. Next, the diene mixture was treated with 0.3 equiv. of BH_3 in THF. Surprisingly, after alkaline work-up, again cyclopentenol **11** was isolated as the sole product in 59% overall yield (four steps starting from cyclopentadiene).

To prove the suitability of cyclopentenol **11** to be a starting material for the synthesis of carbocyclic nucleosides, pyrimidine heterocycles were introduced using the modified Mitsunobu reaction conditions as reported previously[13,14,16]. Thus, 3-benzoylthymine and 3-benzoyluracil were condensed successfully with cyclopentenol **11**. Alkaline treatment of the crude reaction product led to *O*-benzylcyclopentenyl nucleosides **12a** and **12b**, respectively. In parallel, cyclopentenol **11** was reacted with 3-[(benzyloxy)-methyl]thymine[15] under Mitsunobu conditions leading to intermediate **12c** in 90% yield. In the case of 3-benzoyl- and 3-[(benzyloxy)methyl]thymine the $N1/O^2$-regioselectivity was found to be 75:15 and 85:15 while a 9:1 regioselectivity was found for 3-benzoyluracil. The products were identified by HMBC-NMR spectroscopy. These values are identical to those reported before for the couplings to cyclopentanol **8**. This clearly points to an intrinsic property of the pyrimidine rings. Debenzylation of nucleosides **12** proceeded in ca. 70% yield using BCl_3 at –78 °C to give cyclopentenyl nucleoside analogues **13** [19], respectively. Cyclopentenyl nucleosides such as **13** are analogues of the bioactive Neplanocin A, D and F (Chart 1).

Then, 5′-*O*-benzylated *N*3-BOM-nucleoside (BOM = (benzyloxy)methyl) (**12c**) was hydroborated using 9-BBN with anti-Markownikow orientation which led to the formation of protected carbocyclic thymidine **14** and deprotection led to (±)-carba-dT **5** showing identical spectroscopic data as before[10]. The reaction proceeded with anti selectivity with respect to the heterocycle. Consequently, the sterically demanding hydroboration reagent attacks the C=C double bond from the α-face (Scheme 2). On the whole,


BnO
T > 0 °C
6
9
10
1. 9-BBN, THF, 0 °C, 2 h
2. NaOH, H2O2
42 %
59 %
1. BH3, THF, 0 °C, 2 h
2. NaOH, H2O2
1. DIAD, PPh3
2. 3-Bz-base, -40 °C, 2 h, CH3CN
3. 1 % NaOH, CH3OH
50-58 %
(±)-12a: R = CH3
(±)-12b: R = H
(±)-11
1. DIAD, PPh3
2. 3-BOM-thymine, -40 °C to rt, 24 h, CH3CN
90 %
(±)-12c
1. 9-BBN, THF 50 °C, 12 h
2. NaOH, H2O2
76 %
14
H2, Pd/C, rt, 5 h, EtOH
88 %
(±)-carba-dT (5)
BCl3, -78 °C, 5 h, CH2Cl2
66-76 %
1. K2OsO4•2H2O, NMO, DMF, rt, 24 h
2. Pd/C, H2, EtOH, rt, 24 h
41 %
(±)-16
(±)-13a: R = CH3
(±)-13b: R = H
m-CPBA, CH2Cl2
5 h, 20°C
59 %
(±)-trans-15
(±)-cis-15

SCHEME 2

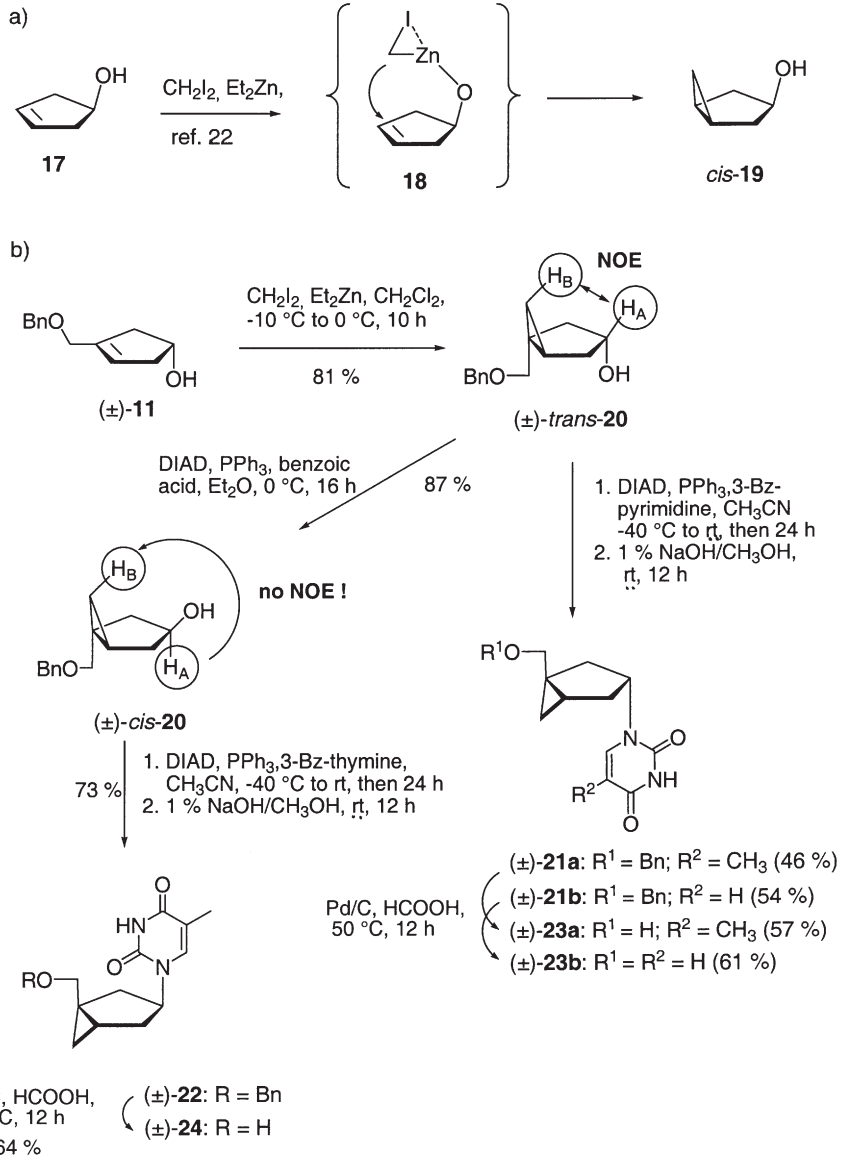
the route starting from a mixture of cyclopentadienes **9** and **10** is even shorter compared to our previously reported synthesis[13].

Moreover, this strategy offers the possibility of synthesizing new carbocyclic nucleosides because before or after introduction of the pyrimidine ring the double bond can be functionalized. To demonstrate that, cyclopentenyl nucleoside **13a** was treated with 3-chloroperbenzoic acid (*m*-CPBA) to form an epoxide **15** (Scheme 2). Such epoxide-containing carbocyclic nucleosides are analogues of the naturally occurring Neplanocin B and C. Surprisingly, we isolated both diastereomeric bicyclic nucleoside analogues **15** as a 1:1 mixture in 59% yield. Thus, in contrast to the hydroboration reaction, the unprotected heterocycle attached to the cyclopentenyl ring in **13a** was not able to hinder the attack from the β-face of the alkene sufficiently. It should be mentioned that *both* epoxides decompose slowly during storage at room temperature.

Cyclopentenyl uracil nucleoside (±)-**12b** was reacted with *N*-methylmorpholine-*N*-oxide (NMO) and $K_2OsO_4 \cdot 2H_2O$ in DMF for *cis*-dihydroxylation. As expected, *cis*-diol **16** was isolated in 41% yield after deprotection by hydrogenolysis in the presence of Pd/C. Taking the results of the epoxidation into account, the *cis*-hydroxylation surprisingly took place exclusively *trans* to the heterocycle. The relative stereochemistry was proven by NOE-experiments (Scheme 2).

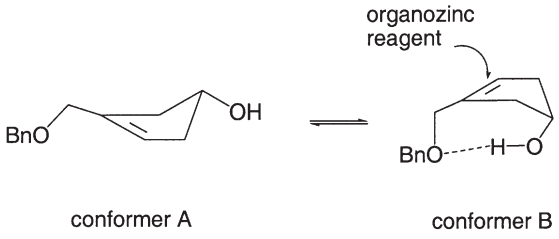
Bicyclic nucleosides attracted recently considerable interest because they are conformationally rigid or at least highly constrained analogues[4,20]. Thus, cyclopropanation of the cyclopentene ring was investigated. In previous reports cyclopent-3-en-1-ol (**17**) was treated with diiodomethane and diethylzinc (Furukawa's reagent)[21] for cyclopropanation (Scheme 3a). Due to complexation of the organo-zinc reagent by the hydroxy group (**18**), the cyclopropanation proceeded independently to the preferred conformation with *cis*-orientation of the two functional groups (*cis*-**19**)[22]. However, treating BOM-cyclopentenol **11** with CH_2I_2 and $ZnEt_2$ the bicyclic system *trans*-**20** was isolated in 81% yield.

This orientation was unambiguously proven by NOE spectroscopy (strong NOE between proton A and proton B; Scheme 3b). Further evidence of the *trans*-configuration was obtained after a conversion of the hydroxy group in compound *trans*-**20** using PPh_3, benzoic acid and diisopropyl azodicarboxylate (DIAD) to *cis*-**20** (87% yield). As expected, *no* NOE was now observed between proton A and B. Consequently, the Zn-reagent does not complex to the hydroxy group. The starting material **11** exists in two energy-low envelope-conformers. In one conformation (conformer B in Scheme 4) the hydroxy group may even form a hydrogen bridge to the oxy-


a)
OH
17
CH_2I_2, Et_2Zn,
ref. 22
I
Zn
O
18
OH
cis-19
b)
BnO
OH
(±)-11
CH_2I_2, Et_2Zn, CH_2Cl_2,
-10 °C to 0 °C, 10 h
81 %
NOE
H_B
H_A
BnO
OH
(±)-trans-20
DIAD, PPh_3, benzoic
acid, Et_2O, 0 °C, 16 h
87 %
1. DIAD, PPh_3,3-Bz-
pyrimidine, CH_3CN
-40 °C to rt, then 24 h
2. 1 % NaOH/CH_3OH,
rt, 12 h
H_B
OH
BnO
H_A
no NOE !
(±)-cis-20
R^1O
N
O
NH
R^2
O
73 %
1. DIAD, PPh_3,3-Bz-thymine,
CH_3CN, -40 °C to rt, then 24 h
2. 1 % NaOH/CH_3OH, rt, 12 h
(±)-21a: R^1 = Bn; R^2 = CH_3 (46 %)
(±)-21b: R^1 = Bn; R^2 = H (54 %)
Pd/C, HCOOH,
50 °C, 12 h
(±)-23a: R^1 = H; R^2 = CH_3 (57 %)
(±)-23b: R^1 = R^2 = H (61 %)
HN
O
N
RO
Pd/C, HCOOH,
50 °C, 12 h
64 %
(±)-22: R = Bn
(±)-24: R = H

SCHEME 3

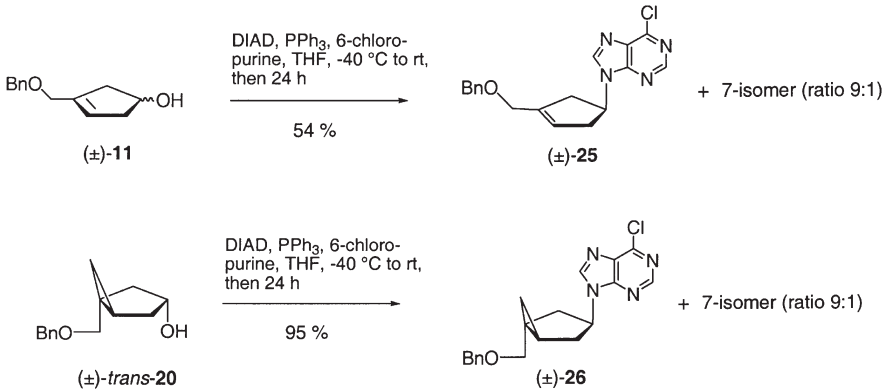
gen atom of the BOM group. In this conformation the lower face of the molecule is shielded by the two substituents while the upper face is less hindered. Thus, the Zn-reagent approaches preferably from that face leading to the anti orientation of the cyclopropane and the hydroxy group. Nevertheless, the reaction led to stereospecific cyclopropanation of the cyclopentene ring which is unprecedented. Attempts to use samarium carbenoid ($ISmCH_2I$) formed from a mixture of samarium, HgI_2 and CH_2I_2 (ref.[23]) for the cyclopropanation failed.



SCHEME 4

Bicyclo[3.1.0]hexanol *trans*-**20** was converted into the pyrimidine nucleoside **21a** (thymine) and **21b** (uracil) in about 50% yield. In the products, the heterocycle and cyclopropane are now in *cis*-orientation. However, if the *trans*-orientation is needed, bicyclo[3.1.0]hexanol *cis*-**20** would be the appropriate starting material leading to nucleoside **23**. The benzyl protecting group in nucleoside analogues **21**, **22** was cleaved using Pd/C and formic acid to give bicyclic nucleoside analogues **23a**, **23b** and **24** in about 60% yield.

Cyclopentenol **11** and bicyclo[3.1.0]hexanol (±)-*trans*-**20** were used for the first syntheses of 6-chloropurine analogues (Scheme 5). Mitsunobu cou-



SCHEME 5

pling of precursors (±)-**11** or *trans*-**20** with 6-chloropurine led to the formation of the protected purine nucleosides **25** and **26** in 54 and 95% yields, respectively. The *cis*-orientation in bicyclo[3.1.0]hexanylpurine **26** was confirmed by a strong NOE signal between H8 of the purine and H_B of the three-membered ring. The coupling of the bicyclic system and the purine ring resulted in a 9:1 mixture of *N*9/*N*7-regioisomers which were separated by column chromatography. The regioisomers were distinguished by their HMBC-NMR spectra. Both compounds will serve in the future as starting materials for the preparation of, e.g., adenine nucleoside analogues using known procedures[6,7,20].

In summary, we have elaborated an interesting new pathway towards the synthesis of functionalized carbocyclic pyrimidine and purine nucleoside analogues. Most interestingly, the route opens an access to the important class of bicyclic nucleoside analogues. The method starts from cheap cyclopentadiene and is a powerful addition to our previously reported methodology. Currently we are working on stereoselective hydroboration of a mixture of alkylated cyclopentadienes **9** and **10**. The biological evaluation of the compounds is under investigation.

EXPERIMENTAL

All experiments involving water-sensitive compounds were conducted under scrupulously dry conditions (nitrogen atmosphere) using 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 and CH_3CN were distilled from CaH_2 and stored over molecular sieves. EtOAc, CH_2Cl_2, petroleum ether and CH_3OH employed in chromatography were distilled before use. Chromatography: Chromatotron (Harrison Research 7924), silica gel 60_{Pf} (Merck, with gypsum), UV detection at 254 nm. TLC: analytical thin layer chromatography was performed on Merck precoated aluminium plates 60 F_{254} with an 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), concentrated H_2SO_4 (0.5 ml), and HOAc (0.1 ml)) by heating with a fan. For column chromatography, Merck silica gel 60, 230–400 mesh was used. NMR spectra were recorded using (^{1}H NMR) Bruker AMX 400 at 400 MHz or Bruker DMX 500 at 500 MHz, (^{13}C NMR) Bruker AMX 400 at 101 MHz or Bruker DMX 500 at 123 MHz. All ^{1}H and ^{13}C NMR chemical shifts (δ-scale) are quoted in ppm and calibrated with solvent signals; coupling constants (*J*) are given in Hz. The spectra were recorded at room temperature. ESI mass spectra were measured on a Finnigan ThermoQuest MAT 95 XL spectrometer and FAB high resolution (HR) mass spectra on a VG Analytical 70–250 F spectrometer (matrix was 3-nitrobenzyl alcohol).

General Procedure 1. Coupling of Pyrimidines

To a suspension of PPh_3 (3 equiv.) in anhydrous CH_3CN, DIAD (3 equiv.) was added slowly and the solution was stirred at 0 °C for 30 min. This preformed complex was slowly added

to a suspension of a protected nucleobase (2 equiv.) and the alcohols (±)-**11**, (±)-*cis*-**20** or (±)-*trans*-**20** (1 equiv.) in anhydrous CH_3CN at –40 °C under nitrogen. The reaction was slowly warmed to room temperature and stirred overnight. The solvent was removed from the reaction mixture and the *N*3-benzoyl nucleoside was chromatographed on silica gel column (petroleum ether–EtOAc, 1:2). This material was dissolved in a methanolic NaOH solution (1%) and stirred at room temperature overnight. The solution was neutralized by addition of 1 M HCl and then concentrated. The crude material was purified on silica gel column (petroleum ether–EtOAc, 2:1) to yield the *N*1-alkylated compounds **12a**, **12b**, **21a**, **21b** and **22** as light yellow syrups.

General Procedure 2. Debenzylation of Cyclopent-3-en-1-yl Nucleosides

BCl_3 (1 M in CH_2Cl_2, 6 equiv.) was added slowly to a stirred solution of the benzylated carba-nucleosides (1 equiv.) in anhydrous CH_2Cl_2 at –78 °C. The reaction mixture was warmed to –25 °C and CH_3OH was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed and the residue with CH_3OH was concentrated three times. The crude product was purified by chromatography on a Chromatotron (CH_2Cl_2–CH_3OH gradient 0→20%) to yield the carba-nucleosides as white solids. After lyophilization (CH_3CN–water), the debenzylated nucleoside analogues were obtained as colorless solids.

General Procedure 3. Debenzylation of Bicyclic Nucleoside Analogues

Formic acid was added to a stirred suspension of benzylated carba-nucleoside (1 equiv.) and palladium on charcoal in CH_3OH. The reaction mixture was warmed to 50 °C for 12 h. The solvent was removed and the crude product was purified by chromatography on a Chromatotron (CH_2Cl_2–MeOH gradient 0→5%) to yield the carba-nucleoside as a white solid. After lyophilization (CH_3CN–water), the debenzylated nucleoside analogues were obtained as colorless solids.

(±)-3-[(Benzyl)oxymethyl]cyclopent-3-en-1-ol (**11**)

To a suspension of NaH (288 mg, 12.0 mmol) in anhydrous THF (10 ml) at 0 °C, was added freshly distilled cyclopentadiene (1.00 ml, 15 mmol) under nitrogen. The slightly pink solution was stirred at 0 °C for 1 h and then added dropwise to a solution of (benzyloxy)methyl chloride (1.7 ml, 12 mmol) in anhydrous THF (15 ml) at –50 °C. The reaction mixture was stirred at –40 °C for 2 h and slowly warmed to room temperature overnight. The solvent was evaporated under reduced pressure. The residue was cooled to 0 °C and a 1 M solution of BH_3·THF in THF (4.0 ml, 4.0 mmol) was added dropwise. The solution was stirred at 0 °C for 1 h, slowly warmed to room temperature and stirred at this temperature for another 16 h. The reaction mixture was quenched with 3 M NaOH (8.0 ml) solution and H_2O_2 (30%; 8.0 ml) at 0 °C and the mixture was stirred overnight. The formed solid was removed by filtration and washed with Et_2O. After phase separation the aqueous layer was washed with Et_2O (3 × 15 ml), the combined organic fractions were dried (anhydrous Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether–EtOAc, 2:1) yielding **11** (1.30 g, 59%) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): 7.38–7.27 (m, 5 H, CH-arom.); 5.66–5.63 (m, 1 H, H-4); 4.58–4.58 (m, 1 H, H-1); 4.51 (s, 2 H, CH_2-benzyl); 4.08 (s, 2 H, O-CH_2); 2.75–2.67 (m, 2 H,

H-2a, H-5a); 2.38–2.30 (m, 2 H, H-2b, H-5b). ^{13}C NMR (101 MHz, $CDCl_3$): 139.9 (C-3); 138.8 (Cq-arom.); 128.5 (C-arom.); 127.9 (C-arom.); 127.8 (C-arom.); 125.1 (C-4); 72.3 (O-CH_2); 72.2 (C-1); 68.9 (CH_2-benzyl); 43.3 (C-2); 42.8 (C-5). IR (film), cm^{-1}: 698, 946, 1168, 1198, 1453, 1496, 2849, 2920, 3030, 3396. HRMS-FAB, *m/z*: calculated for $C_{13}H_{16}O_2$ (M + H) 205.1229, found 205.1224.

(±)-1-{4-[(Benzyloxy)methyl]cyclopent-3-en-1-yl}thymine (**12a**)

See General procedure 1. PPh_3 (1.89 g, 7.21 mmol), DIAD (1.42 ml, 7.21 mmol) in CH_3CN (20 ml), cyclopentenol (±)-**11** (482 mg, 2.40 mmol), 3-benzoylthymine (980 mg, 4.83 mmol) in CH_3CN (20 ml). Yield 370 mg (50%). ^{1}H NMR (400 MHz, C_6D_6): 9.84 (bs, 1 H, NH); 7.28–7.03 (m, 5 H, CH-arom.); 6.44 (d, 1 H, ^4J = 1.3, H-6); 5.28–5.25 (m, 1 H, H-3′); 5.12–5.11 (m, 1 H, H-1′); 4.26 (s, 2 H, CH_2-benzyl); 3.73–3.63 (m, 2 H, H-5′); 2.41–2.30 (m, 2 H, H-6′a, H-2′a); 1.96–1.92 (m, 1 H, H-2′b); 1.91–1.88 (m, 1 H, H-6′b); 1.65 (d, 3 H, ^4J = 1.0, CH_3-thymine). ^{13}C NMR (101 MHz, C_6D_6): 162.3 (C-4); 151.5 (C-2); 138.5 (Cq-arom.); 136.3 (C-6); 128.9 (C-arom.); 128.7 (C-arom.); 125.3 (C-3′); 124.8 (C-4′); 111.5 (C-5); 72.8 (C-5′); 68.6 (O-CH_2); 53.6 (C-1′); 39.4 (C-2′); 39.3 (C-6′); 12.9 (CH_3-thymine). IR (film), cm^{-1}: 700, 1046, 1073, 1118, 1270, 1473, 1694, 2678, 2858, 2930, 3062, 3448. HRMS-FAB, *m/z*: calculated for $C_{18}H_{20}N_2O_3$ (M + H) 313.1552, found 313.1541.

(±)-1-{4-[(Benzyloxy)methyl]cyclopent-3-en-1-yl}uracil (**12b**)

See General procedure 1. PPh_3 (2.20 g, 8.4 mmol), DIAD (1.65 ml, 8.38 mmol) in CH_3CN (20 ml), cyclopentenol (±)-**11** (573 mg, 2.81 mmol), 3-benzoyluracil (1.21 g, 5.60 mmol) in CH_3CN (20 ml). Yield 486 mg (58%). ^{1}H NMR (500 MHz, $CDCl_3$): 8.54 (bs, 1 H, NH); 7.30–7.18 (m, 5 H, CH-arom.); 7.09 (d, 1 H, ^3J = 8.2, H-5); 5.65–5.63 (m, 1 H, H-3′); 5.59 (d, 1 H, ^2J = 7.9, H-6); 5.29–5.24 (m, 1 H, H-1′); 4.44 (s, 2 H, CH_2-benzyl); 4.06–3.95 (m, 2 H, H-5′); 2.91–2.81 (m, 2 H, H-2′a, H-6′a); 2.34–2.28 (m, 2 H, H-2′b, H-6′b). ^{13}C NMR (101 MHz, $CDCl_3$): 163.1 (C-4); 150.8 (C-2); 140.9 (C-5); 140.6 (C-4′); 138.1 (Cq-arom.); 128.6 (C-arom.); 128.0 (C-arom.); 127.8 (C-arom.); 125.4 (C-3′); 103.2 (C-6); 72.9 (CH_2-benzyl); 68.4 (C-5′); 53.4 (C-1′); 40.0 (C-2′); 39.8 (C-6′). IR (film), cm^{-1}: 699, 1028, 1093, 1203, 1383, 1459, 1666, 2081, 3450, 3854. MS-FAB, *m/z*: calculated for $C_{17}H_{18}N_2O_3$ (M + H) 299.1, found 299.2.

(±)-1-{4-[(Benzyloxy)methyl]cyclopent-3-en-1-yl}-3-[(benzyloxy)methyl]thymine (**12c**)

See General procedure 1. PPh_3 (780 g, 2.98 mmol), DIAD (0.56 ml, 2.8 mmol) in CH_3CN (8 ml), cyclopentenol (±)-**11** (204 mg, 1.00 mmol), 3-[(benzyloxy)methyl]thymine (517 mg, 2.10 mmol) in CH_3CN (8 ml). Yield 389 mg (90%). ^{1}H NMR (400 MHz, $CDCl_3$): 7.40–7.30 (m, 10 H, CH-arom.); 6.95 (d, 1 H, ^4J = 1.0, H-6); 5.76–5.72 (m, 1 H, H-3′); 5.52 (s, 2 H, O-CH_2-N); 5.46–5.39 (m, 1 H, H-1′); 4.72 (s, 2 H, CH_2-benzyl-A); 4.55 (s, 2 H, CH_2-benzyl-B); 4.11–4.06 (m, 2 H, 5′-CH_2); 2.96–2.85 (m, 2 H, H-2′a, H-6′a); 2.44–2.39 (m, 1 H, H-2′b); 2.39–2.34 (m, 1 H, H-6′b); 1.88 (d, 3 H, ^4J = 1.0, CH_3-thymine). ^{13}C NMR (101 MHz, $CDCl_3$): 163.3 (C-4); 150.2 (C-2); 145.3 (C4′); 140.8, 138.7 (Cq-arom.); 135.8 (C-6); 128.9, 128.8, 128.7, 128.3, 128.1, 128.0 (CH-arom.); 127.9 (C-3′); 111.2 (C-5); 73.1, 72.7 (CH_2-benzyl); 71.3 (O-CH_2-N); 68.9 (C-5′); 54.0 (C-1′); 40.2 (C-2′); 39.9 (C-6′); 13.7 (CH_3-thymine). IR (film), cm^{-1}: 698, 738, 772, 810, 1028, 1092, 1150, 1211, 1269, 1360, 1453, 1496, 1548,

1663, 1705, 2855, 2924, 3030. HRMS-FAB, *m/z*: calculated for $C_{26}H_{28}N_2O_4$ (M + H) 433.2127, found 433.2143.

(±)-1-[4-(Hydroxymethyl)cyclopent-3-en-1-yl]thymine (**13a**)

See General procedure 2. **12a** (370 mg, 1.20 mmol), BCl_3 (1 M in CH_2Cl_2, 7.2 ml, 7.2 mmol) in anhydrous CH_2Cl_2 (20 ml). Yield 172 mg (66%), m.p. 193–195 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 11.23 (bs, 1 H, NH); 7.29 (d, 1 H, ^4J = 1.3, H-6); 5.86–5.83 (m, 1 H, H-3′); 5.18–5.09 (m, 1 H, H-1′); 4.37–4.31 (m, 2 H, H-5′); 2.83–2.75 (m, 2 H, H-2′a, H-6′a); 2.50–2.43 (m, 2 H, H-2′b, H-6′b); 1.75 (d, 3 H, ^4J = 1.0, CH_3-thymine). ^{13}C NMR (101 MHz, DMSO-d_6): 163.9 (C-4); 150.8 (C-2); 141.4 (C-4′); 137.6 (C-6); 128.7 (C-3′); 109.6 (C-5); 53.3 (C-1′); 43.1 (C-5′); 38.3 (C-6′); 38.3 (C-2′); 12.3 (CH_3-thymine). IR (KBr), cm^{-1}: 627, 762, 824, 1008, 1027, 1054, 1676, 2126, 2252, 3438. HRMS-FAB, *m/z*: calculated for $C_{11}H_{14}N_2O_3$ (M + H) 223.1083, found 223.1100.

(±)-1-[4-(Hydroxymethyl)cyclopent-3-en-1-yl]uracil (**13b**)

See General procedure 2. **13a** (112 mg, 0.342 mmol), BCl_3 (1 M in CH_2Cl_2, 2.0 ml, 2.00 mmol) in anhydrous CH_2Cl_2 (10 ml). Yield 60.0 mg (76%), m.p. 144–147 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 11.25 (s, 1 H, NH); 7.41 (d, 1 H, ^3J = 8.0, H-6); 5.85–5.83 (m, 1 H, H-3′); 5.58 (d, 1 H, ^3J = 8.0, H-5); 5.16–5.08 (m, 1 H, H-1′); 4.34 (s, 2 H, H-5′); 2.87–2.76 (m, 2 H, H-2′a, H-6′a); 2.46–2.42 (m, 2 H, H-2′b, H-6′b). ^{13}C NMR (101 MHz, DMSO-d_6): 163.3 (C-4); 150.8 (C-2); 145.7 (C-4′); 142.0 (C-6); 128.7 (C-3′); 109.3 (C-5); 53.6 (C-1′); 43.0 (C-5′); 38.4 (C-6′) 38.4 (C-2′). IR (KBr), cm^{-1}: 760, 1008, 1055, 1272, 1379, 1460, 1686, 2819, 3006, 3433. HRMS-FAB, *m/z*: calculated for $C_{10}H_{12}N_2O_3$ (M + H) 209.0926, found 209.0925.

(±)-1-{4-[(Benzyloxy)methyl]cyclopent-3-ol-1-yl}-3-[(benzyloxy)methyl]thymine (**14**)

To a solution of protected nucleoside **12c** (100 mg, 0.231 mmol) in anhydrous THF (5 ml) at 0 °C, was added dropwise to a solution of 9-BBN (0.5 M in THF, 920 µl, 0.460 mmol). The reaction mixture slowly warmed to room temperature overnight. The reaction mixture was quenched with 3 M NaOH (170 µl) solution and H_2O_2 (30%; 170 µl) at 0 °C, and the mixture was stirred overnight. The formed solid was removed by filtration and washed with Et_2O. After phase separation the aqueous layer was washed with Et_2O (3 × 5 ml), the combined organic fractions were dried (anhydrous Na_2SO_4) and the solvent was removed under reduced pressure. The crude material was purified by chromatography on a Chromatotron (CH_2Cl_2–CH_3OH gradient 0→10%) yielding **14** (79 mg, 76%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): 7.40–7.27 (m, 10 H, CH-arom.); 6.98 (d, 1 H, ^4J = 1.0, H-6); 5.49 (s, 2 H, O-CH_2-N); 5.19–5.10 (m, 1 H, H-1′); 4.70 (s, 2 H, CH_2-benzyl-A); 4.56 (d, 1 H, J = 12.0, CH_2-benzyl-B); 4.52 (d, 1 H, J = 12.0, CH_2-benzyl-B); 4.32–4.27 (m, 1 H, H-3′); 3.69 (dd, 1 H, ^2J = 9.0, ^3J = 4.1, H-5′a); 3.51 (d, 1 H, ^2J = 9.0, ^3J = 7.0, H-5′b); 2.28–2.17 (m, 2 H, H-4′, H-6′a); 2.09–2.03 (m, 2 H, H-2′); 1.81 (d, 3 H, ^4J = 1.0, CH_3-thymine); 1.54–1.47 (m, 1 H, H-6′b). ^{13}C NMR (101 MHz, $CDCl_3$): 163.8 (C-4); 151.9 (C-2); 138.5, 138.3 (Cq-arom.); 136.4 (C-6); 128.7, 128.4, 128.2, 128.1, 128.1, 128.0 (CH-arom.); 110.8 (C-5); 75.8 (C-3′); 74.0 (CH_2-benzyl-A); 72.9 (C-5′); 72.4 (CH_2-benzyl-B); 71.2 (O-CH_2-N); 55.3 (C-1′); 47.1 (C-4′); 39.6 (C-2′); 32.8 (C-6′); 13.6 (CH_3-thymine). IR (film), cm^{-1}: 468, 611, 698, 736, 774, 1027, 1091, 1151, 1267, 1360, 1454, 1496, 1548, 1661, 2928, 3031, 3062, 3457. HRMS-FAB, *m/z*: calculated for $C_{26}H_{30}N_2O_5$ (M + H) 451.2233, found 451.2256.

(±)-*cis*/*trans*-1-[3,4-Epoxy-3-hydroxymethyl)cyclopentyl]thymine (**15**)

To a solution of *m*-chloroperbenzoic acid (138 mg, 0.82 mol) in anhydrous CH_2Cl_2 (10 ml) under nitrogen, (±)-1-[4-(hydroxymethyl)cyclopent-3-en-1-yl]thymine (**13a**; 140 mg, 0.55 mmol) was slowly added at 0 °C. The reaction mixture was stirred and allowed to warm to room temperature overnight. The reaction mixture was diluted with a saturated solution of sodium sulfite (5 ml) and stirred at room temperature After 1 h the layers were separated, the aqueous phase was extracted with CH_2Cl_2 (3 × 10 ml), the combined organic phases were dried (anhydrous Na_2SO_4) and the solvent was removed under reduced pressure. The crude material was purified by chromatography on a Chromatotron (CH_2Cl_2–CH_3OH gradient 0→5%) to yield the carba-nucleosides as white solids. After lyophilization (CH_3CN–water), the nucleoside analogues were obtained (*trans*-**15** (42.0 mg, 31%) and *cis*-**15** (39.0 mg, 28%)) as colorless solids (diastereomeric ratio: 1:1.2 (*trans*:*cis*)).

trans-**15**: m.p. 186 °C (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6): 11.17 (bs, 1 H, NH); 7.52 (d, 1 H, ^4J = 0.9, 1 H, H-6); 5.18–5.12 (m, 1 H, H-1′); 4.11 (d, 1 H, ^2J = 12.0, H-5′a); 3.79 (d, 1 H, ^2J = 12.3, H-5′b); 3.73–3.69 (m, 1 H, H-3′); 2.55–2.42 (m, 2 H, H-2′a, H-6′a); 2.09–2.01 (m, 2 H, H-2′b, H-6′b); 1.77 (d, 3 H, ^4J = 0.9, CH_3-thymine). ^{13}C NMR (101 MHz, DMSO-d_6): 164.0 (C-4); 151.5 (C-2); 138.4 (C-6); 108.8 (C-5); 68.1 (C-4′); 64.4 (C-3′); 53.0 (C-1′); 45.7 (C-5′); 35.6 (C-6′); 34.4 (C-2′); 12.8 (CH_3-thymine). MS-ESI, *m*/*z*: calculated for $C_{11}H_{14}N_2O_4$ (M + Na) 261.1, found 261.1.

cis-**15**: m.p. 172 °C (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6): 11.22 (bs, 1 H, NH); 7.62 (d, 1 H, ^4J = 0.9, H-6); 4.57–4.49 (m, 1 H, H-1′); 4.14 (d, 1 H, ^2J = 12.0, H-5′a); 3.77 (d, 1 H, ^2J = 12.3, H-5′b); 3.72–3.65 (m, 1 H, H-3′); 2.32–2.22 (m, 2 H, H-2′a, H-6′a); 2.14–2.04 (m, 2 H, H-2′b, H-6′b); 1.76 (d, 3 H, ^4J = 0.9, CH_3-thymine). ^{13}C NMR (101 MHz, DMSO-d_6): 163.8 (C-4); 150.8 (C-2); 138.8 (C-6); 109.4 (C-5); 64.8 (C-4′); 61.4 (C-3′); 51.5 (C-1′); 46.1 (C-5′); 32.0 (C-6′); 31.6 (C-2′); 12.1 (CH_3-thymine). MS-ESI, *m*/*z*: calculated for $C_{11}H_{14}N_2O_4$ (M + Na) 261.1, found 261.2.

(±)-1-[3,4-Dihydroxy-4-(hydroxymethyl)cyclopentyl]uracil (**16**)

To a solution of the benzylated carbocyclic nucleoside (±)-**12b** (106 mg, 0.360 mmol) in anhydrous DMF, *N*-methylmorpholineoxide (NMO; 77 µl, 0.75 mmol) and $K_2OsO_4 \cdot 2H_2O$ (5.00 mg, 0.02 mol) were added. After stirring at room temperature for 24 h, the reaction mixture was quenched with a solution of sodium hydrogensulfite (ten drops) and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (10 ml) and washed with a solution of saturated sodium chloride (3 × 10 ml). The organic layer was dried (anhydrous Na_2SO_4) and the solvent was removed under reduced pressure. The crude material was purified by chromatography on a Chromatotron (CH_2Cl_2–CH_3OH gradient 0→5%) to yield the carba-nucleoside as white solids. ^{1}H NMR (400 MHz, DMSO-d_6): 11.18 (bs, 1 H, NH); 7.63 (d, 1 H, ^3J = 7.9, H-6); 7.56–7.45 (m, 5 H, CH-arom.); 5.50 (d, 1 H, ^3J = 8.0, H-5); 5.21–5.12 (m, 1 H, H-1′); 4.79 (d, 1 H, ^3J = 6.1, 3′-OH); 4.61 (s, 2 H, CH_2-benzyl); 4.53 (bs, 1 H, 4′-OH); 4.16 (dd, 1 H, ^3J = 14.1, ^3J = 7.8, H-3′); 3.62–3.54 (m, 2 H, H-5′); 1.98–1.86 (m, 4 H, H-2′, H-6′). ^{13}C NMR (101 MHz, DMSO-d_6): 163.2 (C-4); 150.9 (C-2); 143.0 (C-6); 138.5 (Cq-arom.); 128.3 (C-arom.); 127.5 (C-arom.); 127.4 (C-arom.); 101.4 (C-5); 78.8 (C-4′); 73.1 (C-5′); 72.6 (CH_2-benzyl); 71.6 (C-3′); 52.7 (C-1′); 38.8 (C-6′); 36.7 (C-2′). IR (film), cm^{-1}: 721, 1118, 1276, 1382, 1466, 1682, 2469, 2978, 3411. MS-FAB, *m*/*z*: calculated for $C_{17}H_{20}N_2O_5$ (M + H) 333.1, found 333.2. A suspension of the benzylated diol and palladium on charcoal (10%; 50 mg) in EtOH (5 ml) was stirred under H_2 atmosphere at

room temperature for 24 h. The mixture was filtered, and the filtrate was evaporated. The residue was purified by chromatography on a Chromatotron (CH_2Cl_2–CH_3OH gradient 0→5%) to yield the carba-nucleoside. After lyophilization (CH_3CN–water), the nucleoside analogue was obtained in the yield 29.0 mg (41%) as colorless solid, m.p. 205 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 11.17 (bs, 1 H, NH); 7.64 (d, 1 H, ^3J = 8.1, H-6); 5.56 (d, 1 H, ^3J = 8.1, H-5); 5.04–4.95 (m, 1 H, H-1′); 4.76 (dd, 1 H, ^3J = 5.5, ^3J = 5.5, 5′-OH); 4.71 (d, 1 H, ^3J = 6.3, 1 H, 3′-OH); 4.24 (s, 1 H, 4′-OH); 4.12 (dd, 1 H, ^3J = 13.7, ^3J = 6.3, H-3′); 3.36 (dd, 1 H, ^2J = 11.0, ^3J = 5.5, H-5′a); 3.28 (dd, 1 H, ^2J = 11.0, ^3J = 5.5, H-5′b); 1.99–1.88 (m, 2 H, H-2′); 1.87–1.79 (m, 2 H, H-6′). ^{13}C NMR (101 MHz, DMSO-d_6): 163.2 (C-4); 150.9 (C-2); 142.8 (C-6); 101.5 (C-5); 79.7 (C-4′); 70.9 (C-3′); 64.3 (C-5′); 52.4 (C-1′); 38.5 (C-2′); 37.0 (C-6′). IR (film), cm^{-1}: 668, 1002, 1048, 1289, 1677, 2256, 2342, 2360, 3439. MS-FAB, *m*/*z*: calculated for $C_{10}H_{14}N_2O_5$ (M + H) 243.1, found 243.1.

(±)-*trans*-1-[(Benzyloxy)methyl]bicyclo[3.1.0]hexan-3-ol (**20**)

A solution of Et_2Zn (1 M in hexane, 4.0 ml, 4.0 mmol) was added dropwise to cyclopentenol **11** (722 mg, 3.60 mmol) in anhydrous CH_2Cl_2 (20 ml) at –10 °C and stirred for 15 min. To this mixture a solution of diiodomethane (322 µl, 4.05 mmol) in anhydrous CH_2Cl_2 (5 ml) was added rapidly. After 15 min, an Et_2Zn solution (1 M in hexane, 4.0 ml, 4.0 mmol) was added dropwise. A solution of diiodomethane (322 µl, 4.0 mmol) in anhydrous CH_2Cl_2 (5 ml) was added rapidly and the reaction mixture was stirred at 0 °C overnight. After quenching with saturated NH_4Cl solution (25 ml), the mixture was stirred at room temperature overnight. The aqueous layer was washed with EtOAc (3 × 20 ml), the organic phase was washed with saturated NH_4Cl solution, dried (anhydrous Na_2SO_4) and concentrated. Purification of the residue was accomplished by chromatography on silica gel column (petroleum ether–EtOAc gradient 0→50%) to yield **20** (636 mg, 83%) as a colorless oil. ^{1}H NMR (400 MHz, C_6D_6): 7.31–7.07 (m, 5 H, CH-arom.); 4.32 (s, 2 H, CH_2-benzyl); 3.80 (m, 1 H, H-1); 3.33 (d, 1 H, ^2J = 9.8, O-CHH); 3.13 (d, 1 H, ^2J = 9.8, O-CHH); 1.99 (dd, 1 H, ^2J = 12.5, ^3J = 6.5, H-2a); 1.84 (dd, 2 H, ^2J = 12.3, ^3J = 6.6, H-2b, H-5a); 1.75–1.69 (m, 1 H, H-5b); 1.05–1.00 (m, 1 H, H-4); 0.36 (dd, 1 H, ^2J = 8.3, ^3J = 5.0, CHH-cyclopropyl); 0.05 (dd, 1 H, ^2J = 4.4, ^3J = 4.4, CHH-cyclopropyl). ^{13}C NMR (101 MHz, C_6D_6): 139.4 (Cq-arom.); 128.6 (C-arom.); 127.7 (C-arom.); 75.2 (O-CH_2); 72.8 (CH_2-benzyl); 72.7 (C-1); 40.0 (C-2); 38.0 (C-5); 28.0 (C-3); 20.8 (C-4); 16.3 (CH_2-cyclopropyl). IR (film), cm^{-1}: 698, 1028, 1272, 1398, 1496, 2491, 2858, 2935, 3062, 3397. MS-FAB, *m*/*z*: calculated for $C_{14}H_{18}O_2$ (M + H) 219.1, found 219.2.

(±)-*cis*-1-[(Benzyloxy)methyl]bicyclo[3.1.0]hexan-3-ol (**20**)

To a suspension of PPh_3 (630 mg, 2.40 mmol) in dry Et_2O (15 ml) at 0 °C under nitrogen was slowly added DIAD (473 µl, 2.40 mmol) and the suspension was stirred for 30 min. This preformed complex was slowly added to a suspension of benzoic acid (293 mg, 2.40 mmol) and alcohol (±)-**11** (175 mg, 0.81 mmol) in anhydrous Et_2O (15 ml) at 0 °C under nitrogen. The reaction was slowly warmed to room temperature and stirred for 16 h. The solid was removed by filtration and washed with Et_2O. The solvent was removed and a methanolic NaOH solution (1%; 20 ml) was added. Stirring was continued at room temperature overnight. The solution was neutralized by addition of 1 M HCl and then concentrated. The crude material was purified on silica gel column (petroleum ether–EtOAc, 2:1) to yield the

alcohol (153 mg, 87%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): 7.38–7.27 (m, 5 H, CH-arom.); 4.53 (s, 2 H, CH_2-benzyl); 4.46–4.41 (m, 1 H, H-1); 3.51 (d, 1 H, ^2J = 10.2, O-CHH); 3.43 (d, 1 H, ^2J = 10.4, O-CHH); 2.27–2.22 (m, 1 H, H-2a); 2.22–2.16 (m, 1 H, H-5a); 1.84 (d, 1 H, ^2J = 14.0, H-2b); 1.73 (d, 1 H, ^2J = 14.2, H-5b); 1.23–1.16 (m, 1 H, H-4); 0.94 (dd, 1 H, ^2J = 4.3, ^3J = 4.3, CHH-cyclopropyl); 0.60–0.56 (m, 1 H, CHH-cyclopropyl). ^{13}C NMR (101 MHz, $CDCl_3$): 139.4 (Cq-arom.); 128.5 (C-arom.); 127.7 (C-arom.); 127.6 (C-arom.); 75.3 (O-CH_2); 74.0 (C-1); 72.6 (C-benzyl); 40.7 (C-2); 38.5 (C-5); 30.2 (C-3); 22.5 (C-4); 16.7 (CH_2-cyclopropyl). IR (film), cm^{-1}: 738, 964, 1028, 1096, 1201, 1258, 1357, 1496, 2853, 2927, 3028, 3422. MS-FAB, *m/z*: calculated for $C_{14}H_{18}O_2$ (M + H) 219.1, found 219.2.

cis-(±)-1-{4-[(Benzyloxy)methyl]bicyclo[3.1.0]hexan-3-yl}thymine (**21a**)

See General procedure 1. PPh_3 (1.10 g, 4.00 mmol), DIAD (788 µl, 4.00 mmol) in CH_3CN (10 ml), (±)-*trans*-1-[(benzyloxy)methyl]bicyclo[3.1.0]hexan-3-ol (**20**; 290 mg, 1.33 mmol), 3-benzoylthymine (653 mg, 3.21 mmol) in CH_3CN (10 ml). Yield 201 mg (46%). ^{1}H NMR (400 MHz, $CDCl_3$): 8.35 (bs, 1 H, NH); 7.37–7.27 (m, 5 H, CH-arom.); 6.95 (d, 1 H, ^4J = 0.9, H-6); 5.19–5.10 (m, 1 H, H-1′); 4.53 (s, 2 H, CH_2-benzyl); 3.41 (d, 1 H, ^2J = 10.1, H-5′a); 3.37 (d, 1 H, ^2J = 10.1, H-5′b); 2.52–2.45 (m, 2 H, H-2′a, H-6′a); 1.91 (d, 3 H, ^4J = 1.0, CH_3-thymine); 1.74 (dd, 1 H, ^2J = 13.4, ^3J = 9.0, H-6′b); 1.57 (dd, 1 H, ^3J = 9.0, ^4J = 2.0, H-2′b); 1.28–1.23 (m, 1 H, H-3′); 1.02 (dd, 1 H, ^2J = 5.4, ^3J = 8.2, CHH-cyclopropyl); 0.62 (dd, 1 H, ^2J = 4.7, ^3J = 4.7, CHH-cyclopropyl). ^{13}C NMR (101 MHz, $CDCl_3$): 165.1 (C-4); 150.8 (C-2); 138.5 (Cq-arom.); 137.1 (C-6); 128.6 (C-arom.); 127.7 (C-arom.); 110.7 (C-5); 75.2 (C-5′); 73.0 (CH_2-benzyl); 60.5 (C-1′); 36.9 (C-6′); 35.0 (C-2′); 29.6 (C-4′); 24.3 (CH_2-cyclopropyl); 22.1 (C-3′); 12.7 (CH_3-thymine). IR (film), cm^{-1}: 699, 740, 909, 1298, 1365, 1685, 2342, 2360, 3188. MS-FAB, *m/z*: calculated for $C_{19}H_{22}N_2O_3$ (M + H) 327.2, found 327.3.

cis-(±)-1-{4-[(Benzyloxy)methyl]bicyclo[3.1.0]hexan-3-yl}uracil (**21b**)

See General procedure 1. PPh_3 (393 mg, 1.50 mmol), DIAD (0.29 ml, 1.50 mmol) in CH_3CN (5 ml), (±)-*trans*-1-[(benzyloxy)methyl]bicyclo[3.1.0]hexan-3-ol (**20**; 113 mg, 0.52 mmol), 3-benzoyluracil (216 mg, 1.00 mmol) in CH_3CN (5 ml). Yield 84 mg (54%). ^{1}H NMR (400 MHz, $CDCl_3$): 9.22 (bs, 1 H, NH); 7.37–7.26 (m, 5 H, CH-arom.); 7.15 (d, 1 H, ^3J = 8.2, H-6); 5.69 (d, 1 H, ^3J = 8.0, H-5); 5.18–5.10 (m, 1 H, H-1′); 4.52 (s, 2 H, CH_2-benzyl); 3.41 (d, 1 H, ^2J = 10.1, H-5′a); 3.37 (d, 1 H, ^2J = 10.1, H-5′b); 2.54–2.47 (m, 2 H, H-6′a, H-2′a); 1.75 (dd, 1 H, ^2J = 13.6, ^3J = 8.5, H-6′b); 1.58 (ddd, 1 H, ^2J = 13.9, ^3J = 8.7, ^3J = 1.7, H-2′b); 1.29–1.23 (m, 1 H, H-3′); 1.02–0.98 (m, 1 H, CHH-cyclopropyl); 0.59 (dd, ^2J = 4.7, ^3J = 4.7, 1 H, CHH-cyclopropyl). ^{13}C NMR (101 MHz, $CDCl_3$): 163.2 (C-4); 150.9 (C-2); 141.2 (C-6); 138.5 (Cq-arom.); 128.6 (C-arom.); 127.9 (C-arom.); 127.8 (C-arom.); 127.7 (C-arom.); 102.2 (C-5); 75.1 (C-5′); 73.0 (CH_2-benzyl); 60.7 (C-1′); 36.9 (C-6′); 35.0 (C-2′); 29.3 (C-4′); 23.9 (CH_2-cyclopropyl); 21.4 (C-3′). IR (film), cm^{-1}: 699, 1028, 1379, 1420, 1686, 2863, 3059, 3449. HRMS-FAB, *m/z*: calculated for $C_{18}H_{20}N_2O_3$ (M + H) 313.1552, found 313.1578.

trans-(±)-1-{4-[(Benzyloxy)methyl]bicyclo[3.1.0]hexan-3-yl}thymine (**22**)

See General procedure 1. PPh_3 (262 mg, 1.00 mmol), DIAD (0.197 ml, 1.02 mmol) in CH_3CN (5 ml), (±)-*cis*-1-[(benzyloxy)methyl]bicyclo[3.1.0]hexan-3-ol (**20**; 75 mg, 0.34 mmol), 3-benzoylthymine (172 mg, 0.66 mmol) in CH_3CN (5 ml). Yield 82 mg (73%). ^{1}H NMR (400 MHz, $CDCl_3$): 8.90 (bs, 1 H, NH); 7.38–7.27 (m, 5 H, CH-arom.); 7.08 (d, ^4J = 1.0, 1 H,

H-6); 4.83–4.73 (m, 1 H, H-1′); 4.56–4.54 (m, 2 H, CH_2-benzyl); 3.62 (d, ^2J = 10.4, 1 H, H-5′a); 3.39 (d, ^2J = 10.4, 1 H, H-5′b); 2.23–2.11 (m, 2 H, H-2′a, H-6′a); 2.04–1.94 (m, 2 H, H-2′b, H-6′b); 1.91 (d, ^4J = 1.0, 3 H, CH_3-thymine); 1.35–1.29 (m, 1 H, H-3′); 0.64 (dd, ^2J = 5.1, ^3J = 4.8, 1 H, CHH-cyclopropyl); 0.54 (dd, ^2J = 5.8, ^3J = 8.1, 1 H, CHH-cyclopropyl). ^{13}C NMR (101 MHz, $CDCl_3$): 163.7 (C-4); 151.1 (C-2); 138.5 (Cq-arom.); 136.9 (C-6); 128.6 (C-arom.); 127.8 (C-arom.); 127.7 (C-arom.); 111.5 (C-5); 75.2 (CH_2-benzyl); 74.6 (C-5′); 52.5 (C-1′); 34.4 (C-6′); 32.9 (C-2′); 27.3 (C-4′); 20.3 (C-3′); 13.5 (CH_2-cyclopropyl); 12.7 (CH_3-thymine). IR (film), cm^{-1}: 700, 739, 1072, 1266, 1299, 1373, 1454, 1578, 1686, 2865, 2933, 3032, 3199. MS-FAB, *m/z*: calculated for $C_{19}H_{22}N_2O_3$ (M + H) 327.2, found 327.2.

cis-(±)-1-[1-(Hydroxymethyl)bicyclo[3.1.0]hexan-3-yl]thymine (**23a**)

See General procedure 3. **21a** (181 mg, 0.55 mmol), formic acid (0.60 ml, 16.0 mmol) in CH_3OH (5 ml). Yield 75 mg (57%), m.p. 195–197 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 11.16 (bs, 1 H, NH); 7.51 (d, 1 H, ^4J = 1.0, H-6); 5.06–4.96 (m, 1 H, H-1′); 4.59 (bs, 1 H, 5′-OH); 3.43 (d, 1 H, ^2J = 11.4, H-5′a); 3.17 (d, 1 H, ^2J = 11.2, H-5′b); 2.27–2.18 (m, 2 H, H-2′a, H-6′a); 1.76 (d, 3 H, ^4J = 1.0, CH_3-thymine); 1.61 (dd, 1 H, ^2J = 12.7, ^3J = 10.2, H-6′b); 1.51–1.45 (m, 1 H, H-2′b); 1.13–1.08 (m, 1 H, H-3′); 0.86–0.83 (m, 1 H, CHH-cyclopropyl); 0.72 (dd, 1 H, ^2J = 4.2, ^3J = 4.2, CHH-cyclopropyl). ^{13}C NMR (101 MHz, DMSO-d_6): 163.8 (C-4); 150.8 (C-2); 138.0 (C-6); 108.9 (C-5); 65.7 (C-5′); 59.7 (C-1′); 35.4 (C-6′); 34.1 (C-2′); 31.0 (C-4′); 23.3 (CH_2-cyclopropyl); 20.2 (C-3′); 12.0 (CH_3-thymine). IR (KBr), cm^{-1}: 1004, 1260, 1363, 1401, 1684, 1749, 2835, 3424. HRMS-FAB, *m/z*: calculated for $C_{12}H_{16}N_2O_3$ (M + H) 237.1239, found 237.1268.

cis-(±)-1-[1-(Hydroxymethyl)bicyclo[3.1.0]hexan-3-yl]uracil (**23b**)

See General procedure 3. **21b** (29 mg, 0.09 mmol), formic acid (0.20 ml, 5.30 mmol) in CH_3OH (5 ml). Yield 13 mg (61%), m.p. 168–170 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 11.23 (s, 1 H, NH); 7.41 (d, 1 H, ^3J = 8.0, H-6); 5.58 (d, 1 H, ^3J = 8.0, H-5); 5.06–4.96 (m, 1 H, H-1′); 4.59 (bs, 1 H, 5′-OH); 3.43 (d, 1 H, ^2J = 11.4, H-5′a); 3.17 (d, 1 H, ^2J = 11.2, H-5′b); 2.27–2.18 (m, 2 H, H-2′a, H-6′a); 1.61 (dd, 1 H, ^2J = 12.7, ^3J = 10.2, H-6′b); 1.51–1.45 (m, 1 H, H-2′b); 1.13–1.08 (m, 1 H, H-3′); 0.86–0.83 (m, 1 H, CHH-cyclopropyl); 0.72 (dd, 1 H, ^2J = 4.2, ^3J = 4.2, CHH-cyclopropyl). ^{13}C NMR (101 MHz, DMSO-d_6): 163.3 (C-4); 150.8 (C-2); 141.6 (C-6); 109.3 (C-5); 65.7 (C-5′); 59.7 (C-1′); 35.4 (C-6′); 34.1 (C-2′); 31.0 (C-4′); 23.3 (CH_2-cyclopropyl); 20.2 (C-3′). HRMS-FAB, *m/z*: calculated for $C_{11}H_{14}N_2O_3$ (M + H) 223.1083, found 223.1097.

trans-(±)-1-[1-(Hydroxymethyl)bicyclo[3.1.0]hexan-3-yl]thymine (**24**)

See General procedure 3. **22** (49.0 mg, 0.15 mmol) in CH_3OH (5 ml). Yield 23 mg (64%), m.p. 182–186 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 11.21 (bs, 1 H, NH); 7.59 (d, 1 H, ^4J = 1.0, H-6); 4.62–4.51 (m, 1 H, H-1′); 3.97 (d, 1 H, ^2J = 10.9, H-5′a); 3.68 (d, 1 H, ^2J = 10.9, H-5′b); 2.81–2.66 (m, 2 H, H-2′a, H-6′a); 2.60–2.54 (m, 2 H, H-2′b, H-6′b); 1.74 (d, 3 H, ^4J = 1.0, CH_3-thymine); 1.46–1.40 (m, 1 H, H-3′); 0.74 (dd, 1 H, ^2J = 4.8, ^3J = 4.8, CHH-cyclopropyl); 0.66 (dd, 1 H, ^2J = 8.3, ^3J = 8.3, CHH-cyclopropyl). ^{13}C NMR (101 MHz, DMSO-d_6): 163.7 (C-4); 150.7 (C-2); 139.0 (C-6); 100.2 (C-5); 64.5 (C-5′); 52.7 (C-1′); 35.0 (C-6′); 33.8 (C-2′); 31.6 (C-4′); 23.8 (CH_2-cyclopropyl); 22.9 (C-3′); 12.0 (CH_3-thymine). IR (film), cm^{-1}: 482,

737, 1026, 1269, 1301, 1393, 1474, 1682, 2939, 3435. HRMS-ESI, *m/z*: calculated for $C_{12}H_{16}N_2O_3$ (M + Na) 259.1059, found 259.1071.

(±)-9-{4-[(Benzyloxy)methyl]cyclopent-3-en-1-yl}-6-chloro-9*H*-purine (**25**)

To a suspension of PPh_3 (783 g, 2.98 mmol) in anhydrous THF (20 ml), DIAD (0.59 ml, 3.0 mmol) was added slowly and the solution was stirred at 0 °C for 30 min. The preformed complex was slowly added to a suspension of 6-chloropurine (464 mg, 2.93 mmol) and (±)-4-[(benzyloxy)methyl]cyclopent-3-en-1-ol (**11**; 300 mg, 1.47 mmol) in anhydrous THF (20 ml) at –40 °C under nitrogen. The reaction was slowly warmed to room temperature and stirred overnight. The solvent was removed from the reaction mixture and the purine nucleoside was purified on silica gel column (petroleum ether–EtOAc, 1:2) to yield the title compound **25** (272 mg, 54%) as slight yellow syrup. ^{1}H NMR: (400 MHz, $CDCl_3$): 8.75 (s, 1 H, H-2); 8.18 (s, 1 H, H-8); 7.38–7.29 (m, 5 H, CH-arom.); 5.86–5.83 (m, 1 H, H-3′); 5.47–5.40 (m, 1 H, H-1′); 4.57 (s, 2 H, CH_2-benzyl); 4.16–4.13 (m, 2 H, H-5′); 3.18–3.06 (m, 2 H, H-2′a, H-6′a); 2.80–2.69 (m, 2 H, H-2′b, H-6′b). ^{13}C NMR (101 MHz, $CDCl_3$): 152.1 (C-2); 151.9 (C-4); 145.7 (C-4′); 143.5 (C-8); 138.6 (Cq-arom.); 134.6 (C-6); 132.2 (C-5); 128.6 (CH-arom.); 128.0 (CH-arom.); 127.8 (CH-arom.); 125.1 (C-3′); 72.9 (CH_2-benzyl); 68.3 (C-5′); 54.2 (C-1′); 40.6 (C-6′); 40.3 (C-2′). IR (film), cm^{-1}: 699, 812, 917, 1028, 1453, 1732, 2854, 2924, 3064. HRMS-FAB, *m/z*: calculated for $C_{18}H_{17}ClN_4O$ (M + H) 341.1169, found 341.1181.

(±)-9-{1-[(Benzyloxy)methyl]bicyclo[3.1.0]hexan-3-yl}-6-chloro-9*H*-purine (**26**)

For preparation see **25**. PPh_3 (865 mg, 3.30 mmol), DIAD (650 µl, 3.30 mmol) in anhydrous THF (20 ml), *trans*-**20** (235 mg, 1.08 mmol), 6-chloropurine (340 mg, 2.22 mmol), anhydrous THF (20 ml). Yield 353 mg (95%). ^{1}H NMR: (400 MHz, $CDCl_3$): 8.73 (bs, 1 H, H-2); 8.13 (s, 1 H, H-8); 7.38–7.27 (m, 5 H, CH-arom.); 5.26–5.18 (m, 1 H, H-1′); 4.55 (s, 2 H, CH_2-benzyl); 3.54 (d, 1 H, ^2J = 10.2, H-5a′); 3.40 (d, 1 H, ^2J = 10.2, H-5b′); 2.79–2.72 (m, 2 H, H-2a′, H-6a′); 2.27 (dd, 1 H, ^2J = 14.0, ^3J = 6.9, H-6b′); 2.14 (ddd, 1 H, ^2J = 14.1, ^3J = 6.6, ^4J = 1.7, H-2b′); 1.44–1.38 (m, 1 H, H-3′); 0.99–0.96 (m, 1 H, CHH-cyclopropyl); 0.75 (dd, 1 H, ^2J = 4.8, ^3J = 4.8, CHH-cyclopropyl). ^{13}C NMR (101 MHz, $CDCl_3$): 151.8 (C-2); 151.2 (C-4); 143.5 (C-8); 138.5 (Cq-arom.); 134.5 (C-6); 132.3 (C-5); 128.6 (C-arom.); 127.8 (C-arom.); 127.7 (C-arom.); 74.8 (C-5′); 73.0 (CH_2-benzyl); 59.2 (C-1′); 37.6 (C-6′); 35.7 (C-2′); 30.0 (C-4′); 22.2 (C-3′); 22.1 (CH_2-cyclopropyl). IR (film), cm^{-1}: 739, 941, 1092, 1195, 1396, 1437, 1653, 1717, 3447. HRMS-FAB, *m/z*: calculated for $C_{19}H_{19}ClN_4O$ (M + H) 355.1326, found 355.1338.

REFERENCES

1. a) Balzarini J.: *Pharm. World Sci.* **1994**, *16*, 113; b) De Clercq E.: *Nat. Rev. Drug Discovery* **2002**, *1*, 13.
2. Herdewijn P., Balzarini J., De Clercq E. in: *Advances in Antiviral Drug Design* (E. De Clercq, Ed.), Vol. 1, p. 233–318. JAI Press Inc., Greenwich, Connecticut, London 1993.
3. For reviews see: a) Agrofoglio L., Suhas E., Farese A., Condom R., Challand S. R., Earl R. A., Guedj R.: *Tetrahedron* **1994**, *50*, 10611; b) Crimmins M. T.: *Tetrahedron* **1998**, *54*, 9229.

4. Marquez V. E., Ezzitouni A., Russ P., Siddiqui M. A., Ford H., Feldman R. J., Mitsuja H., George C., Barchi J. J.: *J. Am. Chem. Soc.* **1998**, *120*, 2780.
5. Simons C. in: *Nucleoside Mimetics* (C. Simons, Ed.), Chap. 7, p. 137. Gordon and Breach Science Publishers, Amsterdam 2001.
6. Vince R., Hua M.: *J. Med. Chem.* **1990**, *33*, 17.
7. Daluge S. M., Martin M. T., Sickles B. R., Livingston D. A.: *Nucleosides Nucleotides Nucleic Acids* **2000**, *19*, 297.
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. 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.
10. Ludek O. R., Balzarini J., Meier C.: *Eur. J. Org. Chem.* **2006**, 932.
11. Béres J., Sági G., Tömösközi I., Gruber L., Baitz-Gács E., Ötvos L., De Clercq E.: *J. Med. Chem.* **1990**, *33*, 1353.
12. a) Biggadike K., Borthwick A. D., Evans D., Exall A. M., Kirk B. E., Roberts S. M., Stephenson L., Younds P.: *J. Chem. Soc., Perkin Trans. 1* **1988**, 549; b) Biggadike K., Borthwick A. D., Exall A. M., Kirk B. E., Roberts S. M., Younds P.: *J. Chem. Soc., Chem. Commun.* **1987**, 1083.
13. Ludek O. R., Meier C.: *Synthesis* **2003**, 2101.
14. Ludek O. R., Meier C.: *Synlett* **2005**, 3145.
15. Ludek O. R., Meier C.: *Eur. J. Org. Chem.* **2006**, 941.
16. Ludek O. R., Meier C.: *Synlett* **2006**, 324.
17. Ludek O. R., Krämer T., Balzarini J., Meier C.: *Synthesis* **2006**, 1313.
18. Collins S., Hong Y., Kataoka M., Nguyen T.: *J. Org. Chem.* **1990**, *55*, 3395.
19. O'Dell C. A., Shealy Y. F.: *Nucleosides Nucleotides* **1994**, *13*, 1929.
20. Rodriguez J. B., Marquez V. E., Nicklaus M. C., Mitsuya H., Barchi J. J.: *J. Med. Chem.* **1993**, *34*, 6233.
21. Furukawa J., Kawabata N., Nishimura J.: *Tetrahedron* **1968**, *24*, 53.
22. Nishimura J., Kawabata N., Furukawa J.: *Tetrahedron* **1969**, *25*, 2647.
23. Garahi M., Badelle F., Noe E. A.: *J. Org. Chem.* **1987**, *52*, 3941.