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151. Carbocyclic Analogs of Nucleosides

Part 2[1])

Synthesis of 2′,3′-Dideoxy-5′-homonucleoside Analogs

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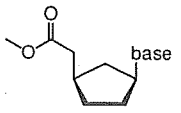
A set of derivatives of cyclopentaneacetic acid *cis*-substituted at position 3 by nucleoside bases (both purines and pyrimidines) were prepared and characterized (see **11**, **14**, and **23a**, **b**; *Schemes 2–4*). These molecules are carbocyclic analogs of 2′,3′-dideoxy-5′-homonucleosides. In this synthesis, the skeleton was constructed from norbornanone and a novel method based on *Mitsunobu* chemistry used for the introduction of nucleoside-base substituents. The scope of this method was further explored *via* the preparation of a cyclobutyl analog of dideoxyguanosine (see **17**, *Scheme 3*).

Introduction. – Analogs of nucleosides have attracted interest as lead compounds for treating diseases where the diseased and normal states differ in the enzymes used to process nucleic acids. Viral diseases fall within this class, and several of these promise to be among the most troubling public health problems in the future. Nucleoside analogs are also important for scientific reasons; systematic variation of the structure of the building blocks of oligonucleotides should help biological chemists understand better the chemical basis for the conformational and binding properties of this remarkable class of molecules.

For such small molecules, it continues to be astonishing how many different structural variations of nucleosides are possible. Focusing only on alterations in the furanose ring, themes in the chemistry of nucleoside analogs include: *i*) removal of heteroatomic substituents from the ring [2], *ii*) replacement of these substituents by other heteroatomic substituents [3], *iii*) opening the ring entirely [4], *iv*) building carbocyclic versions of the ring [5], and *v*) homologating the sugar ring at one or more positions [6]. The first three themes include analogs that presently are the most important antiviral compounds. The last leads to molecules that provide entry into backbone-modified oligonucleotide analogs with potential 'antisense' activity against natural oligonucleotides [7].

As part of an ongoing program to expand the structural versatility of nucleosides, we needed to understand better the reactivity of nucleoside analogs combining the first, fourth, and fifth of these themes, *i.e.* of compounds of the general formula **1**. As



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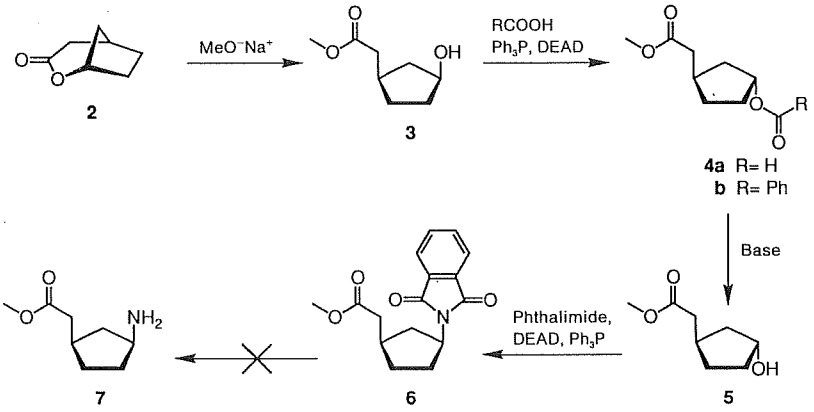
[1]) Part 1: [1].

carbocyclic analogs of 2′,3′-dideoxy-5′-homonucleosides, such molecules lack substituents on the 2′- and 3′-position, and, therefore, must terminate an oligonucleotide chain. Because they are homologated at the 5′-position, derivatives of these molecules can be appended to the 3′-end of an oligonucleotide chain with a modified backbone [6]. As carbocycles, these molecules lack the acid lability characteristic of many nucleoside derivatives.

We report here the synthesis of these molecules wherein a novel method based on *Mitsunobu* chemistry was developed for the introduction of nucleoside-base substituents [1]. Further, a derivative of guanine protected at the O^6-atom by a 2-(4-nitrophenyl)ethyl group [8] was exploited in the synthesis of guanosine analogs [9].

Results and Discussion. – *Cyclopentane Precursor.* In preliminary experiments, the synthesis of the aminocyclopentaneacetate **7** was attempted using a set of variants of the *Beckmann* rearrangement, starting with the oxime of norbornanone [10] and its derivatives. Ideally, the resulting lactam was to be methanolyzed, and pyrimidine [11] and purine [12] rings built around the free amino group using standard procedures. Unfortunately, the nucleoside precursor **7** was not available by this route, and longer reaction sequences had to be explored (*Scheme 1*). The first step involved the formation of lactone

Scheme 1

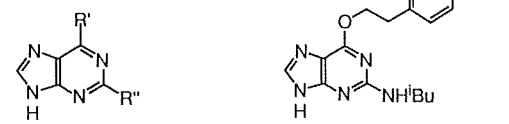


2 from norbornanone *via* a *Baeyer-Villiger* oxidation [13] and the conversion of the lactone with MeOH under base catalysis to hydroxy compound **3** (80% yield). *Mitsunobu* reactions [14] yielded either the formic-acid derivative **4a** or the benzoic-acid derivative **4b** with inversion of configuration at C(3). Methanolysis of the ester functions afforded diastereoisomer **5** in 88% yield. Compound **5** was converted to its phthalimide derivative **6** under *Mitsunobu* conditions in 85% yield. However, deprotection to yield **7** proved not to be possible, neither by methanolysis, by reduction [15], nor by treatment with hydrazine and its derivatives [16].

Because compound **7** was not accessible by this strategy, a method was developed to introduce pyrimidine and purine derivatives directly into a suitably substituted cyclopen-

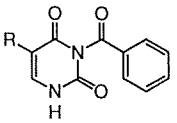
tane derivative (*e.g.* **5**). This led to the development of some novel chemistry that may have general application to the preparation of nucleoside analogs [1].

Nucleoside-Base Introduction. Addition of purine- and pyrimidine-ring systems to carbocyclic skeletons (*e.g. via* S_N2 reactions with tosylates, mesylates [17], and epoxides [18]) is very often low-yielding or, in the case of epoxides, gives ring systems bearing a possibly superfluous OH group [19]. Further, direct alkylation of the purine system often yields both N^7- and N^9-substituted derivatives of the purine ring [20]. Reports that 6-chloropurine (**8**) could replace a primary OH group under standard *Mitsunobu* conditions [21], and success in developing *Mitsunobu*-type conditions for introducing nucleoside bases by replacing the secondary OH group at the anomeric center of sugar derivatives [22] and in allylic cyclopentenol cores [23], encouraged us to test whether the nucleoside bases or their derivatives **8**, **9**, **12**, **20**, or **21** could be introduced in the cyclopentanol derivative **5** under *Mitsunobu* conditions.



8 R′ = Cl, R″ = H
9 R′ = R″ = Cl

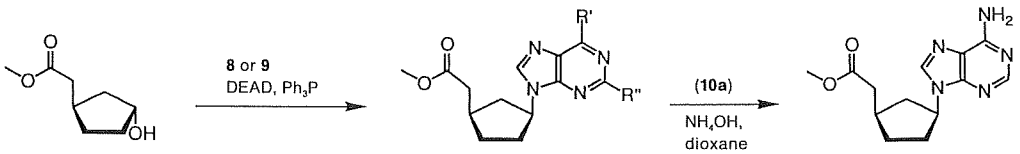
12



20 R = H
21 R = Me

Reacting 6-chloropurine (**8**) with **5** under standard *Mitsunobu* conditions (room temperature, 20% excess of nucleophile, Ph_3P, and diethyl azodicarboxylate (DEAD)) indeed afforded the desired 6-chloropurine derivative **10a** in 80% yield. Amination with either NH_4OH in dioxane under normal pressure [24] or NH_3 in MeOH under high pressure [25] finally afforded the desired adenine derivative **11** in an overall yield of 45% (*Scheme 2*).

Scheme 2



5

10a R′ = Cl, R″ = H
b R′ = R″ = Cl

11

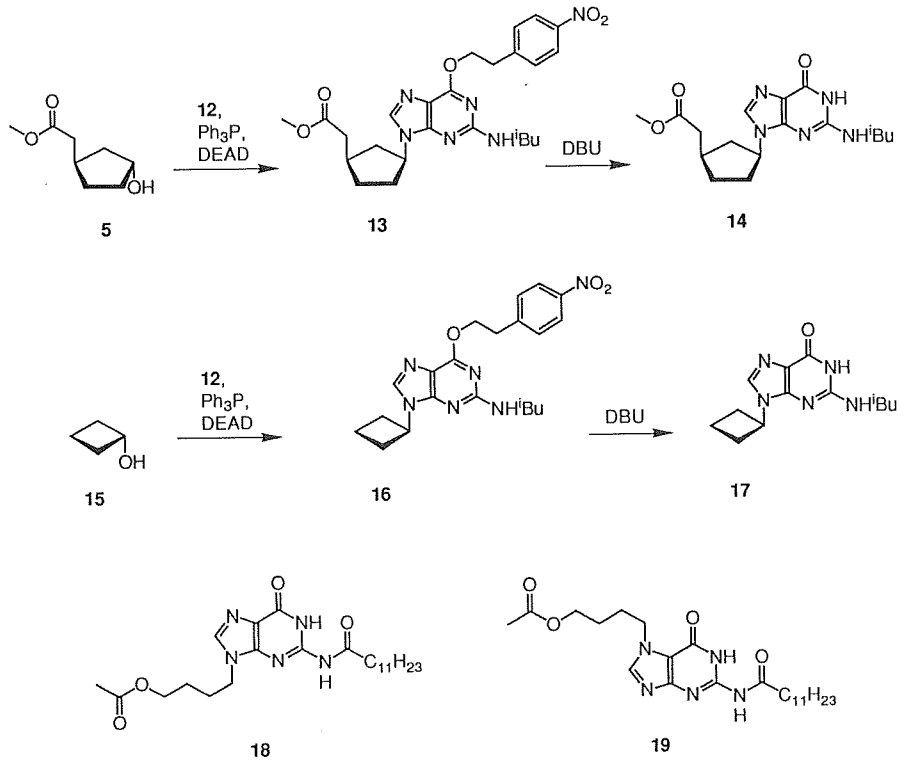
Surprisingly, under the same reaction conditions, 2,6-dichloropurine (**9**) could not be introduced into **5** in an acceptable yield. Instead, the primary product resulted from substitution of the secondary OH group of **5** by DEAD. However, by preformation of the DEAD-Ph_3P complex and lowering the reaction temperature to −20°, a method which was used for CH-acidic nucleophiles [26], the desired 2,6-dichloropurine derivative **10b** could be isolated in 81% yield. Comparison with the ^{13}C-NMR data of known N^7- and N^9-alkylated purines [27] showed that the desired N^9-substituted derivative was formed (*Table 1*). No N^7-substituted product was observed.

Table 1. *^{13}C-NMR Data of Alkylated Dichloropurine Derivatives*

	Chemical shifts [ppm] of purine moiety				
	C(2)	C(4)	C(5)	C(6)	C(8)
2,6-Dichloro-7-methylpurine	153	164	122	144	151
2,6-Dichloro-9-methylpurine	153	153	131	152	146
10b	153	153	131	152	144

In principle, **10b** is a starting material for the synthesis of various kinds of disubstituted purine derivatives. However, substitution of the Cl-atom at position 2 is possible only under very strong conditions, conditions that may compromise the structural integrity of the carbocyclic ring, especially if it bears functional groups. We, therefore, searched for a protected guanine derivative that could be alkylated easily at position N^9 with different carbocyclic OH compounds using *Mitsunobu* conditions. Among the different guanine derivatives tested, N^2-isobutyryl-O^6-[2-(4-nitrophenyl)ethyl]guanine (**12**) [9] yielded by far the most successful results. Its versatility was explored with a number of carbocyclic compounds; this exploration shows that a guanine ring can be added using this reagent to cyclopentanol skeletons as well as cyclobutane skeletons (*Scheme 3*). With cyclopentanol **5**, the guanosine analog **14** was isolated in 69% overall

Scheme 3



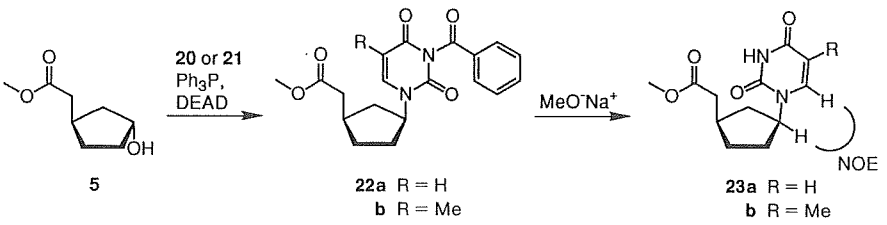
yield after removal of the (4-nitrophenyl)ethyl protective group from **13** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) [8]. With cyclobutanol (**15**), the corresponding product **17**, obtained *via* **16**, was isolated in 53% yield. This result is especially remarkable, because the analogous S_N2 replacement of a leaving group in cyclobutane cores is usually a poor reaction. Comparison of the ^{13}C-NMR data of **14** and **17** with the known N^2-protected, alkylated guanine derivatives **18** and **19** proved that alkylation occurred at the desired N^9-position (*Table 2*). The formation of N^7-substituted products was not observed.

Table 2. *^{13}C-NMR Data of Alkylated Guanine Derivatives*

	Chemical shifts [ppm] of guanine moiety	
	C(5)	C(8)
14	121.7	137.2
17	121.2	137.3
18	121.8	138.8
19	112.4	143.0

A variety of different thymine and uracil derivatives protected at the O-atom(s) (*e.g.* disilylated thymine and uracil [28]) could not be introduced into **5** in an acceptable yield. A search showed, however, that thymine and uracil benzoylated at position N^3 could be alkylated with **5** almost as effectively as the purines discussed above. As already described with 2,6-dichloropurine (**9**), it was crucial to use reaction temperatures lower than those used in standard *Mitsunobu* reactions. For the uracil and thymine derivatives **20** and **21** [29], respectively, best results were obtained at *ca.* −50°. Additional lowering of the temperature to −78° did not increase the yield, but did increase the time required for a completed reaction by a factor of at least 10. The final uridine and thymidine analogs **23a** and **23b** were obtained by removal of the benzoyl protective group from the intermediate **22a, b** with MeOH under basic conditions in an overall yield of 47 and 52%, respectively (*Scheme 4*). These low yields were due in part to the partial loss of the N^3-benzoyl group

Scheme 4



during purification of **22a** and **22b**. If debenzoylation is the desired next step, **22a** and **22b** need not be purified before the deprotection, and the yields of compounds **23a** and **23b** are considerably higher. NOE experiments proved that in both cases, alkylation occurred only at the desired N^1-position. The undesired N^3-alkylated products were not observed.

In *Table 3*, a summary of the different *Mitsunobu* conditions for nucleoside-base introduction into carbocyclic derivatives **5** and **15** is given.

Table 3. *Base Introduction under* Mitsunobu *Conditions*

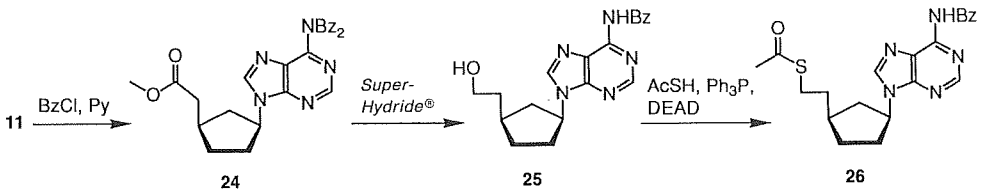
Carbocyclic ring	Nucleoside-base derivative	Product	Base [equiv.]	Ph_3P [equiv.]	DEAD [equiv.]	Time [h]	*T* [°C]	Yield [%]
5	**8**	**10a**	1.2	1.2	1.2	18	25	80[a])
5	**9**	**10b**	2.0	3.0	3.0	96	–20	81
5	**12**	**13**	1.0	4.0	4.0	18	25	69[b])
15	**12**	**16**	1.5	2.0	2.0	18	25	53[b])
5	**20**	**22a**	2.0	2.5	2.5	18	–50	47
5	**21**	**22b**	2.0	2.5	2.5	18	25	52

[a]) A mixture of **10a** and Ph_3PO was obtained. Yield is calculated from NMR data. After reaction with NH_3, the corresponding adenosine analog **11** was obtained in 45% overall yield.

[b]) After removal of the (4-nitrophenyl)ethyl group with DBU in pyridine.

Further Transformations. The adenosine analog **11** was chosen as the starting point to develop methods for converting cyclopentaneacetic acid nucleoside analogs **1** to several derivatives (*Scheme 5*) suitable for attachment to the 3′-end of an oligonucleotide chain.

Scheme 5



24 **25** **26**

The free NH_2 group in the adenine derivative **11** was protected with benzoyl chloride in the presence of pyridine to yield **24** in 80%. Among the different reducing agents tested, lithium triethylborohydride [30] most efficiently reduced the methyl ester and imide functions in **24** to yield N^6-benzoylated derivative **25** in 68% yield. The OH group in **25** was also readily replaced by a thiol function under *Mitsunobu* conditions with thioacetic acid to yield thioester **26** as colorless crystals. Such compounds are related to building blocks needed to prepare oligonucleotide analogs with the phosphodiester linking group replaced by dimethylene sulfone units [6].

The new conditions developed here for incorporating nucleoside bases into carbocyclic ring systems should have applicability to the preparation of other analogs of nucleosides as well as those described here. In particular, appending the heterocyclic ring as a unit to the C-skeleton is far superior to strategies in which the heterocycle is formed around a pendant amino group on the skeleton. The compounds prepared here are potentially interesting for their biological properties, especially as they combine nucleoside-analog structural themes *i*), *iv*), and *v*), mentioned above, in a single nucleoside analog. Further work in this area is in progress.

We are grateful to *Marco Cathomas* for excellent technical assistance, to *Brigitte Brandenberg* for NMR measurements, to the *Stipendienfonds der Basler Chemischen Industrie* for a stipend granted to *T.F.J.*, and to the *Swiss National Science Foundation* and *Sandoz AG* for financial support.

Experimental Part

General. All reactions were carried out under Ar. Solvents (*Fluka*, puriss.) were used without further purification, unless mentioned otherwise. THF and Et_2O were distilled from Na/benzophenone, and pyridine was distilled from CaH_2. For the *Mitsunobu*-type reactions, triphenylphosphine (Ph_3P; *Fluka, puriss.*) and diethyl azodicarboxylate (DEAD; *Fluka, pract.*) were used without further purification. Reactions were monitored by TLC. TLC: *Merck* silica gel *60 F254* precoated plates; visualisation with UV light or with a Ce-Mo staining reagent. Flash column chromatography (FC): *Fluka* silica gel *60* (mesh size 0.040–0.063); once distilled solvents (techn.). M.p.: *Büchi 510*; uncorrected. UV: *Shimadzu UV/VIS 240*; in EtOH; λ_{max} in nm, ε in mol^{-1} lcm^{-1}. IR: *Perkin-Elmer-782* or *-983*; $\tilde{\nu}$ in cm^{-1}. ^{1}H-NMR: *Varian EM-390, XL-300, Bruker WM-300*; chemical shifts in ppm rel. to TMS as internal standard ($\delta = 0$ ppm), J in Hz. ^{13}C-NMR: *Varian EM-390* or *XL-300*, multiplicities from DEPT. MS: *Hitachi-Perkin-Elmer RMU-6M* (70 eV); m/z in %. Microanalysis were performed by the 'Mikroanalytisches Laboratorium', ETH, Zürich.

Methyl cis-*3-Hydroxycyclopentaneacetate* (**3**). A soln. of 2-oxabicyclo[3.2.1]octan-3-one (**2**; 1.01 g, 8 mmol) in MeOH (10 ml) was treated with Na (550 mg, 24 mmol) in MeOH (20 ml) and refluxed overnight. The soln. was brought to pH 8 (AcOH), evaporated to 1/3 of the original volume, diluted with Et_2O, washed twice with sat. $NaHCO_3$ soln. and brine, dried ($MgSO_4$), and evaporated. The residue was distilled (bulb-to-bulb, 100°/1 Torr): **3** (1.0 g, 80%). Colorless liquid. IR (CCl_4): 3625, 3460, 2950, 2865, 1740, 1435, 1415, 1375, 1340, 1275, 1255, 1195, 1175, 1140, 1080, 1015, 995, 965. ^{1}H-NMR ($CDCl_3$): 1.22–1.31 (*m*, 1 H); 1.45–1.54 (*m*, 1 H); 1.63–1.88 (*m*, 4 H incl. OH); 2.15–2.33 (*m*, 2 H); 2.44 (*d*, $J = 7.3$, CH_2CO); 3.67 (*s*, MeO); 4.31–4.36 (*m*, H–C(3)). ^{13}C-NMR ($CDCl_3$): 30.02 (*t*); 34.61 (*d*, C(1)); 35.53 (*t*); 40.47 (*t*); 41.80 (*t*); 51.37 (*q*, MeO); 73.60 (*d*, C(3)); 173.57 (*s*, CO). MS: 158 (< 1, M^+), 126 (18), 115 (26), 109 (14), 108 (11), 98 (23), 97 (21), 85 (10), 84 (15), 83 (41), 82 (42), 81 (28), 80 (17), 79 (11), 74 (81), 70 (20), 69 (28), 68 (10), *67* (100), 66 (12), 59 (20), 57 (16), 56 (11), 55 (48), 54 (31), 53 (17), 44 (10), 43 (40), 42 (25), 41 (74), 40 (10).

Methyl trans-*3-(Formyloxy)cyclopentaneacetate* (**4a**) *and Methyl* trans-*3-Hydroxycyclopentaneacetate* (**5**). To a soln. of Ph_3P (22.86 g, 88 mmol) in anh. THF (25 ml) was added at 0° a soln. of **3** (6.89 g, 44 mmol) in anh. THF (25 ml) and HCOOH (3.29 ml, 88 mmol). Within 1 h, DEAD (14.38 ml, 95%, 88 mmol) was added, the mixture stirred at r.t. for 1 h, adsorbed on silica gel (75 g), and chromatographed (silica gel (1 kg), hexane/AcOEt 8:2): **4a** (7.57 g, 93%) as colorless oil. A soln. of **4a** (7.57 g, 41 mmol) in MeOH (230 ml) was saturated with NH_3 at 0° and stirred at r.t. overnight. Evaporation of the solvent and distillation (bulb-to-bulb, 130°/0.5 Torr) of the residue yielded **5** (6.11 g, 88%). Colorless oil. IR (CCl_4): 3610, 3485, 2950, 2865, 1740, 1435, 1415, 1375, 1335, 1295, 1255, 1195, 1175, 1140, 1070, 1015, 945. ^{1}H-NMR ($CDCl_3$): 1.15–1.27 (*m*, 1 H); 1.42 (*ddd*, $J = 5.7$, 9.6, 13.5, 1 H); 1.53–1.65 (*m*, 2 H incl. OH); 1.81–1.93 (*m*, 1 H); 1.95–2.09 (*m*, 2 H); 2.33 (*d*, $J = 7.4$, CH_2CO); 2.50–2.63 (*m*, 1 H); 3.67 (*s*, MeO); 4.34–4.40 (*m*, H–C(3)). ^{13}C-NMR ($CDCl_3$): 30.26 (*t*); 33.90 (*d*, C(1)); 35.06 (*t*); 40.04 (*t*); 42.28 (*t*); 51.47 (*q*, MeO); 73.45 (*d*, C(3)); 173.48 (*s*, CO). MS: 158 (< 1, M^+), 126 (15), 115 (29), 99 (12), 98 (24), 97 (22), 87 (10), 84 (16), 83 (57), 82 (19), 81 (23), 80 (15), 79 (10), 75 (10), *74* (100), 70 (16), 69 (16), 67 (39), 59 (28), 57 (22), 55 (43), 54 (10), 53 (15), 44 (14), 43 (51), 42 (16), 41 (54).

Methyl trans-*3-(Benzoyloxy)cyclopentaneacetate* (**4b**) *and Methyl* trans-*3-Hydroxycyclopentaneacetate* (**5**). To a soln. of Ph_3P (1.97 g, 7.5 mmol), **3** (790 mg, 5.0 mmol), and benzoic acid (915 mg, 7.5 mmol) in anh. THF (10 ml) was added at 0° a soln. of DEAD (1.25 ml, 95%, 7.5 mmol) in anh. THF (10 ml). The mixture was stirred at 0° for 10 min and chromatographed (silica gel (50 g), pentane/Et_2O 2:1): **4b** (quant.) as a slightly yellow oil. To a soln. of **4b** (1.37 g, max. 5.0 mmol) in anh. MeOH (25 ml) was added at 0° a soln. of Na (115 mg, 5.0 mmol) in anh. MeOH (15 ml). The mixture was stirred overnight at r.t. At 0°, the mixture was adjusted with AcOH to pH 8, evaporated to 1/3 of its volume, and diluted with Et_2O. The org. phase was washed twice with sat. $NaHCO_3$ soln. and brine, dried ($MgSO_4$), evaporated, and chromatographed (silica gel (50 g), pentane/Et_2O 1:9): **5** (690 mg, 87%). Colorless oil. The anal. data were identical with those of the sample described above.

Methyl cis-*3-Phthalimidocyclopentaneacetate* (**6**). To a soln. of **5** (350 mg, 1.9 mmol), Ph_3P (540 mg, 2.0 mmol), and phthalimide (290 mg, 2.0 mmol) in anh. THF (15 ml) was added at 0° a soln. of DEAD (0.38 ml, 95%, 2.3 mmol) in anh. THF (20 ml) within 1 h. The solvent was evaporated and the residue adsorbed onto silica gel and chromatographed (silica gel (40 g), pentane/Et_2O 3:2): **6** (0.46 g, 85%). Colorless semi-solid. M.p. 55–56°. UV: 292 (1700), 221 (37300). IR (KBr): 3450, 2950, 2870, 1770, 1735, 1695, 1610, 1465, 1435, 1395, 1380, 1340, 1290, 1250,

1200, 1180, 1150, 1100, 1080, 1055, 990, 960, 880, 740. ^{1}H-NMR ($CDCl_3$): 1.68–1.80 (*m*, 2 H); 1.86–2.05 (*m*, 2 H); 2.08–2.19 (*m*, 2 H); 2.21–2.41 (*m*, 1 H); 2.51 (*d*, J = 7.4, 2 H); 3.68 (*s*, MeO); 4.63–4.75 (*m*, H–C(3)); 7.72–7.89 (*m*, 4 arom. H). ^{13}C-NMR ($CDCl_3$): 28.7 (*t*); 31.0 (*t*); 35.7 (*d*, C(1)); 36.0 (*t*); 39.7 (*t*); 50.3 (*d*, C(3)); 51.5 (*q*, MeO); 123.1 (*d*, arom. CH); 132.1 (*s*, arom. C); 133.9 (*d*, arom. CH); 168.4 (*s*, CON); 173.4 (*s*, COO). MS: 287 (6, M^+), 256 (12), 214 (60), 186 (12), 161 (15), 160 (15), 149 (17), *148* (100), 147 (44), 140 (37), 130 (36), 108 (23), 105 (20), 104 (69), 103 (18), 81 (17), 80 (29), 79 (14), 77 (22), 76 (81), 75 (17), 74 (37), 67 (36), 66 (21), 50 (36), 41 (17).

*6-Chloro-*N^9-{cis-*3-[(methoxycarbonyl)methyl]cyclopentyl}purine* (= *Methyl* cis-*3-(6-Chloro-9*H-*purin-9-yl)cyclopentaneacetate*; **10a**) *and 2′,3′,5′-Trideoxy-5′-(methoxycarbonyl)-1′a-carbaadenosine* (= *Methyl* cis-*3-(6-Amino-9*H-*purin-9-yl)cyclopentaneacetate*; **11**). A soln. of Ph_3P (598 mg, 2.28 mmol) and 6-chloropurine (**8**; 364 mg, 2.28 mmol) in anh. THF (16 ml) was treated at r.t. with DEAD (0.38 ml, 95%, 2.28 mmol) in anh. THF (3 ml) for 1 h. Methyl *trans*-3-hydroxycyclopentaneacetate (**5**; 300 mg, 1.90 mmol) in anh. THF (7 ml) was then added and the mixture stirred at r.t. overnight. After evaporation, the mixture was chromatographed (silica gel (50 g), Et_2O/EtOH 30:1) to yield **10a** (containing Ph_3PO as a contaminant). A portion of the mixture (250 mg) was dissolved in MeOH (5 ml), the soln. saturated with NH_3 at 0°, sealed in a bomb, and heated (100°) for 1.5 h. The mixture was then cooled, the solvent evaporated, and the crude product purified by FC (silica gel, Et_2O/EtOH 3:1): **11** (65 mg, 45% rel. to **5**). IR (KBr): 3350, 3180, 2945, 1730, 1655, 1595, 1570, 1480, 1435, 1385, 1335, 1310, 1245, 1200, 1145, 800, 735, 650, 605. ^{1}H-NMR ($CDCl_3$): 1.67–1.85 (*m*, 2 H); 2.05–2.16 (*m*, 2 H); 2.31–2.41 (*m*, 1 H); 2.43–2.60 (*m*, 4 H, incl. *d* at 2.51 J = 2.1, CH_2CO); 3.69 (*s*, MeO); 4.88–4.93 (*m*, H–C(1′)); 5.84 (br. *s*, NH_2); 7.86 (*s*, H–C(8)); 8.35 (*s*, H–C(2)). ^{13}C-NMR ($CDCl_3$): 30.13 (*t*), 31.63 (*t*); 34.75 (*d*, C(4′)); 39.22 (*t*); 39.67 (*t*); 51.65 (*q*, MeO); 55.47 (*d*, C(1′)); 120.10 (*s*, C(5)); 138.75 (*d*, C(8)); 150.12 (*s*, C(4)); 152.65 (*d*, C(2)); 155.49 (*s*, C(6)); 172.96 (*s*, CO). MS: 275 (17, M^+), 244 (18), 203 (10), 202 (76), 162 (10), 136 (50), *135* (100), 108 (31), 81 (13), 67 (18), 59 (17), 54 (19), 53 (13), 43 (12), 41 (22), 39 (16), 28 (15), 15 (11).

*2,6-Dichloro-*N^9-{cis-*3-[(methoxycarbonyl)methyl]cyclopentyl}purine* (= *Methyl* cis-*3-(2,6-Dichloro-9*H-*purin-9-yl)cyclopentaneacetate*; **10b**). DEAD (0.48 ml, 95%, 3 mmol) was added within 20 min to a soln. of Ph_3P (790 mg, 3 mmol) in anh. THF (7 ml). The mixture was then stirred at r.t. until the light beige Ph_3P-DEAD complex precipitated. The mixture was cooled to −78° and a soln. of 2,6-dichloropurine (**9**; 380 mg, 2 mmol) and **5** (160 mg, 1 mmol) in THF (4 ml) added over 20 min. The mixture was stirred for 96 h at −20°, warmed to r.t. (with dissolution of a fine precipitate), and the mixture chromatographed (silica gel (120 g), CH_2Cl_2/MeOH 98:2) to yield **10b** (270 mg, 81%), which was crystallized from Et_2O/hexane. M.p. 120°. UV (0.149 mg in 5 ml): 215 (20300), 275 (8800). IR (KBr): 3420 (H_2O), 3110, 2965, 2950, 1725, 1590, 1555, 1495, 1435, 1410, 1360, 1295, 1260, 1225, 1195, 1155, 975, 880, 805, 785, 650, 625. ^{1}H-NMR ($CDCl_3$): 1.67–1.85 (*m*, 2 H); 2.04–2.18 (*m*, 2 H); 2.34–2.46 (*m*, 1 H); 2.48–2.66 (*m*, 4 H, incl. *d* at 2.54, J = 2.2, 2 H, CH_2CO); 3.70 (*s*, MeO); 4.93–5.02 (*m*, H–C(1′)); 8.18 (*s*, H–C(8)). ^{13}C-NMR ($CDCl_3$): 30.11 (*t*); 31.65 (*t*): 34.77 (*d*, C(3′)); 39.04 (*t*); 39.37 (*t*); 51.70 (*q*, MeO); 56.27 (*d*, C(1′)); 131.20 (*s*, C(5)); 144.17 (*d*, C(8)); 151.82 (*s*); 152.73 (*s*); 153.06 (*s*, C(2), C(4), C(6)); 172.73 (*s*, CO). MS: 328 (9, M^+), 257 (44), 255 (67), 193 (12), 191 (65), 190 (23), *189* (100), 188 (25), 153 (23), 108 (11), 86 (10), 81 (58), 80 (20), 79 (40), 77 (21), 74 (23), 67 (74), 66 (22), 65 (17), 59 (69), 55 (16), 54 (15), 53 (35), 43 (15), 42 (17), 41 (55). Anal. calc. for $C_{13}H_{14}Cl_2N_4O_2$ (329.19): C 47.43, H 4.29, N 17.02, O 9.72, Cl 21.54; found: C 47.17, H 4.30, N 17.17.

N^2-*Isobutyryl-2′,3′,5′-trideoxy-5′-(methoxycarbonyl)-*O^6-*[2-(4-nitrophenyl)ethyl]-1′a-carbaguanosine* (= *Methyl* cis-*3-{2-isobutyramido-6-[2-(4-nitrophenyl)ethoxy]-9*H-*purin-9-yl}cyclopentaneacetate*; **13**) *and* N^2-*Isobutyryl-2′,3′-5′-trideoxy-5′-(methoxycarbonyl)-1′a-carbaguanosine* (= *Methyl* cis-*3-(1,6-Dihydro-2-isobutyramido-6-oxo-9*H-*purin-9-yl)cyclopentaneacetate*; **14**). A mixture of *N*^{2}-isobutyryl-*O*^{6}-[2-(4-nitrophenyl)ethyl]-guanine (**12**; 370 mg, 1 mmol), Ph_3P (1.05 g, 4 mmol) and **5** (160 mg, 1 mmol) in anh. dioxane (15 ml) was stirred at r.t. for 1 h. DEAD (0.66 ml, 95%, 4 mmol) was then added and stirring continued overnight. The reaction was quenched with MeOH (4 ml) and **13** (contaminated by Ph_3PO) isolated by FC (silica gel (100 g), CH_2Cl_2/MeOH 98:2). The crude material was directly dissolved in pyridine (10 ml) containing DBU (0.3 ml, 2 mmol) and the mixture stirred overnight. The pyridine was removed by repeated evaporation with toluene and **14** (250 mg, 69% rel. to **5** isolated by FC (silica gel (140 g), CH_2Cl_2/MeOH 92.5:7.5) and crystallized from MeOH/H_2O. M.p. 150° (dec.). UV (0.077 mg in 10 ml): 205 (23700), 261 (15400), 278 (sh, 11300), IR (KBr): 3420, 3200, 2870, 1730, 1680, 1610, 1560, 1470, 1400, 1260, 1215, 1195, 1160, 1145, 950, 785, 650. ^{1}H-NMR ($CDCl_3$): 1.30 (*d*, J = 6.9, Me_2CHCO); 1.60–1.67 (*m*, 1 H); 1.73–1.80 (*m*, 1 H); 1.95–2.04 (*m*, 2 H); 2.16–2.27 (*m*, 1 H); 2.41–2.51 (*m*, 2 H); 2.56–2.63 (*m*, 1 H); 2.75 (*qq* (= *sept.*), J = 6.9, Me_2CHCO); 3.69 (*s*, MeO); 4.66 (*dddd* (= *quint.*), J = 8.1, H–C(1′)); 7.69 (*s*, H–C(8)); 9.3 (*s*, NH–C(2)); 12.04 (*s*, NH(1)). ^{13}C-NMR ($CDCl_3$): 19.02 (*q*, Me_2CHCO); 30.32 (*t*); 31.78 (*t*); 34.78 (*d*, C(4′)); 36.44 (*d*, Me_2CHCO); 38.31 (*t*); 39.72 (*t*); 51.71 (*q*, MeO); 55.77 (*d*, C(1′)); 121.73 (*s*, C(5)); 137.42 (*d*, C(8)); 147.12, 148.24 (*s*, C(2), C(6)); 155.80 (*s*, C(4)); 173.31 (*s*, COO); 178.78 (*s*, Me_2CHCO). MS: 361 (13, M^+), 291 (11), 218 (11), 152 (10), 151 (20), 43 (21), 41 (10), *28* (100). Anal. calc. for $C_{17}H_{23}N_5O_4$ (361.4): C 56.50, H 6.41, N 19.38, O 17.71; found: C 56.18, H 6.44, N 19.52.

N^9-*Cyclobutyl*-N^2-*isobutyryl*-O^6-*[2-(4-nitrophenyl)ethyl]guanine* (**16**) *and* N^9-*Cyclobutyl*-N^2-*isbutyrylguanine* (**17**). A suspension of **12** (555 mg, 1.5 mmol) in anh. dioxane (20 ml) was heated at reflux for 30 min, cooled to r.t., and treated with cyclobutanol (**15**; 72 mg, 1 mmol) and Ph_3P (525 mg, 2 mmol) in anh. dioxane (10 ml) for 2 h. DEAD (0.33 ml, 95%, 2 mmol) was added and the mixture stirred at r.t. overnight. The reaction was quenched with MeOH (2 ml), and **16** contaminated with Ph_3PO was isolated by chromatography (silica gel, CH_2Cl_2/MeOH 97:3). The crude material was directly dissolved in pyridine (5 ml) containing DBU (0.3 ml, 2 mmol) and the mixture stirred overnight at r.t. The pyridine was removed by repeated evaporation with toluene, and **17** (145 mg, 53% rel. to **15**) was isolated as a colorless foam by FC (silica gel, CH_2Cl_2/MeOH 9:1) and crystallized from CH_2Cl_2/pentane. M.p. 206–208°. UV (0.060 mg in 5 ml): 204 (23300), 261 (16100), 280 (sh, 12100). IR (KBr): 3430, 3170, 2975, 2940, 1715, 1680, 1605, 1555, 1475, 1405, 1250, 1200, 1160, 1105, 1035, 950, 820, 785, 645. ^{1}H-NMR ($CDCl_3$): 1.25 (*d*, *J* = 6.9, Me_2CHCO); 1.81–1.90 (*m*, 2 H); 2.40–2.56 (*m*, 4 H); 2.96 (*qq*(= *sept.*), *J* = 6.9, Me_2CHCO); 3.69 (*s*, MeO); 4.74 (*dddd*(= *quint.*), *J* = 8.5, H–C(1′)); 7.80 (*s*, H–C(8)); 10.36 (*s*, NH–C(2)); 12.28 (*s*, NH(1)). ^{13}C-NMR ($CDCl_3$): 15.25 (*t*); 19.10 (*q*, Me_2CHCO); 30.49 (*t*); 36.12 (*d*, Me_2CHCO); 48.69 (*d*, C(1′)); 121.20 (*s*, C(5)); 137.25 (*d*, C(8)); 147.73, 148.74 (*s*, C(2), C(6)); 156.16 (*s*, C(4)); 179.82 (*s*, CO). MS: 276 (15, $[M + 1]^+$), 275 (86), 247 (11), 206 (14), 205 (71), 204 (11), 178 (14), 177 (98), 151 (18), 135 (10), 71 (17), 55 (37), 54 (21), 53 (12), 44 (20), *43* (100), 42 (10), 41 (37). Anal. calc. for $C_{13}H_{17}N_5O_2$ (275.31): C 56.72, H 6.22, N 25.44, O 11.62; found: C 56.27, H 6.24, N 25.30.

N^3-*Benzoyl-2′,3′,5′-trideoxy-5′-(methoxycarbonyl)-1′a-carbauridine* (= *Methyl* cis-*3-(3-Benzoyl-1,2,3,4-tetrahydro-2,4-dioxopyrimidin-1-yl)cyclopentaneacetate*; **22a**). To a soln. of Ph_3P (1.34 g, 5.1 mmol) in anh. THF (15 ml) was added DEAD (0.83 ml, 95%, 5.0 mmol). The mixture was stirred at 0° for 30 min and then cooled to −78°. To the suspension was added a suspension of N^3-benzoyluracil (**20**; 865 mg, 4.0 mmol) and **5** (322 mg, 2.0 mmol) in anh. THF (30 ml) over 10 min. The mixture was then stirred overnight at −50°. The product **22a** (340 mg, 47%) was isolated as a colorless foam following FC (silica gel (300 g), petroleum ether/AcOEt 4:6). UV (0.312 mg in 10 ml): 206 (13300), 253 (18800), 273 (sh, 10300). IR ($CHCl_3$): 3010, 2950, 1750, 1705, 1670, 1630, 1600, 1450, 1440, 1370, 1295, 1275, 1250, 1180, 980, 915. ^{1}H-NMR ($CDCl_3$): 1.41–1.57 (*m*, 2 H); 1.74–1.83 (*m*, 1 H); 1.95–2.03 (*m*, 1 H); 2.12–2.21 (*m*, 1 H); 2.29–2.41 (*m*, 2 H); 2.44–2.46 (*m*, 2 H); 3.68 (*s*, MeO); 4.83–4.91 (*m*, H–C(1′)); 5.83 (*d*, *J* = 8.1, H–C(5)); 7.35 (*d*, *J* = 8.1, H–C(6)); 7.48–7.52 (*m*, 2 arom. H); 7.63–7.67 (*m*, 1 arom. H); 7.92–7.94 (*m*, 2 arom. H). MS: 356 (3, M^+), 217 (10), 189 (11), 106 (11), *105* (100), 77 (35), 67 (10).

2′,3′,5′-Trideoxy-5′-(methoxycarbonyl)-1′a-carbauridine (= *Methyl* cis-3-*(1,2,3,4-Tetrahydro-2,4-dioxopyrimidin-1-yl)cyclopentaneacetate*; **23a**). To a soln. of **22a** (148 mg, 0.84 mmol) in MeOH (5 ml) was added NaOMe (45 mg, 0.31 mmol) in MeOH (5 ml) and the mixture stirred at r.t. overnight. After adsorption on silica gel (500 mg), the crude product was purified by FC (silica gel (30 g), CH_2Cl_2/MeOH 95:5): **23a** (99 mg, 94%) as colorless crystals, which were recrystallized from CH_2Cl_2/hexane. M.p. 133–134°. UV (0.244 mg in 10 ml): 208 (8600), 267 (10200). IR (KBr): 3430, 3170, 3040, 2950, 1720, 1705, 1680, 1625, 1460, 1430, 1395, 1340, 1295, 1270, 1250, 1200, 1140, 990, 875, 810, 760, 645. ^{1}H-NMR ($CDCl_3$): 1.35–1.43 (*m*, 1 H); 1.47–1.56 (*m*, 1 H); 1.68–1.77 (*m*, 1 H); 1.96–2.05 (*m*, 1 H); 2.11–2.20 (*m*, 1 H); 2.29–2.40 (*m*, 2 H); 2.44–2.46 (*m*, 2 H); 3.68 (*s*, MeO); 4.89–4.98 (*m*, H–C(1′)); 5.76 (*d*, *J* = 8.0, H–C(5)); 7.26 (*d*, *J* = 8.0, H–C(6)); 9.58 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 29.95 (*t*); 30.19 (*t*); 34.48 (*d*, C(4′)); 37.94 (*t*); 39.41 (*t*); 51.63 (*q*, MeO); 56.31 (*d*, C(1′)); 102.68 (*d*, C(5)); 141.08 (*d*, C(6)); 151.29 (*s*, C(2)); 163.68 (*s*, C(4)); 172.81 (*s*, COO). MS: 252 (22, M^+), 221 (14), 179 (30), 140 (13), *113* (100), 109 (13), 108 (21), 82 (12), 81 (50), 80 (27), 79 (11), 74 (16), 68 (10), 67 (54), 66 (11), 59 (10), 55 (11), 54 (12), 53 (11), 41 (22). Anal. calc. for $C_{12}H_{16}N_2O_4$ (252.3): C 57.13, H 6.39, N 11.10, O 25.37; found: C 56.86; H 6.35, N 11.10.

N^3-*Benzoyl-2′,3′,5′-trideoxy-5′-(methoxycarbonyl)-1′a-carbathymidine* (= *Methyl* cis-*3-(3-Benzoyl-1,2,3,4-tetrahydro-5-methyl-2,4-dioxopyrimidin-1-yl)cyclopentaneacetate*; **22b**). To a soln. of Ph_3P (1.34 g, 5.1 mmol) in anh. THF (15 ml) was added DEAD (0.83 ml, 95%, 5.0 mmol). The mixture was stirred at 0° for 30 min and then cooled to −45°. To the suspension was added a soln. of N^3-benzoylthymine (**21**; 920 mg, 4.0 mmol) and **5** (335 mg, 2.1 mmol) in anh. THF (14 ml) over 90 min. The mixture was stirred overnight at −50°. The product **22b** (411 mg, 52%) was isolated as a colorless foam following chromatography (silica gel, petroleum ether/AcOEt 55:45). UV (0.238 mg in 10 ml): 204 (17800), 253 (15700), 277 (sh, 8600). IR ($CHCl_3$): 3420 (H_2O), 3005, 2950, 1750, 1700, 1655, 1600, 1460, 1440, 1390, 1370, 1295, 1255, 1130, 985, 910. ^{1}H-NMR ($CDCl_3$): 1.42–1.58 (*m*, 2 H); 1.75–1.84 (*m*, 2 H); 1.96–2.04 (*m*, 4 H, incl. *s* at 1.98, Me–C(5)); 2.11–2.20 (*m*, 1 H); 2.29–2.37 (*m*, 2 H); 2.45–2.37 (*m*, 2 H); 3.68 (*s*, MeO); 4.84–4.93 (*m*, H–C(1′)); 7.15 (*s*, H–C(6)); 7.47–7.51 (*m*, 2 arom. H); 7.62–7.66 (*m*, 1 arom. H); 7.90–7.93 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$): 12.67 (*q*, *Me*–C(5)); 29.80 (*t*); 30.26 (*t*); 34.57 (*d*, C(4′)); 37.88 (*t*); 39.38 (*t*); 51.62 (*q*, MeO); 56.66 (*d*, C(1′)); 111.08 (*s*, C(5)); 129.11 (*d*, arom. CH); 130.43 (*d*, arom. CH); 131.71 (*s*, arom. C); 134.92 (*d*, arom. CH); 136.79 (*d*, C(6)); 149.94 (*s*, C(2)); 162.70 (*s* C(4)); 169.21 (*s*, Ph*C*O); 172.77 (*s*, COO). MS: 370 (14, M^+), 300 (19), 231 (22), 202 (14), 106 (17), *105* (100), 77 (43), 67 (11).

2′,3′,5′-Trideoxy-5′-(methoxycarbonyl)-1′a-carbathymidine (= *Methyl* cis-*3-(1,2,3,4-Tetrahydro-5-methyl-2,4-dioxopyrimidin-1-yl)cyclopentaneacetate*; **23b**). To a soln. of **22b** (230 mg, 0.62 mmol) in MeOH (15 ml) was added NaOMe (17 mg, 0.31 mmol) and the mixture stirred at r.t. overnight. After adsorption on silica gel (700 mg), the crude product was purified by FC (silica gel (30 g), AcOEt): **23b** (125 mg, 76%) as colorless liquid which was crystallized from CH_2Cl_2/pentane at −18°. M.p. 93–95°. IR (KBr): 3440, 3160, 3030, 2950, 1740, 1690, 1480, 1435, 1395, 1375, 1300, 1270, 1200, 1130, 1015, 590. ^{1}H-NMR ($CDCl_3$): 1.35–1.43 (*m*, 1 H); 1.46–1.56 (*m*, 1 H); 1.68–1.77 (*m*, 1 H); 1.94 (*d*, *J* = 1.2, Me–C(5)); 1.97–2.05 (*m*, 1 H); 2.09–2.18 (*m*, 1 H); 2.26–2.32 (*m*, 1 H); 2.33–2.41 (*m*, 1 H); 2.45–2.47 (*m*, 2 H); 3.68 (*s*, MeO); 4.87–4.96 (*m*, H–C(1′)); 7.04 (*d*, *J* = 1.2, H–C(6)); 8.45 (br. *s*, NH); NOE: irr. at 7.04 (H–C(6))→increase in intensity at 4.87–4.96 (H–C(1′)); 1.94 (Me–C(5)), 1.68–1.77, 1.35–1.43. ^{13}C-NMR ($CDCl_3$): 12.64 (*q*, *Me*–C(5)); 29.82 (*t*); 30.25 (*t*); 34.52 (*d*, C(4′)); 37.92 (*t*); 39.52 (*t*); 51.62 (*q*, MeO); 56.02 (*d*, C(1′)); 111.14 (*s*, C(5)); 136.76 (*d*, C(6)); 151.23 (*s*, C(2)); 163.89 (*s*, C(4)); 172.83 (*s*, COO). MS: 267 (48, $[M+1]^+$), 266 (66), 235 (42), 207 (12), 206 (10), 193 (49), 141 (31), 140 (27), 128 (18), *127* (100), 126 (76), 122 (12), 110 (13), 109 (47), 108 (39), 99 (22), 96 (10), 83 (26), 82 (20), 81 (78), 80 (49), 79 (28), 77 (11), 74 (30), 68 (16), 67 (80), 66 (23), 59 (17), 55 (44), 54 (23), 53 (19), 43 (12), 42 (10), 41 (44), 40 (12). Anal. calc. for $C_{13}H_{18}N_2O_4$ (252.3): C 58.63, H 6.81, N 10.52, O 24.03; found: C 58.46, H 6.78, N 10.64.

N^6,N^6-*Dibenzoyl-2′,3′,5′-trideoxy-5′-(methoxycarbonyl)-1′a-carbaadenosine* (= *Methyl* cis-*3-[6-(dibenzoyl-amino)-9H-purin-9-yl]cyclopentaneacetate*; **24**). To a soln. of **11** (245 mg, 0.98 mmol) in anh. CH_2Cl_2 (2 ml) and pyridine (1 ml) was added at 0° a catalytic amount of 4-(dimethylamino)pyridine and benzoyl chloride (0.5 ml, 4.2 mmol). The mixture was stirred at r.t. for 2 h and then taken up in AcOEt. The org. layer was washed 3 times with 10% aq. $CuSO_4$ soln., dried ($MgSO_4$) and evaporated. The residue was chromatographed (silica gel (40 g), Et_2O/EtOH 9:1): **24** (345 mg, 80%). Colorless crystals. IR ($CHCl_3$): 3030, 3000, 2950, 1710, 1600, 1575, 1490, 1450, 1400, 1340, 1280, 1240, 1175, 900, 870, 830. ^{1}H-NMR ($CDCl_3$): 1.65–1.78 (*m*, 1 H); 1.79–1.94 (*m*, 2 H); 2.05–2.24 (*m*, 2 H); 2.31–2.44 (*m*, 1 H); 2.24–2.66 (*m*, 3 H, incl. *d* at 2.52, *J* = 2.6, CH_2CO); 3.68 (*s*, MeO); 4.92–5.02 (*m*, H–C(1′)); 7.31–7.36 (*m*, 4 arom. H); 7.44–7.49 (*m*, 2 arom. H); 7.83–7.87 (*m*, 4 arom. H); 8.12 (*s*, H–C(8)); 8.64 (*s*, H–C(2)). ^{13}C-NMR ($CDCl_3$): 30.07 (*t*); 31.37 (*t*); 34.76 (*d*, C(4′)); 38.91 (*t*); 39.46 (*t*); 51.63 (*q*); 56.15 (*d*, C(1′)); 128.68 (*d* and *s*, arom. CH, C(5)); 129.45 (*d*, arom. CH); 132.93 (*d*, arom. CH); 134.11 (*s*, arom. C); 143.37 (*d*, C(8)); 151.58 (*s*, C(4)); 151.80 (*d*, C(2)); 153.06 (*s*, C(6)); 172.30 (*s*, CO); 172.85 (*s*, CO). MS: 483 (5, M^+), 378 (24), *105* (100), 77 (48).

N^6-*Benzoyl-2′,3′,5′-trideoxy-5′-(hydroxymethyl)-1′a-carbaadenosine* (= *3-[6-(Benzoylamino)-9H-purin-9-yl]cyclopentaneethanol*; **25**). A soln. of **24** (122 mg, 0.25 mmol) in anh. THF (5 ml) was treated at −15° with 1M lithium triethylborohydride in THF (1.5 ml, 1.5 mmol) and warmed up to r.t. After stirring for 2 h, the reaction was quenched with sat. NH_4Cl soln. (1 ml). The mixture was diluted with THF and evaporated. The residue was chromatographed (silica gel (150 g), Et_2O/EtOH 8:2): **25** (61.2 mg, 68%). Colorless foam. UV (0.053 mg in 5 ml): 205 (22500), 279 (22500). IR (KBr): 3380, 2935, 2870, 1690, 1620, 1580, 1520, 1460, 1400, 1315, 1265, 1070, 1030, 900, 800, 715, 645. ^{1}H-NMR ((D_6)DMSO): 1.54–1.65 (*m*, 3 H, incl. *q* at 1.61, *J* = 6.7); 1.79 (*dd*, *J* = 10.7, 11.7, 1 H); 2.03–2.26 (*m*, 3 H); 2.32–2.26 (*m*, 1 H); 3.45 (*dd*, *J* = 5.2, 6.7, CH_2OH); 4.44 (*t*, *J* = 5.2, OH); 4.90–5.01 (*m*, H–C(1′)); 7.52–7.57 (*m*, 2 arom. H); 7.61–7.67 (*m*, 1 arom. H); 8.03–8.06 (*m*, 2 H); 8.59 (*s*, H–C(8)); 8.72 (*s*, H–C(2)); 11.14 (br. *s*, NH). ^{13}C-NMR ((D_6)DMSO): 29.94 (*t*); 30.74 (*t*); 34.78 (*d*, C(4′)); 55.20 (*d*, C(1′)); 59.74 (*t*, CH_2OH); 125.90 (*s*, C(5)); 128.43 (2*d*, 2 arom. CH); 132.33 (*d*, arom. CH); 133.55 (*s*, arom. C); 143.29 (*d*, C(8)); 150.16 (*s*, C(4)); 151.08 (*d*, C(2)); 152.24 (*s*, C(6)); 165.70 (*s*, CON). MS: 351 (6, M^+), 246 (15), 231 (11), 230 (63), 202 (22), 162 (19), 136 (52) *135* (100), 108 (36), 105 (67), 79 (12), 77 (84), 67 (23), 66 (14), 53 (12), 51 (16), 41 (22).

5′-[(Acetylthio)methyl]-N^6-*benzoyl-2′,3′,5′-trideoxy-1′a-carbaadenosine* (**26**). To a soln. of Ph_3P (90 mg, 0.34 mmol) in anh. THF (3 ml) was added at 0° DEAD (50 µl, 95%, 0.34 mmol). The mixture was then stirred at r.t. and treated with **25** (60 mg, 0.17 mmol) and thioacetic acid (24 µl, 0.34 mmol) in anh. THF (3 ml) for 15 min. The soln. was stirred for 1 h and, after evaporation, chromatographed (silica gel (8 g), AcOEt): **26** (32 mg, 46%) as a colorless foam, which was crystallized from AcOEt/hexane in the cold. M.p. 133–136°. UV (0.043 mg in 5 ml): 205 (30800), 229 (sh, 20400), 281 (21000). IR ($CHCl_3$): 3410, 3000, 1705, 1685, 1615, 1585, 1500, 1475, 1455, 1355, 1140, 1095, 1070, 1030, 640. ^{1}H-NMR ($CDCl_3$): 1.60–1.70 (*m*, 1 H); 1.74–1.81 (*m*, 3 H); 1.99–2.19 (*m*, 3 H); 2.30–2.42 (*m*, 4 H, incl. *s* at 2.33, MeCO); 2.49–2.58 (*m*, 1 H); 2.91 (*dd*, *J* = 7.4, 7.7, CH_2S); 4.89–5.01 (*m*, H–C(1′)); 7.43–7.54 (*m*, 3 arom. H); 8.01–8.03 (*m*, 2 arom. H); 8.05 (*s*, H–C(8)); 8.78 (*s*, H–C(2)); 9.09 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 27.77 (*t*); 29.97 (*t*); 30.66 (*q*); 31.50 (*t*); 35.72 (*t*); 37.65 (*d*, C(4′)); 39.28 (*t*, CH_2S); 55.85 (*d*, C(1′)); 123.43 (*s*, C(5)); 127.88 (*d*, arom. CH); 128.84 (*d*, arom. CH); 132.72 (*d*, arom. CH); 133.76 (*s*, arom. C); 141.26 (*d*, C(8)); 149.43 (*s*, C(4)); 152.13 (*s* C(6)); 152.31 (*d*, C(2)); 164.66 (*s*, CON); 195.81 (*s*, COS). MS: 409 (< 1, M^+), 263 (10), 262 (19), 230 (25), 210 (10), 136 (19), 135 (15), *105* (100), 77 (66), 43 (37). Anal. calc. for $C_{21}H_{23}N_5O_2S$ (409.5): C 61.59, H 5.66, N 17.10, O 7.81, S 7.83; found: C 61.14, H 5.42, N 16.95.

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