A New Synthesis of Ciliapterin and Dictyopterin. Ene Reactions of (Alkenylamino)-nitroso-pyrimidines

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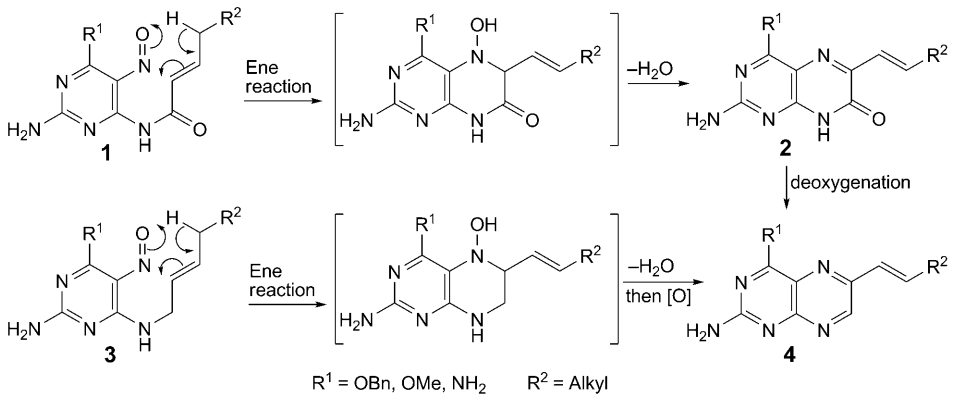
A comparison of the reactivity of (acylamino)-nitroso-pyrimidines **1** and the alkenylamino analogue **17** in intramolecular ene reactions showed the considerably lower reactivity of **17**, leading to the pteridine **18**. Pteridin-7-one **11** resulting from **1** ($R^1 = OBn$, $R^2 = Me$) was transformed into 4-(benzyloxy)-6-[(*E*)-prop-1-enyl]pteridin-2-amine (**13**) by *O*-triflation, followed by reduction with $LiBHEt_3$, while the 4-MeO analogue **18** was prepared by spontaneous oxidation of the initial ene product of **17**. The (alkenylamino)-nitroso-pyrimidine **17** was synthesized by substitution of the dimethoxy-nitroso-pyrimidine **16** with the allylamine **15**. Ciliapterin (**5**) and dictyopterin (**7**) were synthesized from pteridine **18** by a *Sharpless* asymmetric dihydroxylation.

Introduction. – We recently described a high-yielding synthesis of *C(6)*-alkenyl pteridinones **2** by the nitroso-ene reaction of 6-(acylamino)-5-nitrosopyrimidines **1** (*Scheme 1*) [1]. Transforming the pteridinones **2** into pteridines **4**, as required for the synthesis of biopterin (**8**), ciliapterin (**5**), and dictyopterin (**7**) ([2]; *Fig. 1*, see below), appears feasible by deoxygenating the lactam moiety. Pterins might, however, be obtained in a more straightforward way *via* a nitroso-ene reaction of 6-(alkenylamino)-5-nitrosopyrimidines **3**. The expected weaker electrophilicity of **3** as compared to **1** may, however, disfavour the ene reaction, require harsher reaction conditions, and perhaps result in unsatisfactory yields.

Scheme 1



We wished to compare the reactivity of 6-(alkenylamino)-5-nitrosopyrimidines **3** in the nitroso-ene reaction, ultimately providing pteridins **4**, to the nitroso-ene reaction of **1**, and the synthesis of **4** from **3** to the one from the acylamino analogues **1**. The practicality of the synthesis of **4** should be tested by transforming **4** into ciliapterin (**5**) and dictyopterin (**7**).

The name 'ciliapterin' was given in 1968 by *Kidder* and *Dewey* [3] to the pterin they isolated from the ciliate protozoan *Tetrahymena pyriformis*, and to which they had assigned the structure of 6-(L-*threo*-1,2-dihydroxypropyl)pterin (**5**; *Fig. 1*), a known compound that had been synthesized by *Green* and *Rembold* in 1966 [4]. The constitution and absolute configuration of ciliapterin were revised by *Klein et al.* [5] to 6-(D-*threo*-1,2,3-trihydroxypropyl)pterin (**6**), a known compound that had already been given the trivial name of umanopterin [6]. 'Ciliapterin' is still used as trivial name for 6-(L-*threo*-1,2-dihydroxypropyl)pterin, and a natural compound possessing this structure was isolated from human urine in 1992 by *Ogiwara et al.*, and termed 'orinapterin' [6][1]). Several glycosides of ciliapterin (6-(L-*threo*-1,2-dihydroxypropyl)pterin) were then obtained from the cyanobacterium *Alphanizomenon flos-aquae* [11], and the 1-*O*-*β*-L-*N*-acetylglucosaminide of ciliapterin was isolated from *Chlorobium tepidum*, a thermophilic photosynthetic green sulphur bacterium [12].

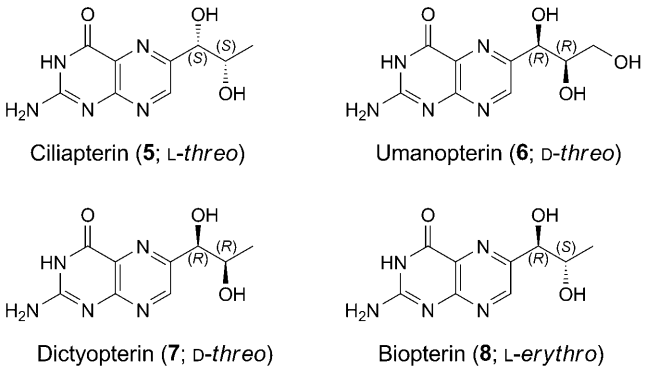


Fig. 1. *Structure of ciliapterin* (**5**), *umanopterin* (**6**), *dictyopterin* (**7**), *and biopterin* (**8**)

Dictyopterin (6-(D-*threo*-1,2-dihydroxypropyl)pterin (**7**); *Fig. 1*) was isolated as the major pterin from extracts of vegetative cells of the myxobacterium *Dictyostelium discoideum* after perchloric acid deproteinization and oxidation with I_2 under acidic conditions [13]. Dictyopterin and tetrahydrodictyopterin are thought to be involved in the transition of this myxobacterium from the unicellular growing phase to the multicellular developmental phase. A G-protein-linked signaling pathway was reported to be involved in the regulation of GTP cyclohydrolase I activity and in the production of tetrahydrodictyopterin during the early development of *D. discoideum* [14].

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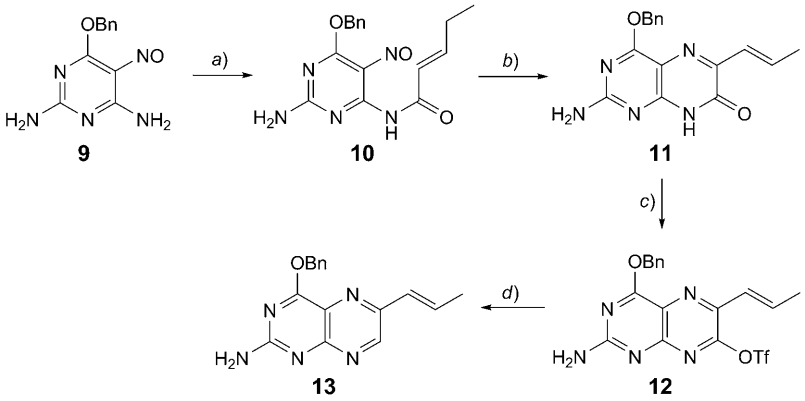
[1]) The separation of diastereoisomers of neopterin and biopterin [7] (**8**; *Fig. 1*) is based on reversed-phase ligand-exchange chromatography [8], and a determination of individual pterins in the urine of cancer patients is of diagnostic relevance [9][10].

Ciliapterin was synthesized in a yield of *ca*. 9% by condensing 2,5,6-triaminopyrimidin-4(3*H*)-one dihydrochloride with 5-deoxy-L-xylose phenylhydrazone, followed by oxidation with $K_3[Fe(CN)_6]$ and H_2O_2 in the presence of KI. Similarly, dictyopterin was synthesized in a yield of *ca*. 4.5% from 5-deoxy-D-xylose phenylhydrazone [4][15]. Ciliapterin was also prepared from biopterin in a yield of *ca.* 32% [16].

Results and Discussion. – We already described the synthesis of pteridinone **11** [1]. It was obtained in almost quantitative yield by nitroso-ene reaction of the pent-2-enamide **10** that was obtained in 60 to 65% yield from the known diamino-nitrosopyrimidine **9** and (*E*)-pent-2-enoyl chloride.

The pteridinone **11** was transformed into the triflate (trifluoromethylsulfonate; **12**; 57%) by treatment with $PhNTf_2$ and DBU (*Scheme 2*). Although this triflate was slowly hydrolysed to **11** upon exposure to H_2O and had to be stored under Ar, it could be isolated by adding H_2O to the reaction mixture and collecting the precipitate. Reduction of the triflate **12** with $LiBHEt_3$ led mostly to an over-reduced product that was, however, readily aromatized *in situ* to yield 86% of **13** that is much better soluble in organic solvents than the pteridinone **11**.

Scheme 2

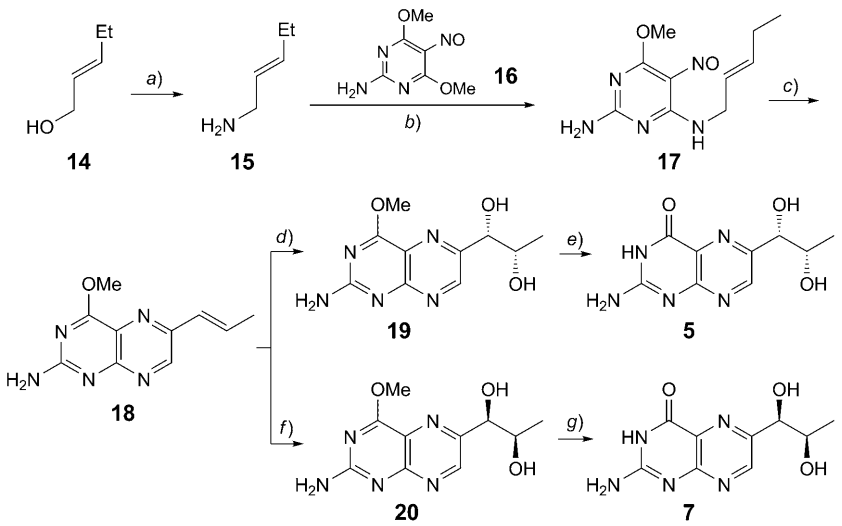


a) (*E*)-Pent-2-enoyl chloride, K_2CO_3, −18°, THF; 63%. *b*) Suspension in toluene, 11 mM, 100°, then 10% I_2, reflux; *ca.* 98%. *c*) 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), $PhNTf_2$ (Tf = trifluoromethylsulfonyl), 0°, DMF; 57%. *d*) $LiBHEt_3$, −78°, THF, then air; 86%.

The direct synthesis of pterins was studied by submitting the more readily available *O*-methyl- (rather than *O*-benzyl-) protected 5-nitroso-4-(pent-2-enylamino) pyrimidine **17** to the conditions of a nitroso-ene reaction. The starting blue-violet nitrosopyrimidine **17** was prepared in a yield of 89% by reaction of 2-amino-4,6-dimethoxy-5-nitrosopyrimidine (**16**) [17] with the pent-2-enamine (**15** [18]; *Scheme 3*). Heating **17** at 200° in 1,2,3,5-tetramethylbenzene for 45 min resulted in a *ca*. 50% transformation of **17**, yielding, besides 54% of starting material, 36% of **18** and some decomposition products. Prolonged heating did not improve the yield, but led to more extensive decomposition. No improvement resulted from adding *Lewis* acids or protic acids, or by using microwaves. The nitroso-ene reaction of **17** required significantly harsher

conditions than that of the (acylamino)-5-nitrosopyrimidine **10** which reacted completely within 3 h at 100°.

Scheme 3



a) Ph_3P, diisopropyl azodicarboxylate (DIAD), phthalimide, THF; 94% then $H_2NNH_2 \cdot H_2O$, MeOH; 70%. *b*) **16**, DMSO; 89%. *c*) 200°, 1,2,3,5-Tetramethylbenzene; 54% of **17**, 36% of **18**. *d*) *AD-Mix-α*, $MeSO_2NH_2$, 0–4°, ^{t}BuOH/H_2O; 48%, ee 96%. *e*) 1N NaOH, dioxane, then AcOH; 93%. *f*) *AD-Mix-β*, $MeSO_2NH_2$, 0–4°, ^{t}BuOH/H_2O; 46%, ee 97%. *g*) 1N NaOH, dioxane, then AcOH; 90%.

The route from the nitrosopyrimidine **9** to pterin **13** (*Scheme 2*), requiring four steps, *viz.*, acylation, ene reaction, triflation, and reduction, resulted in a total yield of 30%. It also required preparing the acyl chloride, and rather expensive reagents for triflation and reduction. The route from the nitroso-pyrimidine **16** to pteridine **18** (*Scheme 3*) involved two steps, *viz.*, substitution and ene reaction, and resulted in a total yield of 32%. It also required the synthesis of the allylamine **15** from the allyl alcohol **14**, but no expensive reagents.

Slow concentration of a solution of **17** in 1,1,1,3,3,3-hexafluoropropan-2-ol/THF 1:1 provided crystals suitable for X-ray analysis (*Fig. 2*). There are two molecules of **17** with a highly disordered pentenyl group, and two molecules of hexafluoropropan-2-ol in the unit cell. The intramolecular H-bond between C(5)–NO and C(4)–NH is characterized by a N=O···H–N distance of 1.907/1.937 Å, and the intermolecular H-bond between C(5)–NO and the OH group of hexafluoropropan-2-ol by a N=O···H–O distance of 1.711/1.689 Å.

The reactivity of **17** in the nitroso-ene reaction is much lower than that of **10**, most probably due to the stronger donor–acceptor interactions between the amino and NO groups of **17**. The stronger interaction could be reflected in the relative bond lengths, and the N=O, C–NO, C=C, and C–NH bond lengths of the crystalline (acylamino)-

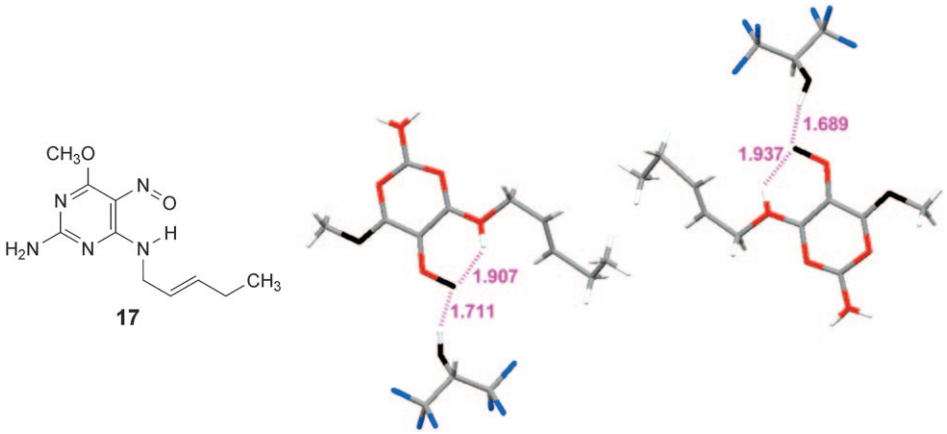
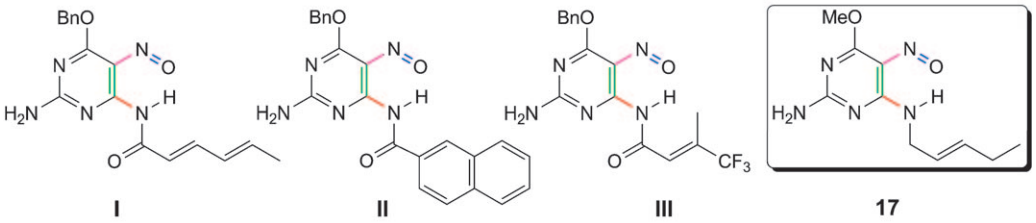


Fig. 2. *Crystal structure of* **17** *showing the inter- and intramolecular H-bonds*

nitroso-pyrimidines **I** [19], **II** [20], and **III** [1] that are similar to **10** were compared to those of **17**, as listed in the *Table*[2]).

Table. *Comparison of Bond Lengths of* **I**, **II**, **III**, *and* **17** (in Å)[2])



	I	**II**	**III**	**17**
N=O	1.263	1.275	1.226 – 1.297	1.302/1.295
C–NO	1.361	1.353	1.352 – 1.371	1.352/1.304
C=C	1.437	1.445	1.409 – 1.478	1.416/1.511
C–NH	1.366	1.368	1.340 – 1.406	1.338/1.318
Δ/σ_{max}	0.017	0.001	0.095	0.020

As shown by the data in the *Table*, there is a slight, but hardly significant tendency for an elongation of the N=O and C=C bonds, and a shortening of the C–NO and C–NH bonds of **17**, as compared to those of **I**, **II**, and **III**, resulting from a combination of the stronger donor – acceptor interaction and the relative strength of the H-bonds, as determined by the less acidic H–N group of **17**.

[2]) There are eight molecules in the unit cell of **III**, and two molecules in the unit cell of **17**. The crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-696734 for **II**, CCDC-696735 for **17**, and CCDC-667942 for **18**. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB21EZ (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

Large amber crystals were obtained by slow evaporation of a solution of **18** in CH_2Cl_2/MeOH 1:1. The crystal-structure analysis showed that, in the unit cell, one molecule of **18** forms two H-bonds with another two molecules between C(2)–NH_2 and the ring N(1) and N(3), with N···H distances of 2.31 and 2.35 Å, respectively, as shown in *Fig. 3*.

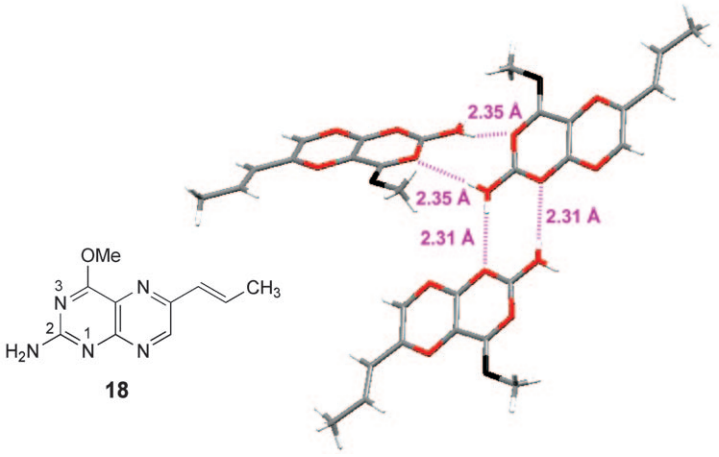


Fig. 3. *Crystal structure of* **18** *showing the intermolecular H-bonds*

The *Sharpless* asymmetric dihydroxylation [21] of a *C(6)*-[(*E*)-alkenyl]-pteridine was reported by *Guiney et al.*, but without determining its enantioselectivity [22], and *Torigoe et al.* dihydroxylated *C(6)*- and *C(7)*-[(*E*)-alkenyl]-lumazines, but without assigning the absolute configuration of the product [23].

The pteridine **18** was dihydroxylated with *ca.* 0.9 mol-% OsO_4 and 2 mol-% ligand at 0–4° for 2 d, providing, in the presence of *AD-mix-α*, the (1*S*,2*S*)-diol **19** (48%, ee[3]) 96%) and, in the presence of *AD-mix-β*, the (1*R*,2*R*)-enantiomer **20** (46%, ee 97%). The unsatisfactory yields of the diols **19** and **20** are due to their poor solubility in organic solvents and good solubility in H_2O, requiring a diol-phased silica-gel chromatography [24] for their separation from organic and inorganic impurities. The imino ethers **19** and **20** were smoothly deprotected by boiling them in 1N NaOH/dioxane [25] to afford ciliapterin (**5**; 93%) and dictyopterin (**7**; 90%), respectively, as off-white precipitates upon neutralization by AcOH. The structure of the products was confirmed by NMR spectroscopy and HR-EI mass spectrometry, by elemental analysis, and by the UV spectra and specific rotation of **5** and **7**, all data being in complete agreement with the published data [4]. The overall yield of ciliapterin (**5**) from the nitrosopyrimidine **16** amounts to 14%, and that of dictyopterin to 13%, while the highest yield of known syntheses (disregarding the preparation of 5-deoxy-L-xylose phenylhydrazone) is 9% [15].

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[3]) The ee values were determined by HPLC, as detailed in the *Exper. Part.*

Experimental Part

General. See [26]. Flash chromatography (FC): *Merck* silica gel *60* (0.063–0.200 mm). FT-IR Spectra: neat (ATR), absorption in cm^{-1}. UV Spectra (MeOH): λ_{max} (log ε). HR-MALDI-MS: in 3-hydroxypicolinic acid (3-HPA) matrix.

*2-Amino-4-(benzyloxy)-6-[(*E*)-prop-1-enyl]pteridin-7-yl Trifluoromethanesulfonate* (**12**). *Method A*. A suspension of **11** (2.03 g, 6.56 mmol) in DMF (250 ml) was cooled to 0° and treated with DBU (2.95 ml, 19.68 mmol). The mixture was stirred for 15 min and treated slowly (syringe pump) with a soln. of $PhNTf_2$ (6.66 g, 18.37 mmol) in DMF (20 ml) over 2 h. The resulting mixture was stirred for 1.5 h at 0° and filtered. Evaporation of the filtrate (30°, 0.5–1 mbar) yielded a brown solid (7.2 g) that was filtered through silica gel (elution with CH_2Cl_2). Evaporation at 30° gave a yellow solid (3.19 g; mixture of **12** and DBU). Recrystallization in AcOEt (dissolved at 35° and precipitated upon stepwise cooling to 25° and then −20°) afforded pure **12** (950 mg, 33%). The yellow residue of the mother liquor (2.02 g) contained *ca.* 40% of **12**.

Method B. A suspension of **11** (90 mg, 0.29 mmol) in DMF (25 ml) was cooled to 0° and treated with DBU (48 µl, 0.32 mmol). The mixture was stirred for 1 h, treated with $PhNTf_2$ (127 mg, 0.35 mmol), stirred for 6 h at 0°, and filtered. The filtrate was cooled to 0°, H_2O (15 ml) was added, and the resulting bright-yellow precipitation was filtered off and dried to afford pure **12** (77 mg, 57%). M.p. 175° (dec.). R_f (CH_2Cl_2/MeOH 20:1) 0.63. UV: 251 (4.17), 293 (4.27), 391 (4.09). IR (ATR): 3486*m*, 3267*w*, 3200*w*, 3162*w*, 3055*m*, 2964*m*, 2912*m*, 2851*m*, 1631*s*, 1599*s*, 1519*s*, 1467*s*, 1430*m*, 1407*s*, 1396*s*, 1364*s*, 1343*s*, 1322*m*, 1309*s*, 1277*s*, 1262*s*, 1247*s*, 1198*w*, 1143*m*, 1125*m*, 1082*m*, 1070*m*, 975*m*, 940*m*, 911*m*, 897*m*, 841*w*, 822*m*, 809*m*. ^{1}H-NMR (300 MHz, (D_6)DMSO): 7.91 (br. *s*, NH_2); 7.50–7.53 (*m*, 2 arom. H); 7.36–7.44 (*m*, 3 arom. H); 6.95 (*dq*, *J* = 15.7, 6.9, H−C(2′)); 6.64 (*dq*, *J* = 15.7, 1.7, H−C(1′)); 5.49 (*s*, PhCH_2); 1.87 (*dd*, *J* = 6.9, 1.7, Me). ^{13}C-NMR (100 MHz, (D_6)DMSO): serious decomposition during measurement. ^{19}F-NMR (282 MHz, (D_6)DMSO): −71.69 (*s*, CF_3). HR-MALDI-MS: 442.0784 (100, $[M+H]^+$, $C_{17}H_{15}F_3N_5O_4S^+$; calc. 442.0791), 464.0615 (10, $[M+Na]^+$, $C_{17}H_{14}F_3N_5NaO_4S^+$; calc. 464.0611).

*4-(Benzyloxy)-6-[(*E*)-prop-1-enyl]pteridin-2-amine* (**13**). A soln. of **12** (662 mg, 1.5 mmol) in THF (60 ml) was cooled to −78°, treated dropwise with 1.0M $LiEt_3BH$ (3.2 ml, 3.2 mmol) over a period of 1 h, and stirred for 0.5 h. Air was slowly bubbled through the soln. during warming to r.t. within 3 h. The mixture was diluted with H_2O (100 ml) and extracted with CH_2Cl_2 (150 ml × 2). The combined org. layers were washed with sat. NH_4Cl (50 ml), dried (Na_2SO_4), and evaporated. FC (CH_2Cl_2/MeOH 100:1 → 50:1) gave **13** (380 mg, 86%). M.p. 172° (dec.). R_f (CH_2Cl_2/MeOH 20:1) 0.49. UV: 206 (4.25), 244 (4.20), 290 (4.27), 387 (3.98). IR (ATR): 3431*w*, 3325*w*, 3224*w*, 3132*w*, 2960*w*, 2847*w*, 1653*s*, 1627*s*, 1593*m*, 1564*m*, 1516*m*, 1430*w*, 1373*m*, 1353*s*, 1317*s*, 1299*m*, 1284*m*, 1273*m*, 1259*m*, 1234*s*, 1208*s*, 1195*m*, 1165*s*, 1121*m*, 1097*w*, 1073*m*, 1028*m*, 968*w*, 942*w*, 898*m*, 851*m*, 827*s*, 804*m*. ^{1}H-NMR (300 MHz, (D_6)DMSO): 8.98 (*s*, H−C(7)); 7.54–7.59 (*m*, 2 arom. H); 7.37–7.45 (*m*, 3 arom. H); 7.20 (br. *s*, NH_2); 6.79 (*dq*, *J* = 16.0, 6.6, H−C(2′)); 6.58 (*dq*, *J* = 16.0, 1.6, H−C(1′)); 5.75 (*s*, PhCH_2); 1.90 (*dd*, *J* = 6.6, 1.6, Me). ^{13}C-NMR (75 MHz, (D_6)DMSO, assignment based on a HMBC spectrum): 166.32 (*s*, C(4)); 160.92 (*s*, C(2)); 156.00 (*s*, C(8a)); 149.29 (*d*, C(7)); 145.69 (*s*, C(6)); 135.89 (*s*); 132.04 (*d*, C(2′)); 128.72 (2*d*); 128.43 (2*d*); 128.23 (*d*); 128.23 (*d*, C(1′)); 121.68 (*s*, C(4a)); 68.25 (*t*, PhCH_2); 18.32 (*q*, C(3′)). HR-MALDI-MS: 294.1346 (100, $[M+H]^+$, $C_{16}H_{16}N_5O^+$; calc. 294.1349), 316.1172 (4, $[M+Na]^+$, $C_{16}H_{15}N_5NaO^+$; calc. 316.1169).

*(*E*)-Pent-2-enamine* (**15**). A soln. of **14** (2.29 ml, 22.5 mmol), phthalimide (4.3 g, 29 mmol), and Ph_3P (7.65 g, 29.0 mmol) in THF (200 ml) was dropwise treated with DIAD (5.75 ml, 29.25 mmol) in the dark at r.t., and stirred for 4 h. The mixture was concentrated to *ca.* 50 ml, diluted with H_2O (400 ml), and extracted with cyclohexane (3 × 300 ml). The combined org. layers were washed with brine, dried ($MgSO_4$), and filtered. The filtrate was evaporated (Ph_3PO was filtered off after concentrating the soln.). FC (cyclohexane/AcOEt 100:1) provided *N*-(pent-2-enyl)phthalimide (4.55 g, 94%) as a white solid.

A soln. of *N*-(pent-2-enyl)phthalimide (5.0 g, 23.2 mmol) in MeOH (100 ml) was treated with $NH_2NH_2 \cdot H_2O$ (1.4 ml, 27.8 mmol) and stirred at r.t. for 12 h. After the addition of 37.5% HCl (5 ml) and H_2O (100 ml), the mixture was stirred for 12 h. The precipitate was filtered off, and the filtrate was diluted with an equal amount of H_2O, acidified (pH < 2), and washed with Et_2O. The aq. layer was basified with solid KOH (pH > 10) and extracted with Et_2O (4 × 200 ml). The combined Et_2O layers

were washed with brine, dried ($MgSO_4$), and concentrated to a 22% soln. of **15** in Et_2O (6.2 g; corresponding to 70% **15**; concentration determined by ^{1}H-NMR). ^{1}H-NMR (300 MHz, $CDCl_3$): 5.62 (*dt*, *J* = 15.6, 5.4, H−C(3)); 5.53 (*dt*, *J* = 15.6, 5.4, H−C(2)); 5.30 (br. *s*, NH_2); 3.26 (*d*, *J* = 5.1, 2 H−C(1)); 2.03 (*quint.*, *J* ≈ 7.2, 2 H−C(4)); 0.98 (*td*, *J* = 7.5, 2.4, Me). ^{13}C-NMR (75 MHz, $CDCl_3$): 133.24, 129.43 (2*d*, CH=CH); 44.03 (*t*, C(1)); 25.46 (*t*, C(4)); 13.77 (*q*, Me).

*6-Methoxy-5-nitroso-4-[(*E*)-(pent-2-enylamino]pyrimidin-2-amine* (**17**). A soln. of **16** (968 mg, 5.25 mmol) in DMSO (12 ml) was treated slowly (syringe pump) over 20 h with a 22% soln. of **15** in Et_2O (1.9 g, 5.52 mmol). The mixture was cooled to 0° and treated with H_2O (25 ml). The resulting violet precipitate was filtered off, dissolved in CH_2Cl_2 (200 ml), and washed with H_2O (2 × 50 ml). Evaporation gave **17** (1.11 g, 89%). M.p. 121–123°. R_f (CH_2Cl_2/MeOH 20:1) 0.43. UV: 203 (4.54), 236 (4.13), 330 (4.35). IR (ATR): 3482*w*, 3316*m*, 3108*m*, 2961*m*, 2933*w*, 2873*w*, 1670*m*, 1649*m*, 1565*s*, 1527*s*, 1448*s*, 1398*m*, 1379*s*, 1352*s*, 1331*s*, 1299*s*, 1207*s*, 1188*m*, 1150*s*, 1079*s*, 1055*s*, 993*m*, 970*m*, 886*w*, 835*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO): 11.33 (*t*, *J* = 5.4, HN−C(4)); 8.02 (br. *s*, NH_2); 5.64 (*dt*, *J* = 15.3, 6.0, H−C(3′)); 5.49 (*dt*, *J* = 15.3, 5.4, H−C(2′)); 4.04 (*s*, MeO); 3.97 (*t*, *J* = 5.4, 2 H−C(1′)); 2.01 (*quint.*, *J* ≈ 7.5, 2 H−C(4′)); 0.93 (*t*, *J* = 7.5, Me). ^{13}C-NMR (75 MHz, (D_6)DMSO): 170.84, 163.21, 150.05, 138.43 (4*s*, 4 C of pyrimidine); 134.14, 124.04 (2*d*, CH=CH); 54.09 (*q*, MeO); 40.43 (*t*, C(1′)); 24.48 (*t*, C(4′)); 13.09 (*q*, Me). HR-EI-MS: 237.1221 (30, M^+, $C_{10}H_{15}N_5O_2^+$; calc. 237.1220).

X-Ray Analysis of **17**. Slow evaporation of a soln. of **17** in $(CF_3)_2$CHOH/THF 1:1 gave suitable crystals. Dimensions: cube 0.4 × 0.16 × 0.08 mm; color: amber. $C_{10}H_{15}N_5O_2 \cdot C_3H_2F_6O$, M_r 405.299, monoclinic $P2_1/c$, *a* = 33.183 (2), *b* = 14.6867 (6), *c* = 7.3473 (3) Å, *α* = 90.00°, *β* = 91.7848 (14)°, *γ* = 90.00°, *V* = 3579.0 (3) Å^3, *Z* = 8, D_x = 1.504 Mg/m^3, *F*(000) = 1664.0, fine-focus sealed tube. Intensities were measured on a *Nonius Kappa CCD* diffractometer, with MoK_α radiation *λ* = 0.71073 Å, Cell parameters from 32263 refl. *θ* = 2.425–27.485 °, *μ* = 0.149 mm^{-1}, *T* = 223 K, 13221 measured reflections, 6841 independent reflections, 2598 observed reflections. Refinement on F^2: full-matrix least-squares refinement, *R*(all) = 0.2417, *R*(*gt*) = 0.1212. Δ/σ_{max} = 0.020. Heavily disordered pentenyl groups. Some constraints on bond lengths. All calculations were performed using maXus (*Bruker Nonius*, *Delft & MacScience*, Japan). Programme used to solve structure: SIR97. Programme used to refine structure: SHELXL-97.

*(*E*)-4-Methoxy-6-(prop-1-enyl)pteridin-2-amine* (**18**). A stirred suspension of **17** (1 g, 4.21 mmol) in 1,2,3,5-tetramethylbenzene (200 ml) was kept in an oil bath at 200° for 45 min. The mixture was passed through a column with dry silica gel (100 g), and 1,2,3,5-tetramethylbenzene was recovered by washing the column first with cyclohexane, then eluting with CH_2Cl_2/MeOH (100:1 → 50:1) to give **17** (540 mg, 54%) and **18** (278 mg, 36% based on starting material, 66% based on recovered starting material). Yellow powder. M.p. > 170° (dec.). R_f (CH_2Cl_2/MeOH 20:1) 0.50. UV: 201 (4.22), 242 (4.27), 289 (4.30), 387 (3.95). IR (ATR): 3367*m*, 3330*m*, 3153*m*, 2966*w*, 1654*s*, 1582*s*, 1567*s*, 1517*s*, 1481*m*, 1427*s*, 1403*s*, 1356*s*, 1308*m*, 1274*m*, 1232*m*, 1201*m*, 1167*s*, 1134*m*, 1097*s*, 1050*m*, 991*w*, 958*s*, 923*w*, 875*w*, 826*m*. ^{1}H-NMR (300 MHz, (D_6)DMSO): 8.95 (*s*, H−C(7)); 7.25 (br. *s*, NH_2); 6.83 (*dq*, *J* = 16.0, 6.9, H−C(2′)); 6.60 (*dq*, *J* = 16.0, 1.5, H−C(1′)); 4.05 (*s*, MeO); 1.93 (*dd*, *J* = 6.9, 1.5, Me). ^{13}C-NMR (75 MHz, (D_6)DMSO; assignment based on a HMBC spectrum): 166.73 (*s*, C(4)); 160.80 (*s*, C(2)); 155.60 (*s*, C(8a)); 149.13 (*d*, C(7)); 145.37 (*s*, C(6)); 131.81 (*d*, C(2′)); 127.96 (*d*, C(1′)); 121.59 (*s*, C(4a)); 54.34 (*q*, MeO); 18.43 (*q*, C(3′)). HR-EI-MS: 216.0881 (100, $[M-H]^+$, $C_{10}H_{10}N_5O^+$; calc. 216.0880). Anal. calc. for $C_{10}H_{11}N_5O \cdot 0.25\ CH_3OH$ (225.24): C 54.66, H 5.37, N 31.09; found: C 54.68, H 5.16, N 30.53.

X-Ray Analysis of **18**. Slow evaporation of a soln. of **18** in CH_2Cl_2/MeOH 1:1 gave suitable crystals. Dimensions: cube 0.5 × 0.4 × 0.3 mm; color: yellow. $C_{10}H_{11}N_5O$, M_r 217.232, monoclinic $P2/c$, *a* = 9.8207 (2), *b* = 7.2210 (2), *c* = 14.9754 (4) Å, *α* = 90.00°, *β* = 105.5742 (11)°, *γ* = 90.00°, *V* = 1022.99 (4) Å^3, *Z* = 4, D_x = 1.410 Mg/m^3, *F*(000) = 456.0, fine-focus sealed tube. Intensities were measured on a *Nonius Kappa CCD* diffractometer, with MoK_α radiation *λ* = 0.71073 Å, Cell parameters from 6979 refl. *θ* = 2.167–27.485°, *μ* = 0.099 mm^{-1}, *T* = 243 K, 4399 measured reflections, 2322 independent reflections, 2064 observed reflections. Refinement on F^2: full-matrix least-squares refinement, *R*(all) = 0.0489, *R*(*gt*) = 0.0446. All calculations were performed using maXus (*Bruker Nonius*, *Delft & MacScience*, Japan). Programme used to solve structure: SIR97. Programme used to refine structure: SHELXL-97.

*(1*S*,2*S*)-1-(2-Amino-4-methoxypteridin-6-yl)propane-1,2-diol* (**19**). A soln. of *AD-mix-α* (18.37 g) in *t*-BuOH (50 ml) and H_2O (50 ml) was stirred at r.t. for 5 min, treated with $MeSO_2NH_2$ (500 mg,

5.25 mmol), stirred for 5 min, and cooled to 0°, whereupon **18** (1.14 g, 5.25 mmol) was added at once. The heterogeneous slurry was stirred vigorously at 4° for 2 d, treated with solid sodium sulfite (20 g), and stirred at r.t. for 60 min. After evaporation of the solvent, the residue was thoroughly washed with MeOH (3 × 100 ml). The combined MeOH extract was evaporated. FC (diol-phased silica gel, CH_2Cl_2/MeOH 50:1 → 10:1) gave **19** (634 mg, 48%). Off-white powder. $[\alpha]_D^{25} = +83.2$ ($c = 0.5$, H_2O). M.p. 219–222° (dec.). R_f (CH_2Cl_2/MeOH 10:1) 0.20. R_f (CH_2Cl_2/MeOH 20:1; diol-phased TLC) 0.36. ee 96% (Anal. *HPLC-Chiral AD–H*; 1.0 ml/min, UV, 254 nm; hexane/i-PrOH 85:15; $t_R = 33.45$ min). UV: 202 (4.39), 236 (4.43), 265 (4.07), 365 (3.84). IR (ATR): 3391*m*, 3316*m*, 3199*m*, 2968*w*, 2916*w*, 1660*m*, 1644*m*, 1605*s*, 1566*m*, 1525*s*, 1479*m*, 1437*s*, 1414*m*, 1363*s*, 1313*s*, 1277*m*, 1255*m*, 1183*s*, 1130*s*, 1094*m*, 1075*m*, 1062*m*, 1041*m*, 1012*m*, 986*m*, 941*w*, 917*w*, 881*w*, 862*w*, 833*m*, 823*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO): 8.86 (*s*, H–C(7)); 7.22 (br. *s*, NH_2); 5.56 (*d*, $J = 5.4$, HO–C(1)); 4.62 (*d*, $J = 5.7$, HO–C(2)); 4.47 (*t*, $J \approx 4.8$, H–C(1)); 4.05 (*s*, MeO); 3.92–3.81 (*m*, H–C(2)); 1.06 (*d*, $J = 6.3$, Me). ^{13}C-NMR (75 MHz, (D_6)DMSO): 166.96 (*s*, C(4′)); 161.23 (*s*, C(2′)); 156.28 (*s*, C(8′a)); 152.34 (*s*, C(6′)); 150.17 (*d*, C(7′)); 120.93 (*s*, C(4′a)); 76.62 (*d*, C(1)); 69.19 (*d*, C(2)); 54.29 (*q*, MeO); 19.40 (*q*, Me). HR-ESI-MS: 274.0910 (10, $[M + Na]^+$, $C_{10}H_{13}N_5NaO_3^+$; calc. 274.0911). Anal. calc. for $C_{10}H_{13}N_5O_3 \cdot 0.25$ MeOH (259.25): C 47.49, H 5.44, N 27.01; found: C 47.65, H 5.32, N 26.85.

*2-Amino-6-[(1S,2S)-1,2-dihydroxypropyl]pteridin-4(3*H*)-one* (**5**) [4]. A suspension of **19** (50 mg, 0.2 mmol) in dioxane (1.2 ml) was treated with 1N NaOH (6 ml) and heated at 100° for 20 min, leading to a dissolution. The mixture was cooled to 70°, treated with AcOH (1 ml), stirred for 5 min, and cooled to 0°. The resulting off-white precipitate was filtered off, providing off-white solid **5** (44 mg, 93%). $[\alpha]_D^{25} = +99.7$ ($c = 0.22$, 0.1N HCl); [4]: +95 ($c = 0.2$, 0.1N HCl). M.p. > 270° (dec.). UV (H_2O): 221 (3.88), 275 (4.14), 345 (3.74). IR (ATR): 3243*m* (br.), 3061*m*, 2794*m*, 2718*m*, 1722*m*, 1673*s*, 1641*s*, 1581*m*, 1537*s*, 1514*m*, 1488*m*, 1415*m*, 1360*m*, 1299*m*, 1279*m*, 1248*m*, 1175*m*, 1126*s*, 1065*m*, 1045*m*, 1001*m*, 973*w*, 957*w*, 924*w*, 881*m*, 867*m*, 846*w*, 822*m*. ^{1}H-NMR (300 MHz, (D_6)DMSO): 11.56 (br. *s*, NH); 8.70 (*s*, H–C(7)); 6.90 (br. *s*, NH_2); 5.49 (*d*, $J = 5.4$, HO–C(1′)); 4.59 (*d*, $J = 5.4$, HO–C(2′)); 4.44 (*t*, $J \approx 4.5$, H–C(1′)); 3.90–3.80 (*m*, H–C(2′)); 1.05 (*d*, $J = 6.0$, Me). ^{13}C-NMR (125 MHz, (D_6)DMSO): 161.17 (*s*, C(4)); 156.05 (br. *s*, C(2)); 153.67 (*s*, C(8a)); 151.72 (*s*, C(6)); 148.35 (*d*, C(7)); 127.03 (*s*, C(4a)); 76.31 (*d*, C(1′)); 69.09 (*d*, C(2′)); 19.22 (*q*, Me). HR-ESI-MS: 238.0936 (15, $[M + H]^+$, $C_9H_{12}N_5O_3^+$; calc. 238.0935); 229.1410 (100). Anal. calc. for $C_9H_{11}N_5O_3 \cdot 0.25$ H_2O (241.72): C 44.72, H 4.80, N 28.97; found: C 44.95, H 4.82, N 28.60.

(1R,2R)-1-(2-Amino-4-methoxypteridin-6-yl)propane-1,2-diol (**20**). Prepared, similarly to **19**, from **18** (114 mg), with *AD-mix-β*. Yield: 61 mg (46%). Off-white powder. $[\alpha]_D^{25} = -86.4$ ($c = 0.5$, H_2O). ee 97% (Anal. *HPLC-Chiral AD–H*; 1.0 ml/min; UV, 254 nm, hexane/i-PrOH 85:15, $t_R = 25.85$ min). IR and NMR spectra identical to those of **19**.

*2-Amino-6-[(1R,2R)-1,2-dihydroxypropyl]pteridin-4(3*H*)-one* (**7**) [4]. Prepared, similarly to **5**, from **20** (50 mg). Yield: 42 mg (90%). Off-white to light-brown powder. $[\alpha]_D^{25} = -101.6$ ($c = 0.22$, 0.1N HCl); [4]: −94 ($c = 0.2$, 0.1N HCl). IR and NMR spectra identical to those of **5**.

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