Transition-Metal-Mediated Synthesis of Novel Carbocyclic Nucleoside Analogues with Antitumoral Activity

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Abstract: A diversity-oriented, enantioselective synthesis of new (monoprotected) carbocyclic nucleoside analogues (CNAs) with the nucleobase attached to a 3-hydroxymethyl-4-trialkylsilyloxymethylcyclopent-2-en-1-yl scaffold was developed. As a key intermediate, racemic (5*SR*,8*RS*)-8-allyloxy-2-trimethylsilyl-7-oxa-bicyclo[3.3.0]-oct-1-en-3-one was prepared from 1,1-diallyloxy-3-trimethylsilyl-2-propyne in a cobalt-mediated Pauson–Khand reaction. The enantiomerically pure material was obtained through efficient kinetic resolution (selectivity factor $s \geq 40$ at −78 °C) by means of an oxazaborolidine-catalyzed borane reduction (CBS reduction) with catecholborane. The absolute configuration of the resolved products was determined by CD spectroscopy, Mosher ester analysis, and chemical correlation. Subsequent steps involve diastereoselective ketone reduction and fully regio- and diastereoselective introduction of the nucleobase through Pd^0-catalyzed allylic substitution. The generality of the method was demonstrated by preparation of CNAs in both enantiomeric series with all five natural nucleobases, as well as 5-bromouracil, 5-fluorouracil, and 6-chloropurine. Screening of the various compounds in a cytotoxicity assay with BJAB and ALL tumor cell lines revealed that some of the compounds possess pronounced antitumoral properties (LD_{50} values down to 9 μM, as determined by lactate dehydrogenase release after 48 h). By measuring DNA fragmentation, it could be shown that the activity results from induction of apoptosis.

Keywords: antitumor agents · kinetic resolution · nucleosides · palladium catalysis · Pauson–Khand reaction

Introduction

Nucleosides and nucleotides are of fundamental importance for all living systems, for example, as structural modules of nucleic acids, cofactors, and messenger substances.[1] Therefore, it is not surprising that nucleoside analogues play an important role in pharmacology, mainly as antiviral and antitumoral drugs.[2]

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Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author. It shows the structures of **11b**, *rac*-**10h**, and the acetate derived from *rac*-**18** in their crystalline states (in color).

While certain nucleoside analogues are incorporated into nucleic acids as chain terminators, thereby interrupting the replication of cancer cells or a virus,[3] others are designed to block certain enzymes necessary for cancer or viral reproduction (for example, (*S*)-adenosyl-L-homocysteine hydrolase[4] or reverse transcriptase).[3,5]

The popularity of nucleoside analogues increased after the Food and Drug Administration (FDA) approval of AZT (Zidovudin, **1**, Scheme 1) against HIV and of acyclovir (Zovirax, **2**) against the Herpes Simplex virus. In the past two decades, carbocyclic nucleoside analogues (CNAs) have also attracted much attention since the natural products aristeromycin (**3**)[6] and neplanocin A (**4**)[7] were shown to exhibit interesting biological activities. In the meantime, a large number of CNAs have been synthesized and tested.[8] Prominent synthetic CNAs are the anti-HIV compounds carbovir (**5**)[9] and abacavir (Ziagen) (**6**).[10]

One advantage of the carbocyclic compounds (CNAs) in comparison to the furanose-derived nucleoside analogues is a generally increased resistance against enzymatic degradation, as well as a decreased toxicity.[8a,11] Even though some CNAs are already in clinical use, this class of compounds still possesses a huge and largely unexploited potential for the development of new pharmaceuticals. The elaboration

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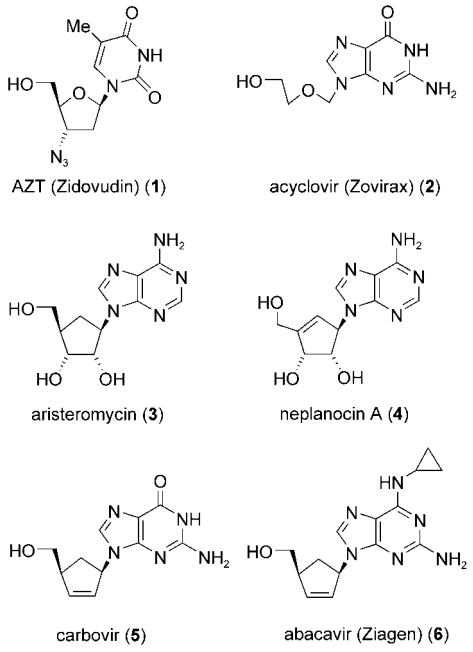
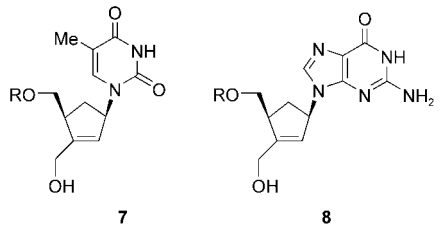


Scheme 1. Some important synthetic and natural nucleoside analogues.

of efficient methods for the diversity-oriented synthesis of new types of carbocyclic nucleoside analogues thus represents an important and challenging research task.

As already indicated in our preliminary communication,[12] we recently became interested in 2′,3′-unsaturated CNAs, such as **7** and **8** (Scheme 2), because these compounds might



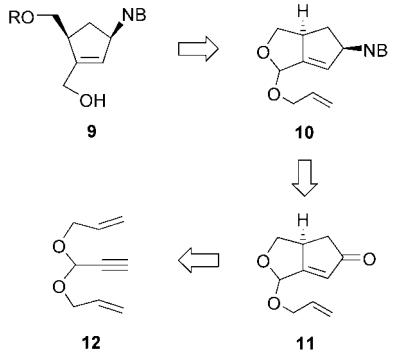
Scheme 2. Examples of projected target structures.

exhibit interesting biological activities. In addition, such structures would represent promising building blocks for the preparation of artificial oligonucleotides[13] and other complex molecules, for instance, hybrids with different pharmacophoric units, which would also be of pharmaceutical interest.

In this article we describe an efficient synthesis of enantiomerically pure CNAs of type **9** (see Scheme 3) by following a novel strategy that is centrally based on transition-metal–organic chemistry. Besides exploiting metal-mediated reactions, the synthesis is characterized by the fact that it is highly stereoselective and generally suited for the preparation of a broad variety of structurally diverse compounds (a scaffold approach).[14] Furthermore, we report the initial results of the biological testing, which demonstrate that some of the novel CNAs possess significant potential as antitumoral agents by inducing apoptosis of cancer cells.

Results and Discussion

Our retrosynthetic analysis (Scheme 3) was based on the consideration that the target structures **9** could be derived



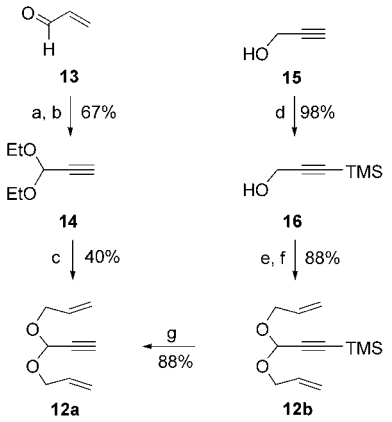
Scheme 3. Retrosynthetic analysis for CNAs of type **9**. NB = nucleobase.

from a precursor of type **10**, in which the two oxy-functionalized side chains are jointly protected within an acetal function. This would also allow for their later differentiation (selective preparation of monoprotected products) because cleavage of the acetal would lead to a hydroxyaldehyde. We predicted a bicyclic enone of type **11** to be a suitable precursor of **10**; **11** would be formally derived from the symmetric (achiral) dienyne **12** through an intramolecular Pauson–Khand reaction (PKR).[15]

While the intramolecular mode of the PKR would guarantee the desired regioselectivity, the (relative) configuration at the acetal stereocenter would not be important because this stereocenter would disappear at a later stage of the synthesis. A crucial issue, however, was the control of the absolute configuration of the lasting stereocenter(s). In order to obtain the target compounds in nonracemic form, we could either try to perform the (chirogenic) PKR in an enantioselective fashion[16] or we had to resolve a racemic intermediate at the stage of *rac*-**11** or beyond.

Synthesis of dienynes as PKR precursors: The synthesis of the CNAs of type **9** began with the preparation of a suitable substrate for the planned PKR, that is, a dienyne of type **12** (Scheme 4). By following a known protocol,[17] acrolein (**13**) was converted in high yield into a dibrominated diethyl acetal, from which the protected propargyl aldehyde **14** was obtained by double elimination with KOH as a base in the presence of $[Oct_4N^+Br^-]$ (1 mol%) as a phase-transfer catalyst.[18] The conversion of **14** into the desired diallyl acetal **12a** was achieved in 40% yield by acid-catalyzed transacetalization[19] with azeotropic removal of EtOH.

Since the overall yield of the sequence for the synthesis of **12a** described above was unsatisfactory, an alternative method was developed (Scheme 4, right). This new route began with the conversion of propargyl alcohol (**15**) into the TMS-protected derivative **16** by double silylation followed by selective O-desilylation.[20] After PCC oxidation of **16**,[21] the resulting (sensitive) aldehyde was directly converted into the stable diallyl acetal **12b**[22] by acid-catalyzed acetali-



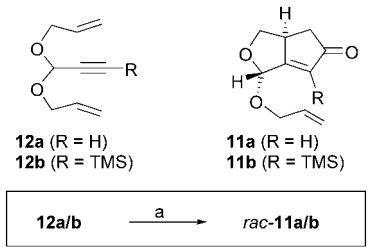
Scheme 4. Synthesis of the precursors of the Pauson–Khand reaction, **12a** and **12b**. a) Br_2, 0–5 °C; then $HC(OEt)_3$, EtOH, RT, 99 %; b) KOH (excess), $[Oct_4N^+Br^-]$ (cat.), CyHex, reflux, 67 %; c) allyl-OH (excess), TsOH (cat.), C_6H_6 (azeotropic removal of EtOH), 40 %; d) *n*BuLi (2.3 equiv), THF/*n*-hexane, −78 °C→RT, 4 h; then TMSCl (2.3 equiv), −78 °C→RT, 18 h; then aq. HCl (1.3 equiv), RT, 1 h, 98 %; e) PCC (1.5 equiv), CH_2Cl_2, RT, 3 h; f) allyl-OH (excess), TsOH (cat.), C_6H_6, Δ, 15 h, 88 % over 2 steps; g) TBAF (1 equiv) in THF, H_2O/allyl-OH (2:1), RT, 1 h, 88 %. CyHex = cyclohexane, Oct = octyl, PCC = pyridinium chlorochromate, TBAF = tetrabutylammonium fluoride, THF = tetrahydrofuran, TMS = trimethylsilyl, Ts = toluene-4-sulfonyl.

zation. This second route provides a highly efficient and operationally attractive synthesis of the C-silylated acetal **12b** (86 % over three steps), from which the desilylated dieneyne **12a** is obtained in high yield (88 %) by treatment with TBAF in allylic alcohol/H_2O (2:1).[23]

The Pauson–Khand reaction: The PKR is one of the oldest and synthetically most valuable transition-metal-mediated reactions, as it allows the construction of substituted cyclopentenones from an alkyne, an alkene, and carbon monoxide in a formal [2+2+1] cycloaddition.[15] While the "classical" PKR involves the thermal reaction of a preformed alkyne–$[Co_2(CO)_6]$ complex with an olefin (thus requiring stoichiometric amounts of the metal), some catalytic methods for Pauson–Khand-type reactions employing different metals (such as Ti, Rh, Ir, and Ru) have recently been developed.[24]

Initial attempts to prepare the bicyclic intermediates *rac*-**11a/b** from the dienynes **12a/b**, respectively, (Scheme 5) under standard literature conditions[25] afforded the expected products in low yields (Table 1, entries 1–4). We therefore had to optimize the conditions for this particular PKR.

As the first experiments had shown that TMANO gave better results than NMO and that the silylated compound **12b** gave rise to somewhat better yields and higher diastereoselectivities (d.r. up to



Scheme 5. Preparation of bicyclic intermediates of type **11** by the Pauson–Khand reaction. Optimized conditions: a) $[Co_2(CO)_8]$ (1.1 equiv), CH_2Cl_2, molecular sieves (4 Å, 8 equiv by weight), RT, 2 h; then TMANO (8.8 equiv), air, 0 °C→RT, 15 h. For yields, see Table 1.

> 98:2) than those with **12a**, the further optimization was carried out employing **12b** and TMANO. While variation of the solvent had some effect (Table 1, entries 5 and 6), a greatly improved yield (72 %) was obtained in dichloromethane when the reaction mixture was exposed to the air once the promoter had been added (entry 8).[25a] A further improvement was finally achieved by adding molecular sieves (4 Å).[26] In this way, the conversion of **12b** into the bicyclic product *rac*-**11b** could be performed in up to 76 % yield, even on a 60 mmol scale. Under the same conditions, the desilylated substrate **12a** afforded the corresponding PKR product in only 45 % yield and with significantly lower diastereoselectivity (Table 1, entry 10). From a variety of other conditions screened for the cobalt-mediated PKR of substrates **12a/b**, only the Sugihara method,[27] which uses *n*BuSMe as a promoter, afforded the desired product (*rac*-**11b** from **12b**) in a reasonable yield (Table 1, entry 11).

All our attempts to convert enynes **12a** and **12b** in catalytic Pauson–Khand-type reactions[24] failed, although control experiments with 1-allyloxy-3-phenyl-2-propyne as a literature-known model substrate proceeded successfully. For instance, by using $[RhCl(cod)]_2$ (5 mol %; cod = cycloocta-1,5-diene) and BINAP (10 mol %; BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl) as a catalyst and cinnamaldehyde (2 equiv) as a CO source[16f,g] (no solvent, 120 °C, 16 h), the product was obtained in 90 % yield and 81 % *ee* in the model series, while none of the desired product could be

Table 1. Optimization of the Pauson–Khand reaction according to Scheme 5.[a]

Entry	R	Solvent	Promoter	*T* [°C]	Conditions[b]	Yield [%]	*dr*
1	H	CH_2Cl_2	NMO	20	A	18	80:20
2	H	CH_2Cl_2	TMANO	0→20	A	28	90:10
3	TMS	CH_2Cl_2	NMO	20	A	28	93:7
4	TMS	CH_2Cl_2	TMANO	0→20	A	31	> 98:2
5	TMS	pentane	TMANO	0→20	A	0	–
6	TMS	THF	TMANO	0→20	A	50	> 98:2
7	TMS	THF	TMANO	0→20	B	27	> 98:2
8	TMS	CH_2Cl_2	TMANO	0→20	B	72	> 98:2
9	TMS	CH_2Cl_2	TMANO	0→20	C	76	> 98:2
10	H	CH_2Cl_2	TMANO	0→20	C	45	72:28
11	TMS	1,2-DCE	*n*BuSMe	reflux	D	57	> 98:2

[a] 1,2-DCE = 1,2-dichloroethane, NMO = *N*-methylmorpholine *N*-oxide, TMANO = trimethylamine *N*-oxide. [b] A: $[Co_2(CO)_8]$ (1.1 equiv), 2 h, RT, then addition of promoter (6 equiv), 15 h at specified temperature; B: same as A, except that the flask was left open to the air after addition of the promoter; C: same as B except that molecular sieves (4 Å, 8 equiv by weight) were added to the reaction mixture in the beginning and 8 equivalents of promoter were used; D: same as A except that 3.5 equivalents of promoter were used.

detected when **12a** or **12b** were used. Also, cationic rhodium species generated in situ from $[RhCl(cod)]_2$ and AgOTf (Tf = triflate = trifluoromethanesulfonyl) in the presence of various ligands (including propane-1,3-diylbis(diphenylphosphane) (dppp) and BINAP)[16d] were not able to catalyze this particular reaction. Therefore, compounds of type **12** represent particularly difficult substrates, especially for catalytic variants of the PKR. Nevertheless, the stoichiometric method with $[Co_2(CO)_8]$ and TMANO in the presence of 4 Å molecular sieves and air (Table 1, entry 9) provides a convenient and highly diastereoselective access to multigram amounts of the bicyclic intermediate *rac*-**11b**.[28]

The relative configuration of *rac*-**11a** and *rac*-**11b** was initially assigned based on 2D NMR spectroscopy experiments (NOESY) and later confirmed by X-ray crystal structure analysis of **11b** (Figure 1 and Supporting Information).[29]

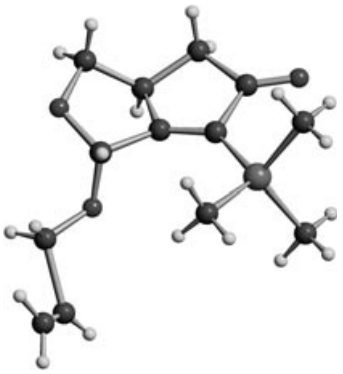
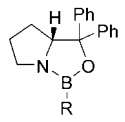


Figure 1. Structure of **11b** in the crystalline state.

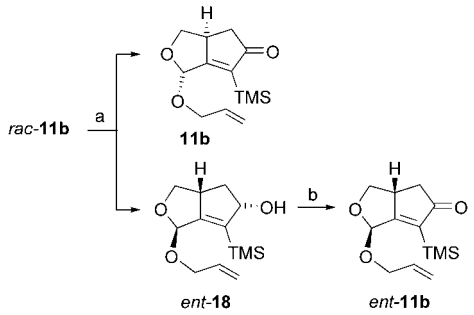
Kinetic resolution of the PKR product *rac*-11b: After the synthesis of CNAs of type **9** had been achieved in the racemic series in the course of our preliminary investigation,[12] a major task was to develop an enantioselective access to the target compounds. Since the chirogenic step[30] of the synthesis, that is, the PKR described above, could not be performed in an enantioselective fashion (so far), resolution of the PKR product *rac*-**11b** was the earliest possibility to enter the nonracemic series. We envisioned that this task could possibly be achieved through kinetic resolution (KR)[31] by means of an asymmetric reduction. As a promising method for this purpose, the oxazaborolidine-catalyzed borane reduction (CBS reduction)[32,33] employing chiral catalysts of type **17** was investigated (Scheme 6).



17a (R = Me)
17b (R = *n*Bu)
17c (R = Ph)

Scheme 6. Oxazaborolidine catalysts used for the reduction.

In order to prevent any hydroboration of a C–C double-bond in the substrate *rac*-**11b** by borane, catecholborane (CB) was used as a less reactive reducing agent (Scheme 7).[34] In an initial experiment, treatment of *rac*-**11b** in toluene with (neat) CB (50 mol%) in the presence of the *B*-methyl CBS catalyst **17a** (20 mol%) at −78°C afforded the enantiomerically enriched ketone **11b** (90% *ee*) and the alcohol *ent*-**18** (76% *ee*) after 45% conversion. When CB (0.85 equiv) was added as a solution



Scheme 7. Preparation of enantiomerically pure **11b** and *ent*-**11b** through kinetic resolution of the ketone *rac*-**11b** by means of a CBS reduction. a) **17a** (20 mol%), CB (0.85 equiv), THF/toluene, −78°C→RT, 6 h, 34% of **11b** (>99% *ee*), 58% of *ent*-**18** (83% *ee*, d.r. = 83:17); b) MnO_2, CH_2Cl_2, 0°C, 2 h, 89%; then *ent*-**17a** (20 mol%), CB (0.85 equiv), THF/toluene, −78°C→RT, 3 h, 72% of *ent*-**11b**.

in THF (which is easier to handle) to *rac*-**11b** in toluene in the presence of **17a** (20 mol%), approximately 60% conversion was observed at −50°C after 16 h, and the slower reacting enantiomer, **11b**, was isolated in virtually pure form (99% *ee*) according to GC analysis on a chiral column.[35] Lowering the amount of catalyst **17a** led to decreased enantioselectivities (after comparable conversions) while larger amounts gave no improvement. The *B*-butyl catalyst **17b** behaved in a similar manner to **17a**, while the *B*-phenyl catalyst **17c** showed no significant enantioselectivity at all in this reaction.

By carefully monitoring the KR of *rac*-**11b** at two temperatures (−78°C and −50°C), the high efficiency and the temperature dependence of these reactions were shown (Figure 2). While the KR of *rac*-**11b** at −78°C requires only 56% conversion to leave behind the slower reacting enantiomer **11b** in greater 99% *ee* (after 3 days), the reaction at −50°C needs 61% conversion to obtain **11b** in such a high enantiopurity (after 16 h). To express the high efficiency of these kinetic resolutions in numbers, the so-called selectivity factors ($s \geq k_{ent\text{-}\mathbf{11b}}/k_{\mathbf{11b}}$, in which k is the rate of reaction) were determined.[31d,e] The values calculated ($s \geq 40$ for −78°C and $s \geq 25$ for −50°C) are remarkably high; they are actually comparable to those obtained in typical enzymatic[31e] or particularly efficient chemical[31c,36] kinetic resolutions.

The most convenient protocol for the KR of *rac*-**11b** (Scheme 7) on a preparative scale (50 mmol) involves adding a solution of CB in THF at −78°C to a solution of **17a** and *rac*-**11b** in toluene and then allowing the mixture to slowly warm up to room temperature (6 h) before the reaction is quenched by addition of MeOH. In this way, ketone **11b** (>99% *ee*) could be obtained in 34% yield along with 58% of the alcohol *ent*-**18** (approximately 83% *ee*; d.r. = 83:17). As shown in Scheme 7, this material could be efficiently converted into the enantiomerically pure ketone *ent*-**11b** by MnO_2 oxidation and a second kinetic-resolution step employing the enantiomeric CBS catalyst *ent*-**17a**.

The stereochemical assignments of the reaction products were carefully proven: While the *relative* configuration of the main alcohol diastereomer (**18**/*ent*-**18**) was secured by

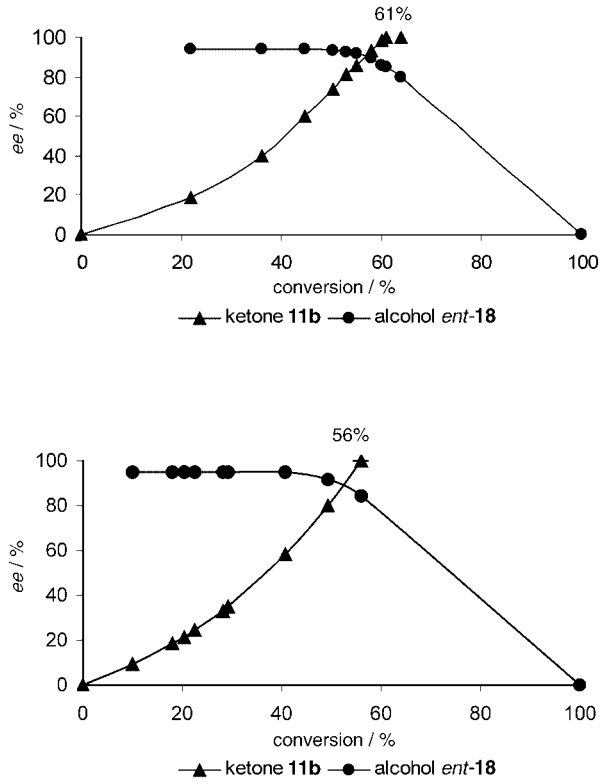


Figure 2. Kinetic resolution of ketone *rac*-**11b** at −78 °C (top) and at −50 °C (bottom).

X-ray crystal structure analysis of the corresponding (racemic) acetate (Figure 3),[37] the *absolute* configurations of the reaction products were determined by CD and NMR spectroscopic techniques and confirmed by chemical correlation (as described below in a separate section).

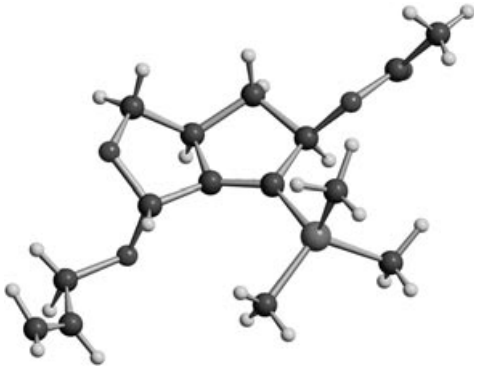
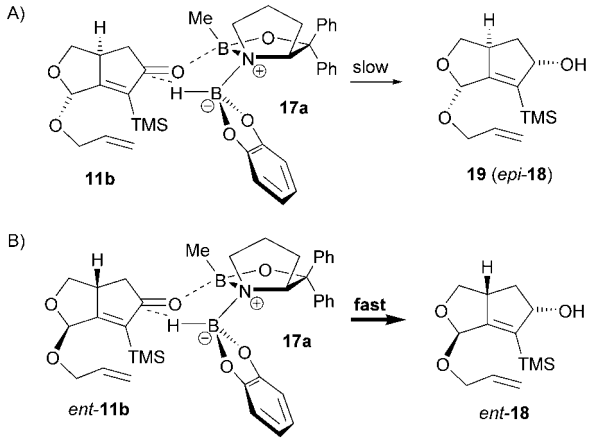


Figure 3. Structure of the acetate derived from *rac*-**18** in the crystalline state.

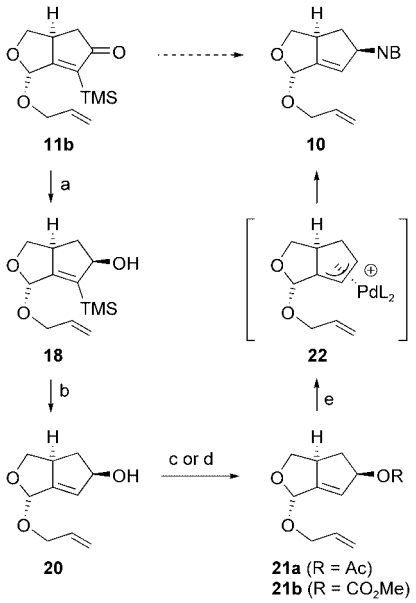
The stereochemical outcome of the CBS kinetic resolution of *rac*-**11b** by using the oxazaborolidine **17a** as a catalyst can be nicely rationalized by applying the Corey model[32b] with the assumption of strong catalyst control[33a] (Scheme 8). In the case of the substrate enantiomer **11b** the resulting transition structure (A) represents a "mismatched" case, because the natural preference of the substrate (substrate control, that is, attack of the hydride from the convex face) to give diastereomer **19** (*epi*-**18**) is frustrated and this results in a slower reaction. In contrast, the other substrate enantiomer (*ent*-**11b**) can participate in transition structure B, in which catalyst and substrate control work synergistically ("matched" case) to form *ent*-**18** in a fast process. Therefore, *ent*-**11b** is rapidly consumed and **11b** is left behind.



Scheme 8. Two competing transition structures in the kinetic resolution of *rac*-**11b** by CBS reduction with catalyst **17a**. Catalyst control is assumed: A) mismatched case (violation of substrate preference); B) matched case.

Planning the further synthesis: Once we had developed an efficient access to the key intermediate **11b** in both racemic and enantiopure forms, the next goal was to elaborate a sequence for the conversion of PKR products **11** into compounds of type **10** according to the general strategic concept (Scheme 3). We envisioned that an allylic ester of type **21** (obtainable from **11b** by reduction, desilylation, and esterification) could be used for the diastereoselective introduction of a nucleobase by means of Pd^0-catalyzed allylic substitution (Scheme 9). Such reactions are known to proceed with retention of configuration via cationic π-allyl intermediates of type **22**.[38,39] The further synthesis was first developed in the racemic series[12] and then applied to the preparation of various enantiomerically pure nucleoside analogues in both enantiomeric forms. For reasons of clarity, however, we will describe only the details for compounds with "natural" stereochemistry in the following sections.

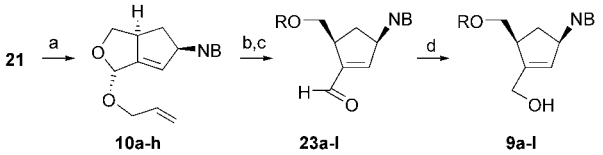
Preparation of the precursor for nucleobase introduction: The conversion of enone **11b** into the allylic esters **21a** or **21b** (Scheme 9) started with its reduction to the allylic alcohol **18**. It was found that this transformation was best achieved by using $NaBH_4$ in the presence of $CeCl_3$ in MeOH[40] at 0 °C. Under these conditions, **18** was obtained in virtually quantitative yield as a single diastereomer. A fully diastereoselective reduction was also achieved with L-Selectride (THF, −78 °C). However, the yield of isolated **18** was only 83 % in this case. The presence of the hydroxy group now allowed for a particularly facile, oxygen-assisted[41] removal of the TMS group under basic conditions. Indeed, when **18** was treated with KH in THF or, better, with *t*BuOK in DMSO, the desilylated product **20** was isolated in 87 % yield. Desi-



Scheme 9. Conversion of **11b** into nucleoside precursors of type **10**. a) $NaBH_4$, $CeCl_3$, MeOH, 0°C, 30 min, 100%; b) *t*BuOK, DMSO/H_2O (19:1), RT, 1 h, 87%; c) Ac_2O, Et_3N, DMAP (cat.), CH_2Cl_2, RT, 1 h, 99%; d) $ClCO_2Me$, pyridine, CH_2Cl_2, 0°C→RT, 1.5 h, 92%; e) nucleobase, Pd^0 (cat.), see Table 2 for further details. DMAP = 4-dimethylaminopyridine, DMSO = dimethylsulfoxide.

lylation with TBAF in THF afforded only impure material in significantly lower yield (66%). In contrast to the silylated alcohol **18**, the desilylated analogue **20** was found to be highly sensitive towards hydrolysis of the acetal function. Therefore, it was usually directly converted into the acetate **21a** under standard acetylation conditions[42] (99% yield). Alternatively, the methyl carbonate **21b** was obtained by treatment of **20** with methyl chloroformate in the presence of pyridine (92% yield).

Pd-catalyzed nucleobase introduction: Compounds **21a** and **21b** proved to be perfectly suited substrates for the introduction of various pyrimidine and purine nucleobases by means of Pd-catalyzed allylic substitution (Scheme 10 and Table 2).



Scheme 10. Final steps of the synthesis of CNAs of type **9**. a) Nucleobase or derivative, Pd^0 (cat.), see Table 2 for further details; b) PPTS, acetone, reflux, 3 h; c) R_3Si–Cl (1.5 equiv), pyridine, RT, 16 h; d) $NaBH_4$, MeOH/CH_2Cl_2, −78°C, 1 h; then RT, 30 min. For details, see Tables 2 and 3. PPTS = pyridinium *p*-toluenesulfonate.

When **21a** was treated with preformed salts of nucleobases in the presence of catalytic amounts of a Pd catalyst at elevated temperatures (50–70°C) in a DMSO/THF solvent mixture, the allylic substitution products of type **10** were formed in good yields with virtually complete regio- and diastereoselectivity (d.r. > 99:1; Table 2). While NaH was used to deprotonate the pyrimidine nucleobases, Cs_2CO_3 proved superior in the case of adenine (→**10g**) due to the better solubility of the resulting amide in organic solvents.[43] The direct introduction of cytosine and guanine failed. However, the N^4-benzoyl derivative of cytosine[44] afforded **10e** in up to 84% yield. For the introduction of guanine, the N^2-acetyl-*O*-diphenylcarbamoyl derivative was employed according to the method of Robins and co-workers[45] to give **10f** as a single regioisomer in 76% yield. In this case, 1,2,2,6,6-pentamethylpiperidine (pempidine) was used as the base.

An important parameter in these reactions was, of course, the Pd catalyst. Initially, we used $[Pd(PPh_3)_4]$ with two additional equivalents of PPh_3 (Method A),[46] a method that was successful for the introduction uracil, bromouracil, thymine, *N*-benzoylthymine, and adenine.[12] However, the formation of $Ph_3P{=}O$ (as a result of Ph_3P oxidation during workup) caused severe separation problems and isolated products **10** were often contaminated with significant amounts of $Ph_3P{=}O$.[47] Therefore, a different catalyst system consisting of $[Pd(dba)_2]$ (2 mol%) and $(i\mathrm{PrO})_3P$ (14 mol%) was applied (Method B).[44] While the yields were comparable to those obtained with $[Pd(PPh_3)_4]$, chromatographic product purification was generally easier. However, some of the less polar compounds tended to retain traces of $(i\mathrm{PrO})_3P$ as an impurity.

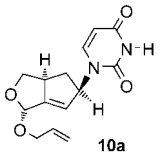
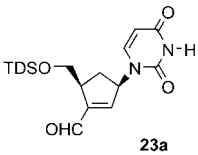
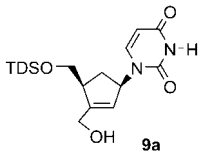
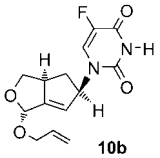
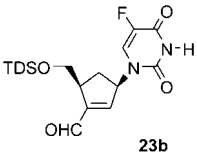
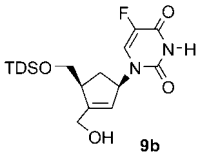
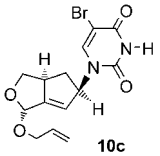
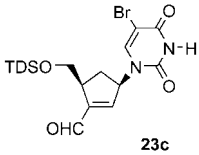
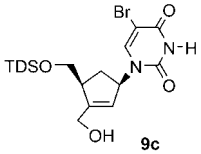
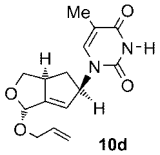
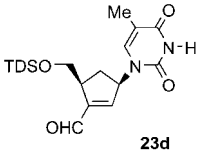
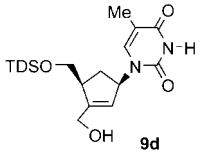
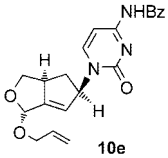
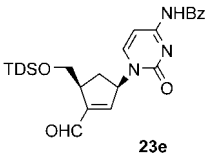
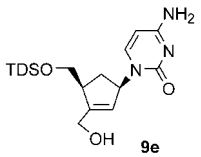
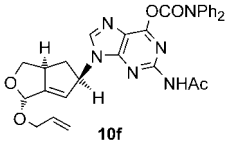
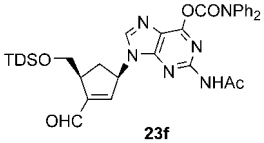
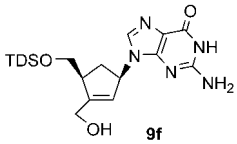
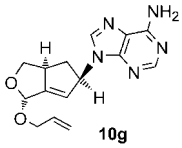
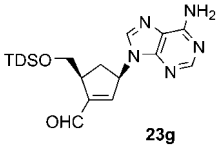
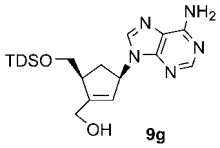
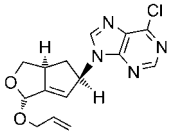
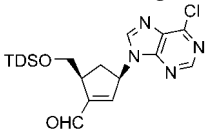
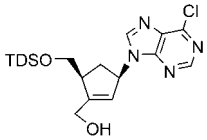
The introduction of chloropurine onto the allylic acetate **21a** under the catalytic conditions decribed above (Methods A and B) turned out to be difficult (approximately 5% yield). However, the product **10h** was obtained in up to 61% yield when the carbonate **21b** was used as the substrate. The catalyst system consisted of $[Pd_2(dba)_3]$ (2.5 mol%) and dppp (10.5 mol%) in DMF at RT (Method C). Here, dppp was a superior ligand to ethane-1,2-diylbis(diphenylphosphane) (dppe), 1,1′-bis(diphenylphosphanyl)butane (dppb), PPh_3, and $(i\mathrm{PrO})_3P$, which afforded **10h** in yields of 8, 0, 51, and 55%, respectively.

The constitution of **10e** and **10f** (and thus the regioselectivity of N-alkylation at the heterocycles) was confirmed by NMR spectroscopy exploiting long-range coupling. Nuclear overhouser effects (NOEs) between the H-3 and H-5 protons confirmed the relative configuration of the products **10a–g**. In addition, the structure of *rac*-**10h** was unequivocally proven by X-ray crystal structure analysis (Figure 4).[48] Thus, the Pd-catalyzed allylic aminations had proceeded with (complete) retention of configuration, as expected.[38,39]

Completing the synthesis of the carbocyclic nucleoside analogues: As shown in Scheme 10, the remaining steps in the synthesis of CNAs of type **9** were the hydrolysis of the acetal function in compounds of type **10**, the subsequent silylation of the free alcohol group, and the final reduction.

The hydrolysis of the bicyclic acetals **10** was best performed by using catalytic amounts of PPTS in refluxing wet acetone.[49] While the resulting hydroxyaldehydes[50] could, in principle, be isolated in pure form by solvent evaporation and chromatography, the crude products were usually converted directly into the corresponding silylethers by treat-

Table 2. Preparation of various TDS-protected CNAs of type **9** by Pd-catalyzed nucleobase introduction, acetal hydrolysis/silylation, and final reduction according to Scheme 10.[a]

Entry	Method[b]	Product **10**	Yield [%]	Product **23**	Yield [%]	Product **9**	Yield [%]
1	A	 **10a**	56	 **23a**	82	 **9a**	78
2	A	*ent*-**10a**	65	*ent*-**23a**	70	*ent*-**9a**	95
3	A	*rac*-**10a**	66	*rac*-**23a**	80	–	–
4	B	 **10b**	73	 **23b**	74	 **9b**	99
5	B	*ent*-**10b**	74	*ent*-**23b**	73	*ent*-**9b**	93
6	A	 **10c**	82	 **23c**	83	 **9c**	99
7	A	*ent*-**10c**	71	*ent*-**23c**	75	*ent*-**9c**	93
8	A	*rac*-**10c**	74	*rac*-**23c**	83	–	–
9	C	*rac*-**10c**	72	–	–	–	–
10	A	 **10d**	63	 **23d**	64	 **9d**	88
11	A	*ent*-**10d**	47	*ent*-**23d**	60	*ent*-**9d**	99
12	A	*rac*-**10d**	56	*rac*-**23d**	65	–	–
13	B	 **10e**	84	 **23e**	67	 **9e**	85[c]
14	A	*ent*-**10e**	65	*ent*-**23e**	75	*ent*-**9e**	95[c]
15	B	 **10f**	76	 **23f**	68	 **9f**	71[c]
16	B	*ent*-**10f**	76	*ent*-**23f**	67	*ent*-**9f**	76[c]
17	B	 **10g**	52	 **23g**	40	 **9g**	93
18	A	*ent*-**10g**	54	*ent*-**23g**	38	*ent*-**9g**	99
19	A	*rac*-**10g**	73	*rac*-**23g**	45	–	–
20	C	 **10h**	63	 **23h**	72	 **9h**	97
21	A	*rac*-**10h**	61	*rac*-**23h**	75	*rac*-**9h**	99 %

[a] Bz = benzoyl, dba = *trans*,*trans*-dibenzylideneacetone, DMF = *N*,*N*-dimethylformamide, TDS = thexyldimethylsilyl. [b] Method A: nucleobase, base (NaH for pyrimidine derivatives; Cs_2CO_3 for adenine), DMSO, 70 °C (50 °C for adenine), 30 min, then addition of $[Pd(PPh_3)_4]$ (5 mol %), PPh_3 (11 mol %), and **21a** in THF, 70 °C (50 °C for adenine), 16 h; Method B: nucleobase, base (NaH for pyrimidines; Cs_2CO_3 for adenine; pempidine for the guanine derivative), DMSO, 70 °C (50 °C for adenine; RT for the guanine derivative), 5–30 min, then $[Pd(dba)_2]$ (2 mol %), $P(OiPr)_3$ (14 mol %), THF, 70 °C (50 °C for adenine), 16 h; Method C: $[Pd_2(dba)_3]$ (2.5 mol %), dppp (10.5 mol %), DMF, 10 min, RT, then **21b**, nucleobase, RT, 16 h. [c] Yield of the deprotected product after treatment of the primary reduction product with NH_3 in MeOH at RT for 16 h.

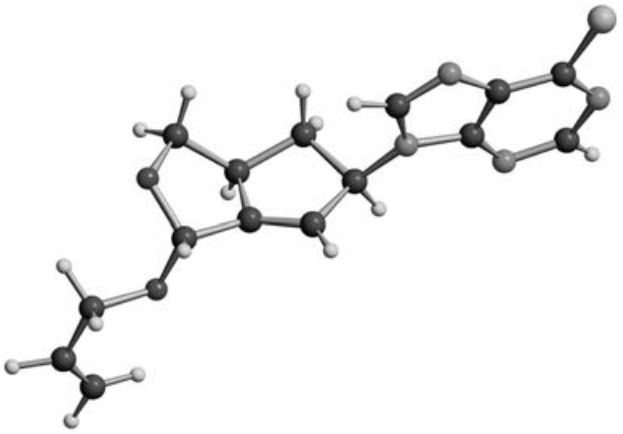


Figure 4. Structure of *rac*-**10h** in the crystalline state.

ment with a chlorosilane in pyridine. Thus, compounds **23a–f** and **23h–l** (Tables 2 and 3) were obtained in satisfactory yields (60–82% over two steps). Only for the hydrolysis of the adenine derivative **10g** were two equivalents of PPTS necessary. In addition, DMAP was employed in this case as a catalyst in the silylation step to give **23g** in acceptable yields (38–45%).

While the TDS group was chosen in most cases as a protecting group for the 5′-OH group (Table 2), intermediates **10b**, **10c**, **10e**, and **10f** were also converted into the corresponding TBDPS ethers **23i–l** (Table 3).

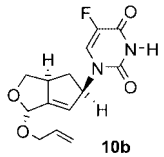
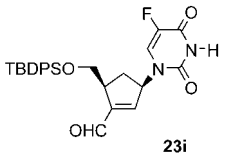
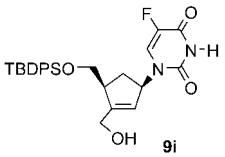
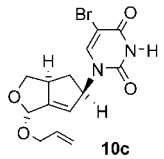
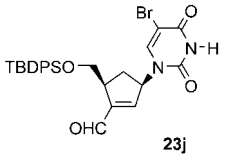
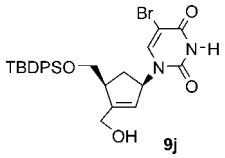
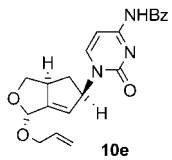
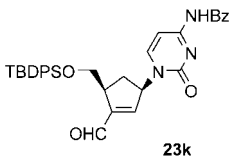
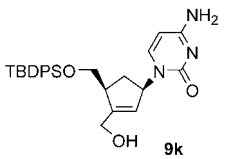
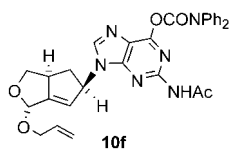
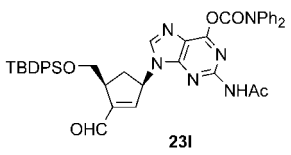
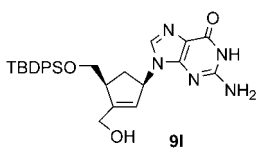
The final reduction of the α,β-unsaturated aldehydes of type **23** to the corresponding CNAs of type **9** (Scheme 10) was initially tried under the Luche conditions ($NaBH_4$/$CeCl_3$),[40] but the yields were rather low (46–67%).[12] Much better results, however, were obtained with $NaBH_4$ in the absence of $CeCl_3$ at −78°C in a solvent mixture of MeOH/CH_2Cl_2.[51] Under these conditions the products of type **9** were formed in 78–99% yields (Tables 2 and 3). When the protected cytosine or guanine derivatives **23e**, **23f**, **23k**, and **23l** were subjected to these conditions, the protecting groups were already partially removed. By exposing the resulting crude product mixtures to ammonolysis[39b,52] the desired products were obtained in high yields (Table 2 entries 13–16 and Table 3 entries 3,4).

Determination of the absolute configuration: As an important part of this work, the absolute configuration of the products obtained from the CBS kinetic resolution of *rac*-**11b** was carefully determined. As the X-ray crystal structure analysis of the optically active ketone **11b** (Figure 1) did not provide information about the absolute stereochemistry, other methods for the configurational assignment had to be applied.

As a first technique, we used CD spectroscopy, which is particularly suitable for cyclic ketones.[53] The CD spectra of ketones **11b** and *ent*-**11b** (Figure 5) show three Cotton effects (CEs): a weak CE at 330 nm corresponding to the carbonyl n→π* transition, a strong CE at 232 nm characteristic for the π→π* band, and a CE at 211 nm.

As the empirical octant rule cannot simply be applied to the analysis of CD spectra of α,β-unsaturated ketones,[53c] the so-called *enone helicity rule* was established.[53b,c] However, cyclohexenones and in particular cyclopentenones with a virtually planar enone chromophore (such as **11b**) obey the *inverse enone helicity rule*.[53b] According to this rule, the sign of the octant sector where the substituent at the "saturated part" of the cyclopentenone is located equals that of the CE for the π→π* transition (230–260 nm). The CE con-

Table 3. Preparation of TBDPS-protected CNAs **9i–l** from intermediates of type **10** according to Scheme 10.[a]

Entry	Starting material **10**	Product **23**	Yield [%]	Product **9**	Yield [%]
1	 **10b**	 **23i**	59	 **9i**	99
2	 **10c**	 **23j**	63	 **9j**	99
3	 **10e**	 **23k**	57	 **9k**	76[b]
4	 **10f**	 **23l**	37	 **9l**	99[b]

[a] TBDPS = *tert*-butyldiphenylsilyl. [b] Yield of the deprotected product after treatment of the primary reduction product with NH_3.

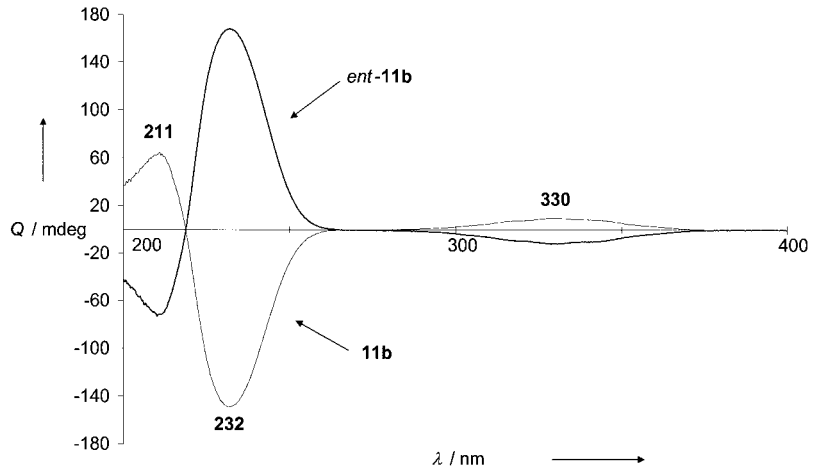
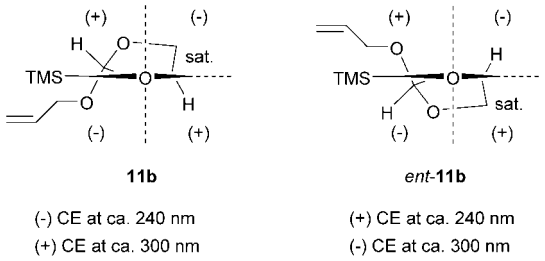


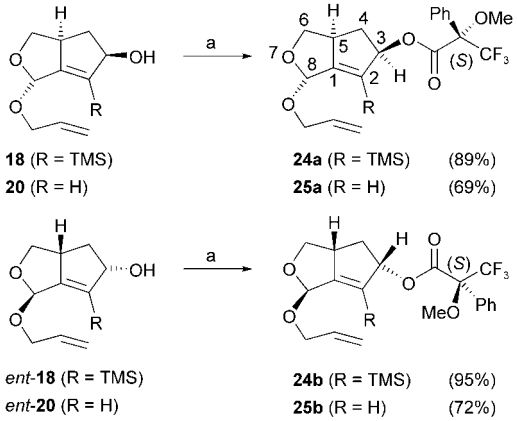
Figure 5. CD-spectra of ketones **11b** and *ent*-**11b** in cyclohexane.

nected to the n→π* transition (at approximately 330 nm) will then have an opposite sign.[53b] As shown in Scheme 11, the respective analysis for enone **11b** allows a clear assignment of the two enantiomorphic CD spectra to the enantiomers. The γ-allyloxy substituent should additionally contribute to the (−) character of the CE at approximately 230 nm.[53c] This analysis is also supported by comparison of the CD spectrum of **11b** with that of a structurally related compound of known configuration.[54]



Scheme 11. Application of the inverse helicity rule to ketones **11b** and *ent*-**11b**, thereby allowing the prediction of the sign of the Cotton effects.

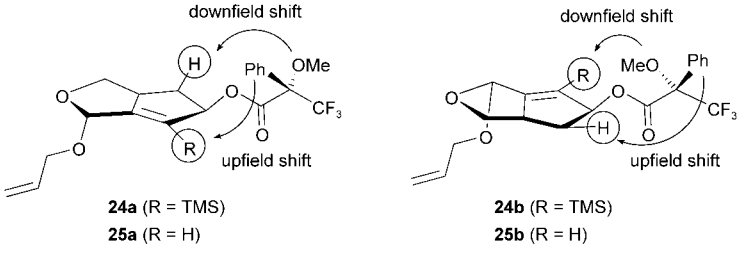
As a second independent technique for the determination of the absolute configuration, the empirical Mosher ester analysis[55] was applied to the alcohols **18** and **20**. This method is based on the comparison by NMR spectroscopy of pairs of diastereomeric esters obtained from a chiral alcohol by esterification with methoxytrifluoromethylphenylacetic acid (MTPA) of known absolute configuration. As both enantiomers of the alcohols to be investigated (**18** and its desilylated analogue **20**) were available, only one form of the chiral reagent (*S*)-MTPA had to be used. The four Mosher esters **24a, 24b, 25a**, and **25b** were obtained in good yields under the standard *N*,*N*′-dicyclohexylcarbidiimide (DCC) coupling conditions[56] (Scheme 12).



Scheme 12. Preparation of the Mosher (MTPA) esters from alcohols **18**, *ent*-**18**, **20**, and *ent*-**20**. a) (*S*)-MTPA (1.1 equiv), DCC (1.1 equiv), DMAP (12 mol %), CH_2Cl_2, 0 °C→RT, 16 h.

Based on the ^{1}H NMR spectroscopic data of the four MTPA esters prepared, the configurational assignments were drawn as follows:

1) One can assume that the esters adopt a preferred conformation, which is characterized by a horseshoe-type arrangement of the carbinol hydrogen atom and the carbonyl group as well as an antiperiplanar position of the CF_3 group with respect to the ester CO single bond (Scheme 13).[55]
2) According to the established rules,[55] the signals of protons on the phenyl side of the plane defined by the ester moiety undergo an upfield shift, while those of the protons on the methoxy side are shifted downfield (Scheme 13).



Scheme 13. Effects of the (S)-MTPA ester group (in its preferred conformation) on the ^{1}H NMR chemical shift of the signals of the adjacent substituents R and H-4_{exo}. See also Table 4.

3) By comparing the ^{1}H NMR spectroscopic data, the two pairs of diastereomers (**24a**/**24b** and **25a**/**25b**) could be clearly assigned. Most characteristic effects were observed for the substituent R at the olefinic position C2 and for the *endo*-hydrogen atom at C4 (Table 4). In accordance with Scheme 13, the signal for substituent R (TMS or H) showed a relative upfield shift ($\Delta\delta < 0$ ppm) in the spectra of **24a** and **25a** as compared to that in their diastereomers, while the signal of H-4$_{endo}$ was shifted downfield ($\Delta\delta > 0$ ppm) at the same time. Figure 6 illustrates the significant shift ($\Delta\delta = -0.07$ ppm) of the H-2 signal in the spectra of **25a** and **25b**.

Table 4. ^{1}H NMR chemical shifts (δ in ppm) of selected signals in the MTPA esters.

	24a	**25a**	**24b**	**25b**	$\Delta\delta$(**24a**/**24b**)	$\Delta\delta$(**25a**/**25b**)
H-2	–	5.71	–	5.78	–	−0.07
H-4$_{endo}$	1.40	1.62	1.27	1.52	+0.13	+0.10
TMS	−0.14	–	0.03	–	−0.17	–

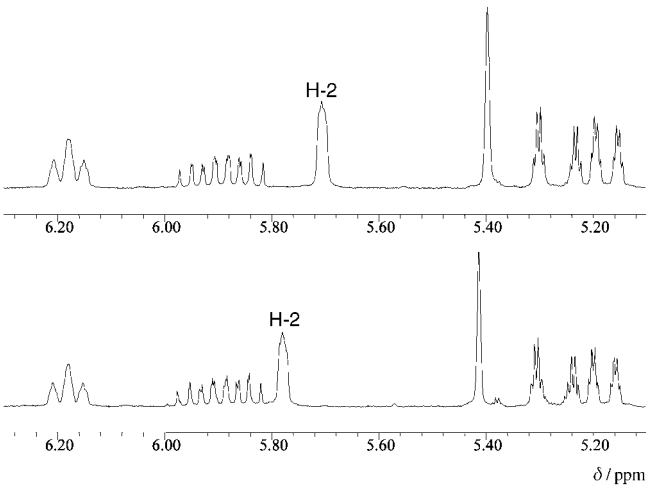
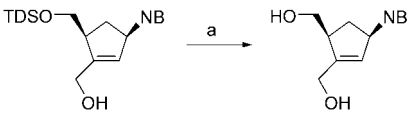


Figure 6. Section of the ^{1}H NMR spectra of MTPA esters **25a** (top) and **25b** (bottom).

4) As the configuration of the MTPA ester moiety was known (*S*), the absolute configuration of the bicyclic alcohols (**18**/*ent*-**18** and **20**/*ent*-**20**) could be directly deduced. It is in agreement with the earlier assignment based on CD spectroscopy.

After the absolute stereochemistry predicted by the Corey model (see above) had been confirmed by two empirical methods (CD spectroscopy and Mosher ester analysis) the correctness of our assignment was additionally supported by chemical correlation. For this purpose, the silylated compounds **9f** and **9g** were converted into the unprotected CNAs **26a** and **26b** by fluoride-induced desilylation (Scheme 14). These compounds had been independently synthesized before by Samuelsson and co-workers in a "stereorational" manner.[57]



9f (NB = guanine) **26a** (NB = guanine) (67%)
9g (NB = adenine) **26b** (NB = adenine) (99%)

Scheme 14. Deprotection of **9f** and **9g**. a) TBAF (2 equiv), THF, RT, 16 h.

The comparison of the specific rotations of **26a** ($[\alpha]_D^{20} = -11.8$; $c = 0.34$ in H_2O) and **26b** ($[\alpha]_D^{20} = -30.3$; $c = 0.33$ in H_2O) with those reported by Samuelsson and co-workers ($[\alpha]_D^{20} = -12.8$ for **26a** and $[\alpha]_D^{20} = -25.8$ for **26b**)[57] confirmed the configurational assignments of all chiral nonracemic compounds described in this work.

Biological investigations: The cytotoxic activity of some of the synthesized CNAs of type **9** was evaluated in vitro by using BJAB cells (Burkitt-like lymphoma cells).[58] The results summarized in Figure 7 indicate that some of the compounds possess a cytotoxic activity in the lower micromolar range. While the TDS-protected compounds **9a–h** showed moderate activity ($LD_{50} = 40$–100 μM) in both enantiomeric series, the TBDPS-protected compounds **9i–l** were generally more active ($LD_{50} = 9$–35 μM). Evidently, apart from the expected influence of the nucleobase on the activity, the silyl protecting group has a significant impact. Among the tested compounds the TBDPS-protected bromouracil and cytosine derivatives, **9j** ($LD_{50} = 9$ μM) and **9k** ($LD_{50} = 15$ μM), were the most active. As a general trend, the pyrimidine-based compounds exhibited a stronger activity than their purine-based relatives. One exception is the chloropurine derivative *rac*-**9h** with an LD_{50} value of 22 μM.

By using the most active compounds (**9i–l**), further experiments assessed whether the observed cell death was due to apoptosis or necrosis. The first evidence for apoptosis[59] was provided by microscopy, which showed a characteristic membrane blebbing and cell shrinkage of the tumor cells (not shown).

As an additional indicator of apoptotic cell death, the ability of compounds **9i–l** to induce DNA fragmentation (hypoploidity) was investigated.[60] As shown in Table 5, incubation with compounds **9i–l** led to substantial hypoploidity in BJAB cells as well as in primary, leukemic lymphoblasts of patients suffering from childhood acute lymphoblastic leukemia (ALL). Consistent with their high cytotoxic potential, compounds **9j** and **9k** were also particularly active in the DNA fragmentation assay. Further evidence for apoptosis was obtained by probing the activation of caspases 3, 8, and 9, which are principal effectors of apoptotic signal transduction and execution. Their activation by proteolytic cleavage after treatment of BJAB cells with compounds **9b** (50 μM) and **9i–l** (30 μM) was investigated by means of Western blot analysis.[61] As shown in Figure 8, compounds **9b** and **9i–l** induced specific processing of procaspase-3 (p32), procaspase-8 (p55), and procaspase-9 (p47) with concomitant appearance of the active subunits of the caspases (p17, p18, and p37, respectively). Interestingly, **9j**

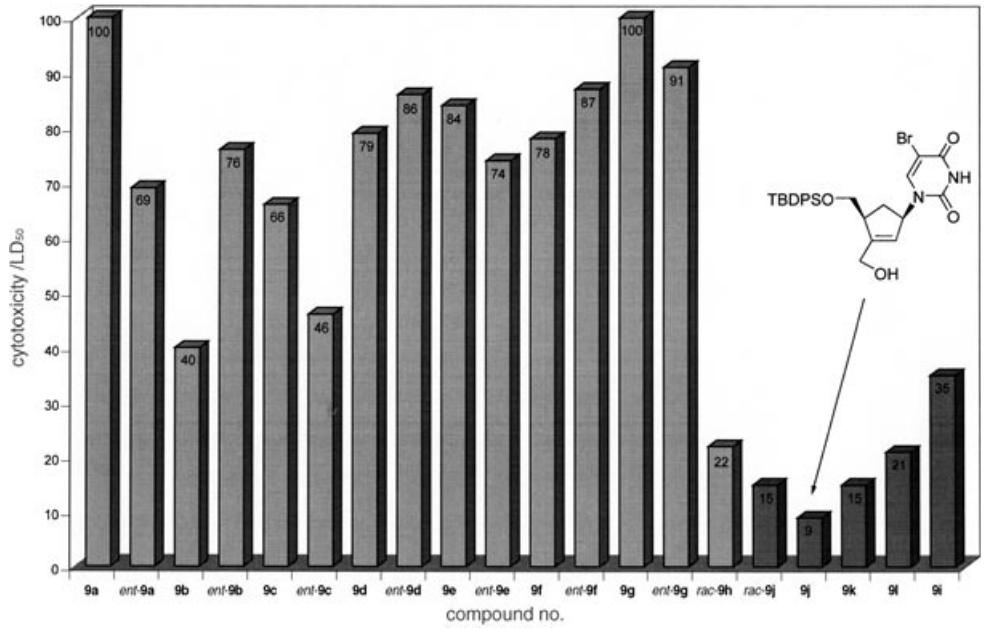


Figure 7. Cytotoxicity data for CNAs of type **9** in BJAB cells after incubation for 48 h. LD_{50} values are given in μM. Light gray is used for the TDS-protected compounds and darker gray for the TBDPS-protected compounds.

Table 5. Additional biological data for compounds **9i–l**.

Entry	Compound	Cytotoxicity[a] LD_{50} [μM]	Cell death [%][a] 10 μM	20 μM	Hypoploidity [%] ALL cells[b]	BJAB cells[c]
1	**9i**	35	1	4	28	55
2	**9j**	9	61	69	44	54
3	**9k**	15	14	72	33	66
4	**9l**	21	2	44	31	59

[a] Measured in BJAB cells after incubation for 48 h. [b] DNA fragmentation after incubation for 60 h at a nucleoside concentration of 20 μM. The hypoploidity of control cells in the presence of the vehicle alone (0.5% ethanol) was 15%. [c] DNA fragmentation after incubation for 72 h at a nucleoside concentration of 30 μM. The hypoploidity of control cells in the presence of the vehicle alone (0.5% ethanol) was 4%.

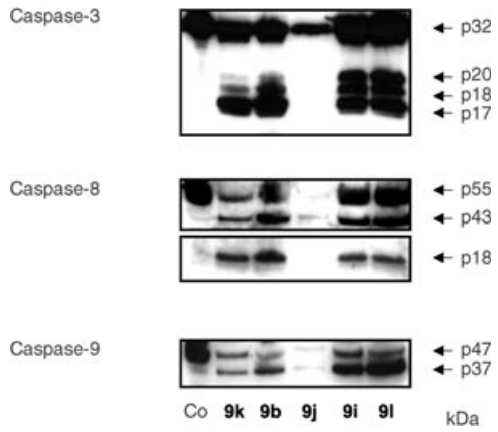


Figure 8. Western blot analysis of CNA-treated BJAB cells after incubation for 36 h. After incubation with 30 μM **9i–l** or with 50 μM **9b**, cells were collected, cellular protein was extracted, and processing of procaspase-3 (upper panel; procaspase: 32 kDa; cleavage products: 20, 18, and 17 kDa), procaspase-8 (middle panels; procaspase: 55 kDa; cleavage products: 43 and 18 kDa), and procaspase-9 (lower panel; procaspase: 47 kDa; cleavage product: 37 kDa) was detected by Western blot analysis. Arrows indicate the positions of procaspases-3, -8, and -9 and the respective cleavage products.

induced complete processing of procaspase-8 and procaspase-9, a result which again demonstrated the high potency of this compound.

Conclusion

We have developed a convergent and enantioselective synthesis of monoprotected, 2′,3′-unsaturated carbocyclic nucleoside analogues of type **9** with a hydroxymethyl substituent in the 3′ position (according to normal nucleoside numbering). Numerous new CNAs were prepared from propargyl alcohol and were fully characterized.

The synthesis in the racemic series involves only 10 linear steps with an average overall yield of approximately 25%. The synthesis centrally exploits transition-metal–organic chemistry, that is, a Co-mediated Pauson–Khand reaction (PKR) and a Pd-catalyzed allylic substitution, with the latter allowing the introduction of various nucleobases with virtually complete regio- and diastereocontrol.

While the chirogenic step, the Pauson–Khand reaction, cannot be directly performed in an enantioselective manner at the moment, an efficient kinetic resolution ($s \geq 30$) of the PKR product through CBS reduction opened an operationally convenient access to the enantiomerically pure compounds in both absolute configurations.

The absolute stereochemistry of the chiral products was carefully determined by three independent methods (CD spectroscopy, Mosher ester analysis, and chemical correlation) and is in accordance with the predictions drawn from the Corey model.

The potential of the new class of compounds as antitumoral agents was shown in a first series of biological assays with a Burkitt-like lymphoma cell line model as well as primary lymphoblastic tumor cells ex vivo. Cytotoxic activities at concentrations in the lower micromolar range specifically result from apoptosis induction and encourage further structural variation and screening in the future.

Indeed, the option of flexibly varying the structural modules (that is, the nucleobase and the substituents at both hydroxy groups) in a late stage of the synthesis provides ample opportunity for a broad structural variation (a diversity-oriented approach).[14] This includes the possibility of using the monoprotected compounds of type **9** as building blocks for the synthesis of oligonucleotides or conjugates with other pharmacophoric units (for example, natural-product hybrids).[62] Furthermore, the allylic alcohol unit in compounds of type **9** provides an anchor for additional structural modification.

Experimental Section

General: Anhydrous solvents were obtained by distillation from sodium/benzophenone (THF), from CaH_2 (CH_2Cl_2), from KOH (pyridine, Et_3N), or by storage over 4 Å MS (DMSO). Reagents (generally 99%) were used as purchased unless otherwise stated. The concentration of organolithium reagents was determined by titration against menthol in THF with 1,10-phenanthroline as an indicator.[63] TMANO was dried by azeotropic removal of water with toluene. Water- and/or air-sensitive compounds were handled under an atmosphere of argon by using Schlenk techniques. Reactions were monitored by analytical TLC with Merck silica gel 60F 254 aluminum plates. Chromatograms were visualized either with UV light, by staining with iodine, or with a "cerium reagent" (prepared by dissolving phosphomolybdic acid (2 g) and $Ce(SO_4)_2$ (1 g) in 100 mL of 10% aqueous H_2SO_4) and subsequent heating. Flash chromatography[64] was performed over silica gel 60 (230–400 mesh) from Merck. Gas chromatography was performed on an HP-6890 apparatus with H_2 as the carrier gas and flame ionization detector. NMR spectroscopy was carried out on Bruker DPX 300, DRX 500, and AC 250 instruments. Chemical shifts (δ) are given in ppm relative to the solvent reference. ^{13}C NMR spectra were measured under proton decoupling and the number of bound protons (multiplicities) was determined by DEPT methods. IR spectroscopy was carried out on a Perkin-Elmer FTIR Paragon 1000 apparatus by using the ATR technique. Mass spectrometry was performed on a Finnigan MAT Incos 50 Galaxy system (DIP-MS) or a Finnigan MAT 900 spectrometer; high-resolution MS was performed on Finnigan HSQ-30 (HR-EI-MS) or Finnigan MAT 900 (HR-ESI-MS) instruments. The method of ionization is given in parentheses. Melting points were measured on a Büchi B-545 apparatus and are uncorrected. Specific optical rotations ([α]) were recorded on a Perkin-Elmer 343 apparatus plus polarimeter; concentrations c are given in g per 100 mL and the cell length was 100 mm. CD spectroscopy was performed on a Jasco J-810 spectrometer. Elemental analyses were recorded on an Elementar Vario EL instrument.

3-Trimethylsilyl-2-propyn-1-ol (16):[20] A solution of propargyl alcohol (**15**; 24.5 mL, 413 mmol) in dry THF (500 mL) was cooled to −78 °C before a 1.6 M solution of *n*BuLi in hexane (600 mL) was added over a period of 1 h. The yellow-colored suspension was allowed to warm to RT for 3 h and then cooled to −78 °C before TMSCl (121 mL, 960 mmol) was added within a period of 5 min. The cooling bath was removed and stirring was continued for 10 h before 1.4 N HCl (385 mL, 1.3 equiv) was added within a period of 5 min. The resulting clear mixture was stirred at RT for 1 h. The water layer was separated and extracted with *tert*-butyl methyl ether (MTBE, 3×200 mL). The combined organic layers were washed with brine (2×200 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give alcohol **16** (73.66 g, 98%) as a colorless liquid. The product thus obtained was pure according to ^1H NMR spectroscopy. For analytical purposes a sample was further purified by vacuum distillation. B.p. 90–92 °C/22 mm Hg (literature value:[20a] 76 °C/20 mm Hg); ^1H NMR (250 MHz, $CDCl_3$): δ = 4.24 (s, 2H; CH_2), 1.70 (s, 1H; OH), 0.15 ppm (s, 9H; Si(CH_3)$_3$); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 103.8/90.7 (C≡C), 51.7 (CH_2OH), −0.2 ppm (CH_3Si); IR (ATR): $\tilde{\nu}$ = 3320 (m, O−H), 2956 (m, C−H), 2174 (m, C≡C), 1248 (s), 1038 (s), 980 (s), 844 (s), 759 (s), 698 cm^{-1} (s); MS (EI, 70 eV): m/z (%): 113 (75) $[M-15]^+$, 85 (100), 75 (91), 73 (76).

3,3-Diallyloxy-1-propynyltrimethylsilane (12b):[21,22] A solution of alcohol **16** (61.15 g, 336 mmol) in dry CH_2Cl_2 (100 mL) was added dropwise to a stirred suspension of pyridinium chlorochromate (111 g, 504 mmol) in dry CH_2Cl_2 (450 mL) at 0 °C. The mixture was allowed to warm to RT for 2 h and then carefully filtered through a plug of silica. (Note: to prevent the filtration being blocked, the black oily residue should not be poured onto the silica.) After evaporation of the solvent, the residue was purified by flash chromatography (EtOAc/CyHex 1:19) to give sensitive 3-trimethylsilyl-2-propyne-1-al as a light-yellow liquid, which was immediately further converted as follows. The crude aldehyde (336 mmol), allyl alcohol (230 mL, 3.36 mol), and *p*TsOH (3.2 g, 16.8 mmol) were dissolved in benzene (500 mL) and the mixture was heated to reflux for 15 h with azeotropic removal of water (Dean–Stark trap). After cooling to RT, the mixture was neutralized by addition of $NaHCO_3$ before it was filtered through a plug of silica and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/CyHex 1:19) to afford the acetal **12b** as a light-yellow oil (66.34 g, 88% over two steps). An analytical sample was further purified by vacuum distillation through a Vigreux column (103–105 °C, 8 mbar). R_f = 0.48 (EtOAc/CyHex 1:4); ^1H NMR (250 MHz, $CDCl_3$): δ = 5.91 (tdd, J_1 = 5.4, J_2 = 17.2, J_3 = 10.3 Hz, 2H; CH=CH$_2$), 5.30 (s, 1H; H-3), 5.29 (tdd, J_1 = 1.6, J_2 = 3.3, J_3 = 17.2 Hz, 2H; CH=CH−H_{trans}), 5.18 (tdd, J_1 = 1.6, J_2 = 2.9, J_3 = 10.3 Hz, 2H; CH=CH−H_{cis}), 4.20 (tdd, J_1 = 1.4, J_2 = 12.6, J_3 = 5.4 Hz, 2H; CH_2−CH=CH$_2$), 4.06 (tdd, J_1 = 1.4, J_2 = 12.6, J_3 = 6.1 Hz, 2H; CH_2−CH=CH$_2$), 0.17 ppm (s, 9H; SiCH_3); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 133.9 (CH=CH$_2$), 117.6 (CH=CH_2), 99.5 (C3), 91.1 (C2), 90.3 (C1), 66.2 (CH_2CH=CH$_2$), −0.4 ppm (SiCH_3); IR (ATR): $\tilde{\nu}$ = 2959 (m, C−H), 1647 (w, C≡C), 1250 (s, C−O), 1098 (s), 1027 (s), 922 (s), 841 (s), 760 cm^{-1} (s); MS (EI, 70 eV): m/z (%): 167 (27) $[M-C_3H_5O]^+$, 73 (100), 57 (57), 55 (74).

1,1-Diallyloxy-2-propyne (12a)

A) By transacetalization of 1,1-diethoxy-2-propyne (14):[19] A solution of 1,1-diethoxy-2-propyne (**14**)[17,18] (2.56 g, 20 mmol), allyl alcohol (13.7 mL, 200 mmol), and *p*TsOH (190 mg, 1 mmol) in benzene (60 mL) was heated to reflux. By using a distillation head, the benzene/ethanol azeotrope (b.p. ≈ 69 °C) was constantly removed from the system until no further azeotrope formed. The mixture was cooled to RT and neutralized by addition of K_2CO_3. The solvent and excess of allyl alcohol were removed under reduced pressure and the residue was purified by flash chromatography (CyHex → CyHex/MTBE 9:1) to give the product **12a** as a colorless oil (1.23 g, 40%).

B) By desilylation of 12b:[23] A 1 M solution of TBAF in THF (10 mL) was added dropwise to a solution of **12b** (2.24 g, 10 mmol) in a mixture of allyl alcohol (8 mL) and H_2O (4 mL) at 0 °C. After stirring for 1 h at RT, H_2O (30 mL) and MTBE (30 mL) were added and the water phase was extracted with MTBE (2×20 mL). The combined organic layers were washed with water (3×30 mL) and brine (30 mL) and then dried ($MgSO_4$). The solvent was removed to give the product **12a** as a colorless oil (1.33 g, 88%). The product was pure according to ^1H NMR spectroscopy and TLC. R_f = 0.35 (EtOAc/CyHex 1:4); ^1H NMR (250 MHz, $CDCl_3$): δ = 5.92 (tdd, J_1 = 5.4, J_2 = 17.2, J_3 = 10.3 Hz, 2H; CH=CH$_2$), 5.33 (d, J = 1.6 Hz, 1H; H-1), 5.29 (tdd, J_1 = 1.6, J_2 = 17.2, J_3 = 3.3 Hz, 2H; CH=CH−H_{trans}), 5.19 (tdd, J_1 = 1.6, J_2 = 10.3, J_3 = 2.9 Hz, 2H; CH=CH−H_{cis}), 4.21 (tdd, J_1 = 1.4, J_2 = 12.6, J_3 = 5.4 Hz, 2H; CH_2−CH=CH$_2$), 4.08 (tdd, J_1 = 1.4, J_2 = 12.6, J_3 = 6.1 Hz, 2H; CH_2−CH=CH$_2$), 2.55 ppm (d, J = 1.6 Hz, 1H; H-3); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 133.7 (CH=CH$_2$), 117.6 (CH=CH_2), 90.1 (C3) 78.5 (C2); 74.0 (C1), 66.2 ppm (CH_2CH=CH$_2$); IR (ATR): $\tilde{\nu}$ = 2922 (m, C−H), 2123 (w, C≡C), 1667 (w, C≡C), 1246 (m, C−O), 1091 (s), 1033 (s), 839 (s), 737 (s), 727 (s), 697 cm^{-1} (s); MS (EI, 70 eV): m/z (%): 151 (1) $[M-H]^+$, 95 (60), 41 (100).

(5*SR*,8*RS*)-8-Allyloxy-2-trimethylsilyl-7-oxa-[3.3.0]-bicyclooct-1-ene-3-one (*rac*-11b): A 2 L 2-necked flask was charged with dry, degassed

CH_2Cl_2 (1.5 L), activated 4 Å molecular sieves (108 g), and $[Co_2(CO)_8]$ (25 g, 69 mmol) under argon. (Note: the $[Co_2(CO)_8]$ must be of high quality, that is, red and nonsticky crystals, to obtain good yields.) The dieneyne **12b** (13.52 g, 60 mmol) was then added all at once and the mixture was stirred at RT for 2 h under argon. After the mixture was cooled to −20 °C, dry TMANO (39.6 g, 528 mmol) was added in small portions over a period of 10 min. A stream of air was bubbled through the dark solution for 10 min before stirring was continued for 15 h at RT (open flask). The mixture was filtered through a plug of silica (in order to remove blue- and violet-colored cobalt byproducts) before the solvent was evaporated and the residue purified by flash chromatography (EtOAc/CyHex 1:4). The PKR product *rac*-**11b** was obtained as a light-yellow oil (11.56 g, 76 %, d.r. > 98:2), which solidified on standing in a fridge at 4 °C. An analytical sample was further purified by Kugelrohr distillation (128–130 °C oven temperature, 14 mbar). M.p. 31.5–32.5 °C; $R_f = 0.13$ (EtOAc/CyHex 1:4); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 5.93$ (tdd, $J_1 = 5.4$, $J_2 = 17.2$, $J_3 = 10.3$ Hz, 1H; C*H*=CH$_2$), 5.58 (s, 1H; H-8), 5.31 (tdd, $J_1 = 1.6$, $J_2 = 17.2$, $J_3 = 1.6$ Hz, 1H; CH=CH−H_{trans}), 5.22 (tdd, $J_1 = 1.2$, $J_2 = 10.3$, $J_3 = 1.8$ Hz, 1H; CH=CH−H_{cis}), 4.38 (dd, $J_1 = 6.6$, $J_2 = 7.2$ Hz, 1H; H-6a), 4.29 (tdd, $J_1 = 12.2$, $J_2 = 5.6$, $J_3 = 1.4$ Hz, 1H; CH*H*a−CH=CH$_2$), 4.10 (tdd, $J_1 = 12.5$, $J_2 = 6.4$, $J_3 = 1.3$ Hz, 1H; CH*H*b−CH=CH$_2$), 3.46 (m, 1H; H-5), 3.42 (dd, $J_1 = 6.2$, $J_2 = 6.7$ Hz, 1H; H-6b), 2.66 (dd, $J_1 = 17.6$, $J_2 = 6.4$ Hz, 1H; H-4a), 2.10 (dd, $J_1 = 17.6$, $J_2 = 3.6$ Hz, 1H; H-4b), 0.21 ppm (s, 9H; $SiCH_3$); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 213.4$ (C3), 184.9 (C1), 137.6 (C2), 133.8 (*C*H=CH$_2$), 118.2 (CH=*C*H$_2$), 96.7 (C8), 71.0 (C6), 68.8 (*C*H$_2$CH=CH$_2$), 42.6 (C5), 41.8 (C4), −1.5 ppm (SiC); IR (ATR): $\tilde{\nu} = 2954$ (m, C−H), 1703 (s, C=O), 1640 (s, C=C), 1247 (s, C−O), 1126 (s), 1073 (s), 997 (s), 838 (s), 762 cm^{-1} (s); MS (EI, 70 eV): *m*/*z* (%): 253 (1) $[M+H]^+$, 237 (2) $[M-CH_3]^+$, 211 (15) $[M-C_3H_5]^+$, 195 (20) $[M-C_3H_5O]^+$, 73 (100); HRMS (EI): calcd for $C_{12}H_{17}O_3Si$: 237.095 $[M-CH_3]^+$; found: 237.095.

Alternative method for the preparation of *rac*-11b by using *n*BuSMe as a promoter:[27] A solution of dieneyne **12b** (757 mg, 3 mmol) in 1,2-dichloroethane (30 mL, freshly filtered through ALOX-B) was added to $[Co_2(CO)_8]$ (1.30 g, 3.6 mmol) all at once under argon. After the mixture was stirred for 1 h at RT, *n*BuSMe (1.31 mL, 10.5 mmol) was added and the resulting mixture was refluxed for 18 h. The solvent was evaporated and the residue was purified by flash chromatography (EtOAc/CyHex 1:9→1:4→1:2) to afford the product *rac*-**11b** as a light-yellow oil (435 mg, 57 %, d.r. = 24:1).

(5*SR*,8*RS*)-8-Allyloxy-7-oxa-[3.3.0]-bicyclooct-1-ene-3-one (*rac*-11a): By following the protocol described above for the preparation of *rac*-**11b**, acetal **12a** (760 mg, 5 mmol) was treated with $[Co_2(CO)_8]$ (with TMANO as a promoter) to afford an inseparable mixture of *rac*-**11a** and *rac-epi*-**11a** (d.r. = 2.6:1) as a colorless oil (333 mg, 45 %). $R_f = 0.16$ (EtOAc/CyHex 1:4).

rac-**11a**: ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 6.09$ (d, $J = 2.4$ Hz, H-2), 5.98–5.85 (m, 1H; C*H*=CH$_2$), 5.58 (s, 1H; H-8), 5.30 (tdd, $J_1 = J_2 = 1.4$, $J_3 = 17.1$ Hz, 1H; CH=CH−H_{cis}), 5.21 (tdd, $J_1 = J_2 = 1.4$, $J_3 = 10.0$ Hz, 1H; CH=CH−H_{trans}), 4.39 (dd, $J_1 = J_2 = 7.8$ Hz, 1H; H-6a), 4.27 (tdd, $J_1 = 12.6$, $J_2 = 5.3$, $J_3 = 1.5$ Hz, 1H; CH*H*a−CH=CH$_2$), 4.10 (tdd, $J_1 = 12.6$, $J_2 = 6.2$, $J_3 = 1.3$ Hz, 1H; CH*H*b−CH=CH$_2$), 3.59–3.50 (m, 1H; H-5), 3.44 (dd, $J_1 = 7.6$, $J_2 = 8.8$ Hz, 1H; H-6b), 2.69 (dd, $J_1 = 17.9$, $J_2 = 6.3$ Hz, 1H; H-4a), 2.16 ppm (dd, $J_1 = 17.9$, $J_2 = 3.5$ Hz, 1H; H-4b); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 209.3$ (C3), 178.3 (C1), 133.7 (*C*H=CH$_2$), 124.8 (C2), 117.9 (CH=*C*H$_2$), 96.4 (C8), 71.2 (C6), 68.7 (*C*H$_2$CH=CH$_2$), 41.1 (C5), 40.8 ppm (C4).

rac-epi-**11a**: ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 6.23$ (m, 1H; H-2), 5.98–5.85 (m, 1H; C*H*=CH$_2$), 5.78 (s, 1H; H-8), 5.30 (tdd, $J_1 = J_2 = 1.4$, $J_3 = 17.1$ Hz, 1H; CH=CH−H_{cis}), 5.21 (tdd, $J_1 = J_2 = 1.4$, $J_3 = 10.0$ Hz, 1H; CH=CH−H_{trans}), 4.29 (m, 1H; CH*H*a−CH=CH$_2$), 4.23 (dd, $J_1 = J_2 = 7.8$ Hz, 1H; H-6a), 4.13 (tdd, $J_1 = 1.3$, $J_2 = 6.2$, $J_3 = 12.6$ Hz, 1H; CH*H*b−CH=CH$_2$), 3.53 (dd, $J_1 = 7.8$, $J_2 = 10.8$ Hz, 1H; H-6b), 3.34–3.25 (m, 1H; H-5), 2.60 (dd, $J_1 = 17.9$, $J_2 = 6.2$ Hz, 1H; H-4a), 2.21 ppm (dd, $J_1 = 17.9$, $J_2 = 3.5$ Hz, 1H; H-4b); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 208.7$ (C3), 182.5 (C1), 133.7 (*C*H=CH$_2$), 127.6 (C2), 117.9 (CH=*C*H$_2$), 98.2 (C8), 70.7 (C6), 69.7 (*C*H$_2$CH=CH$_2$), 45.2 (C5), 39.8 ppm (C4).

Analytical data for the mixture: IR (ATR): $\tilde{\nu} = 2917$ (w, C−H), 1713 (s, C=O), 1660 (s, C=C), 1069 (s), 996 cm^{-1} (s); MS (EI, 70 eV): *m*/*z* (%): 180 (6) $[M]^+$, 163 (8), 151 (11), 147 (15), 139 (28), 123 (100), 109 (36), 95 (24); HRMS (EI): calcd for $C_{10}H_{12}O_3$: 180.078 $[M]^+$; found: 180.078.

CBS kinetic resolution of rac-11b: A Schlenk flask was charged with the azeotropically dried ketone *rac*-**11b** (12.60 g, 50 mmol) and an approximately 0.05 M solution of freshly prepared (*R*)-Me-oxazaborolidine **17a**[65] in toluene (200 mL) was added at RT. The mixture was cooled to −78 °C and after 30 min a solution of catecholborane (42.5 mL, 1 M in THF) was added over a period of 5 min. The mixture was allowed to warm to RT and stirred for another 6 h. GC analysis showed that the slower reacting enantiomer (**11b**) was obtained in > 99 % *ee* while the conversion was 59 %. (Note: When ketone **11b** was not obtained in enantiomerically pure form, additional catecholborane was added at −78 °C.) The reaction was quenched by addition of a 2 M solution of KOH (300 mL). After stirring for 30 min at RT, the mixture was extracted with EtOAc (4 × 150 mL) and the combined organic layers were washed with a 2 M solution of KOH (2 × 200 mL) and saturated solutions of NH_4Cl (200 mL) and $CuSO_4$ (2 × 200 mL). After the washing process was repeated, the mixture was finally washed with brine (2 × 200 mL) and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by flash chromatography (EtOAc/CyHex 1:4) to afford ketone **11b** (4.24 g, 34 %, > 99 % *ee*) and alcohol *ent*-**18** (7.00 g, 58 %, 83 % *ee*, 65 % *de*). Ketone **11b**: $[\alpha]_D^{20} = -290.7$ ($c = 1.185$ in $CHCl_3$), $[\alpha]_{546}^{20} = -342.5$; CD: Θ (λ) = +64 809 (210.9 nm), −148 828 (232.0 nm), +10 071 mdeg nm^{-1} (329.7 nm) ($c = 0.148$ mg dL^{-1} in cyclohexane); the *ee* and *de* were determined by chiral GC (Hydrodex β-PM, 130 °C, isotherm, 15 psi H_2): retention times: **11b**: 24.70; *ent*-**11b**: 25.44; *epi*-**18**: 35.09, 37.56; *ent*-**18**: 41.15; **18**: 44.35 min.

Oxidation of alcohol *ent*-18: A solution of alcohol *ent*-**18** (83 % *ee*, 65 % *de*, 6.10 g, 24 mmol) in dry CH_2Cl_2 (20 mL) was added to a stirred suspension of MnO_2 (68 g, 90 % purity) in dry CH_2Cl_2 (90 mL) at 0 °C under argon. The mixture was allowed to warm to RT and stirred for 2 h. The suspension was filtered through a plug of celite and the solvent was evaporated to give the product *ent*-**11b** (5.37 g, 89 %, 83 % *ee*). The purity was > 98 % according to GC analysis and therefore no further purification was performed.

Repeated CBS kinetic resolution–Preparation of ketone *ent*-11b in enantiomerically pure form: An approximately 0.1 M solution of (*S*)-Me-CBS-*catalyst ent*-**17a** in PhMe (128 mL, 20 mol %) was added to a solution of the azeotropically dried ketone *ent*-**11b** (16.13 g, 64 mmol, 83 % *ee*) under argon and the resulting mixture was cooled to −78 °C. After stirring for 30 min, a 1 M solution of catecholborane in THF (9.25 mL) was added within a period of 5 min. The mixture was allowed to warm to RT and stirred for 3 h. When the ketone *ent*-**11b** was obtained in the desired purity (> 99 % *ee*), the reaction was quenched by addition of a 2 M solution of KOH (300 mL) and the workup was carried out in the same manner as that described previously (for **11b**). After flash chromatography (EtOAc/CyHex 1:4), the ketone *ent*-**11b** (11.56 g, 72 %, > 99 % *ee*) and the alcohol **18** (3.34 g, 21 %) were isolated. *ent*-**11b**: $[\alpha]_D^{20} = +290.0$ ($c = 1.29$ in $CHCl_3$); CD: Θ (λ) = −73076 (210.1), +168312 (232.0), −11831 mdeg nm^{-1} (330.8) ($c = 0.308$ mg dL^{-1} in cyclohexane).

(−)-(3*R*,5*S*,8*R*)-8-Allyloxy-2-trimethylsilyl-7-oxa-[3.3.0]-bicyclooct-1-ene-3-ol (18) (Luche reduction):[40b] $NaBH_4$ (3.23 g, 85 mmol) was added portionwise to a solution of **11b** (8.57 g, 34 mmol) and $CeCl_3 \cdot 7H_2O$ (12.88 g, 34 mmol) in MeOH (340 mL) at −20 °C (ice/salt bath) over a period of 30 min. After stirring the mixture at RT for 10 min, the reaction was quenched by addition of a saturated solution of $NaHCO_3$ (100 mL). The mixture was extracted with MTBE (4 × 100 mL) and the combined organic layers were washed with saturated $NaHCO_3$ (2 × 100 mL) and brine (100 mL), then dried ($MgSO_4$). The solvents were evaporated and the alcohol **18** was obtained as a colorless oil (8.62 g, 99 %, d.r. > 98:2) that was pure according to ^{1}H NMR spectroscopy and GC analysis. $R_f = 0.39$ (EtOAc/CyHex 1:1); $[\alpha]_D^{20} = -247.5$ ($c = 1.69$ in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 5.90$ (tdd, $J_1 = 17.2$, $J_2 = 10.3$, $J_3 = 5.4$ Hz, 1H; C*H*=CH$_2$), 5.38 (s, 1H; H-8), 5.26 (tdd, $J_1 = 17.2$, $J_2 = 1.5$, $J_3 = 1.3$ Hz, 1H; CH=CH−H_{trans}), 5.17/5.16 (m/tdd, $J_1 = 10.3$, $J_2 = 1.8$, $J_3 = 1.1$ Hz, 2H; H-3/CH=CH−H_{cis}), 4.20 (dd, $J_1 = J_2 = 8.2$ Hz, 1H; H-6a), 4.19 (tdd, $J_1 = 12.4$, $J_2 = 5.3$, $J_3 = 1.4$ Hz, 1H; CH*H*a−CH=CH$_2$), 4.00 (tdd, $J_1 = 12.4$, $J_2 = 6.4$, $J_3 = 1.3$ Hz, 1H; CH*H*b−CH=CH$_2$), 3.42 (dd, $J_1 = J_2 = 7.9$ Hz, 1H; H-6b); 3.20 (m, 1H; H-5), 2.69 (ddd, $J_1 = 12.1$, $J_2 = 6.5$, $J_3 = 6.0$ Hz, 1H; H-4a), 1.64 (br s, 1H; OH), 1.22 (ddd, $J_1 = 12.0$, $J_2 = J_3 = 8.6$ Hz, 1H; H-4b), 0.21 ppm (s, 9H; $SiCH_3$); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 156.8$ (C1),

140.3 (C2), 134.3 (*C*H=CH$_2$), 117.7 (CH=*C*H$_2$), 97.3 (C8), 87.61 (C3), 72.1 (C6), 68.3 (*C*H$_2$CH=CH$_2$), 46.4 (C5), 43.9 (C4), −0.6 ppm (SiC); IR (ATR): $\tilde{\nu}$ = 3437 (m, O−H), 2952 (s, C−H), 1657 (m, C=C), 1324 (s), 1245 (s, C−O), 1107 (s), 1064 (s), 989 (s), 834 (s), 753 cm^{-1} (s); MS (EI, 70 eV): *m*/*z* (%): 253 (1) $[M-H]^+$, 197 (22) $[M-C_3H_5O]^+$, 73 (100); elemental analysis: calcd (%) for $C_{13}H_{22}O_3Si$: C 61.38, H 8.72; found: C 61.37, H 8.57.

Alternative method for the reduction of ketone 11b (L-Selectride reduction): A 1 M solution of L-Selectride in THF (750 μL) was added dropwise at −78 °C under argon to a solution of ketone **11b** (126 mg, 0.5 mmol) in dry THF (3 mL) and the mixture was stirred for 6 h at −78 °C followed by 15 h at RT. The reaction was quenched by addition of MeOH (2 mL), 2 M NaOH (6 mL), 30 % H_2O_2 (aq, 12 mL), and finally MTBE (20 mL). The resulting mixture was stirred at RT for 1.5 h. The aqueous phase was extracted with MTBE (2 × 30 mL) and the combined organic phases were washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL). After drying ($MgSO_4$) and removal of the solvent the residue was purified by flash chromatography (EtOAc/CyHex 1:2) to give the alcohol **18** as a colorless oil (105 mg, 83 %, d.r. > 98:2).

(+)-(3*S*,5*R*,8*S*)-8-Allyloxy-2-trimethylsilyl-7-oxa-[3.3.0]-bicyclooct-1-ene-3-ol (*ent*-18): By following the reduction method described above (Luche conditions), ketone *ent*-**11b** (10.08 g, 40 mmol) was converted into alcohol *ent*-**18** (10.2 g, 99 %). $[\alpha]_D^{20}$ = +250.2 (*c* = 0.59 in $CHCl_3$).

(−)-(3*R*,5*S*,8*R*)-8-Allyloxy-7-oxa-[3.3.0]-bicyclooct-1-ene-3-ol (20): *t*BuOK (4.6 g, 40.7 mmol) was added to a solution of **18** (8.62 g, 33.9 mmol) in DMSO/H_2O (19:1, 100 mL) at RT and the color of the mixture turned immediately to brown. After stirring for 30 min at RT the mixture was diluted by addition of water (200 mL) and extracted with EtOAc (4 × 100 mL). The combined organic phases were washed with water (3 × 100 mL) and brine (100 mL), then dried ($MgSO_4$). The solvent was removed under reduced pressure. The product **20**, obtained as a colorless oil (5.03 g, 82 %), was pure according to ^{1}H NMR spectroscopy and TLC and therefore no further purification was necessary. R_f = 0.20 (EtOAc/CyHex 1:1); $[\alpha]_D^{20}$ = −236.4 (*c* = 0.77 in $CHCl_3$), $[\alpha]_{546}^{20}$ = −282.1; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.85 (tdd, J_1 = 17.2, J_2 = 10.3, J_3 = 5.4 Hz, 1H; C*H*=CH$_2$), 5.70 (m, 1H; H-2), 5.36 (s, 1H; H-8), 5.22 (tdd, J_1 = 17.2, J_2 = 1.6, J_3 = 1.2 Hz, 1H; CH=CH−H_{trans}), 5.13/5.12 (m/tdd, J_1 = 10.3, J_2 = 1.6, J_3 = 1.2 Hz, 2H; H-3/CH=CH−H_{cis}), 4.18 (dd, J_1 = J_2 = 8.2 Hz, 1H; H-6a), 4.12 (tdd, J_1 = 12.6, J_2 = 5.3, J_3 = 1.6 Hz, 1H; CH*H*a−CH=CH$_2$), 3.96 (tdd, J_1 = 12.6, J_2 = 6.1, J_3 = 1.6 Hz, 1H; CH*H*b−CH=CH$_2$), 3.38 (dd, J_1 = J_2 = 7.1 Hz, 1H; H-6b), 3.20 (m, 1H; H-5), 2.66 (ddd, J_1 = 12.4, J_2 = 6.3, J_3 = 6.1 Hz, 1H; H-4a), 2.11 (br s, 1H; OH), 1.29 ppm (ddd, J_1 = 12.3, J_2 = J_3 = 8.0 Hz, 1H; H-4b); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 147.9 (C1), 134.0 (*C*H=CH$_2$), 126.8 (C2), 117.3 (CH=*C*H$_2$), 96.8 (C8), 82.2 (C3), 72.7 (C6), 67.8 (*C*H$_2$CH=CH$_2$), 44.9 (C5), 42.9 ppm (C4); IR (ATR): $\tilde{\nu}$ = 3396 (w, O−H), 2920 (s, C−H), 1646 (w, C=C), 1295 (m, C−O), 1033 (s), 985 (s), 823 cm^{-1} (s); MS (EI, 70 eV): *m*/*z* (%): 183 (4) $[M+H]^+$, 125 (13) $[M-C_3H_5O]^+$, 95 (82), 83 (64), 69 (60), 66 (98), 55 (100).

(+)-(3*S*,5*R*,8*S*)-8-Allyloxy-7-oxa-[3.3.0]-bicyclooct-1-ene-3-ol (*ent*-20): By following the desilylation method described for alcohol **20**, alcohol *ent*-**18** (4.32 g, 17 mmol) was converted into alcohol *ent*-**20** (2.49 g, 81 %). $[\alpha]_D^{20}$ = +231.5 (*c* = 0.69 in $CHCl_3$), $[\alpha]_{546}^{20}$ = +276.1.

(−)-(3*R*,5*S*,8*R*)-Acetic acid 8-allyloxy-7-oxa-[3.3.0]-bicyclooct-1-ene-3-yl ester (21a): Ac_2O (4.2 mL, 44 mmol) was added at RT to a stirred solution of **20** (3.64 g, 20 mmol), Et_3N (3.6 mL, 24 mmol), and DMAP (300 mg, 2.4 mmol) in CH_2Cl_2 (80 mL). The resulting mixture was stirred for 1 h at RT and was then quenched by addition of saturated $NaHCO_3$ (50 mL). The water phase was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers were washed with saturated $NaHCO_3$ (2 × 50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (EtOAc/CyHex 1:4) to give the product **21a** as a colorless oil (4.42 g, 99 %). R_f = 0.53 (EtOAc/CyHex 1:1); $[\alpha]_D^{20}$ = −183.6 (*c* = 1.375 in $CHCl_3$), $[\alpha]_{546}^{20}$ = −218.6; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.95 (m, 1H; H-3), 5.87 (ddt, J_1 = 17.2, J_2 = 10.3, J_3 = 5.4 Hz, 1H; C*H*=CH$_2$), 5.73 (m, 1H; H-2), 5.41 (s, 1H; H-8), 5.26 (ddt, J_1 = 17.2, J_2 = 1.6, J_3 = 1.2 Hz, 1H; CH=CH−H_{trans}), 5.17 (ddt, J_1 = 10.3, J_2 = 1.6, J_3 = 1.3 Hz, 1H; CH=CH−H_{cis}), 4.25 (dd, J_1 = J_2 = 8.0 Hz, 1H; H-6a), 4.18 (ddt, J_1 = 12.4, J_1 = 5.4, J_1 = 1.6 Hz, 1H; CH*H*a−CH=CH$_2$), 3.96 (ddt, J_1 = 12.4, J_2 = 6.1, J_3 = 1.4 Hz, 1H; CH*H*b−CH=CH$_2$), 3.44 (dd, J_1 = J_2 = 7.91 Hz, 1H; H-6b), 3.32 (m, 1H; H-5), 2.77 (ddd, J_1 = 12.7, J_2 = J_3 = 6.8 Hz, 1H; H-4a), 2.03 (s, 1H; C*H*$_3$COO), 1.50 ppm (ddd, J_1 = 12.7, J_2 = J_3 = 7.7 Hz, 1H; H-4b); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 170.0 (C=O), 150.2 (C1), 134.2 (*C*H=CH$_2$), 122.6 (C2), 117.4 (CH=*C*H$_2$), 96.8 (C8), 84.1 (C3), 72.6 (C6), 68.0 (*C*H$_2$CH=CH$_2$), 45.0 (C5), 39.0 (C4), 21.1 ppm (*C*H$_3$COO); IR (ATR): $\tilde{\nu}$ = 2973 (m, C−H), 1732 (s, C=O), 1362 (s), 1232 (s, C−O), 1152 (s), 1065 (s), 1023 (s), 991 (s), 891 cm^{-1} (s); MS (EI, 70 eV): *m*/*z* (%): 225 (2) $[M+H]^+$, 167 (42) $[M-C_3H_5O]^+$, 94 (100), 66 (74); elemental analysis: calcd (%) for $C_{12}H_{16}O_4$: C 64.27, H 7.19; found: C 64.12, H 7.13.

(+)-(3*S*,5*R*,8*S*)-Acetic acid 8-allyloxy-7-oxa-[3.3.0]-bicyclooct-1-ene-3-yl ester (*ent*-21a): By following the method described for ester **21a**, alcohol *ent*-**20** (2.37 g, 13 mmol) was converted into ester *ent*-**21a**, which was obtained as a colorless oil (2.77 g, 95 %). $[\alpha]_D^{20}$ = +179.1 (*c* = 0.45 in $CHCl_3$), $[\alpha]_{546}^{20}$ = +205.6.

(−)-(3*R*,5*S*,8*R*)-Carbonic acid 8-allyloxy-7-oxa-[3.3.0]-bicyclooct-1-ene-3-yl ester methyl ester (21b): Pyridine (5 mL) and methyl chloroformate (1.27 mL, 16.5 mmol) were added to a solution of alcohol **20** (1.00 g, 5.48 mmol) in CH_2Cl_2 (75 mL) at 0 °C and the mixture was stirred for 1 h under argon. The reaction was quenched with water (50 mL) and stirred for an additional 30 min. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with brine (50 mL) and dried ($MgSO_4$), then the solvent was removed under reduced pressure. After purification by flash chromatography (CyHex/EtOAc 4:1), compound **21b** was obtained in 92 % yield (1.21 g, 5.05 mmol). R_f = 0.40 (EtOAc/CyHex 1:4); $[\alpha]_D^{20}$ = −141.6 (*c* = 0.820 in $CHCl_3$), $[\alpha]_{546}^{20}$ = −168.8; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.95–5.84 (m, 2H; H-3, C*H*=CH$_2$), 5.76 (m, 1H; H-2), 5.40 (s, 1H; H-8), 5.25 (ddt, J_1 = 17.2, J_2 = 3.2, J_3 = 1.2 Hz, 1H; CH=CH−H_{trans}), 5.15 (ddt, J_1 = 10.4, J_2 = 3.0, J_3 = 1.5 Hz, 1H; CH=CH−H_{cis}), 4.23 (dd, J_1 = J_2 = 8.1 Hz, 1H; H-6a), 4.16 (ddt, J_1 = 12.7, J_2 = 5.4, J_3 = 1.4 Hz, 1H; CH*H*a−CH=CH$_2$), 3.99 (ddt, J_1 = 12.7, J_2 = 6.0, J_3 = 1.3 Hz, 1H; CH*H*b−CH=CH$_2$), 3.75 (s, 1H; C*H*$_3$OCO$_2$), 3.43 (dd, J_1 = J_2 = 7.9 Hz, 1H; H-6b), 3.34–3.28 (m, 1H; H-5), 2.79 (ddd, J_1 = 12.7, J_2 = J_3 = 6.7 Hz, 1H; H-4a), 1.57 ppm (ddd, J_1 = 12.7, J_2 = J_3 = 7.6 Hz, 1H; H-4b); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 155.0 (C=O), 150.6 (C1), 134.1 (*C*H=CH$_2$), 122.1 (C2), 117.4 (CH=*C*H$_2$), 96.7 (C8), 87.6 (C3), 72.4 (C6), 68.0 (*C*H$_2$CH=CH$_2$), 54.7 (*C*H$_3$OCO$_2$), 45.0 (C5), 38.6 ppm (C4); IR (ATR): $\tilde{\nu}$ = 2952 (m, C−H), 1740 (s, C=O), 1687 (m), 1441 (s), 1256 (s, C−O), 1153 (m), 1064 (m), 975 (s), 791 cm^{-1} (m); MS (EI, 70 eV): *m*/*z* (%): 240 (3) $[M]^+$, 239 (13), 183 (57), 134 (36), 119 (23), 107 (28), 95 (23), 79 (100), 67 (39), 59 (58); HRMS (EI): calcd for $C_{12}H_{16}O_5$: 240.100 $[M]^+$; found: 240.100.

Pd-catalyzed introduction of nucleobases

Protocol A: A suspension of a pyrimidine nucleobase (3.3 mmol) and NaH (120 mg, 3 mmol, 60 % dispersion in mineral oil) in dry, degassed DMSO (20 mL) was heated to 70 °C for 30 min under argon to give a clear solution. After cooling to RT, $[Pd(PPh_3)_4]$ (116 mg, 100 μmol, 5 mol %), PPh_3 (58 mg, 220 μmol, 11 mol %) and **21a** (448 mg, 2 mmol, unless stated otherwise) in dry, degassed THF (4 mL) were added under argon and the resulting mixture was stirred at 70 °C (50 °C for adenine) for 16 h. After cooling to RT, the black mixture was filtered and washed with CH_2Cl_2. The filtrate was washed with brine (4 × 25 mL) and dried ($MgSO_4$), then the solvent was evaporated. The residue was purified by flash chromatography (EtOAc/CyHex 1:4→4:1). The purity of products **10** was measured by ^{1}H NMR spectroscopy.

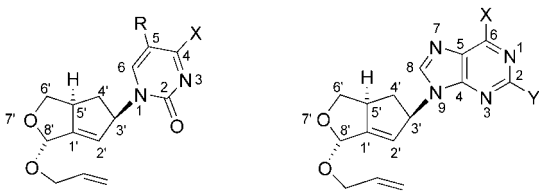
Modifications: For cytosine: N^4-benzoylcytosine (2.2 equiv) and NaH (2 equiv) were used. For adenine: adenine (1.5 equiv) and Cs_2CO_3 (1.5 equiv) were utilized with heating to 50 °C for 30 min. For guanine: N^2-acetyl-*O*-diphenylcarbamoylguanine[45] (1.2 equiv) and pempidine (2.3 equiv) were dissolved in dry, degassed DMSO and stirred at RT for 5 min before use.

Protocol B: P(*i*PrO)$_3$ (68 μL, 95 %, 280 μmol, 14 mol %) was added to a solution of $[Pd(dba)_2]$ (23 mg, 40 μmol, 2 mol %) in dry, degassed THF (4 mL) at RT under argon. (The color of mixture changed from red to green.) The prepared solution of the nucleobase salt (see protocol A) in dry, degassed DMSO (20 mL) and a solution of acetate **21a** (448 mg, 2 mmol, unless stated otherwise) in dry, degassed THF (4 mL) were added to the catalyst mixture at RT under argon. The resulting mixture was heated to 70 °C (50 °C for adenine) for 16 h. After cooling to RT, the same workup as that described in protocol A was carried out.

Protocol C: dppp (87 mg, 0.210 mmol, 10.5 mol %) was added to a solution of $[Pd_2(dba)_3]$ (46 mg, 0.05 mmol, 2.5 mol %) in dry, degassed DMF (10 mL) at RT under argon. The solution was stirred for 5 min. Carbonate **21b** (481 mg, 2 mmol, unless otherwise stated) in DMF (2 mL) and the nucleobase (1.5 equiv) in DMF (2 mL) were added to the mixture. After stirring at RT for 16 h, the reaction was quenched by addition of water (40 mL). The layers were separated and the aqueous phase was extracted with EtOAc (5×30 mL). The combined organic layers were washed with water (3×30 mL) and brine (30 mL), then dried. Finally, the solvent was removed under reduced pressure. The residue was purified by flash chromatography.

Synthesis of compounds of type 10 (Scheme 15)

(−)-(3′*R*,5′*S*,8′*R*)-1-(8′-Allyloxy-7′-oxa-[3.3.0]-bicyclooct-1′-ene-3′-yl)-1*H*-pyrimidine-2,4-dione (10a): When the general protocol A for the Pd-catalyzed introduction of nucleobases was followed, uracil and **21a** afforded



Scheme 15. Numbering used for compounds of type **10**, NB = various nucleobases.

10a (330 mg, 56 %, 94 % purity) as a white solid. M.p. 146–150 °C; R_f = 0.08 (EtOAc/CyHex 4:1); $[\alpha]_D^{20} = -247.0$ (c = 0.495 in $CHCl_3$), $[\alpha]_{546}^{20} = -297.8$; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.09 (brs, 1H; N*H*), 7.17 (d, J = 8.0 Hz, 1H; H-6), 6.04 (dd, J_1 = 7.2, J_2 = 8.7 Hz, 1H; H-3′), 5.86 (tdd, J_1 = 5.4, J_2 = 17.2, J_3 = 10.4 Hz, 1H; C*H*=CH$_2$), 5.70 (d, J = 8.0 Hz, 1H; H-5), 5.57 (m, 1H; H-2′), 5.43 (s, 1H; H-8′), 5.23 (tdd, J_1 = 1.2, J_2 = 17.2, J_3 = 1.6 Hz, 1H; CH=CH−H_{trans}), 5.13 (tdd, J_1 = 1.1, J_2 = 10.3, J_3 = 1.6 Hz, 1H; CH=CH−H_{cis}), 4.24 (dd, $J_1 = J_2$ = 7.4 Hz, 1H; H-6′a), 4.05 (tdd, J_1 = 1.6, J_2 = 12.7, J_3 = 5.4 Hz, 1H; CH*H*a−CH=CH$_2$), 4.04 (tdd, J_1 = 1.3, J_2 = 12.6, J_3 = 6.1 Hz, 1H; CH*H*b−CH=CH$_2$), 3.47 (dd, $J_1 = J_2$ = 7.6 Hz, 1H; H-6′b), 3.44 (m, 1H; H-5′), 2.84 (ddd, J_1 = 12.5, J_2 = 7.0, J_3 = 6.8 Hz, 1H; H-4′a), 1.37 ppm (ddd, J_1 = 12.5, J_2 = 8.3, J_3 = 7.6 Hz, 1H; H-4′b); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 163.5 (C4), 152.4 (C1′), 150.8 (C2), 140.4 (C6), 133.8 (*C*H=CH$_2$), 120.6 (C2′), 117.5 (CH=*C*H$_2$), 103.0 (C5), 96.2 (C8′), 71.8 (C6′), 67.9 (*C*H$_2$CH=CH$_2$), 65.5 (C3′), 45.4 (C5′), 40.4 ppm (C4′); IR (ATR): $\tilde{\nu}$ = 3180/3051 (w, N−H), 2970 (m, C−H), 1681 (s, C=O), 1626 (w, C=C), 1242 cm^{-1} (m, C−O); MS (EI, 70 eV): *m*/*z* (%): 277 (8) $[M+H]^+$, 276 (5) $[M]^+$, 219 (78) $[M-C_3H_5O]^+$, 205 (100), 134 (52), 79 (57).

(+)-(3′*S*,5′*R*,8′*S*)-1-(8′-Allyloxy-7′-oxa-[3.3.0]-bicyclooct-1′-ene-3′-yl)-1*H*-pyrimidine-2,4-dione (*ent*-10a): When the general protocol A for the Pd-catalyzed introduction of nucleobases was followed, uracil and *ent*-**21a** afforded *ent*-**10a** (379 mg, 65 %, 94 % purity) as a white solid. $[\alpha]_D^{20}$ = +230.7 (c = 0.59 in $CHCl_3$), $[\alpha]_{546}^{20}$ = +278.2.

(−)-(3′*R*,5′*S*,8′*R*)-1-(8′-Allyloxy-7′-oxa-[3.3.0]-bicyclooct-1′-ene-3′-yl)-5-fluoro-1*H*-pyrimidine-2,4-dione (10b): When the general protocol B for the Pd-catalyzed introduction of nucleobases was followed, 5-fluorouracil and **21a** afforded **10b** (460 mg, 73 %, 93 % purity) as a white solid. The product **10b** was obtained in 99 % purity after crystallization from EtOAc/Hex. M.p. 155–157 °C; R_f = 0.35 (EtOAc/CyHex 4:1); $[\alpha]_D^{20}$ = −254.5 (c = 0.41 in $CHCl_3$), $[\alpha]_{546}^{20} = -306.9$; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.47 (brs, 1H; N*H*), 7.24 (d, J = 4.8 Hz, 1H; H-6), 6.04 (dd, $J_1 = J_2$ = 7.5 Hz, 1H; H-3′), 5.91 (tdd, J_1 = 5.6, J_2 = 17.2, J_3 = 10.3 Hz, 1H; C*H*=CH$_2$), 5.59 (s, 1H; H-2′), 5.49 (s, 1H; H-8′), 5.28 (dd, J_1 = 17.2, J_2 = 1.6 Hz, 1H; CH=CH−H_{trans}), 5.20 (dd, J_1 = 10.3, J_2 = 1.2 Hz, 1H; CH=CH−H_{cis}), 4.30 (dd, $J_1 = J_2$ = 7.7 Hz, 1H; H-6′a), 4.22 (dd, J_1 = 12.6, J_2 = 5.3 Hz, 1H; CH*H*a−CH=CH$_2$), 4.04 (dd, J_1 = 12.6, J_2 = 6.1 Hz, 1H; CH*H*b−CH=CH$_2$), 3.52 (dd, $J_1 = J_2$ = 7.6 Hz, 1H; H-6′b), 3.50 (m, 1H; H-5′), 2.90 (ddd, J_1 = 12.7, $J_2 = J_3$ = 6.6 Hz, 1H; H-4′a), 1.41 ppm (ddd, J_1 = 12.7, $J_2 = J_3$ = 8.5 Hz, 1H; H-4′b); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 156.4 (d, J(C,F) = 27 Hz, C4), 153.5 (C1′), 149.0 (C2), 140.9 (d, J(C,F) = 238 Hz, C5), 133.9 (*C*H=CH$_2$), 124.5 (d, J(C,F) = 33 Hz, C6), 119.8 (C2′), 117.7 (CH=*C*H$_2$), 96.3 (C8′), 71.9 (C6′), 68.1 (*C*H$_2$CH=CH$_2$), 66.1 (C3′), 45.6 (C5′), 40.3 ppm (C4′); IR (ATR): $\tilde{\nu}$ = 3155 (w, N−H), 3016 (m, N−H), 2890 (w, C−H), 1730 (s), 1704 (s, C=O), 1686 (s, C=O), 1653 (s, C=C), 1243 (s, C−O), 987 cm^{-1} (s); MS (EI, 70 eV): *m*/*z* (%): 709 (82), 677 (100), 655 (13) $[2M+Na]^+$, 317 (58) $[M+H]^+$, 237 (80); elemental analysis: calcd (%) for $C_{13}H_{22}O_3Si$: C 57.14, H 5.14, N 9.52; found: C 57.36, H 5.26, N 9.50.

(+)-(3′*S*,5′*R*,8′*S*)-1-(8′-Allyloxy-7′-oxa-[3.3.0]-bicyclooct-1′-ene-3′-yl)-5-fluoro-1*H*-pyrimidine-2,4-dione (*ent*-10b): When the general protocol B for the Pd-catalyzed introduction of nucleobases was followed, 5-fluorouracil and *ent*-**21a** afforded *ent*-**10b** (468 mg, 74 %, 93 % purity) as a white solid. The product *ent*-**10b** was obtained in 99 % purity after crystallization from EtOAc/Hex. $[\alpha]_D^{20}$ = +259.4 (c = 0.48 in $CHCl_3$), $[\alpha]_{546}^{20}$ = +314.4.

(−)-(3′*R*,5′*S*,8′*R*)-1-(8′-Allyloxy-7′-oxa-[3.3.0]-bicyclooct-1′-ene-3′-yl)-5-bromo-1*H*-pyrimidine-2,4-dione (10c): When the general protocol A for the Pd-catalyzed introduction of nucleobases was followed, 5-bromouracil and **21a** afforded **10c** (590 mg, 83 %, 99 % purity) as a white solid. M.p. 144–146 °C, R_f = 0.43 (EtOAc/CyHex 4:1); $[\alpha]_D^{20} = -160.6$ (c = 0.36 in $CHCl_3$), $[\alpha]_{546}^{20} = -194.0$; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.81 (brs, 1H; N*H*), 7.47 (s, 1H; H-6), 6.03 (m, 1H; H-3′), 5.89 (tdd, J_1 = 5.4, J_2 = 17.1, J_3 = 10.2 Hz, 1H; C*H*=CH$_2$), 5.60 (m, 1H; H-2′), 5.51 (s, 1H; H-8′), 5.28 (tdd, J_1 = 1.2, J_2 = 17.1, J_3 = 1.5 Hz, 1H; CH=CH−H_{trans}), 5.18 (tdd, J_1 = 1.2, J_2 = 10.2, J_3 = 1.5 Hz, 1H; CH=CH−H_{cis}), 4.29 (dd, $J_1 = J_2$ = 7.8 Hz, 1H; H-6′a), 4.21 (tdd, J_1 = 1.5, J_2 = 12.7, J_3 = 5.4 Hz, 1H; CH*H*a−CH=CH$_2$), 4.18 (tdd, J_1 = 1.3, J_2 = 12.7, J_3 = 5.4 Hz, 1H; CH*H*b−CH=CH$_2$), 3.54 (dd, J_1 = 7.8, J_2 = 7.6 Hz, 1H; H-6′b), 3.45 (m, 1H; H-5′), 2.90 (ddd, J_1 = 12.4, $J_2= J_3$ = 6.8 Hz, 1H; H-4′a), 1.42 ppm (ddd, J_1 = 12.4, J_2 = 8.3, J_3 = 8.8 Hz, 1H; H-4′b); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 159.0 (C4), 152.6 (C1′), 150.0 (C2), 140.0 (C6), 133.7 (*C*H=CH$_2$), 120.2 (C2′), 117.3 (CH=*C*H$_2$), 97.1 (C5), 96.1 (C8′), 71.6 (C6′), 67.7 (*C*H$_2$CH=CH$_2$), 65.8 (C3′), 45.3 (C5′), 40.4 ppm (C4′); IR (ATR): $\tilde{\nu}$ = 3167/3046 (w, N−H), 2975 (w, C−H), 1691 (s, C=O), 1615 (m, C=C), 1242 cm^{-1} (m, C−O); MS (EI, 70 eV): *m*/*z* (%): 356 (4) $[^{81}BrM]^+$, 354 (4) $[^{79}BrM]^+$, 135 (55), 119 (51), 79 (100); HRMS (EI): calcd for $C_{14}H_{15}BrN_2O_5$: 354.022 $[^{79}BrM]^+$; found: 354.021.

(+)-(3′*S*,5′*R*,8′*S*)-1-(8′-Allyloxy-7′-oxa-[3.3.0]-bicyclooct-1′-ene-3′-yl)-5-bromo-1*H*-pyrimidine-2,4-dione (*ent*-10c): When the general protocol A for the Pd-catalyzed introduction of nucleobases was followed, 5-bromouracil and *ent*-**21a** afforded *ent*-**10c** (501 mg, 71 %, 99 % purity) as a white solid. $[\alpha]_D^{20}$ = +158.8 (c = 0.56 in $CHCl_3$), $[\alpha]_{546}^{20}$ = +192.5.

(−)-(3′*R*,5′*S*,8′*R*)-1-(8′-Allyloxy-7′-oxa-[3.3.0]-bicyclooct-1′-ene-3′-yl)-5-methyl-1*H*-pyrimidine-2,4-dione (10d): When the general protocol A for the Pd-catalyzed introduction of nucleobases was followed, thymine and **21a** afforded **10d** (140 mg in 99 % purity and 250 mg in 89 % purity, 63 % total yield) as a white solid. M.p. 155–157 °C; R_f = 0.15 (EtOAc/CyHex 4:1); $[\alpha]_D^{20}$ = −234.2 (c = 0.47 in $CHCl_3$), $[\alpha]_{546}^{20} = -282.8$; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.63 (brs, 1H; N*H*), 6.96 (dq, J_1 = 1.3, J_2 = 1.0 Hz, 1H; H-6), 6.04 (dddd, J_1 = 2.2, J_2 = 1.3, J_3 = 6.8, J_4 = 8.5 Hz, 1H; H-3′), 5.91 (tdd, J_1 = 5.4, J_2 = 17.2, J_3 = 10.3 Hz, 1H; C*H*=CH$_2$), 5.60 (m, 1H; H-2′), 5.50 (s, 1H; H-8′), 5.29 (tdd, J_1 = 1.2, J_2 = 17.2, J_3 = 1.6 Hz, 1H; CH=CH−H_{trans}), 5.20 (tdd, J_1 = 1.3, J_2 = 10.3, J_3 = 1.7 Hz, 1H; CH=CH−H_{cis}), 4.30 (dd, $J_1 = J_2$ = 8.1 Hz, 1H; H-6′a), 4.20 (tdd, J_1 = 1.6, J_2 = 12.6, J_3 = 5.4 Hz, 1H; CH*H*a−CH=CH$_2$), 4.04 (tdd, J_1 = 1.3, J_2 = 12.6, J_3 = 6.1 Hz, 1H; CH*H*b−CH=CH$_2$), 3.53 (dd, $J_1 = J_2$ = 7.8 Hz, 1H; H-6′b), 3.45 (m, 1H; H-5′), 2.86 (ddd, J_1 = 12.4, J_2 = 7.0, J_3 = 6.8 Hz, 1H; H-4′a), 1.91 (d, J = 1.0 Hz, 1H; C*H*$_3$), 1.42 ppm (ddd, J_1 = 12.4, $J_2 = J_3$ = 7.7 Hz, 1H; H-4′b); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 163.4 (C4), 152.3 (C1′), 150.5 (C2), 136.1 (C6), 134.0 (*C*H=CH$_2$), 120.9 (C2′), 117.7 (CH=*C*H$_2$), 111.7 (C5), 96.4 (C8′), 72.0 (C6′), 68.1 (*C*H$_2$CH=CH$_2$), 65.4 (C3′), 45.5 (C5′), 40.5 (C4′), 12.5 ppm (*C*H$_3$); IR (ATR): $\tilde{\nu}$ = 3171/3052 (w, N−H), 2923 (w, C−H), 1682 (s, C=O), 1246 cm^{-1} (m, C−O); MS (EI, 70 eV): *m*/*z* (%): 207 (20), 98 (21), 97 (42), 91 (23), 83 (35), 71 (23), 70 (28), 69 (48), 57 (62), 55 (100).

(+)-(3′*S*,5′*R*,8′*S*)-1-(8′-Allyloxy-7′-oxa-[3.3.0]-bicyclooct-1′-ene-3′-yl)-5-methyl-1*H*-pyrimidine-2,4-dione (*ent*-10d): When the general protocol A for the Pd-catalyzed introduction of nucleobases was followed, thymine and *ent*-**21a** afforded *ent*-**10d** (295 mg, 47 %, 92 % purity) as a white solid. $[\alpha]_D^{20}$ = +197.4 (c = 0.49 in $CHCl_3$), $[\alpha]_{546}^{20}$ = +237.9.

(−)-(3′*R*,5′*S*,8′*R*)-*N*-[1-(8′-Allyloxy-7′-oxa-[3.3.0]-bicyclooct-1′-ene-3′-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-benzamide (10e): When the general

protocol A for the Pd-catalyzed introduction of nucleobases was followed, N^4-benzoylcytosine and **21a** (114 mg, 0.5 mmol) afforded **10e** (98 mg, 52%, 99% purity) as a white solid. M.p. 162–164 °C; R_f = 0.22 (EtOAc/CyHex 4:1); $[\alpha]_D^{20} = -205$ (c = 0.065 in $CHCl_3$), $[\alpha]_{546}^{20} = -256$; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.64–7.31 (m, 7H; H-Ph, H-5, H-6), 6.12 (m, 1H; H-3′), 5.89 (dddd, J_1 = 5.4, J_2 = 6.1, J_3 = 17.1, J_4 = 10.2 Hz, 1H; C*H*=CH$_2$), 5.62 (m, 1H; H-2′), 5.43 (s, 1H; H-8′), 5.20 (tdd, J_1 = 1.1, J_2 = 17.1, J_3 = 1.6 Hz, 1H; CH=CH−H_{trans}), 5.10 (tdd, J_1 = 1.2, J_2 = 10.2, J_3 = 1.6 Hz, 1H; CH=CH−H_{cis}), 4.21 (dd, J_1 = 7.1, J_2 = 5.7 Hz, 1H; H-6′a), 4.12 (tdd, J_1 = 1.5, J_2 = 12.7, J_3 = 5.4 Hz, 1H; CH*H*a−CH=CH$_2$), 4.18 (tdd, J_1 = 1.4, J_2 = 12.7, J_3 = 6.0 Hz, 1H; CH*H*b−CH=CH$_2$), 3.45 (dd, J_1 = 7.1, J_2 = 7.5 Hz, 1H; H-6′b), 3.40 (m, 1H; H-5′), 2.93 (ddd, J_1 = 12.5, J_2 = J_3 = 6.5 Hz, 1H; H-4′a), 1.35 ppm (ddd, J_1 = 12.5, J_2 = J_3 = 8.8 Hz, 1H; H-4′b); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 161.8 (PhC=O), 153.0 (C1′), 145.1 (C2), 136.1 (C6), 134.0 (*C*H=CH$_2$), 133.2/130.0/129.0/127.6 (all Ph), 120.7 (C2′), 117.7 (CH=*C*H$_2$), 111.7 (C5), 96.4 (C8′), 72.0 (C6′), 68.1 (*C*H$_2$CH=CH$_2$), 67.3 (C3′), 45.9 (C5′), 41.5 ppm (C4′); IR (ATR): $\tilde{\nu}$ = 3215/3144/3061 (w, N−H), 2942 (w, C−H), 1690 (s, C=O), 1658 (s, C=N), 1620 (s, C=C), 1556 (s), 1483 (s), 1382 (s), 1301 (s), 1244 cm^{-1} (s, C−O); MS (EI, 70 eV): m/z (%): 379 (10) $[M]^+$, 322 (32) $[M-C_3H_5O]^+$, 216 (27), 105 (100), 79 (21), 77 (43); HRMS (ESI): calcd for $C_{21}H_{22}N_3O_4$: 380.161 $[M+H]^+$; found: 380.161.

(+)-(3′*S*,5′*R*,8′*S*)-*N*-[1-(8′-Allyloxy-7′-oxa-[3.3.0]-bicyclooct-1′-ene-3′-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-benzamide (*ent*-10e): When the general protocol A for the Pd-catalyzed introduction of nucleobases was followed, N^4-benzoylcytosine and *ent*-**21a** afforded *ent*-**10e** (490 mg, 65%, 99% purity) as a white solid. $[\alpha]_D^{20} = +229.1$ (c = 0.43 in $CHCl_3$), $[\alpha]_{546}^{20} = +280.5$.

(−)-(3′*R*,5′*S*,8′*R*)-Diphenylcarbamic acid 2-acetylamino-9-(8′-allyloxy-7′-oxa-[3.3.0]-bicyclooct-1′-ene-3′-yl)-9*H*-purin-6-yl ester (10f): When the general protocol B for the Pd-catalyzed introduction of nucleobases was followed, the N^2-acetyl-*O*-diphenylcarbamoylguanine derivative and **21a** (896 mg, 4 mmol) afforded **10f** (1.67 g, 76%, 99% purity) as a pale-yellow solid. M.p. 90–94 °C; R_f = 0.68 (EtOAc/MeOH 4:1); $[\alpha]_D^{20} = -75.1$ (c = 0.58 in $CHCl_3$), $[\alpha]_{546}^{20} = -90.1$; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.02 (s, 1H; N*H*), 7.94 (s, 1H; H-8), 7.40–7.22 (m, 10H; 2×Ph), 5.99–5.86 (m, 2H; H-3′, C*H*=CH$_2$), 5.81 (s, 1H; H-2′), 5.51 (s, 1H; H-8′), 5.30 (tdd, J_1 = 1.7, J_2 = 17.1, J_3 = 3.2 Hz, 1H; CH=CH−H_{trans}), 5.20 (tdd, J_1 = 1.3, J_2 = 10.3, J_3 = 2.5 Hz, 1H; CH=CH−H_{cis}), 4.32 (dd, J_1 = J_2 = 6.4 Hz, 1H; H-6′a), 4.22 (tdd, J_1 = 1.3, J_2 = 12.5, J_3 = 5.3 Hz, 1H; CH*H*a−CH=CH$_2$), 4.06 (tdd, J_1 = 1.3, J_2 = 12.7, J_3 = 6.3 Hz, 1H; CH*H*b−CH=CH$_2$), 3.58 (dd, J_1 = J_2 = 7.7 Hz, 1H; H-6′b), 3.55 (m, 1H; H-5′), 2.96 (ddd, J_1 = 13.0, J_2 = J_3 = 6.4 Hz, 1H; H-4′a), 2.51 (s, 3H; C*H*$_3$), 1.87 ppm (ddd, J_1 = 13.2, J_2 = J_3 = 8.6 Hz, 1H; H-4′b); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 170.8 (CH$_3$*C*=O), 156.3/152.0/150.4 (C2/C6/O−*C*=O), 154.6 (C4), 152.1 (C1′), 142.1 (C8), 141.7/129.2/127.0 (br, all Ph), 134.0 (*C*H=CH$_2$), 121.0 (C5), 120.8 (C2′), 117.7 (CH=*C*H$_2$), 96.5 (C8′), 72.0 (C6′), 68.2 (*C*H$_2$CH=CH$_2$), 65.0 (C3′), 45.9 (C5′), 41.3 (C4′), 25.2 ppm (*C*H$_3$); IR (ATR): $\tilde{\nu}$ = 3262/3095 (w, N−H), 2977 (w, C−H), 1739 (s, C=O), 1687 (m, C=O), 1619 (s, C=C), 1491 (s), 1293 (s), 1186 cm^{-1} (s); MS (ESI, 70 eV): m/z (%): 575 (100) $[M+Na]^+$, 553 (6) $[M+H]^+$; HRMS (ESI): calcd for $C_{30}H_{28}N_6NaO_5$: 575.202 $[M+Na]^+$; found: 575.201.

(+)-(3′*S*,5′*R*,8′*S*)-Diphenylcarbamic acid 2-acetylamino-9-(8′-allyloxy-7′-oxa-[3.3.0]-bicyclooct-1′-ene-3′-yl)-9*H*-purin-6-yl ester (*ent*-10f): When the general protocol B for the Pd-catalyzed introduction of nucleobases was followed, the N^2-acetyl-*O*-diphenylcarbamoylguanine derivative and *ent*-**21a** (896 mg, 4 mmol) afforded *ent*-**10f** (1.31 g in 99% purity and 388 mg in 84% purity, 76% total yield) as a pale-yellow solid. $[\alpha]_D^{20} = +82.8$ (c = 0.43 in $CHCl_3$), $[\alpha]_{546}^{20} = +99.5$.

(−)-(3′*R*,5′*S*,8′*R*)-9-(8′-Allyloxy-7′-oxa-[3.3.0]-bicyclooct-1′-ene-3′-yl)-9*H*-purin-6-ylamine (10g): When the general protocol B for the Pd-catalyzed introduction of nucleobases was followed, adenine and **21a** afforded **10g** (313 mg, 52%, 99% purity) as a pale-yellow solid. M.p. 170–172 °C; R_f = 0.32 (EtOAc/MeOH 4:1); $[\alpha]_D^{20} = -164.9$ (c = 0.45 in $CHCl_3$), $[\alpha]_{546}^{20} = -196.6$; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.29 (s, 1H; H-2), 7.47 (s, 1H; H-8), 6.42 (br s, 2H; N*H*$_2$), 6.04 (tdd, J_1 = 2.0, J_2 = 7.3, J_3 = 8.6 Hz, 1H; H-3′), 5.90 (dddd, J_1 = 5.4, J_2 = 6.1, J_3 = 17.1, J_4 = 10.2 Hz, 1H; C*H*=CH$_2$), 5.83 (m, 1H; H-2′), 5.51 (s, 1H; H-8′), 5.26 (tdd, J_1 = 1.4, J_2 = 17.1, J_3 = 1.8 Hz, 1H; CH=CH−H_{trans}), 5.17 (tdd, J_1 = 1.2, J_2 = 10.2, J_3 = 1.8 Hz, 1H; CH=CH−H_{cis}), 4.29 (dd, J_1 = J_2 = 7.1 Hz, 1H; H-6′a), 4.19 (tdd, J_1 = 1.5, J_2 = 12.6, J_3 = 5.4 Hz, 1H; CH*H*a−CH=CH$_2$), 4.03 (tdd, J_1 = 1.2, J_2 = 12.6, J_3 = 6.1 Hz, 1H; CH*H*b−CH=CH$_2$), 3.56 (dd, J_1 = 7.1, J_2 = 7.5 Hz, 1H; H-6′b), 3.51 (m, 1H; H-5′), 2.99 (ddd, J_1 = 12.4, J_2 = 7.1, J_3 = 6.6 Hz, 1H; H-4′a), 1.75 ppm (ddd, J_1 = 12.4, J_2 = 8.6, J_3 = 9.1 Hz, 1H; H-4′b); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 155.8 (C6), 152.9 (C2), 151.9 (C1′), 149.5 (C4), 138.2 (C8), 133.9 (*C*H=CH$_2$), 121.3 (C2′), 119.6 (C5), 117.6 (CH=*C*H$_2$), 96.5 (C8′), 72.0 (C6′), 68.1 (*C*H$_2$CH=CH$_2$), 64.1 (C3′), 45.9 (C5′), 41.9 ppm (C4′); IR (ATR): $\tilde{\nu}$ = 3315/3162 (m, N−H), 2970 (w, C−H), 1644 (s, C=C), 1596 (s), 1247 cm^{-1} (m, C−O); MS (EI, 70 eV): m/z (%): 299 (3) $[M]^+$, 258 (61) $[M-C_3H_5]^+$, 242 (57) $[M-C_3H_5O]^+$, 164 (63), 136 (100), 135 (63), 79 (39); HRMS (EI): calcd for $C_{15}H_{17}N_5O_2$: 299.138 $[M]^+$; found: 299.139.

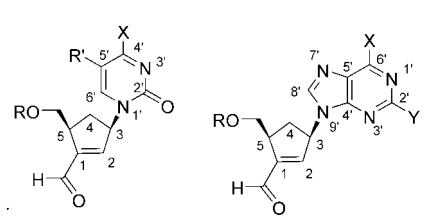
(+)-(3′*S*,5′*R*,8′*S*)-9-(8′-Allyloxy-7′-oxa-[3.3.0]-bicyclooct-1′-ene-3′-yl)-9*H*-purin-6-ylamine (*ent*-10g): When the general protocol A for the Pd-catalyzed introduction of nucleobases was followed, adenine and *ent*-**21a** afforded *ent*-**10g** (324 mg, 54%, 99% purity) as a yellow waxy solid (73% yield was achieved for a racemic version on a 5 mmol scale[12]). $[\alpha]_D^{20} = +164.0$ (c = 0.45 in MeOH), $[\alpha]_{546}^{20} = +195.0$.

(−)-(3′*R*,5′*S*,8′*R*)-9-(8′-Allyloxy-7′-oxa-[3.3.0]-bicyclooct-1′-ene-3′-yl)-9*H*-6-chloropurine (10h): When the general protocol C for the Pd-catalyzed introduction of nucleobases was followed, 6-chloropurine and **21b** (1.06 g, 4.4 mmol) afforded **10h** (880 mg, 63%, >99% purity) as a white, crystalline solid. M.p. 147–149 °C; R_f = 0.50 (EtOAc); $[\alpha]_D^{20} = -92.2$ (c = 0.60 in MeOH), $[\alpha]_{546}^{20} = -99.5$; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.73 (s, 1H; H-2), 8.17 (s, 1H; H-8), 6.15–6.09 (m, 1H; H-3′), 5.92 (dddd, J_1 = 5.4, J_2 = 6.0, J_3 = 17.3, J_4 = 10.3 Hz, 1H; C*H*=CH$_2$), 5.85 (m, 1H; H-2′), 5.54 (s, 1H; H-8′), 5.29 (tdd, J_1 = 1.5, J_2 = 17.3, J_3 = 1.6 Hz, 1H; CH=CH−H_{trans}), 5.20 (tdd, J_1 = 1.2, J_2 = 10.3, J_3 = 1.6 Hz, 1H; CH=CH−H_{cis}), 4.33 (dd, J_1 = J_2 = 6.8 Hz, 1H; H-6′a), 4.23 (tdd, J_1 = 1.5, J_2 = 12.7, J_3 = 5.4 Hz, 1H; CH*H*a−CH=CH$_2$), 4.06 (tdd, J_1 = 1.3, J_2 = 12.7, J_3 = 6.0 Hz, 1H; CH*H*b−CH=CH$_2$), 3.62 (dd, J_1 = J_2 = 7.6 Hz, 1H; H-6′b), 3.60 (m, 1H; H-5′), 3.04 (ddd, J_1 = 12.5, J_2 = J_3 = 6.5 Hz, 1H; H-4′a), 1.91–1.80 ppm (m, 1H; H-4′b); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 151.9 (C2), 151.3/151.1/150.5 (C4/C6/C1′), 143.2 (C8), 133.9 (*C*H=CH$_2$), 128.8 (C5), 120.3 (C2′), 117.7 (CH=*C*H$_2$), 96.4 (C8′), 71.9 (C6′), 68.2 (*C*H$_2$CH=CH$_2$), 65.0 (C3′), 46.0 (C5′), 41.5 ppm (C4′); IR (ATR): $\tilde{\nu}$ = 3361 (m), 2870 (m, C−H), 1684 (m, C=C), 1588 (s), 1556 (s), 1332 (s), 1202 (s), 1039 (s), 951(s), 635 cm^{-1} (m); MS (EI, 70 eV): m/z (%): 318 (15) $[M]^+$, 317 (19), 261 (50) $[M-C_3H_5O]^+$, 219 (23), 164 (94), 155 (51), 135 (38), 79 (100), 65 (41); HRMS (EI): calcd for $C_{15}H_{15}ClN_4O_2$: 318.088 $[M]^+$; found: 318.088.

General one-pot procedure for hydrolysis and silylation: A solution of **10a–f** or **10h–l** (1 mmol, unless otherwise stated) and PPTS (76 mg, 300 μmol) in wet acetone (10 mL) was stirred under reflux for 3 h. The solvent was evaporated and the flask was flushed with argon (3 times). Dry pyridine (3 mL) was added and, after stirring at RT for 5 min, ThxMe$_2$SiCl (310 μL, 1.5 mmol; used for **10a–f** and **10h**) or *t*BuPh$_2$SiCl (79 μL, 300 μmol; used for 200 μmol of **10i–l**) was added. After stirring at RT for 16 h, the reaction was quenched by addition of saturated $NaHCO_3$ (20 mL). After stirring the resulting mixture at RT for 30 min, the water phase was extracted with EtOAc (4×20 mL) and the combined organic layers were washed with 10% HCl (3×20 mL), saturated $NaHCO_3$ (20 mL), and brine (40 mL), dried ($MgSO_4$), and concentrated. The residue was then purified by flash chromatography to yield to **23a–f** and **23h–l**.

Modifications: For adenine derivative **23g**: **10g** (0.8 mmol) and PPTS (2 equiv) were used for the hydrolysis; ThxMe$_2$SiCl (3.3 equiv) and DMAP (33 mg, 260 μmol, 33 mol%) in a solvent mixture consisting of Et$_3$N (0.4 mL) and CH_2Cl_2 (4 mL) were used for the silylation step.

Synthesis of compounds of type 23 (Scheme 16)



Scheme 16. Numbering used for compounds of type **23**, NB = various nucleobases.

(+)-(3*R*,5*S*)-3-(2′,4′-Dioxo-3′,4′-dihydro-2*H*-pyrimidin-1′-yl)-5-[dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-cyclopent-1-enecarbaldehyde (23a): When the general hydrolysis/silylation procedure was followed, **10a** (294 mg, 1 mmol, 94% purity) afforded the aldehyde **23a** (309 mg, 82%) as a white solid. M.p. 115–116°C; R_f=0.24 (EtOAc/CyHex 4:1); $[\alpha]_D^{20}$=+59.3 (c=0.62 in $CHCl_3$), $[\alpha]_{546}^{20}$=+72.2; ^{1}H NMR (250 MHz, $CDCl_3$): δ=9.85 (s, 1H; *H*C=O), 8.78 (brs, 1H; N*H*), 7.47 (d, J_1=8.0 Hz, 1H; H-6′), 5.56 (dd, J_1=J_2=2.2 Hz, 1H; H-2), 5.90 (dddd, J_1=9.5, J_2=7.1, J_3=J_4=2.2 Hz, 1H; H-3), 5.71 (dd, J_1=8.0, J_2=2.4 Hz, 1H; H-5′), 4.27 (dd, J_1=10.0, J_2=3.0 Hz, 1H; SiOC*H*a), 3.58 (dd, J_1=10.0, J_2=2.5 Hz, 1H; SiOC*H*b), 3.18 (m, 1H; H-5), 2.79 (ddd, J_1=14.2, J_2=J_3=9.5 Hz, 1H; H-4a), 1.82 (ddd, J_1=14.2, J_2=J_3=7.5 Hz, 1H; H-4b), 1.56 (septet, J=6.8 Hz, 1H; Me_2CH), 0.81 (d, J=6.8 Hz, 6H; $(CH_3)_2CH$), 0.788/0.786 (2s, 6H; $C(CH_3)_2$), 0.042/0.036 ppm (2s, 6H; $SiCH_3$); ^{13}C NMR (63 MHz, $CDCl_3$): δ=188.9 (CH=O), 163.2 (C4′), 150.8 (C2′), 150.3 (C1), 147.8 (C2), 141.4 (C6′), 103.2 (C5′), 62.2 (CH_2OSi), 58.9 (C3), 44.3 (C5), 34.0 (Me_2CH), 33.3 (C4), 25.4 (Me_2CSi), 20.3/20.2 ($(CH_3)_2CH$), 18.5/18.4 ($(CH_3)_2CSi$), −3.5/−3.6 ppm ($(CH_3)_2Si$); IR (ATR): $\tilde{\nu}$=3038 (w, N−H), 2955 (m, C−H), 1697 (s, C=O), 1680 (s, C=O), 1649 (s, C=C), 1248 cm^{-1} (m, C−O); MS (EI, 70 eV): m/z (%): 293 (100) $[M-C_6H_{13}]^+$, 201 (55), 181 (62); HRMS (EI): calcd for $C_{13}H_{17}N_2O_4Si$: 293.096 $[M-C_6H_{13}]^+$; found: 293.096.

(−)-(3*S*,5*R*)-3-(2′,4′-Dioxo-3′,4′-dihydro-2*H*-pyrimidin-1′-yl)-5-[dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-cyclopent-1-enecarbaldehyde (*ent*-23a): When the general hydrolysis/silylation procedure was followed, *ent*-**10a** (294 mg, 1 mmol, 94% purity) afforded the aldehyde *ent*-**23a** (264 mg, 70%) as a white solid. $[\alpha]_D^{20}$=−55.5 (c=0.45 in $CHCl_3$), $[\alpha]_{546}^{20}$=−67.7.

(+)-(3*R*,5*S*)-3-(5′-Fluoro-2′,4′-dioxo-3′,4′-dihydro-2*H*-pyrimidin-1′-yl)-5-[dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-cyclopent-1-enecarbaldehyde (23b): When the general hydrolysis/silylation procedure was followed, **10b** (176 mg, 0.6 mmol) afforded the aldehyde **23b** (173 mg, 74%) as a white solid. M.p. 148–149°C; R_f=0.50 (EtOAc/CyHex 4:1); $[\alpha]_D^{20}$=+53.6 (c=0.50 in $CHCl_3$), $[\alpha]_{546}^{20}$=+65.2; ^{1}H NMR (250 MHz, $CDCl_3$): δ=9.86 (s, 1H; *H*C=O), 9.06 (brs, 1H; N*H*), 7.55 (d, J=5.6 Hz, 1H; H-6′), 6.56 (dd, J_1=J_2=2.1 Hz, 1H; H-2), 5.90 (m, 1H; H-3), 4.29 (dd, J_1=10.1, J_2=2.9 Hz, 1H; SiOC*H*a), 3.58 (dd, J_1=10.1, J_2=2.2 Hz, 1H; SiOC*H*b), 3.18 (m, 1H; H-5), 2.79 (ddd, J_1=14.2, J_2=J_3=9.4 Hz, 1H; H-4a), 1.82 (ddd, J_1=14.3, J_2=J_3=6.7 Hz, 1H; H-4b), 1.57 (septet, J=6.8 Hz, 1H; Me_2CH), 0.82 (d, J=7.4 Hz, 6H; $(CH_3)_2CH$), 0.798/0.794 (2s, 6H; $C(CH_3)_2$), 0.06 ppm (s, 6H; $SiCH_3$); ^{13}C NMR (63 MHz, $CDCl_3$): δ=188.7 (*C*H=O), 156.6 (d, J(C,F)=27 Hz, C4′), 150.6 (C2′), 149.3 (C1), 147.0 (C2), 145.0 (d, J(C,F)=269 Hz, C5′), 125.2 (d, J(C,F)=32 Hz, C6′), 62.3 (CH_2OSi), 59.4 (C3), 44.3 (C5), 34.0 (Me_2CH), 32.9 (C4), 25.5 (Me_2CSi), 20.4/20.2 ($(CH_3)_2CH$), 18.44/18.37 ($(CH_3)_2CSi$), −3.4/−3.6 ppm (CH_3Si); IR (ATR): $\tilde{\nu}$=3160 (w, N−H), 3049 (m, N−H), 2955 (m, C−H), 1720 (s, C=O), 1711 (s, C=O), 1685 (s, C=O), 1657 (s, C=C), 1248 (s, C−O), 1110 (s), 830 (s), 780 cm^{-1} (s); MS (EI, 70 eV): m/z (%): 397 (49) $[M+H]^+$, 251 (25), 237 (14).

(−)-(3*S*,5*R*)-3-(5′-Fluoro-2′,4′-dioxo-3′,4′-dihydro-2H-pyrimidin-1′-yl)-5-[dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-cyclopent-1-enecarbaldehyde (*ent*-23b): When the general hydrolysis/silylation procedure was followed, *ent*-**10b** (176 mg, 0.6 mmol) afforded the aldehyde *ent*-**23b** (171 mg, 73%) as a white solid. $[\alpha]_D^{20}$=−53.3 (c=0.52 in $CHCl_3$), $[\alpha]_{546}^{20}$=−65.2.

(+)-(3*R*,5*S*)-3-(5′-Bromo-2′,4′-dioxo-3′,4′-dihydro-2H-pyrimidin-1′-yl)-5-[dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-cyclopent-1-enecarbaldehyde (23c): When the general hydrolysis/silylation procedure was followed, **10c** (355 mg, 1 mmol) afforded the aldehyde **23c** (350 mg, 77%) as a white solid. M.p. 80–83°C; R_f=0.55 (EtOAc/CyHex 4:1); $[\alpha]_D^{20}$=+62.6 (c=0.58 in $CHCl_3$), $[\alpha]_{546}^{20}$=+76.3; ^{1}H NMR (250 MHz, $CDCl_3$): δ=9.87 (s, 1H; *H*C=O), 8.52 (brs, 1H; N*H*), 7.54 (s, 1H; H-6′), 6.57 (m, 1H; H-2), 5.85 (dddd, J_1=J_2=2.3, J_3=8.7, J_4=7.6 Hz, 1H; H-3), 4.25 (dd, J_1=10.0, J_2=3.2 Hz, 1H; SiOC*H*a), 3.52 (dd, J_1=10.0, J_2=2.3 Hz, 1H; SiOC*H*b), 3.17 (m, 1H; H-5), 2.75 (ddd, J_1=13.7, J_2=J_3=8.8 Hz, 1H; H-4a), 1.85 (ddd, J_1=13.7, J_2=J_3=7.7 Hz, 1H; H-4b), 1.55 (septet, J=6.8 Hz, 1H; Me_2CH), 0.83 (d, J=6.8 Hz, 6H; $(CH_3)_2CH$), 0.810/0.805 (2s, 6H; $C(CH_3)_2$), 0.06 ppm (s, 6H; $SiCH_3$); ^{13}C NMR (63 MHz, $CDCl_3$): δ=188.9 (*C*H=O), 159.2 (C4′), 150.5 (C2′), 150.4 (C1), 147.3 (C2), 140.2 (C6′), 97.7 (C5′), 61.5 (CH_2OSi), 59.9 (C3), 44.3 (C5), 34.0 (Me_2CH), 33.5 (C4), 25.3 (Me_2CSi), 20.4/20.3 ($(CH_3)_2CH$), 18.5/18.4 ($(CH_3)_2CSi$), −3.5/−3.7 ppm (CH_3Si); IR (ATR): $\tilde{\nu}$=3177/3046 (w, N−H), 2954 (m, C−H), 1704 (s, C=O), 1684 (s, C=O), 1617 (m, C=C), 1249 cm^{-1} (m, C−O); MS (EI, 70 eV): m/z (%): 373 (95), 372 (28), 371 (100) $[M-C_6H_{13}]^+$, 355 (34), 353 (32), 281 (92), 279 (89), 182 (58), 181 (90), 75 (31); HRMS (EI): calcd for $C_{13}H_{16}BrN_2O_4Si$: 371.006 $[M-C_6H_{13}]^+$; found: 371.005.

(−)-(3*S*,5*R*)-3-(5′-Bromo-2′,4′-dioxo-3′,4′-dihydro-2*H*-pyrimidin-1′-yl)-5-[dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-cyclopent-1-enecarbaldehyde (*ent*-23c): When the general hydrolysis/silylation procedure was followed, *ent*-**23c** (355 mg, 1 mmol) afforded the aldehyde *ent*-**23c** (342 mg, 75%) as a white solid. $[\alpha]_D^{20}$=−67.6 (c=0.53 in $CHCl_3$), $[\alpha]_{546}^{20}$=−82.7.

(+)-(3*R*,5*S*)-3-(5′-Methyl-2′,4′-dioxo-3′,4′-dihydro-2*H*-pyrimidin-1′-yl)-5-[dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-cyclopent-1-enecarbaldehyde (23d): When the general hydrolysis/silylation procedure was followed, **10d** (290 mg, 1 mmol) afforded the aldehyde **23d** (252 mg, 64%) as a white solid. M.p. 58–61°C; R_f=0.26 (EtOAc/CyHex 4:1); $[\alpha]_D^{20}$=+28.8 (c=0.53 in $CHCl_3$), $[\alpha]_{546}^{20}$=+35.4; ^{1}H NMR (250 MHz, $CDCl_3$): δ=10.06 (brs, 1H; N*H*), 9.81 (s, 1H; *H*C=O), 6.99 (q, J=1.2 Hz, 1H; H-6′), 6.58 (m, 1H; H-2), 5.83 (dddd, J_1=J_2=8.6, J_3=J_4=2.4 Hz, 1H; H-3), 4.18 (dd, J_1=10.0, J_2=3.4 Hz, 1H; SiOC*H*a), 3.53 (dd, J_1=10.0, J_2=2.4 Hz, 1H; SiOC*H*b), 3.10 (m, 1H; H-5), 2.65 (ddd, J_1=13.4, J_2=J_3=8.8 Hz, 1H; H-4a), 1.85 (d, J=1.2 Hz, 3H; C*H*$_3$), 1.80 (ddd, J_1=13.4, J_2=J_3=8.4 Hz, 1H; H-4b), 1.51 (septet, J=7.1 Hz, 1H; Me_2CH), 0.83 (d, J=7.1 Hz, 6H; $(CH_3)_2CH$), 0.793/0.790 (2s, 6H; $C(CH_3)_2$), 0.058/0.057 ppm (2s, 6H; $SiCH_3$); ^{13}C NMR (63 MHz, $CDCl_3$): δ=188.9 (*C*H=O), 164.1 (C4′), 151.1 (C2′), 149.8 (C1), 148.4 (C2), 136.2 (C6′), 111.8 (C5′), 61.4 (CH_2OSi), 59.0 (C3), 44.2 (C5), 34.0 (Me_2CH), 33.4 (C4), 25.1 (Me_2CSi), 20.2/20.2 ($(CH_3)_2CH$), 18.4/18.4 ($(CH_3)_2CSi$), 12.3 (CH_3), −3.5/−3.7 ppm ($SiCH_3$); IR (ATR): $\tilde{\nu}$=3177/3050 (w, N−H), 2954/2864 (m, C−H), 1683 (s, C=O), 1249 cm^{-1} (m, C−O); MS (EI, 70 eV): m/z (%): 393 (4) $[M+H]^+$, 307 (100) $[M-C_6H_{13}]^+$, 215 (52), 181 (73); HRMS (ESI): calcd for $C_{20}H_{33}N_2O_4Si$: 393.221 $[M+H]^+$; found: 393.221.

(−)-(3*S*,5*R*)-3-(5′-Methyl-2′,4′-dioxo-3′,4′-dihydro-2*H*-pyrimidin-1′-yl)-5-[dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-cyclopent-1-enecarbaldehyde (*ent*-23d): When the general hydrolysis/silylation procedure was followed, *ent*-**10d** (290 mg, 1 mmol) afforded the aldehyde *ent*-**23d** (235 mg, 60%) as a white solid. $[\alpha]_D^{20}$=−23.6 (c=0.54 in $CHCl_3$), $[\alpha]_{546}^{20}$=−29.4.

(+)-(3*R*,5*S*)-*N*-(1-{4-[Dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-3-formyl-cyclopent-2-enyl}-2′-oxo-1′,2′-dihydro-pyrimidin-4′-yl)-benzamide (23e): When the general hydrolysis/silylation procedure was followed, **10e** (403 mg, 1 mmol, 94% purity) afforded the aldehyde **23e** (324 mg, 67%) as a yellow solid. M.p. 78–81°C; R_f=0.28 (EtOAc/CyHex 4:1); $[\alpha]_D^{20}$=+59.5 (c=0.59 in $CHCl_3$), $[\alpha]_{546}^{20}$=+70.5; ^{1}H NMR (250 MHz, $CDCl_3$): δ=9.88 (s, 1H; *H*C=O), 8.23 (brs, 1H; N*H*), 7.89 (d, J=6.3 Hz, 3H; H-6′, 2H-Ph), 7.63–7.46 (m, 4H; H-5′, 3H-Ph), 6.63 (t, J=2.1 Hz, 1H; H-2), 6.10 (m, 1H; H-3), 4.26 (dd, J_1=10.0, J_2=3.2 Hz, 1H; SiOC*H*a), 3.59 (dd, J_1=10.0, J_2=2.3 Hz, 1H; SiOC*H*b), 3.22 (m, 1H; H-5), 2.90 (ddd, J_1=14.0, J_2=J_3=9.3 Hz, 1H; H-4a), 1.84 (ddd, J_1=14.0, J_2=J_3=6.7 Hz, 1H; H-4b), 1.57 (septet, J=6.8 Hz, 1H; Me_2CH), 0.82 (d, J=6.9 Hz, 6H; $(CH_3)_2CH$), 0.80 (s, 6H; $C(CH_3)_2$), 0.05 ppm (s, 6H; $SiCH_3$); ^{13}C NMR (63 MHz, $CDCl_3$): δ=188.9 (*C*H=O), 161.9 (C=O (Bz)), 150.4 (C2′), 147.9 (C6′) 146.1 (C2), 133.3/129.0/127.6 (all Ph), 62.3 (CH_2OSi), 60.6 (C3), 44.5 (C5), 34.3 (C4), 33.0 (Me_2CH), 25.4 (Me_2CSi), 20.4/20.2 ($(CH_3)_2CH$), 18.5/18.4 ($(CH_3)_2CSi$), −3.47/−3.49 ppm ($Si(CH_3)_2$); IR (ATR): $\tilde{\nu}$=3230/3142/3061 (w, N−H), 2954/2864 (m, C−H), 1684 (s, C=O), 1661 (s, C=N), 1622 (s, C=C), 1484 (s), 1249 cm^{-1} (s, C−O); MS (ESI, 70 eV): m/z (%): 1177 (11) $[2M+Na]^+$, 632 (49), 610 (100) $[M+Na]^+$, 578 (27) $[M+H]^+$, 216 (57).

(−)-(3*S*,5*R*)-*N*-(1-{4-[Dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-3-formyl-cyclopent-2-enyl}-2′-oxo-1′,2′-dihydro-pyrimidin-4′-yl)-benzamide (*ent*-23e): When the general hydrolysis/silylation procedure was followed, *ent*-**10e** (379 mg, 1 mmol) afforded the aldehyde *ent*-**23e** (316 mg, 66%) as a yellow solid. $[\alpha]_D^{20}$=−47.1 (c=0.32 in $CHCl_3$), $[\alpha]_{546}^{20}$=−56.3.

(+)-(3*R*,5*S*)-Diphenylcarbamic acid 2′-acetylamino-9′-{4-[dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-3-formyl-cyclopent-2-enyl}-9*H*-purin-6′-yl ester (23f): When the general hydrolysis/silylation procedure was followed, **10f** (1.104 g, 2 mmol) afforded the aldehyde **23f** (895 mg, 68%) as a light-yellow solid. M.p. 79–84°C; R_f=0.33 (EtOAc/CyHex

4:1); $[\alpha]_D^{20}=+5.7$ ($c=0.37$ in $CHCl_3$), $[\alpha]_{546}^{20}=+5.7$; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=9.88$ (s, 1H; *HC*=O), 8.06 (s, 1H; H-8′), 7.99 (s, 1H; N*H*), 7.40–6.72 (m, 10H; 2×Ph), 6.72 (s, 1H; H-2), 5.82 (m, 1H; H-3), 4.17 (dd, $J_1=8.5$, $J_2=3.5$ Hz, 1H; SiOC*H*a), 3.69 (dd, $J_1=8.3$, $J_2=2.3$ Hz, 1H; SiOC*H*b), 3.27 (m, 1H; H-5), 2.89 (ddd, $J_1=11.5$, $J_2=J3=7.5$ Hz, 1H; H-4a), 2.52 (s, 3H; CH_3CO), 2.12 (ddd, $J_1=11.5$, $J_2=J_3=6.0$ Hz, 1H; H-4b), 1.56 (septet, $J=6.8$ Hz, 1H; Me_2CH), 0.81 (d, $J=6.9$ Hz, 6H; $(CH_3)_2$CH), 0.79 (s, 6H; C(CH_3)$_2$), 0.05 ppm (s, 6H; SiCH_3); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta=189.1$ (*C*H=O), 170.6 (CH_3*C*=O), 154.7 (C4′), 156.3/152.1/150.4 (C4′, C6′, Ph_2N*C*=O), 149.7 (C1), 146.8 (C2), 142.1 (C8′), 141.7/129.1/127.0 (br, all Ph), 120.6 (C5′), 62.2 (*C*H$_2$OSi), 57.9 (C3), 44.7 (C5), 35.0 (C4), 34.0 (Me_2CH), 25.3 (Me_2CSi), 25.0 (CH_3C=O), 20.35/20.29 ((CH_3)$_2$CH), 18.45/18.43 ((CH_3)$_2$CSi), −3.55 ppm (Si(CH_3)$_2$); IR (ATR): $\tilde{\nu}=3272/3060$ (w, N−H), 2954/2864 (m, C−H), 1740 (s, C=O); 1685 (s, C=O), 1617 (s, C=C), 1586 (s), 1490 (s), 1374 (s), 1334 (s), 1280 (s, C−O), 1214 (s), 1186 (s), 1167 (s), 1059 (s), 1002 (s), 830 (s), 699 cm^{-1} (s).

(−)-(3*S*,5*R*)-Diphenylcarbamic acid 2′-acetylamino-9′-{4-[dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-3-formyl-cyclopent-2-enyl}-9*H*-purin-6′-yl ester (*ent*-23 f): When the general hydrolysis/silylation procedure was followed, *ent*-**10 f** (1.104 g, 2 mmol) afforded the aldehyde *ent*-**23 f** (877 mg, 67%) as a light-yellow solid. $[\alpha]_D^{20}=-7.0$ ($c=0.60$ in $CHCl_3$), $[\alpha]_{546}^{20}=-7.4$.

(+)-(3*R*,5*S*)-3-(6′-Aminopurin-9′-yl)-5-[dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-cyclopent-1-enecarbaldehyde (23 g): When the modified protocol for the hydrolysis/silylation procedure was followed, **10 g** (150 mg, 0.5 mmol) afforded the aldehyde **23 g** (79 mg, 40%) as a yellow solid. M.p. 148–152 °C; $R_f=0.43$ (EtOAc/CyHex 4:1); $[\alpha]_D^{20}=+40.8$ ($c=0.40$ in MeOH), $[\alpha]_{546}^{20}=+50.1$; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=9.86$ (s, 1H; *HC*=O), 8.30 (s, 1H; H-2′), 7.93 (s, 1H; H-8′), 6.75 (dd, $J_1=J_2=2.2$ Hz, 1H; H-2), 6.40 (s, 2H; NH_2), 5.84 (dddd, $J_1=9.1$, $J_2=6.8$, $J_3=J_4=2.2$ Hz, 1H; H-3), 4.14 (dd, $J_1=10.0$, $J_2=3.8$ Hz, 1H; SiOC*H*a), 3.66 (dd, $J_1=10.0$, $J_2=2.4$ Hz, 1H; SiOC*H*b), 3.24 (m, 1H; H-5), 2.89 (ddd, $J_1=14.0$, $J_2=J_3=9.1$ Hz, 1H; H-4a), 2.10 (ddd, $J_1=14.0$, $J_2=J_3=6.8$ Hz, 1H; H-4b), 1.53 (septet, $J=6.8$ Hz, 1H; Me_2CH), 0.78 (d, $J=6.8$ Hz, 6H; (CH_3)$_2$CH), 0.77 (s, 6H; C(CH_3)$_2$), 0.02 ppm (s, 6H; CH_3Si); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta=189.2$ (*C*H=O), 155.7 (C4′), 152.8 (C2′), 149.5 (C1), 149.5 (C6′), 147.4 (C2), 138.5 (C8′), 119.2 (C5′), 62.2 (*C*H$_2$OSi), 57.5 (C3), 44.7 (C5), 35.1 (C4), 34.0 (Me_2CH), 25.3 (Me_2CSi), 20.3/20.2 ((CH_3)$_2$CH), 18.4/18.4 ((CH_3)$_2$CSi), −3.6 ppm (CH_3Si); IR (ATR): $\tilde{\nu}=3318/3168$ (w, N−H), 2953/2864 (m, C−H), 1683 (s, C=O), 1645 (s, C=C), 1598 (s), 1250 cm^{-1} (s, C−O); MS (EI, 70 eV): *m*/*z* (%): 401 (2) [*M*]$^+$, 316 (100) [*M*+C_6H_{13}]$^+$; HRMS (ESI): calcd for $C_{20}H_{31}N_5O_2Si$: 402.2325 [*M*+H]$^+$; found: 402.2327.

(−)-(3*S*,5*R*)-3-(6′-Aminopurin-9′-yl)-5-[dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-cyclopent-1-enecarbaldehyde (*ent*-23 g): When the modified protocol for the hydrolysis/silylation procedure was followed, *ent*-**10 g** (239 mg, 0.8 mmol) afforded the aldehyde *ent*-**23 g** (123 mg, 38%) as a yellow solid. $[\alpha]_D^{20}=-25$ ($c=0.30$ in MeOH), $[\alpha]_{546}^{20}=-30$.

(+)-(3*R*,5*S*)-3-(6′-Chloropurin-9′-yl)-5-[dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-cyclopent-1-enecarbaldehyde (23 h): When the general protocol for the hydrolysis/silylation procedure was followed, **10 h** (638 mg, 2 mmol) afforded the aldehyde **23 h** (628 mg, 72%) as a pale-yellow solid. M.p. 130–131 °C; $R_f=0.67$ (EtOAc); $[\alpha]_D^{20}=+43.9$ ($c=0.65$ in MeOH), $[\alpha]_{546}^{20}=+53.8$; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=9.91$ (s, 1H; *HC*=O), 8.74 (s, 1H; H-2′), 8.29 (s, 1H; H-8′), 6.76 (dd, $J_1=J_2=2.1$ Hz, 1H; H-2), 5.96 (dddd, $J_1=9.3$, $J_2=6.9$, $J_3=J_4=2.1$ Hz, 1H; H-3), 4.22 (dd, $J_1=10.0$, $J_2=3.8$ Hz, 1H; SiOC*H*a), 3.66 (dd, $J_1=10.0$, $J_2=2.6$ Hz, 1H; SiOC*H*b), 3.30 (m, 1H; H-5), 2.94 (ddd, $J_1=14.0$, $J_2=J_3=9.1$ Hz, 1H; H-4a), 2.16 (ddd, $J_1=14.0$, $J_2=J_3=6.8$ Hz, 1H; H-4b), 1.55 (septet, $J=6.9$ Hz, 1H; Me_2CH), 0.80 (d, $J=6.8$ Hz, 6H; (CH_3)$_2$CH), 0.79 (s, 6H; C(CH_3)$_2$), 0.05 ppm (s, 6H; CH_3Si); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta=188.9$ (*C*H=O), 151.9 (C2′), 151.4/151.2/150.1 (C4′, C6′, C3), 146.1 (C2), 143.5 (C8′), 131.5 (C5′), 62.1 (*C*H$_2$OSi), 58.2 (C1), 44.8 (C4), 34.9 (C5), 34.0 (Me_2CH), 25.4 (Me_2CSi), 20.4/20.3 ((CH_3)$_2$CH), 18.4 ((CH_3)$_2$CSi), −3.5 ppm (CH_3Si); IR (ATR): $\tilde{\nu}=2954/2868$ (m, C−H), 1674 (s, C=O), 1589 (s), 1563 (s), 1396 (m), 1205 (m), 1109 (s), 826 cm^{-1} (s); MS (EI, 70 eV): *m*/*z* (%): 420 (7) [*M*]$^+$, 335 (82) [*M*−C_6H_{13}]$^+$, 243 (24), 181 (53), 167 (16), 151 (16), 75 (100); HRMS (EI): calcd for $C_{20}H_{29}ClN_4O_2Si$: 335.073 [*M*−C_6H_{13}]$^+$; found: 335.073; elemental analysis: calcd (%) for $C_{20}H_{29}ClN_4O_2Si$: C 57.06, H 6.94, N 13.31; found: C 57.01, H 6.95, N 13.25.

(+)-(3*R*,5*S*)-3-(5′-Fluoro-2′,4′-dioxo-3′,4′-dihydro-2*H*-pyrimidin-1′-yl)-5-(*tert*-butyldiphenylsilanyloxymethyl)-cyclopent-1-enecarbaldehyde (23 i): When the general protocol for the hydrolysis/silylation procedure was followed, **10 b** (29 mg, 0.1 mmol) afforded the aldehyde **23 i** (29 mg, 59%) as a white solid. $R_f=0.49$ (EtOAc/CyHex 4:1); $[\alpha]_D^{20}=+63.0$ ($c=0.56$ in $CHCl_3$), $[\alpha]_{546}^{20}=+76.5$; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=9.88$ (s, 1H; *HC*=O), 9.67 (br s, 1H; N*H*), 7.56 (d, $J=5.9$ Hz, 4H; Ph), 7.45–7.31 (m, 6H; Ph), 7.29 (d, $J=5.5$ Hz, 1H; H-6′), 6.61 (dd, $J_1=J_2=2.1$ Hz, 1H; H-2), 5.86 (dd, $J_1=J_2=7.7$ Hz, 1H; H-3), 4.23 (dd, $J_1=10.3$, $J_2=4.1$ Hz, 1H; SiOC*H*a), 3.74 (dd, $J_1=10.3$, $J_2=2.7$ Hz, 1H; SiOC*H*b), 3.19 (m, 1H; H-5), 2.76 (ddd, $J_1=13.9$, $J_2=J_3=9.0$ Hz, 1H; H-4a), 1.85 (ddd, $J_1=13.9$, $J_2=J_3=7.7$ Hz, 1H; H-4b), 1.02 ppm (s, 9H; SiCH_3); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta=188.6$ (*C*H=O), 156.8 (d, J(C,F)=27 Hz, C4′), 150.6 (C2′), 149.5 (C1), 146.8 (C2), 140.9 (d, J(C,F)=241 Hz, C5′), 135.6/135.4/133.1/132.8/129.9/127.78/127,76 (all Ph), 124.8 (d, J(C,F)=33 Hz, C6′), 62.9 (*C*H$_2$OSi), 59.8 (C3), 44.3 (C5), 33.3 (C4), 26.9 ((CH_3)$_3$CSi), 19.3 ppm (Me_2CSi); IR (ATR): $\tilde{\nu}=3181/3166$ (w, N−H), 3065 (m, N−H), 2952/2927 (m, C−H), 1714 (s, C=O), 1683 (s, C=O), 1243 (s, C−O), 1107 (s), 702 cm^{-1} (s); MS (EI, 70 eV): *m*/*z* (%): 1023 (2) [2*M*+K]$^+$, 1007 (1) [2*M*+Na]$^+$, 547 (100), 515 (14) [*M*+Na]$^+$, 493 (2) [*M*+H]$^+$.

(+)-(3*R*,5*S*)-3-(5′-Bromo-2′,4′-dioxo-3′,4′-dihydro-2*H*-pyrimidin-1′-yl)-5-(*tert*-butyldiphenylsilanyloxymethyl)-cyclopent-1-enecarbaldehyde (23 j): When the general protocol for the hydrolysis/silylation procedure was followed, **10 c** (71 mg, 0.2 mmol) afforded the aldehyde **23 j** (55 mg, 50%) as a white solid (76% yield was achieved in a racemic version of the reaction on a 1 mmol scale). M.p. 121–123 °C; $R_f=0.53$ (EtOAc/CyHex 4:1); $[\alpha]_D^{20}=+101.4$ ($c=0.31$ in $CHCl_3$), $[\alpha]_{546}^{20}=+122.4$. ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=9.90$ (s, 1H; *HC*=O), 8.50 (br s, 1H; N*H*), 7.59–7.32 (m, 10H; Ph), 7.46 (s, 1H; H-6′), 6.62 (dd, $J_1=J_2=2.1$ Hz, 1H; H-2), 5.81 (dddd, $J_1=J_2=2.5$, $J_3=J_4=8.4$ Hz, 1H; H-3), 4.20 (dd, $J_1=10.3$, $J_2=4.4$ Hz, 1H; SiOC*H*a), 3.74 (dd, $J_1=10.3$, $J_2=2.6$ Hz, 1H; SiOC*H*b), 3.18 (m, 1H; H-5), 2.74 (ddd, $J_1=13.4$, $J_2=J_3=8.7$ Hz, 1H; H-4a), 1.85 (ddd, $J_1=13.6$, $J_2=J_3=8.2$ Hz, 1H; H-4b), 1.03 ppm (s, 9H; SiCH_3); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta=188.8$ (*C*H=O), 159.3 (C4′), 150.40/150.35 (C1, C2′), 147.1 (C2), 139.9 (C6′), 135.5/135.3/133.0/132.8/129.8/129.4/127.7/127.6 (all Ph), 97.8 (C5′), 62.5 (*C*H$_2$OSi), 60.1 (C3), 44.3 (C5), 34.0 (C4), 26.9 ((CH_3)$_3$CSi), 19.3 ppm (Me_2CSi); IR (ATR): $\tilde{\nu}=3177/3067/3048$ (w, N−H), 2953/2928/2888 (m, C−H), 1704 (s, C=O), 1683 (s, C=O), 1619 (m, C=C), 1110 cm^{-1} (s).

(+)-(3*R*,5*S*)-*N*-{1-[4-(*tert*-Butyldiphenylsilanyloxymethyl)-3-formyl-cyclopent-2-enyl]-2′-oxo-1′,2′-dihydro-pyrimidin-4′-yl}-benzamide (23 k): When the general hydrolysis/silylation procedure was followed, **10 e** (64 mg, 0.16 mmol, 94% purity) afforded the aldehyde **23 k** (52 mg, 57%) as a pale-yellow solid. M.p. 104–108 °C; $R_f=0.25$ (EtOAc/CyHex 4:1); $[\alpha]_D^{20}=+45.1$ ($c=0.32$ in $CHCl_3$), $[\alpha]_{546}^{20}=+52.6$; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=9.89$ (s, 1H; *HC*=O), 7.88 (d, $J=7.2$ Hz, 2H; H-6′, 1H-Ph), 7.63 (d, $J=7.4$ Hz, 1H; H-5′), 7.60–7.33 (m, 14H; Ph), 6.66 (s, 1H; H-2), 6.07 (m, 1H; H-3), 4.28 (dd, $J_1=10.3$, $J_2=3.9$ Hz, 1H; SiOC*H*a), 3.74 (dd, $J_1=10.1$, $J_2=2.7$ Hz, 1H; SiOC*H*b), 3.24 (m, 1H; H-5), 2.92 (ddd, $J_1=14.2$, $J_2=J_3=9.3$ Hz, 1H; H-4a), 1.90 (ddd, $J_1=14.2$, $J_2=J_3=7.1$ Hz, 1H; H-4b), 1.04 ppm (s, 9H; SiCH_3); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta=188.8$ (*C*H=O), 161.9 (NH*C*=O), 150.4 (C2′), 147.7 (C6′) 145.7 (C2), 135.6/135.4/135.2/133.3/133.2/132.8/130.3/130.0/129.1/128.0/127.8/127.6 (all Ph), 97.8 (C5′), 63.2 (*C*H$_2$OSi), 60.8 (C3), 44.5 (C5), 34.4 (C4), 27.0 (SiC(CH_3)$_3$), 19.4 ppm (Si*C*(CH_3)$_3$).

(+)-(3*R*,5*S*)-Diphenylcarbamic acid 2′-acetylamino-9′-[4-(*tert*-butyldiphenylsilanyloxymethyl)-3-formyl-cyclopent-2-enyl]-9*H*-purin-6′-yl ester (23 l): When the general hydrolysis/silylation procedure was followed, **10 f** (228 mg, 0.4 mmol) afforded the aldehyde **23 l** (112 mg, 37%) as a white solid. $R_f=0.41$ (EtOAc/CyHex 4:1); $[\alpha]_D^{20}=+12.1$ ($c=0.75$ in $CHCl_3$), $[\alpha]_{546}^{20}=+13.7$; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=9.84$ (s, 1H; *HC*=O), 8.46 (s, 1H; N*H*), 7.92 (s, 1H; H-8′), 7.99 (s, 1H; N*H*), 7.56–7.18 (m, 20H; 4×Ph), 6.76 (s, 1H; H-2), 5.74 (m, 1H; H-3), 4.05 (dd, $J_1=10.3$, $J_2=6.0$ Hz, 1H; SiOC*H*a), 3.85 (dd, $J_1=10.1$, $J_2=3.2$ Hz, 1H; SiOC*H*b), 3.25 (m, 1H; H-5), 2.85 (ddd, $J_1=13.7$, $J_2=J_3=8.5$ Hz, 1H; H-4a), 2.43 (s, 3H; CH_3CO), 2.06 (ddd, $J_1=13.2$, $J_2=J_3=5.8$ Hz, 1H; H-4b), 1.00 ppm (s, 9H; SiCH_3); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta=188.9$ (*C*H=O), 170.5 (CH_3*C*=O), 156.2 (C4′), 154.6/152.1/150.3 (C2′, C6′, Ph_2N*C*=O), 149.4 (C1), 146.7 (C2), 141.75 (C8′), 141.64/135.5/135.3/133.1/132.9/129.75/

129.772/129.1/127.65/127.60/126.9 (br, all 4×Ph), 120.6 (C5′), 63.2 (CH_2OSi), 58.2 (C3), 44.7 (C5), 35.3 (C4), 26.9 (SiC(CH_3)$_3$), 25.0 (CH_3C=O), 19.2 ppm (SiC(CH_3)$_3$); IR (ATR): $\tilde{\nu}$=3217/3064 (w, N−H), 2929/2854 (w, C−H), 1741 (s, C=O); 1684 (s, C=O), 1617 (s, C=C), 1281 (s), 1213 (s), 1185 (s), 1167 (s), 700 cm^{-1} (s); MS (ESI, 70 eV): *m*/*z* (%): 773 (47) [*M*+Na]$^+$, 411 ppm (100); HRMS (ESI): calcd for $C_{43}H_{42}N_6NaO_5Si$: 773.288 [*M*+Na]$^+$; found: 773.288.

General procedure for the reduction of aldehydes of type 23: A mixture of MeOH (6 mL) and CH_2Cl_2 (12 mL) was added to $NaBH_4$ (76 mg, 2 mmol) and the resulting mixture was stirred at RT for 3 min and then cooled to −78 °C. A solution of **23** (200 μmol) in CH_2Cl_2 (2 mL) was added dropwise. After the mixture was stirred at −78 °C for 1 h, acetone (5 mL) was added and the mixture was allowed to warm to RT and stirred for 30 min. The mixture was poured through a plug of silica and washed with EtOAc. The solvents were then removed under reduced pressure to give the allylic alcohols of type **9** in a high purity according to ^{1}H NMR spectroscopy and TLC.

(−)-(1′*R*,4′*S*)-1-{4′-[Dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-3′-hydroxymethyl-cyclopent-2′-enyl}-1*H*-pyrimidine-2,4-dione (9a): When the general protocol for the reduction was followed, **23a** (76 mg, 0.2 mmol) afforded the alcohol **9a** (59 mg, 78 %) as a white solid. M.p. 60–62 °C; R_f=0.17 (EtOAc/CyHex 4:1); $[\alpha]_D^{20}$=−84.6 (*c*=0.33 in $CHCl_3$), $[\alpha]_{546}^{20}$=−101.3; ^{1}H NMR (250 MHz, $CDCl_3$): δ=9.00 (brs, 1H; N*H*), 7.34 (d, *J*=8.0 Hz, 1H; H-6), 5.67 (dd, J_1=8.0, J_2=2.2 Hz, H-5), 5.62 (ddd, J_1=8.5, J_2=J_3=1.9 Hz, 1H; H-1′), 5.52 (s, 1H; H-2′), 4.26 (s, 2H; CH_2OH), 3.79 (dd, J_1=10.5, J_2=3.6 Hz, 1H; SiOC*H*a), 3.52 (dd, J_1=10.5, J_2=6.1 Hz, 1H; SiOC*H*b), 2.86 (m, 1H; H-4′), 2.71 (ddd, J_1=13.5, J_2=J_3=8.5 Hz, 1H; H-5′a), 1.59 (septet, *J*=6.8 Hz, 2H; OH, Me$_2$C*H*), 1.39 (ddd, J_1=13.5, J_2=J_3=6.9 Hz, 1H; H-5′b), 0.85 (d, *J*=6.8 Hz, 6H; (CH_3)$_2$CH), 0.83 (s, 6H; C(CH_3)$_2$), 0.10/0.09 ppm (2s, 6H; CH_3Si); ^{13}C NMR (63 MHz, $CDCl_3$): δ=163.3 (C4), 152.7 (C3′), 151.0 (C2), 141.2 (C6), 124.7 (C2′), 102.4 (C5), 64.1 (CH_2OSi), 60.5 (CH_2OH), 59.6 (C1′), 46.9 (C4′), 34.1 (C5′), 34.0 (Me$_2$*C*H), 25.3 (Me$_2$*C*Si), 20.3/20.2 ((CH_3)$_2$CH), 18.5/18.4 ((CH_3)$_2$CSi), −3.49/−3.51 ppm (CH_3Si); IR (ATR): $\tilde{\nu}$=3406 (w, O−H), 3178 (w, N−H), 3043 (m, N−H), 2951/2862 (m, C−H), 1693 (s, C=O), 1687 (s, C=O), 1666 (s, C=N), 1651 (m, C=C), 1461 (s), 1248 (s, C−O), 828 (s), 775 cm^{-1} (s); MS (EI, 70 eV): *m*/*z* (%): 295 (10) [*M*−C_6H_{13}]$^+$, 91 (100); HRMS (ESI): calcd for $C_{19}H_{32}N_2NaO_4Si$: 403.203 [*M*+Na]$^+$; found: 403.204.

(+)-(1′*S*,4′*R*)-1-{4′-[Dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-3′-hydroxymethyl-cyclopent-2′-enyl}-1*H*-pyrimidine-2,4-dione (*ent*-9a): When the general protocol for the reduction was followed, *ent*-**23a** (76 mg, 0.2 mmol) afforded the alcohol *ent*-**9a** (72 mg, 95 %) as a white solid. $[\alpha]_D^{20}$=+61 (*c*=0.26 in $CHCl_3$), $[\alpha]_{546}^{20}$=+76.

(−)-(1′R,4′S)-5-Fluoro-1-{4′-[dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-3′-hydroxymethyl-cyclopent-2′-enyl}-1H-pyrimidine-2,4-dione (9b): When the general protocol for the reduction was followed, **23b** (48 mg, 0.1 mmol) afforded the alcohol **9b** (48 mg, 99 %) as a colorless oil. R_f=0.40 (EtOAc/CyHex 4:1); $[\alpha]_D^{20}$=−77.0 (*c*=0.46 in $CHCl_3$), $[\alpha]_{546}^{20}$=−95.3; ^{1}H NMR (250 MHz, $CDCl_3$): δ=9.92 (brs, 1H; N*H*), 7.42 (d, *J*(H,F)=5.9 Hz, 1H; H-6), 5.62 (m, 1H; H-1′), 5.53 (s, 1H; H-2′), 4.31 (d, *J*=14.6 Hz, 1H; C*H*aOH), 4.23 (d, *J*=15.0 Hz, 1H; C*H*bOH), 3.80 (dd, J_1=10.4, J_2=3.4 Hz, 1H; SiOC*H*a), 3.53 (dd, J_1=10.4, J_2=5.2 Hz, 1H; SiOC*H*b), 2.86 (m, 1H; H-4′), 2.70 (ddd, J_1=13.6, J_2=J_3=8.6 Hz, 1H; H-5′a), 1.58 (septet, *J*=6.8 Hz, 1H; Me$_2$C*H*), 1.43 (ddd, J_1=13.7, J_2=J_3=6.6 Hz, 1H; H-5′b), 0.84 (d, *J*=7.0 Hz, 6H; (CH_3)$_2$CH), 0.82 (s, 6H; C(CH_3)$_2$), 0.10/0.08 ppm (2s, 6H; CH_3Si); ^{13}C NMR (63 MHz, $CDCl_3$): δ=157.1 (d, *J*(C,F)=26 Hz, C4), 153.2 (C3′), 149.8 (C2), 140.6 (d, *J*(C,F)=236 Hz, C6), 125.3 (d, *J*(C,F)=32 Hz, C5), 124.2 (C2′), 63.7 (CH_2OSi), 60.4 (CH_2OH), 60.1 (C1′), 46.8 (C4′), 34.0 (Me$_2$*C*H), 33.7 (C5′), 25.3 (Me$_2$*C*Si), 20.3/20.1 ((CH_3)$_2$CH), 18.41/18.36 ((CH_3)$_2$CSi), −3.5/−3.6 ppm (CH_3Si); IR (ATR): $\tilde{\nu}$=3416 (w, O−H), 3178/3056 (w, N−H), 2954/2864 (m, C−H), 1692 (s, C=O), 1659 (s, C=C), 1239 (s, C−O), 830 cm^{-1} (s); MS (ESI, 70 eV): *m*/*z* (%): 835 (4) [2*M*+K]$^+$, 819 (4) [2*M*+Na]$^+$, 421 (100) [*M*+Na]$^+$, 399 (2) [*M*+H]$^+$; HRMS (ESI): calcd for $C_{19}H_{31}FN_2NaO_4Si$: 421.194 [*M*+Na]$^+$; found: 421.194.

(+)-(1′*S*,4′*R*)-5-Fluoro-1-{4′-[dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-3′-hydroxymethyl-cyclopent-2′-enyl}-1*H*-pyrimidine-2,4-dione (*ent*-9b): When the general protocol for the reduction was followed, *ent*-**23b** (48 mg, 0.1 mmol) afforded the alcohol *ent*-**9b** (45 mg, 94 %) as a yellow solid. M.p. 165–167 °C; $[\alpha]_D^{20}$=+71.1 (*c*=0.68 in $CHCl_3$), $[\alpha]_{546}^{20}$=+88.3.

(−)-(1′*R*,4′*S*)-5-Bromo-1-{4′-[dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-3′-hydroxymethyl-cyclopent-2′-enyl}-1*H*-pyrimidine-2,4-dione (9c): When the general protocol for the reduction was followed, **23c** (92 mg, 0.2 mmol) afforded the alcohol **9c** (92 mg, 99 %) as a yellow solid. M.p. 79–82 °C; R_f=0.39 (EtOAc/CyHex 4:1); $[\alpha]_D^{20}$=−25 (*c*=0.30 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ=9.01 (brs, 1H; N*H*), 7.55 (s, 1H; H-6), 5.59 (dddd, J_1=8.6, J_2=7.3, J_3=J_4=2.0 Hz, 1H; H-1′), 5.55 (d, *J*=1.7 Hz, 1H; H-2′), 4.29 (brs, 2H; CH_2OH), 3.78 (dd, J_1=10.6, J_2=3.7 Hz, 1H; SiOC*H*a), 3.52 (dd, J_1=10.0, J_2=5.8 Hz, 1H; SiOC*H*b), 2.87 (m, 1H; H-4′), 2.69 (ddd, J_1=13.4, J_2=J_3=8.2 Hz, 1H; H-5′a), 1.68 (brs, 1H; OH), 1.60 (septet, *J*=6.8 Hz, 1H; Me$_2$C*H*), 1.40 (ddd, J_1=13.4, J_2=J_3=7.6 Hz, 1H; H-5′b), 0.86 (d, *J*=6.8 Hz, 6H; (CH_3)$_2$CH), 0.84 (s, 6H; C(CH_3)$_2$), 0.12/0.10 ppm (2s, 6H; CH_3Si); ^{13}C NMR (63 MHz, $CDCl_3$): δ=159.1 (C4), 153.6 (C3′), 150.3 (C2), 140.4 (C6), 124.0 (C2′), 96.7 (C5), 63.8 (CH_2OSi), 60.5 (CH_2OH), 60.4 (C1′), 46.9 (C4′), 34.3 (C5′), 34.0 (Me$_2$*C*H), 25.2 (Me$_2$*C*Si), 20.3/20.2 ((CH_3)$_2$CH), 18.4 ((CH_3)$_2$CSi), −3.4/−3.5 ppm (CH_3Si); IR (ATR): $\tilde{\nu}$=3427 (w, O−H), 3171/3048 (w, N−H), 2953/2862 (m, C−H), 1693 (s, C=O), 1682 (s, C=O), 1615 (m, C=C), 1249 cm^{-1} (m, C−O); MS (EI, 70 eV): *m*/*z* (%): 375 (48), 373 (58), 183 (100); HRMS (EI): calcd for $C_{13}H_{18}BrN_2O_4Si$: 373.022 [*M*−C_6H_{13}]$^+$; found: 373.020.

(+)-(1′*S*,4′*R*)-5-Bromo-1-{4′-[dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-3′-hydroxymethyl-cyclopent-2′-enyl}-1*H*-pyrimidine-2,4-dione (*ent*-9c): When the general protocol for the reduction was followed, *ent*-**23c** (92 mg, 0.2 mmol) afforded the alcohol *ent*-**9c** (85 mg, 93 %) as a yellow solid. $[\alpha]_D^{20}$=+20.7 (*c*=0.34 in $CHCl_3$), $[\alpha]_{546}^{20}$=+26.1.

(−)-(1′*R*,4′*S*)-1-{4′-[Dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-3′-hydroxymethyl-cyclopent-2′-enyl}-5-methyl-1*H*-pyrimidine-2,4-dione (9d): When the general protocol for the reduction was followed, **23d** (78 mg, 0.2 mmol) afforded the alcohol **9d** (69 mg, 88 %) as a white solid. M.p. 108–109 °C; R_f=0.21 (EtOAc/CyHex 4:1); $[\alpha]_D^{20}$=−67.9 (*c*=0.50 in $CHCl_3$), $[\alpha]_{546}^{20}$=−83.6; ^{1}H NMR (250 MHz, $CDCl_3$): δ=8.62 (brs, 1H; N*H*), 7.05 (d, *J*=1.2 Hz, 1H; H-6), 5.59 (dddd, J_1=7.8, J_2=7.6, J_3=J_4=2.1 Hz, 1H; H-1′), 5.53 (s, 1H; H-2′), 4.27 (d, *J*=5.8 Hz, 2H; CH_2OH), 3.77 (dd, J_1=10.3, J_2=3.7 Hz, 1H; SiOC*H*a), 3.52 (dd, J_1=10.3, J_2=6.3 Hz, 1H; SiOC*H*b), 2.87 (m, 1H; H-4′), 2.65 (ddd, J_1=13.3, J_2=J_3=8.4 Hz, 1H; H-5′a), 1.88 (d, *J*=1.2 Hz, 3H; CH_3), 1.67 (brs, 1H; OH), 1.60 (septet, *J*=6.9 Hz, 1H; Me$_2$C*H*), 1.35 (ddd, J_1=13.6, J_2=J_3=7.7 Hz, 1H; H-5′b), 0.86 (d, *J*=6.9 Hz, 6H; (CH_3)$_2$CH), 0.83 (s, 6H; C(CH_3)$_2$), 0.11/0.10 ppm (2s, 6H; CH_3Si); ^{13}C NMR (63 MHz, $CDCl_3$): δ=163.8 (C4), 152.3 (C3′), 150.1 (C2), 136.6 (C6), 125.2 (C2′), 110.1 (C5), 64.1 (CH_2OSi), 60.6 (CH_2OH), 59.4 (C1′), 46.7 (C4′), 34.2 (C5′), 34.1 (Me$_2$*C*H), 25.2 (Me$_2$*C*Si), 20.2 ((CH_3)$_2$CH), 18.5 ((CH_3)$_2$CSi), 12.4 (CH_3), −3.5/−3.6 ppm (CH_3Si); IR (ATR): $\tilde{\nu}$=3404 (w, O−H), 3173/3042 (w, N−H), 2953/2863 (m, C−H), 1681 (s, C=O), 1249 (s), 1222 (m, C−O), 829 cm^{-1} (s); MS (EI, 70 eV): *m*/*z* (%): 216 (87), 183 (34), 105 (100), 91 (28), 77 (29), 75 (50), 73 (30); HRMS (ESI): calcd for $C_{20}H_{34}N_2NaO_4Si$: 417.2186 [*M*+Na]$^+$; found: 417.219.

(+)-(1′*S*,4′*R*)-1-{4′-[Dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-3′-hydroxymethyl-cyclopent-2′-enyl}-5-methyl-1*H*-pyrimidine-2,4-dione (*ent*-9d): When the general protocol for the reduction was followed, *ent*-**23d** (78 mg, 0.2 mmol) afforded the alcohol *ent*-**9d** (79 mg, 99 %) as a white solid. $[\alpha]_D^{20}$=+70 (*c*=0.16 in $CHCl_3$), $[\alpha]_{546}^{20}$=+87.

(+)-(1′*R*,4′*S*)-4-Amino-1-{4′-[dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-3′-hydroxymethyl-cyclopent-2′-enyl}-1*H*-pyrimidin-2-one (*ent*-9e): When the general protocol for the reduction was followed, *ent*-**23e** (96 mg, 0.2 mmol) afforded the corresponding protected alcohol (97 mg, 99 %; R_f=0.55, EtOAc/CyHex 4:1) as a yellow foam. The resulting intermediate (48 mg, 100 μmol) was treated under argon with a 2 M solution of ammonia in MeOH (2 mL, 4 mmol) and the resulting mixture was stirred for 16 h at RT. The solvent and the ammonia were evaporated and the residue was purified by flash chromatography (EtOAc/CyHex 4:1, then EtOAc/MeOH 4:1). The product *ent*-**9e** was obtained as a yellow oil (36 mg, 95 %). R_f=0.27 (EtOAc/MeOH 4:1); $[\alpha]_D^{20}$=+91.6 (*c*=0.31 in MeOH), $[\alpha]_{546}^{20}$=+112.1; ^{1}H NMR (250 MHz, [D$_4$]MeOH): δ=7.49 (d, *J*=6.0 Hz, 1H; H-6), 5.79 (d, *J*=6.0 Hz, 1H; H-5), 5.50 (brs, 2H; NH_2), 4.25 (d, *J*=13.0 Hz, 1H; C*H*aOH), 4.10 (d, *J*=13.0 Hz, 1H; C*H*bOH), 3.71 (dd, J_1=8.8, J_2=3.5 Hz, 1H; SiOC*H*a), 3.51 (m, 1H; SiOC*H*b), 3.29

(s, 1H; H-2′), 3.23 (m, 1H; H-1′), 2.81 (m, 1H; H-4′), 2.64 (ddd, J_1=11.5, J_2=J_3=7.3 Hz, 1H; H-5′a), 1.54 (septet, J=5.5 Hz, 1H; Me_2CH), 1.46 (ddd, J_1=11.5, J_2=J_3=5.5 Hz, 1H; H-5′b), 0.80 (d, J=5.5 Hz, 6H; $(CH_3)_2CH$), 0.78 (s, 6H; $C(CH_3)_2$), 0.03/0.01 ppm (2s, 6H; CH_3Si); ^{13}C NMR (63 MHz, [D$_4$]MeOH): δ=167.3 (C4), 158.9 (C2), 154.1 (C3′), 143.8 (C6), 124.9 (C2′), 96.0 (C5), 64.4 (CH_2OSi), 62.2 (C1′), 60.9 (CH_2OH), 48.0 (C4′), 35.9 (C5′), 35.4 (Me_2CH), 26.3 (Me_2CSi), 21.0/20.8 ($(CH_3)_2CH$), 19.05/18.98 ($(CH_3)_2CSi$), −3.3 ppm (CH_3Si); IR (ATR): $\tilde{\nu}$= 3330 (br m, O−H), 3199 (m, N−H), 2954/2863 (m, C−H), 1714 (w, C=O), 1640 (s, C=N), 1613 (s, C=C), 1250 cm^{-1} (m, C−O); MS (ESI, 70 eV): *m*/*z* (%): 402 (100) $[M+Na]^+$, 134 (39), 112 (43); HRMS (ESI): calcd for $C_{19}H_{33}N_3O_3NaSi$: 402.219 $[M+Na]^+$; found: 402.218.

(−)-(1′*S*,4′*R*)-4-Amino-1-[4′-[dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-3′-hydroxymethyl-cyclopent-2′-enyl]-1*H*-pyrimidin-2-one (9e): When the general protocol for the reduction was followed, **23e** (96 mg, 0.2 mmol) afforded a mixture of the protected and the deprotected alcohols. This mixture was used directly for the deprotecting step. By following the deprotection method described for *ent*-**9e**, the product **9e** was obtained as a white solid (59 mg, 85% yield). M.p. 189–193 °C; $[\alpha]_D^{20}$=−97.9 (*c*=0.33 in MeOH), $[\alpha]_{546}^{20}$=−120.6.

(−)-(1′*R*,4′*S*)-2-Amino-9-[4′-[dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-3′-hydroxymethyl-cyclopent-2′-enyl]-1,9-dihydro-purin-6-one (9f): Alcohol **9f** (97 mg, 99% yield) was obtained as a white solid from **23f** (65 mg, 0.1 mmol) by following the general procedure for the reduction, except that the solvents were evaporated and the residue was directly subjected to the ammonolysis as described for *ent*-**9e**. M.p. 230 °C; R_f=0.58 (EtOAc/MeOH 4:1); $[\alpha]_D^{20}$=−55.4 (*c*=0.31 in MeOH), $[\alpha]_{546}^{20}$= −66.7; ^{1}H NMR (250 MHz, [D$_4$]MeOH): δ=7.66 (s, 1H; H-8), 5.80 (s, 1H; H-2′), 5.42 (m, 1H; H-1′), 4.37 (d, J=15.0 Hz, 1H; C*H*aOH), 4.21 (d, J=15.0 Hz, 1H; C*H*bOH), 3.77 (dd, J_1=10.3, J_2=4.9 Hz, 1H; SiOC*H*a), 3.66 (dd, J_1=10.2, J_2=4.4 Hz, 1H; SiOC*H*b), 2.95 (m, 1H; H-4′), 2.76 (ddd, J_1=13.7, J_2=J_3=8.5 Hz, 1H; H-5′a), 1.83 (ddd, J_1=13.6, J_2=J_2=5.9 Hz, 1H; H-5′b), 1.60 (septet, J=6.9 Hz, 1H; Me_2CH), 0.87 (d, J=6.9 Hz, 6H; $(CH_3)_2CH$), 0.84 (s, 6H; $C(CH_3)_2$), 0.08/0.07 ppm (2s, 6H; CH_3Si); ^{13}C NMR (63 MHz, [D$_4$]MeOH): δ=159.4 (C6), 155.2 (C2), 153.8 (C4), 152.7 (C3′), 137.3 (C8), 128.8 (C5), 124.4 (C2′), 64.8 (CH_2OSi), 60.9 (CH_2OH), 59.3 (C1′), 48.6 (C4′), 36.7 (C5′), 35.5 (Me_2CH), 26.3 (Me_2CSi), 20.93/20.84 ($(CH_3)_2CH$), 19.00/18.96 ($(CH_3)_2CSi$), −3.4 ppm ($(CH_3)_2Si$); IR (ATR): $\tilde{\nu}$=3364 (m, O−H), 3191 (m, N−H), 2954/2865 (m, C−H), 1686 (s, C=O), 1638 (s, C=N), 1608 (m, C=C), 1251 cm^{-1} (m, C−O); MS (ESI, 70 eV): *m*/*z* (%): 861 (55) $[2M+Na]^+$, 442 (100) $[M+Na]^+$; HRMS (ESI): calcd for $C_{20}H_{33}N_5NaO_3Si$: 442.225 $[M+Na]^+$; found: 442.225.

(+)-(1′S,4′R)-2-Amino-9-[4′-[dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-3′-hydroxymethyl-cyclopent-2′-enyl]-1,9-dihydro-purin-6-one (*ent*-9f): When the protocol for the reduction and deprotection as described for **9f** was followed, *ent*-**23f** (65 mg, 0.1 mmol) afforded the alcohol *ent*-**9f** (32 mg, 76%) as a white solid. $[\alpha]_D^{20}$=+68.1 (*c*=0.42 in MeOH).

(−)-(1′*R*,4′*S*)-9-[4′-[Dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-3′-hydroxymethyl-cyclopent-2′-enyl]-9*H*-purin-6-ylamine (9g): When the general protocol for the reduction was followed, **23g** (40 mg, 0.1 mmol) afforded the alcohol **9g** (37 mg, 93%) as a pale-yellow solid. M.p. 203–205 °C; R_f=0.33 (EtOAc/MeOH 4:1); $[\alpha]_D^{20}$=−27.2 (*c*=0.34 in MeOH), $[\alpha]_{546}^{20}$=−31.4; ^{1}H NMR (250 MHz, [D$_4$]MeOH): δ=8.21 (s, 1H; H-2), 8.06 (s, 1H; H-8), 5.85 (dd, J_1=J_2=1.8 Hz, 1H; H-2′), 5.59 (m, 1H; H-1′), 4.38 (d, J=15.3 Hz, 1H; C*H*aOH), 4.23 (d, J=15.3 Hz, 1H; C*H*bOH), 3.76 (dd, J_1=10.3, J_2=4.7 Hz, 1H; SiOC*H*a), 3.66 (dd, J_1= 10.3, J_2=4.1 Hz, 1H; SiOC*H*b), 2.99 (m, 1H; H-4′), 2.84 (ddd, J_1=13.4, J_2=J_3=8.6 Hz, 1H; H-5′a), 1.85 (ddd, J_1=13.4, J_2=J_2=5.4 Hz, 1H; H-5′b), 1.57 (septet, J=6.8 Hz, 1H; (Me_2CH), 0.84 (d, J=6.8 Hz, 6H; $(CH_3)_2CH$), 0.82 (s, 6H; $C(CH_3)_2$), 0.06/0.04 ppm (2s, 6H; CH_3Si); ^{13}C NMR (63 MHz, [D$_4$]MeOH): δ=155.2/153.7/152.7 (C2, C4, C6), 152.0 (C3′), 137.3 (C8), 136.68/136.64/134.50/134.42/131.00/130.96 (all Ph), 124.4 (C2′), 117.9 (C5), 66.2 (CH_2OSi), 61.0 (CH_2OH), 59.9 (C1′), 48.5 (C4′), 36.7 (C5′), 35.4 ($(CH_3)_2CH$), 26.3 (Me_2CSi), 20.95/20.83 ($(CH_3)_2CH$), 18.99/18.93 ($(CH_3)_2CSi$), −3.4 ppm (CH_3Si); IR (ATR): $\tilde{\nu}$=3357 (s, O−H), 3304 (s, N−H), 2956/2865 (m, C−H), 1643 (m, C=C), 1606 (s), 1250 cm^{-1} (m, C−O); MS (EI, 70 eV): *m*/*z* (%): 318 (28) $[M-C_6H_{13}]^+$, 136 (100); HRMS (ESI): calcd for $C_{20}H_{33}N_5O_2Si$: 404.248 $[M+H]^+$; found: 404.248.

(+)-(1′*S*,4′*R*)-9-[4′-[Dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-3′-hydroxymethyl-cyclopent-2′-enyl]-9*H*-purin-6-ylamine (*ent*-9g): When the general protocol for the reduction was followed, *ent*-**23g** (40 mg, 0.1 mmol) afforded the alcohol *ent*-**9g** (40 mg, 99%) as a yellow solid. $[\alpha]_D^{20}$=+16 (*c*=0.20 in MeOH), $[\alpha]_{546}^{20}$=+18.

(−)-(1′*R*,4′*S*)-9-[4′-[Dimethyl-(1,1,2-trimethylpropyl)-silanyloxymethyl]-3′-hydroxymethyl-cyclopent-2′-enyl]-9*H*-6-chloropurine (9h): When the general protocol for the reduction was followed, **23h** (422 mg, 1 mmol) afforded the alcohol **9h** (412 mg, 97%) as a white solid. M.p. 112–113 °C; R_f=0.48 (EtOAc); $[\alpha]_D^{20}$=−50.8 (*c*=0.665 in $CHCl_3$), $[\alpha]_{546}^{20}$=−62.1; ^{1}H NMR (250 MHz, $CDCl_3$): δ=8.71 (s, 1H; H-2), 8.18 (s, 1H; H-8), 5.80 (m, 1H; H-2′), 5.73 (m, 1H; H-1′), 4.37 (d, J=15.0 Hz, 1H; C*H*aOH), 4.32 (d, J=15.0 Hz, 1H; C*H*bOH), 3.76 (dd, J_1=10.3, J_2= 4.1 Hz, 1H; SiOC*H*a), 3.57 (dd, J_1=10.3, J_2=6.6 Hz, 1H; SiOC*H*b), 3.01 (m, 1H; H-4′), 2.88 (ddd, J_1=13.5, J_2=J_3=8.5 Hz, 1H; H-5′a), 2.74 (s, 1H; O*H*), 1.85 (ddd, J_1=13.5, J_2=J_2=6.4 Hz, 1H; H-5′b), 1.57 (septet, J=6.9 Hz, 1H; $(CH_3)_2CH$), 0.83 (d, J=6.9 Hz, 6H; $(CH_3)_2CH$), 0.81 (s, 6H; $C(CH_3)_2$), 0.09/0.07 ppm (2s, 6H; CH_3Si); ^{13}C NMR (63 MHz, $CDCl_3$): δ=153.3 (C3′), 151.7 (C2), 151.5/150.9 (C4, C6), 143.4 (C8), 131.8 (C5), 123.5 (C2′), 64.5 (CH_2OSi), 60.5 (CH_2OH), 58.6 (C1′), 47.4 (C4′), 35.6 (C5′), 34.0 ($(CH_3)_2CH$), 25.2 (Me_2CSi), 20.3/20.2 ($(CH_3)_2CH$), 18.43/18.41 ($(CH_3)_2CSi$), −3.5 ppm (CH_3Si); IR (ATR): $\tilde{\nu}$=3382 (s, O−H), 2953/2863 (m, C−H), 1588 (s), 1557 (s), 1395 (m), 1194 (s), 831 (s), 777 cm^{-1} (s); MS (EI, 70 eV): *m*/*z* (%): 318 (28) $[M-C_6H_{13}]^+$, 136 (100); HRMS (ESI): calcd for $C_{20}H_{31}ClN_4O_2Si$: 445.180 $[M+Na]^+$; found: 445.181; elemental analysis: calcd (%) for $C_{20}H_{31}ClN_4O_2Si$: C 56.78, H 7.39, N 13.24; found: C 56.63, H 7.41, N 13.18.

(−)-(1′*R*,4′*S*)-5-Fluoro-1-[4′-(*tert*-butyldiphenylsilanyloxymethyl)-3′-hydroxymethyl-cyclopent-2′-enyl]-1*H*-pyrimidine-2,4-dione (9i): When the general protocol for the reduction was followed, **23i** (25 mg, 50 μmol) afforded the alcohol **9i** (25 mg, 99%) as a colorless oil. R_f=0.43 (EtOAc/CyHex 4:1); $[\alpha]_D^{20}$=−42.1 (*c*=0.44 in $CHCl_3$), $[\alpha]_{546}^{20}$=−51.5; ^{1}H NMR (250 MHz, $CDCl_3$): δ=9.20 (br s, 1H; N*H*), 7.64–7.58 (m, 4H; Ph), 7.46–7.35 (m, 6H; Ph), 7.31 (d, J(H,F)=5.9 Hz, 1H; H-6), 5.56 (m, 2H; H-1′, H-2′), 4.35 (d, J=14.7 Hz, 1H; C*H*aOH), 4.25 (d, J=14.8 Hz, 1H; C*H*bOH), 3.73 (dd, J_1=10.5, J_2=4.4 Hz, 1H; SiOC*H*a), 3.64 (dd, J_1= 10.5, J_2=5.9 Hz, 1H; SiOC*H*b), 2.88 (m, 1H; H-4′), 2.63 (ddd, J_1=14.0, J_2=J_3=8.7 Hz, 1H; H-5′a), 1.37 (ddd, J_1=14.0, J_2=J_3=7.3 Hz, 1H; H-5′b), 1.06 ppm (s, 9H; $(CH_3)CSi$); ^{13}C NMR (63 MHz, $CDCl_3$): δ=153.6 (C3′), 149.5 (C2), 135.54/135.48/132.6/130.11/130.08/128.0 (all Ph), 125.0 (d, J(C,F)=33 Hz, C6), 123.9 (C2′), 65.1 (CH_2OSi), 60.7 (CH_2OH), 60.3 (C1′), 46.8 (C4′), 34.0 (C5′), 26.9 ($SiC(CH_3)_3$), 19.2 ppm ($SiC(CH_3)_3$); IR (ATR): $\tilde{\nu}$=3399 (w, O−H), 3176/3065 (m, N−H), 2927/2890/2854 (m, C−H), 1696 (s, C=O), 1659 (s, C=N), 1239 (s, C−O), 1109 (s), 702 cm^{-1} (s); MS (EI, 70 eV): *m*/*z* (%): 437 (14) $[M-C_4H_9]^+$, 229 (41), 199 (100); HRMS (EI): calcd for $C_{23}H_{22}FN_2O_4Si$: 437.133 $[M-C_4H_9]^+$; found: 437.133.

(+)-(1′*R*,4′*S*)-5-Bromo-1-[4′-(*tert*-butyldiphenylsilanyloxymethyl)-3′-hydroxymethyl-cyclopent-2′-enyl]-1*H*-pyrimidine-2,4-dione (9j): When the general protocol for the reduction was followed, **23j** (55 mg, 0.1 mmol) afforded the alcohol **9j** (56 mg, 99%) as a colorless oil. R_f=0.39 (EtOAc/CyHex 4:1); $[\alpha]_D^{20}$=+18.5 (*c*=0.52 in $CHCl_3$), $[\alpha]_{546}^{20}$=+21.7; ^{1}H NMR (250 MHz, $CDCl_3$): δ=9.74 (s, 1H; N*H*), 7.64–7.58 (m, 4H; Ph), 7.52 (s, 1H; H-6), 7.43–7.34 (m, 6H; Ph), 5.58 (d, J=1.7 Hz, 1H; H-2′), 5.55 (dd, J_1=J_2=8.2 Hz, 1H; H-1′), 4.37 (d, J=14.6 Hz, 1H; C*H*aOH), 4.27 (d, J=14.7 Hz, 1H; C*H*bOH), 3.71 (dd, J_1=10.5, J_2= 4.6 Hz, 1H; SiOC*H*a), 3.63 (dd, J_1=10.5, J_2=6.0 Hz, 1H; SiOC*H*b), 2.87 (m, 2H; H-4′, OH), 2.61 (ddd, J_1=13.7, J_2=J_3=8.2 Hz, 1H; H-5′a), 1.33 (ddd, J_1=13.6, J_2=J_3=7.4 Hz, 1H; H-5′b), 1.06 ppm (s, 9H; $(CH_3)_3CSi$); ^{13}C NMR (63 MHz, $CDCl_3$): δ=159.2 (C4), 153.6 (C3′), 150.4 (C2), 140.3 (C6), 135.50/135.48/132.61/132.58/130.07/130.03/127.9 (all Ph), 123.7 (C2′), 96.7 (C5), 65.0 (CH_2OSi), 61.0 (CH_2OH), 60.6 (C1′), 46.8 (C4′), 34.5 (C5′), 26.9 ($(CH_3)_3CSi$), 19.2 ppm ($(CH_3)_3CSi$); IR (ATR): $\tilde{\nu}$=3425 (w, O−H), 3173 (w, N−H), 3065 (m, N−H), 2927/2854 (m, C−H), 1691 (s, C=O), 1683 (s, C=O), 1615 (m, C=C), 702 cm^{-1} (s); MS (ESI, 70 eV): *m*/*z* (%): 583 (100), 581 (92), 579 (46), 577 (42) $[M+Na]^+$, 501 (67); HRMS (ESI): calcd for $C_{27}H_{31}BrN_2NaO_4Si$: 577.113 $[M+Na]^+$; found: 577.114.

(−)-(1′*R*,4′*S*)-4-Amino-1-[4′-(*tert*-butyldiphenylsilanyloxymethyl)-3′-hydroxymethyl-cyclopent-2′-enyl]-1*H*-pyrimidin-2-one (9k): When the general protocol for the reduction was followed, **23k** (29 mg, 50 μmol) afforded the corresponding protected alcohol (23 mg, 79%) as a light-

yellow solid (m.p. 190–193 °C; R_f = 0.54, EtOAc/MeOH 4:1). By using the ammonolysis method described for *ent*-**9e**, the protected alcohol (20 mg, 35 μmol) was converted into the alcohol **9k** (16 mg, 96 %), which was obtained as a white solid. M.p. 198–201 °C; R_f = 0.33 (EtOAc/MeOH 4:1); $[\alpha]_D^{20} = -54.5$ (c = 0.31 in MeOH), $[\alpha]_{546}^{20} = -67.6$; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.60–7.56 (m, 4H; Ph-H), 7.42–7.33 (m, 7H; H-6, Ph-H), 5.61–5.48 (m, 3H; H-1′, H-2′, H-5), 4.34 (d, J = 14.6 Hz, 1H; C*H*aOH), 4.24 (d, J = 14.6 Hz, 1H; C*H*bOH), 3.74–3.52 (m, 4H; SiOCH_2, NH_2), 2.84 (m, 1H; H-4′), 2.64 (m, 1H; H-5′a), 1.28 (m, 1H; H-5′b), 1.03 ppm (s, 9H; Si(CH_3)$_3$); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 153.4 (C3′), 142.8 (C6), 135.53/135.48/132.9/132.6/130.06/129.94/127.89/127.83 (all Ph), 125.1 (C2′), 94.6 (C5), 65.5 (*C*H_2OSi), 61.7 (C1′), 60.8 (*C*H_2OH), 46.9 (C4′), 34.8 (C5′), 26.9 (SiC(*C*H_3)$_3$), 19.2 ppm (Si*C*(CH$_3$)$_3$); IR (ATR): $\tilde{\nu}$ = 3338 (br s, O–H/N–H), 2953/2928/2854 (m, C–H), 1714 (w, C=O), 1640 (s, C=N), 1486 (s), 778 (s), 738 cm^{-1} (s); MS (ESI, 70 eV): m/z (%): 973 (14) [2M+Na]$^+$, 951 (3) [2M+H]$^+$, 498 (100) [M+Na]$^+$; HRMS (ESI): calcd for $C_{27}H_{33}N_3NaO_3Si$: 498.219 [M+Na]$^+$; found: 498.219.

(−)-(1′*R*,4′*S*)-2-Amino-9-[4′-(*tert*-butyldiphenylsilanyloxymethyl)-3′-hydroxymethyl-cyclopent-2′-enyl]-1,9-dihydro-purin-6-one (9l): When the one-pot procedure described for **9f** was followed, **23l** (38 mg, 50 μmol) afforded the alcohol **9l** (26 mg, 99 % over 2 steps) as a white solid. M.p. > 260 °C (decomp.); R_f = 0.50 (EtOAc/MeOH 4:1); $[\alpha]_D^{20} = -34.8$ (c = 0.72 in MeOH), $[\alpha]_{546}^{20} = -40.6$; ^{1}H NMR (250 MHz, [D$_4$]MeOH): δ = 7.60–7.32 (m, 11H; Ph, H-8), 5.84 (s, 1H; H-2′), 5.39 (m, 1H; H-1′), 4.37 (d, J = 15.6 Hz, 1H; C*H*aOH), 4.19 (d, J = 15.7 Hz, 1H; C*H*bOH), 3.79 (dd, J_1 = 10.3, J_2 = 4.9 Hz, 1H; SiOC*H*a), 3.69 (dd, J_1 = 10.3, J_2 = 5.7 Hz, 1H; SiOC*H*b), 2.99 (m, 1H; H-4′), 2.72 (ddd, J_1 = 13.7, J_2 = J_3 = 8.5 Hz, 1H; H-5′a), 1.81 (ddd, J_1 = 13.3, J_2 = J_2 = 6.2 Hz, 1H; H-5′b), 1.02 ppm (s, 9H; Si(CH_3)$_3$); ^{13}C NMR (63 MHz, [D$_4$]MeOH): δ = 155.2/153.7/152.7 (C2, C4, C6), 152.0 (C3′), 137.1 (C8), 136.68/136.64/134.50/134.42/131.00/130.96 (all Ph), 124.4 (C2′), 117. 9 (C5), 66.2 (*C*H_2OSi), 61.0 (*C*H_2OH), 59.9 (C1′), 48.5 (C4′), 36.7 (C5′), 27.4 (SiC(*C*H_3)$_3$), 20.1 ppm (Si*C*(CH$_3$)$_3$); IR (ATR): $\tilde{\nu}$ = 3350 (m, O–H), 3317/3191 (m, N–H), 2934/2891 (m, C–H), 1683 (s, C=O), 1603 (m, C=C), 701 cm^{-1} (s); MS (ESI, 70 eV): m/z (%): 339 (100).

(−)-(2*S*,3′*R*,5′*S*,8′*R*)-3,3,3-Trifluoro-2-methoxy-2-phenyl propionic acid (8′-allyloxy-2′-trimethylsilyl-7′-oxa-[3.3.0]-bicyclooct-1′-ene-3′-yl) ester (24a): A solution of DCC (46 mg, 220 μmol) in dry CH_2Cl_2 (0.5 mL) was added at 0 °C to a solution of alcohol **18** (51 mg, 200 μmol), (*S*)-MTPA (52 mg, 97 % *ee*, 220 μmol), and DMAP (3 mg, 98 %, 24 μmol) in dry CH_2Cl_2 (0.5 mL). The formation of a white suspension was observed. The mixture was allowed to warm to RT and was stirred for 16 h. The mixture was purified directly by flash chromatography (EtOAc/CyHex 1:9) to afford the ester **24a** as a colorless oil (84 mg, 89 %). R_f = 0.72 (EtOAc/CyHex 1:1); $[\alpha]_D^{20} = -154.6$ (c = 0.875 in $CHCl_3$), $[\alpha]_{546}^{20} = -184.4$; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.53 (m, 2H; Ph), 7.37 (m, 3H; Ph), 6.08 (tdd, J_1 = 7.8, J_2 = 5.9, J_3 = 1.7 Hz, 1H; H-3), 5.89 (tdd, J_1 = 16.8, J_2 = 10.3, J_3 = J_4 = 6.6 Hz, 1H; C*H*=CH$_2$), 5.38 (s, 1H; H-8), 5.26 (ddd, J_1 = 17.1, J_2 = 1.7, J_3 = 1.5 Hz, 1H; CH=CH–H_{trans}), 5.17 (tdd, J_1 = 10.3, J_2 = 1.7, J_3 = 1.0 Hz, 1H; CH=CH–H_{cis}), 4.22 (dd, J_1 = J_2 = 8.1 Hz, 1H; H-6a), 4.12 (ddd, J_1 = 12.5, J_2 = 5.4, J_3 = 1.2 Hz, 1H; CH*H*a–CH=CH$_2$), 3.99 (ddd, J_1 = 12.5, J_2 = 6.6, J_3 = 1.2 Hz, 1H; CH*H*b–CH=CH$_2$), 3.58 (d, J(H,F) = 1.5 Hz, 3H; *C*H_3O), 3.45 (dd, J_1 = J_2 = 7.8 Hz, 1H; H-6b), 3.33 (m, 1H; H-5), 3.03 (ddd, J_1 = 12.2, J_2 = 6.8, J_3 = 5.9 Hz, 1H; H-4a), 1.40 (ddd, J_1 = 12.2, J_2 = J_3 = 8.5 Hz, 1H; H-4b), −0.14 ppm (s, 9H; SiCH$_3$); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 177.5 (*C*=O), 158.8 (C1), 135.4 (C2), 134.1 (*C*H=CH$_2$), 132.4/129.5/128.3/126.9 (all Ph), 123.3 (d, J(C,F) = 289 Hz, *C*F$_3$), 118.0 (CH=*C*H$_2$), 97.0 (C8), 91.3 (C3), 84.7 (d, J(C,F) = 28 Hz, CF$_3$*C*), 71.7 (C6), 68.4 (*C*H$_2$CH=CH$_2$), 55.7 (O*C*H$_3$), 46.8 (C5), 40.7 (C4), −1.4 ppm (SiC); IR (ATR): $\tilde{\nu}$ = 2947 (s, C–H), 2892/2849 (w, C–H), 1742 (C=O), 1662 (w, C=C), 1268 (s), 1246 (s, C–O), 1165 (s), 1118 (s), 1077 (s), 1020 (s), 987 (s), 941 (s), 837 (s), 762 (s), 720 (s), 696 cm^{-1} (s); MS (EI, 70 eV): m/z (%): 189 (41) [CF$_3$C(Ph)OMe]$^+$, 91 (100), 77 (11) [Ph]$^+$; GC (HP-5 column, 50→300 °C over 2 min, gradient: 25 °C min^{-1}): R_t = 9.20 min.

(+)-(2*S*,3′*S*,5′*R*,8′*S*)-3,3,3-Trifluoro-2-methoxy-2-phenyl propionic acid (8′-allyloxy-2′-trimethylsilyl-7′-oxa-[3.3.0]-bicyclooct-1′-ene-3′-yl) ester (24b): Ester **24b** (89 mg, 95 %) was obtained from the alcohol *ent*-**18** (51 mg, 200 μmol) as a colorless oil, by using the DCC method described for the preparation of **24a**. R_f = 0.56 (EtOAc/CyHex 1:1); $[\alpha]_D^{20} = +106.1$ (c = 0.90 in $CHCl_3$), $[\alpha]_{546}^{20} = +125.7$; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.48 (m, 2H; Ph), 7.39 (m, 3H; Ph), 6.16 (dddd, J_1 = J_2 = 7.6, J_3 = 5.9, J_4 = 2.0 Hz, 1H; H-3), 5.89 (tdd, J_1 = 17.1, J_2 = 10.3, J_3 = 6.3 Hz, 1H; C*H*=CH$_2$), 5.37 (s, 1H; H-8), 5.26 (ddd, J_1 = 17.1, J_2 = 1.5, J_3 = 1.2 Hz, 1H; CH=CH–H_{trans}), 5.17 (ddd, J_1 = 10.3, J_2 = J_3 = 1.2 Hz, 1H; CH=CH–H_{cis}), 4.20 (dd, J_1 = J_2 = 7.8 Hz, 1H; H-6a), 4.18 (m, 1H; CH*H*a–CH=CH$_2$), 3.99 (dd, J_1 = 12.2, J_2 = 6.3 Hz, 1H; CH*H*b–CH=CH$_2$), 3.43 (d, J = 0.7 Hz, 3H; CH_3O), 3.40 (dd, J_1 = J_2 = 7.3 Hz, 1H; H-6b), 3.31 (m, 1H; H-5), 3.00 (ddd, J_1 = 12.7, J_2 = J_3 = 6.6 Hz, 1H; H-4a), 1.27 (ddd, J_1 = 12.2, J_2 = J_3 = 8.1 Hz, 1H; H-4b), 0.03 ppm (s, 9H; SiCH$_3$); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 177.3 (*C*=O), 159.1 (C1), 135.0 (C2), 134.1 (*C*H=CH$_2$), 131.6/129.7/128.5/127.6 (all Ph), 123.4 (d, J(C,F) = 289 Hz, *C*F$_3$), 118.0 (CH=*C*H$_2$), 97.0 (C8), 91.5 (C3), 84.9 (d, J(C,F) = 27 Hz, CF$_3$*C*), 71.7 (C6), 68.4 (*C*H$_2$CH=CH$_2$), 55.2 (O*C*H$_3$), 46.7 (C5), 40.1 (C4), −1.1 ppm (SiC); IR (ATR): $\tilde{\nu}$ = 2945/2891/2851 (m, C–H), 1742 (C=O), 1662 (m, C=C), 1268 (s), 1248 (s), 1167 (s), 1117 (s), 1077 (s), 1021 (s), 941 (s), 838 (s), 762 (s), 721 (s), 697 cm^{-1} (s); MS (EI, 70 eV): m/z (%): 455 (2) [M−CH$_3$]$^+$, 189 (100) [CF$_3$C(Ph)OMe]$^+$, 170 (64), 126 (42), 83 (87), 77 (29) [Ph]$^+$.

(−)-(2*S*,3′*R*,5′*S*,8′*R*)-3,3,3-Trifluoro-2-methoxy-2-phenyl propionic acid (8′-allyloxy-7′-oxa-[3.3.0]-bicyclooct-1′-ene-3′-yl) ester (25a): Ester **25a** (53 mg, 67 %) was obtained from alcohol **20** (36 mg, 200 μmol) as a colorless oil by using the DCC method described for the preparation of **24a**. R_f = 0.59 (EtOAc/CyHex 1:1); $[\alpha]_D^{20} = -123.1$ (c = 0.99 in $CHCl_3$), $[\alpha]_{546}^{20} = -146.5$; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.51 (m, 2H; Ph), 7.39 (m, 3H; Ph), 6.18 (dddd, J_1 = J_2 = 7.1, J_3 = 6.6, J_4 = 1.5 Hz, 1H; H-3), 5.89 (dddd, J_1 = 17.1, J_2 = 10.3, J_3 = 5.9, J_4 = 5.4 Hz, 1H; C*H*=CH$_2$), 5.71 (s, 1H; H-2), 5.40 (s, 1H; H-8), 5.27 (ddt, J_1 = 17.1, J_2 = 1.7, J_3 = 1.5 Hz, 1H; CH=CH–H_{trans}), 5.17 (ddt, J_1 = 10.3, J_2 = 1.5, J_3 = 1.2 Hz, 1H; CH=CH–H_{cis}), 4.25 (dd, J_1 = J_2 = 7.6 Hz, 1H; H-6a), 4.18 (ddt, J_1 = 12.7, J_2 = 5.4, J_3 = 1.5 Hz, 1H; CH*H*a–CH=CH$_2$), 4.01 (ddt, J_1 = 6.1, J_2 = 2.7, J_3 = 1.5 Hz, 1H; CH*H*b–CH=CH$_2$), 3.52 (d, J = 1.0 Hz, 3H; CH_3O), 3.45 (dd, J_1 = J_2 = 7.6 Hz, 1H; H-6b), 3.36 (m, 1H; H-5), 2.87 (ddd, J_1 = 12.9, J_2 = J_3 = 6.8 Hz, 1H; H-4a), 1.62 ppm (ddd, J_1 = 12.7, J_2 = J_3 = 7.6 Hz, 1H; H-4b); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 166.0 (*C*=O), 151.1 (C1), 134.1 (*C*H=CH$_2$), 132.0/129.6/128.4/127.3 (all Ph), 123.2 (d, J(C,F) = 289 Hz, *C*F$_3$), 121.3 (C2), 117.5 (CH=*C*H$_2$), 96.6 (C8), 86.1 (C3), 84.3 (CF$_3$*C*), 72.2 (C6), 68.1 (*C*H$_2$CH=CH$_2$), 55.4 (O*C*H$_3$), 45.0 (C5), 38.7 ppm (C4); IR (ATR): $\tilde{\nu}$ = 2977/2926/2848 (w, C–H), 1743 (s, C=O), 1664 (w, C=C), 1251 (s, C–O), 1166 (s), 1018 (s), 993 cm^{-1} (s); MS (EI, 70 eV): m/z (%): 398 (2) [M]$^+$, 190 (42), 189 (100) [CF$_3$C(Ph)OMe]$^+$, 170 (45), 105 (51), 83 (91), 77 [Ph]$^+$ (35).

(+)-(2*S*,3′*S*,5′*R*,8′*S*)-3,3,3-Trifluoro-2-methoxy-2-phenyl propionic acid (8′-allyloxy-7′-oxa-[3.3.0]-bicyclooct-1′-ene-3′-yl) ester (25b): Ester **25b** (57 mg, 72 %) was obtained from alcohol *ent*-**20** (36 mg, 200 μmol) as a colorless oil by using the DCC method described for preparation of **24a**. R_f = 0.48 (EtOAc/CyHex 1:1); $[\alpha]_D^{20} = +33.2$ (c = 1.05 in $CHCl_3$), $[\alpha]_{546}^{20} = +39.4$; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.50 (m, 2H; Ph), 7.39 (m, 3H; Ph), 6.18 (dddd, J_1 = J_2 = 6.8, J_3 = J_4 = 1.5 Hz, 1H; H-3), 5.90 (ddt, J_1 = 17.3, J_2 = 10.5, J_3 = 6.1 Hz, 1H; C*H*=CH$_2$), 5.78 (s, 1H; H-2), 5.41 (s, 1H; H-8), 5.27 (ddd, J_1 = 17.3, J_1 = 1.7, J_3 = 1.5 Hz, 1H; CH=CH–H_{trans}), 5.18 (tdd, J_1 = 10.3, J_2 = J_3 = 1.2 Hz, 1H; CH=CH–H_{cis}), 4.24 (dd, J_1 = J_2 = 7.6 Hz, 1H; H-6a), 4.19 (ddt, J_1 = 12.7, J_2 = 5.4, J_3 = 1.5 Hz, 1H; CH*H*a–CH=CH$_2$), 4.01 (ddt, J_1 = 12.7, J_2 = 6.1, J_3 = 1.5 Hz, 1H; CH*H*b–CH=CH$_2$), 3.54 (d, J(H,F) = 1.2 Hz, 3H; CH_3O), 3.42 (dd, J_1 = J_2 = 7.1 Hz, 1H; H-6b), 3.36 (m, 1H; H-5); 2.83 (ddd, J_1 = 12.9, J_2 = J_3 = 6.8 Hz, 1H; H-4a), 1.52 ppm (ddd, J_1 = 12.7, J_2 = J_3 = 7.6 Hz, 1H; H-4b); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 166.0 (*C*=O), 151.3 (C1), 134.1 (*C*H=CH$_2$), 132.1/129.7/128.5/127.2 (all Ph), 123.2 (d, J(C,F) = 289 Hz, *C*F$_3$), 121.2 (C2), 117.5 (CH=*C*H$_2$), 96.6 (C8), 86.2 (C3), 84.5 (d, J(C,F) = 28 Hz, CF$_3$*C*), 72.2 (C6), 68.1 (*C*H$_2$CH=CH$_2$), 55.4 ppm (O*C*H$_3$), 45.0 (C5), 38.5 (C4); IR (ATR): $\tilde{\nu}$ = 2976/2944/2848 (w, C–H), 1743 (s, C=O), 1250 (s, C–O), 1180 (s), 1166 (s), 1018 (s), 993 cm^{-1} (s); MS (EI, 70 eV): m/z (%): 341 (19) [M−C$_3$H$_5$O]$^+$, 189 (100) [CF$_3$C(Ph)OMe]$^+$, 119 (55), 105 (41), 91 (42), 79 (49), 77 (34) [Ph]$^+$.

(−)-(1′*R*,4′*S*)-2-Amino-9-[3′,4′-bis(hydroxymethyl)-2′-cyclopenten-1′-yl]-9*H*-purine-6-one (26a): A 1 M solution of TBAF in THF (150 μL) was added to a solution of alcohol **9f** (33 mg, 75 μmol) in THF (0.5 mL) at RT and the mixture was stirred for 16 h. The solvent was evaporated and the residue purified by flash chromatography (EtOAc→EtOAc/MeOH 4:1→3:2→2:3). The diol **26a** was obtained as a white solid (14 mg, 67 % yield over 3 steps from aldehyde **23f**). R_f = 0.22 (EtOAc/MeOH 1:1); $[\alpha]_D^{20} = -11.8$ (c = 0.34 in H_2O; literature value:[57a] $[\alpha]_D^{20} = -12.8$ (c = 0.25

in H_2O)); the spectral data were in accordance with those reported in the literature.[57a]

(−)-(1′*R*,4′*S*)-9-[3′,4′-Bis(hydroxymethyl)-2′-cyclopenten-1′-yl]-9*H*-purine-6-ylamine (26b): When the desilylation procedure described for the preparation of **26a** was followed, **9g** (10.5 mg, 25 μmol) afforded the diol **26b** (6.5 mg, 99%) as a white solid. For purification, flash chromatography (EtOAc/MeOH 4:1) was used. $R_f = 0.40$ (EtOAc/MeOH 1:1); $[\alpha]_D^{20} = -30.3$ (c = 0.33 in H_2O; literature value:[57a] $[\alpha]_D^{20} = -25.8$ ($c = 0.66$ in H_2O)); the spectral data were in accordance with those reported in the literature.[57a]

Materials and methods for the biological investigations

Materials: Polyclonal rabbit anti-human-caspase-3 antibody (developed against the human recombinant protein) was from PharMingen (Hamburg, Germany), murine monoclonal anti-human-caspase-8 antibody has been described previously,[58] and polyclonal goat anti-human-caspase-9 antibody was from R&D Systems (Wiesbaden, Germany). Primary antibodies were used at 1:2000. Secondary anti-mouse and anti-rabbit antibodies conjugated with horseradish peroxidase (HRP) were from Promega (Mannheim, Germany) and secondary anti-goat HRP-conjugated antibodies were from Santa Cruz (Heidelberg, Germany) and were used at 1:5000. RNase A was from Roth (Karlsruhe, Germany).

Cell culture: Leukemic lymphoblasts were obtained from bone marrow aspirations of patients with childhood acute lymphoblastic leukemia (ALL) and were separated by centrifugation over Ficoll (Biochrom KG, Berlin, Germany). ALL cells or BJAB cells were grown in RPMI 1640 medium (RPMI = Rosewell Park Memorial Institute) supplemented with 10% fetal calf serum, 0.56 g L^{-1} L-glutamine, 100000 U L^{-1} penicillin, and 0.1 g L^{-1} streptomycin. Media and culture reagents were from Life Technologies GmbH (Karlsruhe, Germany). BJAB cells were subcultured every 3–4 days by dilution of the cells to a concentration of 1×10^5 cells mL^{-1}.

Microscopy: BJAB cell suspensions (100 μL) were applied to a slide and centrifuged for 5 min at 200 *g*. The cytospins were Haemalaun–Eosin stained and then analyzed under a microscope.

Measurement of cell death: Cytotoxicity was measured by release of LDH as described previously.[58] After incubation with different concentrations of the nucleosides, LDH activity released by BJAB cells was measured in the cell-culture supernatants by using a Cytotoxicity Detection Kit from Boehringer-Mannheim (Mannheim, Germany). The supernatants were centrifuged at 300 *g* for 5 min. Cell-free supernatants (20 μL) were diluted with phosphate-buffered saline (PBS, 80 μL) and a reaction mixture containing 2-[4-iodophenyl]-3-[4-nitrophenyl]-5-phenyltetrazolium chloride (INT), sodium lactate, oxidized nicotinamide adenine dinucleotide (NAD^+), and diaphorase (100 μL) was added. Time-dependent formation of the reaction product was then quantified photometrically at 490 nm. The maximum amount of LDH activity released by the cells was determined by lysis of the cells by using 0.1% Triton X-100 in culture medium; this value was set as 100% cell death.

Measurement of DNA fragmentation: DNA fragmentation was measured essentially as described.[60] After treatment with different concentrations of the nucleosides for 48 h, cells were collected by centrifugation at 300 *g* for 5 min. Cells were washed with PBS at 4 °C. Cells were fixed in 0.74% formaldehyde in PBS on ice for 30 min, pelleted, incubated with ethanol/PBS (2:1) for 15 min, pelleted, and resuspended in PBS containing 40 μg mL^{-1} RNase A. The RNA was digested for 30 min at 37 °C. Cells were pelleted again and finally resuspended in PBS containing 50 μg mL^{-1} propidium iodide. Nuclear DNA fragmentation was quantified by flow-cytometric determination of hypodiploid DNA (Fluorescence-activated cell sort, FACS). Data were collected and analyzed by using a FACScan (Becton Dickinson; Heidelberg, Germany) apparatus equipped with CELLQuest software. Data are given in % hypoploidy (subG1), a value which reflects the number of apoptotic cells.

Western blot analysis: Cytosolic protein (15 μg) was loaded in each lane and was separated by sodium dodecylsulfate (SDS) PAGE as previously described in detail.[61] After blotting of proteins onto nitrocellulose membranes (Schleicher and Schuell, Dassel, Germany), the membrane was blocked for 1 h in PBST (PBS containing 0.05% Tween-20) containing 3% nonfat dry milk and incubated with primary antibody for 1 h. After the membrane had been washed three times in PBST, secondary antibody in PBST was applied for 1 h. Finally, the membrane was washed in PBST again and the ECL (enhanced chemiluminescence) system from Amersham Buchler (Braunschweig, Germany) was used to visualize the protein bands in question.

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were $R1 = 0.045$ and $wR2 = 0.097$ (for 1980 observed reflections with $I > 2\sigma(I)$, 260 parameters) with GOF 1.017, largest residual peak 0.185 e Å^{-3}, and largest residual hole -0.269 e Å^{-3}.[66]

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