Synthesis and Biological Study of 6-Polyhydroxyalkylpteridines

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6-Polyhydroxyalkylpteridines are synthesised by oxidation of the corresponding pyrano[3,2-*g*]pteridines, the latter ones having been obtained by condensation between 5,6-diaminopyrimidines **1a,b** and phenylhydrazones **2a-e**. The relative configuration at the chiral centers of the pyrano[3,2-*g*]pteridines has been determined by nmr study and X-ray analysis. The anti-AIDS activity of several of these compounds has been tested.

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Introduction.

As part of our programme for the synthesis of new heterocyclic compounds as potential anti-AIDS agents, we have recently reported [1] the preparation and anti-AIDS activity of several 7-polyhydroxyalkyl-2-methoxy-3-methylpteridin-4(3*H*)-ones. Latter compounds were prepared by the condensation of 5,6-diamino-2-methoxy-3-methylpyrimidin-4(3*H*)-one, **1b**, with the pentoses of D- and L- series, in ethanol using acetic acid as a catalyst. None of them have shown anti-AIDS activity at subtoxic concentrations. Our investigations in pyrimidine and pteridine chemistry, have lead us to prepare the corresponding regioisomeric 6-polyhydroxyalkylpteridines with a view to their evaluation as anti-AIDS compounds.

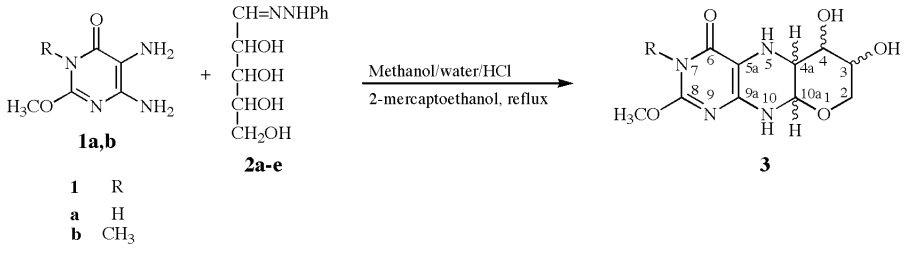
It has been known for some time that 6-substituted pteridines [2-7] are interesting biological and pharmacological heterocyclic compounds, this fact also applies to 6-polyhydroxyalkylpteridines [8-10]. Thus it is important to find a regioselective route leading to 6-polyhydroxyalkylpteridines. From studies describing the regioselective synthesis of 6-polyhydroxyalkylpteridines [11-17], we have investigated those starting from pyrano[3,2-*g*]-pteridines [16].

In this paper, we describe the synthesis of pyrano[3,2-*g*]-pteridines **3** by condensation of 5,6-diamino-2-methoxy-pyrimidin-4(3*H*)-one, **1a**, or 5,6-diamino-2-methoxy-3-methylpyrimidin-4(3*H*)-one, **1b,** with D-xylosephenylhydrazone, **2a**, L-xylosephenylhydrazone, **2b**, D-ribosephenylhydrazone, **2c**, D-arabinosephenylhydrazone, **2d**, and L-arabinosephenylhydrazone, **2e**. To examine the structures of chiral pyrano[3,2-*g*]pteridines **3**, we have carried out their acetylation under two different conditions yielding compounds **4** and **5.** Lastly, the oxidation of compounds **3** has produced the 6-polyhydroxyalkylpteridines **6**. Some of the compounds **3**, **6** and **7** were tested as "*in vitro*" anti-HIV agents.

Results and Discussion.

The reactions between **1a** and phenylhydrazones **2a-e** in a 50% mixture of methanol/water, hydrochloric acid and 2-mercaptoethanol under reflux, produced the diasteromeric pairs of pyrano[3,2-*g*]pteridines **3a/3b**, **3c/3d**, **3e/3f** and **3g/3h** (Scheme 1). It was not possible to separate these pairs due to their poor solubility in organic solvents. Although elemental analysis are not available, the solids appeared homogeneous in thin layer chromatography. When we used as 5,6-diaminopyrimidine **1b** only the reactions with **2c** (or **2d**) and **2e** gave the diasteromeric pairs **3k/3l** and **3m/3n** respectively, which were separable; whereas reactions with **2a** and **2b** yielded only the pure compounds **3i** and **3j** (Scheme 1).

Scheme 1



1a,b **2a-e** **3**

1 R
a H
b CH_3

	Starting Material	Reaction Product		Starting Material	Reaction Product
1a	**2a**	**3a/3b**	**1b**	**2a**	**3i**
	2b	**3c/3d**		**2b**	**3j**
	2c or 2d	**3e/3f**		**2c or 2d**	**3k + 3l**
	2e	**3g/3h**		**2e**	**3m + 3n**

The structures of pyrano[3,2-*g*]pteridine of compounds **3** were established by nmr spectroscopy. In their ^{13}C-nmr spectra the resonance corresponding to C-2 is observed in the range of 64.7-68.1 ppm and C-10a in the 75.8-79.8 ppm range, which is consistent with this class of compounds [15,17]. In their ^{1}H-nmr spectra the signal for H-10 appears as a doublet (7.21-7.73 ppm, $J_{10,10a-}$= 2.7-4.9 Hz) and H-10a as a broad signal or a doublet, after deuterium oxide was added, with a small coupling constant ($J_{10a,4a}$= 1.5 Hz), supported the proposed structure [15,17] (Table 1).

In an attempt to determine the relative configurations of the diasteromeric pairs **3a/3b**, **3c/3d**, **3e/3f** and **3g/3h** and the pure compounds **3i-n**, all of them were acetylated in a 50% mixture of acetic anhydride and pyridine yielding the acetyl derivatives **4**. As we can see, two types of compounds were formed: triacetyl derivatives and diacetyl derivatives (R'=COCH$_3$, R'=H, see Scheme 2); as well as, for **3a/3b**, **3c/3d**, **3e/3f** and **3g/3h** only one type of diasteromer could be isolated. Alternatively, when acetylation of **3a/3b**, **3c/3d**, **3e/3f** and **3g/3h** was carried out in acetic anhydride (27.5%) and pyridine (72.5%) using dimethylaminopyridine as catalyst (Scheme 2), only the tetraacetyl derivatives **5** of one type of diasteromer were isolated.

The structures and relative configurations for compounds **4** and **5** have been established from their behaviour in ^{1}H-nmr, ^{13}C-nmr, DEPT, COSY (H-H), HMQC, HMBC experiments, by X-ray diffraction studies of compounds **4g**, **4i**, **5c** and using bibliographic data of similar products [15,17].

In the ^{13}C-nmr spectra of **4**, the signal appearing between 74.1-79.8 ppm is typical for C-10a [15,17]. In their ^{1}H-nmr, the signal corresponding to H-10 appears as a broad singlet between 7.80-8.20 ppm in dimethyl-d$_6$ sulfoxide or 5.02-5.48 ppm in deuteriochloroform, thus confirming the structure of pyrano[3,2-*g*]pteridine for compounds **4** [15,17] (see Tables 2 and 3).

Table 1

^{1}H-nmr and ^{13}C-nmr Selected Data for Compounds **3** (tetramethylsilane as internal standard in dimethyl-d$_6$ sulfoxide)

Compound	^{1}H-nmr d(ppm), J(Hz)	^{13}C-nmr d(ppm)
3a/3b	7.45 [a] (d, 1H, $J_{10,10a}$= 4.2, *H*-10), 4.81 (m, 1H, + deuterium oxide→bs, *H*-10a) for **3a** and	66.0 (*C*-2), 75.8 (*C*-10a) for **3a**
	7.48 [a] (d, 1H, $J_{10,10a}$= 4.8, *H*-10), 4.63 (m, 1H, + deuterium oxide→bs, *H*-10a) for **3b**	67.1 (*C*-2), 79.8 (*C*-10a) for **3b**
3c/3d	7.42 [a] (d, 1H, $J_{10,10a}$= 3.9, *H*-10), 4.66 (m, 1H, + deuterium oxide→bs, *H*-10a) for **3c** and	66.0 (*C*-2), 75.8 (*C*-10a) for **3c**,
	7.47 [a] (d, 1H, $J_{10,10a}$= 2.7, *H*-10), 4.81 (m, 1H, + deuterium oxide→bs, *H*-10a) for **3d**	67.1 (*C*-2), 79.8 (*C*-10a) for **3d**
3e/3f	7.23 [a] (d, 1H, $J_{10,10a}$= 4.5, *H*-10), 4.81 (m, 1H, + deuterium oxide→bs, *H*-10a) for **3e** and	64.7 (*C*-2), 76.1 (*C*-10a) for **3e**
	7.73 [a] (d, 1H, $J_{10,10a}$= 4.8, *H*-10), 4.63 (m, 1H, + deuterium oxide→bs, *H*-10a) for **3f**	67.9 (*C*-2), 79.8 (*C*-10a) for **3f**
3g/3h	7.22 [a] (d, 1H, $J_{10,10a}$= 3.9, *H*-10), 4.81 (m, 1H, + deuterium oxide→bs, *H*-10a) for **3g** and	67.9 (*C*-2), 79.0 (*C*-10a) for **3g**
	7.71 [a] (d, 1H, $J_{10,10a}$= 4.5, *H*-10), 4.63 (m, 1H, + deuterium oxide→bs, *H*-10a) for **3h**	65.0 (*C*-2), 76.2 (*C*-10a) for **3h**
3i	7.45 [a] (d, 1H, $J_{10,10a}$= 4.9, *H*-10), 4.67 (m, 1H, + deuterium oxide→bs, *H*-10a)	67.1 (*C*-2), 79.7 (*C*-10a)
3j	7.48 [a] (d,1H, $J_{10,10a}$= 4.9, *H*-10), 4.65 (m, 1H, + deuterium oxide→bs, *H*-10a)	67.1 (*C*-2), 79.7 (*C*-10a)
3k	7.22 [a] (d,1H, $J_{10,10a}$= 4.5, *H*-10), 4.83 (m, 1H, + deuterium oxide→d, $J_{10a,4a}$= 1.5, *H*-10a)	64.8 (*C*-2), 76.1 (*C*-10a)
3l	7.71 [a] (d, 1H, $J_{10,10a}$= 4.8, *H*-10), 4.64 (m, 1H, + deuterium oxide→d, $J_{10a,4a}$= 1.5, *H*-10a)	68.0 (*C*-2), 79.0 (*C*-10a)
3m	7.21 [a] (d, 1H, $J_{10,10a}$= 4.5, *H*-10), 4.81 (m, 1H, + deuterium oxide→d, $J_{10a,4a}$= 1.5, *H*-10a)	64.9 (*C*-2), 76.3 (*C*-10a)
3n	7.69 [a] (d, 1H, $J_{10,10a}$= 4.8, *H*-10), 4.62 (m, 1H, + deuterium oxide→d, $J_{10a,4a}$= 1.5, *H*-10a)	68.1 (*C*-2), 79.1 (*C*-10a)

[a] Deuterium exchangeable.

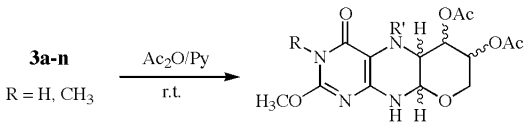
Table 2

^{1}H-nmr and ^{13}C-nmr Selected Data for Compounds **4a-h** (tetramethylsilane as internal standard)

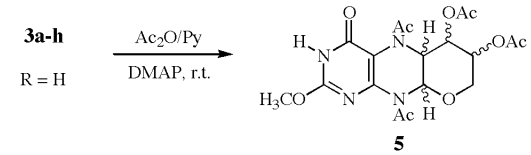
Compound	^{1}H-nmr δ(ppm), J(Hz)	^{13}C-nmr δ(ppm)
4a [a]	5.47 [c] (bs, 1H, *H*-10), 5.13 (d, 1H, $J_{10a,4a}$ = 5.7, *H*-10a), 5.28 (pst, 1H, J = 3.9, *H*-4), 4.72 (bs, 1H, *H*-3), 5.44 (pst, 1H, J = 5.4, *H*-4a), 4.04 (d, 1H, $J_{2a,\ 2e}$ = 13.2, *H*-2e), 3.75 (d, 1H, $J_{2a,\ 2e}$ = 13.2, *H*-2a)	56.3 (*C*-2), 67.6, 67.2 (*C*-3, *C*-4), 40.0 (*C*-4a), 75.5 (*C*-10a)
4b [a]	5.48 [c] (bs, 1H, *H*-10), 5.13 (d, 1H, $J_{10a,4a}$ = 6.0, *H*-10a), 5.28 (pst, 1H, J = 3.9, *H*-4), 4.18 (bs, 1H, *H*-3), 5.44 (pst, 1H, J = 5.4, *H*-4a), 4.04 (d, 1H, $J_{2a,\ 2e}$ = 13.2, *H*-2e), 3.75 (d, 1H, $J_{2a,\ 2e}$ = 13.2, *H*-2a)	56.9 (*C*-2), 67.7, 67.8 (*C*-3, *C*-4), 39.6 (*C*-4a), 75.0 (*C*-10a)
4c [b]	8.10 [c] (s, 1H, *H*-10), 5.00-4.93 (m, 3H, *H*-10a, *H*-4, *H*-3), 5.40 (bs, 1H, *H*-4a), 3.76 (t, 1H, $J_{2a,\ 3}$ = 10.9, $J_{2a,\ 2e}$ = 10.9, *H*-2a), 3.49 (dd, 1H, $J_{2e,3}$ = 4.8, $J_{2a,\ 2e}$ = 10.9, *H*-2e)	54.6 (*C*-2), 66.7, 68.2 (*C*-3, *C*-4), 42.4 (*C*-4a), 79.1 (*C*-10a)
4d [b]	7.80 [c] (s, 1H, *H*-10), 4.98 [c] (s, 1H, *H*-5), 4.72-4.64 (m, 3H, *H*-10a, *H*-4, *H*-3), 4.10 (bs, 1H, *H*-4a), 3.83 (t, 1H, $J_{2a,\ 3}$ = 12.0, $J_{2a,\ 2e}$ = 12.0, *H*-2a), 3.56 (dd, 1H, $J_{2e,3}$ = 3.0, $J_{2a,\ 2e}$ = 12.0, *H*-2e)	54.3 (*C*-2), 66.4, 69.9 (*C*-3, *C*-4), 44.4 (*C*-4a), 74.8 (*C*-10a)
4e [b]	8.20 [c] (s, 1H, *H*-10), 5.05-5.00 (m, 3H, *H*-10a, *H*-4, *H*-3), 5.40 (bs, 1H, *H*-4a), 3.83 (t, 1H, $J_{2a,\ 3}$ = 10.5, $J_{2a,\ 2e}$ = 10.5, *H*-2a), 3.56 (dd, 1H, $J_{2e,3}$ = 3.0, $J_{2a,\ 2e}$ = 12.0, *H*-2e)	54.6 (*C*-2), 66.7, 68.2 (*C*-3, *C*-4), 42.6 (*C*-4a), 74.1 (*C*-10a)
4f [b]	7.81 [c] (s, 1H, *H*-10), 4.98 [c] (s, 1H, *H*-5), 4.72-4.64 (m, 3H, *H*-10a, *H*-4, *H*-3), 4.10 (bs, 1H, *H*-4a), 3.76 (t, 1H, $J_{2a,\ 3}$ = 10.5, $J_{2a,\ 2e}$ = 10.5, *H*-2a), 3.49 (dd, 1H, $J_{2e,3}$ = 4.5, $J_{2a,\ 2e}$ = 10.3, *H*-2e)	54.3 (*C*-2), 66.4, 69.8 (*C*-3, *C*-4), 44.3 (*C*-4a), 74.7 (*C*-10a)
4g [b]	8.20 [c] (s, 1H, *H*-10), 4.60 (m, 1H,+deuterium oxide→d $J_{10a,4a}$ = 1.5, *H*-10a), 4-90-5.10 (m, 3H, *H*-4, *H*-3, *H*-4a), 3.95 (d, 1H, $J_{2a,\ 2e}$ = 10.3, *H*-2e), 3.50 (d, 1H, $J_{2a,\ 2e}$ = 10.3, *H*-2a)	56.3 (*C*-2), 65.7, 67.5 (*C*-3, *C*-4), 51.6 (*C*-4a), 74.1 (*C*-10a)
4h [a]	5.30 [c] (d, 1H, $J_{10,10a}$ = 4.2, *H*-10), 3.90 [c] (s, 1H, *H*-5), 4.84 (m, 1H, +deuterium oxide→d $J_{10a,4a}$ = 0.9, *H*-10a), 5.36 (dd, 1H, $J_{4,3}$ = 9.9, $J_{4,4a}$ = 3.9, *H*-4), 5.50 (td, 1H, $J_{3,4}$ = 9.9, $J_{3,2a}$ = 10.0, $J_{3,2e}$ = 5.4, *H*-3), 3.60 (bs, 1H, *H*-4a), 4.16 (dd, 1H, $J_{2e,3}$ = 5.4, $J_{2a,\ 2e}$ = 11.4, *H*-2e), 3.38 (m, 1H, *H*-2a)	64.6 (*C*-2), 66.4, 72.7 (*C*-3, *C*-4), 51.6 (*C*-4a), 79.8 (*C*-10a)

[a] Deuteriochloroform as solvent; [b] Dimethyl-d$_6$ sulfoxide as solvent; [c] Deuterium exchangeable.

Scheme 2



Starting Material	Reaction Product	R'
3a/3b	**4a**	$COCH_3$
3c/3d	**4b**	$COCH_3$
3e/3f	**4c**	$COCH_3$
	4d	H
3g/3h	**4e**	$COCH_3$
	4f	H
3i	**4g**	$COCH_3$
	4h	H
3j	**4i**	$COCH_3$
	4j	H
3k	**4k**	$COCH_3$
3l	**4l**	$COCH_3$
3m	**4m**	$COCH_3$
3n	**4n**	$COCH_3$



Starting Material	Reaction Product
3a/3b	**5a**
3c/3d	**5b**
3e/3f	**5c**
3g/3h	**5d**

Table 3

^{1}H-nmr and ^{13}C-nmr Selected Data for compounds **4i-n** (tetramethylsilane as internal standard)

Compound	^{1}H-nmr δ(ppm), J(Hz)	^{13}C-nmr δ(ppm)
4i [b]	8.20 [c] (s, 1H, *H*-10), 4.60 (m, 1H, + deuterium oxide → d, $J_{10a,4a}$ = 1.5, *H*-10a), 5.06-4.98 (m, 3H, *H*-4, *H*-3, *H*-4a), 3.94 (m, 1H, *H*-2e), 3.52 (d, 1H, $J_{2a,\ 2e}$ = 13.1, *H*-2a)	56.3 (*C*-2), 66.8, 68.3 (*C*-3, *C*-4), 42.7 (*C*-4a), 74.1 (*C*-10a)
4j [a]	5.62 [c] (d, 1H, $J_{10,10a}$ = 4.8, *H*-10), 3.68 [c] (s, 1H, *H*-5), 4.93 (m, 1H, + deuterium oxide → s, *H*-10a), 5.27 (dd, 1H, $J_{4,3}$ = 9.8, $J_{4,4a}$ = 3.6, *H*-4), 5.50 (td, 1H, $J_{3,4}$ = 9.9, $J_{3,2e}$ = 5.4, $J_{3,2a}$ = 10.0, *H*-3), 3.60 (bs, 1H, *H*-4a), 3.45 (t, 1H, $J_{2a,\ 3}$ = 10.6, $J_{2a,\ 2e}$ = 10.6, *H*-2a), 3.63 (dd, 1H, $J_{2e,3}$ = 5.2, $J_{2a,\ 2e}$ = 10.6, *H*-2e)	63.6 (*C*-2), 66.5, 72.4 (*C*-3, *C*-4), 51.3 (*C*-4a), 78.9 (*C*-10a)
4k [a]	5.02 [c] (bs, 1H, *H*-10), 5.26 (m, 1H, + deuterium oxide → d, $J_{10a,4a}$ = 5.7, *H*-10a), 4.78 (dd, 1H, $J_{4,3}$ = 3.3, $J_{4,4a}$ = 11.4, *H*-4), 5.22 (bs, 1H, *H*-3), 5.44 (m, 1H, *H*-4a), 4.00 (m, 1H, *H*-2a), 3.80 (dd, 1H, $J_{2e,3}$ = 2.1, $J_{2a,\ 2e}$ = 13.2, *H*-2e)	60.5 (*C*-2), 64.5, 67.9 (*C*-3, *C*-4), 42.9 (*C*-4a), 77.0 (*C*-10a)
4l [b]	8.15 [c] (s, 1H, *H*-10), 5.00-5.11 (m, 3H, *H*-10a, *H*-4, *H*-3), 5.40 (bs, 1H, *H*-4a), 3.75 (t, 1H, $J_{2a,\ 3}$ = 10.9, $J_{2a,\ 2e}$ = 10.9, *H*-2a), 3.50 (dd, 1H, $J_{2e,3}$ = 4.7, $J_{2a,\ 2e}$ = 10.9, *H*-2e)	54.7 (*C*-2), 66.8, 68.3 (*C*-3, *C*-4), 42.7 (*C*-4a), 74.2 (*C*-10a)
4m [a]	5.06 [c] (bs, 1H, *H*-10), 5.26 (m, 1H, + deuterium oxide → d $J_{10a,4a}$= 5.5, *H*-10a), 4.78 (dd, 1H, $J_{4,3}$ =3.3, $J_{4,4a}$ = 11.3, *H*-4), 5.22 (bs, 1H, *H*-3), 5.44 (m, 1H, *H*-4a), 3.98 (m, 1H, *H*-2a), 3.80 (dd, 1H, $J_{2e,3}$ = 2.7, $J_{2a,\ 2e}$ = 13.2, *H*-2e)	61.4 (*C*-2), 64.7, 68.4 (*C*-3, *C*-4), 43.7 (*C*-4a), 78.0 (*C*-10a)
4n [b]	8.15 [c] (s, 1H, *H*-10), 5.02-4.94 (m, 3H, *H*-10a, *H*-4, *H*-3), 5.42 (bs, 1H, *H*-4a), 3.77 (t, 1H, $J_{2a,\ 3}$ = 10.5, $J_{2a,\ 2e}$ = 10.5, *H*-2a), 3.63 (dd, 1H, $J_{2e,3}$ = 4.8, $J_{2a,\ 2e}$ = 10.5, *H*-2e)	54.6 (*C*-2), 66.7, 68.2 (*C*-3, *C*-4), 42.6 (*C*-4a), 74.1 (*C*-10a)

[a] Deuteriochloroform as solvent; [b] Dimethyl-d_6 sulfoxide as solvent; [c] Deuterium exchangeable.

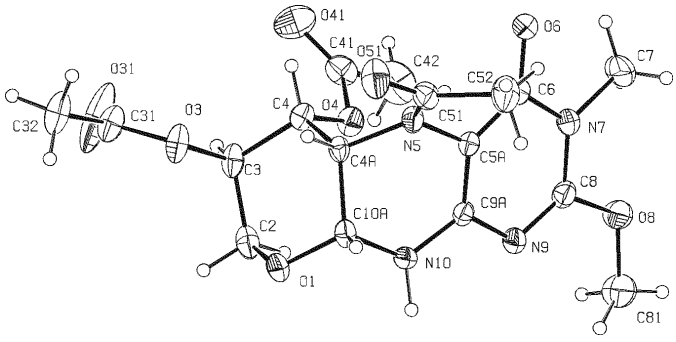


Figure 1. A view of the compound **4g** with the numbering scheme.

The similar ^{1}H-nmr and ^{13}C-nmr spectra and the sign and value of the optical rotation demonstrated that **4a** and **4b, 4g** and **4i, 4h** and **4j** are enantiomeric pairs. The structures of **4g** and **4i** have been determined by X-ray diffraction [18,19] (see Figures 1 and 2). For compound **4g** we could assign the configuration 3*R*,4*R*,4a*S*,10a*R* (as well as for **4a**, **4h**) and for **4i** 3*S*,4*S*,4a*R*,10a*S* (as well as for **4b**, **4j**).

From the ^{1}H-nmr spectra of the above compounds we can obtain additional information about the conformation that these compounds could adopt in dimethyl-d_6 sulfoxide or deuteriochloroform. We have proposed as probable two conformations: I and II (in Scheme 3 only are shown **4a**, **4g** and **4h** and not their enantiomers **4b**, **4i** and **4j**).

From the ^{1}H-nmr spectra of **4h**, (Table 2) more information has been obtained leading to the following discussion. Proton H-10a exhibits a small coupling constant to the vicinal proton H-4a ($J_{10a,4a}$ = 0.9 Hz) that is possible if both protons are *cis* or equatorial-axial in a chair conformer (we assume that a chair conformer is more favourable than a boat conformer). Protons H-3 and H-4 are both axial according to their large coupling constant $J_{3,4}$ = 9.9 Hz, and $J_{4,4a}$ = 3.9 Hz indicating that H-4 and H-4a are both *cis*. Then, this fixes the

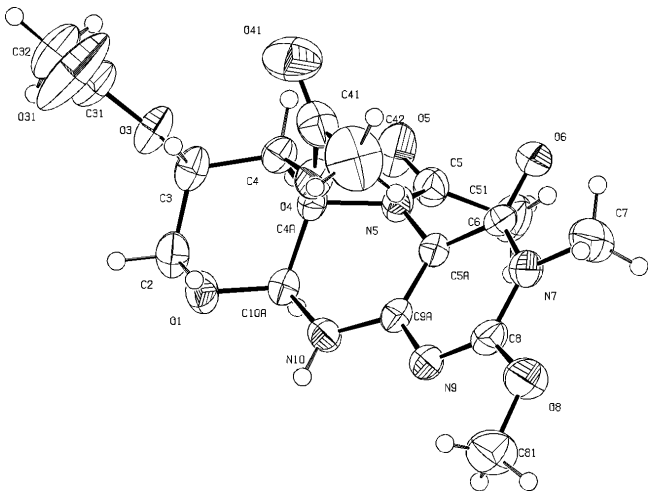


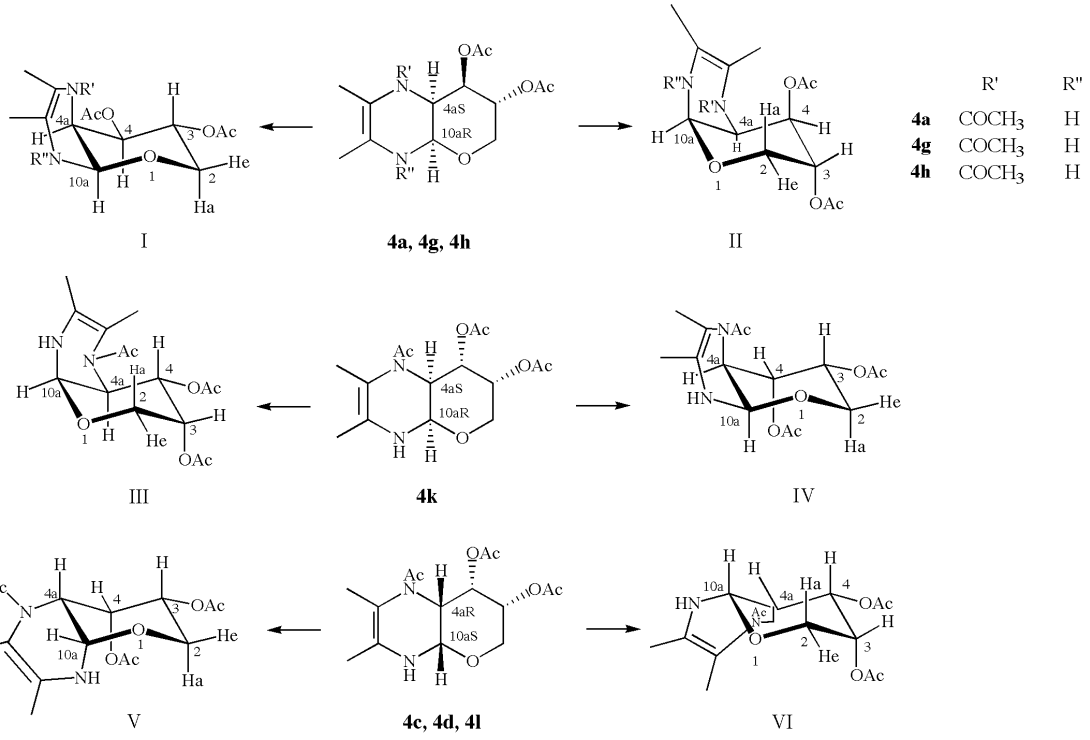
Figure 2. A view of the compound **4i** with the numbering scheme.

for **4g**). This implies a dihedral angle between H-3 and H-2a, H-3 and H-2e of sixty degrees. This is possible only if these compounds adopt the conformation II [15,17] implying that they are 3,4-*trans* diequatorial, 4,4a-*cis* equatorial-axial. The same conclusion could be made for the corresponding enantiomers of the above compounds, **4b**, **4i** and **4j**, which are not represented in Scheme 3.

The relative configuration and conformational conclusions for compound **4k** are essentially the same as those for compound **4m**, because they are an enantiomeric pair, in Scheme 3 (only the enantiomer **4k** is shown) we have proposed two probable conformations III and IV.

The ^{1}H-nmr spectra of **4k** (Table 3) recorded in deuteriochloroform exhibits a small coupling constant between H-4 and H-3 ($J_{4,3}$ = 3.3 Hz) indicating that these protons are in axial-equatorial arrangement. A large coupling constant between H-4 and H-4a ($J_{4,4a}$ = 11.4 Hz) indicates that these protons are in axial arrangement in a classical chair conformation. These considerations suggest a 3,4-*cis* equatorial-axial 4,4a-*trans* diaxial disposition as is depicted in Scheme

Scheme 3



conformation of this compound as the 3,4-*trans* diaxial, 4,4a-*cis* axial-equatorial, as depicted with I in Scheme 3. Further confirmation can be obtained from the signals for H-2a and H-2e, which appear in asymmetrical multiplicity. That is in accord with the fixed conformation I [15,17]. For compounds **4a** and **4g** (see Table 2), the key for the conformational analysis is the symmetrical multiplicity for the signals of H-2a and H-2e protons which appear as doublets with a large coupling constant ($J_{2a,2e}$ = 13.2 Hz for **4a** and 10.3 Hz for **4g**). This implies a dihedral angle between H-3 and H-2a, H-3 and H-2e of sixty degrees. This is possible only if these compounds adopt the conformation II [15,17] implying that they are 3,4-*trans* diequatorial, 4,4a-*cis* equatorial-axial. The same conclusion could be made for the corresponding enantiomers of the above compounds, **4b**, **4i** and **4j**, which are not represented in Scheme 3.

The relative configuration and conformational conclusions for compound **4k** are essentially the same as those for compound **4m**, because they are an enantiomeric pair, in Scheme 3 (only the enantiomer **4k** is shown) we have proposed two probable conformations III and IV.

The ^{1}H-nmr spectra of **4k** (Table 3) recorded in deuteriochloroform exhibits a small coupling constant between H-4 and H-3 ($J_{4,3}$ = 3.3 Hz) indicating that these protons are in axial-equatorial arrangement. A large coupling constant between H-4 and H-4a ($J_{4,4a}$ = 11.4 Hz) indicates that these protons are in axial arrangement in a classical chair conformation. These considerations suggest a 3,4-*cis* equatorial-axial 4,4a-*trans* diaxial disposition as is depicted in Scheme 3 (conformation III) with the configuration 3*R*,4*S*,4a*S*,10a*R*. The coupling constant $J_{10a,4a}$ = 5.7 Hz, is in agreement and gives further weight to this suggestion.

Similar discusion can be made from the ^{1}H-nmr spectra data of compounds **4c-f** and **4l,n**, (see Tables 2 and 3). In Scheme 3, only enantiomers **4c**, **4d** and **4l** are represented, because compounds **4c** and **4e**, **4d** and **4f**, **4l** and **4n** are enantiomeric pairs. To ilustrate this discusion we will use the information from the ^{1}H-nmr spectra of **4c**.

In the ^{1}H-nmr spectra of **4c,** the H-3 proton exhibits a large coupling constant with H-2a ($J_{3,2a}$ = 10.9 Hz), therefore we could assume an axial position. Proton H-4a appears as a broad singlet meaning that the coupling constant with H-3 and H-4 must be small, therefore **4c** exists in 3,4 *cis* axial-equatorial, conformation V as shown in Scheme 3. Further confirmation has been found in bibliographic data [14,15].

The ^{1}H-nmr and ^{13}C-nmr spectra of compounds **5** are in accordance with the pyrano[3,2-*g*]pteridine structure (see Table 4) [15,17]. In addition **5a** and **5b**, **5c** and **5d** are enantiomeric pairs.

In the ^{1}H-nmr spectrum of **5a**, H-3 shows three small coupling constants with H-4, H-2e and H-2a meaning these three protons are *cis*. Similarly, coupling constants between H-4 and H-4a are small. These results suggest a 3,4 *cis* diequatorial 4,4a equatorial-axial disposition (similar to conformation VI in Scheme 3). The structure of **5c** has been determined by X-ray diffraction [20] and the 3*R*,4*S*, 4a*R*,10a*S* configuration has been assigned (see Figure 3). From the nmr spectra of **5c** or **5d**, it has not been possible to obtain additional information about the conformation.

Finally, we have performed the regioselective synthesis of 6-polyhydroxyalkylpteridines **6**, by oxidation of pyrano[3,2-*g*]-pteridines **3**. Reaction of compounds **3a-h** in a buffer solution (sodium carbonate/sodium bicarbonate pH=10) with bubbling oxygen [16] produced the 6-polyhydroxyalkylpteridines **6a-d**; oxidation of **3i-n** with *p*-benzoquinone in water solution led to the 6-polyhydroxyalkylpteridines **6e-h** (see Scheme 4).

The structure of compounds **6** has been demonstrated on the basis of their ^{13}C- and ^{1}H-nmr data: C-7 (146.7-149.8) and H-7 (8.90-9.02) ppm (Table 5), and by comparing with their 7-polyhydroxyalkyl regioismer previously published by us [1]. The structures of 6-polyhydroxy-alkylpteridines **6** have been confirmed by studying the acetyl derivatives **7** (see Scheme 4).

Biological Results.

Biological tests were undertaken to establish the anti-HIV properties of pyrano[3,2-*g*]pteridines and 6-poly-

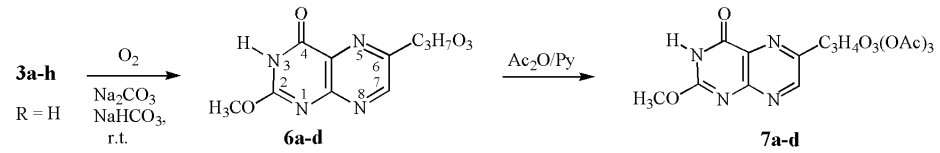
Table 4

^{1}H-nmr and ^{13}C-nmr Selected Data for Compounds **5** (tetramethylsilane as internal standard)

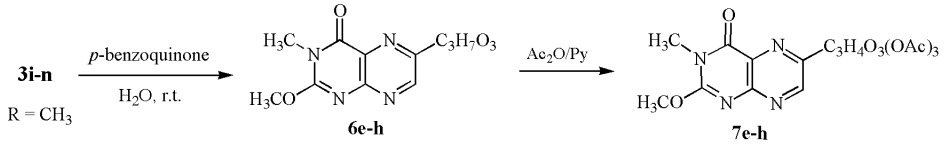
Compound	^{1}H-nmr δ(ppm), J(Hz)	^{13}C-nmr δ(ppm)
5a [a]	6.25 (d, 1H, $J_{4a,10a}$= 7.5, *H*-10a), 5.47 (pst, 1H, J = 6.0, *H*-4), 4.97 (td, 1H, $J_{3,4}$= 5.7, $J_{2a,3}$ =5.7, $J_{2e,3}$ = 3.0, *H*-3), 5.35 (pst, 1H, J=6.0, *H*-4a), 4.16 (dd, 1H, $J_{2a,3}$ = 6.0, $J_{2a,\ 2e}$ = 13.2, *H*-2a), 3.70 (dd, 1H, $J_{2e,3}$ = 3.0, $J_{2a,\ 2e}$ = 13.2, *H*-2e)	68.9 (*C*-2), 65.8, 67.3 (*C*-3, *C*-4), 54.9 (*C*-4a), 81.4 (*C*-10a)
5b [a]	6.25 (d, 1H, $J_{4a,10a}$ = 7.5, *H*-10a), 5.47 (pst, 1H, J= 6.0, *H*-4), 4.97 (td, 1H, $J_{3,4}$= 5.7, $J_{2a,3}$=5.7, $J_{2e,3}$=3.0, *H*-3), 5.35 (pst, 1H, J= 6.0, *H*-4a), 4.15 (dd, 1H, $J_{2a,3}$ = 6.0, $J_{2a,\ 2e}$ = 12.9, *H*-2a), 3.70 (dd, 1H, $J_{2e,3}$ = 3.3, $J_{2a,\ 2e}$ = 12.9, *H*-2e)	66.7 (*C*-2), 66.5, 68.2 (*C*-3, *C*-4), 55.5 (*C*-4a), 80.4 (*C*-10a)
5c [b]	6.16 (d, 1H, $J_{4a,10a}$ = 6.9, *H*-10a), 5.46 (dd, 1H, J= 3.2, 5.3, *H*-4), 4.70 (m, 2H, *H*-3, *H*-4a), 3.87 (m, 1H, *H*-2e), 3.59 (dd, 1H, $J_{2a,3}$ = 5.0, $J_{2a,\ 2e}$ = 12.0, *H*-2a)	65.8 (*C*-2), 65.7, 66.7 (*C*-3, *C*-4), 54.9 (*C*-4a), 80.8 (*C*-10a)
5d [b]	6.16 (d, 1H, $J_{4a,10a}$ = 6.9, *H*-10a), 5.45 (dd, 1H, J = 3.0, 5.3, *H*-4), 5.05 (m, 2H, *H*-3), 4.70 (m, 2H, *H*-3, *H*-4a), 3.88 (m, 1H, *H*-2e), 3.59 (dd, 1H, $J_{2a,3}$ = 5.1, $J_{2a,\ 2e}$ = 12.0, *H*-2a)	63.5 (*C*-2),65.8, 66.8 (*C*-3, *C*-4), 55.0 (*C*-4a), 79.9 (*C*-10a)

[a] Dimethyl-d_6 sulfoxide as solvent.; [b] Deuteriochloroform as solvent.

Scheme 4



Starting Material	Reaction Product
3a/3b	**6a**
3c/3d	**6b**
3e/3f	**6c**
3g/3h	**6d**



Starting Material	Reaction Product
3i	**6e**
3f	**6f**
3k	**6g**
3l	**6g**
3m	**6h**
3n	**6h**

hydroxyalkylpteridines. The "*in vitro*" anti-HIV activity of compounds **3i**, **3l**, **4j**, **6a**, **6d**, **6g**, **7a**, **7g** and **7h** was determined by the National Cancer Institute (NCI) against T4 lymphocytes (CEM cell line) exposed to HIV at virus-to-cell ratio of approximately 0.05, in accord with the general procedure described by this institution [21]. Approximate values for 50% effective concentration (EC_{50}), 50% inhibitory concentration (IC_{50}) and therapeutic index (TI= IC_{50}/EC_{50}) were calculated for each test. These compounds have not shown activity at subtoxic concentration.

Table 5

^{1}H-nmr and ^{13}C-nmr Selected Data for Compounds **6** and **7** (tetramethylsilane as internal standard)

Compound	^{1}H-nmr δ(ppm), J(Hz)	^{13}C-nmr δ(ppm)
6a [a]	8.87 (s, 1H, *H*-7), 4.84 (d, 1H, $J_{1',2'}$ = 2.4, *H*-1')	146.7 (*C*-7), 151.2 (*C*-6)
6b [a]	8.87 (s, 1H, *H*-7), 4.80 (d, 1H, $J_{1',2'}$ = 2.1, *H*-1')	148.4 (*C*-7), 153.9 (*C*-6)
6c [a]	8.91 (s, 1H, *H*-7), 4.65 (d, 1H, $J_{1',2'}$ = 6.2, *H*-1')	147.3 (*C*-7), 150.8 (*C*-6)
6d [a]	8.97 (s, 1H, *H*-7), 4.65 (d, 1H, $J_{1',2'}$ = 5.7, *H*-1')	149.1 (*C*-7), 153.9 (*C*-6)
6e [a]	8.95 (s, 1H, *H*-7), 4.87 (d, 1H, $J_{1',2'}$ = 2.4, *H*-1')	149.8 (*C*-7), 152.9 (*C*-6)
6f [a]	9.02 (s, 1H, *H*-7), 4.87 (d, 1H, $J_{1',2'}$ = 2.4, *H*-1')	149.8 (*C*-7), 153.0 (*C*-6)
6g [a]	8.90 (s, 1H, *H*-7), 4.45 (d, 1H, $J_{1',2'}$ = 5.0, *H*-1')	149.3 (*C*-7), 152.1 (*C*-6)
6h [a]	8.98 (s, 1H, *H*-7), 4.40 (d, 1H, $J_{1',2'}$ = 5.0, *H*-1')	149.3 (*C*-7), 152.1 (*C*-6)
7a [b]	8.88 (s, 1H, *H*-7) , 6.31 (d, 1H, $J_{1',2'}$ = 3.8, *H*-1')	148.8 (*C*-7), 159.3 (*C*-6)
7b [b]	8.87 (s, 1H, *H*-7) , 6.34 (d, 1H, $J_{1',2'}$ = 3.8, *H*-1')	149.4 (*C*-7), 149.1 (*C*-6)
7c [b]	8.97 (s, 1H, *H*-7), 6.27 (d, 1H, $J_{1',2'}$ = 6.9, *H*-1')	148.8 (*C*-7), 149.3 (*C*-6)
7d [b]	8.97 (s, 1H, *H*-7), 6.27 (d, 1H, $J_{1',2'}$ = 6.8, *H*-1')	148.8 (*C*-7), 149.1 (*C*-6)
7e [b]	8.80 (s, 1H, *H*-7), 6.30 (d, 1H, $J_{1',2'}$ = 4.1, *H*-1')	149.0 (*C*-7), 148.5 (*C*-6)
7f [b]	8.90 (s, 1H, *H*-7), 6.36 (d, 1H, $J_{1',2'}$ = 4.8, *H*-1')	149.0 (*C*-7), 148.5 (*C*-6)
7g [b]	8.92 (s, 1H, *H*-7), 6.22 (d, 1H, $J_{1',2'}$ = 6.2, *H*-1')	149.9 (*C*-7), 149.1 (*C*-6)
7h [b]	8.92 (s, 1H, *H*-7), 6.20 (d, 1H, $J_{1',2'}$ = 6.2, *H*-1')	149.1 (*C*-7), 148.9 (*C*-6)

[a] Dimethyl-d_6 sulfoxide as solvent; [b] Deuteriochloroform as solvent.

EXPERIMENTAL

Melting Points were determined using a digital melting points apparatus electrothermal IA9000 and were uncorrected. The ^{1}H- and ^{13}C- nmr were recorded on a Bruker DPX-300 spectrometer operating at 300 MHz and 75 MHz respectively using tetramethylsilane as internal standard. The following abbreviations are used to describe signal coupling: d = doublet, dd = double doublet, m = multiplet, s = singlet, bs = broad singlet, t = triplet, td = three doublets, pst = pseudotriplet. Ultraviolet (uv) spectra were recorded in a GBC UV/VIS spectrophotometer. Optical rotation was measured in a Perkin Elmer 241 polarimeter. The elemental analyses have been obtained using a Perkin Elmer 240 C analyzer. The mass spectra were recorded on a Hewlet Packard HP Engine 5988-A spectrometer equipped with a direct inlet probe operating at 70 eV. Flash column chromatography was perfomed on Merck Silica Gel 60 (0.040-0.030 mm) using the solvent system indicated in each case. Reaction progress and product purity were monitored by thin layer chromatography (tlc) on Merck Silica Gel 60GF_{254} (0.2 mm) aluminium pre-coated sheets with fluorescent indicator, the spots were observed by ultraviolet irradiation and by spraying the sheets with 4% sulphuric acid/ methanol solution and subsequent heating.

General Procedure for the Synthesis of Pyrano[3,2-*g*]pteridines **3**.

5,6-Diaminopyrimidine **1** (17.0 mmol), phenylhydrazone **2** (18.8 mmol) and four drops of 2-mercaptoethanol were added to a 50% mixture (150 ml) of methanol/water previously purged with argon gas. The mixture was stirred under reflux in an argon atmosphere for one hour, then tlc (ethyl acetate/*n*-propanol/water 4:2:1) showed no evidence of the starting material. The reaction crude was kept at room temperature under an inert atmosphere and the resulting white solid which appeared was collected by filtration, washed with cold methanol and then with diethyl ether. The isolation and purification of each reaction product is indicated on each case.

3*R*,4*R*,4a(*S*,*R*)10a(*R*,*S*)-3,4,4a,5,6,7,10,10a-Octahydro-3,4-dihydroxy-8-methoxy-2*H*-pyrano[3,2-*g*]pteridin-6(7H)-ones (**3a**/**3b**).

Starting with 2.66 g of **1a** and 4.18 g of **2a**, after neutralization with amberlite IR-400, 2.34 g (51%) of **3a**/**3b** was obtained, without further purification. uv (methanol): λ max (nm) (ε) 209 (11510), 260 (sh), 295 (5130).

3*S*,4*S*,4a(*S*,*R*)10a(*R*,*S*)-3,4,4a,5,6,7,10,10a-Octahydro-3,4-dihydroxy-8-methoxy-2*H*-pyrano[3,2-*g*]pteridin-6(7*H*)-ones (**3c**/**3d**).

Starting with 2.66 g of **1a** and 4.18 g of **2b**, after neutralization with amberlite IR-400, 2.29 g (50%) of **3c**/**3d** was obtained, without further purification. uv (methanol): λ max (nm) (ε) 209 (17210), 260 (sh), 295 (7800).

3*R*,4*S*,4a(*S*,*R*),10a(*R*,*S*)-3,4,4a,5,6,7,10,10a-Octahydro-3,4-dihydroxy-8-methoxy-2*H*-pyrano[3,2-*g*]pteridin-6(7*H*)-ones (**3e/3f**).

Starting with 2.66 g of **1a** and 4.18 g of **2c**, after neutralization with sodium bicarbonate, 1.88 g (41%) of **3e**/**3f** was obtained. The same product was also obtained from **2d** obtaining 2.98 g (65%), without further purification. uv (methanol): λ max (nm) (ε) 209 (10320), 250 (sh), 295 (4360).

3*S*,4*R*,4a(*R*,*S*),10a(*S*,*R*)-3,4,4a,5,6,7,10,10a-Octahydro-3,4-dihydroxy-8-methoxy-2*H*-pyrano[3,2-*g*]pteridin-6(7*H*)-ones (**3g/3h**).

Starting with 2.66 g of **1a** and 4.18 g of **2e**, after neutralization with sodium bicarbonate, 2.91 g (63%) of **3g**/**3h** was obtained, without further purification. uv (methanol): λ max (nm) (ε) 213 (18750), 264 (sh), 298 (8220).

(3*R*,4*R*,4a*S*,10a*R*)-3,4,4a,5,6,7,10,10a-Octahydro-3,4-dihydroxy-7-methyl-8-methoxy-2*H*-pyrano[3,2-*g*]pteridin-6(7*H*)-one (**3i**.).

Starting with 1.70 g of **1b** and 4.18 g of **2a**, after neutralization with sodium bicarbonate, 2.51 g (49%) of **3i** was obtained which had analytical purity, mp 228 °C. $[\alpha]_D^{20}$ = +14.5° (c 1, dimethyl sulfoxide). ms (70 eV): m/z(%) 284 (100, molecular ion), 209 (45), 194 (13). uv (water): λ max (nm) (ε) 213 (18840), 264 (sh), 298 (8120).

Anal. Calcd. for $C_{11}H_{16}N_4O_5 \cdot H_2O$: C, 43.71; H, 6.00; N, 18.53; Found: C, 43.58; H, 5.99; N, 18.54.

(3*S*,4*S*,4a*R*,10a*S*)-3,4,4a,5,6,7,10,10a-Octahydro-3,4-dihydroxy-7-methyl-8-methoxy-2*H*-pyrano[3,2-*g*]pteridin-6(7*H*)-one (**3j**).

Starting with 1.70 g of **1b** and 4.18 g of **2b**, after neutralization with sodium bicarbonate, 2.49 g (50%) of **3j** was obtained which had analytical purity, mp 230 °C. $[\alpha]_D^{20}$ = -13.6° (c 1, dimethyl sulfoxide). ms (70 eV): m/z(%) 284 (12, molecular ion), 209 (6), 194 (7). u.v (water): λ max (nm) (ε) 212 (20500), 264 (sh), 298 (8400).

Anal. Calcd. for $C_{11}H_{16}N_4O_5 \cdot 1/2H_2O$: C, 45.04; H, 5.50; N, 19.10. Found: C, 44.41; H, 5.94; N, 18.68.

(3*R*,4*S*,4a*S*,10a*R*)-3,4,4a,5,6,7,10,10a-Octahydro-3,4-dihydroxy-7-methyl-8-methoxy-2*H*-pyrano[3,2-*g*]pteridin-6(7*H*)-one **3k** and (3*R*,4*S*,4a*R*,10a*S*)-3,4,4a,5,6,7,10,10a-Octahydro-3,4-dihydroxy-7-methyl-8-methoxy-2*H*-pyrano[3,2-*g*]pteridin-6(7*H*)-one **3l**.

Starting with 1.70 g of **1b** and 4.18 g of **2c** or **2d**, 1.44 g (28%) of **3k** was obtained which had analytical purity, mp 234 °C. $[\alpha]_D^{20}$ = +98.2° (c 1, dimethyl sulfoxide). ms (70 eV): m/z(%) 284 (34, molecular ion), 209 (15), 194 (19). u.v (water): λ max (nm) (ε) 211 (23250), 262 (sh), 293 (8990).

Anal. Calcd. for $C_{11}H_{16}N_4O_5 \cdot H_2O$: C, 43.71; H, 6.00; N, 18.53. Found: C, 44.06; H, 5.82; N, 18.13.

Neutralization of the mother liquors of **3k**, with sodium bicarbonate, led to 1.85 g (36%) of **3l** which had analytical purity, mp 220 °C. $[\alpha]_D^{20}$ = -130.5° (c 1, dimethyl sulfoxide). ms (70 eV): m/z(%) 284 (21, molecular ion), 209 (7), 194 (13). uv (water): λ max (nm) (ε) 211 (23260), 262 (sh), 293 (8980).

Anal. Calcd. for $C_{11}H_{16}N_4O_5 \cdot H_2O$: C, 43.71; H, 6.00; N, 18.53. Found: C, 43.46; H, 6.03; N, 18.75.

(3*S*,4*R*,4a*R*,10a*S*)-3,4,4a,5,6,7,10,10a-Octahydro-3,4-dihydroxy-7-methyl-8-methoxy-2*H*-pyrano[3,2-*g*]pteridin-6(7*H*)-one **3m** and (3*S*,4*R*,4a*S*,10a*R*)-3,4,4a,5,6,7,10,10a-Octahydro-3,4-dihydroxy-7-methyl-8-methoxy-2*H*-pyrano[3,2-*g*]pteridin-6(7*H*)-one **3n**.

Starting with 1.70 g of **1b** and 4.18 g of **2e**, 1.49 g (29%) of **3m** was obtained which had analytical purity, mp 234 °C. $[\alpha]_D^{20}$ = -96.2° (c 1, dimethyl sulfoxide). ms (70 eV): m/z(%) 284 (19, molecular ion), 209 (6), 194 (9). uv (water): λ max (nm) (ε) 212 (14150), 260 (sh), 304 (5850).

Anal. Calcd. for $C_{11}H_{16}N_4O_5 \cdot H_2O$: C, 43.71; H, 6.00; N, 18.53. Found: C, 43.72; H, 5.82; N, 18.77.

Neutralization of the mother liquors of **3m**, with sodium bicarbonate, led to 1.82 g (35.5%) of **3n** which had analytical purity, mp 223 °C. $[\alpha]_D^{20}$ = +132.8° (c 1, dimethyl sulfoxide). ms (70 eV): m/z(%) 284 (4, molecular ion), 209 (3), 194 (77). uv (water): λ max (nm) (ε) 214 (19380), 262 (sh), 296 (7590).

Anal. Calcd. for $C_{11}H_{16}N_4O_5$: C, 46.48; H, 5.67; N, 19.70. Found: C, 46.81; H, 5.80; N, 19.45.

General Procedures for the Acetylation Reaction of Pyrano[3,2-*g*]pteridines **3**.

Method A.

The corresponding pyrano[3,2-*g*]pteridine **3** (5 mmol) was added to 25 ml of a 50% mixture of acetic anhydride/pyridine. The resulting solution was stirred at room temperature for 24 hours and then evaporated under vacuum. The residue was coevaporated several times with methanol. The isolation and purification of each reaction product is indicated on each case.

(3*R*,4*R*,4a*S*,10a*R*)-5-Acetyl-3,4,4a,5,6,7,10,10a-octahydro-8-methoxy-6-oxo-2*H*-pyrano[3,2-*g*]pteridin-3,4-diyl Diacetate **4a**.

Starting from 1.35 g of **3a**/**3b** led to an oily residue which was purified by silicagel flash column chromatography using dichloromethane/ethanol mixtures 100:5 to 100:7; after ethanol crystallization, 1.08 g (52%) of **4a** was obtained, mp 237 °C (d). $[\alpha]_D^{20}$ = +19.9° (c 1, dimethyl sulfoxide). uv (methanol): λ max (nm) (ε) 218 (21730), 254 (sh), 282 (11520).

Anal. Calcd. for $C_{16}H_{20}N_4O_8 \cdot H_2O$: C, 46.37; H, 5.35; N, 13.52. Found: C, 45.96; H, 5.42; N, 13.28.

(3*S*,4*S*,4a*R*,10a*S*)-5-Acetyl-3,4,4a,5,6,7,10,10a-octahydro-8-methoxy-6-oxo-2*H*-pyrano[3,2-*g*]pteridin-3,4-diyl Diacetate (**4b**).

Starting from 1.35 g of **3c**/**3d** led to an oily residue. Flash column (5 x 10 cm) chromatography using dichloromethane/ethanol mixtures 100:5 to 100:7 afforded 1.50 g (73%) of **4b** which crystallized from ethanol, mp 242 °C (d). $[\alpha]_D^{20}$ = -20.4° (c 1, dimethyl sulfoxide). uv (methanol): λ max (nm) (ε) 219 (20540), 250 (sh), 284 (10750).

Anal. Calcd. for $C_{16}H_{20}N_4O_8 \cdot H_2O$: C, 46.37; H, 5.35; N, 13.52. Found: C, 46.13; H, 5.32; N, 13.62.

(3*R*,4*S*,4a*R*,10a*S*)-5-Acetyl-3,4,4a,5,6,7,10,10a-octahydro-8-methoxy-6-oxo-2*H*-pyrano[3,2-*g*]pteridin-3,4-diyl Diacetate **4c** and (3*R*,4*S*,4a*R*,10a*S*)-3,4,4a,5,6,7,10,10a-Octahydro-8-methoxy-6-oxo-2*H*-pyrano[3,2-*g*]pteri-din-3,4-diyl Diacetate **4d**.

Starting from 1.35 g of **3e**/**3f** led to an oily residue for which thin layer chromatography indicated two products, which were separated by flash column chromatography (5 x 10 cm). Elution with dichloromethane/ethanol mixtures 100:7 to 100:9 afforded by order of elution two pure fractions (called I and II).

Fraction I produced 1.39 g (70%) of **4c** that crystallized from ethanol, mp 227 °C (d). $[\alpha]_D^{30}$ = +21.4° (c 1, dimethyl sulfoxide). u.v (methanol): λ max (nm) (ε) 219 (19990), 259 (sh), 281 (9810).

Anal. Calcd. for $C_{16}H_{20}N_4O_8$: C, 48.48; H, 5.09; N, 14.13. Found: C, 48.18; H, 5.12; N, 14.32.

Fraction II generated 0.35 g (19%) of **4d** that crystallized from ethyl acetate, mp 272 °C (d). $[\alpha]_D^{30}$ = +5.0° (c 1, dimethyl sulfoxide). uv (methanol): λ max (nm) (ε) 219 (18230), 260 (sh), 285 (6200).

Anal. Calcd. for $C_{14}H_{18}N_4O_7 \cdot H_2O$: C, 45.03; H, 5.66; N, 15.01. Found: C, 45.24; H, 5.21; N, 14.72.

(3*S*,4*R*,4a*S*,10a*R*)-5-Acetyl-3,4,4a,5,6,7,10a,10-octahydro-8-methoxy-6-oxo-2*H*-pyrano[3,2-*g*]pteridin-3,4-diyl Diacetate **4e** and (3*S*,4*R*,4a*S*,10a*R*)-3,4,4a,5,6,7,10a,10-Octahydro-8-methoxy-6-oxo-2*H*-pyrano[3,2-*g*]pteridin-3,4-diyl Diacetate **4f**.

Starting from 1.35 g of **3g**/**3h** led to an oily residue for which thin layer chromatography indicated two products, after separation by flash column chromatography, as described above, two pure fractions were collected (called I and II).

Fraction I generated 0.51 g (25%) of **4e** that crystallized from ethanol, mp 272 °C (d). $[\alpha]_D^{30}$ = -16.3° (c 1, dimethyl sulfoxide). u.v (methanol): λ max (nm) (ε) 219 (20410), 250 (sh), 284 (10780).

Anal. Calcd. for $C_{16}H_{20}N_4O_8 \cdot 1/2H_2O$: C, 47.40; H, 5.22; N, 13.82. Found: C, 47.77; H, 4.97; N, 13.86.

Fraction II generated 0.12 g (7%) of **4f** that crystallized from ethyl acetate, mp 220 °C (d). $[\alpha]_D^{30}$ = -9.6° (c 1, dimethyl sulfoxide). uv (methanol): λ max (nm) (ε) 219 (20100), 250 (sh), 284 (11110).

Anal. Calcd. for $C_{14}H_{18}N_4O_7$: C, 47.32; H, 5.09; N, 15.77. Found: C, 46.99; H, 5.00; N, 16.08.

(3*R*,4*R*,4a*S*,10a*R*)-5-Acetyl-3,4,4a,5,6,7,10,10a-octahydro-7-methyl-8-methoxy-6-oxo-2*H*-pyrano[3,2-*g*]pteridin-3,4-diyl Diacetate **4g** and (3*R*,4*R*, 4a*S*,10a*R*)-3,4,4a,5,6,7,10a,10-Octahydro-7-methyl-8-methoxy-6-oxo-2*H*-pyrano[3,2-*g*]-pteridin-3,4-diyl Diacetate **4h**.

Starting from 1.47 g of **3i** led to a suspension. The solid was collected by filtration and washed with methanol, 1.35 g (70%) of **4h** pure was obtained, mp 240 °C (d). $[\alpha]_D^{22}$ = -13.9° (c 1, dimethyl sulfoxide). ms (70 eV): m/z(%) 368 (9, molecular ion), 194 (15), 43 (100). u.v (methanol): λ max (nm) (ε) 216 (17120), 269 (sh), 304 (8080).

Anal. Calcd. for $C_{15}H_{20}N_4O_7 \cdot 3/2H_2O$: C, 45.45; H, 5.10; N, 14.13. Found: C, 45.58; H, 4.74; N, 14.10.

Examination of the mother liquors of **4h** by thin layer chromatography indicated two products. The solvents were evaporated *in vacuo* to dryness, a solid residue was obtained; this residue was treated with boiling acetone to give a further residue of **4h**, from the acetone solution of the latter 0.14 g (7%) of **4g** was obtained as a crystalline compound, mp 220 °C (d). $[\alpha]_D^{30}$ = +15.8° (c 1, dimethyl sulfoxide). ms (70 eV): m/z(%) 410 (1, molecular ion), 368 (36), 194 (18), 43 (100). uv (methanol): λ max (nm) (ε) 216 (13900), 304 (2850).

Anal. Calcd. for $C_{17}H_{22}N_4O_8$: C, 49.75; H, 5.40; N, 13.65. Found: C, 49.48; H, 5.40; N, 13.65.

(3*S*,4*S*,4a*R*,10a*S*)-5-Acetyl-3,4,4a,5,6,7,10a,10-octahydro-7-methyl-8-methoxy-6-oxo-2*H*-pyrano[3,2-*g*]pteridin-3,4-diyl Diacetate **4i** and (3*S*,4*S*,4a*R*,10a*S*)-3,4,4a,5,6,7,10a,10,10-Octahydro-7-methyl-8-methoxy-6-oxo-2*H*-pyrano[3,2-*g*]-pteridin-3,4-diyl Diacetate **4j**.

Starting from 1.51 g of **3j** led to a suspension. The solid was collected by filtration and washed with methanol, 1.24 g (64%) of **4j** was obtained, mp 233 °C (d). $[\alpha]_D^{22}$ = +15.3° (c 1, dimethyl sulfoxide). uv (methanol): λ max (nm) (ε) 214 (21350), 268 (sh), 304 (8080).

Anal. Calcd. for $C_{15}H_{20}N_4O_7 \cdot H_2O$: C, 46.50; H, 5.98; N, 14.46. Found: C, 46.48; H, 5.49; N, 14.32.

Examination of the mother liquors of **4j** by thin layer chromatography indicated two products. The solvents were evaporated *in vacuo* to dryness, a solid residue was obtained which was treated with boiling acetone to give a further residue of **4j**, from the acetone solution of the latter, 0.27 g (13%) of **4i** was obtained as a crystalline compound, mp 224 °C (d). $[\alpha]_D^{20}$ = -13.3° (c 1, dimethyl sulfoxide). uv (methanol): λ max (nm) (ε) 222 (25690), 258 (sh), 285 (11580).

Anal. Calcd. for $C_{17}H_{22}N_4O_8$: C, 49.75; H, 5.40; N, 13.65. Found: C, 49.90; H, 5.37; N, 13.54.

(3*R*,4*S*,4a*S*,10a*R*)-5-Acetyl-3,4,4a,5,6,7,10a,10-octahydro-7-methyl-8-methoxy-6-oxo-2*H*-pyrano[3,2-*g*]pteridin-3,4-diyl Diacetate (**4k**).

Starting from 1.51 g of **3k**, 1.91 g (93%) of **4k** was obtained which crystallized from ethyl acetate/petroleum ether 1:2, mp 196 °C. $[\alpha]_D^{22}$ = -46.1° (c 1, dimethyl sulfoxide). ms (70 eV): m/z(%) 410 (2, molecular ion), 368 (30), 194 (16), 43 (100). uv (methanol): λ max (nm) (ε) 221 (24080), 280 (9700).

Anal. Calcd. for $C_{17}H_{22}N_4O_8$: C, 49.75; H, 5.40; N, 13.65. Found: C, 49.66; H, 5.45; N, 13.68.

(3*R*,4*S*,4a*R*,10a*S*)-5-Acetyl-3,4,4a,5,6,7,10a,10-octahydro-7-methyl-8-methoxy-6-oxo-2*H*-pyrano[3,2-*g*]pteridin-3,4-diyl Diacetate (**4l**).

Starting from 1.51 g of **3l**, 1.30 g (63%) of **4l** was obtained which crystallized from ethanol, mp 245 °C (d). $[\alpha]_D^{22}$ = -22.5° (c 1, dimethyl sulfoxide). ms (70 eV): m/z(%) 410 (1, molecular ion), 368 (43), 194 (24), 43 (100). uv (methanol): λ max (nm) (ε) 221 (14130), 280 (5670).

Anal. Calcd. for $C_{17}H_{22}N_4O_8$: C, 49.75; H, 5.40; N, 13.65. Found: C, 49.90; H, 5.45; N, 13.87.

(3*S*,4*R*,4a*R*,10a*S*)-5-Acetyl-3,4,4a,5,6,7,10a,10-octahydro-7-methyl-8-methoxy-6-oxo-2*H*-pyrano[3,2-*g*]pteridin-3,4-diyl Diacetate (**4m**).

Starting from 1.51 g of **3m**, 2.08 g (96%) of **4m** was obtained which crystallized from ethyl acetate/petroleum ether 1:2, mp 190 °C (d). $[\alpha]_D^{20}$ = +47.0° (c 1, dimethyl sulfoxide). ms (70 eV): m/z(%) 410 (3, molecular ion), 368 (100), 194 (24), 43 (20). uv (methanol): λ max (nm) (ε) 221 (27360), 251 (sh), 280 (10410).

Anal. Calcd. for $C_{17}H_{22}N_4O_8 \cdot H_2O$: C, 48.69; H, 5.53; N, 13.36. Found: C, 48.83; H, 5.43; N, 13.26.

(3*S*,4*R*,4a*S*,10a*R*)-5-Acetyl-3,4,4a,5,6,7,10a,10-octahydro-7-methyl-8-methoxy-6-oxo-2*H*-pyrano[3,2-*g*]pteridin-3,4-diyl Diacetate (**4n**).

Starting from 1.51 g of **3n**, 1.15 g (56%) of **4n** was obtained which crystallized from ethanol, mp 243 °C (d). $[\alpha]_D^{20}$ = +26.0° (c 1, dimethyl sulfoxide). ms (70 eV): m/z(%) 410 (5, molecular ion), 368 (93), 194 (25), 43 (100). uv (methanol): λ max (nm) (ε) 222 (20490), 255 (sh), 284 (8630).

Anal. Calcd. for $C_{17}H_{22}N_4O_8$: C, 49.75; H, 5.40; N, 13.65. Found: C, 49.73; H, 5.47; N, 13.89.

Method B.

A mixture of 8.4 ml (27.5%) of acetic anhydride and 22 ml (72.5%) of pyridine and a catalytic amount of dimethylaminopyridine was added to 2.8 mmol of the corresponding pyrano[3,2-*g*]pteridines **3a-h**. The solution was stirred at room temperature for 24 hours; then the acetic anhydride and pyridine were evaporated *in vacuo* to dryness. The residue was coevaporated several times with methanol giving an oily residue that was purified by flash column (4x12 cm) chromatography. Elution with dichloromethane/ethanol mixtures 100:1 to 100:8 afforded the compounds **5**, which crystallized from ethanol.

(3*R*,4*R*,4a*S*,10a*R*)-5,10-Diacetyl-3,4,4a,5,6,7,10a,10-octahydro-8-methoxy-6-oxo-2*H*-pyrano-[3,2-*g*]pteridin-3,4-diyl Diacetate (**5a**).

Starting from **3a/3b**, 1.10 g (90%) of **5a** was obtained, mp 225 °C (d). $[\alpha]_D^{18}$ = -5.6° (c 1, dimethyl sulfoxide). u.v (methanol): λ max (nm) (ε) 221 (25200), 298 (11260).

Anal. Calcd. for $C_{18}H_{22}N_4O_9$: C, 49.31; H, 5.06; N, 12.78. Found: C, 49.18; H, 5.17; N, 12.70.

(3*S*,4*S*,4a*R*,10a*S*)-5,10-Diacetyl-3,4,4a,5,6,7,10a,10-octahydro-8-metho-xy-6-oxo-2*H*-pyrano-[3,2-*g*]pteridin-3,4-diyl Diacetate (**5b**).

Starting from **3c/3d** 0.96 g (78%) of **5b** was obtained, mp 230 °C (d). $[\alpha]_D^{20}$ = +3.2° (c 1, dimethyl sulfoxide). uv (methanol): λ max (nm) (ε) 219 (17250), 285 (14620).

Anal. Calcd. for $C_{18}H_{22}N_4O_9$: C, 49.31; H, 5.06; N, 12.78. Found: C, 49.08; H, 5.14; N, 12.74.

(3*R*,4*S*,4a*R*,10a*S*)-5,10-Diacetyl-3,4,4a,5,6,7,10a,10-octahydro-8-metho-xy-6-oxo-2*H*-pyrano-[3,2-*g*]pteridin-3,4-diyl Diacetate (**5c**).

Starting from **3e/3f**, 1.10 g (90%) of **5c** was obtained, mp 236 °C (d). $[\alpha]_D^{30}$ = -27.0° (c 1, dimethyl sulfoxide). uv (methanol): λ max (nm) (ε) 218 (18000), 288 (9840).

Anal. Calcd. for $C_{18}H_{22}N_4O_9$: C, 49.31; H, 5.06; N, 12.78. Found: C, 49.18; H, 5.12; N, 13.02.

(3*S*,4*R*,4a*S*,10a*R*)-5,10-Diacetyl-3,4,4a,5,6,7,10a,10-octahydro-8-metho-xy-6-oxo-2*H*-pyrano-[3,2-*g*]pteridin-3,4-diyl Diacetate (**5d**).

Starting from **3g/3h**, 0.65 g (53%) of **5d** was obtained, mp 230 °C (d). $[\alpha]_D^{20}$ = +27.0° (c 1, dimethyl sulfoxide). uv (methanol): λ max (nm) (ε) 222 (15620), 297 (9420).

Anal. Calcd. for $C_{18}H_{22}N_4O_9$: C, 49.31; H, 5.06; N, 12.78. Found: C, 49.22; H, 5.15; N, 12.86.

General Procedures for the Synthesis of 6-Polyhydroxyalkylpteridines **6**.

Method A.

Oxygen was bubbled through a suspension of 1.50 g (5.5 mmol) of **3a-h** in 150 ml of a buffer solution formed by sodium carbonate/sodium bicarbonate (pH=10) until the starting material was dissolved, then the mixture was neutralized with acetic acid followed by evaporation to dryness. The oily residue was coevaporated several times with methanol until a solid was obtained. This was suspended in a few millilitres of methanol and filtered off, washed with methanol and diethyl ether affording the compounds **6a-d**. These were purified by redisolution in hot methanol followed by addition of acetone until a white solid began to appear, and then the resulting suspension was cooled to room temperature affording the 6-polyhydroxyalkylpteridines **6a-d**.

6-[D-*threo*]-α,β,γ-Trihydroxypropyl-2-methoxypteridin-4(3*H*)-one (**6a**).

Starting from **3a/3b**, 0.84 g (57%) of **6a** was obtained, mp 178 °C (d). $[\alpha]_D^{18}$ = +81.2° (c 1, water). uv (water): λ max (nm) (ε) 245 (7840), 268, (sh), 334 (5240).

Anal. Calcd. for $C_{10}H_{12}N_4O_5$•1/2 H_2O: C, 43.32; H, 4.72; N, 20.20. Found: C, 43.55; H, 4.38; N, 20.34.

6-[L-*threo*]-α,β,γ-Trihydroxypropyl-2-methoxypteridin-4(3*H*)-one **6b**.

Starting from **3c/3d**, 0.70 g (46%) of **6b** was obtained, mp 179ºC (d). $[\alpha]_D^{18}$ = –80.4º (c 1, water). u.v (water): λ max (nm) (ε) 245 (15490), 270, (sh), 336 (5400).

Anal. Calcd. for $C_{10}H_{12}N_4O_5$•1/2 H_2O: C, 43.32; H, 4.72; N, 20.20. Found: C, 43.75; H, 4.48; N, 20.24.

6-[D-*erythro*]-α,β,γ-Trihydroxypropyl-2-methoxypteridin-4(3*H*)-one (**6c**).

Starting from **3e/3f**, 0.73 g (48%) of **6c** was obtained, mp 171 °C (d). $[\alpha]_D^{30}$ = –46.0° (c 1, water). uv (water): λ max (nm) (ε) 244 (4810), 273, (sh), 331 (2100).

Anal. Calcd. for $C_{10}H_{12}N_4O_5$•1/2H_2O: C, 43.32; H, 4.72; N, 20.20. Found: C, 43.79; H, 4.65; N, 19.75.

6-[L-*erythro*]-α,β,γ-Trihydroxypropyl-2-methoxypteridin-4(3*H*)-one (**6d**).

Starting from **3g/3h,** 0.75 g (49%) of **6d** was obtained, mp 171 °C (d). $[\alpha]_D^{18}$ = –45.0° (c 1, water). ms (70 eV): m/z(%) 269 (5, molecular ion +1), 222 (34), 208 (100). uv (water): λ max (nm) (ε) 232 (10180), 260 (sh), 327 (5730).

Anal. Calcd. for $C_{10}H_{12}N_4O_5$•1/2H_2O: C, 43.32; H, 4.72;N, 20.20. Found: C, 42.89; H, 4.47; N, 19.75.

Method B.

To a suspension of 1.06 g (3.5 mmol) of **3a-h** in 100 ml of water, were added 0.52 g (4.8 mmol) of *p*-benzoquinone. The mixture was stirred at room temperature until total dissolution, and then the reaction crude was extracted with chloroform (25 ml x 3). The organic layer was dried over sodium sulphate and evaporated to dryness. Flash column chromatography (3x10 cm, dichloromethane/ethanol 4:1) led to a solid residue, which crystallized from ethanol to give compounds **6e-h**.

6-[D-*threo*]-α,β,γ-Trihydroxypropyl-2-methoxy-3-methylpteridin-4(3*H*)-one **6e**.

Starting from **3i**, 0.78 g (79%) of **6e** was obtained, mp 173 °C (d). $[\alpha]_D^{30}$ = –101.4° (c 1, water). ms (70 eV): m/z(%) 283 (16, molecular ion + 1), 222 (100). uv (water): λ max (nm) (ε) 238 (18090), 258 (sh), 328 (7010).

Anal. Calcd. for $C_{11}H_{14}N_4O_5$: C, 46.81; H, 5.00; N, 19.85. Found: C, 46.82; H, 5.06; N, 19.47.

6-[L-*threo*]-α,β,γ-Trihydroxypropyl-2-methoxy-3-methylpteridin-4(3*H*)-one (**6f**).

Starting from **3j**, 0.59 g (60%) of **6f** was obtained, mp 173 °C (d). $[\alpha]_D^{30}$ = +102.0° (c 1, water). ms (70 eV): m/z(%) 283 (40, molecular ion + 1), 222 (100). uv (water): λ max (nm) (ε) 238 (16250), 258 (sh), 329 (6310).

Anal. Calcd. for $C_{11}H_{14}N_4O_5$: C, 46.81; H, 5.00; N, 19.85. Found: C, 46.64; H, 5.13; N, 19.27.

6-[D-*erythro*]-α,β,γ-Trihydroxypropyl-2-methoxy-3-methylpteridin-4(3*H*)-one (**6g**).

Starting from **3k** or **3l**, 0.78 g (78%) of **6g** was obtained, mp 171 °C (d). $[\alpha]_D^{28}$ = +48.0° (c 1, water). ms (70 eV): m/z(%) 283 (15, molecular ion + 1), 222 (100). uv (water): λ max (nm) (ε) 238 (16090), 259 (sh), 328 (6480).

Anal. Calcd. for $C_{11}H_{14}N_4O_5$: C, 46.81; H, 5.00; N, 19.85. Found: C, 46.94; H, 4.98; N, 19.78.

6-[L-*erythro*]-α,β,γ-Trihydroxypropyl-2-methoxy-3-methylpteridin-4(3*H*)-one (**6h**).

Starting from **3m** or **3n**, 0.89 g (90%) of **6h** was obtained, mp 173 °C (d). $[\alpha]_D^{28}$ = –48.0° (c 1, water). ms (70 eV): m/z(%) 283 (1, molecular ion + 1), 222 (100). uv (water): λ max (nm) (ε) 238 (16130), 260 (sh), 328 (6290).

Anal. Calcd. for $C_{11}H_{14}N_4O_5$•1/2H_2O: C, 45.36; H, 5.19; N, 19.23. Found: C, 45.75; H, 4.86; N, 19.22.

General Procedure for the Acetylation of 6-Polyhydroxyalkylpteridines.

To a 50% mixture of acetic anhydride/pyridine (20 ml), the corresponding 6-polyhydroxyalkylpteridine **6** (1.1 mmol) was added. The resulting solution was stirred at room temperature for 24 hours and then evaporated under reduced pressure. The residue was coevaporated several times with methanol. Flash column chromatography (2x10 cm, dichloromethane/ethanol 100:7) afforded compounds **7**.

6-[D-*threo*]-α,β,γ-Tri-*O*-acetylpropyl-2-methoxypteridin-4(3*H*)-one (**7a**).

Starting from 0.30 g of **6a** generated 0.19 g (40%) of **7a**, after crystallization from ethanol, mp 103 °C. $[\alpha]_D^{18}$ = –43.0° (c 1, chloroform). uv (methanol): λ max (nm) (ε) 235 (11080), 265 (9710), 327 (6160).

Anal. Calcd. for $C_{16}H_{18}N_4O_8$•ethanol: C, 49.09; H, 5.49; N, 12.72. Found: C, 48.85; H, 5.33; N, 12.65.

6-[L-*threo*]-α,β,γ-Tri-*O*-acetylpropyl-2-methoxypteridin-4(3*H*)-one **7b**.

Starting from 0.30 g of **6b** generated 0.27 g (59%) of **7b**, after crystallization from ethanol, mp 100 °C (d). $[\alpha]_D^{28}$ = +40.8° (c 1, chloroform). uv (methanol): λ max (nm) (ε) 234 (9770), 265 (8740), 326 (5540).

Anal. Calcd. for $C_{16}H_{18}N_4O_8$•1/2ethanol: C, 48.92; H, 5.07; N, 13.42. Found: C, 48.26; H, 5.45; N, 12.84.

6-[D-*erythro*]-α,β,γ-Tri-*O*-acetylpropyl-2-methoxypteridin-4(3*H*)-one (**7c**).

Starting from 0.30 g of **6c** generated 0.21 g (43%) of **7c**, after crystallization from ethanol, mp 147 °C. $[\alpha]_D^{28}$ = +69.3° (c 1, chloroform). ms (70 eV): m/z(%) 222 (63), 208 (2). uv (methanol): λ max (nm) (ε) 234 (10550), 264 (9330), 326 (5860).

Anal. Calcd. for $C_{16}H_{18}N_4O_8$ · ethanol: C, 49.09; H, 5.49; N, 12.72. Found: C, 49.19; H, 5.12; N, 12.68.

6-[L-*erythro*]-α,β,γ-Tri-*O*-acetylpropyl-2-methoxypteridin-4(3*H*)-one (**7d**).

Starting from 0.30 g of **6d** generated 0.26 g (57%) of **7d**, after crystallization from ethanol, mp 149 °C. $[\alpha]_D^{28}$ = –66.8° (c 1, chloroform). ms (70 eV): m/z(%) 222 (44), 208 (100). uv (methanol): λ max (nm) (ε) 234 (10800), 264 (9770), 325 (6090).

Anal. Calcd. for $C_{16}H_{18}N_4O_8$•1/2ethanol: C, 48.92; H, 5.07; N, 13.42. Found: C, 48.65; H, 5.12; N, 13.13.

6-[D-*threo*]-α,β,γ-Tri-O-acetylpropyl-2-methoxy-3-methylpteridin-4(3*H*)-one (**7e**).

Starting from 0.31 g of **6e** generated 0.31 g (70%) of **7e**, as an oily residue.

6-[L-*threo*]-α,β,γ-Tri-*O*-acetylpropyl-2-methoxy-3-methylpteridin-4(3*H*)-one (**7f**).

Starting from 0.31 g of **6f** generated 0.35 g (78%) of **7f**, as an oily residue.

6-[D-*erythro*]-α,β,γ-Tri-*O*-acetylpropyl-2-methoxy-3-methylpteridin-4(3*H*)-one (**7g**).

Starting from 0.31 g of **6g** generated 0.34 g (76%) of **7g**, after crystallization from ethanol, mp 149 °C. $[\alpha]_D^{28}$ = –67.2° (c 1, chloroform). ms (70 eV): m/z(%) 222 (63), 208 (2). uv (methanol): λ max (nm) (ε) 240 (15390), 267 (sh), 327 (5980).

Anal. Calcd. for $C_{17}H_{20}N_4O_8$: C, 50.00; H, 5.18; N, 13.72. Found: C, 49.62; H, 4.87; N, 13.61.

6-[L-*erythro*]-α,β,γ-Tri-*O*-acetylpropyl-2-methoxy-3-methylpteridin-4(3*H*)-one (**7h**).

Starting from 0.31 g of **6h** generated 0.20 g (45%) of **7h**, after crystallization from ethanol, mp 149 °C. $[\alpha]_D^{28}$ = –66.8° (c 1, chloroform). uv (methanol): λ max (nm) (ε) 240 (15190), 267 (sh), 327 (5790).

Anal. Calcd. for $C_{17}H_{20}N_4O_8$: C, 50.00; H, 5.18; N, 13.72. Found: C, 50.00; H, 4.81; N, 13.28.

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REFERENCES AND NOTES

[1] M. D. López, M. L. Quijano, A. Sánchez and M. Nogueras, *J. Heterocyclic. Chem.*, In press.

[2] D. J. Brown, Fused Pyrimidines (part three Pteridines), ed. John Wiley & Sons, New York, 1988.

[3] W. Pfleiderer and E. C. Taylor, Pteridine Chemistry, ed. Pergamon Press, Oxford, 1964.

[4] J. A. Montgomery, *Heterocycles*, **21**, 137, (1984).

[5] M. Viscontini, Biochemical and Clinical Aspects of Pteridines, M. Watcher, W. Pfleiderer and H. C. De Curtius, ed. Walter de Gruyter, Berlín, 1984.

[6] E. C. Taylor, *J. Heterocyclic Chem.*, **27**, 1, (1990).

[7] R. L, Kisliuk and G. M. Brown, Chemistry and Biology of Pteridines, ed. Elsevier North Holland, New York, 1979.

[8] A. Hausen, D. Fuchs, G. Reibneger, E. R. Werner and H. Watcher, *Pteridines*, **1**, 3, (1989).

[9] S. Ogiwara, T. Nagatsu, R. Teradaira, K. Fugita and T. Sugimoto, *Tetrahedron Lett.*, **33(10)**, 1341, (1992).

[10] Kanegafuchi Chemical Industry Co., Ltd., Japan. Jpn. Kokai Tokkyo Koho JP 61293982. *Chem. Abstr.*, 1987, **107**, 7009.

[11] M. Viscontini and R. Provenzale. *Helv. Chim. Acta.*, **51**, 1495, (1968).

[12] M. Viscontini, R. Provenzale and S. Olhgart. *Helv. Chim. Acta.*, **53**, 1202, (1970).

[13] W. Pfleiderer, Comprehensive Heterocyclic Chemistry, Vol **3**, ed. Pergamon Press, Oxford, 1984, pp 312.

[14] S. Matsuura, H. Traube and W. L. F. Amarego, *Pteridines*, **1**, 73, (1989).

[15] R. Soyka and W. Pfleiderer, *Pteridines*, **2**, 129, (1990).

[16] S. Murata, T. Sugimoto, S. Ogiwara, K. Mogi and H. Wasada., *Synthesis*, **3**, 303, (1992).

[17] R. Soyka, W. Pfleiderer and R. Prewo, *Helv. Chim. Acta.*, **73**, 809, (1990).

[18] J. N. Low, E. Cadoret, G. Ferguson, M. D. López, M. L. Quijano, A. Sánchez and M. Nogueras, *Acta Cryst.* **C51**, 2141, (1995).

[19] J. N. Low, E. Cadoret, G. Ferguson, M. D. López, M. L. Quijano, A. Sánchez, M. Nogueras and J. Cobo, *Acta Cryst*. **C54**, IUC9800060, (1998).

[20] J. N. Low, E. Cadoret, G. Ferguson, M. D. López, M. L. Quijano, A. Sánchez and M. Nogueras, *Acta Cryst*. **C55**, 452, (1999).

[21] Weislow, R. Kiser, D. Fine, J. Bader, R. H. Shoemaker and M. R. Boyd, *J. Natl. Cancer Inst*., **81**, 577, (1989).