17. Carbocyclic Analogs of Nucleosides

Part 3[1])

Synthesis of a New Sulfone Analog of Cyclic Adenosine 3′,5′-Monophosphate

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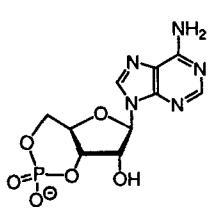
The novel uncharged analog **2** of adenosine 3′,5′-monophosphate (**1**) was prepared in its racemic form. To increase membrane permeability, the phosphate diester monoanion group of **1** was replaced by a dimethylene sulfone unit (= methanosulfonylmethano group), and the 2′-OH group was removed. To decrease lability against acid-catalyzed depurination, the ring O-atom was replaced by a CH_2 group. All three modifications are also expected to increase the stability of analog **2** towards enzymatic degradation. The carbocyclic skeleton of **2** was constructed from trinorbornenecarbaldehyde **3** (see *Scheme 1–3*), and the adenine precursor 6-chloropurine was introduced in the carbocyclic unit *via* an S_N2 reaction based on *Mitsunobu* chemistry (*Schemes 4* and *5*).

Introduction. – In living organisms, adenosine cyclic 3′,5′-monophosphate (cAMP = Ado-3′:5′-*P*; **1**), isolated and purified in 1957 [2], plays an important role in the regulation of metabolic processes. The observation that exogenously added **1** causes a dramatic effect on the growth of tumor cells [3] was the beginning of much research directed at this molecule. Under *in vivo* conditions, however, the desired antitumor effect of exogenously applied **1** was not observed, perhaps due to the poor penetration of natural **1** into cells and its rapid degradation by extracellular and intracellular phosphodiesterases. To circumvent these problems, analogs of **1** have attracted considerable interest [4]. *E.g.*, N^6,2′-*O*-dibutyryladenosine 3′,5′-monophosphate has various pharmacological activities *in vivo* [5–7]. Mixtures of 8-chloro- and N^6-benzyl-substituted derivatives of **1** are potent growth inhibitors of cancer cells [8] [9]. Recently, a number of groups focused on analogs where the negatively charged phosphate bridge is modified (*e.g.*, to a methyl phosphonate [10] [11] or a phosphorothioate [12]) or is replaced completely by an uncharged isosteric and/or isoelectronic unit (*e.g.*, a lactone [13] or a sulfate [14]).



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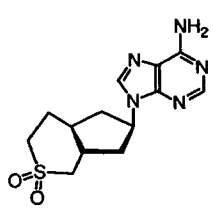


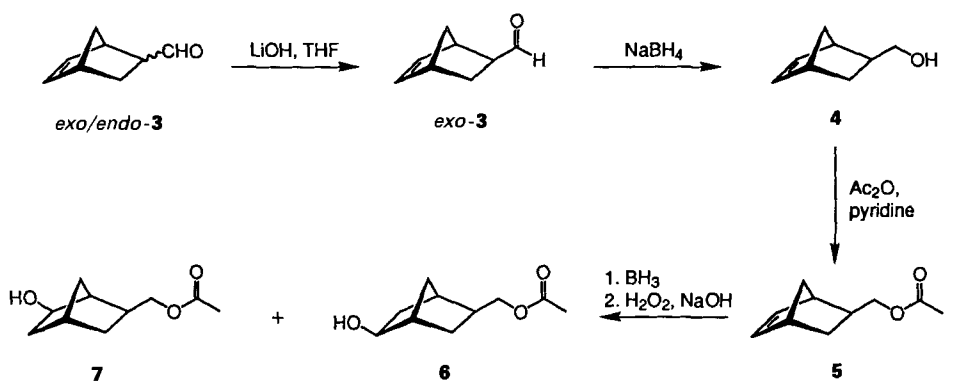
2

[1]) Part 2: [1].

In this paper, the synthesis of a novel analog of **1**, 2′,3′,5′-trideoxy-3′,5′-(methanosulfonylmethano)-1′a-carbaadenosine (**2**), in its racemic form is described. In the design of analog **2**, several structural modifications of **1** are incorporated. First, the sulfone functionality is introduced so as to be analogous in shape and electronic properties to the corresponding phosphate group in **1** itself. Thus, **2** is the first analog of **1** described so far in which the *P*-atom is replaced by an S-atom, yielding a nonionic, achiral, and isosteric analog of the phosphate-diester bridge which is stable to both chemical and biochemical hydrolysis. A report on an analog with a non-isosteric sulfone unit was published recently [15]. Second, removing the polar 2′-OH group and replacing the negatively charged phosphate-diester bridge by an uncharged dimethylene-sulfone unit should increase membrane permeability. Third, replacement of the furanose sugar unit by a carbocyclic system permits the construction of nucleoside analogs (*e.g.* adenine derivatives) that are less labile towards acid-catalyzed depurination. All three modifications should increase stability against degradation by phosphodiesterases.

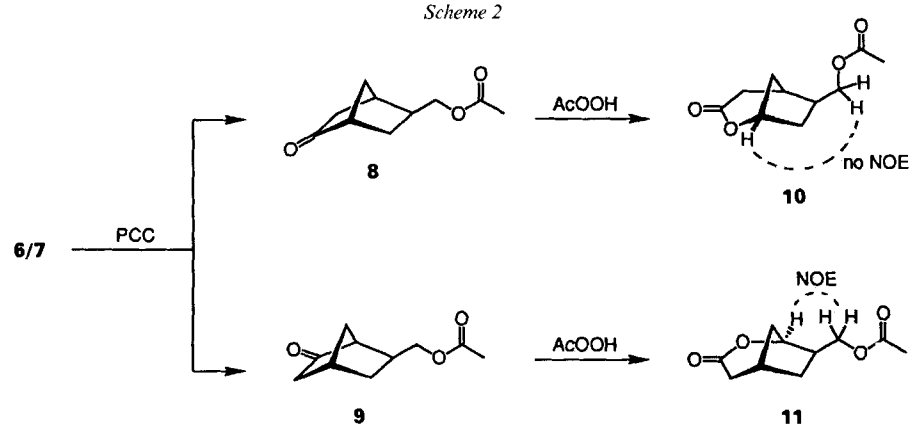
Results. – Beginning with an *exo/endo*-mixture **3**, pure *exo*-**3** was available by base-catalyzed epimerisation (*Scheme 1*). To avoid any epimerisation back to the starting mixture, regioisomer *exo*-**3** was immediately reduced to **4** in 97% yield with $NaBH_4$. The free OH group in **4** was protected with Ac_2O in the presence of pyridine to afford **5** in 78% yield. Hydroboration [16] of unsaturated **5** yielded a mixture of two diastereoisomers **6** and **7** in quantitative yield; however, it was not possible to separate the two compounds by chromatography or distillation.

Scheme 1



By converting **6** and **7** with pyridinium chlorochromate (PCC) [17] [18] to the corresponding ketones in 97% yield, a mixture **8**/**9** was obtained, which could be resolved by crystallization following flash chromatography (*Scheme 2*). Further experiments showed, that protection of the OH group in **4** with a (*tert*-butyl)diphenylsilyl or a trityl instead of an acetyl group yielded, after hydroboration, a mixture of diastereoisomers that could be resolved more easily [19]. It was impossible to assign the relative position of the keto group in **8** and **9** from the spectral data at this stage of the synthesis, because both bridgehead protons showed chemical shifts around 2.6 ppm in the ^{1}H-NMR spectra.

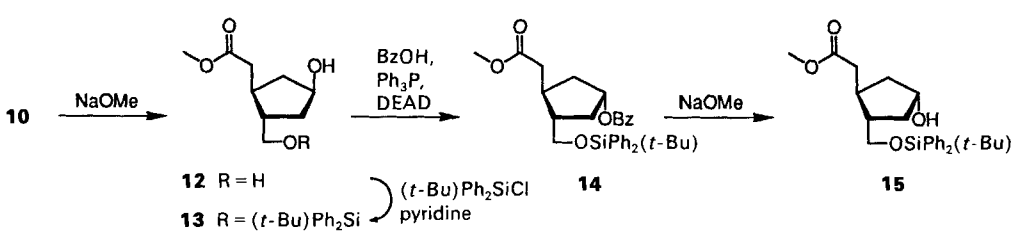
Scheme 2



Therefore, both derivatives were converted *via Baeyer-Villiger* oxidation [20] with peracetic acid or, more effectively, with 3-chloroperbenzoic acid to the bicyclic lactones **10** and **11** in 67 and 60% yield, respectively. In **10**, no nuclear *Overhauser* effect (NOE) between the bridgehead H-atom next to the lactone (H–C(1)) and the methylene group in the side chain (CH_2OAc) was observed. On the other hand, **11** showed a strong NOE between these H-atoms. The relative configuration of **8** and **9** could be assigned by correlation to the structures of **10** and **11**.

Opening of the lactone ring in **10** and removal of the acetyl protective group with MeOH under base catalysis yielded cyclopentaneacetate **12** in 94% yield (*Scheme 3*). Protection of the free primary OH group in **12** with (*tert*-butyl)diphenylsilyl chloride ((*t*-Bu)Ph_2SiCl) [21] in the presence of imidazole provided silyl ether **13** in 67% yield. Under these reaction conditions, silylation of the secondary OH group in **12** was not

Scheme 3

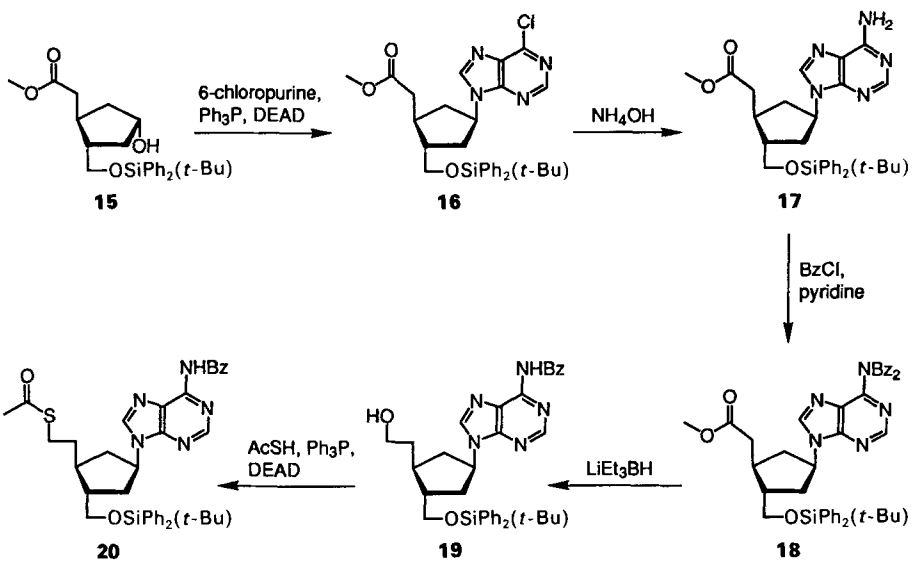


observed. A *Mitsunobu*-type reaction [22] yielded the benzoate **14** with inversion of configuration at C(4). The deprotected diastereoisomer **15** was obtained by methanolysis under base catalysis in 87% yield.

In principle, **15** can be viewed as a precursor for various carbocyclic 3′,5′-bis-(methylene)-substituted nucleoside analogs. Introduction of nucleoside bases into such systems can be readily achieved by *Mitsunobu*-type reactions under modified conditions [23]. Starting from **15**, the synthesis towards the 3′,5′-bis(methylene)-substituted

adenosine analog **20** was achieved in the same manner as already described for the 2′,3′-dideoxy series [1]. The 6-chloropurine was introduced into **15** in the presence of triphenylphosphine (Ph_3P) and diethyl azodicarboxylate (DEAD) to afford the desired N^9-alkylated derivative **16** in 78% yield (*Scheme 4*). Formation of the N^7-substituted derivative could not be observed. Amination at position 6 of the purine ring with aq. NH_4OH solution in dioxane [24] afforded adenine derivative **17** in 71% yield. Surprisingly, essentially no hydrolysis of the methyl-ester function was observed under these conditions. The free amino group in **17** was protected with benzoyl chloride in the presence of pyridine to furnish dibenzamide **18** in 79% yield. Lithium triethylborohydride (*Super Hydride*®) [25] efficiently reduced the methyl ester as well as the dibenzamide function to afford **19** in 78% yield. Finally, the primary OH group on the longer side chain could be substituted by thioacetic acid under *Mitsunobu* conditions [26] to yield thioester **20** in 80% yield.

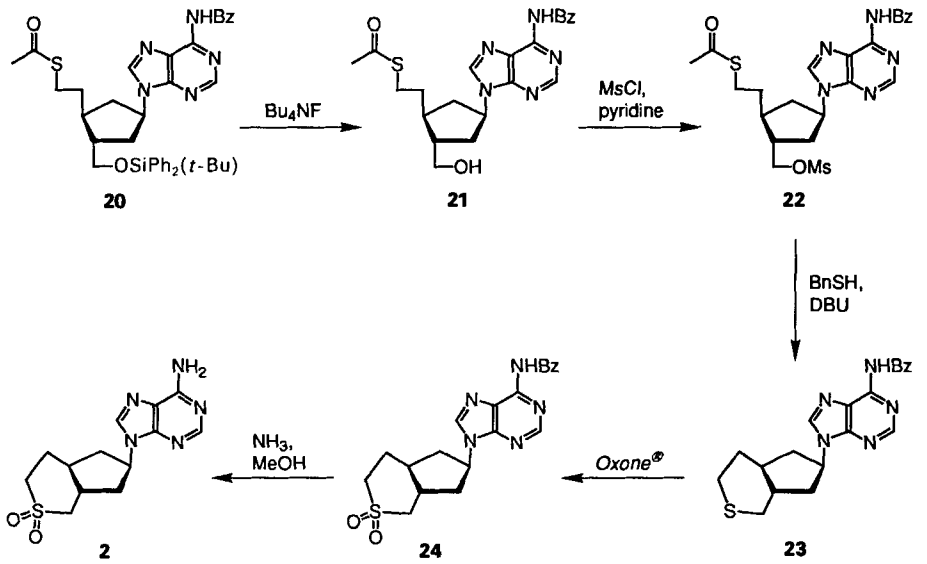
Scheme 4



After deprotection, **20** is either the starting material for the synthesis of title compound **2**, or, in its enantiomerically pure form, a building block needed to prepare oligonucleotide analogs with the phosphodiester linking groups replaced by dimethylene sulfide, sulfoxide, or sulfone units [19] [27] [28].

Removal of the silyl group in **20** was selectively achieved with Bu_4NF to furnish derivative **21** in 77% yield (*Scheme 5*). The free OH group was activated with methanesulfonyl chloride to afford **22** in quantitative yield. Treatment of **22** with phenylmethanethiol in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) led to an exclusive nucleophilic attack of benzyl thiolate at the carbonyl C-atom of the thioester function. Side products, formed by direct substitution of the mesylate group with deprotonated phenylmethanethiol could not be observed at all. Finally, intramolecular ring

Scheme 5



closure produced sulfide **23** in 83% yield. Oxidation of the sulfide bridge with potassium peroxomonosulfate (*Oxone®*) [29] in a buffered solution afforded sulfone **24** quantitatively; oxidation of the purine ring under these conditions could not be detected (UV data). Removal of the amino-protecting group in **24** with NH_3 in MeOH finally afforded the uncharged carbocyclic sulfone analog **2** of **1**.

Discussion. – The synthesis of **2** described here contains two somewhat unusual steps. The incorporation of a nucleoside derivative in a carbocyclic system under modified *Mitsunobu* conditions, introduced recently for the synthesis of 2′,3′-dideoxy-1′a-carbanucleosides [1], was proven highly satisfactory, even for more hindered precursors such as **15** that contain very large side chains at position C(3′). Second, the ready formation of the thioether to form a *trans*-fused ring system in **23** is especially remarkable, as such bicyclic derivatives are generally viewed as being strained. Similar formation of a thioether linkage by intramolecular cyclization was observed previously in an other bicyclic thiosugar nucleoside [15]. Because of the ability of sulfones (such as dimethyl sulfone and sulfolane) as cosolvents to help nucleosides and nucleotides penetrate across membranes [30], it is very likely that compounds that incorporate sulfone units such as **2** can pass biological membranes more easily than the analogous natural products. Work in this area is in progress.

Sincere thanks are due to Prof. *Steven A. Benner*, in whose laboratories this work was carried out, for generous support and helpful discussion, and to *Marco Cathomas* for excellent technical assistance. The author is also indepted to *Brigitte Brandenberg*, *Manfred Welti*, and PD Dr. *Bernhard Jaun* for NMR measurements, to *Josefa Stalder-Weber* for obtaining MS data, to *Beatrix Suter* and *Dieter Manser* for performing elemental analysis, to *Hans-Ulrich-Hediger* for IR spectroscopy, and to Dr. *Engelbert Zass* for CAS on-line searches. Financial support from the *Stipendienfonds der Basler Chemischen Industrie*, the *Swiss National Science Foundation*, and *Sandoz AG* is gratefully acknowledged.

Experimental Part

General. See [1]. If not stated otherwise, org. extracts were worked up by washing with brine, drying ($MgSO_4$), and evaporating.

*Bicyclo[2.2.1]hept-5-ene-2-*exo*-carbaldehyde (exo-***3***).* A soln. of *exo/endo-***3** (24.4 g, 200 mmol) in anh. THF (500 ml) was treated with LiOH (960 mg, 20 mmol) in H_2O (20 ml) and refluxed for 18 h. The pH of the mixture was adjusted to 7.5 with conc. H_2SO_4 soln., and the solvents were evaporated. FC (silica gel (1800 g), pentane/Et_2O 30:1) yielded *exo-***3** (11.0 g, 45%) as a colorless oil. Alternatively, large amounts of *exo-***3** (300 g, 60%; > 95% *exo*) were obtained by distillation of *exo/endo-***3** (500 g, 4.1 mol) and 1,8-bis(dimethylamino)naphthalene (*Proton-Sponge®*; 50 g, 0.23 mol) in sulfolane (420 ml) using a spinning-band distillation apparatus (*Fischer*-'Labor-Spaltrohrkolonne' *104 S*, 100 theoretical plates, reflux ratio 5, pot temp. 79°, mantle temp. 43°, head temp. 51°, pressure 10 mbar). Time of distillation: 4 weeks.

*Bicyclo[2.2.1]hept-5-ene-2-*exo*-methanol* (**4**). A soln. of *exo-***3** (11 g, 90 mmol) in MeOH (50 ml) was added to a soln. of $NaBH_4$ (1.7 g, 45 mmol) in 2N aq. NaOH (20 ml) at 0° within 1 h. The mixture was stirred at r.t. for 1 h. The pH was adjusted to 6 with conc. H_2SO_4 soln. at 0°. The mixture was extracted twice with Et_2O, washed with sat. $NaHCO_3$ soln., and worked up as usual: **4** (10.8 g, 97%). Colorless oil. IR (CCl_4): 3630, 3340, 3060, 2960, 2865, 1445, 1380, 1330, 1255, 1080, 1025, 980, 900, 860, 705. ^{1}H-NMR ($CDCl_3$): 1.11 (*ddd*, J = 3.4, 4.4, 11.6, 1 H); 1.22–1.37 (*m*, 3 H); 1.54 (br. *s*, OH); 1.57–1.67 (*m*, 1 H); 2.75 (br. *s*, 1 bridgehead H); 2.82 (br. *s*, 1 bridgehead H); 3.54 (*dd* = *t*, J = 9.5, 1 H, CH_2O); 3.70 (*dd*, J = 6.7, 9.5, 1 H, CH_2O); 6.07 (*dd*, J = 2.9, 5.5, 1 olef. H); 6.11 (*dd*, J = 2.9, 5.5, 1 olef. H). ^{13}C-NMR ($CDCl_3$): 29.48 (*t*); 41.46 (*d*); 41.81 (*d*); 43.22 (*d*); 44.92 (*t*); 67.48 (*t*, CH_2O); 136.40 (*d*, *C*H=CH); 136.76 (*d*, CH=*C*H). MS: 124 (2, M^+), 91 (8), 77 (8), 67 (8), *66* (100), 39 (11).

*Bicyclo[2.2.1]hept-5-ene-*2-exo*-methyl Acetate* (**5**). A stirred soln. of **4** (9.82 g, 79 mmol) and 4-(dimethylamino)pyridine (0.75 g, 1.6 mmol) in pyridine (13 ml) was treated at 0° with Ac_2O (10 ml, 103 mmol) for 30 min. The mixture was stirred at r.t. for 30 min, hydrolyzed with ice (50 g), and extracted twice with Et_2O. The org. phases were washed 3 times with 2N aq. HCl, twice with sat. $NaHCO_3$ soln., and worked up as usual. Distillation (87°/12 Torr) gave **5** (10.3 g, 78%). Colorless oil. IR (CCl_4): 3020, 2980, 2835, 1740, 1459, 1385, 1365, 1330, 1230, 1090, 1030, 970, 900, 850, 830. ^{1}H-NMR ($CDCl_3$): 1.16 (*ddd*, J = 3.4, 4.5, 12.2, 1 H); 1.23–1.39 (*m*, 3 H); 1.66–1.79 (*m*, 1 H); 2.07 (*s*, Ac); 2.70 (br. *s*, 1 bridgehead H); 2.84 (br. *s*, 1 bridgehead H); 3.97 (*dd*, J = 9.1, 11.1, 1 H, CH_2O); 4.16 (*dd*, J = 6.4, 11.1, 1 H, CH_2O); 6.06–6.14 (*m*, 8 lines, 2 olef. H). ^{13}C-NMR ($CDCl_3$): 21.01 (*q*, *M*eCO); 29.51 (*t*); 37.88 (*d*); 41.50 (*d*); 43.57 (*d*); 44.88 (*t*); 68.50 (*t*, CH_2O); 135.96 (*d*, *C*H=CH); 136.67 (*d*, CH=*C*H); 170.93 (*s*, Me*C*O). MS: 167 (2, $[M + 1]^+$), 106 (12), 105 (16), 91 (11), *66* (100), 43 (16). Anal. calc. for $C_{10}H_{14}O_2$ (166.2): C 72.26, H 8.49, O 19.25; found: C 72.16, H 8.38.

*5-*exo*- and 6-*exo*-Hydroxybicyclo[2.2.1]heptane-2-*exo*-methyl Acetate* (**6** and **7**, resp.). Diborane, prepared by reaction of $NaBH_4$ (2.3 g, 67 mmol) in anh. THF (40 ml) with $BF_3 \cdot Et_2O$ (15.0 ml), was bubbled through a soln. of **5** (10.3 g, 62 mmol) in anh. THF (60 ml) over 30 min, with cooling (temp. < 5°). After 30 min stirring at 0°, the mixture was slowly treated with H_2O (10 ml, temp. < 10°), 2N aq. NaOH (10 ml), and 30% aq. H_2O_2 soln. (8 ml, temp. < 30°). The mixture was stirred at 30° for 30 min, sat. with NaCl, extracted twice with Et_2O, and worked up as usual: **6**/**7** (12.0 g, quant.). Colorless liquid.

*5-Oxobicyclo[2.2.1]heptane-2-*exo*-methyl Acetate* (**8**) *and 6-Oxobicyclo[2.2.1]heptane-2-*exo*-methyl Acetate* (**9**). A mixture **6**/**7** (12.0 g, 62 mmol) in CH_2Cl_2 (70 ml) was added dropwise to a strongly stirred suspension of pyridinium chlorochromate (21.5 g, 100 mmol) and *Celite* (15 g) in CH_2Cl_2 (140 ml). After 1 h stirring at r.t., the liquid was decanted from the dark brown precipitate, filtered through silica gel (60 g), and evaporated: **8**/**9** (10.9 g, 97% rel. to **5**) in a ratio of 52:48 (GLC). Repeated FC (silica gel (400 g each), pentane/Et_2O 1:1) gave **8** as colorless crystals and **9** as a colorless oil.

Data of **8**: R_f 0.25 (pentane/Et_2O 1:2). IR (CCl_4): 2965, 2895, 1740, 1450, 1410, 1390, 1370, 1240, 1160, 1080, 1030, 970, 910. ^{1}H-NMR ($CDCl_3$): 1.40 (*dt*, J = 13.3, 4.9, 1 H); 1.68–1.92 (*m*, 4 H); 2.01–2.09 (*m*, 1 H); 2.07 (*s*, Ac); 2.13 (*dd*, J = 4.6, 17.8, 2 H); 2.46–2.64 (*m*, 3 lines, 2 bridgehead H); 3.85 (*s*, 1 H, CH_2OAc); 3.96 (*d*, J = 1.2, 1 H, CH_2OAc). ^{13}C-NMR ($CDCl_3$): 20.89 (*q*, *Me*CO); 28.13 (*t*); 34.48 (*t*); 37.44 (*d*); 39.14 (*d*); 45.16 (*t*); 49.60 (*d*); 66.78 (*t*, CH_2O); 170.72 (*s*, Me*C*O); 216.63 (*s*, CO). MS: 182 (25, M^+), 141 (10), 140 (74), 122 (12), 104 (12), 94 (18), 93 (32), 81 (31), *80* (100), 79 (64), 78 (42), 67 (13), 66 (11), 43 (82).

Data of **9**: R_f 0.31 (pentane/Et_2O 1:2). ^{1}H-NMR ($CDCl_3$): 1.32–1.44 (*m*, 1 H); 1.64–1.78 (*m*, 3 H); 1.87 (*dd*, J = 3.8, 17.9, 1 H); 2.06 (*s*, Ac); 2.15–2.23 (*m*, 2 H); 2.56 (br. *s*, 1 bridgehead H); 2.70 (br. *s*, 1 bridgehead H); 3.91 (*dd*, J = 9.0, 11.0, 1 H, CH_2OAc); 4.00 (*dd*, J = 6.1, 11.0, 1 H, CH_2OAc). ^{13}C-NMR ($CDCl_3$): 20.89 (*q*, *Me*CO); 31.81 (*t*); 34.33 (*t*); 35.22 (*d*); 44.49 (*t*); 52.09 (*d*); 65.67 (*t*, CH_2O); 171.02 (*s*, Me*C*O); 216.61 (*s*, CO). MS: 182 (2, M^+), 154 (31), 122 (39), 112 (10), 104 (11), 94 (28), 93 (19), 81 (33), 80 (24), 78 (70), 77 (10), 67 (13), 66 (13), 53 (12), *43* (100), 41 (16).

*3-Oxo-2-oxabicyclo[3.2.1]octane-6-*exo*-methyl Acetate* (**10**). To a stirred suspension of **8** (3.3 g, 18 mmol) and anh. NaOAc (9 g) in 30% aq. H_2O_2 soln. (27 ml) was added AcOH (9 ml) at 5°. Stirring was continued at r.t. in the

dark for 40 h. The mixture was treated at 0° with 10% aq. $Na_2S_2O_3$ soln. (50 ml), extracted twice with AcOEt, washed with 10% aq. $Na_2S_2O_3$ soln. and sat. $NaHCO_3$ soln., and worked up as usual. FC (silica gel (380 g), Et_2O) yielded **10** (2.4 g, 67%). Colorless solid. M.p. 55–56° (after recrystallization from Et_2O). IR ($CHCl_3$): 3010, 2950, 1760, 1440, 1380, 1360, 1240, 1170, 1140, 1105, 1080, 1055, 1040, 990, 980, 955, 930. ^{1}H-NMR ($CDCl_3$): 1.49–1.58 (*m*, 1 H); 1.74–1.84 (*m*, 1 H); 1.90–2.00 (*m*, 1 H); 2.07 (*s*, Ac); 2.31–2.45 (*m*, 3 H); 2.55 (*dt*, *J* = 18.5, 2.1, 1 H); 2.77 (*dd*, *J* = 5.1, 18.5, 1 H); 3.89 (*dd*, *J* = 7.8, 11.0, 1 H, CH_2OAc); 3.95 (*dd*, *J* = 4.9, 11.0, 1 H, CH_2OAc); 4.85–4.88 (*m*, H–C(1)); NOE: irrad. at 4.85–4.88 (H–C(1))→no increase intensity at 3.86–3.98 (CH_2OAc). ^{13}C-NMR ($CDCl_3$): 20.76 (*q*, *Me*CO); 33.57 (*t*); 34.46 (*d*); 40.84 (*t*); 41.54 (*d*); 66.52 (*t*); 80.69 (*d*, C(1)); 169.46 (*s*, CO); 170.78 (*s*, CO). MS: 198 (< 1, M^+), 138 (22), 128 (11), 110 (35), 97 (11), 96 (15), 95 (14), 94 (25), 85 (12), 82 (12), 81 (12), 79 (44), 69 (21), 68 (17), 67 (17), 66 (11), *43* (100), 41 (25). Anal. calc. for $C_{10}H_{14}O_4$ (198.2): C 60.59, H 7.12, O 32.29; found: C 60.59, H 7.22.

3-Oxo-2-oxabicyclo[3.2.1]octane-7-exo-*methyl Acetate* (**11**). As described for **10**, with **9** (3.3 g, 18 mmol), anh. NaOAc (9 g), 30% aq. H_2O_2 soln. (27 ml), AcOH (9 ml), and 10% aq. $Na_2S_2O_3$ soln. (50 ml). FC (silica gel (380 g), Et_2O) yielded **11** (2.2 g, 60%). Colorless foam. IR (CCl_4): 2950, 1890, 1445, 1385, 1375, 1365, 1345, 1225, 1195, 1160, 1140, 1070, 1040, 995, 985. ^{1}H-NMR ($CDCl_3$): 1.45–1.53 (*m*, 1 H); 1.76 (*dq*, *J* = 13.2, 2.4, 1 H); 1.93–2.01 (*m*, 2 H); 2.08 (*s*, Ac); 2.54 (*dt*, *J* = 2.0, 18.6, 1 H); 2.58 (*q*, *J* = 5.6, 1 H); 2.70–2.82 (*m*, 2 H); 3.76 (*dd*, *J* = 9.3, 11.3, 1 H, CH_2OAc); 4.01 (*dd*, *J* = 5.5, 11.3, 1 H, CH_2OAc); 4.68–4.69 (*m*, H–C(1)); NOE: irrad. at 4.68–4.69 (H–C(1))→increase in intensity at 3.76, 4.01 (CH_2OAc). ^{13}C-NMR ($CDCl_3$): 20.76 (*q*, *Me*CO); 31.94 (*d*); 33.36 (*t*); 33.59 (*t*); 39.97 (*t*); 44.53 (*d*); 64.86 (*t*), 81.82 (*d*, C(1)); 169.97 (*s*, CO); 170.78 (*s*, CO). MS: 198 (< 1, M^+), 138 (26), 110 (33), 97 (11), 95 (29), 94 (29), 82 (16), 79 (21), 68 (13), 67 (21), *43* (100), 41 (29).

Methyl c-*4-Hydroxy*-t-*2-(hydroxymethyl)cyclopentane*-r-*1-acetate* (**12**). A soln. of **10** (2.4 g, 12 mmol) in anh. MeOH (100 ml) was treated at 0° with a soln. of NaOMe (1.3 g, 24 mmol) in anh. MeOH (50 ml). The mixture was heated under reflux overnight. The pH of the mixture was adjusted to 8.5 with AcOH at 0°, and the solvents were evaporated. FC (silica gel (350 g), Et_2O/EtOH 19:1) yielded **12** (2.12 g, 94%). Colorless oil. IR ($CHCl_3$): 3620, 3450, 3000, 2955, 2930, 1725, 1440, 1230, 1060, 1015, 880. ^{1}H-NMR ($CDCl_3$): 1.37–1.46 (*m*, 1 H); 1.52–1.67 (*m*, 1 H); 1.81–1.89 (*m*, 1 H); 2.05–2.28 (*m*, 3 H); 2.39–2.51 (*m*, 3 H, incl. 2 OH and *dd* at 2.44, *J* = 6.5, 26.7, 1 H); 2.63 (*dd*, *J* = 6.3, 16.0, 1 H); 3.57 (*d*, *J* = 5.7, CH_2O); 3.68 (*s*, MeO); 4.29–4.37 (*m*, H–C(4)). ^{13}C-NMR ($CDCl_3$): 36.64 (*d*), 39.14 (*t*); 39.97 (*t*); 41.74 (*t*); 45.58 (*d*); 51.70 (*q*, MeO); 65.48 (*t*, CH_2O); 72.47 (*d*, C(4)); 174.48 (*s*, CO). MS: 170 (2, $[M - 18]^+$), 139 (16), 138 (13), 129 (12), 127 (10), 110 (15), 108 (11), 105 (12), 97 (70), 96 (31), 95 (15), 93 (33), 92 (23), 84 (15), 83 (17), 82 (13), 81 (20), 80 (13), 79 (44), 74 (62), 71 (12), 70 (16), 69 (33), 68 (19), 67 (57), 66 (27), 59 (31), 57 (23), 55 (36), 54 (12), 53 (18), *28* (100).

Methyl t-*2-{[(*tert-*Butyl)diphenylsilyloxy]methyl}*-c-*4-hydroxycyclopentane*-r-*1-acetate* (**13**). A soln. of **12** (430 mg, 2.3 mmol) and imidazole (340 mg, 5 mmol) in anh. DMF (2.5 ml) was treated with (*t*-Bu)Ph_2SiCl (0.65 ml, 2.52 mmol) at 0° for 30 min. The mixture was stirred at r.t. for 2 h, treated with ice (1 g), extracted twice with AcOEt, and worked up as usual. FC (silica gel (40 g), pentane/Et_2O 1:1) yielded **13** (640 mg, 67%). Colorless oil. IR (CCl_4): 3620, 3500, 3070, 2955, 2930, 2895, 2860, 1740, 1540, 1470, 1435, 1425, 1250, 1190, 1115, 1085, 1000, 825. ^{1}H-NMR ($CDCl_3$): 1.05 (*s*, *t*-Bu); 1.36–1.43 (*m*, 1 H); 1.64 (br. *s*, OH); 1.70 (*dd*, *J* = 5.6, 8.9, 1 H); 1.75–1.84 (*m*, 1 H); 2.07–2.30 (*m*, 1 H); 2.37 (*dd*, *J* = 8.1, 15.5, 1 H); 2.60 (*dd*, *J* = 1.0, 5.2, CH_2OSi); 3.63 (*s*, MeO); 4.27–4.33 (*m*, H–C(4)); 7.35–7.46 (*m*, 6 arom. H); 7.63–7.68 (*m*, 4 arom. H). ^{13}C-NMR ($CDCl_3$): 19.24 (*s*, Me_3C); 26.84 (*q*, Me_3C); 36.74 (*d*); 39.04 (*t*); 39.66 (*t*); 41.80 (*t*), 45.05 (*d*); 51.41 (*q*, MeO); 66.27 (*t*, CH_2OSi); 72.77 (*d*, C(4)); 127.64 (*d*, arom. CH); 129.61 (*d*, arom. CH); 133.66 (*s*, arom. C); 135.59 (*d*, arom. CH); 173.77 (*s*, CO). MS: 411 (< 1, $[M - 15]^+$), 370 (28), *369* (100), 214 (13), 213 (69), 199 (42), 197 (13), 183 (23), 181 (14), 161 (10), 153 (16), 139 (13), 135 (17), 105 (12), 93 (21), 91 (12), 79 (25), 77 (16), 57 (11), 41 (20). Anal. calc. for $C_{25}H_{34}O_4Si$ (426.6): C 70.38, H 8.03, O 15.00, Si 6.58; found: C 70.36, H 8.17.

Methyl t-*4-(Benzoyloxy)*-t-*2-{[(*tert-*butyl)diphenylsilyloxy]methyl}cyclopentane*-r-*1-acetate* (**14**). A soln. of DEAD (1.87 ml, 95%, 11.1 mmol) in anh. THF (15 ml) was added to a stirred soln. of **13** (3.16 g, 7.4 mmol), Ph_3P (2.9 g, 11.1 mmol), and benzoic acid (1.35 g, 11.1 mmol) in anh. THF (75 ml) over 30 min at 0°. After 30 min stirring at 0° and evaporation, the crude product was resolved by FC (silica gel (300 g), pentane/Et_2O 2:1): crude **14** (4.0 g, quant.).

Methyl t-*2-{[(*tert-*Butyl)diphenylsilyloxy]methyl}*-t-*4-hydroxycyclopentane*-r-*1-acetate* (**15**). To a stirred soln. of crude **14** (4.0 g, 7.4 mmol) in anh. MeOH (35 ml) was added dropwise a soln. of NaOMe (0.42 g, 7.7 mmol) in anh. MeOH (25 ml) at 0°. The mixture was stirred at r.t. overnight. The pH of the mixture was adjusted to 8 with AcOH at 0°. After evaporation, the crude product was resolved by FC (silica gel (300 g), pentane/Et_2O 1:2): **15** (2.74 g, 87% rel. to **13**). Colorless liquid. IR (CCl_4): 3620, 3460, 3070, 2950, 2930, 2895, 2860, 1740, 1590, 1470, 1425, 1190, 1110, 1035, 1020, 940, 700, 615. ^{1}H-NMR ($CDCl_3$): 1.07 (*s*, *t*-Bu); 1.41–1.50 (*m*, 8 lines, 1 H); 1.55–1.63 (*m*, 10 lines, 1 H); 1.84–1.94 (*m*, 1 H); 1.94–2.06 (*m*, 1 H); 2.09–2.30 (*m*, 3 H); 2.43–2.57 (*m*, 2 H); 3.59 (*s*, MeO);

3.62 (*dd*, J = 2.5, 4.5, CH_2OSi); 4.23–4.27 (*m*, 7 lines, H–C(4)); 7.35–7.46 (*m*, 6 arom. H); 7.65–7.70 (*m*, 4 arom. H). ^{13}C-NMR ($CDCl_3$): 19.36 (*s*, Me_3C); 27.02 (*q*, Me_3C); 36.09 (*d*); 38.96 (*t*); 39.67 (*t*); 43.10 (*t*), 45.58 (*d*); 51.42 (*q*, MeO); 66.72 (*t*, CH_2OSi); 72.73 (*d*, C(4)); 127.80 (*d*, arom. CH); 129.83 (*d*, arom. CH); 133.39 (*s*, arom. C); 135.81 (*d*, arom. CH); 173.21 (*s*, CO). MS: 425 (< 1, $[M-1]^+$), 395 (10), 370 (68), *369* (100), 351 (16), 337 (12), 291 (19), 229 (10), 213 (36), 200 (18), 199 (90), 197 (14), 183 (17), 182 (15), 153 (47), 139 (13), 135 (19), 121 (33), 105 (11), 93 (70), 91 (12), 79 (50), 77 (17), 75 (18), 43 (11), 41 (10). Anal. calc. for $C_{25}H_{34}O_4Si$ (426.6): C 70.38, H 8.03, O 15.00, Si 6.58; found: C 70.36, H 8.23.

Methyl t-*2*-{[(tert-*Butyl*)*diphenylsilyloxy*]*methyl*}-c-*4*-(*6-chloro-9*H-*purin-9-yl*)*cyclopentane*-r-*1*-*acetate* (**16**). A soln. of DEAD (0.46 ml, 95%, 2.8 mmol) in anh. THF (3.5 ml) was added to a stirred soln. of Ph_3P (730 mg, 2.8 mmol) and 6-chloropurine (430 mg, 2.8 mmol) in anh. THF (16 ml). The mixture was stirred at r.t. for 2 h. Then, **15** (800 mg, 1.9 mmol) in anh. THF (9 ml) was added and the mixture stirred at r.t. overnight. After evaporation, the residue was resolved by FC (silica gel (60 g), pentane/Et_2O 1:5): **16** (820 mg, 78%). Pale yellow viscous oil.

rac-*3'*-{[(tert-*Butyl*)*diphenylsilyloxy*]*methyl*}-*2',3',5'-trideoxy-5'*-(*methoxycarbonyl*)-*1'a-carbaadenosine* (= *Methyl* c-*4*-(*6-Amino-9*H-*purin-9-yl*)-t-*2*-{[(tert-*butyl*)*diphenylsilyloxy*]*methyl*}*cyclopentane*-r-*1*-*acetate*; **17**). An aq. soln. of 25% NH_4OH soln. (40 ml) was added to a soln. of **16** (480 mg, 0.85 mmol) in dioxane (40 ml) at r.t. and the mixture stirred at 60° for 24 h under an atmosphere of NH_3. After addition of dioxane (100 ml), the H_2O/dioxane azeotrope was removed by evaporation. FC (silica gel (70 g), Et_2O/EtOH 4:1) yielded **17** (330 mg, 71%). Colorless crystals. M.p. 184° (after recrystallization from THF). UV (0.064 mg in 5 ml): 207 (40700), 261 (15100). IR (KBr): 3380, 3320, 3190, 2950, 2860, 1715, 1650, 1600, 1470, 1430, 1410, 1330, 1360, 1250, 1110, 1075, 1005, 825, 740, 700, 615, 500. ^{1}H-NMR ($CDCl_3$): 1.08 (*s*, *t*-Bu); 1.90–2.00 (*m*, 1 H); 2.10–2.41 (*m*, 5 H); 2.56–2.67 (*m*, 2 H); 3.64 (*s*, MeO); 3.67 (*ddd*, J = 5.0, 6.6, 10.4, CH_2OSi); 4.85–4.91 (*m*, 7 lines, H–C(1')); 5.91 (br. *s*, NH_2); 7.36–7.47 (*m*, 6 arom. H); 7.65–7.69 (*m*, 4 arom. H); 7.86 (*s*, H–C(8)); 8.34 (*s*, H–C(2)). ^{13}C-NMR ($CDCl_3$): 19.27 (*s*, Me_3C); 26.90 (*q*, Me_3C); 34.79 (*t*); 37.15 (*d*, C(4')); 38.72 (*t*); 39.53 (*t*); 44.88 (*d*, C(3')); 51.58 (*q*, MeO); 54.56 (*d*, C(1')); 65.76 (*t*, CH_2OSi); 120.02 (*s*, C(5)); 127.75 (*d*, arom. CH); 129.79 (*d*, arom. CH); 133.38 (*s*, arom. C); 135.61 (*d*, arom. CH); 139.30 (*d*, C(8)); 149.99 (*s*, C(4)); 151.46 (*d*, C(2)); 154.80 (*s*, C(6)); 172.85 (*s*, CO). MS: 542 (< 1, $[M-1]^+$), 488 (10), 487 (35), *486* (100), 213 (40), 199 (10), 183 (14), 136 (37), 135 (18). Anal. calc. for $C_{30}H_{37}N_5O_3Si$ (543.7): C 66.27, H 6.86, N 12.88, O 32.29, Si 5.17; found: C 65.98, H 6.87, N 12.89.

rac-N^6,N^6-*Dibenzoyl-3'*-{[(tert-*butyl*)*diphenylsilyloxy*]*methyl*}-*2',3',5'-trideoxy-5'*-(*methoxycarbonyl*)-*1'a-carbaadenosine* (= *Methyl* t-*2*-{[(tert-*Butyl*)*diphenylsilyloxy*]*methyl*}-c-*4*-[*6*-(*dibenzoylamino*)-*9*H-*purin-9-yl*]-*cyclopentane*-r-*1*-*acetate*; **18**). Benzoyl chloride (0.55 ml, 4.6 mmol) was slowly added to a stirred soln. of **17** (420 mg, 0.77 mmol) in pyridine (4 ml) at 0°. After 3 h stirring at r.t., the mixture was diluted with Et_2O, washed 3 times with 10% aq. $CuSO_4$ soln., and worked up as usual. FC (silica gel (50 g), pentane/Et_2O 1:5) yielded **18** (455 mg, 79%). Colorless crystals. UV (0.500 mg in 25 ml): 217 (70100), 250 (45200), 271 (sh, 37100). IR ($CHCl_3$): 3070, 3000, 2950, 2935, 2860, 1730, 1710, 1600, 1575, 1450, 1430, 1305, 1285, 1240, 1180, 1110, 900, 870, 830. ^{1}H-NMR ($CDCl_3$): 1.08 (*s*, *t*-Bu); 1.94–2.05 (*m*, 1 H); 2.21–2.43 (*m*, 5 H, incl. *dd* at 2.33, J = 8.0, 23.3); 2.58–2.69 (*m*, 2 H); 3.63 (*s*, MeO); 3.64 (*dd*, J = 5.2, 9.7, 1 H, CH_2OSi); 3.71 (*dd*, J = 4.7, 10.2, 1 H, CH_2OSi); 4.88–5.00 (*m*, H–C(1')); 7.37–7.50 (*m*, 12 arom. H); 7.63–7.68 (*m*, 4 arom. H); 7.84–7.88 (*m*, 4 arom. H); 8.07 (*s*, purine H); 8.63 (*s*, purine H). ^{13}C-NMR ($CDCl_3$): 19.29 (*s*, Me_3C); 26.93 (*q*, Me_3C); 34.66 (*t*); 37.00 (*d*, C(4')); 38.66 (*t*); 39.29 (*t*); 44.83 (*d*, C(3')); 51.61 (*q*, MeO); 55.07 (*d*, C(1')); 65.62 (*t*, CH_2OSi); 127.80 (*d*, arom. CH, Ph_2Si); 128.71 (*d*, arom. CH, Bz; overlapping with C(5)); 129.48 (*d*, arom. CH, Bz); 129.83 (*d*, arom. CH, Ph_2Si); 132.95 (*d*, arom. CH, Bz); 133.30 (*s*, arom. C, Ph_2Si); 134.17 (*s*, arom. C, Ph_2Si); 135.63 (*d*, arom. CH, Ph_2Si); 143.56 (*d*, C(8)); 151.66 (*s*, C(4)); 151.76 (*d*, C(2)); 153.19 (*s*, C(6)); 172.38 (*s*, CO); 172.83 (*s*, CO). MS: 751 (< 1, M^+), 695 (10), 694 (20), 590 (19), 213 (21), *105* (100), 77 (28).

rac-N^6-*Benzoyl-3'*-{[(tert-*butyl*)*diphenylsilyloxy*]*methyl*}-*2',3',5'-trideoxy-5'*-(*hydroxymethyl*)-*1'a-carbaadenosine* (= c-*4*-[*6*-(*Benzoylamino*)-*9*H-*purin-9-yl*]-t-*2*-{[(tert-*butyl*)*diphenylsilyloxy*]*methyl*}*cyclopentane*-r-*1*-*ethanol*; **19**). A soln. of 1M $LiEt_3BH$ in THF (0.85 ml, 0.85 mmol) was added at −10° within 30 min to a stirred soln. of **18** (129 mg, 0.17 mmol) in anh. THF (3 ml). The mixture was stirred for 30 min at −10°, additional reducing agent (0.2 ml) was added at 0°, and stirring continued at r.t. for 30 min. After treatment with sat. NH_4Cl soln. (0.5 ml), the mixture was evaporated and resolved by FC (silica gel (15 g), Et_2O/EtOH 9:1): **19** (83 mg, 78%). Pale yellow crystals. UV (0.16 mg in 10 ml): 205 (39200), 279 (14900). IR (KBr): 3420, 3070, 2930, 2860, 1690, 1620, 1580, 1525, 1460, 1425, 1320, 1265, 1110, 835, 800, 740, 705. ^{1}H-NMR ((D_6)DMSO): 1.04 (*s*, *t*-Bu); 1.43–1.57 (*m*, 6 lines, 1 H); 1.69–1.82 (*m*, 6 lines, 1 H); 1.87–2.04 (*m*, 1 H); 2.13–2.24 (*m*, 1 H); 2.25–2.35 (*m*, 2 H); 2.42–2.51 (*m*, 1 H); 3.38–3.46 (*m*, CH_2O); 3.66 (*dd*, J = 5.9, 10.0, 1 H, CH_2OSi); 3.72 (*dd*, J = 5.4, 10.0, 1 H, CH_2OSi); 4.35–4.40 (*m*, OH); 4.92–5.04 (*m*, H–C(1')); 7.42–7.48 (*m*, 6 arom. H); 7.52–7.59 (*m*, 2 arom. H); 7.61–7.70 (*m*, 5 arom. H); 8.04–8.07 (*m*, 2 arom. H); 8.58 (*s*, purine H); 8.73 (*s*, purine H); 11.11 (br. *s*, NH). ^{13}C-NMR ((D_6)DMSO): 18.81 (*s*, Me_3C); 26.67 (*q*, Me_3C); 34.15 (*t*); 36.51 (*d*, C(4')); 37.89 (*t*); 38.63 (*t*); 45.03 (*d*, C(3')); 54.05 (*d*, C(1')); 59.63 (*t*,

CH_2OH); 65.87 (*t*, CH_2OSi); 125.79 (*s*, C(5)); 127.83 (*d*, arom. CH, Ph_2Si); 128.35 (*d*, 2 arom. CH, Bz); 129.77 (*d*, arom. CH, Ph_2Si); 132.27 (*d*, arom. CH, Bz); 133.07 (*s*, arom. C, Ph_2Si); 133.46 (*s*, arom. C, Bz); 135.05 (*d*, arom. CH, Ph_2Si); 143.14 (*d*, C(8)); 150.06 (*s*, C(4)); 151.01 (*d*, C(2)); 152.24 (*s*, C(6)); 165.61 (*s*, CO). MS: 619 (< 1, M^+), 564 (13), 563 (43), *562* (100), 458 (21), 303 (17), 199 (18), 136 (58), 135 (19), 107 (15), 105 (60), 77 (16).

rac-*5'-[(Acetylthio)methyl]*-N^6-*benzoyl-3'*-{[(tert-*butyl)diphenylsilyloxy]methyl*}-*2',3',5'-trideoxy-1'a-carbaadenosine* (= S-{c-*4-[6-(Benzoylamino)-9*H-*purin-9-yl]-t-2-*{[(tert-*butyl)diphenylsilyloxy]methyl*}*cyclopentane*-r-*1-ethyl*} *Thioacetate*; **20**). A stirred soln. of Ph_3P (47 mg, 0.18 mmol) in anh. THF (0.5 ml) was treated at 0° with DEAD (0.03 ml, 95%, 0.18 mmol). Then, **19** (55 mg, 0.09 mmol) in anh. THF (0.5 ml) and thioacetic acid (14 mg, 0.18 mmol) in anh. THF (0.5 ml) were simultaneously added within 15 min. The mixture was stirred at 0° for 1 h and at r.t. for another h. Evaporation and FC (twice; silica gel (15 g), Et_2O/EtOH 30:1, and silica gel (15 g), AcOEt) yielded **20** (48 mg, 80%). Colorless foam. UV (0.126 mg in 5 ml); 207 (44300), 281 (20700). IR (KBr): 3410, 3070, 2930, 2855, 1690, 1610, 1580, 1515, 1485, 1470, 1455, 1425, 1335, 1310, 1250, 1110, 1030, 825, 800, 740, 700. ^{1}H-NMR ($CDCl_3$): 1.09 (*s*, *t*-Bu); 1.60–1.71 (*m*, 1 H); 1.79–1.98 (*m*, 2 H); 2.01–2.12 (*m*, 1 H); 2.13–2.20 (*m*, 1 H); 2.27–2.41 (*m*, 2 H); 2.31 (*s*, Ac); 2.58–2.68 (*m*, 1 H); 2.74–2.94 (*m*, 2 H); 3.64 (*dd*, *J* = 5.3, 10.4, 1 H, CH_2OSi); 3.70 (*dd*, *J* = 4.6, 10.4, 1 H, CH_2OSi); 4.93–5.05 (*m*, H–C(1')); 7.38–7.45 (*m*, 6 arom. H); 7.47–7.62 (*m*, 3 arom. H); 7.66–7.71 (*m*, 4 arom. H); 8.02–8.07 (*m*, 2 arom. H, 1 purine H); 8.77 (*s*, purine H); 9.17 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 19.32 (*s*, Me_3C); 26.95 (*q*, Me_3C); 27.68 (*t*); 30.65 (*q*, *Me*CO); 34.71 (*t*); 35.06 (*t*); 39.27 (*t*, CH_2S); 39.48 (*d*, C(4')); 45.29 (*d*, C(3')); 55.03 (*d*, C(1')); 65.74 (*t*, CH_2OSi); 123.54 (*s*, C(5)); 127.79 (*d*, arom. CH, Ph_2Si); 127.89 (*d*, arom. CH, Bz); 128.85 (*d*, arom. CH, Bz); 129.81 (*d*, arom. CH, Ph_2Si); 132.72 (*d*, arom. CH, Bz); 133.44 (*s*, arom. C, Ph_2Si); 133.76 (*s*, arom. CH, Bz); 135.65 (*d*, arom. CH, Ph_2Si); 141.43 (*d*, C(8)); 149.42 (*s*, C(4)); 152.18 (*s*, C(6)); 152.24 (*d*, C(2)); 164.64 (*s*, CONH); 195.60 (*s*, *Me*CO). MS: 677 (< 1, M^+), 621 (14), 620 (31), 580 (10), 578 (12), 558 (11), 518 (12), 517 (30), 516 (80), 476 (12), 475 (11), 474 (31), 240 (19), 200 (19), *199* (100), 197 (14), 183 (20), 181 (13), 137 (12), 136 (83), 135 (30), 107 (13), 105 (89), 91 (14), 77 (44), 43 (43), 41 (10). Anal. calc. for $C_{38}H_{43}N_5O_3SiS$ (677.95): C 67.32, H 6.39, N 10.33, O 7.08, Si 4.14, S 4.73; found: C 67.11, H 6.61, N 10.11, S 4.48.

rac-*5'-[(Acetylthio)methyl]*-N^6-*benzoyl-2',3',5'-trideoxy-3'-(hydroxymethyl)-1'a-carbaadenosine* (= S-{c-*4-[6-(Benzoylamino)-9*H-*purin-9-yl]*-t-*2-(hydroxymethyl)cyclopentane*-r-*1-ethyl*} *Thioacetate*; **21**). A soln. of **20** (98 mg, 0.15 mmol) and $Bu_4NF \cdot 3\ H_2O$ (70 mg, 0.22 mmol) in anh. THF (3 ml) was stirred at r.t. for 15 h. Evaporation and FC (silica gel (40 g), Et_2O/EtOH 4:1) yielded **21** (90 mg, 77%). Colorless foam. IR (KBr): 3410, 2920, 2870, 1675, 1620, 1580, 1520, 1455, 1400, 1310, 1250, 1100, 1070, 1050, 1030, 955, 800. ^{1}H-NMR ((D_6)DMSO): 1.57–1.70 (*m*, 1 H); 1.79–2.31 (*m*, 6 H); 2.33 (*s*, Ac); 2.39–2.46 (*m*, 1 H); 2.84–2.91 (*m*, CH_2S); 3.38–3.49 (*m*, CH_2O); 4.68–4.72 (*m*, OH); 4.87–4.98 (*m*, H–C(1')); 7.52–7.57 (*m*, 2 arom. H); 7.62–7.67 (*m*, 1 arom. H); 8.04–8.06 (*m*, 2 arom. H); 8.60 (*s*, purine H); 8.73 (*s* purine H); 11.16 (br. *s*, NH). ^{13}C-NMR ((D_6)DMSO): 27.13 (*t*); 30.53 (*q*, *Me*CO); 34.28 (*t*); 34.68 (*t*); 38.21 (*t*); 38.40 (*d*, C(4')); 44.87 (*d*, C(3')); 53.99 (*d*, C(1')); 63.51 (*t*, CH_2O); 125.78 (*s*, C(5)); 128.37 (*d*, arom. CH); 132.31 (*d*, arom. CH); 133.41 (*s*, arom. C); 143.20 (*d*, C(8)); 150.05 (*s*, C(4)); 151.02 (*d*, C(2)); 152.21 (*s*, C(6)); 165.58 (*s*, CONH); 195.26 (*s*, *Me*CO). MS: 439 (< 1, M^+), 396 (17), 364 (12), 334 (15), 318 (22), 293 (14), 292 (77), 260 (55), *136* (100), 135 (61), 119 (11), 105 (41), 93 (12), 79 (22), 77 (35), 67 (16), 43 (47), 41 (15). Anal. calc. for $C_{22}H_{25}N_5O_3S$ (439.54): C 60.12, H 5.73, N 15.93, O 10.92, S 7.30; found: C 59.12, H 5.74, N 15.72.

rac-*5'-[(Acetylthio)methyl]*-N^6-*benzoyl-2',3',5'-trideoxy-3'-[(methylsulfonyloxy)methyl]-1'a-carbaadenosine* (= S-{c-*4-[6-(Benzoylamino)-9*H-*purin-9-yl]*-t-*2-[(methylsulfonyloxy)methyl]cyclopentane*-r-*1-ethyl*} *Thioacetate*; **22**). A soln. of **21** (15 mg, 0.035 mmol) in CH_2Cl_2 (0.3 ml) and pyridine (50 µl) was treated at 0° with MsCl (12 µl, 0.14 mmol) and stirred at r.t. for 2 h. Filtration through silica gel (3 g, CH_2Cl_2/MeOH 9:1) yielded crude **22** (18 mg, quant.).

rac-N^6-*Benzoyl-2',3',5'-trideoxy-3',5'-(methanothiomethano)-1'a-carbaadenosine* (= N^6-*Benzoyl-9-(*trans-*perhydrocyclopenta[*c*]thiin-6-yl)-9*H-*adenine*; **23**). A soln. of crude **22** (18 mg, 0.035 mmol) in anh. DMF (1 ml) was rapidly treated at r.t. with phenylmethanethiol (47 µl, 0.40 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (24 µl, 0.16 mmol). The mixture was stirred at r.t. for 12 h, concentrated, and resolved by FC (silica gel (8 g), CH_2Cl_2/MeOH 98:2): **23** (11 mg, 83% rel. to **21**). UV (0.027 mg in 2 ml): 205 (30900), 234 (sh, 14000), 281 (18800). IR ($CHCl_3$): 3410, 3000, 2930, 1710, 1610, 1585, 1505, 1480, 1455, 1305, 1160, 1095, 1075, 1030, 910. ^{1}H-NMR ($CDCl_3$): 1.30–1.41 (*m*, 1 H); 1.64 (*ddt*, *J* = 4.0, 12.8, 11.7, 1 H); 1.82 (*dt*, *J* = 8.5, 12.6, 1 H); 1.96–2.07 (*m*, 1 H); 2.19–2.30 (*m*, 3 H); 2.50–2.58 (*m*, 2 H); 2.65–2.82 (*m*, 3 H); 5.05–5.12 (*m*, H–C(1')); 7.49–7.52 (*m*, 2 arom. H); 7.53–7.70 (*m*, 1 arom. H); 7.96–8.03 (*m*, 2 arom. H); 8.05 (*s*, purine H); 8.76 (*s*, purine H); 9.12 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 28.67 (*t*); 32.70 (*t*); 33.29 (*t*); 38.88 (*t*); 40.28 (*t*); 44.74 (*d*); 45.08 (*d*); 51.93 (*d*, C(1')); 123.43 (*s*, C(5)); 127.88 (*d*, arom. CH); 128.85 (*d*, arom. CH); 132.74 (*d*, arom. CH); 133.73 (*s*, arom. C); 141.39 (*d*, C(8)); 149.45 (*s*, C(4)); 151.92 (*s*, C(6)); 152.37 (*d*, C(2)); 164.68 (*s*, CO). MS: 380 (17, $[M + 1]^+$), 379 (29), 378 (14), 352 (14), 351 (32), 350 (60), 241 (30), *240* (100), 238 (11), 212 (18), 211 (18), 210 (29), 140 (16), 137 (16), 136 (27), 135

(10), 108 (11), 107 (19), 106 (22), 105 (99), 94 (11), 93 (38), 92 (12), 91 (29), 85 (10), 81 (10), 80 (15), 79 (27), 78 (20), 77 (83), 67 (14), 66 (10), 65 (13), 55 (12), 53 (12), 51 (24), 47 (11), 45 (14), 41 (21).

rac-N^6-*Benzoyl-2′,3′,5′-trideoxy-3′,5′-(methanosulfonylmethano)-1′a-carbaadenosine* (= N^6-*Benzoyl-9-(*trans-*2,2-dioxoperhydrocyclopenta[c]thiin-6-yl)-9*H-*adenine*; **24**). A soln. of **23** (10 mg, 0.026 mmol) in MeOH (0.5 ml) and CH_2Cl_2 (0.05 ml) was treated at 0° with 0.5M potassium peroxomonosulfate (0.3 ml) in 1M aq. NaOAc buffer (pH 4.7). The mixture was stirred at r.t. for 2 h and adsorbed on silica gel (100 mg). FC (silica gel (12 g), CH_2Cl_2/MeOH 95:5) afforded **24** (11 mg, quant.). UV (0.035 mg in 2 ml): 204 (23300), 233 (sh, 9900), 282 (14100). IR (KBr): 3420, 3180, 3070, 2925, 1700, 1655, 1610, 1575, 1515, 1455, 1405, 1330, 1300, 1280, 1235, 1130, 865, 800, 725, 650, 530. ^{1}H-NMR ($CDCl_3$): 1.66–1.71 (*m*, 1 H); 2.03 (*dt*, *J* = 8.8, 12.6, 1 H); 2.08–2.19 (*m*, 2 H); 2.26–2.38 (*m*, 2 H); 2.56 (*ddd*, *J* = 6.0, 8.2, 13.0, 1 H); 2.89–3.07 (*m*, 3 H); 3.17 (*dq*, *J* = 3.5, 14.3, 1 H); 3.34–3.38 (*m*, 1 H); 5.15–5.23 (*m*, H–C(1′)); 7.51–7.55 (*m*, 2 arom. H); 7.59–7.63 (*m*, 1 arom. H); 8.01–8.03 (*m*, 2 arom. H); 8.05 (*s*, purine H); 8.79 (*s*, purine H); 8.92 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 26.94 (*t*); 37.66 (*t*); 38.25 (*t*); 41.67 (*d*); 43.84 (*d*); 51.40 (*t*, CH_2S); 53.87 (*d*, C(1′)); 56.82 (*t*, CH_2S); 123.63 (*s*, C(5)); 127.89 (*d*, arom. CH); 128.93 (*d*, arom. CH); 132.85 (*d*, arom. CH); 133.65 (*s*, arom. C); 141.49 (*d*, C(8)); 149.62 (*s*, C(4)); 151.76 (*s*, C(6)); 152.55 (*d*, C(2)); 164.61 (*s*, CO). MS: 411 (3, M^+), 383 (14), 382 (29), 347 (20), 319 (11), 290 (10), 240 (13), 210 (14), 105 (42), 86 (11), 84 (17), 79 (10), 77 (32), 57 (11), 43 (10), *18* (100).

rac-*2′,3′,5′-Trideoxy-3′,5′-(methanosulfonylmethano)-1′a-carbaadenosine* (= *9-(*trans-*2,2-Dioxoperhydrocyclopenta[c]thiin-6-yl)-9*H-*adenine*; **2**). A soln. of **24** (8 mg, 0.02 mmol) in anh. MeOH (10 ml) was saturated at 0° with NH_3 and stirred at 50° overnight. After removal of the solvents, the crude product was purified by prep. TLC (CH_2Cl_2/MeOH 9:1): **2** (quant.). UV (0.040 mg in 5 ml): 207 (21400), 261 (14300). ^{1}H-NMR (CD_3OD): 1.74–1.85 (*m*, 1 H); 1.89–2.00 (*m*, 2 H); 2.09–2.18 (*m*, 1 H); 2.20–2.29 (*m*, 10 lines, 2 H); 2.49 (*ddd*, *J* = 5.8, 8.2, 12.6, 1 H); 2.73–2.85 (*m*, 1 H); 3.05–3.21 (*m*, 3 H); 3.27–3.31 (*m*, 1 H, overlapping with MeOH); 5.12–5.20 (*m*, H–C(1′)); 8.20 (*s*, purine H); 8.23 (*s*, purine H). MS: 308 (< 1, $[M + 1]^+$), 244 (16), 243 (91), 216 (11), 215 (76), 162 (35), *136* (100), 135 (87), 108 (24), 80 (18), 79 (14), 44 (31), 41 (13).

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