

45. Synthesis of 3-Adenyl- and 3-Thyminylcyclobutane-1,1-dimethanols and Their Homo-octameric Phosphodiesters

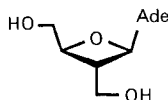
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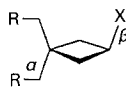
(31.X.91)

Starting from 3-(benzyloxy)cyclobutane-1,1-dimethanol, 3-thyminyl- and 3-adenylcyclobutane-1,1-dimethanol were synthesized by direct introduction of the heterocycles (*Scheme 1*). The mono-*O*-substituted methoxytrityl derivatives were separately converted to octameric phosphodiesters on an aminomethyl-polystyrene carrier by the phosphotriester method. These oligomers of carba-nucleosides were prepared in order to study their annealing behaviour towards ribo- and deoxyribo-nucleic acids as well as their potential for homologous hybridization.

Introduction. – Since the discovery of oxetanocin [1] (**I**), nucleoside analogues with a four-membered ring replacing deoxyribose became objects of intense research. Apart from the synthesis of **I** itself [2] [3], several publications of cyclobutane analogues appeared with the aim to find new compounds with antibiotic and especially antiviral activity [4–7]. In contrast, we wished to explore the additional potential of such compounds as building blocks of oligonucleotides in order to test their annealing behaviour towards deoxy- and ribonucleic acids. We were attracted by the symmetry of 3-(heterocyclyl)cyclobutane-1,1-dimethanols¹⁾ **II**. Homo-oligonucleotides made from such monomers should not give rise to α - and β -configured isomers, *e.g.*, which may differ drastically in their annealing behaviour toward RNA. In this communication, we describe the synthesis of 3-adenyl- and 3-thyminylcyclobutane-1,1-dimethanol which differs from that which was recently reported [8] [9].



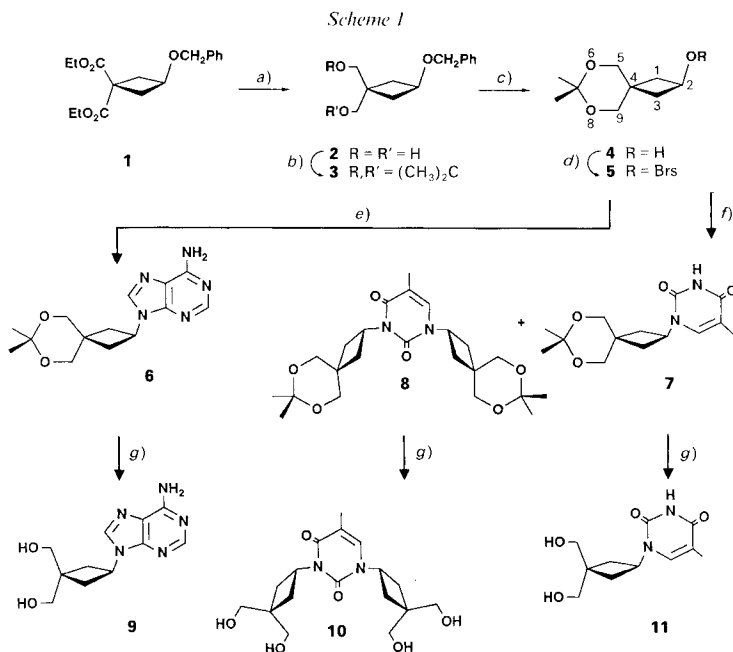
I Ade = Adenin-9-yl, Oxetanocin



II R = OH, X = base

Results. – Starting from the known 3-(benzyloxy)cyclobutane-1,1-dimethanol [10] [11], we prepared diester **1** and then, *via* **2** and **3**, the 6,8-dioxaspiro[3.5]nonan-2-ol (**4**; *Scheme 1*). Various sulfonate esters of **4** were examined for the introduction of the thymine or adenine moiety. In the series methanesulfonate, benzenesulfonate, 4-bromo-

¹⁾ Throughout the *General Part*, compounds of type **II** are considered to be 3-substituted cyclobutane-1,1-dimethanols (except spiro compounds); systematic names are given in the *Exper. Part*. The symbols α and β refer to the side below and above the mean plane of the cyclobutane ring.

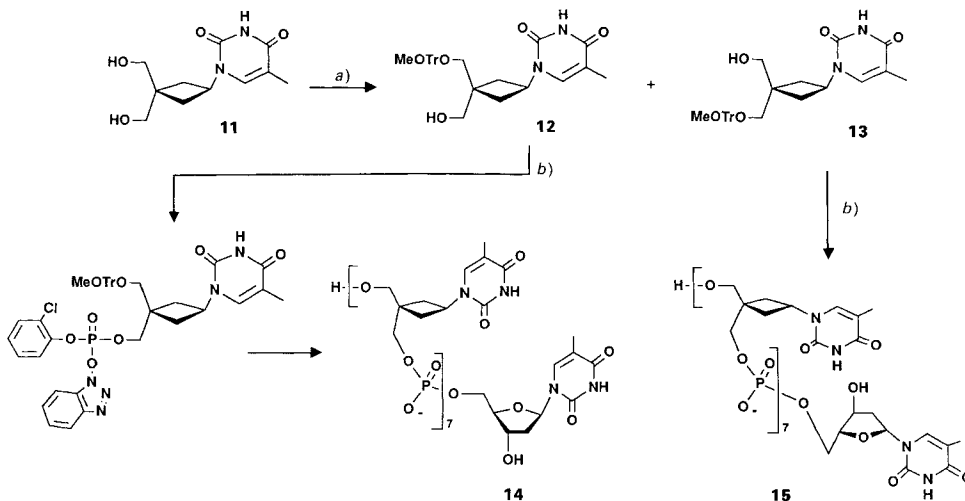


a) $LiAlH_4$, DME, 48 h, 90° (85%). *b)* TsOH (cat), 2,2-dimethoxypropane (96–98%). *c)* H_2 , Pd/C, AcOEt, r.t. (90–97%). *d)* BrsCl, Et_3N , CH_2Cl_2 , 16 h, r.t. (44%). *e)* Adenine (3 equiv.), DBU (3 equiv.), DMSO, 24 h, 80° (90%). *f)* Thymine (3 equiv.), DBU (3 equiv.), DMSO, 24 h, 80° ; **7**: (55%); **8**: (34.2%). *g)* 1. HCl, dioxane/ H_2O ; 2. Na_2CO_3 , CH_2Cl_2/H_2O ; 3. Chromatography (**9**, **10**: 70%; **11**: 78%).

benzenesulfonate, and 4-nitrobenzenesulfonate, the best properties with respect to stability and reaction conditions for substitution were observed with the 4-bromobenzenesulfonate (BrsO) **5**. Introduction of adenine was accomplished in 90% yield in DMSO at 80° for 24 h: we detected N^9 -substituted product **6** only (TLC). Substitution using 3 equiv. of thymine under the same conditions led to a mixture of 3 products: N^1 -substituted **7** (75%), the disubstituted **8** (34%), and traces of N^3 -substituted product. Even a 4-fold excess of thymine did not suppress the formation of **8**. The desired compounds **6** and **7** could be purified by flash chromatography and were deprotected with HCl in dioxane to give the dimethanols **9** and **11**. Deprotection of **8** yielded **10**.

Reaction of **11** with 1.3 equiv. of monomethoxytrityl chloride (MeOTrCl) in pyridine led to two mono-*O*-substituted products **12** (35%) and **13** (42%) as well as to the di-*O*-substituted derivative (9%) together with unreacted **11** (6.5%). Addition of more MeOTrCl did not diminish the amount of diol **11** appreciably, but rather increased the amount of di-*O*-substituted product (*Scheme 2*). Compounds **12** and **13** were each processed by the phosphotriester method [12] to octameric phosphodiester on a solid support with thymidine as a starting nucleoside. Because of the asymmetry of the resulting oligonucleotides, **12** led to a pseudo- β - (see **14**), whereas **13** led to a pseudo- α - oligomer (see **15**). We purposely used these commercially available resins because we hoped to get further information on the degree of disorder introduced by the natural

Scheme 2

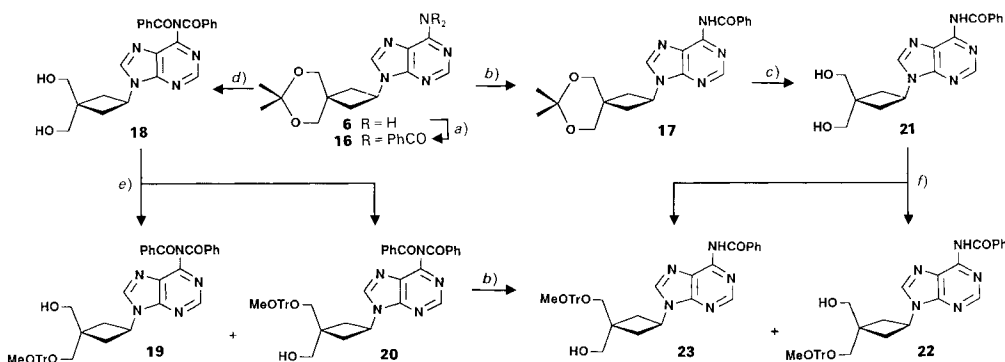


a) MeOTrCl, pyridine; **12**: 35%; **13**: 42%. b) Solid-phase synthesis: 95–98% per coupling step.

nucleosides by measuring the melting behaviour of the pseudo- α - and pseudo- β -oligomers in the presence of complementary RNA's and DNA's.

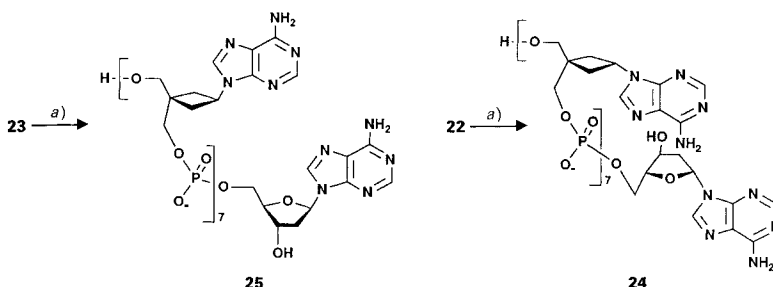
In the adenine series, we first protected the base moiety of **6** by benzylation giving the N^6,N^6 -dibenzoate **16** in 95% yield (Scheme 3). Further conversion to the desired N^6 -benzoyl-*O*-methoxytrityl derivatives **22** and **23** was achieved in two different ways. Removal of the isopropylidene group of **16** (\rightarrow **18**) and monomethoxytritylation (\rightarrow **19/20**) prior to mono-debenzylation with ammonia in THF proved to be more efficient, giving the

Scheme 3



a) PhCOCl/pyridine (95%). b) NH₄OH, THF/H₂O. c) 2M HCl, dioxane, then Na₂CO₃ (40%). d) 2M HCl, dioxane, then Na₂CO₃ (78%). e) MeOTrCl, pyridine; **19**: 15%; **20**: 15%. f) MeOTrCl, pyridine; **22**: 9%; **23**: 27%.

Scheme 4



a) Solid-phase synthesis: 80–87% per coupling step.

desired **22** and **23** each in 11% overall yield. The route *via* **17** and **21** gave **23** in 10% and **22** in 3.5% overall yield. Alcohols **22** and **23** were again separately processed to octameric phosphodiester on a solid support with 2'-deoxyadenosine as a starting nucleoside, **23** giving a pseudo- β - (see **25**) and **22** giving a pseudo- α -oligomer (see **24**; Scheme 4).

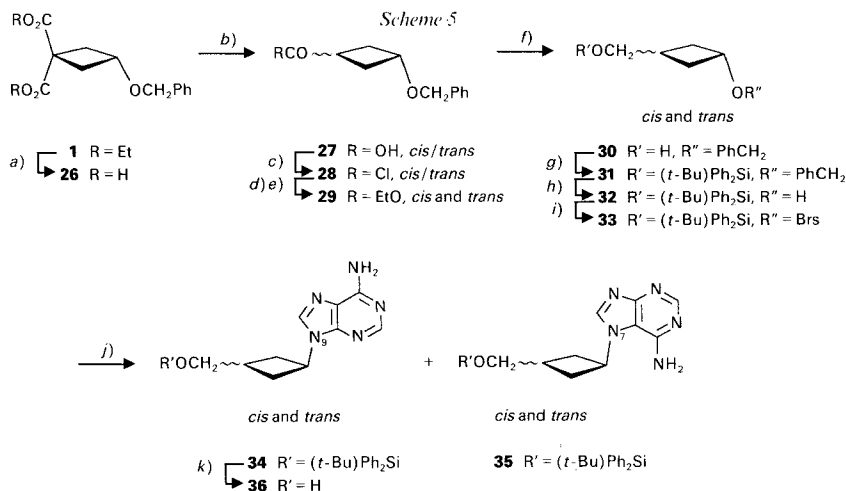
The structure of **12** and **13** was deduced from NOE experiments. With **12**, irradiation at the $H_x-C(3)^1$ signal gave a positive effect on the CH_2 protons of CH_2OH as well as on $H_x-C(2)$ and $H_x-C(4)$, whereas in **13** this effect was seen on $CH_2OTrOMe$, $H_x-C(2)$, and $H_x-C(4)^1$. The substitution pattern of **22** and **23** was revealed similarly by irradiation at the $H_x-C(3)^1$ signal giving NOE's on protons *cis* to $H_x-C(3)$.

All oligomers were characterized by mass spectrometry and by their mobility relative to xylenecyanol and bromophenol blue in polyacrylamide gel electrophoresis (PAGE). Specifically, **14** and **15** were measured by laser-ionisation desorption MS and run on 12% PAGE, whereas for **24** and **25** we used electrospray-ionisation MS and 20% PAGE (Table).

Table. Molecular Masses M and Electrophoresis Mobilities of Oligonucleotides **14**, **15**, **24**, and **25**

	Rel. mobility on PAGE (12%)	M by laser MS		Rel. mobility on PAGE (20%)	M by electrospray MS	
		found	calc.		found	calc.
Xylenecyanol	0			(dA) ₈	0.89	
Bromophenol blue	1			24	0.80	2429.2 2429.9
(dT) ₈	0.95			25	0.83	2429.7 2429.9
14	0.90	2357.7	2357.8			
15	0.90	2356.9	2357.8			

Furthermore, we also prepared the adenylyl-cyclobutanemethanols *cis*- and *trans*-**36** (Scheme 5). In our hands, the best route to the desired intermediates *cis*- and *trans*-**30** was *via* **26–29** and chromatographic separation of the ethyl carboxylates *cis*- and *trans*-**29**. The following procedure was applied separately to both *cis*- and *trans*-**29**. Reduction of the COOEt group with $LiAlH_4$ (\rightarrow **30**), protection with (*tert*-butyl)diphenylsilyl chloride (\rightarrow **31**), hydrogenolytic removal of the benzyl group (\rightarrow **32**), introduction of the leaving group with 4-bromobenzenesulfonyl chloride (\rightarrow **33**), and substitution with adenine in the presence of DBU in DMSO led to the silyl-protected N^9 -substituted derivatives **34**



a) KOH, EtOH/H₂O, reflux for 5 h. b) CO₂, 180°/0.02 Torr (80% for 2 steps). c) ClCOCOCl, CCl₄. d) EtOH, CCl₄. e) Chromatography. f) LiAlH₄ (0.75 equiv.), DME, 15 h, r.t. (80%). g) (t-Bu)Ph₂SiCl, imidazole, DMF. h) H₂, Pd/C, DME (72% for 2 steps). i) BrsCl, Et₃N, CH₂Cl₂ (95%). j) Adenine, DBU, DMSO, 35 h, 80° (46%). k) HF/urea, THF.

together with the corresponding *N*⁷-substituted derivatives **35**. In both the *cis*- and the *trans*-series, **34** and **35** were separated by chromatography. Final deprotection of **34** with HF in urea gave **36**.

For the introduction of *N*⁴-isobutyryl-cytosine and 2-amino-6-(methoxyethoxy)-purine into **32**, the benzenesulfonate rather than **33** proved to be the more efficient (unpublished).

Discussion. – While some oxetane- and cyclobutane-derived nucleosides obviously behave as antimetabolites in antiviral tests, it is not clear if oligomeric phosphodiester of such nucleoside derivatives are able to function as surrogates of oligonucleotides and would hybridize, *e.g.*, with RNA or DNA. Moreover, we wished to know if pairing between homologous complementary species were possible. With no reliable prognosis of computer-assisted molecular modelling at hand, we relied on inspection of *Dreiding* models, observing the well accepted stereochemical and stereoelectronic (phospho diesters) rules. However, the final answer had to come from synthesis and physicochemical tests²⁾.

The recently reported syntheses of 3-adenylcyclobutane-1,1-dimethanol both make use of the 3-amino derivative which is elaborated to the end products by stepwise synthesis of the heterocyclic-base moiety [8] [9]. In contrast, we introduced the base moiety directly by exploiting the preferential alkylation of adenine at *N*⁹ and of thymine at *N*¹. The isomeric *N*³-substituted thymine was expected to be formed; however, the relatively high proportion of *N*¹,*N*³-disubstituted derivative **8** was unexpected.

²⁾ Results with oligonucleotides containing three-, five-, and six-membered rings in place of deoxyribose will be reported later.

After proper protection of the adenine group, elaboration of the monomeric cyclobutanedimethanols to oligomeric phosphodiester followed the well established phosphotriester method. In particular, the methoxytrityl-carbanucleosides were phosphorylated according to the method described by *van Boom et al.* [12]. The resulting carbanucleotide benzotriazolyl esters were assembled to oligomers by a solid-phase process in a semiautomated continuous-flow synthesizer. While the oligomers containing thymine were formed in good yield (95–98% per coupling step) and could be purified by simple gel chromatography, the coupling procedure was less suitable for the adenine derivatives. Coupling yields were low (75–90% per step) for unknown reasons, and the mixture of oligomers had to be fractionated by ion-exchange chromatography on *Mono Q HR 5/5 (Pharmacia)*. In view of this, the phosphoramidite method may be a viable alternative.

With the octamers in hand, the pairing behaviour toward various ribonucleic and deoxyribonucleic acids was studied. The corresponding results are to be reported elsewhere.

We thank Prof. *H. Fritz*, Drs. *H. Fuhrer*, and *E. Keller* for NMR measurements, Dr. *D. Mueller* for mass-spectrometric determinations, Mr. *M. Faupel* for capillary electrophoresis, and Mr. *F. Ossola* for skilled assistance in some experiments.

Experimental Part

General. Flash chromatography (FC): silica gel *Merck 60*, 230–400 Mesh ASTM; alumina *B*, act. I (*JCN Biomedicals* No. 02072), *Hyflo (Fluka* No. 56678), molecular sieves (0.4 and 0.3 nm, beads *ca.* 2 mm; *Merck* No. 5704 and 5708). TLC: *Merck* silica gel 60 F_{254} precoated, layer thickness 0.25 mm. CH_2Cl_2 was stored over 0.4-nm molecular sieves, 1,2-dimethoxyethane (DME) passed over basic alumina before use, dimethylsulfoxide (DMSO) distilled under vacuum and stored over 0.4-nm molecular sieves, dioxane passed over basic alumina before use, EtOH stored over 0.3-nm molecular sieves, pyridine distilled and stored over 0.4-nm molecular sieves, tetrahydrofuran (THF) distilled over potassiumnaphthalene and stored over 0.4-nm molecular sieves, toluene distilled and stored over 0.4-nm molecular sieves, and Et_3N distilled and stored over 0.4-nm molecular sieves. Solvents for chromatography (ratios in *v/v*) were distilled before use. Melting point: *Büchi* apparatus by Dr. *Tottoli*. UV spectra: *Perkin-Elmer-Lambda-9* UV/VIS/NIR spectrometer; λ_{max} in nm (ϵ). IR spectra: *Perkin-Elmer* model 881; film, 1 drop of substance between 2 NaCl plates. NMR spectra: 200 MHz, *Varian GEM 200*; 300 MHz, *Varian GEM 300*; 400 MHz, *Bruker WM 400*; δ in ppm, *J* in Hz; solvent internal reference CDCl_3 , ^1H 7.265 ppm, ^{13}C 77.00 ppm; CD_3OD , ^1H 3.34 ppm, ^{13}C 49.00 ppm; DMSO, ^1H 2.50 ppm, ^{13}C 39.70 ppm; ^{13}C , completely decoupled and APT spectra, off-resonance decoupled spectra only if necessary. Mass spectra: *2 AB, HF* apparatus, FAB technique, thioglycerol as solvent.

Diethyl 3-(Benzyloxy)cyclobutane-1,1-dicarboxylate (1) was prepared according to [10] [11] with some improvements: Diethyl malonate (258.6 ml, 1.703 mol) was added neat within 2 h to a suspension of NaH (51.10 g, 1.703 mol; *Fluka* No. 71614, 80% NaH in oil) in dioxane (1000 ml). This soln. was stirred 90 min at r.t. Then 2-(benzyloxy)-1-bromo-3-chloropropane (500 g, 1.789 mol) was added neat within 1 h. The mixture was stirred for 1 h at r.t., followed by 24 h at 125°. After slow cooling to r.t., the same quantity of NaH was added neat in 5-g portions within 1 h. The suspension was then slowly heated to 125°, mechanically stirred for 120 h at this temp. and worked up as described. The product was first purified by distillation at 172°/0.6 Torr, followed by FC ((*t*-Bu)-OMe/hexane 1:99 to 2:8): 382.5 g (73.3%) of **1**. Colourless oil.

3 β -(Benzyloxy)cyclobutane-1,1-dimethanol (2). A soln. of **1** (95.8 g, 313 mmol) in DME (80 ml) was added dropwise at r.t. under Ar to a suspension of LiAlH_4 (15 g, 395 mmol) in DME (360 ml), so as to maintain the temp. < 50° (TLC control (AcOEt): R_f 0.30). The mixture was stirred under Ar at r.t. for 48 h. After completion of the reaction, H_2O (10 ml) was slowly added with vigorous stirring. The mixture was then transferred into a 2-l flask containing silica gel (800 ml) and the solvent removed under vacuum until a fine powder was obtained. This powder was added to a 5-cm *Hyflo* pad on a fritteglass and washed with AcOEt (400 ml fractions, TLC control). The fractions containing product were evaporated to give 55 g (79%) of crude crystalline **2**. Recrystallization from AcOEt/hexane gave 43.2 g (62%) of colourless crystals. The mother liquors were purified by FC (AcOEt/hexane

5:5 to 7:3); 5 g (7.2%) of crystals. M.p. 67.5–68.5°. IR (film): 3368, 3031, 2928, 2870, 1721, 1496, 1454. ¹H-NMR (CDCl₃, 200 MHz): 7.30 (s, 5 arom. H); 4.40 (s, PhCH₂); 4.06 (*quint.*, H–C(3)); 3.66 (s, β-CH₂OH); 3.62 (s, α-CH₂OH); 3.15 (2OH); 2.16 (*m*, ABX, H_β–C(2), H_β–C(4)); 1.78 (*m*, ABX, H_α–C(2), H_α–C(4)). ¹³C-NMR (CDCl₃, 50 MHz): 138.56 (C_{ipso}); 128.95 (C_o); 128.45 (C_m); 128.25 (C_p); 71.01 (β-CH₂OH); 70.48 (α-CH₂OH); 69.43 (PhCH₂); 69.00 (C(3)); 37.35 (C(1)); 34.55 (C(2), C(4)). Anal. calc. for C₁₃H₁₈O₃ (222.285): C 70.25, H 8.16, O 21.60; found: C 70.09, H 8.22, O 21.64.

2β-(Benzyloxy)-7,7-dimethyl-6,8-dioxaspiro[3.5]nonane (3). To a soln. of **2** (12 g, 54 mmol) and TsOH (1 g) in dimethylformamide (DMF; 240 ml), 2,2-dimethoxypropane (19.9 ml, 162 mmol) was slowly added (TLC control (AcOEt): R_f 0.15). The mixture was stirred under Ar at r.t. for 20 h. AcOEt (500 ml) was then added and the resulting soln. washed 4 times with brine (4 × 150 ml). The org. phase was dried (MgSO₄) and evaporated: **3** (13.7 g, 96.5%) as a colourless oil which crystallized after a few days in the refrigerator (no further purification required). M.p. 54–56°. IR (film): 3419, 3030, 2997, 2955, 2922, 2866, 2350, 1728, 1606, 1584, 1497. ¹H-NMR (CDCl₃, 200 MHz): 7.32 (s, 5 arom. H); 4.38 (s, PhCH₂); 4.02 (*quint.*, J = 6.5, H–C(2)); 3.70 (s, CH₂(5)); 3.67 (s, CH₂(9)); 2.19 (*m*, ABX, J = 13.5, 6.5, H_β–C(1), H_β–C(3)); 1.80 (*m*, ABX, J = 13.5, 6.5, H_α–C(1), H_α–C(3)); 1.37 (s, 2 Me). ¹³C-NMR (CDCl₃, 50 MHz): 138.56 (C_{ipso}); 128.93 (C_m); 128.40 (C_o); 128.20 (C_p); 98.17 (C(7)); 70.48 (CH₂(5)); 70.42 (CH₂(9)); 69.26 (C(2)); 68.94 (PhCH₂); 36.54 (C(1), C(3)); 30.80 (C(4)); 24.04 (2 Me). Anal. calc. for C₁₆H₂₂O₃ (262.350): C 73.25, H 8.45, O 18.30; found: C 73.10, H 8.56, O 18.60.

7,7-Dimethyl-6,8-dioxaspiro[3.5]nonan-2β-ol (4). Degussa Pd (2 g) in DME (350 ml) was first placed under H₂. Then, **3** (44 g, 168 mmol) was added neat. The mixture was shaken vigorously at r.t. under 1 atm H₂ until 1 equiv. H₂ was absorbed (ca. 1 h). After filtration of the catalyst over *Hyflo*, the soln. was evaporated: **4** (28.1 g, 97%). Colourless sirup. IR (film): 3336, 2930, 2873, 1712, 1652, 1465. ¹H-NMR (CDCl₃, 200 MHz): 4.20 (*quint.*, H–C(2)); 3.68 (s, CH₂(5)); 3.64 (s, CH₂(9)); 2.25 (*m*, ABX, H_β–C(1), H_β–C(3)); 1.65 (*m*, ABX, H_α–C(1), H_α–C(3)); 1.35 (s, 2 Me). ¹³C-NMR (CDCl₃, 50 MHz): 98.22 (C(7)); 70.50 (CH₂(5)); 68.79 (CH₂(9)); 63.51 (C(2)); 39.05 (C(1), C(3)); 30.00 (C(4)); 24.02 (2 Me).

7,7-Dimethyl-6,8-dioxaspiro[3.5]non-2-yl 4-Bromobenzenesulfonate (5). A mixture of **4** (65 g, 37.8 mmol) and Et₃N (15.8 ml, 113.2 mmol) in CH₂Cl₂ (150 ml) was stirred under Ar at 0°. A soln. of 4-bromobenzenesulfonyl chloride (11.57 g, 45.3 mmol) in CH₂Cl₂ (50 ml) was slowly added at 0°. The mixture was stirred for 60 h at r.t. (TLC control (AcOEt/hexane 5:5): R_f 0.5). AcOEt (400 ml) was added, the soln. washed 4 times with brine (4 × 200 ml), the org. phase dried (MgSO₄), and the solvent evaporated. The obtained sirup was purified by FC (AcOEt/hexane/Et₃N 7:3:0.1 to 1:1:0.1): **5** (11.4 g, 77.2%). Colourless crystals. M.p. 99–101°. IR (KBr): 2970, 2920, 2840, 1570, 1365, 1185. ¹H-NMR (CDCl₃, 200 MHz): 7.72 (*m*, 4 arom. H); 4.84 (*quint.*, J = 6.9, H–C(2)); 3.67 (s, CH₂(5)); 3.65 (s, CH₂(9)); 2.28 (*m*, ABX, H_β–C(1), H_β–C(3)); 1.95 (*m*, ABX, H_α–C(1), H_α–C(3)); 1.35 (s, 2 Me). ¹³C-NMR (CDCl₃, 50 MHz): 136.44 (C_{ipso}); 133.18 (C_m); 129.77 (C_o); 129.63 (C_p); 98.39 (C(7)); 72.11 (CH₂(5)); 69.83 (CH₂(9)); 67.98 (C(2)); 36.99 (C(1), C(3)); 31.52 (C(4)); 23.90 (2 Me). Anal. calc. for C₁₅H₁₉BrO₅S (391.285): C 46.05, H 4.90, Br 20.42, O 20.45, S 8.19; found: C 46.09, H 5.05, Br 20.42, O 20.32, S 8.20.

9-(7,7-Dimethyl-6,8-dioxaspiro[3.5]non-2β-yl)-9H-purin-6-amine (6). A mixture of **5** (20 g, 51.1 mmol), adenine (= 1H-purin-6-amine; 20.72 g, 153.3 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 23 ml, 23.34 mmol) in DMSO (800 ml) was stirred under Ar at 80° for 48 h (TLC control (AcOEt/MeOH 8:2): R_f 0.29; detection by 1) Cl₂, 2) KI). Sat. NaHCO₃ soln. (200 ml) and H₂O (800 ml) were added, and the soln. was extracted 7 times with AcOEt (7 × 200 ml). The collected org. fractions were washed with brine (200 ml), dried (Na₂SO₄), and purified by FC (AcOEt/MeOH/Et₃N 95:5:0.1): **6** (11.1 g, 75%). Colourless crystals. M.p. 251°, after crystallization from H₂O/EtOH. UV (H₂O, 0.5 · 10⁻⁴ mol/l): 205 (19820), 259 (13940). IR (KBr): 3490, 3420, 3180, 2990, 2850, 2750, 1650, 1600, 1580, 1480. ¹H-NMR (CDCl₃, 200 MHz): 8.30 (s, H–C(2), Ade); 7.82 (s, H–C(8), Ade); 5.60 (s, NH₂); 4.95 (*quint.*, H–C(2)); 3.90 (s, CH₂(5)); 3.87 (s, CH₂(9)); 2.55 (*m*, ABX, CH₂(1), CH₂(3)); 1.40 (s, 2 Me). ¹³C-NMR (CDCl₃, 50 MHz): 155.8 (C(6), Ade); 152.2 (C(2), Ade); 149.4 (C(4), Ade); 138.8 (C(8), Ade); 120.0 (C(5), Ade); 97.8 (C(7)); 68.9 (CH₂(5)); 66.8 (CH₂(9)); 44.3 (C(2)); 39.7 (C(4)); 35.2 (C(3)); 31.3 (C(1)); 23.1 (2 Me). Anal. calc. for C₁₄H₁₉N₅O₂ (289.339): C 58.12, H 6.62, N 24.21, O 11.06%; found: C 58.18, H 6.88, N 24.19, O 11.30.

1-(7,7-Dimethyl-6,8-dioxaspiro[3.5]non-2β-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (7) and 1,3-Bis(7,7-dimethyl-6,8-dioxaspiro[3.5]non-2β-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (8). As described for **6**, with **5** (20.26 g, 51.8 mmol), thymine (= 5-methylpyrimidine-2,4(1H,3H)-dione; 26.12 g, 207.1 mmol), DBU (31 ml, 31.5 mmol), and DMSO (800 ml) (TLC control (MeOH/AcOEt 1:9): R_f 0.52 and 0.48; detection by 1) Cl₂, 2) KI). FC (AcOEt/hexane/Et₃N 5:5:0.1 to 7:3:0.1) afforded first **8** (3.85 g, 34.2%; R_f 0.47 (MeOH/AcOEt 1:9)) and then **7** (7.92 g, 54.6%; R_f 0.52).

Data of 7: M.p. 198–201°. UV (MeOH, 0.5 · 10⁻⁴ mol/l): 209 (15200), 270 (18000). IR (KBr): 3190, 3000, 2950, 2860, 1680. ¹H-NMR (CDCl₃, 200 MHz): 9.94 (s, NH); 7.07 (s, H, Thy); 4.74 (*quint.*, H–C(2)); 3.78 (s, CH₂(5));

3.69 (s, CH₂(9)); 2.36 (m, ABX, H_β-C(1), H_β-C(3)); 1.99 (m, ABX, H_z-C(1), H_z-C(3)); 1.78 (s, Me-C(5), Thy); 1.35 (s, 2 Me). ¹³C-NMR (CDCl₃, 50 MHz): 164.71 (CO); 151.60 (CO); 137.15 (C(6), Thy); 111.12 (C(5), Thy); 98.54 (C(7)); 69.80 (CH₂(5)); 67.60 (CH₂(9)); 47.21 (C(2)); 35.06 (C(1), C(3)); 31.66 (C(4)); 23.94 (2 Me); 12.73 (Me-C(5), Thy). Anal. calc. for C₁₄H₂₀N₂O₄ (280.326): C 59.99, H 7.19, N 10.00, O 22.83; found: C 59.64, H 7.22, N 9.71, O 22.55.

Data of 8: M.p. 154–155°. UV (MeOH, 0.5 · 10⁻⁴ mol/l): 215 (5520), 265 (3940). IR (KBr): 3000, 2940, 1610, 1570. ¹H-NMR (CDCl₃, 200 MHz): 7.90 (s, H, Thy); 5.25 (quint., H-C(2)); 5.07 (quint., H-C(2)); 3.70 (s, 4CH₂O); 2.42 (m, ABX, 4H, H_β-C(1), H_β-C(3)); 1.98 (m, ABX, 4H, H_z-C(1), H_z-C(3)); 1.78 (s, Me-C(5), Thy); 1.35 (s, 4 Me). ¹³C-NMR (CDCl₃, 50 MHz): 168.69 (CO); 163.26 (CO); 157.93 (C(6), Thy); 111.58 (C(5), Thy); 98.16 (C(7)); 98.11 (C(7)); 68.78 (CH₂(5)); 68.72 (CH₂(5)); 67.70 (CH₂(9)); 67.64 (CH₂(9)); 53.60 (C(2)); 36.77 (C(3)); 36.72 (C(1)); 31.87 (C(4)); 31.39 (C(4)); 23.98 (2 Me); 12.06 (Me-C(5), Thy). Anal. calc. for C₂₃H₃₄N₂O₆ (434.536): C 63.57, H 7.89, N 6.45, O 22.09; found: C 63.76, H 7.77, N 6.46, O 22.12.

3β-(6-Amino-9H-purin-9-yl)cyclobutane-1,1-dimethanol (9). Aq. 2M HCl (10 drops) was added at r.t. to a soln. of **6** (1.09 g, 2.77 mmol) in dioxane (5 ml). The soln. was stirred for 1 h, neutralized with NaHCO₃, evaporated and the residue crystallized from H₂O. The crystals obtained were not pure as shown by TLC (CHCl₃/MeOH/H₂O 70:30:5), therefore, the mixture **9**/NaCl was purified by FC (CHCl₃/MeOH/H₂O 93:6:1 to 70:30:5): **9** (650 mg, 70%). Colourless crystals. M.p. 217–218°. UV (H₂O, 0.5 · 10⁻⁴ mol/l): 194 (21200), 206 (21000), 262 (13780). IR (film): 3304, 3145, 2993, 2856, 1673, 1603, 1569. ¹H-NMR (CD₃OD, 200 MHz): 8.05 (s, H-C(2), Ade); 7.95 (s, H-C(8), Ade); 4.80 (quint., H-C(3)); 3.48 (s, β-CH₂OH); 3.42 (s, α-CH₂OH); 2.35 (m, CH₂(2), CH₂(4)). ¹³C-NMR (CD₃OD, 50 MHz): 156.67 (C(2), Ade); 143.97 (C(8), Ade); 70.40 (β-CH₂OH); 69.59 (α-CH₂OH); 48.27 (C(3)); 43.64 (C(1)); 37.12 (C(2), C(4)). Anal. calc. for C₁₁H₁₅N₅O₂ (249.275): C 53.00, H 6.07, N 28.10, O 12.84; found: C 53.05, H 6.29, N 27.87, O 12.71.

1,3-Bis[3,3-bis(hydroxymethyl)cyclobut-1β-yl]-5-methylpyrimidine-2,4(1H,3H)-dione (10). As described for **9**, with 2M HCl (10 drops), **8** (1.48 g, 3.41 mmol), and dioxane (5 ml): **10** (846 mg, 70%). Colourless crystals. M.p. 128–130°. UV (H₂O, 0.5 · 10⁻⁴ mol/l): 268 (9640). IR (film): 3346, 2934, 2870, 1604, 1575, 1435, 1329, 1293. ¹H-NMR (CD₃OD, 200 MHz): 7.70 (s, H, Thy); 5.05 (quint., H-C(1)); 4.87 (quint., H-C(1)); 3.44 (s, β-CH₂OH); 3.42 (s, β-CH₂OH); 3.38 (s, α-CH₂OH); 3.36 (s, α-CH₂OH); 2.15 (m, H_β-C(2), H_β-C(4)); 1.78 (m, H_z-C(2), H_z-C(4)); 1.76 (s, Me-C(5), Thy). ¹³C-NMR (CD₃OD, 50 MHz): 173.87 (CO); 167.06 (CO); 161.08 (C(6), Thy); 115.45 (C(5), Thy); 72.27 (β-CH₂OH); 71.59 (α-CH₂OH); 70.05 (C(1)); 69.97 (C(1)); 42.87 (C(3)); 42.66 (C(3)); 38.34 (C(2), C(4)); 38.19 (C(2), C(4)); 15.62 (Me-C(5), Thy). Anal. calc. for C₁₇H₂₆N₂O₆ (240.261): C 57.61, H 7.39, N 7.90, O 27.09; found: C 57.24, H 7.38, N 7.89, O 27.12.

1-[3,3-Bis(hydroxymethyl)cyclobut-1β-yl]-5-methylpyrimidine-2,4(1H,3H)-dione (11). As described for **9**, with aq. 2M HCl (10 drops), **7** (1.05 g, 3.73 mmol), and dioxane (5 ml): **11** (700 mg, 78%). Colourless crystals. M.p. 207–208°. R_f 0.23 (MeOH/AcOEt 1:9). UV (H₂O, 0.5 · 10⁻⁴ mol/l): 211 (8840), 274 (10520). IR (KBr): 3170, 3040, 2990, 2950, 2870, 1690, 1660. ¹H-NMR (CD₃OD, 400 MHz): 7.33 (q, H, Thy); 4.72 (quint., J = 8.5, H-C(1)); 3.47 (s, β-CH₂OH); 3.37 (s, α-CH₂OH); 2.07 (d, J = 8.5, CH₂(2), CH₂(4)); 1.78 (s, Me-C(5), Thy). ¹³C-NMR (CD₃OD, 50 MHz): 176 (CO); 167 (CO); 142.29 (CH, Thy); 70.45 (β-CH₂OH); 69.84 (α-CH₂OH); 49.68 (C(1)); 43.2 (C(3)); 35.77 (C(2), C(4)); 16.27 (Me-C(5), Thy). Anal. calc. for C₁₁H₁₆N₂O₄ (354.406): C 54.99, H 6.71, N 11.66, O 26.64; found: C 54.86, H 6.74, N 11.65, O 26.56.

1-{3α-(Hydroxymethyl)-3β-[(methoxytrityloxy)methyl]cyclobut-1β-yl}-5-methylpyrimidine-2,4(1H,3H)-dione (12) and 1-{3β-(Hydroxymethyl)-3α-[(methoxytrityloxy)methyl]cyclobut-1β-yl}-5-methylpyrimidin-2,4(1H,3H)-dione (13). Compound **11** (314 mg, 1.307 mmol) was evaporated 3 times with pyridine (3 × 10 ml). Methoxytrityl chloride (MeOTrCl) (316.5 mg, 1.03 mmol) was added under Ar to a soln. of **11** in pyridine (10 ml). The mixture was stirred at r.t. for 8 h (TLC control (AcOEt/hexane 8:2)). More MeOTrCl (100 mg, 0.32 mmol) was added in 2 portions after 5 h. The mixture was stirred 15 h at r.t. TLC (CHCl₃/MeOH/Et₃N 95:5:1): R_f 0.99 (degradation product of MeOTrCl), 0.95 (bis(methoxytrityl)derivative), 0.40 (**12**), 0.35 (**13**), and 0.05 (**11**). (Adding more MeOTrCl did not diminish the amount of **11** but increased the amount of bis(methoxytrityl) derivative.) NaHCO₃ (10 ml, 1M) was added, the soln. extracted 4 times with AcOEt (4 × 20 ml), and the org. phase dried (Na₂SO₄). The products were separated by FC (CHCl₃/acetone/Et₃N 99:1:1 slowly to 80:20:1): *1*-{3,3-bis-[(methoxytrityloxy)methyl]cyclobut-1-yl}-5-methylpyrimidine-2,4(1H,3H)-dione (70 mg, 8.9%), then **12** (234 mg, 34.9%), **13** (281 mg, 41.9%), and **11** (20 mg, 6.4%).

Data of 12: M.p. 126°. UV (MeOH, 0.5 · 10⁻⁴ mol/l): 274 (10720). ¹H-NMR (CDCl₃, 400 MHz): 8.25 (s, NH); 7.43 (m, 4 arom. H); 7.31 (dd, 6 arom. H); 7.25 (m, 2 arom. H); 7.13 (q, J = 1.5, H, Thy); 6.85 (d, 2 arom. H); 4.94 (quint., J = 9.0, H-C(1)); 3.78 (s, MeO); 3.72 (d, J = 4.5, CH₂OH); 3.24 (s, CH₂OTrOMe); 2.31 (ddd, ABX, J = 3.0, 9.0, 11.0, H_β-C(2), H_β-C(4)); 2.10 (ddd, ABX, J = 3.0, 9.0, 10.2, H_z-C(2), H_z-C(4)); 2.01 (t, J = 4.5, OH); 1.72 (d, J = 1.5, Me-C(5), Thy); irradi. on H-C(1) → pos. NOE on CH₂OH, H_z-C(2), H_z-C(4), but no effect on

H_{β} -C(2), H_{β} -C(4); irradi. on CH_2OH → pos. NOE on H-C(1), H_x -C(2), H_x -C(4); irradi. on $CH_2OTrOMe$ → pos. NOE on CH_2OH , H_{β} -C(2), H_{β} -C(4), no effect on H-C(1); irradi. on H_{β} -C(2), H_{β} -C(4) → pos. NOE on H_x -C(2), H_x -C(4), $CH_2OTrOMe$, no effect on H-C(1); irradi. on H_x -C(2), H_x -C(4) → pos. NOE on H_{β} -C(2), H_{β} -C(4), H-C(1), CH_2OH , no effect on $CH_2OTrOMe$. FAB-MS: 513 (MH^+), 535 ($[M + Na]^+$), 435 ($[M - Ph]^+$), 273 ($MeOTr^+$), 241 ($[M - TrOMe]^+$), 195 ($[MeOTr - Ph]^+$), 165 ($[MeOTr - PhOMe]^+$), 127 ($[Thy + H]^+$). Anal. calc. for $C_{31}H_{32}N_2O_5$ (512.608) + 0.42 H_2O : C 71.58, H 6.36, N 5.39, O 16.67; found: C 71.58, H 6.37, N 5.46, O 16.72.

Data of 13: M.p. 120°. UV (MeOH, $0.5 \cdot 10^{-4}$ mol/l): 274 (10740). 1H -NMR ($CDCl_3$, 400 MHz): 8.25 (s, NH); 7.43 (m, 4 arom. H); 7.36 (q, $J = 1.5$, H, Thy); 7.31 (m, 6 arom. H); 7.23 (m, 2 arom. H); 6.86 (m, 2 arom. H); 4.81 (quint., $J = 8.5$, H-C(1)); 3.82 (s, MeO); 3.64 (d, $J = 3.5$, CH_2OH); 3.26 (s, $CH_2OTrOMe$); 2.28 (m, A_2X , $CH_2(2)$, $CH_2(4)$); 2.06 (t, $J = 3.7$, OH); 1.94 (d, $J = 1.5$, Me-C(5), Thy); irradi. on H-C(1) → pos. NOE on $CH_2OTrOMe$, $CH_2(2)$, $CH_2(4)$; irradi. on CH_2OH → pos. NOE on $CH_2OTrOMe$, $CH_2(2)$, $CH_2(4)$, no effect on H-C(1); irradi. on $CH_2OTrOMe$ → pos. NOE on H-C(1), $CH_2(2)$, $CH_2(4)$, CH_2OH . FAB-MS: 513 ($[M + H]^+$), 535 ($[M + Na]^+$), 435 ($[M - Ph]^+$), 241 ($[M - TrOMe]^+$), 273 ($MeOTr^+$), 241 ($[M - TrOMe]^+$), 195 ($[MeOTr - Ph]^+$), 165 ($[MeOTr - PhOMe]^+$), 127 ($[Thy + H]^+$). Anal. calc. for $C_{31}H_{32}N_2O_5$ (512.608) + 0.50 H_2O : C 71.38, H 6.38, N 5.37, O 16.87; found: C 71.26, H 6.48, N 5.44, O 16.65.

6-(Dibenzoylamino)-9-(7,7-dimethyl-6,8-dioxaspiro[3.5]non-2 β -yl)-9H-purine (16). A pyridine soln. of **6** (707 mg, 2.44 mmol) was evaporated 3 times to dryness (3×15 ml). Benzoyl chloride (700 μ l, 6.02 mmol) was added neat dropwise to soln. of **6** in pyridine (5 ml). The mixture was stirred 15 h at r.t. (TLC control (MeOH)/AcOEt 2:8): R_f 0.55). H_2O (20 ml) was added and the soln. extracted twice with AcOEt (2×40 ml). The org. phase was dried (Na_2SO_4) and evaporated. The compound was crystallized from $CHCl_3/MeOH$: **16** (1.205 g, 99%). Colourless crystals. M.p. 221–222°, after crystallization from $CHCl_3/MeOH$. UV (MeOH, $0.5 \cdot 10^{-4}$ mol/l): 249 (21700). IR (KBr): 3060, 2990, 2930, 2850, 1700, 1600. 1H -NMR ($CDCl_3$, 200 MHz): 8.64 (s, H-C(2), Ade); 8.08 (s, H-C(8), Ade); 7.85 (d, H_o , PhCO); 7.48 (t, H_p , PhCO); 7.33 (m, H_m , PhCO); 5.03 (quint., H-C(2)); 3.92 (s, 2 CH_2O); 2.63 (d, $CH_2(1)$, $CH_2(3)$); 1.42 (s, 2 Me). ^{13}C -NMR ($CDCl_3$, 50 MHz): 172.94 (CO); 164.00 (C(6), Ade); 152.43 (C(2), Ade); 144.14 (C(8), Ade); 141.80 (C(4), Ade); 134.64 (C_{ipso} , PhCO); 134.09 (C_p , PhCO); 133.52 (C_p , PhCO); 130.66 (C_o , PhCO); 130.02 (C_m , PhCO); 129.24 (C_m , PhCO); 128.95 (C_m , PhCO); 112.80 (C(5), Ade); 98.56 (C(7)); 69.90 ($CH_2(5)$); 67.79 ($CH_2(9)$); 55.02 (C(2)); 45.83 (C(4)); 35.80 (C(3)); 32.24 (C(1)); 24.01 (2 Me). Anal. calc. for $C_{28}H_{24}N_2O_4$ (494.533): C 67.59, H 5.47, N 14.08, O 12.86; found: C 67.60, H 5.50, N 14.10, O 12.90.

6-(Benzoylamino)-9-(7,7-dimethyl-6,8-dioxaspiro[3.5]non-2 β -yl)-9H-purine (17). Conc. NH_3 soln. (3 ml, 29%) was added dropwise to a soln. of **16** (718 mg, 1.47 mmol) in THF (7.3 ml) and H_2O (1.5 ml). The mixture was stirred 4 h at r.t. TLC (AcOEt and AcOEt/MeOH 9:1): R_f 0.46 and 0.54, resp. (PhCONH $_2$), 0.36 and 0.45, resp. (**16**), 0.10 and 0.42, resp. (**17**), 0.02 and 0.26, resp. (PhCOO-NH $_4^+$). H_2O (20 ml) was added and the soln. extracted 4 times with AcOEt (2×40 ml). The org. phase was dried (Na_2SO_4) and evaporated. The compounds were separated by FC (AcOEt/hexane 5:5 to AcOEt/MeOH 8:2). **17**: M.p. 180–182°, after crystallization from AcOEt/hexane. UV (MeOH, $0.5 \cdot 10^{-4}$ mol/l): 281 (20180). IR (film): 3500–3100, 2991, 2941, 2856, 1695, 1613. 1H -NMR ($CDCl_3$, 200 MHz): 9.75 (s, NH); 8.23 (s, H-C(2), Ade); 8.08 (s, H-C(8), Ade); 8.02 (d, H_o , PhCO); 7.48 (m, H_p , H_m , PhCO); 5.02 (quint., H-C(2)); 3.43 (s, 2 CH_2O); 2.57 (d, $CH_2(1)$, $CH_2(3)$); 1.47 (s, 2 Me). ^{13}C -NMR ($CDCl_3$, 50 MHz): 165.84 (C=O); 152.54 (C(2), Ade); 152.37 (C(6), Ade); 150.26 (C(4), Ade); 142.17 (C(8), Ade); 134.15 (C_{ipso} , PhCO); 132.94 (C_p , PhCO); 128.95 (C_m , PhCO); 128.55 (C_o , PhCO); 123.91 (C(5), Ade); 98.45 (C(7)); 69.71 ($CH_2(5)$); 67.76 ($CH_2(9)$); 62.64 (C(2)); 45.71 (C(4)); 35.88 (C(3)); 32.26 (C(1)); 24.01 (2 Me). Anal. calc. for $C_{21}H_{23}N_3O_3$ (393.448): C 64.11, H 5.89, N 17.80, O 12.20; found: C 64.07, H 6.04, N 17.33, O 12.47.

3 β -[6-(Dibenzoylamino)-9H-purin-9-yl]-1 α -[(methoxytrityloxy)methyl]cyclobutane-1 β -methanol (19) and 3 β -[6-(Dibenzoylamino)-9H-purin-9-yl]-1 β -[(methoxytrityloxy)methyl]cyclobutane-1 α -methanol (20). Aq. 4M HCl (10 drops) was added to a soln. of **16** (209.5 mg, 0.421 mmol) in dioxane (5 ml). The mixture was stirred at r.t. for 5 h (TLC control ($CH_2Cl_2/MeOH$) 9:1) and neutralized with pyridine. The compound formed, 3-[6-(dibenzoylamino)-9H-purin-9-yl]cyclobutane-1,1-dimethanol (**18**), was not stable and could not be stored in the refrigerator. Thus, a pyridine soln. of **18** was evaporated 3 times to dryness (3×10 ml). Then, MeOTrCl (130 mg, 0.421 mmol) was added in one portion to the pyridine soln. (5 ml) of **18** in the presence of 4-(dimethylamino)pyridine (20 mg). The mixture was stirred 15 h at r.t. TLC ($(t-Bu)OMe/hexane$ 2:8, then $(t-Bu)OMe/EtOH$ 8:2): R_f 0.61 (degradation product of MeOTrCl), 0.48 (bis(methoxytrityl)derivative), 0.44 (**19**), 0.39 (**20**), 0.21 (unreacted **18**), H_2O (20 ml), 1M $NaHCO_3$ (20 ml), and AcOEt (50 ml) were added. The aq. phase was extracted 3 more times with AcOEt (3×50 ml), the org. phase dried (Na_2SO_4) and evaporated. Separation by FC ($(t-Bu)OMe/hexane$ 2:8 to $(t-Bu)OMe/MeOH$ 2:8) gave bis(methoxytrityl) derivative (40 mg, 9.5%), **19** (46 mg, 15.0%), **20** (46 mg, 15.0%), and **18** (30 mg, 14.3%).

Data of 3 β -[6-(Dibenzoylamino)-9H-purin-9-yl]-1,1-bis[(methoxytrityloxy)methyl]cyclobutane: 1H -NMR ($CDCl_3$, 200 MHz): 8.62 (s, H-C(2), Ade); 8.22 (s, H-C(8), Ade); 7.85 (m, H_o , PhCO); 7.50–7.20 (m, 30 arom. H);

6.82 (*m*, 4 arom. H); 4.96 (*quint.*, H–C(3)); 3.78 (*s*, MeO); 3.72 (*s*, MeO); 3.35 (*s*, β -CH₂O); 3.30 (*s*, α -CH₂O); 2.50 (*m*, A₂X, CH₂(2), CH₂(4)).

Data of 19: ¹H-NMR (CDCl₃, 200 MHz): 8.63 (*s*, H–C(2), Ade); 8.24 (*s*, H–C(8), Ade); 7.85 (*m*, 4 arom. H); 7.50–7.20 (*m*, 18 arom. H); 6.82 (*m*, 2 arom. H); 4.98 (*quint.*, H–C(3)); 3.80 (*s*, MeO); 3.70 (*s*, CH₂OH); 3.30 (*s*, CH₂OTrOMe); 2.80 (*m*, ABX, H_α–C(2), H_α–C(4)); 2.50 (*m*, ABX, H_β–C(2), H_β–C(4)). ¹³C-NMR (CDCl₃, 50 MHz): 172.97 (2CO); 159.30 (C(6), Ade); 153.79 (C_p, PhOMe); 152.34 (C(2), Ade); 152.27 (C(4), Ade); 144.66 (C(8), Ade); 144.31 (C_{ipso}, Ph of Tr); 135.78 (C_{ipso}, MeOC₆H₄); 134.69 (C_{ipso}, PhCO); 133.49 (C_p, PhCO); 130.84 (C_o, MeOC₆H₄); 130.00 (C_o, PhCO); 129.23 (C_m, PhCO); 128.87 (C_m, Ph of Tr); 128.51 (C_o, Ph of Tr); 127.65 (C_p, Ph of Tr); 113.82 (C(5), Ade); 113.75 (C_m, MeOC₆H₄); 69.55 (β -CH₂OH); 67.62 (α -CH₂O); 55.58 (C(3)); 45.94 (C(1)); 38.44 (C(2)); 34.39 (C(4)).

Data of 20: ¹H-NMR (CDCl₃, 200 MHz): 8.55 (*s*, H–C(2), Ade); 8.04 (*s*, H–C(8), Ade); 7.87 (*m*, 4 arom. H); 7.50–7.20 (*m*, 18 arom. H); 6.80 (*m*, 2 arom. H); 5.06 (*quint.*, H–C(3)); 3.80 (*s*, CH₂OH); 3.76 (*s*, MeO); 3.46 (*s*, CH₂OTrOMe); 2.55 (*m*, A₂X, CH₂(2), CH₂(4)).

3-[6-(Benzoylamino)-9H-purin-9-yl]cyclobutane-1,1-dimethanol (**21**). Aq. 4M HCl (200 μ l) was added to a soln. of **17** (1.00 g, 2.54 mmol) in dioxane (10 ml) and H₂O (1 ml). This mixture was stirred at r.t. for 5 h (TLC control (AcOEt/MeOH 7:3)). After the reaction was complete, the soln. was neutralized with solid NaHCO₃ and evaporated. The obtained oil was purified by FC (AcOEt to AcOEt/MeOH 4:1): **21** (700 mg, 78%). Colourless crystals. This compound was not very stable and could not be stored in the freezer for a longer time. ¹H-NMR (CD₃OD, 200 MHz): 9.00 (*s*, H–C(2), Ade); 8.70 (*s*, H–C(8), Ade); 7.80 (*d*, H_o, PhCO); 7.55 (*dd*, H_p, PhCO); 7.35 (*t*, H_m, PhCO); 5.08 (*quint.*, H–C(3)); 3.70 (*s*, β -CH₂OH); 3.58 (*s*, α -CH₂OH); 2.50 (*d*, CH₂(2), CH₂(4)). ¹³C-NMR (CD₃OD, 50 MHz): 171.80 (CO), 154.22 (C(6), Ade); 152.52 (C(2), Ade); 149.14 (C(4), Ade); 146.58 (C(8), Ade); 136.87 (C_{ipso}, PhCO); 133.81 (C_p, PhCO); 131.62 (C_m, PhCO); 131.03 (C_o, PhCO); 120.81 (C(5), Ade); 67.88 (β -CH₂OH); 66.55 (α -CH₂OH); 48.54 (C(3)); 41.85 (C(1)); 34.88 (C(2), C(4)).

3β-[6-(Benzoylamino)-9H-purin-9-yl]-1α-[methoxytrityloxy)methyl]cyclobutane-1β-methanol (**22**) and 3β-[6-(Benzoylamino)-9H-purin-9-yl]-1β-[methoxytrityloxy)methyl]cyclobutane-1α-methanol (**23**). MeOTrCl (481 mg, 1.56 mmol) was added under Ar in 100-mg portions every 2 h to a soln. of **17** (500 mg, 1.41 mmol) in pyridine (5 ml) in the presence of 4-(dimethylamino)pyridine (100 mg). The mixture was stirred at r.t. for 15 h. TLC (AcOEt/MeOH 8:2): R_f 0.95 (degradation product of MeOTrCl), 0.80 (bis(methoxytrityl)derivative), 0.40 (**22**), 0.35 (**23**), 0.10 (unreacted **17**). Two more additions of MeOTrCl (2 × 100 mg) did not show further reaction. H₂O (1 ml) was added, the soln. extracted 6 times with AcOEt (6 × 15 ml), dried (Na₂SO₄) and evaporated. The mixture was separated by FC (AcOEt/hexane 1:1 to AcOEt/MeOH 7:3): bis(methoxytrityl)derivative (100 mg, 8%), **22** (240 mg, 27%), **23** (80 mg, 9%), and **17** (50 mg, 10%).

Data of 3β-[6-(Benzoylamino)-9H-purin-9-yl]-1,1-bis[methoxytrityloxy)methyl]cyclobutane: ¹H-NMR (CDCl₃, 200 MHz): 9.55 (*s*, NH); 8.70 (*s*, H–C(2), Ade); 8.05 (*d*, 2 arom. H); 7.95 (*s*, H–C(8), Ade); 7.45 (*m*, 10 arom. H); 7.25 (*m*, 17 arom. H); 6.85 (*m*, 4 arom. H); 4.95 (*quint.*, H–C(3)); 3.75 (*s*, 2 MeO); 3.47 (*s*, β -CH₂O); 3.42 (*s*, α -CH₂O); 2.55 (*m*, CH₂(2), CH₂(4)).

Data of 22: M.p. 194°. UV (EtOH, 0.5 · 10⁻⁴ mol/l): 231 (22740), 281 (17060). IR (film): 3396, 2935, 1700, 1611, 1581, 1508, 1453. ¹H-NMR (CDCl₃, 360 MHz): 9.10 (*s*, NH); 8.79 (*s*, H–C(2), Ade); 8.12 (*s*, H–C(8), Ade); 8.05 (*d*, H_p, PhCO); 7.61 (*t*, H_p, PhCO); 7.53 (*t*, 2 arom. H); 7.49 (*d*, 4 arom. H); 7.39–7.25 (*m*, 8 arom. H); 6.90 (*d*, H_m, PhOMe); 4.98 (*quint.*, H–C(3)); 3.83 (*s*, MeO); 3.76 (*s*, CH₂OH); 3.32 (*s*, CH₂OTrOMe); 2.90 (*m*, ABX, H_β–C(2), H_β–C(4)); 2.52 (*m*, ABX, H_α–C(2), H_α–C(4)). ¹³C-NMR (CDCl₃, 50 MHz): 165.29 (CO); 159.16 (C(6), Ade); 152.61 (C(2), Ade); 152.55 (C_p, MeOC₆H₄); 150.80 (C(4), Ade); 144.71 (C(8), Ade); 142.65 (C_{ipso}, Ph of Tr); 135.70 (C_{ipso}, MeOC₆H₄); 134.16 (C_{ipso}, PhCO); 133.20 (C_p, PhCO); 130.95 (C_m, PhCO); 129.28 (C_o, PhCO); 128.88 (C_m, Ph of Tr); 128.44 (C_o, Ph of Tr, MeOC₆H₄); 127.58 (C_p, Ph of Tr); 123.50 (C(5), Ade); 113.71 (C_m, MeOC₆H₄); 67.77 (β -CH₂OH); 67.29 (α -CH₂O); 55.77 (C(3)); 45.36 (C(1)); 39.32 (C(2)); 33.68 (C(4)); irradi. on H–C(3) → pos. NOE on CH₂OTrOMe, H_β–C(2), H_β–C(4), H–C(8) of Ade, no effect on CH₂OH; irradi. on CH₂OTrOMe → pos. NOE on CH₂OH, H–C(3). FAB-MS: 626 (MH⁺), 522 ([M – PhCO]⁺), 352 ([M – TrOMe]⁺), 273 (MeOTr⁺), 240 ([bz⁶Ade + 2H]⁺).

Data of 23: M.p. 112°. UV (EtOH, 0.5 · 10⁻⁴ mol/l): 230 (24880), 281 (18040). ¹H-NMR (CDCl₃, 360 MHz): 9.16 (*s*, NH); 8.73 (*s*, H–C(2), Ade); 8.05 (*d*, H_o, PhCO); 7.98 (*s*, H–C(8), Ade); 7.47–7.15 (*m*, 13 arom. H); 6.87 (*d*, H_m, MeOC₆H₄); 5.10 (*quint.*, H–C(3)); 3.85 (*s*, CH₂OH); 3.72 (*s*, MeO); 3.33 (*s*, CH₂OTrOMe); 2.53 (*d*, CH₂(2), CH₂(4)). ¹³C-NMR (CDCl₃, 50 MHz): 165.30 (CO); 159.12 (C(6), Ade); 150.80 (C(2), Ade); 150.40 (C_p, MeOC₆H₄); 148.00 (C(4), Ade); 142.05 (C(8), Ade); 135.83 (C_{ipso}, MeOC₆H₄); 134.29 (C_{ipso}, PhCO); 133.13 (C_p, PhCO); 130.81 (C_m, PhCO); 129.19 (C_o, PhCO); 128.89 (C_m, Ph of Tr); 128.54 (C_o, Ph of Tr); 128.43 (C_o, MeOC₆H₄); 127.58 (C_p, Ph of Tr); 123.52 (C(5) of Ade); 113.70 (C_m, MeOC₆H₄); 68.82 (β -CH₂O); 67.19 (α -CH₂OH); 55.72 (C(3)); 45.77 (C(1)); 38.95 (C(2)); 34.53 (C(4)); irradi. on H–C(3) → pos. NOE on CH₂OH, CH₂(2),

CH₂(4), H–C(8) of Ade, no effect on CH₂OTrOMe; irradi. on CH₂OTrOMe → pos. NOE on CH₂OH, CH₂(2), CH₂(4), no effect on H–C(3); irradi. on CH₂OH → pos. NOE on CH₂OTrOMe, CH₂(2), CH₂(4), OH, H–C(3). FAB-MS: 626 (MH⁺), 522 ([M – PhCO]⁺), 352 ([M – TrOMe]⁺), 273 (MeOTr⁺), 240 ([bz⁶Ade + 2H]⁺).

22 and 23 from 19 and 20, resp. Conc. aq. NH₃ soln. (200 μl) was added to a soln. of **19** (200 mg, 0.274 mmol) in THF (2 ml) and H₂O (500 μl). The mixture was stirred at r.t. for 5 h (TLC control (AcOEt/MeOH 8:2)) and evaporated. The obtained oil was purified by FC (AcOEt to AcOEt/MeOH 7:3): 100 mg (59%) of **22**. Colourless crystals.

Analogously **20** (200 mg, 0.274 mmol) afforded **23** (100 mg, 59%). Colourless crystals.

3α-(Benzyloxy)cyclobutane-1,1-dicarboxylic Acid (26). Aq. KOH (4M, 77.4 ml, 309.6 mmol) was added to a soln. of **1** (23.71 g, 77.39 mmol) in H₂O (57 ml) and EtOH (171 ml). The mixture was stirred at reflux for 5 h and evaporated. The residue (ca. 21 g) was brought to pH 3 with 2M aq. HCl (ca. 160 ml). AcOEt (150 ml) was added, the aq. phase extracted 4 times with AcOEt (4 × 150 ml), the org. phase dried (Na₂SO₄) and evaporated. The oily residue was evaporated twice with toluene (2 × 100 ml), and it crystallized (**26**). Yellow crystals. M.p. 160–162°. IR (film): 3470, 2926, 2856, 1728, 1497, 1453. ¹H-NMR (DMSO, 200 MHz): 7.32 (s, 5 arom. H); 4.98 (s, COOH); 4.45 (s, PhCH₂); 4.15 (quint., H–C(3)); 2.75 (m, ABX, H_α–C(2), H_α–C(4)); 2.45 (m, ABX, H_β–C(2), H_β–C(4)). ¹³C-NMR (DMSO, 50 MHz): 176.10 (CO); 175.60 (CO); 139.78 (C_{ipso}); 129.72 (C_o); 129.66 (C_m); 129.38 (C_p); 71.49 (C(3)); 69.33 (PhCH₂); 47.25 (C(1)); 39.08 (C(2), C(4)).

3-(Benzyloxy)cyclobutane-1-carboxylic Acid (cis/trans-27). In a bulb-to-bulb distillation apparatus at 215°/0.4 Torr, **26** was decarboxylated to *cis/trans*-**27** 1:1 (14.69 g, 88.6%). The isomers could not be separated by FC. TLC (CHCl₃/MeOH/H₂O 65:30:5): one spot. IR (film): 3200, 2926, 2854, 2350, 1732, 1603, 1496, 1454. ¹H-NMR (CDCl₃, 200 MHz): 11.40 (s, COOH); 7.35 (s, 5 arom. H); 4.45 (s, PhCH₂); 4.35 (quint., H–C(3)); 3.98 (quint., H–C(3)); 3.10 (m, H–C(1)); 2.68 (m, H–C(1)); 2.55 (m, ABX, H_α–C(2), H_α–C(4)); 2.35 (m, ABX, H_β–C(2), H_β–C(4)). ¹³C-NMR (CDCl₃, 50 MHz): 182.85 (CO); 181.13 (CO); 138.51 (C_{ipso}); 138.45 (C_{ipso}); 129.00 (C_o); 128.45 (C_m); 128.33 (C_p); 71.78 (C(3)); 70.70 (PhCH₂); 70.52 (PhCH₂); 68.78 (C(3)); 34.24 (C(2)); 34.13 (C(2)); 33.60 (C(4)); 33.46 (C(4)); 31.95 (C(1)); 29.56 (C(1)).

3-(Benzyloxy)cyclobutane-1-carbonyl Chloride (cis/trans-28). Neat oxalyl chloride (42.3 ml, 485 mmol) was added slowly over 1 h at 0° to a soln. of *cis/trans*-**27** (28.61 g, 133.5 mmol) in CCl₄ (230 ml). The reaction started immediately with evolution of CO₂. The mixture was stirred 1 h at 0° and 12 h at r.t. This soln. was evaporated: *cis/trans*-**28** 1:1 (31.13 g, 99.5%). ¹H-NMR (CDCl₃, 200 MHz): 7.35 (s, 5 arom. H); 4.48 (s, PhCH₂); 4.42 (s, PhCH₂); 4.22 (quint., H–C(3)); 3.98 (quint., H–C(3)); 3.55 (m, H–C(1)); 3.08 (m, H–C(1)); 2.68 (m, ABX, H_α–C(2), H_α–C(4)); 2.35 (m, ABX, H_β–C(2), H_β–C(4)). ¹³C-NMR (CDCl₃, 50 MHz): 157.00 (CO); 156.22 (CO); 138.17 (C_{ipso}); 138.14 (C_{ipso}); 129.09 (C_o); 128.79 (C_o); 128.61 (C_m); 128.52 (C_m); 128.12 (C_p); 70.93 (C(3)); 70.70 (PhCH₂); 67.72 (C(3)); 44.37 (C(1)); 41.86 (C(1)); 35.14 (C(2)); 34.08 (C(4)).

Ethyl 3-(Benzyloxy)cyclobutane-1-carboxylate (cis- and trans-29). *cis/trans*-**28** (1:1; 31.13 g, 132.8 mmol) was twice evaporated in the presence of CCl₄ (50 ml) and toluene (50 ml). EtOH (100 ml) was slowly added at 0° under Ar to the soln. of *cis/trans*-**28** in CCl₄ (50 ml). The mixture was stirred for 5 h at r.t. (TLC control ((*t*-Bu)OMe/hexane 2:8)) and evaporated. The isomers were separated by FC ((*t*-Bu)OMe/hexane 2:8 to 8:2). The fraction containing both isomers was rechromatographed with the same solvent: *trans*-**29** (R_f 0.28; 12.02 g, 38.4% rel. to *cis/trans*-**27**) and *cis*-**29** (R_f 0.22; 11.94 g, 38.2% rel. to *cis/trans*-**27**).

Data of trans-29 (1β,3α): IR (film): 2986, 2945, 1731, 1604, 1496, 1374, 1354. ¹H-NMR (CDCl₃, 400 MHz): 7.35 (s, Ph); 4.48 (s, PhCH₂); 4.32 (quint., H–C(3)); 4.18 (q, CH₃CH₂); 3.08 (tt, H–C(1)); 2.55 (m, H_β–C(2), H_β–C(4)); 2.35 (m, H_α–C(2), H_α–C(4)); 1.35 (t, CH₃CH₂); irradi. on H_β–C(2) → pos. NOE on H–C(3), no effect on H–C(1) and Et; irradi. on H_α–C(2) → pos. NOE on H–C(1), Et, no effect on H–C(3). ¹³C-NMR (CDCl₃, 100 MHz): 176.8 (CO); 138.0 (C_{ipso}); 128.2 (C_o); 127.6 (C_m); 127.5 (C_p); 71.5 (C(3)); 70.4 (PhCH₂); 60.2 (CH₃CH₂); 33.4 (C(2), C(4)); 32.0 (C(1)); 14.1 (CH₃CH₂). Anal. calc. for C₁₄H₁₈O₃ (234.296) + 0.06 H₂O: C 71.44, H 7.76, O 20.80; found: C 71.26, H 7.78, O 20.63.

Data of cis-29 (1α,3α): IR (film): 2986, 2943, 2865, 1731, 1604, 1496, 1454. ¹H-NMR (CDCl₃, 400 MHz): 7.35 (s, Ph); 4.38 (s, PhCH₂); 4.08 (q, CH₃CH₂); 3.86 (quint., H–C(3)); 2.60 (m, H–C(1)); 2.40 (m, H_β–C(2), H_β–C(4)); 2.20 (m, H_α–C(2), H_α–C(4)); 1.32 (t, CH₃CH₂); irradi. on H_β–C(2) → pos. NOE on H–C(1), H–C(3); irradi. on H_α–C(2) → no effect on H–C(1), H–C(3). ¹³C-NMR (CDCl₃, 100 MHz): 174.38 (CO); 138.02 (C_{ipso}); 128.32 (C_o); 127.67 (C_m); 127.60 (C_p); 69.82 (C(3)); 68.28 (PhCH₂); 60.29 (CH₃CH₂); 33.69 (C(2), C(4)); 29.04 (C(1)); 13.88 (CH₃CH₂). Anal. calc. for C₁₄H₁₈O₃ (234.296) + 0.11 H₂O: C 71.17, H 7.77, O 21.06; found: C 71.06, H 7.65, O 20.93.

cis- and trans-29 from 1. A soln. of **1** (11.56 g, 37.76 mmol), H₂O (1.30 ml, 75.52 mmol), and NaCl (2.21 g, 37.76 mmol) in DMSO (19 ml) was heated at 210° for 48 h. TLC ((*t*-Bu)OMe/hexane 2:8): R_f 0.28 (*trans*-**29**), 0.22 (*cis*-**29**), 0.18 (**1**). Brine (150 ml) was added and the soln. extracted 7 times with Et₂O (7 × 100 ml), which was dried

(MgSO₄) and evaporated. The mixture was separated by FC ((*t*-Bu)OMe/hexane 2:8 to 8:2). The fraction containing both isomers was chromatographed a second time with the same solvent: *trans*-**29** (3.34 g, 37.9%) and *cis*-**29** (4.43 g, 50.1%).

3-(*Benzyloxy*)cyclobutane-1-methanol (*cis/trans*-**30**). LiAlH₄ (1.39 g, 36.36 mmol) was stirred under Ar in DME (50 ml), *cis/trans*-**27** 1:1 (5.19 g, 24.21 mmol) in DME (10 ml) added dropwise without cooling, and the suspension mechanically stirred at 85° for 60 h (TLC control ((*t*-Bu)OMe/hexane 9:1): only 1 spot). After cooling, H₂O (100 ml) was slowly added until the suspension turned from gray to white. This suspension was evaporated, THF/AcOEt 9:1 (100 ml) added, and the suspension filtered over *Hyflo*. The precipitate was washed 3 times with the same solvent mixture (3 × 50 ml) and the obtained soln. evaporated. The isomer mixture was purified by FC ((*t*-Bu)OMe/hexane 1:1 to (*t*-Bu)OMe): *cis/trans*-**30** 1:1 (4.60 g, 98.8%). ¹H-NMR (CDCl₃, 200 MHz): 7.36 (*s*, Ph); 4.32 (*s*, PhCH₂); 4.30 (*s*, PhCH₂); 4.15 (*quint.*, H-C(3)); 3.85 (*quint.*, H-C(3)); 3.60 (*d*, CH₂OH); 2.33 (*m*, H_β-C(2), H_β-C(4)); 2.08 (*m*, H_α-C(2), H_α-C(4)); 1.90 (*m*, H-C(1)). ¹³C-NMR (CDCl₃, 50 MHz): 138.79 (C_{ipso}); 138.74 (C_{ipso}); 128.93 (C_o); 128.46 (C_m); 128.41 (C_p); 128.18 (C_p); 72.22 (C(3)); 69.85 (C(3)); 70.37 (PhCH₂); 67.36 (CH₂OH); 66.85 (CH₂OH); 32.25 (C(2)); 32.00 (C(4)); 30.01 (C(1)); 28.52 (C(1)). Anal. calc. for C₁₂H₁₆O₂ (192.258): C 74.97, H 8.39, O 16.64; found: C 75.00, H 8.40, O 16.69.

3α-(*Benzyloxy*)cyclobutane-1α-methanol (*cis*-**30**). LiAlH₄ (607 mg, 16.00 mmol) was stirred under Ar in DME (50 ml), *cis*-**29** (5.13 g, 21.90 mmol) added neat dropwise without cooling, and the suspension mechanically stirred at 85° for 60 h (TLC control ((*t*-Bu)OMe/hexane 9:1)). After cooling, H₂O (100 ml) was slowly added until the suspension turned from gray to white. This suspension was evaporated, THF/AcOEt 9:1 (100 ml) added, and the obtained suspension filtered over *Hyflo*. The precipitate was washed 3 times with the same solvent mixture (3 × 50 ml), the soln. evaporated, and the residue purified by FC ((*t*-Bu)OMe/hexane 1:1 to (*t*-Bu)OMe): *cis*-**30** (3.87 g, 91.9%). IR (film): 3398, 2974, 2991, 2933, 2861, 1951, 1878, 1812. ¹H-NMR (CDCl₃, 200 MHz): 7.33 (*s*, Ph); 4.30 (*s*, PhCH₂); 3.86 (*quint.*, H-C(3)); 3.60 (*d*, CH₂OH); 2.33 (*m*, H_β-C(2), H_β-C(4)); 2.08 (*m*, H_α-C(2), H_α-C(4)); 1.90 (*m*, H-C(1)). ¹³C-NMR (CDCl₃, 50 MHz): 138.72 (C_{ipso}); 128.93 (C_o); 128.42 (C_m); 128.14 (C_p); 69.85 (C(3)); 70.37 (PhCH₂); 66.85 (CH₂OH); 32.25 (C(2)); 32.00 (C(4)); 28.52 (C(1)). Anal. calc. for C₁₂H₁₆O₂ (192.258): C 74.97, H 8.39, O 16.64; found: C 75.00, H 8.40, O 16.69.

3α-(*Benzyloxy*)cyclobutane-1β-methanol (*trans*-**30**). As described for *cis*-**30**, *trans*-**29** (5.0 g, 21.34 mmol) afforded *trans*-**30** (3.70 g, 90.2%). IR (film): 3415, 3031, 2970, 2934, 2863, 1954, 1877, 1812. ¹H-NMR (CDCl₃, 200 MHz): 7.35 (*s*, Ph); 4.37 (*s*, PhCH₂); 4.12 (*quint.*, *J* = 6.5, H-C(3)); 3.59 (*d*, *J* = 7.0, CH₂OH); 2.35 (*m*, H-C(1)); 2.11 (*m*, CH₂(2), CH₂(4)). ¹³C-NMR (CDCl₃, 50 MHz): 138.78 (C_{ipso}); 128.90 (C_o); 128.36 (C_m); 128.12 (C_p); 72.15 (C(3)); 70.34 (PhCH₂); 67.05 (CH₂OH); 31.99 (C(2), C(4)); 29.96 (C(1)). Anal. calc. for C₁₂H₁₆O₂ (192.258): C 74.97, H 8.39, O 16.64; found: C 75.00, H 8.40, O 16.69.

1α-(*Benzyloxy*)-3α-{[(*tert*-butyl)diphenylsilyloxy]methyl}cyclobutane (*cis*-**31**). (*t*-Bu)Ph₂SiCl (16.39 ml, 63.00 mmol) was added neat at 0° under Ar to a soln. of *cis*-**30** (10.09 g, 52.49 mmol) and imidazole (7.15 g, 105.0 mmol) in DMF (250 ml). The mixture was stirred at r.t. for 20 h. TLC ((*t*-Bu)OMe/hexane 5:95): 2 spots (*cis*-**31** and (*t*-Bu)Ph₂SiOH). H₂O (250 ml) was added and the soln. extracted 3 times with AcOEt (3 × 300 ml). The combined org. phases were washed with H₂O (150 ml) and brine (150 ml), dried (MgSO₄), and evaporated. FC ((*t*-Bu)OMe/hexane 1:99 to 5:95) afforded *cis*-**31** (18.50 g, 81.2%). Colourless oil. UV (MeOH, 0.5 · 10⁻⁴ mol/l): 259 (840), 265 (920). IR (film): 3070, 3049, 2931, 2892, 2857, 1959, 1890, 1824, 1722, 1589, 1568. ¹H-NMR (CDCl₃, 200 MHz): 7.68 (*m*, 4 arom. H); 7.38 (*m*, 11 arom. H); 4.42 (*s*, PhCH₂); 3.95 (*quint.*, *J* = 6.0, H-C(1)); 3.67 (*d*, *J* = 6.0, CH₂OSi); 2.33 (*q*, H_α-C(2), H_α-C(4)); 2.10 (*m*, H-C(3)); 1.87 (*t*, H_β-C(2), H_β-C(4)); 1.10 (*s*, *t*-Bu); ¹³C-NMR (CDCl₃, 50 MHz): 139.04 (C_{ipso}, PhCH₂); 136.18 (C_o, PhSi); 134.54 (C_{ipso}, PhSi); 130.10 (C_p, PhSi); 128.89 (C_o, PhCH₂); 128.40 (C_m, PhCH₂); 128.17 (C_m, PhSi); 128.07 (C_p, PhCH₂); 70.19 (PhCH₂); 69.87 (C(1)); 67.94 (CH₂OSi); 33.16 (C(2), C(4)); 28.53 (C(3)); 27.21 (Me₃C); 19.64 (Me₃C). Anal. calc. for C₂₈H₃₄O₂Si (430.665): C 78.09, H 7.96, Si 6.52; found: C 78.02, H 8.18, Si 6.67.

1α-(*Benzyloxy*)-3β-{[(*tert*-butyl)diphenylsilyloxy]methyl}cyclobutane (*trans*-**31**). As described for *cis*-**31**, with (*t*-Bu)Ph₂SiCl (3.24 ml, 12.48 mmol), *trans*-**30** (2 g, 10.40 mmol), imidazole (1.42 g, 20.80 mmol), and DMF (80 ml; 64 h at r.t.), AcOEt (200 ml) and H₂O (50 ml) were added, and the aq. phase was extracted twice with AcOEt (2 × 200 ml). The combined org. phase was washed twice with brine (2 × 50 ml), dried (MgSO₄), and evaporated. FC ((*t*-Bu)OMe/hexane 1:99 to 5:95) afforded *trans*-**31** (4.40 g, 98.2%). Colourless oil. UV (MeOH, 0.5 · 10⁻⁴ mol/l): 253 (800), 259 (960), 264 (760), 270 (640). IR (film): 3071, 3050, 3032, 2932, 2892, 2857, 1958, 1889, 1821, 1721, 1589. ¹H-NMR (CDCl₃, 200 MHz): 7.68 (*m*, 4 arom. H); 7.50–7.30 (*m*, 11 arom. H); 4.38 (*s*, PhCH₂); 4.17 (*quint.*, *J* = 6.0, H-C(1)); 3.67 (*d*, *J* = 6.0, CH₂OSi); 2.42 (*m*, H-C(3)); 2.15 (*m*, CH₂(2), CH₂(4)); 1.05 (*s*, *t*-Bu). ¹³C-NMR (CDCl₃, 50 MHz): 138.50 (C_{ipso}, PhCH₂); 136.18 (C_o, PhSi); 133.04 (C_{ipso}, PhSi); 130.13 (C_p, PhSi); 128.90 (C_o, PhCH₂); 128.39 (C_m, PhCH₂); 128.17 (C_m, PhSi); 128.07 (C_p, PhCH₂); 72.08 (C(1)); 70.30 (PhCH₂);

67.43 (CH₂OSi); 32.11 (C(2), C(4)); 30.06 (C(3)); 27.18 (Me₃C); 19.58 (Me₃C). Anal. calc. for C₂₈H₃₄O₂Si (430.665): C 78.09, H 7.96, Si 6.52; found: C 77.80, H 7.95, Si 6.48.

3 α -{[(tert-Butyl)diphenylsilyloxy]methyl}cyclobutane-1 α -ol (*cis*-**32**). Degussa Pd (500 mg) in DME (250 ml) was placed under H₂, *cis*-**31** (1.0 g, 23.27 mmol) added neat, and the mixture shaken vigorously at r.t. at 1 atm H₂ until 1 equiv. of H₂ (209 ml) was absorbed (ca. 8 h). After filtration of the catalyst over *Hylflo*, the soln. was evaporated: *cis*-**32** (7.80 g, 99.2%). Colourless sirup. TLC ((*t*-Bu)OMe/hexane 2:8): R_f 0.11. UV (MeOH, 0.5 · 10⁻⁴ mol/l): 259 (600), 264 (640), 270 (440). IR (film): 3342, 3135, 3071, 3050, 2929, 2893, 2856, 1959, 1888, 1824, 1776, 1741. ¹H-NMR (CDCl₃, 200 MHz): 7.70 (*dd*, 4 arom. H); 7.40 (*s*, C_p, PhSi); 7.30 (*dd*, 4 arom. H); 4.27 (*quint.*, *J* = 7.0, H-C(1)); 3.67 (*d*, *J* = 7.0, CH₂OSi); 2.30 (*m*, *ABX*, H_z-C(2), H_z-C(4)); 2.20 (*m*, H-C(3)); 1.95 (*m*, *ABX*, H_β-C(2), H_β-C(4)); 1.10 (*s*, *t*-Bu). Anal. calc. for C₂₁H₂₈O₂Si (340.54): C 74.07, H 8.29, Si 8.25; found: C 74.29, H 8.12, Si 8.33.

3 β -{[(tert-butyl)diphenylsilyloxy]methyl}cyclobutane-1 α -ol (*trans*-**32**). As described for *cis*-**32**, *trans*-**31** (1.0 g, 23.27 mmol) afforded *trans*-**32** (7.95 g, 99.7%). Colourless sirup. TLC ((*t*-Bu)OMe/hexane 2:8): R_f 0.11. UV (MeOH, 0.5 · 10⁻⁴ mol/l): 259 (760), 264 (800), 270 (560). IR (film): 3070, 3050, 2960, 2920, 2850, 1960, 1890, 1820, 1770, 1740. ¹H-NMR (CDCl₃, 200 MHz): 7.70 (*dd*, 4 arom. H); 7.45 (*s*, C_p, PhSi); 7.40 (*dd*, 4 arom. H); 4.47 (*quint.*, *J* = 7.0, H-C(1)); 3.67 (*d*, *J* = 7.0, CH₂OSi); 2.44 (*m*, H-C(3)); 2.25 (*m*, *ABX*, H_z-C(2), H_z-C(4)); 2.05 (*m*, *ABX*, H_β-C(2), H_β-C(4)); 1.10 (*s*, *t*-Bu). ¹³C-NMR (CDCl₃, 50 MHz): 136.16 (C_o, PhSi); 134.32 (C_{ipso}, PhSi); 130.18 (C_p, PhSi); 128.16 (C_m, PhSi); 67.31 (CH₂OSi); 66.72 (C(1)); 35.26 (C(2), C(4)); 29.36 (C(3)); 27.15 (Me₃C); 19.58 (Me₃C). Anal. calc. for C₂₁H₂₈O₂Si (340.54): C 74.07, H 8.29, Si 8.25; found: C 74.06, H 8.21, Si 7.99.

3 α -{[(tert-Butyl)diphenylsilyloxy]methyl}cyclobut-1 α -yl 4-Bromobenzenesulfonate (*cis*-**33**). At r.t., 4-bromobenzenesulfonyl chloride (3.02 g, 11.82 mmol) was added neat under Ar to a soln. of *cis*-**32** (3.35 g, 9.85 mmol) and Et₃N (9.60 ml, 68.96 mmol) in CH₂Cl₂ (50 ml). The mixture was stirred at r.t. for 15 h. TLC ((*t*-Bu)OMe/hexane 2:8): R_f 0.40; no *cis*-**32**. Brine (50 ml) was added and the mixture extracted 3 times with AcOEt (3 × 200 ml). The combined org. fractions were washed with brine (50 ml), dried (Na₂SO₄), and evaporated. FC ((*t*-Bu)OMe/hexane 5:95 to 1:9) afforded *cis*-**33** (4.20 g, 76.2%). M.p. 83.5–84.5°, after crystallization from Et₂O. UV (MeOH, 0.5 · 10⁻⁴ mol/l): 221 (23400), 256 (1200), 263 (1300). IR (film): 3071, 2931, 2893, 2857, 1576, 1471. ¹H-NMR (CDCl₃, 200 MHz): 7.80–7.60 (*m*, 8 arom. H); 7.45–7.32 (*m*, 6 arom. H); 4.70 (*quint.*, *J* = 7.0, H-C(1)); 3.52 (*d*, *J* = 7.0, CH₂OSi); 2.30–1.95 (*m*, CH₂(2), H-C(3), CH₂(4)); 1.05 (*s*, *t*-Bu). ¹³C-NMR (CDCl₃, 50 MHz): 136.50 (C_{ipso}, Brs); 136.10 (C_o, PhSi); 134.06 (C_{ipso}, PhSi); 133.08 (C_m, Brs); 130.24 (C_p, PhSi); 129.81 (C_o, Brs); 129.20 (C_p, Brs); 128.22 (C_m, PhSi); 72.39 (C(1)); 65.85 (CH₂OSi); 32.85 (C(2), C(4)); 28.81 (C(3)); 27.13 (Me₃C); 19.59 (Me₃C). Anal. calc. for C₂₇H₃₁BrO₄SSi (559.598): C 57.95, H 5.58, Br 14.28, S 5.73, Si 5.02; found: C 57.73, H 5.63, Br 14.11, S 5.67, Si 4.85.

3 β -{[(tert-Butyl)diphenylsilyloxy]methyl}cyclobut-1 α -yl 4-Bromobenzenesulfate (*trans*-**33**). At r.t., 4-bromobenzenesulfonyl chloride (2.08 g, 8.14 mmol) was added neat under Ar to a soln. of *trans*-**32** (2.31 g, 6.78 mmol) and Et₃N (6.61 ml, 47.48 mmol) in CH₂Cl₂ (50 ml). The mixture was stirred at r.t. for 36 h. TLC ((*t*-Bu)OMe/hexane 2:8): R_f 0.40. Another two portions of 4-bromobenzenesulfonyl chloride (2 × 200 mg, 2 × 0.81 mmol) were added. TLC: no *trans*-**32** left. Brine (30 ml) was added and the mixture extracted 3 times with AcOEt (3 × 200 ml). The combined org. fractions were washed with brine (50 ml), dried (Na₂SO₄), and evaporated: *trans*-**33** (3.04 g, 80.1%). M.p. 80–81°, after crystallization from Et₂O. UV (MeOH, 0.5 · 10⁻⁴ mol/l): 220 (23060), 233 (16500), 259 (1300), 265 (1400). IR (film): 3070, 2940, 2880, 2860, 1580, 1470. ¹H-NMR (CDCl₃, 200 MHz): 7.80–7.60 (*m*, 8 arom. H); 7.45–7.32 (*m*, 6 arom. H); 4.98 (*quint.*, *J* = 7.0, H-C(1)); 3.58 (*d*, *J* = 7.0, CH₂OSi); 2.30 (*m*, CH₂(2), H-C(3), CH₂(4)); 1.05 (*s*, *t*-Bu). ¹³C-NMR (CDCl₃, 50 MHz): 136.51 (C_{ipso}, Brs); 136.13 (C_o, PhSi); 134.02 (C_{ipso}, PhSi); 133.08 (C_m, Brs); 131.12 (C_o, Brs); 130.51 (C_p, PhSi); 129.20 (C_p, Brs); 128.20 (C_m, PhSi); 75.46 (C(1)); 65.92 (CH₂OSi); 32.90 (C(2), C(4)); 30.15 (C(3)); 27.16 (Me₃C); 19.56 (Me₃C). Anal. calc. for C₂₇H₃₁BrO₄SSi (559.598): C 57.95, H 5.58, Br 14.28, S 5.73, Si 5.02; found: C 57.96, H 5.69, Br 14.00, S 5.61, Si 4.85.

9- and 7-{3 β -{[(tert-Butyl)diphenylsilyloxy]methyl}cyclobut-1 β -yl}-9H-purin-6-amine (*cis*-**34** and *cis*-**35**, resp.) A mixture of *trans*-**33** (2.78 g, 4.96 mmol), adenine (19.84 g, 26.82 mmol), and DBU (3.02 ml, 2.96 mmol) in DMSO (28 ml) was stirred under Ar at 80° for 15 h. TLC ((*t*-Bu)OMe/MeOH 8:2; detection by 1) Cl₂, 2) KI): R_f 0.95 (*trans*-**33**), 0.88 (*cis*-**34**), and 0.57 (*cis*-**35**). Brine (200 ml) and H₂O (800 ml) were added, and the soln. was extracted 7 times with AcOEt (4 × 75 ml). The combined org. phase was washed with brine (50 ml), dried (Na₂SO₄), and purified by FC ((*t*-Bu)OMe/MeOH 98:2 to 1:1): *trans*-**33** (735 mg, 26.0%), *cis*-**34** (1.06 g, 46.8%), and *cis*-**35** (190 mg, 8.4%).

Data of *cis*-**34** (1 β ,3 β): M.p. 181–182°. UV (H₂O, 0.5 · 10⁻⁴ mol/l): 204 (34780), 258 (12920). IR (KBr): 3324, 3160, 2929, 2855, 1662, 1601, 1571. ¹H-NMR (CDCl₃, 200 MHz): 8.35 (*s*, H-C(2), Ade); 7.88 (*s*, H-C(8), Ade); 7.67 (*m*, 4 arom. H); 7.37 (*m*, 6 arom. H); 5.98 (*s*, NH₂); 4.92 (*quint.*, H-C(1)); 3.22 (*s*, CH₂OSi); 2.65–2.35 (*m*,

CH₂(2), H–C(3), CH₂(4)); 1.10 (s, *t*-Bu). ¹³C-NMR (CDCl₃, 50 MHz): 156.11 (C(6), Ade); 153.46 (C(2), Ade); 152.05 (C(4), Ade); 139.16 (C(8), Ade); 136.16 (C_o, PhSi); 134.07 (C_{ipso}, PhSi); 130.21 (C_p, PhSi); 128.27 (C_m, PhSi); 118.43 (C(5), Ade); 65.85 (CH₂OSi); 45.13 (C(1)); 32.61 (C(2), C(4)); 30.82 (C(3)); 27.21 (Me₃C); 19.62 (Me₃C). Anal. calc. for C₂₆H₃₁N₅O₂Si (457.65): C 68.24, H 6.83, N 15.30, Si 6.14; found: C 68.09, H 6.84, N 15.43, Si 6.18.

Data of cis-35 (1β,3β): UV (H₂O, 0.5 · 10⁻⁴ mol/l): 214 (29800), 277 (16280). IR (KBr): 3071, 2931, 2857, 1922, 1895, 1870, 1844, 1800, 1773, 1751, 1654, 1619, 1578. ¹H-NMR (CDCl₃, 200 MHz): 8.10 (s, H–C(2), Ade); 8.02 (s, H–C(8), Ade); 7.65 (m, 4 arom. H); 7.37 (m, 6 arom. H); 5.12 (quint., H–C(1)); 3.71 (s, CH₂OSi); 2.70 (m, H_β–C(2), H_β–C(4)); 2.45 (m, H_α–C(2), H–C(3), H_α–C(4)); 1.05 (s, *t*-Bu).

9- and 7-{3α-{[(tert-butyl)diphenylsilyloxy]methyl}cyclobut-1β-yl}-9H-purin-6-amine (*trans-34* and *trans-35*, resp.). As described for *cis-34* and *-35*, with *cis-33* (3.81 g, 6.81 mmol), adenine (3.68 g, 27.22 mmol), DBU (4.05 ml, 4.14 mmol), and DMSO (38 ml), 35 h at 80°: *cis-33* (R_f 0.95; 1.29 g, 33.9%), *trans-34* (R_f 0.88; 1.46 g, 46.9%), *trans-35* (R_f 0.57; 401 mg, 12.9%).

Data of trans-34 (1β,3α): M.p. 129.5–130.5°. UV (H₂O, 0.5 · 10⁻⁴ mol/l): 205 (40000), 258 (13940). IR (KBr): 3138, 2929, 2857, 1660, 1651, 1645, 1650, 1600, 1574. ¹H-NMR (CDCl₃, 200 MHz): 8.35 (s, H–C(2), Ade); 7.90 (s, H–C(8), Ade); 7.67 (m, 4 arom. H); 7.37 (m, 6 arom. H); 6.78 (s, NH₂); 5.10 (quint., H–C(1)); 3.77 (s, CH₂OSi); 2.60–2.45 (m, CH₂(2), H–C(3), CH₂(4)); 1.10 (s, *t*-Bu). ¹³C-NMR (CDCl₃, 50 MHz): 156.98 (C(6), Ade); 153.34 (C(2), Ade); 150.53 (C(4), Ade); 139.28 (C(8), Ade); 136.16 (C_o, PhSi); 134.14 (C_{ipso}, PhSi); 130.30 (C_p, PhSi); 128.29 (C_m, PhSi); 120.43 (C(5), Ade); 66.54 (CH₂OSi); 47.98 (C(1)); 31.82 (C(2), C(4)); 31.48 (C(3)); 27.23 (Me₃C); 19.60 (Me₃C). Anal. calc. for C₂₆H₃₁N₅O₂Si (457.65): C 68.24, H 6.82, N 15.30, Si 6.14; found: C 68.45, H 7.07, N 14.95, Si 5.93.

Data of trans-35 (1β,3α): UV (H₂O, 0.5 · 10⁻⁴ mol/l): 214 (29800), 265 (9500). IR (KBr): 3322, 2933, 2894, 2857, 2244, 2218, 1658, 1618, 1549. ¹H-NMR (CDCl₃, 200 MHz): 8.10 (s, H–C(2), Ade); 8.02 (s, H–C(8), Ade); 7.65 (m, 4 arom. H); 7.37 (m, 6 arom. H); 5.22 (quint., H–C(1)); 3.81 (s, CH₂OSi); 2.87 (m, H_α–C(2), H_α–C(4)); 2.60 (m, H_β–C(2), H–C(3), H_β–C(4)); 1.05 (s, *t*-Bu).

3β-(6-Amino-9H-purin-9-yl)cyclobutane-1β-methanol (*cis-36*). A soln. of *cis-34* (500 mg, 1.09 mmol) and aq. HF-urea (3 ml, 9 mmol) in THF (10 ml) was stirred for 15 h at r.t. TLC (AcOEt/MeOH 2:8); R_f 0.12. The mixture was neutralized with NaHCO₃ and evaporated. Purification by FC (AcOEt/MeOH 9:1) afforded *cis-36*/NaF. FC (hydrophobic silica gel) with H₂O gave NaF and then with MeOH *cis-36* (60 mg). Glassy solid. UV (EtOH, 0.5 · 10⁻⁴ mol/l): 206 (16580), 262 (11160). ¹H-NMR (CD₃OD, 200 MHz): 8.22 (s, H–C(2), Ade); 8.18 (s, H–C(8), Ade); 4.95 (quint., H–C(3)); 3.62 (s, CH₂OH); 2.55 (m, H_β–C(2), H_β–C(4)); 2.40 (m, H_α–C(2), H–C(1), H_α–C(4)). ¹³C-NMR (CD₃OD, 50 MHz): 157.20 (C(6), Ade); 153.92 (C(2), Ade); 149.10 (C(4), Ade); 141.22 (C(8), Ade); 111.60 (C(5), Ade); 66.05 (CH₂OH); 46.73 (C(3)); 35.57 (C(2), C(4)); 31.84 (C(1)). FAB-MS: 242 ([M + Na]⁺), 220 ([M + H]⁺), 188 ([M – MeOH]⁺), 136 ([Ade + H]⁺).

3β-(6-Amino-9H-purin-9-yl)cyclobutane-1α-methanol (*trans-36*). As described for *cis-36*, *trans-34* (500 mg, 1.09 mmol) afforded *trans-36* (60 mg). Glassy solid. UV (EtOH, 0.5 · 10⁻⁴ mol/l): 206 (16250), 262 (11056). ¹H-NMR (CD₃OD, 200 MHz): 8.25 (s, H–C(2), Ade); 8.16 (s, H–C(8), Ade); 5.15 (quint., H–C(3)); 3.62 (s, CH₂OH); 2.60 (m, H_β–C(2), H_β–C(4)); 2.45 (m, H_α–C(2), H–C(1), H_α–C(4)). ¹³C-NMR (CD₃OD, 50 MHz): 157.3 (C(6), Ade); 153.90 (C(2), Ade); 149.20 (C(4), Ade); 141.44 (C(8), Ade); 112.40 (C(5), Ade); 66.21 (CH₂OH); 48.5 (C(3)); 35.75 (C(2), C(4)); 31.80 (C(1)). FAB-MS: 242 ([M + Na]⁺), 220 ([M + H]⁺), 188 ([M – MeOH]⁺), 136 ([Ade + H]⁺).

Oligonucleotides. 1. Phosphorylation. A typical experiment was performed as follows: Cyclobutanemethanol **22** (0.25 mmol, 156.4 mg) was co-evaporated with pyridine to remove traces of H₂O and phosphorylated with 2-chlorophenyl bis(benzotriazol-1-yl) phosphate (1.00 ml, 0.25M) in THF at r.t. for 30 min (activated nucleotide) [12]. This intermediate, which can be kept in soln. for several h, was further processed *in situ*.

2. Assembling of the Nucleotides on a Solid Phase. The 3'-[5'-(monomethoxytrityl)-N⁶-benzoyladenosyl]-succinyl-amidomethyl-polystyrene (1% DVB cross-linked; 11.5 mg, functionalization, 2.24 μmol) [13] was subjected to the following washing (3 ml/min) and reaction procedures: CH₂Cl₂/i-PrOH 85:15 (3 min); MeOTr cleavage: 1M ZnBr₂, 0.02M 1,2,4-triazole in CH₂Cl₂/i-PrOH 85:15 (1.5–2 min) [14]; CH₂Cl₂/i-PrOH 85:15 (3 min); 0.5M (Et₃NH)OAc in DMF (3 min); MeCN (< 0.005% H₂O; 3 min); N₂ flow, 50° (10 min); coupling: 64 μl of activated carba-nucleotide (16 μmol) and 6.4 μl of *N*-methylimidazole (80 μM), 12–15 min, 50°, no flow, MeCN (4 min). This solid-phase process was repeated seven times. Yield per coupling step: 80–87%, giving 0.6 μmol or 46 OD units calculated yield.

The oligomer was cleaved from the carrier and the protecting groups were removed by sequentially reacting the resin with 1M tetramethylguanidinium 2-nitrobenzaldehyde oximate in 200 μl of 95% pyridine during 7 h at 60° and with 0.8 ml 33% NH₃/H₂O for 24 h at 60°. The mixture was extracted 3 times with Et₂O (2 ml each), the aq.

phase applied to a *Biogel P4* (50–100 mesh) column (3×26 cm), and the product eluted with H_2O . Fractions were checked for correct size of the oligomer and homogeneity by polyacrylamide gel electrophoresis with 12 or 20% acrylamide on 1-mm layers in 5M urea and $E = 37$ V/cm or by capillary electrophoresis. No further purification was usually needed, but due to low coupling yields with **22**, additional fractionation was performed on a *Mono Q HR5/5* anion exchanger. The applied gradient was: $A = 10$ mM NaOH, 0.05M NaCl; $B = 10$ mM NaOH, 2M NaCl; 0% $B \rightarrow 40\%$ B linear within 45 min. Fractions homogeneous in electrophoresis were checked with electrospray-ionization or laser-ionization desorption MS for the presence of the expected oligomer and were appropriately pooled and desalted on a *Biogel P4* column. Thus, 10 *OD*'s (optical-density units at 259 nm) of octamer **24** and 7 *OD*'s of the heptamer were isolated.

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