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Reaction of Pteridine and Its 8-Oxide with Grignard Reagents, Regioselective 7-Alkylation of Pteridine

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Summary

Reaction of 2-amino-4-butoxypteridine (**1**) with alkyl- or phenylmagnesium bromide followed by protonative and oxidative work-up with a solution of iodine in acetic acid gives 7-alkyl- or 7-phenylpteridines (**2**). Regioselective oxidation of **1** to 2-amino-4-butoxypteridine 8-oxide (**3**) by hydrogen peroxide proceeds in trifluoroacetic acid, and reaction of **3** with Grignard reagent or an organolithium compound affords **2** together with its 8-oxide **4**. The products (**2** and **4**) are easily derived to 7-substituted 2-amino-4-hydroxypteridines. The mechanism of the regioselectivity can be explained based on electron density and molecular orbitals (MO) which are obtained by calculation on the methoxy analogs of **1** and **3**.

Key Words: Alkylation, Oxidation, 4-Alkoxypteridine, Nucleophilic Addition, Grignard Reagent, Pteridine 8-oxide, Molecular orbital calculation

Introduction

Pterins, 2-amino-4-hydroxypteridine, are one of the most important heterocyclic compounds, and especially 6-substituted derivatives, such as biopterin, neopterin, and folic acids, have been attracting a lot of attentions in biochemistry and medicinal chemistry. In many cases, syntheses of these 6-substituted pteridines have been carried out by using the pyrazine ring-forming condensation of 6-hydroxy-2,4,5-triaminopyrimidine with a synthetic equivalent of α-dicarbonyl compound (1—6). On the other hand, methanopterin which is a cofactor of methanation enzyme in a microorganisms is known to be a 6,7-disubstituted pterin structure (7,8). Thus, regioselective synthesis of 6- and/or 7-substituted pteridines is a very important problem in pteridine chemistry. Methodologies of regioselective synthesis of 7-substituted pteridine are not known so many as those of 6-substituted pteridine. Since control of the direction in the pyrazine ring-formation by using condensation with asymmetric α-diketones (R^1-CO-CO-R^2) was generally difficult, the regioselective introduction of the substituents on the 7-position should be considered as a useful technique. Several methods for carbon-carbon bond-forming substitution on 6-and/or 7-position of the pteridines have been reported, but all of these procedures have to require the regioselective introduction of the activating or blocking groups on the desired or undesired positions (9—12). In the previous communication, we have briefly reported that the addition of Grignard reagents to 2-amino-4-butoxypteridine (**1**) regioselectively proceeded on the 7-position and 7-alkyl-2-amino-4-butoxypteridines (**2**) were obtained after the oxidative work-up (13). In this

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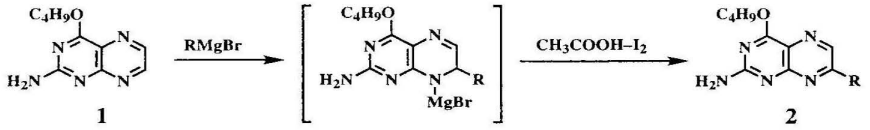
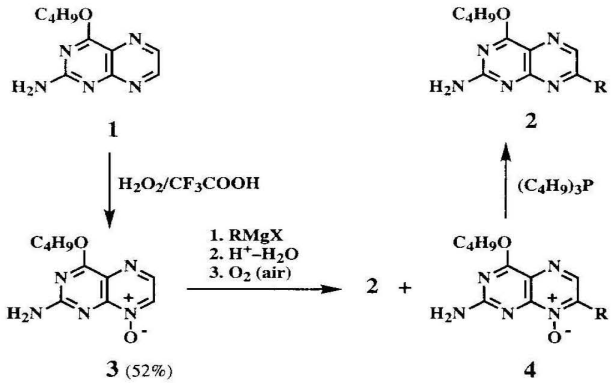


product No.	R	yield/%
2a	CH_3	16
2b	C_4H_9	14
2c	$(CH_3)_2CH$	16
2d	$(CH_3)_3C$	8
2e	C_6H_5	20

Scheme 1. Reaction of **1** Grignard Reagent.



R	products (yield/%)	
CH_3	**2a** (16)	**4a** (0)
C_4H_9	**2b** (9)	**4b** (21)
$(CH_3)_2CH$	**2c** (19)	**4c** (29)
$(CH_3)_3C$	**2d** (17)	**4d** (33)
C_6H_5	**2e** (20)	**4e** (23)

Seheme 2. Reaction of **3** with Grignard Reagent.

paper, we would like to describe the mechanism of the regioselectivity and the improved procedure for the introduction of alkyl groups on the 7-position of the pteridine.

Results and Discussion

Reaction of 1 with Grignard Reagents: Regioselective Addition to the C(7) Position

The reaction of **1** with 3 equivalents of alkyl- and phenylmagnesium bromides occurred in THF at 20°C to give 7-alkyl- and phenylpteridines (**2a-2e**) in 8 - 20% yield (see Scheme 1) after oxidative work-up by a solution of iodine in acetic acid. The regioselectivities of the 7-substituted pteridine **2a-2e** were perfect, and formation of regioisomerically 6-alkylated and 6,7-dialkylated pteridines was not detected in the crude reaction mixture by HPLC analyses. Even less nucleophilic *t*-C_4H_9-MgBr could give the product **2d** (8% yield), but vinylmagnesium bromide and allymagnesium chloride did not give the substituted products. Organolithium reagents, such as butyllithium and phenyllithium, were not suitable to the addition reaction, and the isolated yields of **2b** and **2e** were only 3% and 8%, respectively. The work-up operation by I_2 and CH_3COOH is essential for isolation of **2**. Indeed, yield of **2d** was significantly decreased when the reaction mixture of **1** with *t*-C_4H_9-MgBr was treated by water and I_2. Since products (**2**) were easily purified by silica gel column chromatography and the 4-butoxy group was easily converted to hydroxyl group by the treatment with aqueous KOH (**6**), this reaction is worth as a synthetic procedure of 7-substituted pterins.

Oxidation of 1 to the N(8)-Oxide (3) and Reaction of 3 with Grignard Reagents

Since *N*-oxides of pteridines are used as facile substrates for substitution at the neighboring carbon atom by various nucleophiles (14, 15), the *N*-oxide of **1** is considered to be a better substrate for addition of Grignard reagents. Oxidation of **1** was carried out by 2 equivalents of hydrogen peroxide in trifluoroacetic acid at 25°C to give pteridine 8-oxide (**3**) as an exclusive product in 52% yield. Formations of the isomeric 5-oxide

and the 5,8-dioxide were not recognized even under forcing conditions. The following oxidants and conditions were intact to the oxidation of **1** to **3**: *m*-chloroperoxybenzoic acid in 1,4-dioxane at 60°C; trifluoroperoxyacetic acid in CH_2Cl_2 at 20°C; 90% H_2O_2 in acetone or acetonitrile at 20°C.

The reaction of **3** with Grignard reagent or an organolithium compound in THF at 20°C followed by aqueous work-up under atmospheric oxygen gave a mixture of **2** and its 8-oxide (**4**) in 15—50% total yields (see Scheme 2). Yields were lower when Grignard reagent was replaced by an organolithium reagent, and, for example, the yield of **2b**+**4b** and **2e**+**4e** were 10+0% and 6+6%, respectively. Since compound **4** could be reduced to **2** by tributylphosphine in high yield, the reaction is considered to be an improved method of **2**. In this reaction, the 6-substituted isomers and the 6,7-disubstituted products were not obtained like the reaction of **1**. Although some Grignard reagents and organolithium reagents, especially *t*-C_4H_9-MgBr, *i*-C_3H_7-MgBr, and C_6H_5Li, behave not only as nucleophiles but also as strong reducing agents, formation of **1** resulting from simple reduction (deoxygenation) of **3** did not detected any more in the reaction mixture.

Confirmation of the Geometries of the Substituent in 2 and 3

The structure of **2a** were confirmed by the comparison of ^{1}H NMR spectra to that of authentic 2-amino-4-butoxy-6-methylpteridine as follows. Since the chemical shift of C(7)*H* of 2-amino-4-butoxy-6-methyl isomer was 8.72 ppm (6), the two doublets (at δ=8.54 and 8.82 ppm) of **1** could be assigned as C(6)*H* and C(7)*H*, respectively. Compound **2a** has the proton which resonated at the relatively high field (8.41 ppm), and the signal is assignable as C(6)*H*. The chemical shifts of **2b**—**2d** which were higher than 8.66 ppm were in the region of C(6)*H*. The low-field shift of **2e** (δ=9.03 ppm) was explained by the anisotropic effect of benzene ring, because both pteridine and benzene rings did not exist in the same plane. The tendency that the nuclei on the 6-position resonates at higher field than the 7-position in ^{1}H NMR spectra of **1** and **2** is same in ^{13}C NMR. The high field shifts (^{1}H: 0.41 ppm; ^{13}C: 15.78 ppm) caused by the enolate like electron donating nature of the *N*-oxide were observed on C(7) of **3**, and the variations of the chemical shifts of *C*(6) and *C(6)H* were smaller

Table 1. ^{1}H and ^{13}C NMR Chemical Shifts in $CDCl_3$

compound				
1	8.54	140.41	8.82	150.73
2-amino-4-butoxy-6-methylpteridine*			8.72	
2a	8.41	141.20		161.02
2b	8.40	141.26		164.87
2c	8.44	140.48		169.14
2d	8.66	138.76		171.03
2e	9.03	138.49		156.85
3	8.28	139.69	8.41	134.95
4b	8.27	-**		-**
4c	8.30	138.58		129.87
4d	8.41	-**		-**
4e	8.43	141.02		129.70

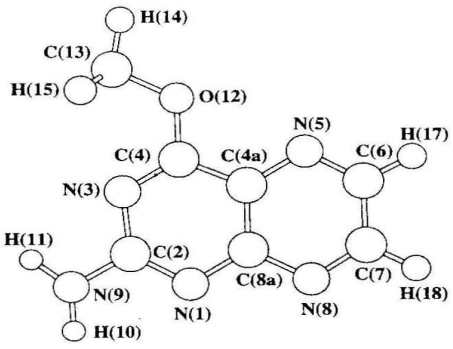
* See ref.6. ** ^{13}C NMR was not observed.

(^{1}H: 0.26 ppm;^{13}C: 0.72 ppm). Such high field shifts (^{1}H: 0.63 ppm and ^{13}C: 9.0 ppm) are also observed on C(6) and C(6)H of 1,3-dimethyl-2,4(1*H*,3*H*)-pteridinedione 5-oxide whose structure was determined by X-ray crystallographic analysis (16). In compounds **4**, the same high field shifts are recognized on the C(6) position. Thus, the structure of **3** was confirmed as the 8-oxide. The chemical shifts of the pteridines concerning to this paper are listed in Table 1.

Molecular Orbital Calculations and the Mechanistic Aspects

Molecular orbital (MO) calculations of the pteridine and its 8-oxide were carried out on their 4-methoxy analogs (**5** and **6**). The structures of **5** and **6** were optimized by using AM1 method, and were shown in Figure 1 with atom numberings. All atoms, except hydrogens (H(15) and H(16)), of **5** and **6** were existing nearly on the same plane, and the orbital of lone pair electrons of N(9) and O(12) which were omitted in the Figure 1 were perpendicular to the plane. These structures indicate that the hetero atom substituents are fully resonate to the pteridine ring. The atomic charges concerning to the electron density and the molecular orbital coefficients of each LUMO (lowest unoccupied molecular orbital) were obtained by using both AM1 and *ab-initio* methods on these structures, and the results are summarized in Table 2.

In compound **5**, the electron density of the following atoms were found to be relatively low: C(2), C(4), C(8a), and C(7). The atoms, N(5), C(4), N(8), and C(7), have large LUMO coefficients. Accordingly, Grignard reagents are possible to attack



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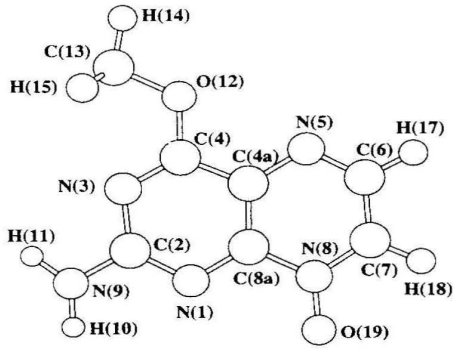

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Figuer 1. Structures and Atom Numbering of **5** and **6**.

Table 2. Atomic Charges and Coefficients of LUMO of 5 and 6

atomic numbering	compound **5**				compound **6**			
	AM1		*ab-initio*		AM1		*ab-initio*	
	charge	UMOL	charge	LUMO	charge	LUMO	charge	LUMO
N(1)	-0.270	0.316	-0.300	0.318	-0.256	0.304	-0.292	0.303
C(2)	0.292	0.225	0.334	0.246	0.287	0.014	0.331	0.206
N(3)	-0.353	0.310	-0.321	0.297	-0.337	0.361	-0.313	0.285
C(4)	0.297	0.505	0.269	0.472	0.284	0.379	0.266	0.424
C(4a)	-0.194	0.147	0.031	0.125	-0.105	0.336	0.056	0.139
N(5)	-0.075	0.427	-0.209	0.488	-0.129	0.321	-0.258	0.411
C(6)	-0.203	0.184	0.023	0.257	-0.093	0.025	0.053	0.200
C(7)	-0.107	0.433	0.049	0.389	-0.289	0.473	-0.018	0.338
N(8)	-0.144	0.407	-0.230	0.453	0.275	0.394	0.012	0.486
C(8a)	0.128	0.135	0.186	0.061	0.050	0.356	0.174	0.099

to the C(4) or C(7) position of **5**. The nucleophilic attack on the C(4) position, where is the almost lowest electron density and largest LUMO, gives dihydropyrimidine derivative **7**. However, the anionic intermediate (**7**) is not so stable, because the aromatic system of the pyrimidine is lost. On the other hand, nucleophilic addition of the Grignard reagent on the C(7) position, although that is the even less favored process, performs the anionic dihydropteridine intermediate (**8**) which is able to be stabilized by the electron withdrawing pyrimidine. The intermediate (**8**) is not suffered the attack of excess Grignard reagent (dialkylation) since it is already anionic species. When **8** is protonated by relatively nucleophilic water, the resulting 7,8-dihydropteridine might easily accept the nucleophilic attack of H_2O on C(6). Less nucleophilic acetic acid could not carry out the side reaction. Thus, the yields of **2** decreased significantly when the reaction was quenched by water. In comparison to electron density on N(5) and N(8) of **5**, the latter is more electron negative and electron donative. It is obvious that more electron rich and steric less hindered N-8 would be favorably converted to the *N*-oxide in the oxidation of **5** (17).

Although the C(7) atom of **6** is found to be electron negative and that is obvious also by the high-field shift of the ^{13}C NMR spectrum, the almost largest LUMO on the position is able to control the direction of the nucleophilic attack there. The electronic and molecular orbital situations on the C(6) positions of both **1** and **3** are not suitable for acceptance of the nucleophilic attack.

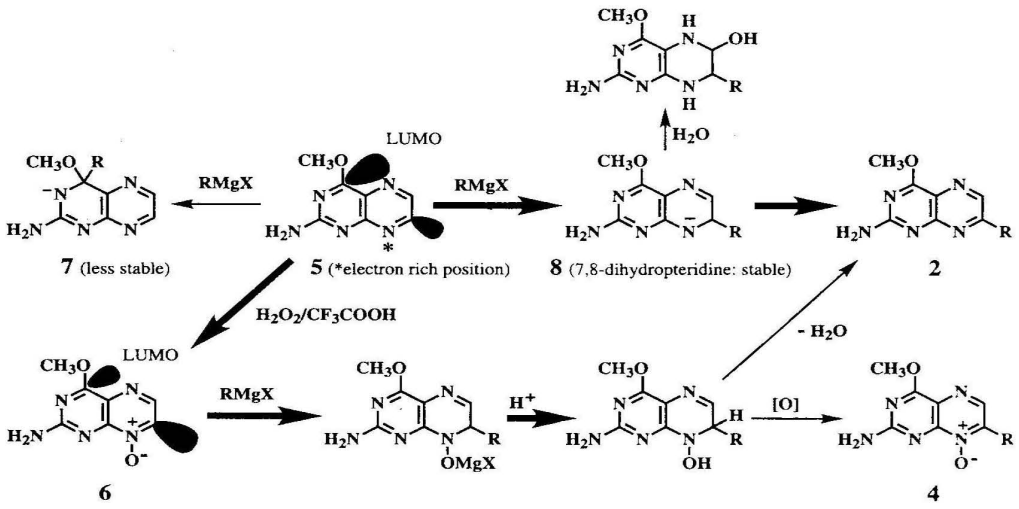
Acknowledgment

We thank to Professor Nobuaki Koga in School of Informatics and Sciences, Nagoya University for valuable suggestions to the molecular orbital study. The author, S. M., acknowledges to Fujisawa Pharmaceutical Co., Ltd. for kindly measurements of elementary analyses.

Experimental Part

General Methods

Both the ^1H and ^{13}C NMR spectra were taken



Scheme 3. Mechanism of Regioselectivity.

on a JEOL Ex-270 spectrometer, and chemical shifts were measured relative to internal tetramethylsilane ($\delta = 0$). The assignments of the ^{13}C signals were confirmed by C-H COSY observations. The IR and UV spectra were recorded on a JASCO FT/IR-5300 and a JASCO Ubest-55 spectrometers in the noted conditions, respectively. Micro elemental analyses were performed at Micro Analytical Center in Faculty of Agriculture of Nagoya University and Research Center of Fujisawa Pharmaceutical Co., Ltd. Flash column chromatography was carried out on silica gel 60 (Nakarai Co., Ltd., 230-400 mesh). Silica-gel TLC was performed by using Merck $60F_{254}$ glass plate (0.25 mm), and spots were detected by UV absorption (254 nm) and fluorescent (irradiating by a 330 nm UV lamp). Analytical HPLC was performed on a JASCO Gulliver HPLC System attached with a column of Inertsil-ODS (250 × 4.6 mm), and UV absorption at 350 nm were recorded. THF for Grignard reactions was distilled over Na-benzophenone, and dry ether for Grignard reactions was obtained from Sanraku Co., Ltd. Hydrogen peroxide (35%) was freshly obtained from Mitsubishi Gas Chemicals Co., Ltd. 6-Butoxy-2,4,5-triaminopyrimidine was prepared *in situ* by the procedures descried in the reference (6).

Molecular Orbital Calculation

The molecular orbital calculations of **5** and **6** were performed on a Sun 4/2 work station by using AM1 and *ab-initio* (STO-3G) programs available from Gaussian®92. The optimized atomic coordinates of **5** and **6** are given in Table 3.

Preparation of 2-Amino-4-butoxypteridine (1)

To a catalyst free solution of 6-butoxy-2,4,5-triaminopyrimidine(**6**), prepared from 6-butoxy-2,4-diamino-5-nitrosopyrimidine (10.1 g, 0.048 mol), in methanol (300 ml) was added a solution of glyoxal trimer dihydrate (5.0 g, 0.024 mol) in methanol (100 ml), and the mixture was heated under reflux for 30 min. After removal of methanol by a rotary evaporator, water (150 ml) was added to the residue, and the mixture was extracted with trichloromethane (3 × 300 ml). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to flash column chromatography eluting with a 19:1 mixture of dichloromethane and methanol. Recrystalization of the crude products from toluene gave pure **1** (6.52 g, 63%) as yellow crystals: mp 121-122°C: *Rf* 0.43 ($CHCl_3$: CH_3OH = 9:1): HPLC retention volume 14.8 ml (H_2O:CH_3CN = 3:1): UV (CH_3OH) λ/nm ($\varepsilon \times 10^{-3}$) 363 (7.1), 263 (9.3), 232 (21): IR (KBr disk) ν/cm^{-1} 3308, 3127, 2963, 1638, 1595, 1532, 1437, 1366, 1325, 1190, 1071: ^1H NMR ($CDCl_3$) δ/ppm 1.01 (3H, t, J = 7.4 Hz, CH_3), 1.53 (2H, sext like, J = 7.4 Hz, CH_2), 1.93 (2H, tt, J = 7.4 and 6.9 Hz, CH_2), 4.60 (2H, t, J = 6.9 Hz, CH_2-O), 5.70 (2H, br, NH_2), 8.54 (1H, d, J = 2.0 Hz, C(6)*H*), 8.82 (1H, d, J = 2.0 Hz, C(7)*H*): ^{13}C NMR ($CDCl_3$) δ/ppm 13.80 (CH_3), 19.16 (CH_2), 30.53 (CH_2), 68.34 (CH_2-O), 124.51 (C(4a)), 140.41 (C(6)), 150.73 (C(7)), 157.32 (C(8a)), 161.65 (C(4)), 167.83 (C(2)). Anal. calc. for $C_{10}H_{13}N_5O$: C54.78, H5.98, N31.94; found: C54.67, H5.93, N31.72.

Table 3. Atomic Coordinates of **5** and **6***

compound **5**				compound **6**			
atom	X	Y	Z	atom	X	Y	Z
N(1)	0.000000	0.000000	0.000000	N(1)	0.000000	0.000000	0.000000
C(2)	0.000000	0.000000	1.371900	C(2)	0.000000	0.000000	1.371100
N(3)	1.141643	0.000000	2.199226	N(3)	1.149587	0.000000	2.185797
C(4)	2.324731	-0.000225	1.585718	C(4)	2,325826	-0.000924	1.561175
C(4a)	2.474882	0.000001	0.135068	C(4a)	2.473883	-0.001219	0.103776
N(5)	3.702307	-0.000013	-0.481538	N(5)	3.707573	-0.001931	-0.501109
C(6)	3.699386	0.000916	-1.803635	C(6)	3.709324	-0.002033	-1.821208
C(7)	2.472432	0.001930	-2.566354	C(7)	2.529701	-0.001224	-2.623502
N(8)	1.274441	0.001384	-2.015665	N(8)	1.277677	-0.000650	-2.069050
C(8a)	1.228625	0.000397	-0.613814	C(8a)	1.225331	-0.000604	-0.613491
N(9)	-1.222136	-0.000380	2.014973	N(9)	-1.220608	-0.000232	2.016642
H(10)	-2.057168	0.000203	1.485400	H(10)	-2.056365	0.000624	1.487842
H(11)	-1.258572	0.000448	3.003101	H(11)	-1.253944	0.000798	3.005080
O(12)	3.494699	-0.000416	2.295431	O(12)	3.502920	-0.001370	2.259202
C(13)	3.413686	-0.000281	3.726841	C(13)	3.343755	-0.000941	3.691881
H(14)	4.454872	-0.000286	4.130789	H(14)	4.479823	-0.001437	4.085959
H(15)	2.873112	-0.925540	4.041353	H(15)	2.896750	-0.0926270	4.010915
H(16)	2.873188	0.925081	4.041183	H(16)	2.897818	0.925181	4.010412
H(17)	4.676485	0.000944	-2.314304	H(17)	4.961460	-0.002753	2.328473
H(18)	2.509399	0.002964	-3.671336	H(18)	2.573356	-0.001156	-3.725138
				O(19)	0.270889	-0.000076	-2.747591

*Numbering of atoms were shown in Fig. 1.

Preparation of 2-Amino-6-butoxypteridine 8-Oxide (3)

To a solution of **1** (3.0 g, 0.014 mol) in trifluoroacetic acid (20 ml) was added 35% hydrogen peroxide (2.3 ml) at 25 °C, and the mixture was stirred for 4 h. The mixture was concentrated, and to this were added trichloromethane (50 ml) and saturated $NaHCO_3$ (30 ml). The organic solution was dried over $MgSO_4$ and subjected to flash column chromatography eluting with a mixture of toluene and ethanol (19:1). Recrystalization of the crude products from toluene gave pure **3** as colorless crystals (1.66 g, 52%): mp 190 °C (dec.): R_f 0.33 (toluene:C_2H_5OH = 4:1): UV (CH_3OH) λ/nm ($\varepsilon \times 10^{-3}$) 390 (7.4), 300 (4.4), 269 (15), 240 (9.6), 226 (14); IR (KBr disk) ν/cm^{-1} 3299, 3198, 1634, 1605, 1557, 1501, 1462, 1400, 1370, 1318, 1236, 1182, 1071: ^{1}H NMR ($CDCl_3$) δ/ppm 1.00 (3H, t, J=7.4 Hz, CH_3), 1.53 (2H, sext like, J=7.4 Hz, CH_2), 1.93 (2H, tt, J=7.4 and 6.9 Hz, CH_2), 4.60 (2H, t, J=6.9 Hz, CH_2-O), 5.72 (2H, br, NH_2), 8.28 (1H, d, J=3.6 Hz, C(6)*H*), 8.41 (1H, d, J=3.6 Hz, C(7)*H*): ^{13}C NMR ($CDCl_3$) δ/ppm 13.76 (CH_3), 19.12 (CH_2), 30.44 (CH_2), 69.15 (CH_2-O), 126.88 (*C*(4a)), 134.95 (*C*(7)), 139.69 (*C*(6)), 152.36 (*C*(8a)), 161.00 (*C*(4)), 168.03 (*C*(2)). Anal. calc. for $C_{10}H_{13}N_5O_2$: C51.06, H5.57, N29.77; found C51.11, H5.44, N29.46.

Reaction of 1 with Methylmagnesium Bromide, a General Procedure

Under an Ar atmosphere, to a solution of **1** (0.5 g, 2.3 mmol) in THF (15 ml) was added an ether solution of CH_3MgBr (3.0 *M*, 3.0 ml, 9.0 mmol) at 25°C, and the mixture was stirred for 11 h. To this were added acetic acid (15 ml) and iodine (1.2 g, 4.7 mmol). After 4-h stirring, solvent was removed *in vacuo*, and the residue was subjected to flash column chromatography eluting with a 9:1 mixture of ethyl acetate (EtOAc) and petroleum ether (PE). 2-Amino-4-butoxy-7-methylpteridine (**2a**, 0.09g, 16%) was obtained as yellow crystals: mp 162-163°C (toluene):R_f 0.15 (EtOAc:PE = 19:1): HPLC retention volume 20.0 ml (H_2O:CH_3CN = 3:1) (18): ^{1}H NMR ($CDCl_3$) δ/ppm 1.00 (3H, t, J=7.4 Hz, CH_3), 1.52 (2H, sext like, J=7.4 Hz, CH_2), 1.92 (2H, tt, J=7.4 and 6.9 Hz, CH_2), 2.69 (3H, s, CH_3-C(7)), 4.57 (2H, t, J=6.9 Hz, CH_2-O), 5.55 (2H, br, NH_2), 8.41 (1H, s, C(6)*H*): ^{13}C NMR (in $CDCl_3$) δ/ppm = 13.82 (CH_3), 19.18 (CH_2), 22.84 (CH_3-C(7)), 30.59 (CH_2), 68.12 (CH_2-O), 121.76

(*C*(4a)), 141.20 (*C*(6)), 156.80 (*C*(8a)), 161.02 (*C*(7)), 161.61 (*C*(4)), 167.87 (*C*(2)). Anal. calc. for $C_{11}H_{15}N_5O$: C56.64, H6.48, N30.02; found: C56.65, H6.51, N29.81.

*2-Amino-4-butoxy-7-butylpteridine (**2b**)*

Yellow crystals: mp 105-107°C (toluene): R_f 0.27 (EtOAc:PE = 7:3): UV (CH_3OH) λ/nm (ε×10^{-3}) 357 (6.8), 263 (7.2), 234 (21): IR (KBr disk) ν/cm^{-1} 3364, 3128, 2957, 2932, 1667, 1595, 1545, 1489, 1460, 1435, 1350, 1294, 1242, 1217, 1180, 1105, 1061: ^{1}H NMR ($CDCl_3$) δ/ppm 0.95 (3H, t, *J* = 6.9 Hz, C*H*$_3$ of the butyl group on C(7)), 1.00 (3H, t, *J* = 7.4 Hz, C*H*$_3$), 1.41 (2H, sext like, *J* = 6.9 Hz, C*H*$_2$ of the butyl group on C(7)), 1.52 (2H, sext like, *J* = 7.4 Hz, C*H*$_2$), 1.83 (2H, quint like, *J* = 6.9 Hz,C*H*$_2$ of the butyl group on C(7)), 1.92 (2H, tt, *J* = 7.4 and 6.9 Hz, C*H*$_2$), 2.93 (2H, t, *J* = 6.9 Hz,C*H*$_2$-C(7)), 4.57 (2H, t, *J* = 6.9 Hz, *CH*$_2$-O), 5.34 (2H, br, N*H*$_2$), 8.40 (1H, s, *C(6)H*): ^{13}C NMR ($CDCl_3$) δ/ppm 13.82 (*C*H$_3$), 13.85 (*C*H$_3$ of the butyl group on C(7)),19.17 (*C*H$_2$), 22.44 (*C*H$_2$ of the butyl group on C(7)), 30.60 (CH$_2$), 30.82 (*C*H$_2$ of the butyl group on C(7)), 36.10 (*C*H$_2$-C(7)), 68.12 (*C*H$_2$-O),121.96 (*C*(4a)), 141.26 (*C*(6)), 156.91 (*C*(8a)), 161.45 (*C*(4)), 164.87 (*C*(7)), 167.85 (*C*(2)). Anal. calc. for $C_{14}H_{21}N_5O$: C61.07, H7.69, N25.43; found: C61.19, H7.40, N, 25.14.

*2-Amino-4-butoxy-7-i-propylpteridine (**2c**)*

Yellow crystals: mp 132-133°C (toluene): R_f 0.36 (EtOAc:PE = 7:3): UV (CH_3OH) λ/nm (ε×10^{-3}) 357 (12), 263 (11), 235 (31): IR (KBr disk) ν/cm^{-1} 3371, 3324, 3160, 2963, 1672, 1649, 1597, 1545, 1487, 1460, 1431, 1399, 1365, 1348, 1194, 1105: ^{1}H NMR ($CDCl_3$) δ/ppm 1.00 (3H, t, *J* = 7.4 Hz, C*H*$_3$), 1.40 (6H, d, *J* = 6.9 Hz, (C*H*$_3$)$_2$CH), 1.52 (2H, sext like, *J* = 7.4 Hz,C*H*$_2$), 1.92 (2H, tt, *J* = 7.4 and 6.9 Hz, C*H*$_2$), 3.23 (1H, sept, *J* = 6.9 Hz, C*H*-C(7)), 4.57 (2H, t, *J* = 6.9 Hz, C*H*$_2$-O), 5.29 (2H, br, N*H*$_2$), 8.44 (1H, s, *C(6)H*): ^{13}C NMR ($CDCl_3$) δ/ppm 13.82 (*C*H$_3$), 19.17 (*C*H$_2$), 21.73 ((*C*H$_3$)$_2$CH), 30.60 (*C*H$_2$), 34.75 ((CH$_3$)$_2$*C*H-C(7)), 68.12 (*C*H$_2$-O), 122.14 (*C*(4a)), 140.48 (*C*(6)), 156.85 (*C*(8a)), 161.42 (*C*(4)), 167.83 (*C*(2)), 169.14 (*C*(7)). Anal. calc. for $C_{13}H_{19}N_5O$: C59.75, H7.33, N26.80: found: C59.78, H7.37, N26.61.

*2-Amino-4-butoxy-7-t-butylpteridine (**2d**)*

Yellow crystals: mp 141-142°C (toluene).: R_f 0.48 (EtOAc:PE = 7:3): UV (CH_3OH) λ/nm (ε×10^{-3}) 356 (6.7), 262 (6.3), 235 (18):IR (KBr disk) ν/cm^{-1} 3368, 3317, 3131, 2961, 1663, 1593, 1545, 1489, 1460, 1431, 1400, 1368, 1224, 1175, 1136, 1096: ^{1}H NMR ($CDCl_3$) δ/ppm 1.00 (3H, t, *J* = 7.4 Hz, C*H*$_3$), 1.47 (9H, s, *J* = 6.9 Hz, (C*H*$_3$)$_3$C), 1.52 (2H, sext like, *J* = 7.4 Hz, C*H*$_2$), 1.92 (2H, tt, *J* = 7.4 and 6.9 Hz, C*H*$_2$), 4.57 (2H, t, *J* = 6.9 Hz, C*H*$_2$-O), 5.43 (2H, br, N*H*$_2$), 8.66 (1H, s, C(6)*H*): ^{13}C NMR ($CDCl_3$) δ/ppm 13.82 (*C*H$_3$), 19.17 (*C*H$_2$), 29.54 ((*C*H$_3$)$_3$C), 30.60 (*C*H$_2$), 37.56 ((CH$_3$)$_3$*C*-C(7)), 68.09 (*C*H2-O), 121.58 (*C*(4a)), 138.76 (*C*(6)), 156.24 (*C*(8a)), 161.51 (*C*(4)), 167.74 (*C*(2)), 171.03 (*C*(7)). Anal. calc. for $C_{14}H_{21}N_5O$: C61.07, H7.69, N25.43; found: C 61.11, H7.80, N, 25.43.

*2-Amino-4-butoxy-7-phenylpteridine (**2e**)*

Yellow crystals: mp 189-191°C (toluene): R_f 0.44 (EtOAc:toluene = 4:1): UV (CH_3OH) λ/nm (ε×10^{-3}) 363 (7.1), 263 (9.3), 232 (21): IR (KBr disk) ν/cm^{-1} 3495, 3268, 3065, 2957, 1630, 1589, 1545, 1446, 1424, 1397, 1366, 1345, 1308, 1290, 1256, 1204, 1177, 1101: ^{1}H NMR ($CDCl_3$) δ/ppm 1.01 (3H, t, *J* = 7.4 Hz, C*H*$_3$), 1.54 (2H, sext like, *J* = 7.4 Hz, C*H*$_2$), 1.94 (2H, tt, *J* = 7.4 and 6.9 Hz, C*H*$_2$), 4.60 (2H, t, *J* = 6.9 Hz, C*H*$_2$O), 5.48 (2H, br, N*H*$_2$), 7.54 (3H, m, *o*-and *p*-*H* of Ph), 8.25 (2H, m, *m*-*H* of Ph), 9.03 (1H, s, C(6)*H*): ^{13}C NMR ($CDCl_3$) δ/ppm 13.92 (*C*H$_3$), 19.21 (*C*H$_2$), 30.62 (*C*H$_2$), 68.28 (*C*H$_2$-O), 122.64 (*C*(4a)), 128.01 (*m*-*C* of Ph), 129.00 (o-*C* of Ph), 131.17 (*p*-*C* of Ph), 135.76 (*C*-C(7)), 138.49 (*C*(6)), 156.85 (*C*(7)), 157.53 (*C*(8a)), 161.76 (*C*(4)), 167.79 (*C*(2)). Anal. calc. for $C_{16}H_{17}N_5O$: C65.07, H5.80, N23.71; found: C65.02, H5.61, N23.11.

*Reaction of **3** with Butylmagnesium Bromide, a Typical Example*

Under an Ar atmosphere, to a solution of **3** (0.30 g, 1.3 mmol) in THF (10 ml) was added a solution of butylmagnesium bromide in ether (0.64 M, 7.0 ml, 4.5 mmol) at 25°C. After 4-h stirring, the mixture was allowed to contact with air and stirred for additional 8 h. The solvent was removed, and to the residue was added trichloromethane (50 ml). The solution was washed with saturated NH_4Cl (3×30 ml) and dried over $MgSO_4$. Flash column chromatography gave pure **2b** (0.03 g, 9%) and pure 2-amino-4-butoxy-7-butylpteridine 8-oxide (**4b**, 0.08 g, 21%) as yellow oily solid (19): ^{1}H

NMR ($CDCl_3$): δ/ppm 0.95 (3H, t, J = 6.9 Hz, CH_3 of the butyl group on C(7)), 1.00 (3H, t, J = 7.4 Hz, CH_3), 1.41 (2H, sext like, J = 6.9 Hz, CH_2 of the butyl group on C(7)), 1.52 (2H, sext like, J = 7.4 Hz, CH_2), 1.83 (2H, quint like, J = 6.9 Hz, CH_2 of the butyl group on C(7)), 1.92 (2H, tt, J = 7.4 and 6.9 Hz, CH_2), 3.00 (2H, t, J = 6.9 Hz, CH_2-C(7)), 4.58 (2H, t, J = 6.9 Hz, CH_2-O), 5.48 (2H, br, NH_2), 8.27 (1H, s, C(6)*H*).

*2-Amino-4-butoxy-7-i-propylpteridine 8-Oxide (**4c**)*

The crude product was purified by preparative HPLC with an ODS column. Yellow prisms: mp 185-187°C: ^{1}H NMR ($CDCl_3$) δ/ppm 1.00 (3H, t, J = 7.4 Hz, CH_3), 1.38 (6H, d, J = 6.9 Hz, $(CH_3)_2CH$), 1.52 (2H, sext like, J = 7.4 Hz, CH_2, 1.92 (2H, tt, J = 7.4 and 6.9 Hz, CH_2), 3.78 (1H, sept, J = 6.9 Hz, C*H*-C(7)), 4.59 (2H, t, J = 6.9 Hz, CH_2-O), 5.96 (2H, br, NH_2), 8.30 (1H, s, C(6)*H*):^{13}C NMR ($CDCl_3$) δ/ppm 13.81 (CH_3), 19.17 (CH_2), 19.33 ($(CH_3)_2CH$), 27.28 ($(CH_3)_2C$), 30.54 (CH_2), 68.89 (CH_2O), 124.60 (*C*(4a) or *C*(7)), 129.87 (*C*(4a) or *C*(7)), 138.58 (*C*(6)), 154.03 (*C*(8a)), 160.88 (*C*(4)), 168.46 (*C*(2)). Anal. calc. for $C_{13}H_{19}N_5O_2$: C56.30, H 6.91, N25.25; found: C56.30, H6.81, N25.14.

*2-Amino-6-butoxy-7-t-butylpteeridine 8-Oxide (**4d**)*

Yellow oily solid (17): ^{1}H NMR ($CDCl_3$) δ/ppm 1.00 (3H, t, J = 7.4 Hz, CH_3), 1.52 (2H, sext like, J = 7.4 Hz, CH_2), 1.56 (9H, s, J = 6.9 Hz, $(CH_3)_3C$), 1.92 (2H, tt, J = 7.4 and 6.9 Hz, CH_2), 4.59 (2H, t, J = 6.9 Hz, CH_2-O), 5.60 (2H, br, NH_2), e8.41 (1H, s, C(6)*H*).

*2-Amino-6-butoxy-7-phenylpteridine 8-Oxide (**4e**)*

Yellow crystals: mp 135-138°C (dec) (toluene): ^{1}H NMR ($CDCl_3$) δ/ppm 1.00 (3H, t, J = 7.4 Hz, CH_3), 1.52 (2H, sext like, J = 7.4 Hz, CH_2), 1.92 (2H, tt, J = 7.4 and 6.9 Hz, CH_2), 4.59 (2H, t, J = 6.9 Hz, CH_2-O), 5.88 (2H, br, NH_2), 7.55 (3H, m, *o*-and *p-H* of Ph), 7.93 (2H, m, *m-H* of Ph), 8.43 (1H, s, C(6)*H*): ^{13}C NMR ($CDCl_3$) δ/ppm 13.82 (CH_3), 19.17 (CH_2), 30.53 (CH_2), 68.95 (CH_2O), 124.58 (*C*(4a) or *C*(7)), 128.73 (*m-C* of Ph), 129.34 (*o-C* of Ph), 129.70 (*C*(4a) or *C* (7)), 130.76 (*p-C* of Ph), 141.02 (*C*(6)), 145.06 (*ipso-C* of Ph), 152.86 (*C*(8a)), 161.36 (*C*(4)), 168.24 (*C*(2)). Anal. calc. for $C_{16}H_{17}N_5O_2$: C61.72, H5.50, N22.49; found: C61.97, H5.47, N22.11.

*Conversion of **4** to **2**, a General Procedure*

A mixture of **4e** (0.10 g, 0.32 mmol), tributylphosphine (0.15 ml), and 1,4-dioxane (0.5 ml) was heated at 100°C for 4 h. The volatile components were removed under vacuum (0.1 mmHg) at 100°C, and the residue was subjected to flash chromatography (EtOAc:toluene = 1:1). Pure **2e** (0.08g, 85%) was obtained.

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18. The retention volume of 2-amino-4-butoxy-6-methylpteridine was 20.6 ml (H_2O:CH_3CN = 3:1). See: ref. 6.
19. The isolated product was almost pure in ^{1}H NMR analysis. However, small amounts of **2b** (or **2d**) and unknown compounds which had bright yellow fluorescent were contaminated in the isolated **4b** (or **4d**).