Synthesis and Reactivity in [3 + 2] Cycloadditions of Isoxanthopterin *N(5)*-Oxides – A New Synthesis of 6-Substituted Pteridinediones

by **Thomas Steinlin**, **Tiziana Sonati**, and **Andrea Vasella***

Laboratorium für Organische Chemie, Departement Chemie und Angewandte Biowissenschaften, ETH-Zürich, HCI, CH-8093 Zürich (e-mail: vasella@org.chem.ethz.ch)

Intramolecular condensation of the *N*-(4-amino-5-nitrosopyrimidin-4-yl)-2-chloroacetamide **2** led to the pteridinone *N(5)*-oxide **4**, while treatment of **2** with Me_3P yielded the 8-(chloromethyl)purine **3**. A high-yielding [3 + 2] dipolar cycloaddition of the *N(5)*-oxide **4** to electron-poor dipolarophiles, followed by spontaneous N,O-bond cleavage, gave the *C(6)*-substituted pteridinones **8a** – **8d** that were deprotected to provide the pteridine-4,7(3*H*,8*H*)-diones **9a** – **9d**, constituting a new synthesis of pterinones possessing a functionalised side chain at C(6).

Introduction. – The first pteridine *N*-oxides were isolated in 1963 by *Pachter et al.* [1] who prepared a range of 6-substituted pteridine *N(5)*-oxides by condensation of acetonyl-, phenacyl-, and α-cyanobenzylpyridinium salts with a 6-amino-5-nitrosopyrimidine under basic conditions. The structure of the *N*-oxides was established by deoxygenating the *N*-oxides with *Raney*-Ni to the corresponding known pteridine. The synthesis of *N*-oxides of lumazines[1]) was studied in detail by *Pfleiderer et al.* [2 – 4]. They observed that oxidation of lumazines occurs preferentially at N(8), and that the regioselectivity of the oxidation depends strongly on steric factors. As illustrated by the oxidation of 7-oxolumazine with H_2O_2 to produce 6,7-dioxolumazine [5] rather than the expected *N*-oxide, pteridinone *N*-oxides are not readily available.

In 1972, *Mason* and *Tennant* described the reaction of quinoxalin-3(4*H*)-one *N(1)*-oxides with benzyne and with aryl isocyanates [6]. Benzyne led to 2-substituted phenols by [3 + 2] dipolar cycloaddition and N,O-bond cleavage. A [3 + 2] dipolar cycloaddition with aryl isocyanates led to secondary diarylamines by loss of CO_2. Subsequently, *Kim et al.* explored the 1,3-dipolar cycloaddition of benzopyrazine *N*-oxides in the synthesis of annulated quinoxalines [7 – 9], while *Hisano* and co-workers studied [3 + 2] dipolar cycloadditions of aromatic *N*-oxides [10 – 12]. Surprisingly, however, the reactivity of pteridine *N*-oxides as 1,3-dipoles was never explored.

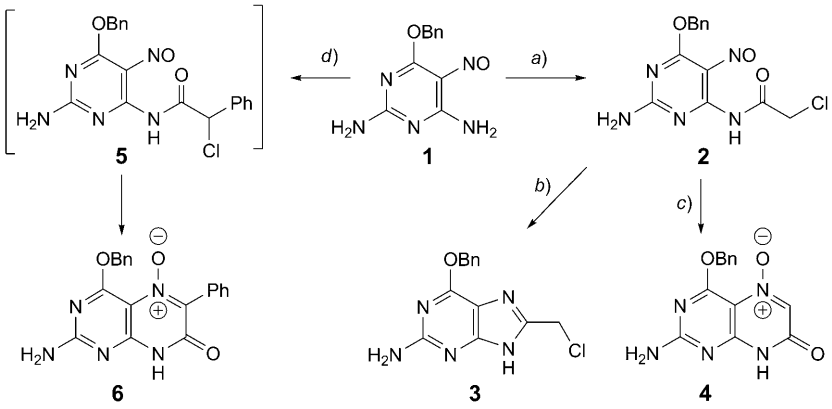
We described a synthesis of 6-substituted pteridinones by *Diels – Alder* cycloaddition of *N*-dienoyl-amino(nitroso)pyrimidines and by ene reactions of *N*-alkenoyl amino(nitroso)pyrimidines [13][14], while heating the same *N*-acylated pyrimidines with phosphines led to 8-substituted guanines [15]. Evaluating new approaches to 6-substituted pteridines, we have considered that the intramolecular (formal) condensa-

[1]) Lumazin = pteridin-2,4(1*H*,3*H*)-dione; pterin = 2-aminopteridin-4(1*H*)-one; isoxanthopterin = 2-aminopteridin-4,7(1*H*,8*H*)-dione.

tion of [(chloroacetyl)amino](nitroso)pyrimidines should lead to pterinone *N(5)*-oxides while treating the 6-[(chloroacetyl)amino]-5-nitrosopyrimidines with phosphines should lead to 8-(chloromethyl)purines. The *N*-oxides are acylnitrones, and should readily undergo [3+2] dipolar cycloadditions. We expected the resulting isoxazolidines to react further by reductive scission of the N,O bond, as it was observed for similar intermediates [6][16]. Such a *β*-elimination would lead to pterinones possessing a differently functionalised 6-substituent. We report the results of this study.

Results and Discussion. – Acylation of 4-(benzyloxy)-2,6-diamino-5-nitrosopyrimidine (**1**) [17] with chloroacetic anhydride in THF gave a blue precipitate of the chloroacetamide **2** (*Scheme 1*). Treating its suspension in *o*-xylene in a flame-dried *Schlenk*-tube with Me_3P in THF yielded 62% of 8-(chloromethyl)purine **3**, according to the known reductive cyclisation of such nitrosoamides [18]. The chloromethyl compound **3** was isolated by filtration and purified by washing with toluene and Et_2O, but it proved too highly reactive to allow purification by chromatography on silica gel.

Scheme 1



a) Chloroacetic anhydride, THF; 94%. *b*) Me_3P, *o*-xylene; 62%. *c*) DMSO; *ca.* 98%. *d*) 2-Chloro-2-phenylacetyl chloride, THF; 68%.

The precipitate of the chloroacetamide **2** proved poorly soluble in most organic solvents[2]), except DMSO and DMF. The deep blue colour of its solution in DMSO faded progressively, and **2** was transformed, within 24 h, to yield 98% of the acyl nitrone **4**. That this transformation is not restricted to solutions in DMSO is suggested by the transformation of the 5-nitrosopyrimidine **1** in THF to the 6-phenylpteridinone *N(5)*-oxide **6**. Treating a suspension of **1** with 2-chloro-2-phenylacetyl chloride led first to a

[2]) Insoluble in THF, AcOEt, MeOH, EtOH, CH_2Cl_2, 1,2-dichloroethane, $CHCl_3$, hexane, pentane, and toluene; moderatly soluble, upon heating, in acetone, MeCN, and dioxane.

greenish solution, presumably of the 5-nitrosopyrimidine **5**, and then to a colourless precipitate of nitrone **6**[3]) that was isolated in a yield of 68%.

The chloroacetamide **2** is characterised by the $ClCH_2$ *s* at 4.86 ppm and, in the HR-MALDI-MS, by a ^{37}Cl isotope peak with 31% intensity of the ^{35}Cl signal. The 8-(chloromethyl)purine **3** is characterised by a $[M+2]$ signal with 28% intensity of the parent HR-MALDI-MS signal, a broad NH *s* at 12.77 ppm, and a sharp $ClCH_2$ *s* at 4.75 ppm. C(6) of the nitrones **4** and **6** is shielded by 23 and 20 ppm, respectively, as compared to the average chemical shift for C(6) of the pteridines **8a**–**8d** (*cf. Scheme 2*), evidencing the higher electron density at C(6) of **4** and **6**. The H–C(6) signal of **4** is hidden under the Ph signals of the Bn group.

Heating a suspension of the nitrone **6** in the presence of the electron-poor dipolarophiles **10**–**13** yielded, after filtration, the 6-substituted pteridinones **8a**–**8d** as pure, poorly soluble products (*Scheme 2*). The isoxazole **7** could not be detected, similarly to the dihydro-1,2-oxazines initially resulting from the *Diels–Alder* cycloaddition of *N*-dienoyl-amino(nitroso)pyrimidines [18]. The elimination transforming **7** into the products removes two stereogenic centers and thereby the information about the *endo*/*exo* selectivity. The regioselectivity of the cycloaddition was predicted by semiempirical calculations, as shown for methyl acrylate in *Table 1*.

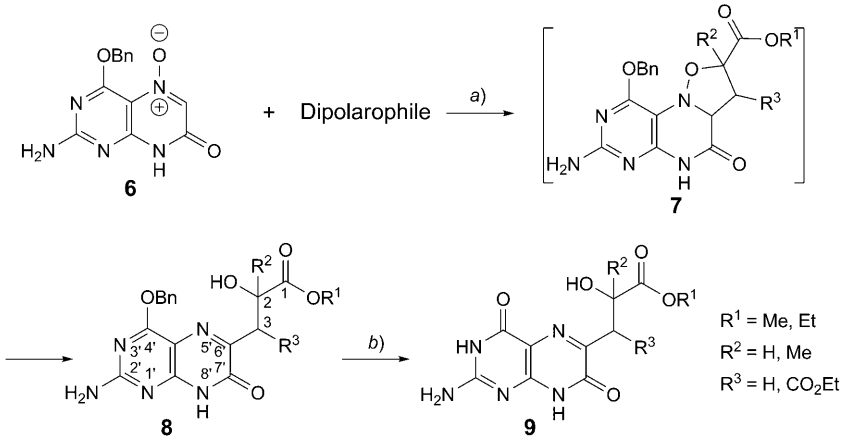
The poor solubility of **8a**–**8d** in many common organic solvents caused significant difficulties in separating product mixtures, and only dipolarophiles leading to single products were considered useful. Reactions of other dipolarophiles, such as enamines, enol ethers, alkenes, and alkynes, yielded complex mixtures and were not examined any further.

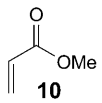
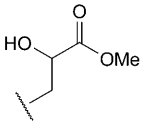
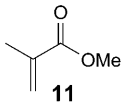
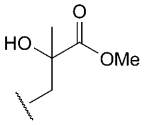
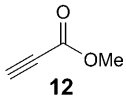
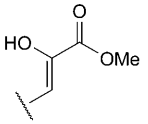
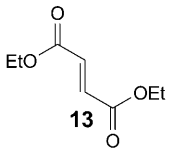
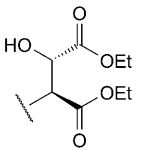
The structure of the pteridine derivatives **8a**–**8d** follows unambiguously from their spectroscopic data. The alcohols **8a** and **8b**, giving rise to very similar analytical data, are characterised by OH ATR-IR bands at 3413 or 3411 cm^{-1}, HR-MALDI-MS, and a *d* at 5.53 ppm ($J = 6.0$ Hz) or a *s* at 5.29 ppm of the OH group that slowly exchanged with D_2O. The diastereotopic H of the CH_2 group resonate at 3.03 and 2.88 ppm as two *dd* ($J = 14.4$, 6.3 and 14.4, 7.5 Hz, resp.) in **8a** and as two *d* ($J = 14.4$ Hz) at 3.09 and 2.93 ppm in **8b**. The pteridinone **8a** displays an additional *q* at 4.49 ppm ($J \approx 6.3$ Hz) for H–C(2) and **8b** a Me *s* at 1.31 ppm. The ^{13}C signals (*Table 2* in the *Exper. Part*) were assigned by comparison to known data [15]. The ^1H-NMR spectrum of **8c** shows *s*s at 13.81 and 6.80 ppm, in keeping with a *s* at 155.02 ppm (C(2)) and a *d* at 97.66 ppm (C(3)). Most probably, the enol **8c** of the α-keto ester is the more stable tautomer, as the OH group forms a strong H-bond to N(5), as reflected by a ^1H-NMR OH signal at 13.81 ppm. The UV spectrum of **8c** shows a maximum at 422 nm ($\log \varepsilon$ 3.45) as compared to λ_{max} at 342–344 nm for **8a**, **8b**, and **8d**, indicating an extended chromophore of **8c**. The constitution of **8d** is established by a HR-MALDI-MS, and by ATR-IR, UV, and NMR spectra. The *(R*,R*)* configuration of **8d** is suggested by the reaction mechanism, but could not be unambiguously derived from the ^1H-NMR spectrum in (D_6)DMSO.

---

[3]) It is not clear if these *N*-oxides result from nucleophilic substitution of the Cl substituent by the NO group and deprotonation, or by addition of an enol to the NO group and elimination. A relatively facile enolisation of the formal acylamino group is suggested by the electrophilic nature of the amide resulting from substitution of the formal amide N-atom by a pyrimidylnitroso moiety.

Scheme 2

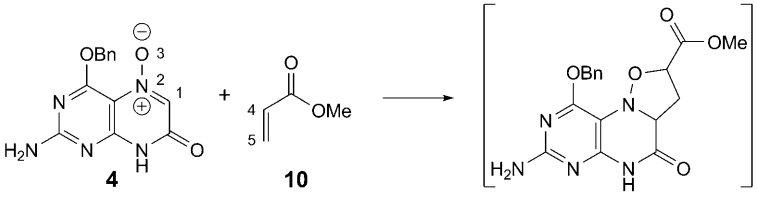


Entry	Dipolarophile	Product	R^1	R^2	R^3	Yield of **8**	Yield of **9**
a	 **10**		Me	H	H	95%	93%
b	 **11**		Me	Me	H	95%	95%
c	 **12**		Me	–	–	93%	94%
d	 **13**		Et	H	CO_2Et	97%	93%

a) Dipolarophile, toluene, 100°. *b*) Me_3SiCl, LiBr, MeCN.

The pteridinones **8a**–**8d** were debenzylated with *in situ* generated Me_3SiBr to yield 93–95% of the pteridine-4,7(3*H*,8*H*)-diones **9a**–**9d**. Their structure was established by their ATR-IR, and ^{13}C- and ^1H-NMR spectra (disappearance of the Bn and appearance of an additional NH signal between 10.96 and 11.36 ppm) and by the similarity of the UV spectra to those of **8a**–**8d**. The very poor solubility of **9a**–**9d** resulted in a HR-MALDI-MS $[M+H]^+$ peak of low intensity relative to the matrix signals.

Table 1. *LUMO and HOMO Energies and Orbital Coefficients of* **4** *and* **10** *Obtained from AM1 Calculations* [19]



		E [eV]	p^Z Coefficients[a])				
			C(1)	N(2)	O(3)	C(4)	C(5)
4	LUMO	– 1.032	0.326	– 0.332	0.264		
	HOMO	– 9.285	*– 0.670*	– 0.1591	*0.366*		
10	LUMO	– 0.014				*0.483*	*– 0.658*
	HOMO	– 11.073				0.680	0.649

[a]) Figures in italics refer to favourable HOMO – LUMO interactions.

This transformation of the 2,6-diamino-4-(benzyloxy)-5-nitrosopyrimidine (**1**) provides a facile access to a variety 6-substituted pteridines.

We thank *Novartis AG*, Basel, for a fellowship, the *ETH-Zürich* for financial support, and *Dr. Bruno Bernet* for checking the analytical data.

Experimental Part

General. Solvents were distilled before use. Reactions were carried out under N_2, unless stated otherwise. Qual. TLC: precoated silica-gel plates (*Merck* silica gel *60* F_{254}); detection under UV (254 nm). Flash chromatography (FC): silica gel *Fluka 60* (0.04 – 0.063 mm). M.p.: uncorrected. UV Spectra: λ_{max} (log ε). FT-IR Spectra: neat (ATR), absorption in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: chemical shifts δ in ppm rel. to Me_4Si as external standard, and coupling constants *J* in Hz. HR-MALDI-MS: in gentisic acid (=2,5-dihydroxybenzoic acid (DHB)) or 3-hydroxypropionaldehyde (3-HPA) matrix.

N-*[2-Amino-6-(benzyloxy)-5-nitrosopyrimidin-4-yl]-2-chloroacetamide* (**2**). A soln. of **1** (490 mg, 2 mmol) in THF (20 ml) was treated at 0° with a soln. of chloroacetic anhydride (410 mg, 2.4 mmol) in THF (5 ml), stirred for 15 min at 0° and for 1 h at amb. temp., and diluted with Et_2O (40 ml). The blue precipitate was filtered off, and drying afforded **2** (606 mg, 94%). Blue powder. R_f (CH_2Cl_2/MeOH 9 : 1) 0.58. M.p. > 170° (dec.). UV (MeOH): 209 (4.28), 256 (4.01), 347 (4.31). IR (ATR): 3432*m*, 3289*w*, 3133*m*, 3100*m*, 2962*w*, 1723*m*, 1643*m*, 1585*s*, 1552*s*, 1497*m*, 1471*s*, 1451*s*, 1392*m*, 1322*s*, 1285*s*, 1212*s*, 1157*s*, 1080*m*, 1051*s*, 1029*m*, 943*m*, 914*m*, 872*w*, 850*m*, 832*m*, 800*m*, 762*s*, 722*s*, 696*s*, 627*w*, 619*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO): 12.42 (*s*, NH); 8.81 (*s*, NH_2)); 7.36 – 7.56 (*m*, 5 arom. H); 5.63 (*s*, PhCH_2); 4.85 (*s*, CH_2Cl). ^{13}C-NMR (75 MHz, (D_6)DMSO): 168.35 (*s*, C=O); 163.24 (*s*, C(6)); 138.66 (*s*, C(4)); 135.5 (*s*); 128.50 (2*d*); 128.30 (2*d*); 127.66 (*d*); 68.60 (*t*, PhCH_2); 46.38 (*t*, CH_2Cl); signals of C(2′) and C(5′) not visible due to coalescence. HR-MALDI-MS: 324.0664 (24, $[M+H]^+$, $C_{13}H_{13}{}^{37}ClN_5O_3^+$; calc. 324.0671), 322.0696 (78, $[M+H]^+$, $C_{13}H_{13}{}^{35}ClN_5O_3^+$; calc. 322.0701), 293.0617 (24, $[M-NO]^+$, $C_{13}H_{12}{}^{37}ClN_4O_2^+$; calc. 293.0614), 291.0632 (100, $[M-NO]^+$, $C_{13}H_{12}{}^{35}ClN_4O_2^+$; calc. 291.7124).

*2-Amino-6-(benzyloxy)-8-(chloromethyl)-9*H*-purine* (**3**). A suspension of **2** (320 mg, 1.0 mmol) in *o*-xylene was treated with Me_3P (1M in THF, 2.2 ml, 2.2 mmol), and stirred for 2 h at 23°. The colourless precipitate was filtered off (washing with toluene and Et_2O), and dried to afford **3** (178 mg, 62%). Pale yellow powder. R_f (CH_2Cl_2/MeOH 9 : 1) 0.42. IR (ATR): 3472*w*, 3316*w*, 3176*w*, 2953*w*, 2926*w*, 1727*w*,

1622*s*, 1579*s*, 1526*m*, 1469*m*, 1454*m*, 1398*s*, 1350*s*, 1330*m*, 1265*s*, 1154*m*, 1083*m*, 992*m*, 944*w*, 910*w*, 844*w*, 790*w*, 736*m*, 695*m*, 641*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO): 12.77 (*s*, H–N(9)); 7.50–7.29 (*m*, 5 arom. H); 6.47 (*s*, NH_2); 5.48 (*s*, PhCH_2); 4.75 (*s*, CH_2Cl). ^{13}C-NMR (100 MHz, (D_6)DMSO): 159.68 (br. *s*, C(2)); 159.55 (*s*, C(6)); 156.27 (br. *s*, C(4)); 145.80 (br. *s*, C(8)); 136.52 (*s*); 128.35 (2*d*); 128.33 (2*d*); 127.99 (*d*); 112.86 (br. *s*, C(5)); 66.90 (*t*, PhCH_2); 38.52 (*t*, CH_2Cl). HR-MALDI-MS: 292.0779 (28, $[M+H]^+$, $C_{13}H_{13}{}^{37}ClN_5O^+$; calc. 292.0774), 290.0806 (100, $[M+H]^+$, $C_{13}H_{13}{}^{35}ClN_5O^+$; calc. 290.0803).

*2-Amino-4-(benzyloxy)-pteridin-7(8*H*)-one 5-Oxide* (**4**). A soln. of **2** (642 mg, 2.0 mmol) in DMSO (10 ml) was stirred at 23° for 16 h and diluted with H_2O (15 ml). The pale precipitate was filtered off, suspended in ^{i}PrOH (15 ml), heated to reflux for 10 min, cooled to 23°, and filtered. Drying *in vacuo* gave **4** (556 mg, 98%). Colourless solid. M.p. 290° (dec.). UV (MeOH): 211 (4.33), 265 (3.92), 355 (3.91). IR (ATR): 3295*w*, 3113*w*, 2774*w*, 1661*s*, 1612*s*, 1574*s*, 1574*s*, 1521*s*, 1497*m*, 1437*m*, 1399*m*, 1381*s*, 1348*s*, 1308*m*, 1279*m*, 1239*m*, 1193*m*, 1173*m*, 1111*m*, 1007*m*, 957*m*, 888*m*, 788*s*, 764*w*, 749*w*, 730*m*, 692*m*, 682*w*, 659*m*, 630*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO): 12.34 (*s*, H–N(8)); 7.26–7.53 (*m*, 5 arom. H, NH_2, H–C(6)); 5.46 (*s*, PhCH_2). ^{13}C-NMR (75 MHz, (D_6)DMSO): see *Table 2*; additionally, 136.11 (*s*); 128.28 (2*d*); 127.79 (*d*); 127.67 (2*d*); 67.81 (*t*, PhCH_2). HR-MALDI-MS: 308.0747 (71, $[M+Na]^+$, $C_{13}H_{11}N_5NaO_3^+$; calc. 308.0754), 286.0929 (100, $[M+H]^+$, $C_{13}H_{12}N_5O_3^+$; calc. 286.0935).

Table 2. *Selected ^{13}C-NMR Chemical Shifts* [ppm] *of the Pteridin-7(8*H*)-ones* **4**, **6**, **8a**–**8d** *and the Pteridine-4,7(3*H*,8*H*)-diones* **9a**–**9d** *in (D_6)DMSO*

	4	**6**	**8a**	**8b**	**8c**
C(2′)	160.94	160.70	161.23	161.28	161.19
C(4′)	161.66	161.81	164.32	164.29	162.17
C(4a′)	107.50	107.48	106.97	106.92	103.95
C(6′)	125.31	129.11	149.64	149.66	147.62
C(7′)	157.79	155.45	157.13	157.43	156.73
C(8a′)	153.61	152.28	151.28	151.07	150.61
C(1), C(4)	–	–	173.60	175.11	162.89
C(2)	–	–	68.19	73.80	155.01
C(3)	–	–	37.33	41.39	97.66
	8d[a])	**9a**	**9b**	**9c**	**9d**[a])
C(2′)	161.55	158.58	158.43	157.05	158.52
C(4′)	164.52	154.60	154.76	154.57	154.94
C(4a′)	107.05	110.26	110.25	106.80	110.41
C(6′)	147.62	147.64	147.68	145.51	145.77
C(7′)	156.70	157.12	157.45	156.69	156.72
C(8a′)	151.46	150.88	150.71	149.93	151.27
C(1), C(4)	171.51, 168.97	173.81	175.18	163.13	171.66, 169.20
C(2)	69.05	68.18	73.92	155.15	69.30
C(3)	52.25	37.32	41.49	97.10	51.30

[a]) Numbering according to *Scheme 2*.

*2-Amino-4-(benzyloxy)-6-phenylpteridin-7(8*H*)-one 5-Oxide* (**6**). A soln. of **1** (245 mg, 1.0 mmol) in THF (10 ml) was cooled to 0°, treated with 2-chloro-2-phenylacetyl chloride (174 µl, 1.2 mmol), and stirred for 1 h at 0° and 2 h at 23°. The white precipitate was repeatedly filtered off (washing with CH_2Cl_2/MeOH 9:1). Drying *i. v.* gave **6** (242 mg, 68%). Colourless solid. M.p. 285°. UV (MeOH): 209 (4.25), 247 (3.98), 270 (3.93), 367 (3.96). IR (ATR): 3492*w*, 3283*w*, 3117*w*, 2900*w*, 2798*w*, 1635*s*, 1614*s*, 1575*s*, 1518*m*, 1496*m*, 1479*m*, 1430*m*, 1395*m*, 1354*s*, 1309*m*, 1281*w*, 1261*m*, 1206*m*, 1177*w*, 1163*m*, 1100*w*, 1014*w*, 981*m*, 870*m*, 785*m*, 765*w*, 733*m*, 719*m*, 692*m*, 650*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO): 12.44 (*s*, H–N(8)); 7.52–7.33 (*m*, 10 arom. H, NH_2); 5.45 (*s*, PhCH_2). ^{13}C-NMR (75 MHz, (D_6)DMSO): see *Table 2*;

additionally, 136.09, 135.19 (2*s*); 130.47–127.35 (several *d*); 67.94 (*t*, Ph*C*H$_2$). HR-MALDI-MS: 384.1072 (30, $[M+Na]^+$, $C_{19}H_{15}N_5NaO_3^+$; calc. 384.1067), 362.1248 (100, $[M+H]^+$, $C_{19}H_{16}N_5O_3^+$; calc. 362.1248). Anal. calc. for $C_{19}H_{15}N_5O_3 \cdot 0.167\ CH_2Cl_2$ (361.36): C 61.30, H 4.12, N 18.65; found: C 61.30, H 4.28, N 18.65.

Methyl 3-[2-Amino-4-(benzyloxy)-7,8-dihydro-7-oxopteridin-6-yl]-2-hydroxypropanoate (**8a**). A suspension of **6** (300 mg, 1.05 mmol) in methyl prop-2-enoate (1 ml, 11.1 mmol) and toluene (2 ml) was stirred for 5 h at 100°, and filtered (washing with pentane). Drying *i. v.* gave **8a** (370 mg, 95%). M.p. > 260°. UV (MeOH): 211 (4.48), 228 sh (4.15), 285 (3.79), 344 (4.25). IR (ATR): 3413*m,* 3329*w*, 3208*m*, 2899*w*, 2833*w*, 2766*w*, 1745*m*, 1666*m*, 1610*s*, 1571*s*, 1555*s*, 1499*s*, 1469*m*, 1431*s*, 1386*s*, 1356*s*, 1309*m*, 1262*m*, 1183*s*, 1147*m*, 1093*s*, 1057*s*, 1022*m*, 987*m*, 920*m*, 837*w*, 822*w*, 799*m*, 733*m*, 718*m*, 693*m*, 634*w*, 611*w*. ^{1}H-NMR (300 MHz, (D$_6$)DMSO): 12.36 (*s*, H–N(8′)); 7.52–7.35 *(m*, 5 arom. H); 7.13 (*s*, NH$_2$); 5.53 (*d*, *J* = 6.0, OH); 5.46 (*s*, PhC*H*$_2$); 4.49 (*q*, *J* ≈ 6.3, H–C(2)); 3.52 (*s*, MeO); 3.03 (*dd*, *J* = 14.4, 6.3, H$_a$–C(3)); 2.88 (*dd*, *J* = 14.1, 7.5, H$_b$–C(3)). ^{13}C-NMR (75 MHz, (D$_6$)DMSO): see *Table 2*; additionally, 136.30 (*s*); 128.53 (2*d*); 128.38 (*d*); 128.08 (2*d*); 67.38 (*t*, Ph*C*H$_2$); 51.27 (*q*, MeO). HR-MS-MALDI: 394.1116 (100, $[M+Na]^+$, $C_{17}H_{17}N_5NaO_5^+$; calc. 394.1122).

Methyl 3-[2-Amino-4-(benzyloxy)-7,8-dihydro-7-oxopteridin-6-yl]-2-hydroxy-2-methyl-3-propanoate (**8b**). A suspension of **6** (300 mg, 1.05 mmol) in methyl 2-methylprop-2-enoate (1 ml, 9.3 mmol) and toluene (10 ml) was stirred for 5 h at 100° and filtered (washing with pentane). Drying *in vacuo* gave **8a** (384 mg, 95%). M.p. > 260° (dec). UV (MeOH): 211 (4.31), 228 (4.13), 284 (3.78), 345 (4.21). IR (ATR): 3411*w*, 3307*w*, 3191*m*, 3006*w*, 2936*w*, 2839*w*, 2770*w*, 1714*m*, 1689*m*, 1671*m*, 1643*s*, 1627*s*, 1577*s*, 1564*s*, 1518*m*, 1498*s*, 1443*s*, 1407*s*, 1384*s*, 1348*s*, 1305*s*, 1232*m*, 1196*s*, 1147*s*, 1112*s*, 1059*s*, 1009*m*, 985*m*, 954*m*, 898*m*, 824*m*, 793*s*, 729*s*, 692*s*, 657*m*, 633*s*. ^{1}H-NMR (300 MHz, (D$_6$)DMSO): 12.32 (*s*, H–N(8′)); 7.50–7.40 (*m*, 5 arom. H); 7.12 (*s*, NH$_2$); 5.44 (*s*, PhC*H*$_2$); 5.29 (*s*, OH); 3.42 (*s*, MeO); 3.09, 2.93 (2*d*, *J* = 14.4, 2 H–C(3)); 1.31 (*s,* Me–C(2)). ^{13}C-NMR (75 MHz, (D$_6$)DMSO): see *Table 2*; additionally, 136.24 (*s*); 128.42 (2*d*); 128.32 (2*d*); 127.66 (*d*); 67.43 (*t*, Ph*C*H$_2$); 51.38 (*q*, MeO); 26.09 (*q*, *Me*–C(2)). HR-MALDI-MS: 408.1274 (100, $[M+Na]^+$, $C_{18}H_{19}N_5NaO_5^+$; calc. 408.1278), 386.1447 (94, $[M+H]^+$, $C_{18}H_{20}N_5O_5^+$; calc. 386.1447).

Methyl (Z)-3-[2-Amino-4-(benzyloxy)-7,8-dihydro-7-oxopteridin-6-yl]-2-hydroxyprop-2-enoate (**8c**). A suspension of **6** (300 mg, 1.05 mmol) in methyl prop-2-ynoate (1.0 ml, 11 mmol) and toluene (10 ml) was heated to 100° for 10 h, cooled to r.t., and filtered (washing with pentane). Drying *i. v.* gave **8c** (359 mg, 93%). M.p. > 200° (dec.). UV (MeOH): 209 (4.41), 230 sh (4.10), 293 (3.84), 328 (3.94), 405 (3.48), 422 (3.45). IR (ATR): 3329*m*, 3191*m*, 2953*m*, 2843*m*, 2764*m*, 1659*s*, 1614*s*, 1563*s*, 1528*s*, 1498*s*, 1471*s*, 1438*s*, 1396*s*, 1348*s*, 1283*s*, 1253*s*, 1176*m*, 1087*m*, 1065*m*, 1015*m*, 948*w*, 909*w*, 846*w*, 783*w*, 768*w*, 732*w*, 695*m*, 641*w*. ^{1}H-NMR (300 MHz, (D$_6$)DMSO): 13.81 (*s*, OH); 12.67 (*s*, H–N(8)); 7.52–7.34 (*m*, 5 arom. H, NH$_2$); 6.80 (*s*, H–C(3)); 5.50 (*s*, PhC*H*$_2$); 3.78 (*s*, MeO). ^{13}C-NMR (75 MHz, (D$_6$)DMSO): see *Table 2*; additionally, 136.04 (*s*); 128.49 (2*d*); 128.15 (*d*); 127.95 (2*d*); 67.77 (*t*, Ph*C*H$_2$); 52.39 (*q*, MeO). HR-MALDI-MS: 392.0983 (51, $[M+Na]^+$, $C_{17}H_{15}N_5NaO_5^+$; calc. 392.0965), 370.1152 (100, $[M+H]^+$, $C_{17}H_{16}N_5O_5^+$; calc. 370.1146).

*Diethyl (2*R**,3*R**)-2-[2-Amino-4-(benzyloxy)-7,8-dihydro-7-oxopteridin-6-yl]-3-hydroxybutanedioate* (**8d**). A suspension of **6** (300 mg, 1.05 mmol) in diethyl (*E*)-but-2-enedioate (1.0 ml, 6.0 mmol) and toluene (10 ml) was heated to 100° for 10 h, cooled to r.t., and filtered (washing with pentane). Drying *i.v.* gave **8d** (465 mg, 97%). M.p. 190° (dec). UV (MeOH): 213 (4.42), 226 (4.42), 262 (3.79), 274 (3.75), 342 (4.25). IR (ATR): 3330*w*, 3209*m*, 2981*w*, 2934*w*, 2904*w*, 2835*w*, 2734*w*, 1732*s*, 1670*s*, 1626*s*, 1552*s*, 1498*s*, 1469*m*, 1395*m*, 1355*s*, 1326*m*, 1306*m*, 1271*m*, 1202*s*, 1183*s*, 1153*s*, 1089*m*, 1063*s*, 1022*s*, 990*m*, 970*m*, 928*m*, 869*m*, 832*m*, 799*m*, 731*s*, 693*s*, 653*m*, 624*m*. ^{1}H-NMR (300 MHz, (D$_6$)DMSO): 12.53 (*s*, H–N(8)); 7.53–7.35 (*m*, 5 arom. H); 7.26 (*s*, NH$_2$); 5.85 (*d*, *J* = 6.9, OH); 5.48 (*s*, PhC*H*$_2$); 4.68 (*dd*, *J* = 9.0, 6.9, H–C(3)); 4.22 (*d*, *J* = 9.0, H–C(2)); 4.10–3.98 (*m*, 2 MeC*H*$_2$O); 1.15 (*t*, *J* = 7.1, Me); 1.06 (*t*, *J* = 6.9, Me). ^{13}C-NMR (75 MHz, (D$_6$)DMSO): see *Table 2*; additionally, 136.18 (*s*); 128.47 (2*d*); 128.37 (2*d*); 128.10 (*d*); 67.50 (*t*, Ph*C*H$_2$); 60.46, 60.23 (2*t*, 2 Me*C*H$_2$O); 13.83, 13.77 (2*q*, 2 Me). HR-ESI-MS: 480.1489 (100, $[M+Na]^+$, $C_{21}H_{24}N_5NaO_7^+$; calc. 480.1490).

Methyl 3-(2-Amino-3,4,7,8-tetrahydro-4,7-dioxopteridin-6-yl)-2-hydroxypropanoate (**9a**). A suspension of **8a** (100 mg, 0.27 mmol) and LiBr (59 mg, 0.67 mmol) in MeCN (5 ml) was cooled to 0°, treated with Me_3SiCl (104 µl, 0.81 mmol), and stirred for 10 min at 0° and for 20 h at amb. temp. The suspension

was diluted with MeOH (3 ml), stirred for 15 min, filtered (washing with MeOH and pentane). Drying *in vacuo* gave **9a** (71 mg, 93%). M.p. > 200° (dec). UV (MeOH): 214 (4.30), 292 (3.87), 340 (3.99). IR (ATR): 3314*w*, 3131*m*, 2844*m*, 2760*m*, 1731*w*, 1627*s*, 1567*s*, 1479*m*, 1439*m*, 1390*m*, 1265*m*, 1230*m*, 1202*m*, 1153*w*, 1087*m*, 1064*m*, 1033*m*, 889*w*, 851*w*, 789*w*, 712*w*, 667*m*, 609*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO): 12.28 (*s*, H−N(8′)); 10.96 (*s*, H−N(3′)); 6.99 (*s*, NH_2); 6–5 (br. *s*, OH); 4.53 (*dd*, *J* = 6.0, 7.5, H−C(2)); 3.60 (*s*, MeO); 2.96 (*dd*, *J* = 13.8, 6.3, H_a−C(3)); 2.87 (*dd*, *J* = 14.1, 7.8, H_b−C(3)). ^{13}C-NMR (75 MHz, (D_6)DMSO): see *Table 2*; additionally, 51.36 (*q*, MeO). HR-MS-MALDI: 304.0652 (89, $[M+Na]^+$, $C_{10}H_{11}N_5NaO_5^+$; calc. 304.0653), 288.0917 (100, $[M+Li]^+$, $C_{10}H_{11}LiN_5O_5^+$; calc. 288.0915).

Methyl 3-(2-Amino-3,4,7,8-tetrahydro-4,7-dioxopteridin-6-yl)-2-hydroxy-2-methylpropanoate (**9b**). A suspension of **8b** (130 mg, 0.34 mmol) and LiBr (73 mg, 0.84 mmol) in MeCN (5 ml) was cooled to 0°, treated with Me_3SiCl (129 µl, 1.01 mmol), and stirred for 10 min at 0° and for 19 h at 23°. The suspension was diluted with MeOH (3 ml), stirred for 15 min, and filtered (washing with MeOH and pentane). Drying *in vacuo* gave **9b** (94 mg, 95%). UV (MeOH): 215 (4.33), 230 sh (3.98), 292 (3.91), 342 (4.05). IR (ATR): 3323*w*, 3155*w*, 2845*w*, 2771*w*, 1708*m*, 1680*m*, 1631*s*, 1602*s*, 1562*s*, 1475*m*, 1454*m*, 1393*m*, 1373*m*, 1313*m*, 1282*w*, 1225*m*, 1179*m*, 1114*m*, 957*w*, 900*w*, 863*w*, 821*w*, 791*w*, 704*m*, 679*w*, 639*w*, 610*w*. ^{1}H-NMR (400 MHz, (D_6)DMSO): 12.24 (*s*, H−N(8′)); 11.00 (*s*, H−N(3′)); 7.04 (br. *s*, NH_2); 5.37 (br. *s*, OH); 3.60 (*s*, MeO); 3.02, 2.95 (2*d*, *J* = 14.1, 2 H−C(3)); 1.33 (*s*, Me). ^{13}C-NMR (100 MHz, (D_6)DMSO): see *Table 2*; additionally, 51.60 (*q*, MeO); 25.88 (*q*, Me). HR-MS-MALDI: 318.0809 (87, $[M+Na]^+$, $C_{11}H_{13}N_5NaO_5^+$; calc. 318.0809), 302.1072 (63, $[M+Li]^+$, $C_{11}H_{13}LiN_5O_5^+$; calc. 302.1072), 296.0989 (100, $[M+H]^+$, $C_{11}H_{14}N_5O_5^+$; calc. 296.0989).

Methyl 3-(2-Amino-3,4,7,8-tetrahydro-4,7-dioxopteridin-6-yl)-2-hydroxyprop-2-enoate (**9c**). A suspension of **8c** (100 mg, 0.26 mmol) and LiBr (56 mg, 0.67 mmol) in MeCN (5 ml) was cooled to 0°, treated with Me_3SiCl (104 µl, 0.81 mmol), and stirred for 10 min at 0° and for 21 h at 23°. The suspension was diluted with MeOH (3 ml), stirred for 15 min, and filtered (washing with MeOH and pentane). Drying *in vacuo* gave **9c** (71 mg, 94%). UV (MeOH): 213 (4.11), 293 (3.53), 307 (3.52) 406 (3.71), 420 (3.70). IR (ATR): 3312*m*, 3135*m*, 2957*m*, 2846*m*, 2747*m*, 1637*s*, 1582*s*, 1546*s*, 1473*m*, 1435*m*, 1381*s*, 1275*s*, 1247*s*, 1178*s*, 1105*m*, 1023*w*, 975*m*, 936*w*, 874*w*, 824*w*, 824*w*, 791*w*, 775*m*, 761*m*, 712*w*, 680*m*. ^{1}H-NMR (300 MHz, (D_6)DMSO): 13.82 (br. *s*, OH); 11.61 (*s*, H−N(8′)); 11.36 (*s*, H−N(3′)); 7.19 (br. *s*, NH_2); 6.75 (*s*, H-C(3)); 3.79 (*s*, MeO). ^{13}C-NMR (75 MHz, (D_6)DMSO): see *Table 2*; additionally, 52.29 (*q*, MeO). HR-MS-MALDI: 280.0609 (30, $[M+H]^+$, $C_{10}H_{10}N_5O_5^+$; calc. 280.0672).

Diethyl (2R,3R*)-2-(2-Amino-3,4,7,8-tetrahydro-4,7-dioxopteridin-6-yl)-3-hydroxybutanedioate* (**9d**). A suspension of **8d** (100 mg, 0.22 mmol) and LiBr (48 mg, 0.55 mmol) in MeCN (5 ml) was cooled to 0°, treated with Me_3SiCl (84 µl, 0.66 mmol), and stirred for 10 min at 0° and for 20 h at 23°. The suspension was diluted with MeOH (3 ml), and filtered (washing with MeOH and pentane). Drying *in vacuo* gave **9d** (75 mg, 93%). M.p. > 270° (dec.). UV (MeOH): 214 (4.23), 292 (3.77), 340 (3.89). IR (ATR): 3433*w*, 3318*w*, 3147*w*, 2984*w*, 2876*m*, 2757*m*, 1738*m*, 1629*s*, 1572*s*, 1538*m*, 1475*w*, 1391*m*, 1370*m*, 1340*w*, 1303*w*, 1278*m*, 1255*m*, 1228*w*, 1201*m*, 1182*m*, 1164*m*, 1114*w*, 1094*w*, 1048*m*, 1020*m*, 967*w*, 882*m*, 852*m*, 817*w*, 777*w*, 734*w*, 704*w*, 675*m*, 650*w*, 612*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO): 12.43 (*s*, H−N(8′)); 11.04 (*s*, H−N(3′)); 7.07 (br. *s*, NH_2); 5.86 (br. *s*, OH); 4.66 (*d*, *J* = 9.3, H−C(3)); 4.27 (*d*, *J* = 9.3, H−C(2)); 4.09, 4.03 (2*q*, *J* = 6.9, 2 MeCH_2O); 1.18, 1.08 (2*t*, *J* = 7.2, 2 Me). ^{13}C-NMR (75 MHz, (D_6)DMSO): see *Table 2*; additionally, 60.43, 60.23 (2*t*, 2 MeCH_2O); 13.87, 13.83 (2*q*, 2 Me). HR-MALDI-MS: 390.1019 (100, $[M+Na]^+$, $C_{14}H_{17}N_5NaO_7^+$; calc. 390.1020), 374.1283 (66, $[M+Li]^+$, $C_{14}H_{17}LiN_5O_7^+$; calc. 374.1283).

REFERENCES

[1] I. J. Pachter, P. E. Nemeth, A. J. Villani, *J. Org. Chem.* **1963**, *28*, 1197.
[2] W. Pfleiderer, W. Hutzenlaub, *Angew. Chem., Int. Ed.* **1965**, *4*, 1075.
[3] S. K. Saha, W. Pfleiderer, *Tetrahedron Lett.* **1973**, 1441.
[4] W. Pfleiderer, W. Hutzenlaub, *Chem. Ber.* **1973**, *106*, 3149.
[5] W. Hutzenlaub, H. Yamamoto, G. B. Barlin, W. Pfleiderer, *Chem. Ber.* **1973**, *106*, 3203.
[6] J. C. Mason, G. Tennant, *J. Chem. Soc., Chem. Commun.* **1972**, 218.

[7] H. S. Kim, Y. Kurasawa, A. Takada, *J. Heterocycl. Chem.* **1989**, *26*, 1511.
[8] H. S. Kim, Y. Kurasawa, A. Takada, *J. Heterocycl. Chem.* **1989**, *26*, 871.
[9] Y. Kurasawa, J. Takizawa, Y. Maesaki, A. Kawase, Y. Okamoto, H. S. Kim, *Heterocycles* **2002**, *58*, 359.
[10] T. Hisano, K. Harano, T. Matsuoka, H. Yamada, M. Kurihara, *Chem. Pharm. Bull.* **1987**, *35*, 1049.
[11] T. Matsuoka, M. Shinada, F. Suematsu, K. Harano, T. Hisano, *Chem. Pharm. Bull.* **1984**, *32*, 2077.
[12] T. Hisano, T. Matsuoka, K. Tsutsumi, K. Muraoka, M. Ichikawa, *Chem. Pharm. Bull.* **1981**, *29*, 3706.
[13] M. Xu, A. Vasella, *Helv. Chim. Acta* **2006**, *89*, 1140.
[14] F.-L. Zhang, A. Vasella, *Helv. Chim. Acta* **2007**, *90*, 2315.
[15] T. Steinlin, A. Vasella, *Helv. Chim. Acta* **2008**, *91*, 435.
[16] R. Huisgen, H. Seidl, I. Bruening, *Chem. Ber.* **1969**, *102*, 1102.
[17] W. Pfleiderer, R. Lohrmann, *Chem. Ber.* **1961**, *94*, 12.
[18] M. Xu, F. De Giacomo, D. E. Paterson, T. G. George, A. Vasella, *Chem. Commun.* **2003**, 1452.
[19] Program AMPAC 8.16, *Semichem*, Shawnee Mission.

Received July 8, 2008