HETEROCYCLES, Vol. 71, No. 4, 2007, pp. 911 - 918. © The Japan Institute of Heterocyclic Chemistry
Received, 16th January, 2007, Accepted, 23rd February, 2007, Published online, 23rd February, 2007. COM-07-11003

CHEMOSELECTIVE OXIDATION OF 6-HYDROXYALKYLPTERIDINE AND ITS APPLICATION TO SYNTHESIS OF 6-ACYL-7,8-DIHYDROPTERIDINE

Sudhir S. Landge, Kazunari Kudoh, Yuri Yamada, and Shizuaki Murata*

Graduate School of Environmental Studies, Nagoya University, Chikusa Nagoya 464-8601 Japan, murata@urban.env.nagoya-u.ac.jp

Abstract – Alcohol-selective oxidation of 6-1'-hydroxyalkylpteridines catalyzed by ruthenium (IV), RuO_4^-, gives 6-acylpteridines in high yields. Partial reduction of the products affords 6-acyl-7,8-dihydropteridine derivatives, such as a lipophilic derivative of sepiapterin, deoxysepiapterin, and sepiapterin-C.

INTRODUCTION

Figure 1 shows some examples of naturally occurring 6-acyl-7,8-dihydropteridine derivatives. Deoxysepiapterin (**1**, 2-amino-7,8-dihydro-6-2'-oxopropyl-pteridin-4(3H)-one) and sepiapterin-C (**2**, 2-amino-7,8-dihydro-6-acetylpteridin-4(3H)-one) have been isolated, together with sepiapterin (**3**), as yellow pigments from higher animals, e.g. *Drosophia meranogaster*.[1] In these animals, **3** is known to be present in a methabolic pathway of (6*R*)-tetrahydrobiopterin (**4**).[2] Compound **4** is of interest in biochemistry and medicinal chemistry, because it is a key cofactor in the biosynthesis of not only neurotransmitting catecolamines and serotonin but also smooth-muscle extending nitrogen monooxide (NO) in the human body.[3] The deficiency of **4** in the human body may cause cardiovascular diseases and hypertension as well as various nervous disorders, for example hyperphenylalania, dystonia, and Parkinson's disease. In some patients the existence of a salvage process through **3** relieves the symptoms, and **3** and related 6-acylpteridine derivatives are required for studies on such diseases.[4,5]

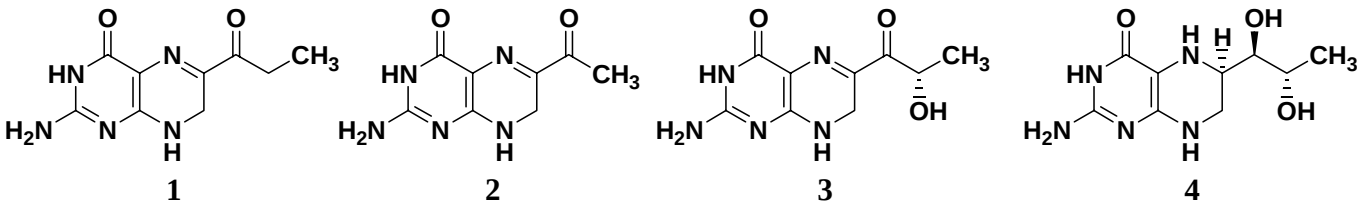
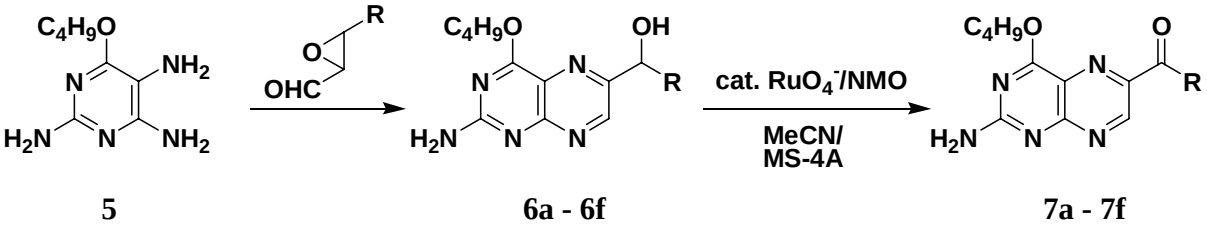


Figure 1. Naturally occurring 7,8-dihydro-6-acylpteridine and (6*R*)-5,6,7,8-tetrahydrobiopterin.

However, the practical supply of such pteridine derivatives by means of chemical synthesis is not well established, so far, mainly because only a few methods for the synthesis of 6-acylpteridine have been reported.[6] Although oxidation of 6-hydroxyalkylpteridine to 6-acylpteridine seems to be the most accessible and straightforward method, it has not attracted the attention of synthetic chemists due to the existence of many possible side reactions, such as *N*-oxide formation[7] and oxidative C–C bond cleavage.[8] In addition, the fact that such pteridine derivatives are generally insoluble in common organic solvents causes further difficulty in choosing reagents and reaction conditions. Our research on pteridine synthesis has overcome the second problem using a protective group which makes the pteridine derivative soluble in organic solvents and applicable to normal chromatographic purification on silica gel.[9] Hence, we have the opportunity to look for a chemoselective oxidation process. In this paper, we describe the Ru(IV) catalyzed side-chain selective oxidation of 6-hydroxyalkylpteridine and its application to the synthesis of 7,8-dihydro-6-acylpteridine derivatives.

RESULTS AND DISCUSSION

2-Amino-4-butoxy-6-1'-hydroxyalkylpteridines (**6a** – **6d**) prepared from the reaction of 2,5,6-triamino-4-butoxypyrimidine (**5**) and corresponding epoxyaldehydes (R: alkyl and phenyl)[9] reacted with 10 mol % of tetrapropylammonium peroxyruthenate (TPAP: $(^nC_3H_7)_4N^+$ RuO_4^-)[10] and 2 equiv. *N*-methylmorpholine oxide (NMO) in the presence of dry molecular sieves (MS-4A) in dry acetonitrile, and gave corresponding 6-acylpteridine derivatives **7a** – **7d** in high yields. The oxidation of 2'-protected 6-1',2'-dihydroxypropylpteridine derivatives **6e** and **6f** under the same conditions gave α-hydroxyketone derivatives **7e** and **7f**, which were considered to be the protected aromatic derivative of **3**. The results are shown in Scheme 1 and Table 1. The formation of either *N*-oxide or pteridin-6-carboxylic acid resulting from oxidative side-chain cleavage was not recommended in the crude products. The butyl protective group for good solubility in acetonitrile and the addition of MS-4A are essential to carry out the reaction.



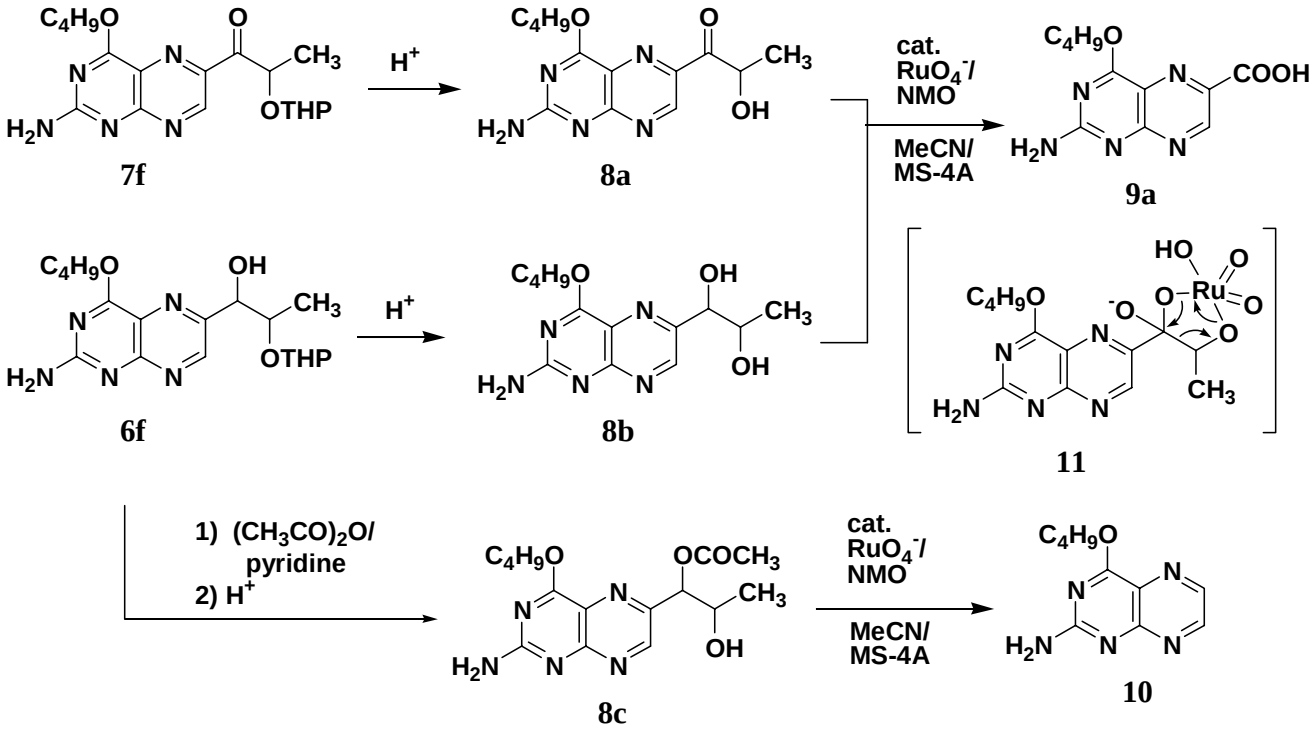
5 **6a - 6f** **7a - 7f**

Scheme 1. Oxidation of 6-1'-hydroxyalkylptrerin to 6-acylpterin.

Table 1. Results of TPAP oxidation of **6a** – **6f**.

Entry	Alcohol	R	Ketone	Yield/%
1	**6a**	CH_3	**7a**	95
2	**6b**	CH_2CH_3	**7b**	99
3	**6c**	$CH_2CH_2CH_3$	**7c**	92
4	**6d**	C_6H_5	**7d**	98
5	**6e**	$CH(OCOCH_3)CH_3$	**7e**	90
6	**6f**	$CH(OTHP)CH_3$	**7f**	91

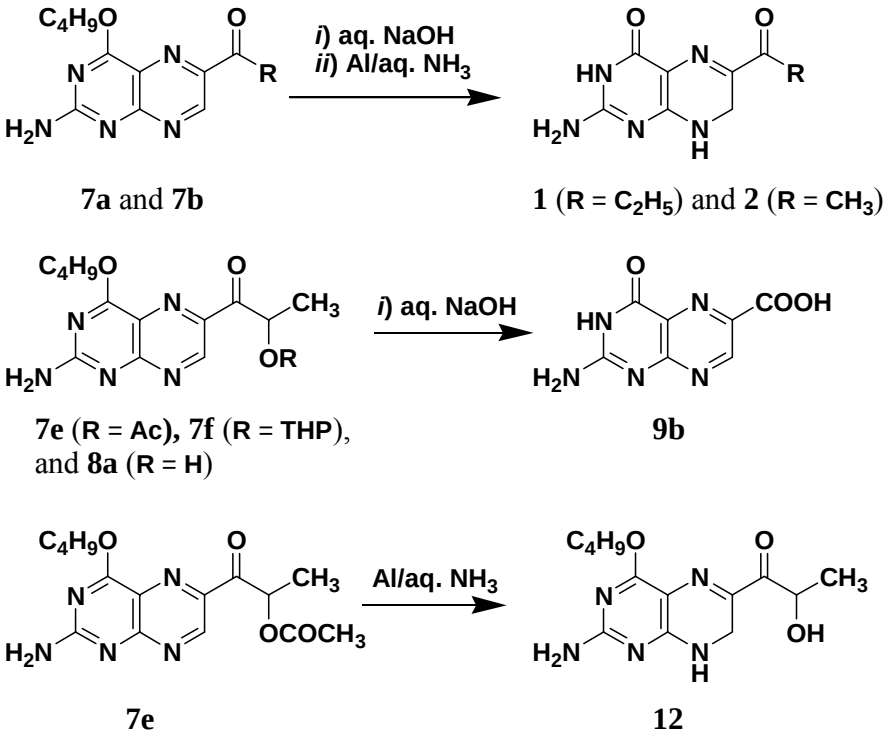
The chemoselective TPAP oxidation was applied to syntheses of 6-1',2'-dioxopropylpteridine and 6-1'-hydroxy-2'-oxopropylpteridine derivatives, both of which were recognized as key intermediates in the biosynthesis of **4** but had not been chemically synthesized. The substrates **8a** – **8c** with a free OH group at the 2'-position were prepared from **6f** and **7f** as follows. Acidic deprotection of **6f** and **7f** by the action of pyridinium *p*-toluenesulfonate in ethanol gave **8a** and **8c** in 90% and 94% yields, respectively, and the treatment of **6f** with acetic anhydride in pyridine followed by the acidic deprotection yielded **8c** in a 92% yield. In contrast to the cases of **6e** and **6f** having the free OH group at the 1'-position, the oxidation of **8a** – **8c** under the same conditions did not afford the desired products, but rather pteridin-6-carboxylic acid (**9a**) or pteridine (**10**) in almost quantitative yields as shown in Scheme 2. These results indicated that the C—C bond cleavage of α-hydroxyketone was facilitated in the cyclic intermediate **11**.



Scheme 2. Attempts to synthesize α-diketone derivative.

The transformation of the obtained 6-acylpteridines **7** to corresponding 6-acyl-7,8-dihydropteridine derivatives was performed by the following 2-step reactions, which are shown in Scheme 3. The protective group (*n*-C_4H_9) was removed by alkaline hydrolysis (0.1 M NaOH) in 85 – 98% yields (step *i*), and partial reduction of the products to 7,8-dihydropteridines was carried out using dissolving metal reduction with activated aluminum in aqueous NH_3 in 30 – 35% yields (step *ii*). Since 7,8-dihydropteridines are easily oxidized to pteridines during isolation and purification under aerobic conditions, the yields of the products were optimal. Catalytic hydrogenation on 5% Pd-C in methanol also afforded the partially hydrogenated product, but the yield was unsatisfactory (10%). Thus, naturally occurring deoxysepiapterin (**1**) and sepiapterin-C (**2**) were synthesized from **7a** and **7b** in 30 and 32 % overall yields, respectively. However, the derivation of **7** to sepiapterin (**3**) has not been successful yet. Due to high instability of the side chain, the same treatment of **7e**, **7f** and **8a** with NaOH did not give the desired products but rather produced pteridine-6-carboxylic acid (**9b**).[11] The reduction of **7e** under similar conditions afforded 7,8-dihydropteridine **12**, which is regarded as a lipophilic derivative of **3**, in a 50 % yield. Further attempts to synthesize **3** are in progress.

In conclusion, we have succeeded in oxidizing 6-hydroxyalkylpteridine to 6-acylpteridine selectively, and the products were transformed to 6-acyl-7,8-dihydropteridine derivatives which are considered to be precursors of biolochemically and pharmaceutically interesting derivatives of pteridine and folic acids.



Scheme 3. Deprotection and partial reduction of **7**.

EXPERIMENTAL

General methods. NMR spectra were recorded on a JEOL® A-400 (^{1}H 400 MHz, ^{13}C 100 MHz) spectrometer in $CDCl_3$ or CF_3COOD solutions, and signals of $CDCl_3$ (δ: 7.27 for ^{1}H; δ: 77.1 for ^{13}C) and tetramethylsilane (δ: 0) were employed for the calibration of chemical shifts. A quintet coupling pattern was abbreviated as qnt. IR and UV spectra were recorded on a JASCO® FT/IR-5300 and JASCO® V-550 spectrometers, respectively. Elemental analyses were carried out at the Analytical Center, the Faculty of Agriculture at Nagoya University. Melting points were uncorrected. Acetonitrile was distilled over P_4O_{10}, and MS-4A was dried over P_4O_{10} at 200 Pa at 200 °C prior to use. Using the method cited in the reference,[9] 6-1'-hydroxyalkylpteridine **6a** – **6f** were synthesized.

*Oxidation of **6b** to **7b**; a typical example.* Under an Ar atmosphere, dry MS-4A (200 mg) was placed in a 50 mL Schlenk tube, and to this was added a solution of tetrapropylammonium peroxyruthenate (10 mg, 0.035 mmol) and 4-methylmorpholine *N*-oxide (NMO) (100 mg, 0.71 mmol) in dry MeCN (10 mL). The mixture was heated at 60 °C for 5 min, and **6b** (100 mg, 0.35 mmol) was added. After 1 h of stirring at 60 °C, the mixture was filtered through a short column of Celite®. The filtrate was poured into a 10% NH_4Cl solution, and organic substances were extracted with CH_2Cl_2 (20 mL x 5). Column chromatography on silica gel (eluant: EtOAc) gave pure **7b** (94 mg, 99% yield) as yellow powder.

*2-Amino-4-butoxy-6-acetylpteridine (**7a**).* Yellow powder, 95%; Mp 246 °C (decomp); ^{1}H NMR ($CDCl_3$) δ: 1.05 (3H, t, *J* = 7.6 Hz), 1.58 (2H, tq, *J* = 6.8, 7.6 Hz), 1.93 (2H, qnt, *J* = 7.2 Hz), 2.77 (3H, s), 4.61 (2H, t, *J* = 6.8 Hz), 9.46 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 14.1, 19.5, 25.7, 30.8, 41.2, 68.9, 141.0, 150.1, 153.8, 153.9, 158.8, 163.7, 168.6. 198.6; IR (KBr) ν cm^{-1}: 3401, 3135, 1696, 1658, 1454, 1356, 1266, 1212, 1092, 957, 826; UV (MeOH) λ_{max} nm (ε): 304 (9500), 364 (8000); Anal. Calcd for $C_{12}H_{15}N_5O_2$: C, 55.10; H, 5.70; N, 26.80. Found: C, 55.11; H, 5.74; N, 26.76.

*2-Amino-4-butoxy-6-1'-oxopropylpteridine (**7b**).* Yellow powder, 99%; Mp 224 °C (decomp); ^{1}H NMR ($CDCl_3$) δ: 1.04 (3H, t, *J* = 7.6 Hz), 1.25 (3H, t, *J* = 7.2 Hz), 1.56 (2H, m), 1.93 (2H, qnt, *J* = 7.1 Hz), 3.27 (2H, q, *J* = 7.2 Hz), 4.59 (2H, t, *J* = 6.8 Hz), 9.45 (1H, s); ^{13}C NMR ($CDCl_3$) δ 13.8, 17.5, 19.4, 30.4, 39.4, 68.7, 142.8, 149.9, 154.8, 158.6, 162.8, 168.4, 200.5; IR (KBr) ν cm^{-1}: 3400–2900, 1693, 1654, 1594, 1508, 1442, 1326, 1211, 1087, 889, 826, 801; UV (MeOH) λ_{max} nm (ε): 301 (10500), 364 (8900); Anal. Calcd for $C_{13}H_{17}N_5O_2$: C, 56.70; H, 6.10; N, 25.40. Found: C, 56.71; H, 5.95; N, 25.57.

*2-Amino-4-butoxy-6-1'-oxobutylpteridine (**7c**).* Yellow powder, 99%; Mp 256 °C (decomp); ^{1}H NMR ($CDCl_3$) δ: 1.03 (3H, t, *J* = 7.6 Hz), 1.05 (3H, t, *J* = 7.2 Hz), 1.58 (2H, m), 1.80 (2H, m), 1.91 (2H, m), 3.20 (2H, t, *J* = 7.2 Hz), 4.58 (2H, t, *J* = 6.8 Hz), 9.43 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 13.8, 13.9, 17.5, 19.3, 30.5, 39.3, 68.5, 143.1, 149.9, 153.7, 158.5, 162.8, 168.3, 200.5; IR (KBr) ν cm^{-1}: 3400–2900, 1694, 1654, 1591, 1505, 1487, 1365, 1327, 1269, 1090, 968, 935, 903; UV (MeOH) λ_{max} nm (ε): 303 (5000), 364 (4200); Anal. Calcd for $C_{14}H_{19}N_5O_2$: C, 58.12; H, 6.62; N, 24.21. Found: C, 58.07; H, 6.55; N, 24.26.

*2-Amino-4-butoxy-6-benzoylpteridine (**7d**).* Yellow powder, 98%; Mp 261 °C (decomp); ^{1}H NMR ($CDCl_3$) δ: 1.03 (3H, t, *J* = 7.3 Hz), 1.60 (2H, tq, *J* = 6.9, 7.3 Hz), 1.89 (2H, qnt, *J* = 6.9 Hz), 4.57 (2H, t, *J* = 6.9 Hz), 7.50 (2H, dd, *J* = 8.2, 1.6 Hz), 7.63 (1H, dd, *J* = 8.2, 1.6 Hz), 8.32 (2H, d, *J* = 8.2 Hz), 9.56 (1H,s); ^{13}C NMR ($CDCl_3$) δ: 14.1, 19.4, 30.8, 68.8, 128.4, 131.7, 133.6, 136.1, 152.5, 152.7, 155.7, 158.0, 163.2, 168.7, 187.6; IR (KBr) ν cm^{-1}: 3400–2900, 1656, 1592, 1506, 1436, 1328, 1269, 1090, 968, 934, 902, 861; UV (MeOH) λ_{max} nm (ε): 311 (7300), 366 (7000); Anal. Calcd for $C_{17}H_{17}N_5O_2$: C, 63.10; H, 5.20; N, 21.60. Found: C, 63.11; H, 5.34; N, 21.74.

*2-Amino-4-butoxy-6-2'-acetoxy-1'-oxopropylpteridine (**7e**).* Yellow powder, 90%; Mp 213 °C (decomp); ^{1}H NMR ($CDCl_3$) δ: 1.05 (3H, t, *J* = 7.6 Hz), 1.58 (2H, m), 1.64 (3H, d, *J* = 7.2 Hz), 1.92 (2H, qnt, *J* = 6.8 Hz), 2.19 (3H, s), 4.58 (2H, t, *J* = 6.8 Hz), 6.35 (1H, q, *J* = 6.8 Hz), 9.45 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 13.8, 16.8, 19.2, 20.7, 30.4, 68.5, 71.4, 140.6, 150.3, 153.7, 158.6, 163.1, 168.2, 170.4, 195.6; IR (KBr) ν cm^{-1}: 3400–2900, 1746, 1700, 1653, 1589, 1506, 1440, 1370, 1352, 1254, 1226, 1091, 988, 936, 914; UV (MeOH) λ_{max} nm (ε): 308 (9100), 364 (8500); Anal. Calcd for $C_{15}H_{19}N_5O_4$: C, 54.00; H, 5.70; N, 21.00. Found: C, 54.00; H, 5.76; N, 20.99.

*2-Amino-4-butoxy-6-2'-tetrahydropyran-2''-yloxy-1'-oxopropylpteridine (**7f**).* Yellow powder, 91%; Mp 213 °C (decomp); ^{1}H NMR ($CDCl_3$) δ: 1.03 (3H, t, *J* = 7.6 Hz), 1.55 (2H, m), 1.59 (3H, d, *J* = 6.7 Hz), 1.64 (6H, m), 1.92 (2H, qnt, *J* = 6.8 Hz), 1.99 (2H, brs), 3.54 (1H, dt, *J* = 11.3, 5.0 Hz), 3.95 (1H, ddd, *J* = 11.2, 9.2, 2.2 Hz), 4.58 (2H, t, *J* = 6.8 Hz), 4.80 (1H, t, *J* = 3.4 Hz), 5.65 (1H, q, *J* = 6.8 Hz), 9.44 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 13.8, 18.5, 19.2, 19.4, 25.5, 26.7, 30.5, 62.7, 68.7, 73.0, 98.7, 141.9, 150.4, 157.6, 157.9, 162.6, 168.3, 198.8; IR (KBr) ν cm^{-1}: 3400–2900, 1698, 1656, 1590, 1509, 1441, 1320, 1289, 1215, 1082, 980, 935, 829; Anal. Calcd for $C_{18}H_{25}N_5O_4$: C, 57.59; H, 6.71; N, 18.65. Found: C, 57.60; H, 6.63; N, 18.62.

*Deprotection and partial reduction of **7b**; a typical example for 6-acylpteridine.* Under an Ar atmosphere, 0.1 M aq. NaOH (10 mL) was added to a solution of **7b** (89 mg, 0.32 mmol) in MeOH (10 mL), and the solution was stirred at 30 °C for 24 h. The mixture was neutralized with 0.1 M HCl, and the resulting pale yellow precipitates were separated by centrifugation. The residue was washed with 50% MeOH and dried under ca. 200 Pa at 50 °C. 2-Amino-6-1-oxopropylpteridin-4(3*H*)-one (68 mg, 98%) was obtained as pale yellow powder. Aluminum turnings (200 mg) were immersed in an aqueous solution of $HgCl_2$ (25 mg in 5 mL) for 15 min and washed 3 times with water. Under an Ar atmosphere, Al turnings were added to a solution of 2-amino-6-1'-oxopropylpteridin-4(3*H*)-one (50 mg, 0.22 mmol) in 1M NH_3 (100 mL). The mixture was stirred at 30 °C for 1.5 h and filtered. The filtrate was concentrated to ca. 75 mL, and the pH was adjusted to 3 – 4 by the addition of CH_3COOH. The mixture was charged to a column of Florisil® (60–100 mesh, 25 mm i.d. x 150 mm), and the column was washed with water (500 mL). Then the column was eluted with 10% aq. acetone to give a yellow fraction.

After evaporation of the fraction, extraction of the residue with hot MeOH (10 mL x 5) gave pure deoxysepiapterin (**2**, 15 mg, 30%) as yellow powder.

2-Amino-6-1'-oxopropylpteridin-4(3H)-one.[12] Pale yellow powder, Mp 315 °C; ^{1}H NMR (CF_3COOD) δ: 1.29 (3H, t, *J* = 7.3 Hz), 3.38 (2H, q, *J* = 7.3 Hz), 9.45 (1H, s); ^{13}C NMR (CF_3COOD) δ: 8.27, 34.1, 128.6, 149.1, 151.3, 152.1, 154.7, 162.4, 207.0.

*Deoxysepiapterin (**2**).*[13] Pale yellow powder, Mp 258 °C (decomp); ^{1}H NMR (CF_3COOD) δ: 1.57 (3H, t, *J* = 6.7 Hz), 3.65 (2H, q, 6.7 Hz) 4.88 (2H,s).

2-Amino-6-1'-oxopropylpteridin-4(3H)-one. Pale yellow powder, Mp 306 °C; ^{1}H NMR (CF_3COOD) δ: 3.12 (3H, s), 9.70 (1H, s); ^{13}C NMR (CF_3COOD) δ: 26.7, 128.6, 149.0, 151.4, 152.2, 154.7, 162.3, 204.5.

*Sepiapterin-C (**3**).*[14] Pale yellow powder, Mp 253 °C (decomp); ^{1}H NMR (CF_3COOD) δ: 2.83 (3H, s), 4.10 (2H, s); IR (KBr) ν cm^{-1}: 3400–2900, 1698, 1656, 1572, 1516, 1426, 1338, 1289, 1259, 1080; UV (MeOH) λ_{max} nm (ε): 264 (1700), 408 (700).

*2-Amino-4-butoxy-6-2'-hydroxy-1'-oxopropylpteridin-4(3H)-one (**8a**).* Pale yellow powder, Mp 261 °C; ^{1}H NMR ($CDCl_3$) δ: 1.04 (3H, t, *J* = 7.6 Hz), 1.53 (2H, m), 1.58 (3H, d, *J* = 6.8 Hz), 1.91 (2H, qnt, *J* = 6.8 Hz), 4.21 (2H, t, *J* = 7.5 Hz), 5.37 (1H, q, *J* = 6.8 Hz), 9.47 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 13.8, 19.2, 21.1, 30.4, 68.7, 70.5, 140.4, 150.6, 150.8, 158.4, 163.0, 168.2, 200.7; IR (KBr) ν cm^{-1}: 3400, 3355, 1700, 1656, 1572, 1516, 1426, 1338, 1259, 1080, 968, 924, 902, 861, 810; UV (MeOH) λ_{max} nm (ε): 310 (8300), 408 (6300); HRMS Calcd for the Na^+ adduct, $C_{13}H_{17}N_5O_3Na$: 314.1229; Found: 314.1236.

*2-Amino-4-butoxypteridin-6-carboxylic acid (**9a**).* Pale yellow powder, 80%, Mp 298 °C; ^{1}H NMR ($CDCl_3$) δ: 1.03 (3H, t, *J* = 7.4 Hz), 1.57 (2H, m), 1.94 (2H, qnt, *J* = 6.8 Hz), 4.65 (2H, t, *J* = 6.8 Hz), 9.38 (1H, 2), 10.17 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 13.8, 19.1, 30.5, 69.0, 142.9, 149.4, 150.9, 159.0, 162.6, 168.3, 191.1; IR (KBr) ν cm^{-1}: 3400–2900, 1712, 1658, 1586, 1506, 1413, 1339, 1284, 1070, 939, 820; UV (MeOH) λ_{max} nm (ε): 310 (10200), 368 (9600).

*2-Amino-4-butoxy-7,8-dihydro-6-2'-hydroxy-1'-oxopropylpteridine (**11**).* Yellow powder, 50%, Mp 154 °C (decomp); ^{1}H NMR ($CDCl_3$) δ: 0.99 (3H, t, *J* = 7.5 Hz), 1.13 (3H, d, *J* = 7.3 Hz), 1.47 (2H, dt, *J* = 7.5, 7.1 Hz), 1.79 (2H, qnt, *J* = 7.1 Hz), 2.98 (1H, q, *J* = 7.1 Hz), 4.36 (2H, t, *J* = 6.8 Hz), 4.41 (2H, s), 4.89 (1H, brs); ^{13}C NMR ($CDCl_3$) δ: 8.1, 13.9, 19.2, 29.2, 31.0, 40.3, 66.8, 146.0, 148.4, 152.1, 155.8, 165.4, 200.8; IR (KBr) ν cm^{-1}: 3400–2900, 1700, 1656, 1592, 1506, 1416, 1318, 1259, 1080, 968, 930, 902, 851, 820; UV (MeOH) λ_{max} nm (ε): 266 (4500), 389 (1900); HRMS Calcd for the Na^+ adduct, $C_{13}H_{19}N_5O_3Na$: 316.1386; Found: 316.1372.

ACKNOWLEDGEMENTS

We thank Shiratori Pharmaceutical Co., Ltd. for the observation of high resolution mass spectra (HRMS). One of the authors (S. S. L.) thanks Japanese Government Scholarship Fund for financial support.

REFERENCES

1. D. J. Brown, 'The Chemistry of Heterocyclic Compounds,' Vol. 24, ed. by E. C. Taylor and A. Weissberger, Wiley, New York, 1988, pp. 273-275.
2. M. K. Demos, P. J. Waters, H. D. Vallance, L Y. Illquist, N. Makhseed, K. Hyland, N. Blau, and M. B. Connolly, *Annals Neurology*, 2005, **58**, 164.
3. T. Yamaguchi, T. Nagatsu, T. Sugimoto, S. Matsuura, T. Kondo, R. Iizuka, and H. Narabayashi, *Science*, 1983, **219**, 75; W. Enders, H. Ibel, L. Kierat, N. Blau, and H.-Ch. Curtius, *Lancet*, 1987, **2**, 223; T. Nagatsu, S. Matsuura, and T. Sugimoto, 'Medical Research Reviews,' Vol. 9, ed. by G. De Stevens, John Wiley, New York, 1989, pp. 25-44; B. Thoeny, G. Auerbach, and N. Blau, *Biochem. J*., 2000, **347**, 1.
4. H. Ichinose, T. Ohye, E. Takahashi, N. Seki, T. Hori, M. Segawa, Y. Nomura, K. Endo, H. Tanaka, S. Tsuji, K. Fujita, and T. Nagatsu, *Nature Genetics*, 1994, **8**, 236; N. Blau, B. Thoeny, R. G. H. Cotton, and K. Hyland, 'The Metabolic Basis of Inherited Diseases,' ed. by C. R. Scriver, A. L. Beaudet, W. S. Slv, D. Valle, B. Childs, K. W. Kinzler, and B. Vogelstein, McGraw Hill: London, 2000, pp. 1725-1776; L. Bonafe, B. J. Thoeny, M. Penzin, B. Czarnecki, and N. Blau, *Am. J. Human Genetics*, 2001, **69**, 269.
5. H. Shintaku, *Current Drug Metabolism*, 2002, **3**, 123.
6. B. Schircks, J. H. Bieri, and M. Viscontini, *Helv. Chim. Acta*, 1978, **43**, 680; W. Pfleiderer, *Chem. Ber.*, 1979, **112**, 2750; H. J. Woo, J. Y. Kang, Y. K. Choi, and Y. S. Park, *Microbiology*, 2002, **68**, 3138.
7. E. C. Taylor and R. Kobylecki, *J. Org. Chem.*, 1978, **43**, 680; K. Kiguchi, S. Murata, and T. Sugimoto, *Pteridine*, 1995, **6**, 160.
8. D. J. Brown, 'The Chemistry of Heterocyclic Compounds,' Vol. 24, ed. by E. C. Taylor and A. Weissberger, Wiley, New York, 1988, pp. 378-380.
9. S. Murata, T. Sugimoto, S. Ogiwara, K. Mogi, and H. Wasada, *Synthesis*, 1992, 303.
10. I. E. Marko, P. R. Giles, M. Tsukazaki, I. C.-Regnaut, C. J. Urch, and S. M. Brown, *J. Am. Chem. Soc.*, 1997, **119**, 12661.
11. M. Kuse, A. Kanakubo, S. Suwan, K. Koga, M. Isobe, and O. Shimomura, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1037.
12. R. Baur, T. Sugimoto, and W. Pfleiderer, *Helv. Chim. Acta*, 1988, **71**, 531.
13. M. Viscontini and E. Mohlmann, *Helv. Chim. Acta*, 1959, **42**, 836.
14. K. Sugiura, S. Takikawa, M. Tsusue, and M. Goto, *Bull. Chem. Soc. Jpn.*, 1973, **46**, 3312.