Pteridines

Part CXVIII[1])

Methanopterin, Chemical Approach and Partial Synthesis

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Our approach to achieve a partial synthesis of methanopterin (**1**) started from 6-acetyl-O^4-isopropyl-7-methylpterin (**20**) which was obtained either by condensation from 6-isopropoxypyrimidine-2,4,5-triamine (**19**) and pentane-2,3,4-trione (**6**) or from 6-isopropoxy-5-nitrosopyrimidine-2,4-diamine (**21**) and pentane-2,4-dione (=acetylacetone; **22**) (*Scheme 2*). $NaBH_4$ reduction of **20** led to 6-(1-hydroxyethyl)-O^4-isopropyl-7-methylpterin (**23**) which was converted into the corresponding 6-(1-chloroethyl) and 6-(1-bromoethyl) derivatives **24** and **25**. A series of nucleophilic displacement reactions in the side chain and at position 4 were performed as model reactions to give **26**–**29**, **32**–**35**, and **39**–**41**. Hydrolysis of the substituents at C(4) led to the corresponding pterin derivatives **30**, **31**, **36**–**38**, and **42**. Analogously, **25** reacted with 1-(4-aminophenyl)-1-deoxy-2,3:4,5-di-*O*-isopropylidene-D-ribitol (**43**), prepared from *N*-(4-bromophenyl)benzamide (**47**) *via* **49** and **50** to give 1-{4-{{1-[2-amino-7-methyl-4-(1-methylethoxy)pteridin-6-yl]ethyl}amino}phenyl}-1-deoxy-D-ribitol (**44**) in 62% yield (*Scheme 3*). Acid cleavage of the isopropylidene groups at room temperature led to **45** and on boiling to 1-{4-{[1-(2-amino-3,4-dihydro-7-methyl-4-oxopteridin-6-yl)ethyl]amino}phenyl}-1-deoxy-D-ribitol (**46**). The next step, however, attachment of the ribofuranosyl moiety with **55** or **56** to the terminal 1-deoxy-D-ribitol OH group could not been achieved. The second component, bis(4-nitrobenzyl) 2-{[(2-cyanoethoxy)(diisopropylamino)phosphino]oxy}pentanedioate (**61**), to built-up methanopterin (**1**) was synthesized from 2-hydroxypentanedioic acid (**59**) and worked well in another model reaction on phosphitylation with N^6-benzoyl-2′,3′-*O*-isopropylideneadenosine and oxidation to give **62** (*Scheme 6*).

1. Introduction. – Methanogenic bacteria comprise a very selected unique group of microorganisms which derive their energy for growth from the hydrogen-dependent reduction of CO_2 to produce methane. In this process, a series of unique coenzymes are involved which remind structurally 5,6,7,8-tetrahydrofolic acid functioning as a C_1 carrier in the biosynthesis of serine, thymidylate, purines, and methionine. One of these bacterial coenzymes is 5,6,7,8-tetrahydromethanopterin acting as C_1 carrier in methanogenesis. In the reduction steps at the formyl, hydroxymethyl, and methyl level, this pterin derivative plays an important role and keeps the C_1 unit bound during these transformation processes. The biochemistry of methane production is known and has been summarized [2].

Methanopterin (MPT; **1**), an oxidation product of the natural coenzyme, was isolated from *Methanobacterium thermoautotrophicum* and first described by *Vogels et al.* [3] and its structure elucidated by the same research group [4]. The structure of

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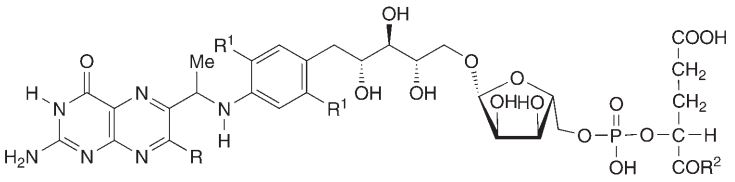
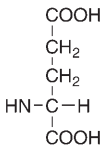
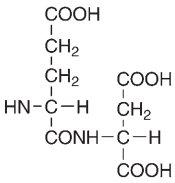
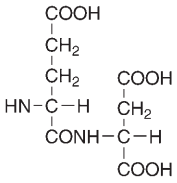
methanopterin (**1**) is complex and was identified as 1-{4-{[(1*R*)-1-(2-amino-3,4-dihydro-7-methyl-4-oxopteridin-6-yl)ethyl]amino}phenyl}-1-deoxy-5-*O*-{5-*O*-{[(1*S*)-1,3-dicarboxypropoxy]hydroxyphosphinyl}-α-D-ribofuranosyl}-D-ribitol in which the phosphate group is esterified with α-hydroxyglutaric acid (=2-hydroxypentanedioic acid). Structural analogs have been found in *Methanosarcina barkeeri*, *i.e.*, sarcinapterin (**2**) [5], in *Methanogenium tationis*, *i.e.*, tatiopterin (**3**) [6], and in *Methanocullens thermophilicum*, *i.e.*, thermopterin (**4**) [7].

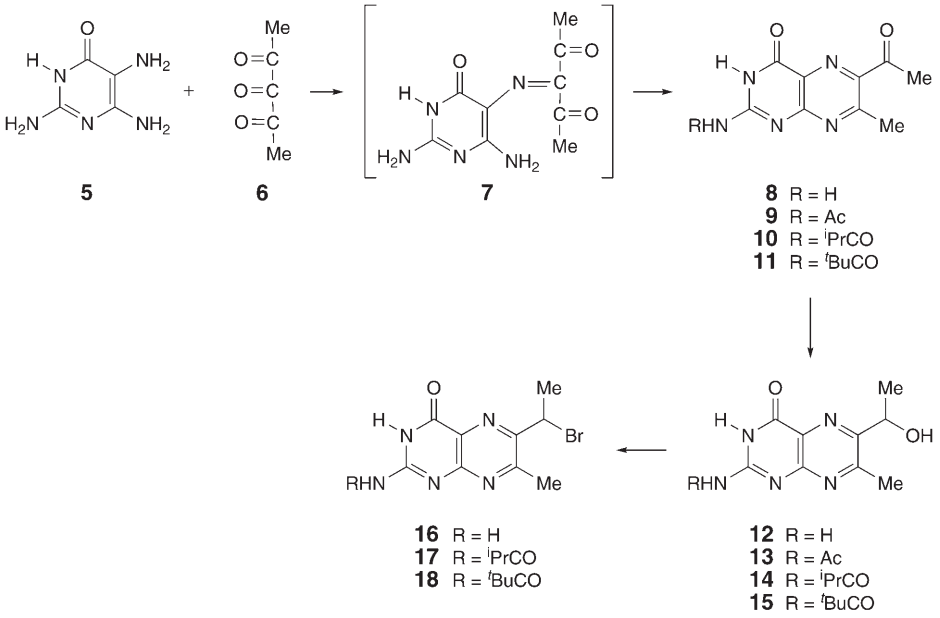


	Methanopterin (**1**)	Sarcinapterin (**2**)	Tatiopterin-O (**3**)	Thermopterin (**4**)
R	Me	Me	H	H
R^1	H	H	H	OH
R^2	OH			

The structural relationship between methanopterin (**1**) and folic acid is obvious since both molecules basically consist of a 2-aminopteridin-4(3*H*)-one (= pterin) and a *p*-substituted benzenamine derivative connected to each other by a C-atom attached to C(6) of the pterin and the amino group of the benzenamine moiety, respectively. Major differences between MPT and folic acid concern the presence in MPT of two additional Me groups at C(7) and at the linking C-atom as well as the extended side chain bound to the benzene ring. The configuration of this side chain was identified as being that of a 1-deoxy-D-ribitol (=D-ribityl) [8] moiety, the terminal hydroxy group of which is connected to C(1) of a D-ribofuranose unit by an α-glycosidic linkage. Finally, C(5) of this latter ribose moiety is phosphylated and connected to α-hydroxyglutaric acid.

2. Synthesis. – We decided to achieve the chemical synthesis of this interesting natural product by approaching the composition from the side of the pterin moiety by stepwise condensation reactions of various building units [9]. We started with a *Gabriel–Isay* reaction [10] between 2,5,6-triaminopyrimid-4(3*H*)-one (**5**) and pentane-2,3,4-trione (**6**) under neutral aqueous conditions to achieve a regioselective condensation between the most nucleophilic 5-amino group and the 3-oxo group to the intermediary *Schiff* base **7** which cyclized to 6-acetyl-7-methylpterin (**8**) [11] (*Scheme 1*). Since **8** is a very insoluble compound, especially in organic solvents, we improved solubility by acylation of the 2-amino group by acetic, isopropionic, and pivaloic anhydride to give **9**–**11** in good yields.

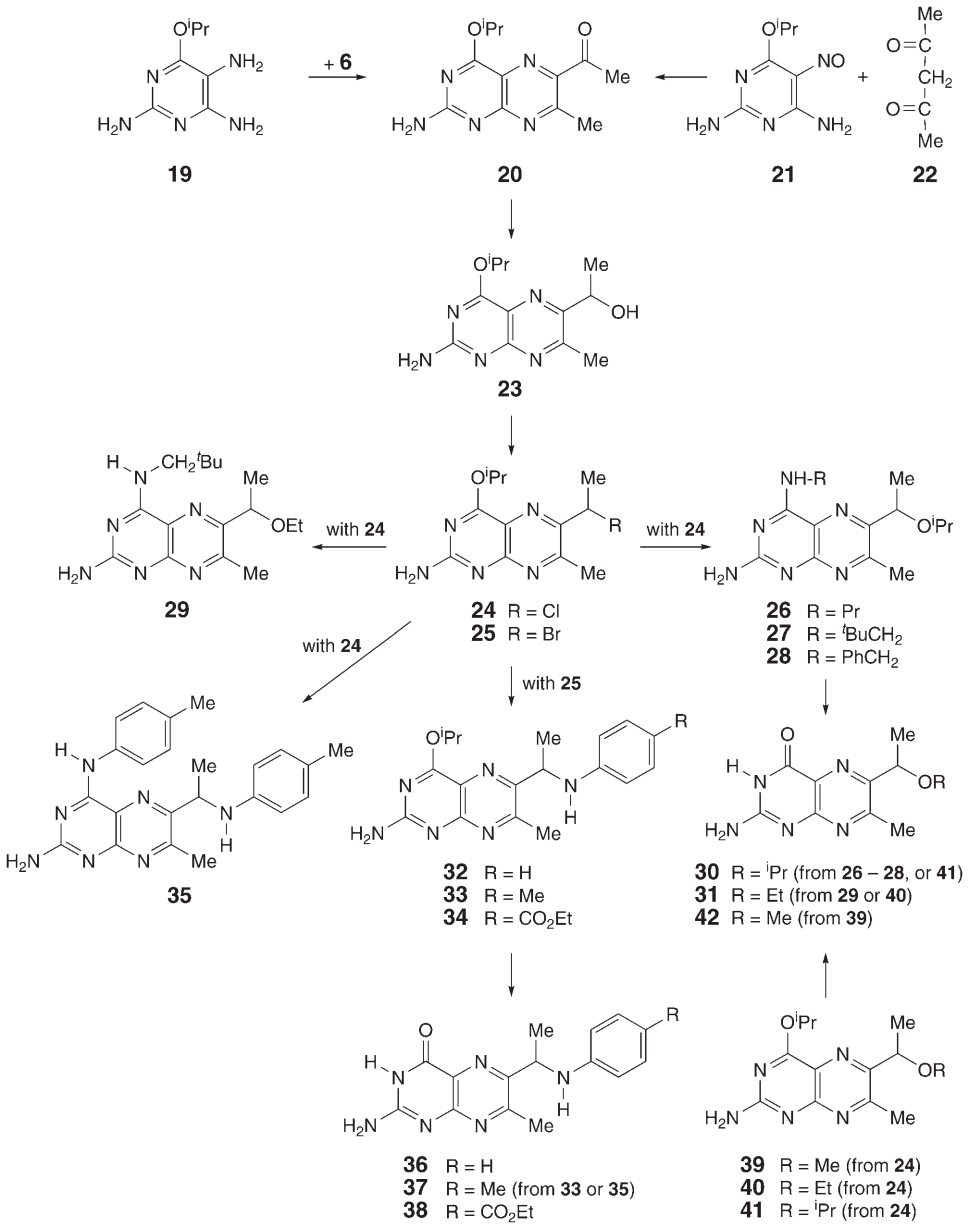
Scheme 1



The $NaBH_4$ reduction of **8**–**11** proceeded well to give the corresponding 6-(1-hydroxyethyl)pterin derivatives **12**–**15** (*Scheme 1*). The interconversion of **8** to 6-(1-bromoethyl)-7-methylpterin (**16**) with conc. HBr solution worked only in low yield, whereas the reaction of **10** and **11** in $CHCl_3$ with thionyl bromide gave **17** and **18**, respectively, in yields of 70–90%.

All attempts to displace the Br-atom in **16**–**18** by primary amines were very disappointing and let to complex mixtures from which no clean substances could be isolated. We switched then to O^4-alkylpterin derivatives which are known as readily soluble substances [12]. The 6-isopropoxypyrimidine-2,4,5-triamine (**19**) was condensed with **6** to form 1-(2-amino-4-isopropoxy-7-methylpteridin-6-yl)ethanone (**20**) in 79% yield (*Scheme 2*). The same substance resulted also from a *Timmis* reaction between 6-isopropoxy-5-nitroso-pyrimidine-2,4-diamine (**21**) and propane-2,4-dione (=acetylacetone; **22**). Reduction of the oxo group of **20** by $NaBH_4$ gave **23**, and subsequent treatment with $SOCl_2$ and $SOBr_2$ led to the valuable synthons **24** and **25**, respectively. Nucleophilic substitution reactions with **24** and aliphatic primary amines such as propan-1-amine, neopentylamine (=2,2-dimethylpropan-1-amine), and benzylamine (=benzenemethanamine) in ^{i}PrOH as solvent gave unexpected results. The amines replaced the isopropoxy group in 4-position, and the Cl-atom in the side chain was substituted by the isopropoxy residue leading to **26**–**28**. In an analogous experiment between **24** and neopentylamine in EtOH resulted 6-(1-ethoxyethyl)-7-methyl-N^4-neopentylpteridine-2,4-diamine (**29**). The structures of **26**–**29** were established by ^{1}H-NMR spectra and elemental analyses and further confirmed by basic hydrolysis forming the corresponding pterin derivatives **30** and **31**.

Scheme 2



The change from alcohol solvents to aprotic solvents like DMF or MeCN was some kind of a break-through in our efforts since now primary aromatic amines like aniline (=benzenamine), *p*-toluidine (=4-methylbenzenamine) and ethyl 4-aminobenzoate

reacted with **25** in the expected manner substituting the Br-atom to form the corresponding 6-[1-(arylamino)ethyl] derivatives **32**–**34** (*Scheme 2*). Excess of amine and extended reaction time led to disubstitution as shown with **24** and *p*-toluidine giving **35**. Basic hydrolysis of **32**–**35** in 1N NaOH/dioxane again resulted in the formation of the pterin derivatives **36**–**38**. Furthermore, the Cl-atom in **24** was easily displaced by alkoxy residues on treatment in the appropriate alcohol in the presence of Et_3N yielding **39**–**41**. The subsequent hydrolysis in 1N NaOH led to the pterin derivatives **30**, **31**, and **42**.

Knowing the side-chain reactivity of **24** and **25**, the next step was the introduction of the 1-(4-aminophenyl)-1-deoxy-D-ribitol residue into **25** (*Scheme 3*). For this purpose, we synthesized the 1-(4-aminophenyl)-1-deoxy-2,3:4,5-di-*O*-isopropylidene-D-ribitol (**43**) by a similar approach as that reported by *White* [8] in a short communication without giving experimental details for the various steps of the preparation of 1-(4-aminophenyl)-1-deoxy-D-ribitol which has not been characterized by chemical and physical means. We started from *N*-(4-bromophenyl)benzamide (**47**) [13] which was treated with 2 equiv. of BuLi and then with 2,3:4,5-di-*O*-isopropylidene-D-ribose (**48**) [14] to give *N*-{4-[(1*S*)-2,3:4,5-di-*O*-isopropylidene-D-ribitol-1-*C*-yl]phenyl}benzenamide (**49**) in 62% yield. Subsequent $LiAlH_4$ treatment in THF resulted in 1-deoxy-2,3:4,5-di-*O*-isopropylidene-1-{4-[(phenylmethyl)amino]phenyl}-D-ribitol (**50**) which gave, on further reduction with Pd/H_2 under debenzylation, 1-(4-aminophenyl)-1-deoxy-2,3:4,5-di-*O*-isopropylidene-D-ribitol (**43**) in 90% yield. The nucleophilic displacement in the side chain of **25** with **43** proceeded well in THF to give in 62% yield 1-{4-{{1-[2-amino-7-methyl-4-(1-methylethoxy)pteridin-6-yl]ethyl}amino}phenyl}-1-deoxy-2,3:4,5-di-*O*-isopropylidene-D-ribitol (**44**). The ribitol moiety could be deprotected by mild acid treatment with 0.5N HCl at room temperature to give **45**, whereas heating of **44** in 1N HCl afforded full deprotection to 1-{4-{[1-(2-amino-3,4-dihydro-7-methyl-4-oxopteridin-6-yl)ethyl]amino}phenyl}-1-deoxy-D-ribitol (**46**) in 78% yield.

Expectedly, all O^4-isopropylpterin derivatives showed very similar UV spectra in MeOH (*Table*). The pterins **30**, **31**, **36**–**38**, **42**, and **45** were further characterized by the determination of their pK_a values [15] to measure the UV absorption of the cation, neutral form, and monoanion (*Table*) showing the specific spectral shifts. An interesting fact is observed in the cations of **30**, **31**, and **42** which consist of a mixture of two cation forms showing the normal N(1)-protonated species with the absorption band at 320 nm and the N(8)-protonated form with its long wavelength band at 384–386 nm reflecting the long cross-conjugated π-electron system [16] (*Scheme 4*).

The next step in the anticipated methanopterin (**1**) synthesis was the stereoselective glycosylation of the terminal OH group of **45** to form an α-glycosidic linkage. Various trials under different reaction conditions with 2,3,5-tri-*O*-benzyl-D-ribofuranose-1-acetate [17] according to *Mukaiyama et al.* [18–25] did not proceed in the expected manner. We also tried the trichloroacetimidate method according to *Schmidt* and *Reichrath* [26] and synthesized for this purpose from 2,3-*O*-isopropylidene-5-*O*-(monomethoxytrityl)- (**53**) and 5-*O*-benzoyl-2,3-*O*-isopropylidene-D-ribofuranose (**54**) the corresponding β-D-configurated 1-(trichloroacetimidates) **55** and **56**, respectively (*Scheme 5*). Unfortunately, glycosylations with these building blocks were again

Scheme 3

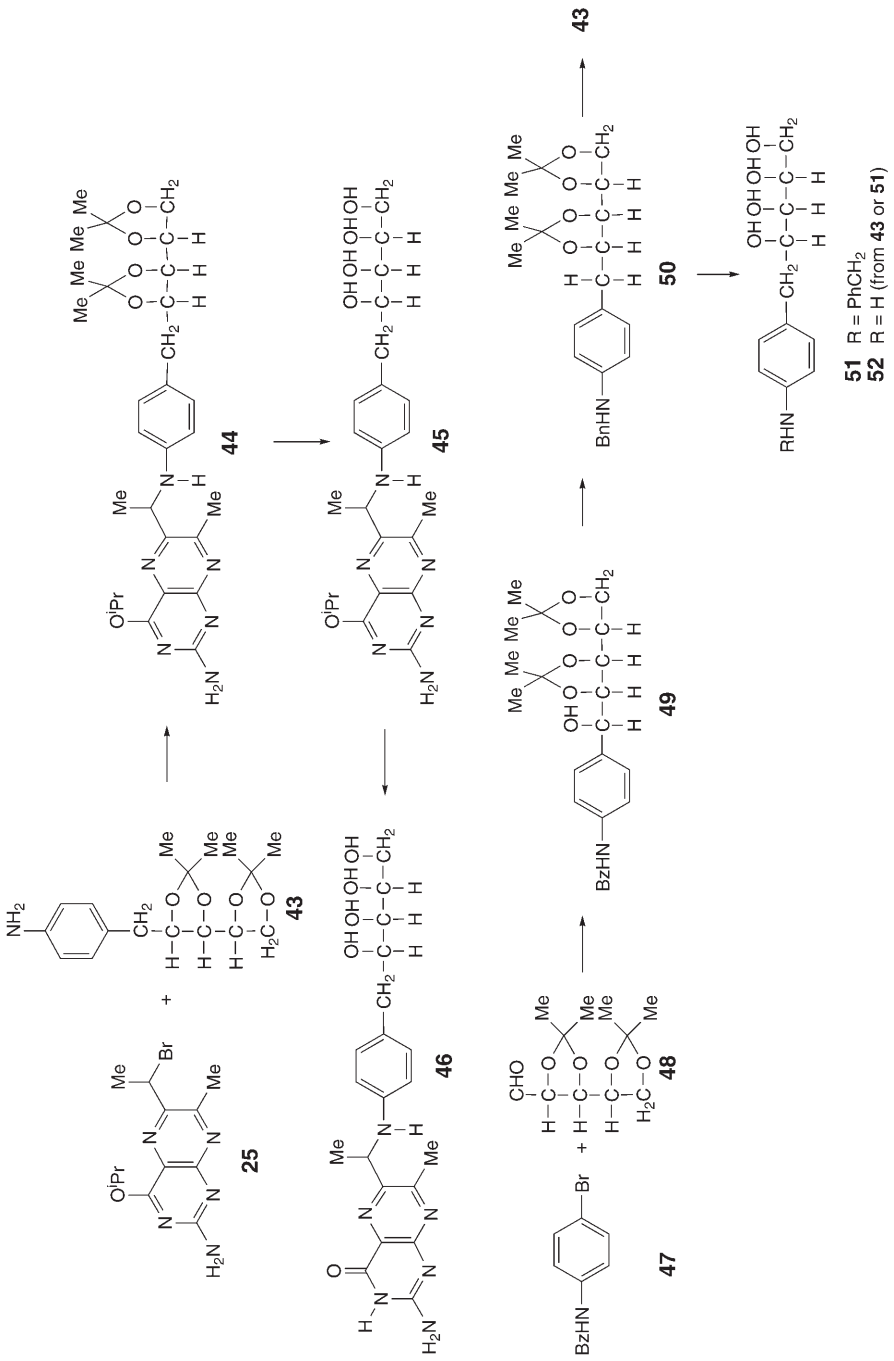


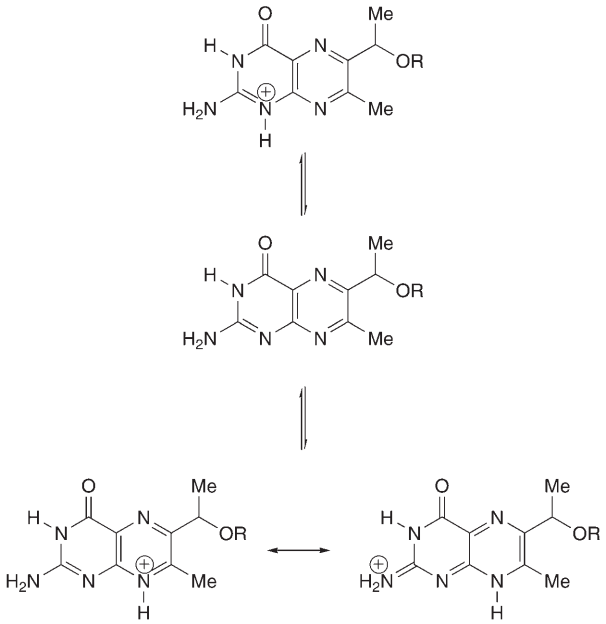
Table. *UV-Absorption Spectra* (MeOH) *of Pterin Derivatives*. Values in parentheses are those of shoulders.

	λ_{max} [nm]			log ε			Solvent or pH	pK_a	Molecular form
23	235	266	357	4.36	4.00	3.92	MeOH		
24	239	273	358	4.33	4.03	3.97	MeOH		
25	236	271	359	4.29	3.98	3.94	MeOH		
39	236	266	356	4.40	4.06	3.95	MeOH		
40	236	266	357	4.40	4.06	3.97	MeOH		
41	237	266	358	4.37	4.03	3.92	MeOH		
26	229	263	371	4.16	4.30	3.96	MeOH		
27	230	265	372	4.13	4.24	3.92	MeOH		
28	228	264	371	4.16	4.23	3.91	MeOH		
29	228	265	371	4.11	4.24	3.92	MeOH		
35	244	276	388	4.52	4.16	4.10	MeOH		
32	240	(260)	362	4.46	(4.09)	3.90	MeOH		
33	239	(266)	361	4.52	(4.17)	3.97	MeOH		
34	230	300	359	4.40	4.41	3.97	MeOH		
43	241	(268)	364	4.52	(4.15)	3.94	MeOH		
44	246	(261)	361	4.61	(4.58)	3.93	MeOH		
36	(220)	251	320	(4.27)	4.02	4.00	−1	1.60	+
	234	276	342	4.29	4.16	3.84	5	8.53	0
	251	(276)	359	4.46	(3.93)	3.93	11		−
37	251	(308)	321	4.05	(3.93)	4.01	−1	1.80	+
	236	278	342	4.21	4.18	3.84	3	8.70	0
	251	(276)	321	4.46	(3.95)	3.95	12		−
38	220	(250)	320	4.44	(4.08)	4.01	−2	0.60	+
	219	280	300	4.33	4.32	4.33	3	4.73	0
	(238)	277	344	(4.16)	4.40	3.90	7	8.63	−
	254	273	360	4.42	4.35	3.98	11		− −
45		251	320		4.05	4.01	−1	1.80	+
	238	274	342	4.35	4.17	3.87	6	8.43	0
	250	(276)	359	4.46	(3.97)	3.94	11		−
30	251	320	386	3.97	3.97	2.62	0	2.53	+
	(232)	274	342	(4.10)	4.12	3.86	5	8.47	0
	251	(276)	357	4.35	(3.77)	3.93	11		−
31	251	320	384	3.98	3.98	2.71	0	2.42	+
	234	274	342	4.10	4.13	3.87	5	8.47	0
	251	(275)	357	4.36	(3.83)	3.94	11		−
42	251	320	386	4.00	4.02	2.85	−1	2.38	+
	234	275	341	4.10	4.15	3.88	5	8.38	0
	251	(276)	358	4.36	(3.80)	3.94	11		−

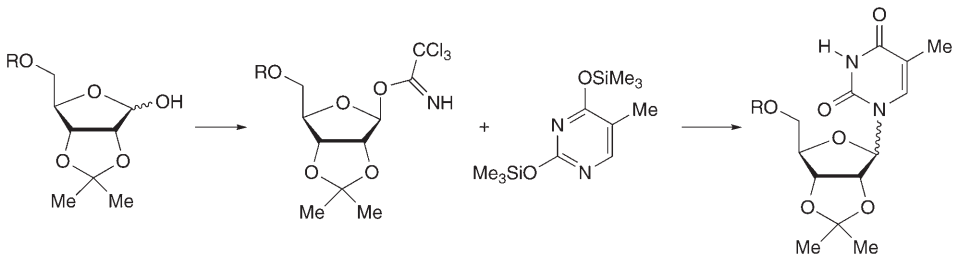
unsuccessful. However, in a model reaction between **55** and O^2,O^4-bis(trimethylsilyl)thymine (**57**) under BF_3 catalysis, an α,β-D-anomer mixture **58** was obtained.

The terminal component for the synthesis of **1** was synthesized from 2-hydroxyglutaric acid (**59**) which gave with 4-nitrobenzyl chloride the bis(4-nitrobenzyl) α-hydroxyglutarate (**60**) (*Scheme 6*). The latter was transformed with 2-cyanoethyl *N*,*N*,*N*′,*N*′-tetraisopropylphosphorodiamidite into the corresponding phosphoramidite **61**. To establish its reactivity, a phosphoramidite synthesis of **61** with N^6-benzoyl-2′,3′-

Scheme 4



Scheme 5



53 R = (MeO)Tr
54 R = Bz

55 R = (MeO)Tr
56 R = Bz

57

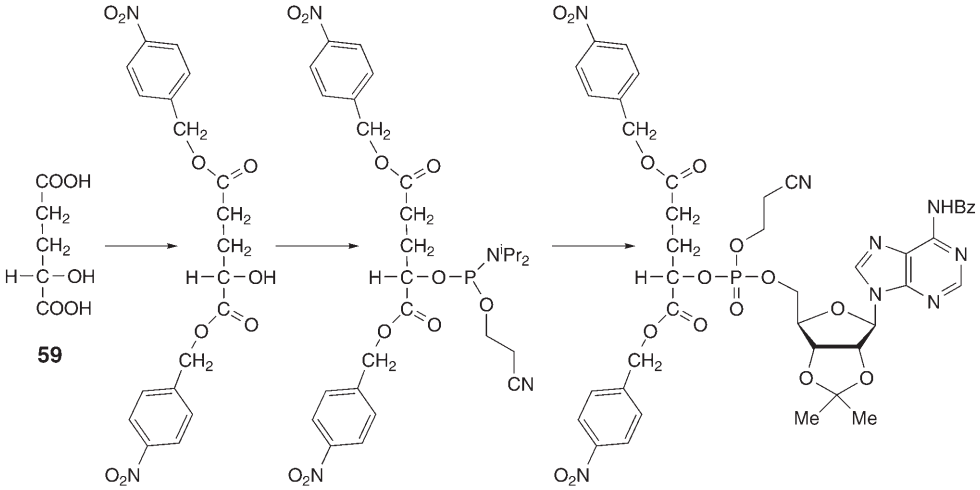
58

di-*O*-isopropylideneadenosine followed by oxidation to the corresponding phosphotriester **62** was successfully performed.

Experimental Part

General. TLC: precoated cellulose thin-layer sheets *F 1440b LS 254* and silica gel thin-layer sheets *F 1500 LS 254* from *Schleicher & Schüll*. Column chromatography (CC): silica gel *60* from *Merck*; FC = flash chromatography. M.p.: *Büchi* apparatus, model Dr. *Totteli*; no corrections. The pK_a measurements were performed by the spectrophotometric method [15]. UV: *Uvikon-820* from *Kontron* and *Lambda-5*

Scheme 6



spectrometer from *Perkin-Elmer*; λ_{max} (log ε) in nm. ^{1}H-NMR: *Bruker WM-250* spectrometer; chemical shifts δ in ppm rel. to $SiMe_4$, coupling constants J in Hz. Elemental analyses were performed in the Microanalytical Laboratory of Konstanz University.

*6-Acetyl-2-amino-7-methylpteridin-4(3*H*)-one* (**8**) [11]. A soln. of 2,5,6-triamino-pyrimidin-4(3*H*)-one dihydrochloride (**5**·2 HCl) [12] (11.0 g, 51.4 mmol) in H_2O (400 ml) was neutralized by conc. ammonia to pH 5, and then pentane-2,3,4-trione (**6**) [27] (7.0 g, 61.3 mmol) in EtOH (75 ml) was added under stirring. The mixture was heated under reflux for 30 min. The formed yellow precipitate was collected after cooling and purified by reprecipitation from hot 1N NaOH with AcOH to give, after washing with H_2O and EtOH and drying at 100°, 8.2 g (73%) of **8**. Yellowish crystal powder. M.p. >320°. pK_a 1.62, 7.52. UV (pH 4): 240 (4.04), 300 (4.11), 358 (3.97). ^{1}H-NMR (0.5N NaOD): 2.73 (*s*, Ac–C(6)); 2.61 (*s*, Me–C(7)).

*6-Acetyl-2-(acetylamino)-7-methylpteridin-4(3*H*)-one* (**9**). A mixture of **8** (2.5 g, 11.4 mmol) and Ac_2O (25 ml) was heated under reflux in an oil bath with stirring for 6 h. After cooling, evaporation, and treatment of the residue with MeOH, the yellowish solid was recrystallized from AcOH (100 ml) with charcoal: 2.6 g (71%) of **9**·AcOH. Colorless needles. M.p. >200° (dec.). R_f ($CHCl_3$/MeOH 95:5) 0.72. UV (MeOH): 240 (sh, 4.08), 303 (4.18), 335 (4.22). ^{1}H-NMR ($CDCl_3$): 12.30 (br. *s*, 1 NH); 12.01 (br. *s*, 1 NH); 2.76 (*s*, Ac–C(6)); 2.65 (*s*, Me–C(7)); 2.23 (*s*, AcN). Anal. calc. for $C_{11}H_{11}N_5O_3$·AcOH (321.2): C 48.59, H 4.70, N 21.80; found: C 48.52, H 4.60, N 22.11.

*6-Acetyl-7-methyl-2-[(2-methyl-1-oxopropyl)amino]pteridin-4(3*H*)-one* (**10**). A suspension of **8** (1.0 g, 4.57 mmol) in abs. pyridine (20 ml) was treated with isobutyric acid anhydride (=2-methylpropanoic acid anhydride; 3.8 ml, 22.6 mmol) and heated under reflux at 130–140° for 12 h. After cooling, MeOH (10 ml) was added, the mixture stirred for 30 min and then evaporated, and the residue twice co-evaporated with AcOEt. The residue was crystallized from hexane/AcOEt 2:1: 1.06 g (80%) of **10**. Colorless crystals. M.p. 196–197°. R_f ($CHCl_3$/MeOH 95:5) 0.88. ^{1}H-NMR ($CDCl_3$): 12.55 (br. *s*, 1 NH); 10.00 (br. *s*, 1 NH); 2.92 (*s*, Ac–C(6)); 2.85 (*m*, Me_2CH); 2.82 (*s*, Me–C(7)); 1.28 (*d*, Me_2CH). Anal. calc. for $C_{13}H_{15}N_5O_3$ (289.3): C 53.97, H 5.23, N 24.21; found: C 54.24, H 5.33, N 24.18.

*6-Acetyl-2-[(2,2-dimethyl-1-oxopropyl)amino]-7-methylpteridin-4(3*H*)-one* (**11**). As described for **10**, with **8** (7.0 g, 31.9 mmol), pivalic anhydride (=2,2-dimethylpropanoic acid anhydride; 27 ml, 133 mmol), and abs. pyridine (110 ml) for 9 h. After cooling, MeOH (50 ml) was slowly added with stirring. Evaporation and treatment with hexane gave 8.62 g (89%) of **11**. Colorless crystals. M.p. 118°. R_f

($CHCl_3$/MeOH 95:5) 0.62. ^{1}H-NMR ($CDCl_3$): 12.75 (br. *s*, 1 NH); 8.80 (br. *s*, 1 NH); 2.94 (*s*, Ac–C(6)); 2.81 (*s*, Me–C(7)); 1.36 (*d*, *Me*$_3$C). Anal. calc. for $C_{14}H_{17}N_5O_3$ (303.3): C 55.44, H 5.65, N 23.09; found: C 55.01, H 5.70, N 22.82.

*2-Amino-6-(1-hydroxyethyl)-7-methylpteridin-4(3*H*)-one* (**12**). A suspension of **8** (13.0 g, 59.3 mmol) in H_2O (1.2 l) was heated to 90°, and then, under stirring, $NaBH_4$ (7.6 g, 0.2 mol) was added in small portions. A clear soln. was obtained, and, on cooling, a yellowish precipitate separated. The mixture was acidified by AcOH to pH 5–6, the solid collected, washed with H_2O, and then reprecipitated from hot 1N NaOH/AcOH to give, after drying at 100°, 10.5 g (80%) of **12**. Yellowish crystal powder. M.p. >350°. R_f (cellulose, PrOH/1% aq. NH_3 soln. 2:1) 0.42. ^{1}H-NMR (0.5N NaOD): 5.35–5.15 (*m*, 1 H–C(1′)); 2.61 (*s*, Me–C(7)); 1.54 (*d*, Me(2′)). Anal. calc. for $C_9H_{11}N_5O_2 \cdot 0.5\ H_2O$ (230.2): C 46.96, H 4.81, N 30.43; found: C 46.88, H 5.20, N 30.51.

*2-(Acetylamino)-6-(1-hydroxyethyl)-7-methylpteridin-4(3*H*)-one* (**13**). To a suspension of **9** (0.82 g, 3.13 mmol) in MeOH (20 ml), $NaBH_4$ (0.38 g, 10 mmol) was added slowly in small portions while stirring. After consumption of **9** (TLC monitoring), the soln. was evaporated, the residue treated with 10% AcOH, and the solid collected, washed with little H_2O, and dried in a vacuum desiccator: 0.625 g (76%) of **13**. Colorless crystal powder. M.p. >210° (dec.). R_f (silica gel, $CHCl_3$/MeOH 95:5) 0.32. ^{1}H-NMR ($CDCl_3$): 12.30 (br. *s*, 1 NH); 12.05 (br. *s*, 1 NH); 5.15 ((*m*, H–C(1′)); 4.70 (br. *s*, OH); 2.76 (*s*, Me–C(7)); 2.21 (*s*, AcN); 1.61 (*d*, Me(2′)). Anal. calc. for $C_{11}H_{13}N_5O_3$ (263.3): C 50.18, H 4.98, N 26.60; found: C 49.33, H 5.02, N 26.23.

*6-(1-Hydroxyethyl)-7-methyl-2-[(2-methyl-1-oxopropyl)amino]pteridin-4(3*H*)-one* (**14**). As described for **13**, with **10** (0.867 g, 3 mmol) in MeOH (20 ml) and $NaBH_4$ (0.38 g, 10 mmol). After evaporation, the residue was extracted with $CHCl_3$, the extract washed with H_2O, dried (Na_2SO_4), and evaporated, and the residue dried at 60°: 0.685 g (84%) of **14**. Colorless crystal powder. M.p. 177–180°. R_f ($CHCl_3$/MeOH 95:5) 0.38. ^{1}H-NMR ($CDCl_3$): 12.54 (br. *s*, 1 NH); 9.29 (br. *s*, 1 NH); 5.16 (*m*, H–C(1′)); 4.10 (br. *s*, OH); 2.75 (*m*, Me_2CH); 2.72 (*s*, Me–C(7)); 1.53 (*d*, Me(2′)); 1.29 (*d*, *Me*$_2$CH). Anal. calc. for $C_{13}H_{17}N_5O_3$ (291.3): C 53.60, H 5.88, N 24.04; found: C 55.53, H 5.55, N 23.81.

*2-[(2,2-Dimethyl-1-oxopropyl)amino]-6-(1-hydroxyethyl)-7-methylpteridin-4(3*H*)-one* (**15**). As described for **13**, with **11** (8.7 g, 28.65 mmol), $NaBH_4$ (3.8 g, 0.1 mol), and MeOH (150 ml). After evaporation, the residue was extracted with $CHCl_3$, the extract washed with H_2O, dried (Na_2SO_4), and evaporated, and the residue dried in a vacuum desiccator: 5.95 g (68%) of **15**. Colorless crystal powder. M.p. 119–121°. R_f ($CHCl_3$/MeOH 95:5) 0.65. ^{1}H-NMR ($CDCl_3$): 12.53 (br. *s*, 1 NH); 9.18 (br. *s*, 1 NH); 5.15 ((*m*, H–C(1′)); 4.50 (br. *s*, OH); 2.73 (*s*, Me–C(7)); 1.53 (*d*, Me(2′)); 1.37 (*s*, Me_3C). Anal. calc. for $C_{14}H_{19}N_5O_3$ (305.3): C 55.07, H 6.27, N 22.94; found: C 54.75, H 6.37, N 22.64.

*2-Amino-6-(1-bromoethyl)-7-methylpteridin-4(3*H*)-one Hydrobromide* (**16**·HBr). A suspension of **12** (3.5 g, 15.8 mmol) in conc. (48%) HBr soln. (7 ml) was heated under reflux for 10 min (→dark brown soln.). On cooling, an almost colorless precipitate was obtained. The solid was washed with little EtOH and Et_2O and then recrystallized from conc. HBr soln.: 1.65 g (29%) **16**·HBr. Colorless crystals. M.p. >350°. ^{1}H-NMR (CF_3COOD): 8.29 (br. *s*, NH_2); 5.57–5.37 (*q*, H–C(1′)); 2.92 (*s*, Me–C(7)); 2.20 (*d*, Me(2′)). Anal. calc. for $C_9H_{10}BrN_5O \cdot HBr$ (365.0): C 29.61, H 3.04, N 19.19; found: C 30.10, H 3.00, N 19.06.

*6-(1-Bromoethyl)-7-methyl-2-[(2-methyl-1-oxopropyl)amino]pteridin-4(3*H*)-one* (**17**). A soln. of **14** (0.37 g, 1.27 mmol) in $CHCl_3$ (10 ml) was cooled in an ice bath, and then thionyl bromide (0.11 mml, 1.4 mmol) was added under stirring. The mixture was stirred for 15 min at 0–5°, then for 1 h at r.t. After evaporation, the residue was purified by CC (silica gel (10 g), CH_2Cl_2/MeOH 50:1). The product was dried in a vacuum desiccator: 0.324 g (72%) of **17**. Yellowish powder. M.p. >180° (dec.). R_f ($CHCl_3$/MeOH 95:5) 0.67. UV (MeOH): 203 (4.31), 240 (sh, 4.05), 276 (4.03), 333 (3.81). ^{1}H-NMR ($CDCl_3$): 12.53 (br. *s*, 1 NH); 9.22 (br. *s*, 1 NH); 5.41 (*m*, H–C(1′)); 2.85–2.75 (*m*, Me_2CH); 2.82 (*s*, Me–C(7)); 2.22 (*d*, Me(2′)); 1.32 (*d*, *Me*$_2$CH). Anal. calc. for $C_{13}H_{16}BrN_5O_2$ (354.2): C 44.08, H 4.55, N 19.77; found: C 44.19, H 4.71, N 19.01.

*6-(1-Bromoethyl)-2-[(2,2-dimethyl-1-oxopropyl)amino]-7-methylpteridin-4(3*H*)-one* (**18**). As described for **17**, with **15** (4.4 g, 14.4 mmol) in CH_2Cl_2 (100 ml) and thionyl bromide (1.34 ml, 17.3 mmol) for 15 min at 0–5° and 2 h at r.t. Purification by CC (silica gel (50 g), CH_2Cl_2/MeOH 100:1) gave, after drying in a vacuum desiccator over KOH, 4.79 g (90%) of **18**. Colorless powder. M.p. >165° (dec.). R_f

($CHCl_3$/MeOH 95:5) 0.80. UV (MeOH): 203 (4.34), 240 (sh, 4.07), 276 (4.09), 333 (3.83). ^{1}H-NMR ($CDCl_3$): 12.30 (br. *s*, 1 NH); 9.45 (br. *s*, 1 NH); 5.34 (*m*, H–C(1′)); 2.84 (*s*, Me–C(7)); 2.24 (*d*, Me(2′)); 1.24 (*s*, Me_3C). Anal. calc. for $C_{14}H_{18}BrN_5O_2$ (368.2): C 45.66, H 4.93, N 19.12; found: C 45.31, H 4.87, N 18.98.

1-[2-Amino-7-methyl-4-(1-methylethoxy)pteridin-6-yl)ethanone (**20**). *a*) A mixture of 6-(1-methylethoxy)pyrimidine-2,4,5-triamine (**19**) [12] (10.8 g, 59 mmol) and pentane-2,3,4-trione (**6**; 10.0 g, 87.6 mmol) in EtOH (300 ml) was heated to 60° for 30 min. The mixture was evaporated and the residue recrystallized from MeOH/H_2O: 12.1 g (79%) of **20**. Yellowish crystals. M.p. 218–219°.

b) A mixture of 6-(1-methylethoxy)-5-nitrosopyrimidine-2,4-diamine (**21**) [12] (16.1 g, 67.4 mmol) in pentane-2,4-dione (**22**; 165 ml) was heated under reflux for 5 h until the educt was consumed. The mixture was evaporated and the brown residue recrystallized from MeOH/H_2O with charcoal: 12.6 g (72%) of **20**. Yellowish crystals. M.p. 220°. R_f ($CHCl_3$/MeOH 95:5) 0.74. UV (MeOH): 207 (4.25), 252 (4.17), 298 (4.03), 357 (4.11). ^{1}H-NMR ($CDCl_3$): 5.65 (br. *s*, 2 NH_2); 5.56 (*m*, Me_2CH); 2.91 (*s*, Ac–C(6)); 2.76 (*s*, Me–C(7)); 1.51 (*d*, Me_2CH). Anal. calc. for $C_{12}H_{15}N_5O_2$ (262.3): C 55.16, H 5.79, N 26.80; found: C 54.81, H 5.68, N 26.38.

2-Amino-α,7-dimethyl-4-(1-methylethoxy)pteridine-6-methanol (**23**). To a suspension of **20** in MeOH (200 ml), $NaBH_4$ was added in small portions under stirring until the educt had disappeared (TLC monitoring). The soln. was evaporated and the residue dissolved in $CHCl_3$. The extract was washed with H_2O, dried (Na_2SO_4), and evaporated, and the residue recrystallized from H_2O (400 ml): 7.42 g (70%) of **23**. Colorless crystals. M.p. 222–223°. R_f ($CHCl_3$/MeOH 95:5) 0.43. ^{1}H-NMR ($CDCl_3$): 5.61 (*m*, Me_2CH); 5.31 (br. *s*, NH_2); 5.12 (*m*, H–C(1′)); 4.40 (*d*, OH); 2.71 (*s*, Me–C(7)); 1.48 (*m*, Me(2′), Me_2CH). Anal. calc. for $C_{12}H_{17}N_5O_2$ (264.3): C 54.74, H 6.51, N 26.60; found: C 54.70, H 6.46, N 26.37.

6-(1-Chloroethyl)-7-methyl-4-(1-methylethoxy)pteridin-2-amine (**24**). A soln. of **23** (7.5 g, 28.5 mmol) in $CHCl_3$ (350 ml) was cooled to 0–5°, and then thionyl chloride (10.5 ml, 158 mmol) in $CHCl_3$ (120 ml) was added dropwise under stirring. After warming to r.t., the mixture was stirred for 1 h followed by evaporation. The yellowish residue was purified by CC (silica gel (100 g), $CHCl_3$/MeOH 50:1). The product fractions (2 l) were evaporated: solid **24** (6.55 g, 83%), pure enough for the following reactions. An anal. sample was obtained by recrystallization from toluene: crystals. M.p. >200° (dec.). R_f ($CHCl_3$/MeOH 95:5) 0.60. ^{1}H-NMR ($CDCl_3$): 9.55 (br. *s*, 1 NH); 7.32 (br. *s*, 1 NH); 5.52 ((*m*, Me_2CH); 5.39 (*q*, H–C(1′)); 2.81 (*s*, Me–C(7)); 2.03 (*d*, Me(2′)); 1.48 (*m*, Me_2CH). Anal. calc. for $C_{12}H_{16}ClN_5O$ (281.7): C 51.16, H 5.72, N 24.86; found: C 51.21, H 5.74, N 24.90.

6-(1-Bromoethyl)-7-methyl-4-(1-methylethoxy)pteridin-2-amine (**25**). A soln. of **23** (6.2 g, 23.55 mmol) in abs. $CHCl_3$ (250 ml) was cooled to 0–5°, and then thionyl bromide (5.65 g, 27.1 mmol) in $CHCl_3$ (20 ml) was added dropwise under stirring. After warming to r.t., the mixture was stirred for another how and then evaporated to a yellowish foam which was purified by CC (silica gel (50 g), CH_2Cl_2/MeOH 50:1). The product was dried under high vacuum: 6.55 g (85%) of **25**, pure enough for the subsequent reactions. Amorphous solid. M.p. >180° (dec.). R_f ($CHCl_3$/MeOH 95:5) 0.68. ^{1}H-NMR ($CDCl_3$): 9.36 (br. *s*, 1 NH); 6.91 (br. *s*, 1 NH); 5.64 (*m*, Me_2CH); 5.36 (*q*, H–C(1′)); 2.76 (*s*, Me–C(7)); 2.15 (*d*, Me(2′)); 1.49 (*m*, Me_2CH).

*7-Methyl-6-[1-(1-methylethoxy)ethyl]-*N^4*-propylpteridine-2,4-diamine* (**26**). To a soln. of **24** (0.5 g, 1.77 mmol) in ^{i}PrOH (20 ml) was added propan-1-amine (0.35 ml, 4.3 mmol) and then heated to 80° for 24 h. The mixture was evaporated, and the residue purified by CC (silica gel (20 g), $CHCl_3$/MeOH 50:1). The product was recrystallized from toluene (25 ml): 0.284 g (53%) of **26**. Yellow crystals. M.p. 144–145°. R_f ($CHCl_3$/MeOH 95:5) 0.32. ^{1}H-NMR ($CDCl_3$): 6.93 (br. *s*, NH); 5.06 (br. *s*, NH_2); 4.89 (*m*, H–C(1′)); 3.54 (*m*, Me_2CH, $MeCH_2CH_2N$); 2.75 (*s*, Me–C(7)); 1.73 (*m*, $MeCH_2CH_2N$); 1.54 (*d*, Me(2′)); 1.19–107 (*m*, Me_2CH); 1.02 (*t*, $MeCH_2CH_2N$). Anal. calc. for $C_{15}H_{24}N_6O$ (304.4): C 59.19, H 7.95, N 27.61; found: C 58.78, H 7.86, N 27.42.

N^4*-(2,2-Dimethylpropyl)-7-methyl-6-[1-(1-methylethoxy)ethyl]pteridin-2,4-diamine* (**27**). As described for **26**, with **24** (0.5 g, 1.77 mmol), 2,2-dimethylpropan-1-amine (0.5 ml, 4.3 mmol), and ^{i}PrOH (20 ml) for 14 h under reflux. Purification by CC (silica gel (20 g), $CHCl_3$/MeOH 50:1), followed by treatment of the product with Et_2O, gave 0.355 g (60%) of **27**. Yellow powder. M.p. 154–155°. R_f ($CHCl_3$/MeOH 95:5) 0.47. ^{1}H-NMR ($CDCl_3$); 7.08 (br. *s*, NH); 5.06 (br. *s*, NH_2); 4.86 (*m*, CH(1′)); 3.75–3.30 (*m*,

Me_2CH, CH_2N); 2.74 (*s*, Me–C(7)); 1.54 (*d*, Me(2′)); 1.16 (*m*, Me_2CH); 1.02 (*s*, Me_3C). Anal. calc. for $C_{17}H_{28}N_6O$ (332.5): C 61.42, H 8.49, N 25.28; found: C 61.12, H 8.62, N 25.11.

7-Methyl-6-[1-(1-methylethoxy)ethyl]-N^4*-(phenylmethyl)pteridine-2,4-diamine* (**28**). As described for **26**, with **24** (0.5 g, 1.77 mmol), benzenemethanamine (0.6 ml, 5.35 mmol), and ^{i}PrOH (20 ml) for 24 h at 100°. Purification by CC (silica gel (20 g), $CHCl_3$/MeOH 50:1), followed by treatment of the product with Et_2O, gave 0.36 g (58%) of **28**. Yellow crystals. M.p. 137–139°. R_f ($CHCl_3$/MeOH 95:5) 0.26. ^{1}H-NMR ($CDCl_3$): 7.38 (*m*, Ph); 7.20 (br. *s*, NH); 5.11 (br. *s*, NH_2); 4.84 (*m*, H–C(1′), CH_2N); 3.55 (*m*, Me_2CH); 2.78 (*s*, Me–C(7)); 1.51 (*d*, Me(2′)); 1.13 (*m*, Me_2CH). Anal. calc. for $C_{19}H_{24}N_6O$ (352.4): C 64.75, H 6.86, N 23.85; found: C 64.66, H 6.75, N 23.84.

N^4*-(2,2-Dimethylpropyl)-6-(1-ethoxyethyl)-7-methylpteridine-2,4-diamine* (**29**). As described for **26**, with **24** (0.2 g, 0.71 mmol), 2,2-dimethylpropan-1-amine (0.5 ml, 4.3 mmol), and EtOH (20 ml) for 14 h under reflux. Purification by CC (silica gel (20 g), $CHCl_3$/MeOH 50:1), followed by recrystallization from toluene (15 ml), gave 0.135 g (60%) of **29**. Yellow crystals. M.p. 168–169°. R_f ($CHCl_3$/MeOH 95:5) 0.53. ^{1}H-NMR ($CDCl_3$): 7.01 (br. *s*, NH); 5.06 (br. *s*, NH_2); 4.78 (*m*, H–C(1′)); 3.60–3.38 (*m*, $MeCHO_2$, CH_2N); 2.74 (*s*, Me–C(7)); 1.58 (*d*, Me(2′)); 1.22 (*t*, $MeCH_2O$); 1.02 (*s*, Me_3C). Anal. calc. for $C_{16}H_{26}N_6O$ (318.4): C 60.35, H 8.23, N 26.39; found: C 60.09, H 8.18, N 26.23.

*2-Amino-7-methyl-6-[1-(1-methylethoxy)ethyl]pteridin-4(3*H*)-one* (**30**). *a*) A soln. of 7-methyl-4-(1-methylethoxy)-6-[1-(1-methylethoxy)ethyl]pteridin-2-amine (**41**; 0.5 g, 1.64 mmol) in 0.2N NaOH (20 ml) and dioxane (10 ml) was heated under reflux for 2 h. The warm soln. was acidified by AcOH, and the precipitate collected after cooling. Washing with H_2O and MeOH followed by drying at 100° gave 0.335 g (75%) of **30**. Yellowish powder. M.p. >300°.

b) A soln. of 0.1 g of **26**, **27**, or **28** in 1N NaOH (5 ml) and dioxane (5 ml) was heated under reflux for 2 h. The mixture was diluted with H_2O (10 ml) and the hot soln. acidified by AcOH. The precipitate was collected after cooling and dried at 100°: 68–72 mg (81–88%) of **30**. Yellowish powder. M.p. >300°. R_f (cellulose, PrOH/1% aq. NH_3 soln. 2:1) 0.70. ^{1}H-NMR (0.5N NaOD): 4.84 (*m*, H–C(1′)); 3.45 (*m*, Me_2CH); 2.41 (*s*, Me–C(7)); 1.26 (*d*, Me(2′)); 0.90 (*d*, Me_2CH). Anal. calc. for $C_{12}H_{17}N_5O_2 \cdot 0.5\ H_2O$ (272.3): C 52.93, H 6.66, N 25.72; found: C 52.86, H 6.41, N 25.75.

*2-Amino-6-(1-ethoxyethyl)-7-methylpteridin-4(3*H*)-one* (**31**). *a*) A soln. of 6-(1-ethoxyethyl)-7-methyl-4-(1-methylethoxy)pteridin-2-amine (**40**; 0.2 g, 0.69 mmol) in 0.2N NaOH (10 ml) and dioxane (10 ml) was refluxed for 2 h. After concentration to half of the volume, H_2O (20 ml) was added and the mixture heated and then acidified by AcOH. The resulting precipitate was collected after cooling, washed with H_2O and MeOH, and dried at 100°: 0.143 g (83%) of **31**. Yellowish powder. M.p. >260°.

b) Analogous treatment of **29** gave 0.124 g (73%) of **31**. Yellowish powder. M.p. >260°. R_f (cellulose, PrOH/1% aq. NH_3 soln. 2:1) 0.65. ^{1}H-NMR (0.5N NaOD): 4.73 (*m*, H–C(1′)); 3.35–3.22 (*m*, $MeCH_2O$); 2.38 (*s*, Me–C(7)); 1.26 (*d*, Me(2′)); 0.94 (*t*, $MeCH_2O$). Anal. calc. for $C_{11}H_{15}N_5O_2 \cdot 0.5\ H_2O$ (258.3): C 51.15, H 6.24, N 27.12; found: C 51.16, H 6.11, N 27.22.

*2-Amino-α,7-dimethyl-4-(1-methylethoxy)-*N*-phenylpteridine-6-methanamine* (**32**). To a soln. of **25** (0.328 g, 1 mmol) in MeCN (15 ml) was added freshly distilled benzenamine (0.146 g, 1.6 mmol), and the mixture was heated to 60° for 4 h. After evaporation, the residue was treated with H_2O and the solid collected and purified by CC (silica gel (10 g), CH_2Cl_2/MeOH). The product was recrystallized from toluene: 0.231 g (68%) of **32**. Yellowish crystal powder. M.p. 201–202°. R_f (silica gel, $CHCl_3$/MeOH 95:5) 0.46. ^{1}H-NMR ($CDCl_3$): 7.13 (*m*, 2 H *o* to NH); 6.73 (*m*, 3 arom. H); 5.53 (*m*, Me_2CH); 5.22 (br. *s*, NH_2); 4.95 (*m*, H–C(1′)); 2.77 (*s*, Me–C(7)); 1.49 (*m*, Me(2′), Me_2CH). Anal. calc. for $C_{18}H_{22}N_6O$ (338.4): C 63.89, H 6.55, N 24.83; found: C 63.94, H 6.55, N 24.22.

*2-Amino-α,7-dimethyl-4-(1-methylethoxy)-*N*-(4-methylphenyl)pteridine-6-methanamine* (**33**). As described for **32**, with **25** (0.29 g, 0.9 mmol), 4-methylbenzenamine (0.14 g, 1.35 mmol), and DMF (15 ml) for 1 h: 0.203 g (65%) of **33**. Yellowish solid. M.p. >210° (dec.). R_f (silica gel, $CHCl_3$/MeOH 95:5) 0.63. ^{1}H-NMR ($CDCl_3$): 6.96 (*m*, 2 H *o* to NH); 6.61 (*m*, 2 arom. H); 5.52 (*m*, Me_2CH); 5.30 (br. *s*, NH_2); 4.98 (*m*, H–C(1′)); 2.75 (*s*, Me–C(7)); 2.21 (*s*, MeC_6H_4); 1.51 (*m*, Me(2′), Me_2CH). Anal. calc. for $C_{19}H_{24}N_6O$ (352.4): C 64.75, H 6.86, N 23.85; found: C 64.41, H 6.87, N 23.65.

Ethyl 4-{[1-[2-Amino-7-methyl-4-(1-methylethoxy)pteridin-6-yl]ethyl}amino}benzoate (**34**). As described for **32**, with **25** (0.328 g, 1 mmol), ethyl 4-aminobenzoate (0.265 g, 1.6 mmol), and DMF (20 ml) for 3 h: 0.202 g (49%) of **34**. Yellowish solid. M.p. >220° (dec.). R_f (silica gel, $CHCl_3$/MeOH 95:5) 0.58.

^{1}H-NMR ($CDCl_3$): 7.89 (*d*, 2 H *o* to COOEt); 6.67 (*d*, 2 H *o* to NH); 5.60 (br. *d*, NH); 5.55 (*m*, Me_2CH); 5.35 (br. *s*, NH_2); 5.03 (*m*, H–C(1′)); 4.30 (*q*, $MeCH_2O$); 2.77 (*s*, Me–C(7)); 1.51 (*m*, Me(2′), Me_2CH); 1.36 (*t*, $MeCH_2O$). Anal. calc. for $C_{21}H_{26}N_6O_3$ (410.4): C 61.44, H 6.38, N 20.48; found: C 61.41, H 6.35, N 20.10.

7-Methyl-N^4-(4-methylphenyl)-6-{1-[(4-methylphenyl)amino]ethyl}pteridine-2,4-amine (**35**). A soln. of **24** (0.5 g, 1.77 mmol) and 4-methylbenzenamine (1.5 g, 13.8 mmol) in MeCN (50 ml) was heated to 70° for 18 h. After evaporation, the residue was dissolved in $CHCl_3$, the soln. washed with H_2O, dried (Na_2SO_4), concentrated and the residue recrystallized from toluene (80 ml): 0.416 g (61%) of **35**. Yellow crystals. M.p. 244–245°. R_f (silica gel, $CHCl_3$/MeOH 95:5) 0.65. ^{1}H-NMR ($CDCl_3$): 8.58 (br. *s*, NH); 7.69 (*d*, 2 H *o* to Me); 7.21 (*d*, 2 H *o* to Me); 6.96 (*d*, 2 H *o* to NH); 6.58 (*d*, 2 H *o* to NH); 5.24 (br. *s*, NH_2); 4.97 (*m*, H–C(1′)); 2.67 (*s*, Me–C(7)); 2.38 (*s*, MeC_6H_4); 2.19 (*s*, MeC_6H_4); 1.55 (*d*, Me(2′)). Anal. calc. for $C_{23}H_{25}N_7$ (399.5): C 69.15, H 6.31, N 24.54; found: C 68.99, H 6.29, N 24.08.

*2-Amino-7-methyl-6-[1-(phenylamino)ethyl]pteridin-4(3*H*)-one* (**36**). A soln. of **32** (0.12 g, 0.35 mmol) in dioxane (10 ml) was treated with 0.1N NaOH (10 ml) and heated to 80° for 5 h. The mixture was concentrated to a small volume, diluted with H_2O (20 ml), heated, and acidified with AcOH. On cooling, the precipitate was collected and recrystallized from DMF/H_2O: 88 mg (84%) of **36**. Yellow powder. M.p. >300°. R_f (cellulose, PrOH/1% aq. NH_3 soln. 2:1) 0.76. ^{1}H-NMR (CF_3COOD): 8.70 (br. *s*, NH_2); 7.64 (*m*, 5 arom. H); 5.41 (*q*, H–C(1′)); 2.80 (*s*, Me–C(7)); 1.76 (*d*, Me(2′)). Anal. calc. for $C_{15}H_{16}N_6O$ (296.3): C 60.79, H 5.44, N 28.36; found: C 60.56, H 5.40, N 28.28.

*2-Amino-7-methyl-6-{1-[(4-methylphenyl)amino]ethyl}pteridin-4(3*H*)-one* (**37**). *a*) A soln. of **33** (0.17 g, 0.48 mmol) in dioxane (15 ml) and 0.1N NaOH (15 ml) was heated under reflux for 5 h. After evaporation to a small volume, addition of H_2O, heating, and acidifying with AcOH, the precipitate was collected, washed with H_2O, and dried at 100°: 0.142 g (90%) of **37**. Yellow powder. M.p. >300°.

b) Analogously to procedure *a*), with **35** (0.2 g, 0.5 mmol): 0.135 g (82%) of **37**. Yellow powder. M.p. >300°. R_f (cellulose, PrOH/1% aq. NH_3 soln. 2:1) 0.84. ^{1}H-NMR (0.5N NaOD): 6.70 (*d*, 2 H *o* to NH); 6.50 (*d*, 2 H *o* to Me); 4.67 (*m*, H–C(1′)); 2.38 (*s*, Me–C(7)); 1.85 (*s*, MeC_6H_4); 1.20 (*s*, Me(2′)). Anal. calc. for $C_{16}H_{18}N_6O \cdot H_2O$ (328.4): C 58.53, H 6.14, N 25.59; found: C 58.75, H 5.89, N 25.23.

Ethyl 4-{[1-(2-Amino-3,4-dihydro-7-methyl-4-oxopteridin-6-yl)ethyl]amino}benzoate (**38**). As described for **37**, with **34** (0.2 g, 0.48 mmol), 0.1N NaOH (20 ml), and dioxane (20 ml) for 4 h: 0.155 g (89%) of **38**. Yellowish powder. M.p. >300°. R_f (cellulose, PrOH/1% aq. NH_3 soln. 2:1) 0.27. ^{1}H-NMR (0.5N NaOD): 6.70 (*d*, 2 H *o* to COOH); 6.63 (*d*, 2 H *o* to NH); 4.68 (*m*, H–C(1′)); 2.43 (*s*, Me–C(7)); 1.23 (*s*, Me(2′)). Anal. calc. for $C_{16}H_{16}N_6O_3 \cdot H_2O$ (358.3): C 53.62, H 4.85, N 23.45; found: C 53.35, H 5.06, N 23.12.

6-(1-Methoxyethyl)-7-methyl-4-(1-methylethoxy)pteridin-2-amine (**39**). To a soln. of **24** (0.5 g, 1.77 mmol) in abs. MeOH (10 ml) was added Et_3N (1 ml) and then heated under reflux for 2 h. The insoluble solid was filtered off and the filtrate concentrated. The residue was treated with H_2O (20 ml) to form a microcrystalline material which was dried and then recrystallized from toluene: 0.295 g (60%) of **39**. Colorless crystals. M.p. 216–217°. R_f (silica gel, $CHCl_3$/MeOH 95:5) 0.75. ^{1}H-NMR ($CDCl_3$): 5.52 (*m*, Me_2CH); 5.31 (br. *s*, NH_2); 4.74 (*q*, H–C(1′)); 3.29 (*s*, MeO); 2.75 (*s*, Me–C(7)); 1.56 (*s*, Me(2′)); 1.46 (*m*, Me_2CH). Anal. calc. for $C_{13}H_{19}N_5O_2$ (277.3): C 56.30, H 6.91, N 25.25; found: C 55.99, H 6.85, N 25.43.

6-(1-Ethoxyethyl)-7-methyl-4-(1-methylethoxy)pteridin-2-amine (**40**). As described for **39**, with **24** (0.5 g, 1.77 mmol), Et_3N (1 ml), and abs. EtOH (10 ml): 0.28 g (54%) of **40**. Colorless crystals. M.p. 207–208°. R_f (silica gel, $CHCl_3$/MeOH 95:5) 0.48. ^{1}H-NMR ($CDCl_3$): 5.56 (*m*, Me_2CH); 5.30 (br. *s*, NH_2); 4.82 (*q*, H–C(1′)); 3.51–3.34 (*m*, $MeCH_2O$); 2.77 (*s*, Me–C(7)); 1.57 (*s*, Me(2′)); 1.46 (*m*, Me_2CH); 1.18 (*t*, $MeCH_2O$). Anal. calc. for $C_{14}H_{21}N_5O_2$ (291.4): C 57.71, H 7.26, N 24.04; found: C 57.92, H 7.13, N 24.19.

7-Methyl-4-(1-methylethoxy)-6-[1-(1-methylethoxy)ethyl]pteridin-2-amine (**41**). A soln. of **24** (0.28 g, 1 mmol) and Et_3N (0.8 ml) in abs. ^{i}PrOH (20 ml) was heated under reflux for 6 h. After evaporation, the residue was treated with H_2O, and the crystals were collected and purified by CC (silica gel (30 g), CH_2Cl_2/MeOH 50:1). The product was recrystallized from toluene (30 ml): 0.182 g (60%) of **41**. Colorless crystals. M.p. 200–202°. R_f (silica gel, $CHCl_3$/MeOH 95:5) 0.51. ^{1}H-NMR ($CDCl_3$): 5.56 (*m*, Me_2CH); 5.20 (br. *s*, NH_2); 4.95 (*q*, H–C(1′)); 3.57 (*m*, Me_2CH); 2.83 (*s*, Me–C(7)); 1.62 (*s*, Me(2′)); 1.48

(*m*, *Me*$_2$CH); 1.18 (*m*, *Me*$_2$CH). Anal. calc. for $C_{15}H_{23}N_5O_2$ (305.4): C 59.00, H 7.59, N 22.93; found: C 59.02, H 7.50, N 22.72.

*2-Amino-6-(1-methoxyethyl)-7-methylpteridin-4(3*H*)-one* (**42**). A soln. of **39** (0.15 g, 1.54 mmol) in 0.2N NaOH (10 ml) and dioxane (15 ml) was heated under reflux for 2 h. The mixture was concentrated to a small volume, then diluted with H_2O (20 ml), heated, and acidified with AcOH. The precipitate was collected after cooling, washed with H_2O and MeOH, and dried at 100°: 0.102 g (80%) of **42**. Yellow powder. M.p. >260°. R_f (cellulose, PrOH/1% aq. NH_3 soln. 2:1) 0.56. ^{1}H-NMR (0.5N NaOD): 4.63 (*m*, H–C(1′)); 3.06 (*s*, MeO); 2.36 (*s*, Me–C(7)); 1.26 (*d*, Me(2′)). Anal. calc. for $C_{11}H_{15}N_5O_2 \cdot 0.25\ H_2O$ (239.8): C 50.10, H 5.68, N 29.21; found: C 50.45, H 5.57, N 28.94.

*1-(4-Aminophenyl)-1-deoxy-2,3:4,5-di-*O*-isopropylidene-*D*-ribitol* (**43**). A soln. of 1-deoxy-2,3:4,5-di-*O*-isopropylidene-1-{4-[(phenylmethyl)amino]phenyl}-D-ribitol (**50**; 0.5 g, 1.26 mmol) in EtOH (30 ml) was treated with 10% Pd/C (0.1 g) under H_2 in a shaking apparatus until the H_2 uptake ceased (2 h). The catalyst was filtered off and washed with EtOH, the combined filtrate evaporated, the obtained syrup dissolved in acetone, and hexane was slowly added until crystallization took place. The colorless crystals were dried in a vacuum desiccator: 0.348 g (90%) of **43**. M.p. 102–104°. R_f (silica gel, hexane/AcOEt 1:1) 0.51. ^{1}H-NMR ($CDCl_3$): 7.10 (*d*, 2 H *o* to ribitol); 6.63 (*d*, 2 H *o* to NH); 4.39–390 (*m*, H–C(2), H–C(3), H–C(4), CH_2(5)); 3.40 (br. *s*, NH_2); 3.01–2.68 (*dd*, CH_2(1)); 1.44 (*s*, 1 Me); 1.41 (*s*, 1 Me); 1.37 (*s*, 1 Me); 1.29 (*s*, 1 Me). Anal. calc. for $C_{17}H_{25}NO_4$ (307.4): C 66.42, H 8.20, N 4.56; found: C 66.24, H 8.28, N 4.45.

*1-{4-{{1-[2-Amino-7-methyl-4-(1-methylethoxy)pteridin-6-yl]ethyl}amino}phenyl}-1-deoxy-2,3:4,5-di-*O*-isopropylidene-*D*-ribitol* (**44**). To a soln. of **25** (0.2 g, 0.61 mmol) in abs. THF (5 ml) was added **43** (0.282 g, 0.91 mmol), and then the mixture was stirred at r.t. overnight (18 h). The mixture was evaporated and the residue purified by CC (silica gel (10 g), CH_2Cl_2/MeOH 50:1). The product was dried under high vacuum at 40°: 0.21 g (62%) of **44**. Yellowish powder. M.p. >180° (dec.). R_f (silica gel, $CHCl_3$/MeOH 95:5) 0.67). ^{1}H-NMR ($CDCl_3$): 7.10 (*d*, 2 H *o* to ribitol); 6.66 (*d*, 2 H *o* to NH); 5.51 (*m*, Me$_2$C*H*); 5.25 (br. *s*, NH_2); 4.97 (*m*, MeC*H*–C(6′)); 4.40–3.88 (*m*, H–C(2), H–C(3), H–C(4), CH_2(5)); 2.95 (*dd*, 1 H–C(1)); 2.76 (*s*, Me(7)); 2.70 (*m*, 1 H–C(1)); 1.52 (*m*, *Me*CH–C(6′), *Me*$_2$CH); 1.44 (*s*, 1 Me); 1.40 (*s*, 1 Me); 1.36 (*s*, 1 Me); 1.29 (*s*, 1 Me). Anal. calc. for $C_{29}H_{40}N_6O_5$ (552.7): C 63.02, H 7.30, N 15.21; found: C 63.20, H 7.32, N 14.64.

*1-{4-{{1-[2-Amino-7-methyl-4-(1-methylethoxy)pteridin-6-yl]ethyl}amino}phenyl}-1-deoxy-*D*-ribitol* (**45**). To a soln. of **44** (0.4 g, 0.72 mmol) in dioxane (4 ml) was added 0.5N HCl (4 ml), and then the mixture was stirred at r.t. for 3 h. After neutralization with sat. $NaHCO_3$ soln., the mixture was extracted several times with AcOEt, the combined org. phase evaporated, and the resulting solid purified by FC (silica gel (*Baker*), CH_2Cl_2/MeOH 9:1 → 4:1). The product was dried under high vacuum: 0.19 g (55%) of **45**. Yellowish powder. M.p. >200° (dec.). R_f (silica gel, CH_2Cl_2/MeOH 9:1) 0.12. ^{1}H-NMR ((D$_6$)DMSO): 7.04 (br. *s*, NH_2); 6.91 (*d*, 2 H *o* to ribitol); 6.54 (*d*, 2 H *o* to NH); 5.66 (br. *s*, NH–CH–C(6′)); 5.48 (*m*, Me$_2$C*H*); 4.87 (*m*, NHC*H*–C(6′)); 4.60–4.30 (*m*, 4 OH); 3.68–3.30 (*m*, H–C(2), H–C(3), H–(4), CH_2(5)); 2.75 (*dd*, 1 H–C(1)); 2.60 (*s*, Me–C(7)); 2.40 (*m*, 1 H–C(1)); 1.46 (*d*, *Me*CH–C(6′)); 1.41 (*d*, *Me*$_2$CH). Anal. calc. for $C_{23}H_{32}N_6O_5$ (472.6): C 58.46, H 6.83, N 17.78; found: C 48.30, H 6.26, N 17.51.

*1-{4-{[1-(2-Amino-3,4-dihydro-7-methyl-4-oxopteridin-6-yl)ethyl]amino}phenyl}-1-deoxy-*D*-ribitol* (**46**). To a soln. of **44** (0.12 g, 0.22 mmol) in dioxane (10 ml) was added 1N HCl (10 ml), and then the mixture was heated to 100° with stirring for 3.5 h. The mixture was evaporated to a small volume and then neutralized with dil. $NaHCO_3$ soln. The precipitate was collected, washed with H_2O and MeOH, and dried under high vacuum at 40°: 76 mg (78%) of **46**. Yellowish powder. M.p. >260° (dec.). R_f (cellulose, PrOH/1% aq. NH_3 soln. 2:1) 0.41. ^{1}H-NMR (0.5N NaOD): 6.89 (*d*, 2 H *o* to ribitol); 6.66 (*d*, 2 H *o* to NH); N*H*–CH–C(6′) and O–CH covered by HDO; 4.87 (*m*, MeC*H*–C(6′)); 3.70–3.38 (*m*, H–C(2), H–C(3), H–C(4′), CH_2(5)); 2.75–2.27 (*m*, CH_2(1)); 2.49 (*s*, Me(7)); 1.32 (*d*, *Me*CH–C(6′)). Anal. calc. for $C_{20}H_{26}N_6O_5 \cdot H_2O$ (430.5): C 53.56, H 6.29, N 18.74; found: C 53.28, H 6.27, N 18.47.

N-*4-(Bromophenyl)benzamide* (**47**) [13]. A soln. of 4-bromobenzenamine (20 g, 0.116 mmol) in pyridine (100 ml) was cooled to 0–5°, and then benzoyl chloride (14.5 ml) was added dropwise under stirring. The mixture was stirred at r.t. for 30 min, and then H_2O was added gradually whereby a precipitate separated. The solid was collected, washed with H_2O, and recrystallized from EtOH (800 ml)

with charcoal: 25.5 g (81%) of **47**. Colorless crystals. M.p. 200–201° ([13]: 200–202°). R_f (silica gel, hexane/AcOEt 2:1) 0.55. ^{1}H-NMR ((D$_6$)DMSO): 9.30 (br. *s*, BzN*H*); 7.45–7.12 (*m*, 9 arom. H).

N-*{4-[(1*S*)-2,3:4,5-di*-O-*isopropylidene*-D-*ribitol-1*-C-*yl]phenyl}benzenamide* (**49**). A soln. of **47** (3.7 g, 13.7 mmol) in abs. THF (200 ml) was cooled to −60°, and then 1.6M BuLi in hexane (17.1 ml) was slowly added under stirring, followed by 2,3:4,5-di-*O*-isopropylidene-D-ribose (**48**) [14] (2.0 g, 8.7 mmol). The mixture was stirred for 15 min at −60° and then warmed to r.t. within 90 min. Subsequently, Et_2O (200 ml) and H_2O (100 ml) were added. The org. phase was washed with H_2O, dried (Na_2SO_4), and concentrated, and the residue purified by CC (silica gel (140 g), hexane/AcOEt 4:1 (→ by-products), then hexane/AcOEt 2:1): 2.32 g (62%) of **49**. Solid. M.p. 136–137°. R_f (silica gel, cyclohexane/AcOEt 2:1) 0.23. ^{1}H-NMR ($CDCl_3$): 7.99–7.28 (*m*, 9 arom. H, NH); 5.08 (*dd*, 1 H–C(1′)); 4.66–3.78 (*m*, H–C(2), H–C(3), H–C(4′), CH_2(5′)); 2.91 (*d*, OH); 1.52 (*s*, 1 Me); 1.40 (*s*, 1 Me); 1.35 (*s*, 2 Me). Anal. calc. for $C_{24}H_{29}NO_6$ (427.5): C 67.43, H 6.84, N 3.28; found: C 66.83, H 6.90, N 3.25.

*1-Deoxy-2,3:4,5-di-*O-*isopropylidene-1-{4-[(phenylmethyl)amino]phenyl}-*D-*ribitol* (**50**). A soln. of **49** (0.5 g, 1.18 mmol) in abs. THF (40 ml) was treated with $LiAlH_4$ (0.8 g, 21.2 mmol) in a glass autoclave at 80° for 30 h. H_2O was slowly added to the mixture until H_2 evolution ceased. The $Al(OH)_3$ was filtered off and washed with Et_2O, and the combined org. phase dried (Na_2SO_4) and concentrated to give an oil which crystallized on standing: 0.352 g (75%) of **50**. Colorless crystal powder. M.p. 97–98°. R_f (silica gel, cyclohexane/AcOEt 2:1) 0.20. ^{1}H-NMR ($CDCl_3$): 7.37–7.26 (*m*, 5 arom. H); 7.11 (*d*, 2 H *o* to NH); 6.59 (*d*, 2 H *o* to NH); 4.36–3.91 (*m*, H–C(2), H–C(3), H–C(4), CH_2(5)); 4.31 (*d*, Ph*C*H$_2$); 2.99–2.68 (2*dd*, 2 H–C(1)); 1.44 (*s*, 1 Me); 1.42 (*s*, 1 Me); 1.37 (*s*, 1 Me); 1.29 (*s*, 1 Me). Anal. calc. for $C_{24}H_{31}NO_4$ (397.5): C 72.52, H 7.86, N 3.52; found: C 72.69, H 8.10, N 3.53.

*1-Deoxy-1-{4-[(phenylmethyl)amino]phenyl}-*D-*ribitol* (**51**). A soln. of **50** (0.7 g, 1.76 mmol) in 1N HCl (50 ml) was stirred at 100° for 1 h. After cooling, the mixture was filtered and the filtrate neutralized with solid K_2CO_3. Then the soln. was brought to pH 12 with 1N NaOH followed by extraction with AcOEt (2 × 100 ml). The extract was dried (Na_2SO_4) and concentrated, the residue dissolved in little acetone, and hexane added slowly until turbidity. After standing in the icebox for several hours, the solid was collected and dried in a vacuum desiccator: 0.463 g (83%) of **50**. Crystal powder. M.p. 129–130°. R_f (silica gel, $CHCl_3$/MeOH 1:1) 0.82. ^{1}H-NMR ((D$_6$)DMSO): 7.36–7.19 (*m*, *Ph*CH$_2$); 6.88 (*d*, 2 H *o* to NH, 2 H *o* to ribitol); 5.99 (*t*, NH); 4.59 (*d*, 1 OH); 4.54 (*d*, 1 OH); 4.35 (*m*, 2 OH); 4.31 (*d*, PhC*H*$_2$); 3.60–3.25 (*m*, 3 CH, 1 CH$_2$); 2.72–2.32 (2*dd*, 2 H–C(1)). Anal. calc. for $C_{18}H_{23}NO_4$ (317.4): C 68.11, H 7.30, N 4.41; found: C 68.18, H 7.35, N 4.54.

*1-(4-Aminophenyl)-1-deoxy-*D-*ribitol* (**52**). *a*) A mixture of **43** (0.2 g, 0.66 mmol) in dioxane (10 ml) and 1N HCl (10 ml) was refluxed for 3 h. After cooling, the mixture was evaporated, the residue dissolved in H_2O, and the soln. adjusted to pH 11 with 1N NaOH. The soln. was adsorbed on silica gel (10 g) and subjected to CC (silica gel, $CHCl_3$/MeOH 1:1). The product was dried under high vacuum: 0.102 g (69%) of **52**.

b) To a suspension of **51** (0.2 g, 0.62 mmol) in EtOH (50 ml, 96%) was added 10% Pd/C (0.1 g), and the mixture was hydrogenated under H_2 in a shaking apparatus. The consumption of H_2 ceased after 1 h. The catalyst was filtered off through silica gel, the filtrate evaporated, and the resulting syrup crystallized from acetone/hexane: 0.116 g (81%) of **52**. R_f (silica gel, $CHCl_3$/MeOH 1:1) 0.59. ^{1}H-NMR ((D$_6$)DMSO): 6.87 (*d*, 2 H *o* to ribitol); 6.43 (*d*, 2 H *o* to NH); 4.76 (br. *s*, NH_2); 4.62 (*d*, 1 OH); 4.55 (*t*, OH–C(5)); 4.38 (*m*, 2 OH); 3.65–3.25 (*m*, 3 CH, 1 CH$_2$); 2.73–2.28 (*m*, 2 H–C(1)). Anal. calc. for $C_{11}H_{17}NO_4$ (227.3): C 58.13, H 7.54, N 6.16; found: C 58.55, H 7.28, N 6.08.

*2,3-*O-*Isopropylidene-5-*O-*(monomethoxytrityl)-*D-*ribofuranose* (**53**). A soln. of 2,3-*O*-isopropylidene-D-ribofuranose [28] (4.2 g, 22.1 mmol) in abs. pyridine (10 ml) was treated with monomethoxytrityl chloride (8.2 g, 26.5 mmol) by stirring at r.t. overnight. After evaporation, dil. $NaHCO_3$ soln. was added, and the mixture several times extracted with Et_2O. The extract was dried (Na_2SO_4) and again evaporated, and the residue purified by CC (silica gel (100 g), hexane/AcOEt 9:1 → 6:1). The product was dried under high vacuum: 8.62 g (84%) of **53**. Amorphous solid. R_f (silica gel, hexane/AcOEt 4:1) 0.51. ^{1}H-NMR ($CDCl_3$): 7.41–7.23 (*m*, 12 arom H); 6.85 (*m*, 2 H *o* to MeO); 5.33 (*d*, H–C(1)); 4.80 (*d*, OH); 4.67 (*d*, H–C(2)); 4.33 (‘*t*’, H–C(3)); 4.08 (*d*, H–C(4)); 3.80 (*s*, MeO); 3.36 (*m*, 2 H–C(5)); 1.48 (*s*, 1 Me); 1.35 (*s*, 1 Me). Anal. calc. for $C_{28}H_{30}O_6$ (462.5): C 72.71, H 6.54; found: C 72.75, H 6.64.

2,3-O-*Isopropylidene*-D-*ribofuranose 5-Benzoate* (**54**) [29]. A soln. of 2,3-*O*-isopropylidene-D-ribofuranose [28] (2.1 g, 11 mmol) were co-evaporated in abs. pyridine (5 ml) to remove any moisture. The resulting syrup was dissolved in abs. pyridine (10 ml) and cooled in ice. Then benzoyl chloride (1.72 g, 12.1 mmol) was added dropwise with stirring followed by warming to r.t. After 30 min, the mixture was poured on ice and extracted several times with Et_2O. The extract was dried (Na_2SO_4) and concentrated, and the residue purified by CC (silica gel (50 g), hexane/AcOEt 5:1 → 4:1). The product was dried under high vacuum: 2.87 g (88%) of **54**. Colorless oil. R_f (silica gel, hexane/AcOEt 2:1) 0.59. ^{1}H-NMR ($CDCl_3$): 8.03 (*m*, 2 H *o* to CO); 7.56–7.38 (*m*, 3 arom H); 5.52 (*d*, H–C(1)); 4.80 (*d*, H–C(3)); 4.67 (*d*, H–C(2)); 4.52 (*m*, 2 H–C(5)); 4.35 (*d*, H–C(4)); 3.55 (*d*, OH); 1.47 (*s*, 1 Me); 1.34 (*s*, 1 Me).

2,3-O-*Isopropylidene-5-(monomethoxytrityl)-β*-D-*ribofuranose 1-(1,1,1-Trichloroethanimidate)* (**55**). To a soln. of **53** (3.0 g, 6.5 mmol) in CH_2Cl_2 (10 ml) was added 1,1,1-trichloroacetonitrile (3.87 g, 26.7 mmol), followed by a small amount of NaH (10 mg) to start the reaction. After stirring for 30 min, more NaH (0.2 g) was added, and the mixture was stirred at r.t. for 4 h. Insoluble material was filtered off, and the filtrate was evaporated. The residue was purified by CC (silica gel (80 g), hexane/AcOEt 7:1 → 5.5:1). The product was dried under high vacuum: 3.11 g (79%) of **55**. Amorphous solid. R_f (silica gel, hexane/AcOEt 4:1) 0.66. ^{1}H-NMR ($CDCl_3$): 8.42 (*s*, NH); 7.44–7.20 (*m*, 12 arom. H); 6.80 (*m*, 2 H *o* to MeO); 6.22 (*d*, H–C(1)); 4.71 (*m*, 2 H–C(5)); 4.61 (*d*, H–C(2)); 3.79 (*s*, MeO); 3.40 (*dd*, H–C(3)); 3.09 (*t*, H–C(4)); 1.53 (*s*, Me); 1.34 (*s*, Me). Anal. calc. for $C_{30}H_{30}Cl_3NO_6$ (406.9): C 59.37, H 4.98, N 2.31; found: C 59.47, H 5.18, N 2.32.

2,3-O-*Isopropylidene-β*-D-*ribofuranose 5-Benzoate 1-(1,1,1-Trichloroethanimidate)* (**56**). As described for **55**, with **54** [29] (0.8 g, 2.72 mmol), CH_2Cl_2 (10 ml), and NaH (0.5 g; 1 batch). Purification by CC (silica gel (10 g), CH_2Cl_2/Et_2O) gave 1.08 g (91%) of **56**. Amorphous solid. M.p. 130°. R_f (silica gel, hexane/AcOEt 4:1) 0.62. ^{1}H-NMR ($CDCl_3$): 8.55 (*s*, NH); 8.03 (*m*, 2 H *o* to CO); 7.55–7.41 (*m*, 3 arom. H); 6.37 (*d*, H–C(1)); 4.93 (*d*, H–C(3)); 4.87 (*d*, H–C(2)); 4.61 (*d*, H–C(4)); 4.40 (*m*, 2 H–C(5)); 1.52 (*s*, 1 Me); 1.35 (*s*, 1 Me). Anal. calc. for $C_{17}H_{18}Cl_3NO_6$ (438.7): C 46.55, H 4.14, N 3.19; found: C 46.82, H 4.26, N 3.37.

2′,3′-O-*Isopropylidene-5-methyl-5′*-O-*(monomethoxytrityl)uridine* (**58**). A mixture of thymine (0.51 g, 4 mmol) in hexamethyldisilazane (HMDS; 5 ml) and $(NH_4)_2SO_4$ (20 mg) was heated under reflux overnight to form 5-methyl-2,4-bis[(trimethylsilyl)oxy]pyrimidine (**57**). The mixture was evaporated under high vacuum and the residue combined with a soln. of **55** (2.4 g, 4 mmol) in CH_2Cl_2 (20 ml). Then $BF_3 \cdot Et_2O$ (0.16 ml, 1.28 mmol) was added under stirring, and the mixture was stirred at r.t. for 5 h. The mixture was treated with sat. $NaHCO_3$ soln. and then extracted several times with AcOEt, the org. phase dried (Na_2SO_4) and concentrated, and the oil purified by FC (silica gel (30 g), CH_2Cl_2/MeOH 9:1). The product was dried under high vacuum: 1.05 (46%) of **58**. Amorphous solid consisting of an *α*/*β*-D-anomer mixture. R_f (silica gel, hexane/AcOEt 2:1) 0.21. UV (MeOH): 230, (sh, 4.28), 266 (4.08). ^{1}H-NMR ($CDCl_3$): 8.28 (*s*, NH(3)); 7.41–7.22 (*m*, 12 arom. H, H–C(6)); 6.83 (*m*, 2 arom. H); 6.50 (*d*, H–C(1′)); 4.96 (*d*, H–C(3′)); 4.56 (*dd*, H–C(2′)); 4.40 (*m*, H–C(4′)); 3.98 (*s*, MeO); 3.49 (*dd*, 1 H–C(5′)); 3.10 (*dd*, 1 H–C(5′)); 1.93 (*s*, Me–C(5)); 1.40 (*s*, Me); 1.26 (*s*, Me). Anal. calc. for $C_{33}H_{34}N_2O_7$ (570.6): C 69.46, H 6.01, N 4.91; found: C 69.00, H 6.16, N 4.54.

2-Hydroxypentanedioic Acid (**59**) *Disodium Salt* [30]. A soln. of L-glutamic acid (75 g, 0.5 mol) in 37.5% H_2SO_4 soln. (150 ml) was cooled to −10°, and then a soln. of KNO_2 (85 g, 1 mol) in H_2O (150 ml) was added dropwise slowly with stirring. After addition, the soln. was concentrated to 200 ml at <40°. The precipitating K_2SO_4 was filtered off and the filtrate continuously extracted with Et_2O for 20 h. The extract was evaporated and the residue treated with 1N NaOH (100 ml). After evaporation and co-evaporation with EtOH, a colorless powder was obtained which was dried in a vacuum desiccator over P_4O_{10}: 60.5 g (62%) of the disodium salt of **59**. ^{1}H-NMR (D_2O): 3.86 (*dd*, H–C(2)); 2.11 (*m*, CH_2(4)); 1.86–1.66 (*m*, CH_2(3)). Anal. calc. for $C_5H_6Na_2O_5$ (192.1): C 31.24, H 3.14; found: C 30.60, H 3.18.

Bis(4-nitrobenzyl) 2-Hydroxypentanedioate (**60**). A suspension of the disodium salt of **59** (10 g, 52 mmol) and 4-nitrobenzyl chloride (19.7 g, 0.115 mol) in DMF (10 ml) was stirred in at 120° for 6 h. The hot soln. was filtered, the filtrate concentrated, and the residue dissolved in excess of AcOEt. After washing with H_2O, drying (Na_2SO_4), and evaporation, the resulting solid was recrystallized from toluene: 16.7 g (77%) of **60**. Colorless crystals. M.p. 89–90°. R_f (silica gel, hexane/AcOEt 1:1) 0.64. ^{1}H-NMR ($CDCl_3$): 8.22 (*m*, 4 H *o* to NO_2); 7.49 (*m*, 4 H *m* to NO_2); 5.28 (*dd*, CH_2O); 5.19 (*s*, CH_2O); 4.30 (*m*,

H–C(2)); 2.56 (*m*, CH_2(4)); 2.50–2.32 (*m*, CH_2(3)); 1.56 (br. *s*, OH). Anal. calc. for $C_{19}H_{18}N_2O_9$ (418.4): C 54.55, H 4.34, N 6.70; found: C 55.03, H 4.48, N 6.55.

Bis(4-nitrobenzyl) 2-{[(2-Cyanoethoxy)(diisopropylamino)phosphino]oxy}pentanedioate (**61**). To a soln. of **60** (0.42 g, 1 mmol) in CH_2Cl_2 (10 ml) was added 2-cyanoethyl *N,N,N′,N′*-tetraisopropylphosphorodiamidite (0.47 g, 1.55 mmol). After 5 min stirring, 1*H*-tetrazole (0.28 g, 4 mmol) was added for activation, and the mixture was stirred at r.t. overnight. The mixture was diluted with $CHCl_3$, washed with phosphate buffer pH 7 and then H_2O, the org. phase dried (Na_2SO_4) and concentrated, and the residue purified by CC (silica gel (20 g), hexane/AcOEt 4:1 → 2.5:1 containing a few drops of Et_3N). The product was dried under high vacuum: 0.53 g (85%) of **61**. Colorless amorphous solid. R_f (silica gel, hexane/AcOEt 2:1) 0.50. ^{1}H-NMR ($CDCl_3$): 8.21 (*m*, 4 H *o* to NO_2); 7.51 (*m*, 4 H *m* to NO_2); 5.25 (*dd*, CH_2O); 5.18 (*s*, CH_2O); 4.50–4.32 (*m*, H–C(2)); 3.89–3.52 (*m*, NCCH_2CH$_2$, 2 Me$_2$C*H*); 2.59 (*m*, NCCH$_2$CH_2, CH_2(4)); 2.16 (*m*, CH_2(3)); 1.12 (*m*, 2 *Me*$_2$CH). Anal. calc. for $C_{28}H_{35}N_4O_{10}P$ (618.6): C 54.37, H 5.70, N 9.06; found: C 53.70, H 5.70, N 9.00.

*Bis(4-nitrobenzyl) 2-{[(*N^6*-Benzoyl-2′,3′-*O*-isopropylideneadenosin-5′-*O*-yl)(2-cyanoethoxy)phosphinyl]oxy}pentanedioate* (**62**). *N*^{6}-Benzoyl-2′,3′-*O*-isopropylideneadenosine [31] (92 mg, 0.22 mmol) was dried under high vacuum overnight and then dissolved under Ar in MeCN (3 ml). To this soln., **61** (0.2 g, 0.32 mmol) and then 1*H*-tetrazole (70 mg, 1 mmol) were added. After stirring for 2 h, a soln. of I_2 (0.5 g) in CH_2Cl_2/H_2O/pyridine 1:1.3 was added dropwise until decoloration ceased. The mixture was diluted with $CHCl_3$ and washed with sat. NaCl soln. containing some $Na_2S_2O_3$. The aq. solns. were reextracted with $CHCl_3$. The combined org. phase was dried (Na_2SO_4) and evaporated, and the resulting residue purified by FC (silica gel (10 g), CH_2Cl_2/MeOH 49:1). The product was dried under high vacuum: 0.136 g (66%) of **62**. Amorphous solid. R_f (silica gel, CH_2Cl_2/MeOH 97:3) 0.24. UV (MeOH): 270 (4.53). ^{1}H-NMR ($CDCl_3$): 9.09 (br. *s*, NH); 8.77 (*d*, H–C(8) (ado)); 8.15 (*m*, 4 H *o* to NO_2, H–C(2) (ado)); 7.51 (*m*, 9 arom. H); 6.17 (*t*-like, H–C(1′)); 5.43 (*m*, H–C(2′)); 5.22 (*s*, CH_2O); 5.14 (*s*, CH_2O, H–C(3′)); 4.90 (*m*, H–C(2)); 4.43 (*m*, H–C(4′)); 4.41–4.06 (*m*, CH_2(5′), NCCH_2CH$_2$); 2.68 (*m*, CH_2(4)); 2.50 (*m*, NCCH$_2$CH_2); 2.29–2.04 (*m*, CH_2(3); 1.60 (*s*, 1 Me); 1.37 (*s*, 1 Me). ^{31}P-NMR($CHCl_3$): –1.58; –1.64.

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