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SYNTHESIS OF 6-HYDROXYMETHYLPTERIN α- AND β-D-GLUCOSIDES

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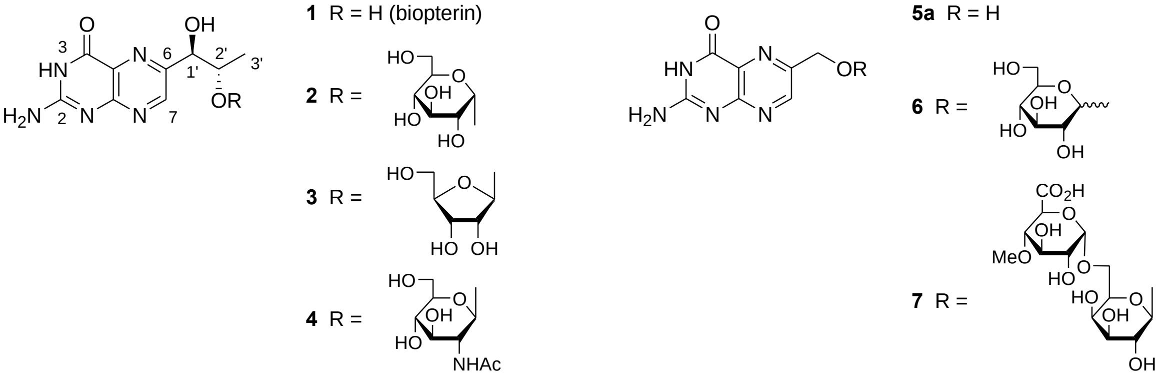
Abstract – The key precursor, N^2-(*N*,*N*-dimethylaminomethylene)-6-hydroxymethyl-3-[2-(4-nitrophenyl)ethyl]pterin (**11**) was efficiently prepared from 2,5,6-triamino-4-hydroxypyrimidine (**8**) in 5 steps. The first, unequivocal synthesis of 6-hydroxymethylpterin α-D-glucoside (**6a**) was achieved by treatment of **11** with 4,6-di-*O*-acetyl-2,3-di-*O*-(4-methoxybenzyl)-α-D-glucopyranosyl bromide (**16**) in the presence of tetraethylammonium bromide and *N*-ethyldiisopropylamine, followed by removal of the protecting groups, while 6-hydroxymethylpterin β-D-glucoside (**6b**) was prepared by means of selective glycosylation of **11** with 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (**12**) in the presence of silver triflate and tetramethylurea.

INTRODUCTION

Certain pterin glycosides carrying various kinds of sugars attached to the side-chain at C-6 of the pteridine ring were found to be produced by some prokaryotes as exemplified by glycosides of biopterin (**1**): 2'-*O*-(α-D-glucopyranosyl)biopterin (**2**)[1-4] and its β-D-ribofuranosyl analog (**3**)[5] isolated from various cyanobacteria and 2'-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)biopterin (**4**)[6] from a green sulfur photosynthetic bacterium. As for glycosides of other pterins, 2-acetamido-2-deoxy-β-D-glucoside of ciliapterin (tepidopterin)[7] and 2-amino-2-deoxy-α-D-glucoside of neopterin (solfapterin)[8] were isolated from a green sulfur photosynthetic bacterium and a thermophilic archaebacterium, respectively, whereas

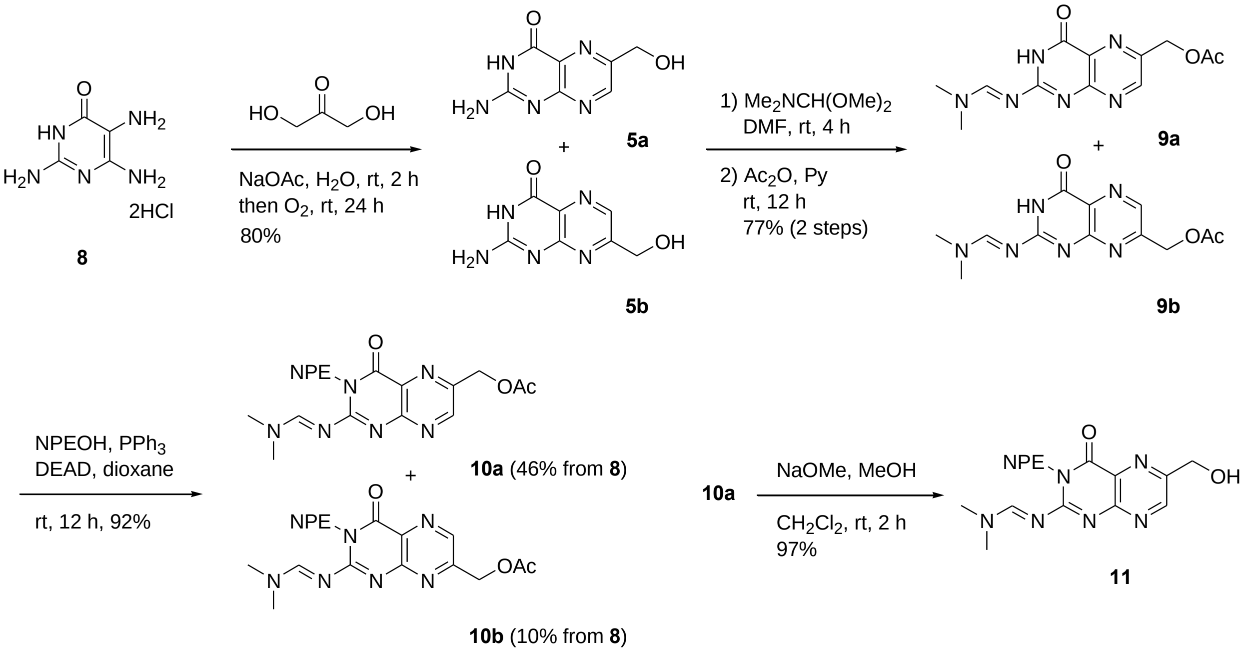


glycosides of 6-hydroxymethylpterin (**5a**), such as D-glucoside (**6**)[9,10] and cyanopterin (**7**),[11] were found in cyanobacterium *Synechocysts* sp.

As shown in these examples, anomeric structures of some pterin glycosides are α-type and those of others are β-type depending on the combination of the pterin and sugar moieties. Despite a considerable interest from the viewpoint of their biological activities and functions,[12] attempts at preparation of natural pterin glycosides including selective glycosylation have so far scarcely been made, except for our synthetic studies on biopterin and ciliapterin glycosides.[5,13-15] Therefore we undertook to explore an efficient protocol for selective α- and β-glycosilation of pterin derivatives by employing 6-hydroxymethylpterin (**5a**) as a model pterin substrate. In addition, we give herein the first synthesis of a natural pterin glycoside, 6-[(D-glucopyranosyloxy)methyl]pterin (**6**).

RESULTS AND DISCUSSION

Although the preparation of 6-hydroxymethylpterin (**5a**) has been achieved by the condensation of 2,5,6-triamino-4-hydroxypyrimidine dihydrochloride (**8**) with dihydroxyacetone and the subsequent oxidation,[16] formation of 7-hydroxymethyl isomer (**5b**) and the detailed regioselectivity of the condensation have not been reported because **5a** was isolated by repeated recrystallizations. We therefore checked the selectivity of the pteridine-ring formation by treatment of compound **8** with dihydroxyacetone in the presence of sodium acetate, followed by air-oxidation (Scheme 1). The resulting products were confirmed by ^{1}H NMR spectrum to be an 82:18 mixture consisting of **5a** and **5b**. On the contrary, the same condensation in an aqueous sodium bicarbonate solution resulted in the predominant formation of the 7-subsituted pterin (**5b**) in a ratio of 11:89. The reversal of the selectivity is most likely caused by the condensation of **8** with glyceraldehyde transformed from dihydroxyacetone under the basic conditions.

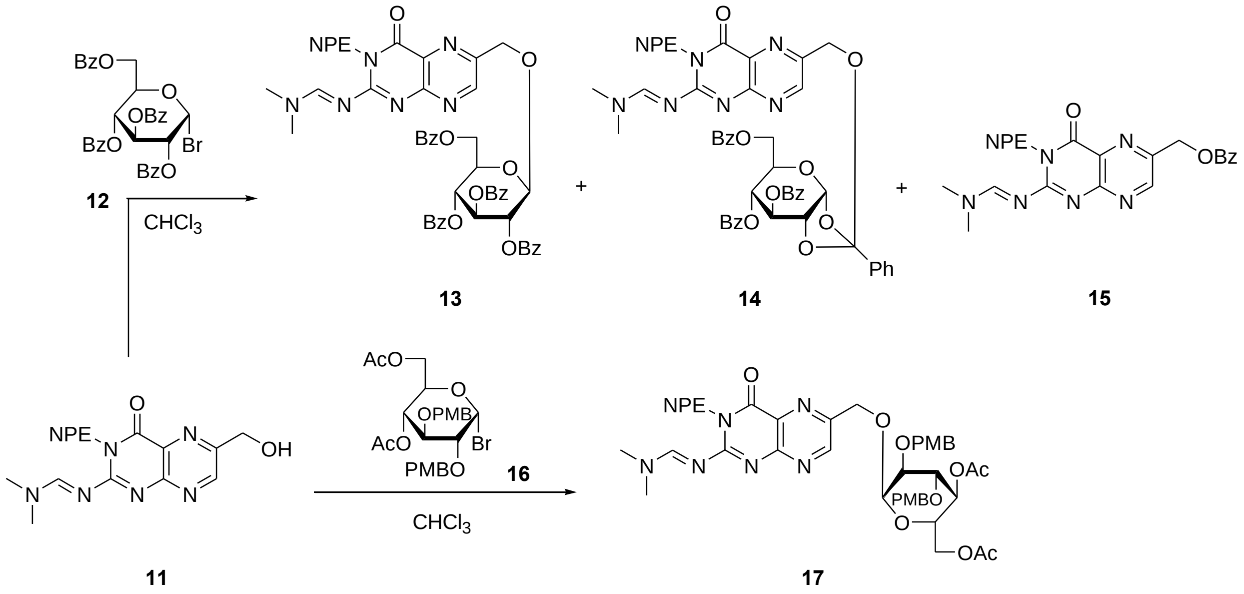


Scheme 1

Due to the effectively stabilized intramolecular hydrogen bonding in the solid state,[17] pterin derivatives including **1** and **5a** are generally little soluble in nonpolar aprotic solvents used for conventional glycosylation. To overcome this problem, we tried to introduce appropriate protecting groups into **5a**: *N*,*N*-dimethylaminomethylene group for 2-amino and 2-(4-nitrophenyl)ethyl (NPE) group for N(3) of the ring.[18] Thus, treatment of the 82:18 mixture of **5a,b** with *N*,*N*-dimethylformamide dimethyl acetal in DMF, followed by acetylation of a hydroxy group, afforded 6-acetoxymethyl-N^2-(*N*,*N*-dimethylamino-methylene) derivatives (**9a,b**), whose N(3) position was then protected with NPE group by Mitsunobu reaction with 2-(4-nitrophenyl)ethanol in the presence of triphenylphoshine and diethyl azodicarboxylate (DEAD) to give the fully protected products **10a** and **10b**. These were then separated by column chromatography over silica gel into the desired 6-acetoxymethyl derivative (**10a**) (46% overall yield from **8**) and the 7-acetoxymethyl isomer (**10b**) (10%).

The structural assignments of **10a** and **10b** were made primarily on the basis of their ^{13}C-NMR spectral data (see, Experimental). The signals of C-6 and C-7 of 6-alkylpteridines generally appear at a similar field, whereas C-7 signals of 7-alkyl derivatives shifts to a lower field (ca. 20 ppm) from those of C-6.[14,19] Therefore, the close values of **10a** (C-6: δ 147.35, C-7: δ 149.48) and the distant values of **10b** (C-6: δ 139.28, C-7: δ 158.12) indicate the 6-substituted pterin for the former and the 7-substituted pterin for the latter.

Methanolysis of 6-acetoxymethylpterin derivative (**10a**) in the presence of sodium methoxide provided the 6-hydroxymethyl derivative (**11**), a versatile precursor for glycosylation. Glycosylation of **11** with two glycosyl donors (**12** and **16**) in chloroform[20] was then extensively investigated under various conditions in the presence of activators (Scheme 2, Table 1).



Scheme 2

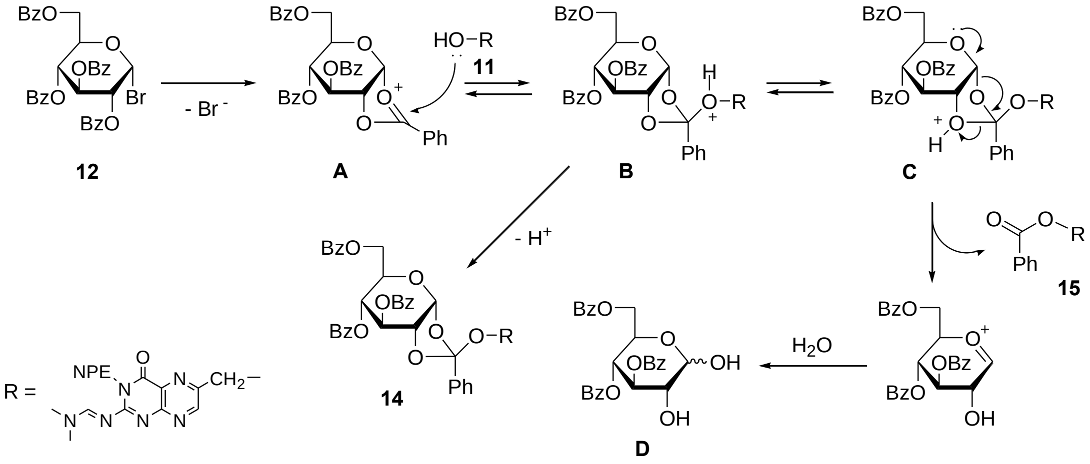
Table 1. Glycosylation of 6-hydroxymethylpterin derivative (**11**) [a]

Entry	Glycosyl donor (mol equiv.)	Activator (mol equiv.)	Conditions	Products (yield) [b]
1	**12** (3.0)	$SnCl_4$ (2.0)	rt, 24 h	**13** (0%), **11** (88% recovery)
2	**12** (3.0)	$SnCl_4$ (2.0)	reflux, 8 h	**13** (0%) [b]
3	**12** (3.0)	AgOTf (2.0), TMU (1.0)	rt, 12 h	**13** (5%), **11** (81% recovery)
4	**12** (3.0)	AgOTf (2.0), TMU (1.0)	rt, 3 h, then reflux, 3h	**13** (63%), **11** (16% recovery)
5	**12** (4.5)	AgOTf (4.0), TMU (2.0)	rt, 3 h, then reflux, 3h	**13** (43%), **15** (34%)
6	**12** (3.0)	Et_4NBr (2.0), iPr_2NEt (2.0)	reflux, 24 h	**14** (93%)
7	**16** (3.0)	AgOTf (2.0), TMU (1.0)	rt, 3 h	**17** (12%), **11** (70% recovery)
8	**16** (3.0)	AgOTf (2.0), TMU (1.0)	rt, 3 h, then reflux, 3h	**17** (0%) [b]
9	**16** (3.0)	Et_4NBr (2.0), iPr_2NEt (2.0)	rt, 48 h	**17** (3%), **11** (82% recovery)
10	**16** (3.0)	Et_4NBr (2.0), iPr_2NEt (2.0)	reflux, 24 h	**17** (69%)

[a] All reactions were carried out in $CHCl_3$. [b] Formation of an inseparable mixture of unidentified products.

Glycosylation of **11** with 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (**12**)[21] (3.0 mol equiv.) in chloroform at room temperature in the presence of tin(IV) chloride (2.0 mol equiv.)[5,13] did not proceed apparently due to deposition of the substrate, whereas the same reaction under reflux conditions resulted in the formation of unidentified, decomposed compounds (Entries 1,2). On the other hand, while treatment of **11** with **12** at room temperature in the presence of siver triflate (2.0 mol equiv.) and tetramethylurea (TMU) (1.0 mol equiv.)[22] scarcely proceeded, efficient glycosylation of **11** was attained by refluxing the same reaction mixture after having been left at room temperature to generate an acyloxonium ion intermediate, furnishing 6-*O*-[(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyloxy)methyl]-pterin derivative (**13**) in 63% yield (Entries 3,4). Use of larger amounts of the glycosyl donor (4.5 equiv.) and the activator (4.0 equiv.) brought about production of 6-benzoyloxymethylpterin derivative (**15**) (Entry 5). Refluxing of **11** with **12** in chloroform in the presence of tetraethylammonium bromide (2.0 mol equiv.) and *N*-ethyldiisopropylamine (2.0 mol equiv.)[23] afforded α-D-glucopyranose-1,2-orthobenzoate derivative (**14**) (in 93% yield) instead of the pterin glycoside (Entry 6).

A possible pathway for the formation of **14** and **15** from the glycosyl donor (**12**) is illustrated in Scheme 3. Namely, the tetra-*O*-benzoylglucopyranosyl bromide (**12**) reacts with the glycosyl accepter (**11**) under Koenigs-Knorr conditions to initially yield a 1,2-orthobenzoate intermediate (**B**) via acyloxonium ion (**A**).[24] Although the intermediate (**B**) isomerizes to yield the thermodynamic product, 1,2-*trans*-glycoside (**13**) by the action of Lewis acid, the presence of an amine is likely to prompt the intermediate (**B**) to cause deprotonation leading to the production of 1,2-orthobenzoate derivative (**14**). Meanwhile, formation of benzoylated alcohol (**15**) may result from an alternative pathway involving intramolecular rearrangement from the intermediate **C**, which was supported by the fact of recovery of 2-*O*-debenzoylated compound (**D**) from the reaction mixture.



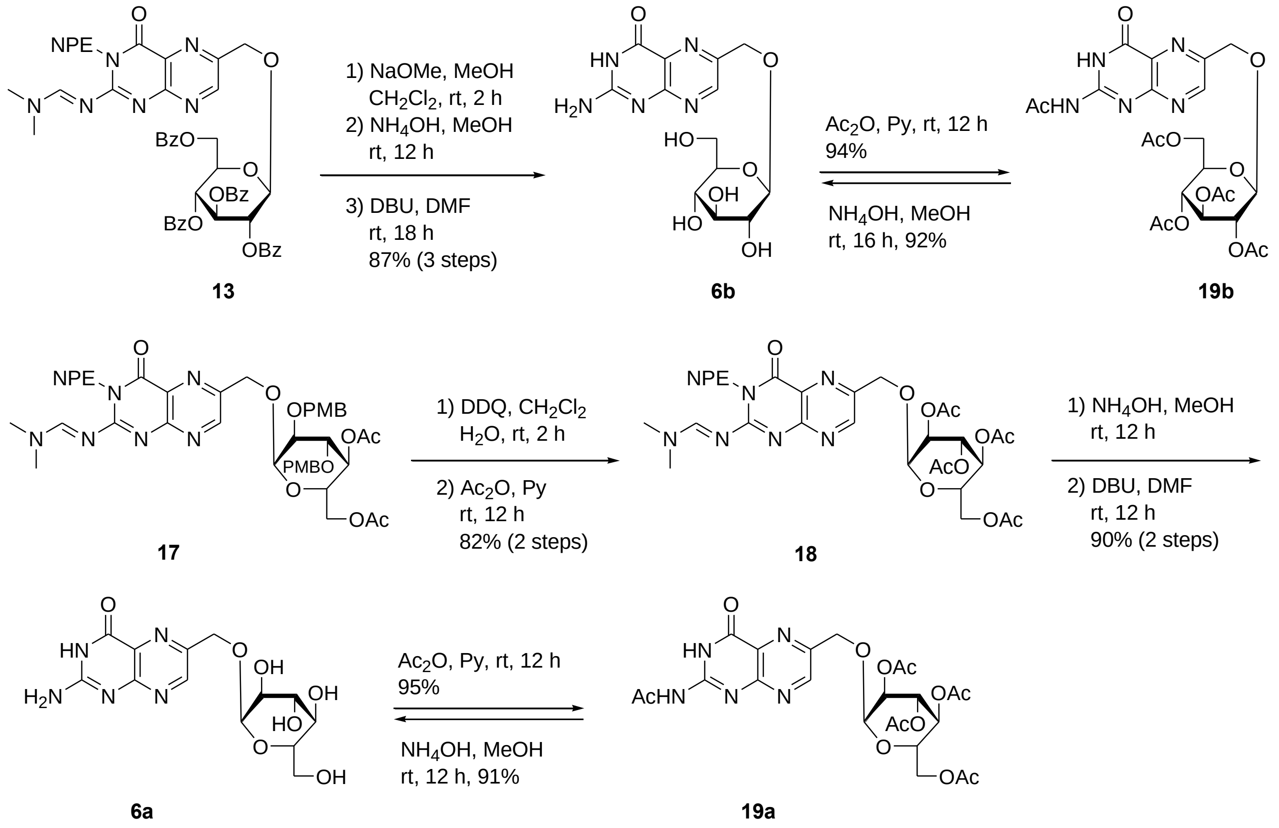
Scheme 3

As the stereoselective formation of the β-glycoside (**13**) from **11** was mainly caused by participation of the 2-*O*-benzoyl group of the glycosyl donor (**12**) through the formation of an acyloxonium ion intermediate, glycosylation of **11** was then examined by use of a glycosyl donor whose 2-OH was protected with an ether substituent having no neighboring group participation. 4,6-Di-*O*-acetyl-2,3-di-*O*-(*p*-methoxybenzyl)-α-D-glucopyranosyl bromide (**16**),[15] a novel glycosyl donor developed for preparation of pterin α-glycoside, was thus employed.

Glycosylation of **11** with the glycosyl donor (**16**) in chloroform in the presence of siver triflate (2.0 mol equiv.) and tetramethylurea (TMU) (1.0 mol equiv.) scarcely proceeded at room temperature, whereas the same reaction under reflux conditions resulted in the formation of decomposed compounds (Entries 7,8). The carboxonium ion intermediate derived from **16** having no stabilization by the neighboring 2-*O*-(*p*-methoxybenzyl) group suggests the facile decomposition at a higher temperature. While treatment of **11** with **16** in the presence of tetraethylammonium bromide (2.0 mol equiv.) and *N*-ethyldiisopropylamine (2.0 mol equiv.) facilitated no glycosylation at room temperature, the same reaction under refluxing conditions resulted in the formation of 6-[(2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyloxy)-methyl]pterin derivative (**17**) as a sole product (69% yield) (Entries 9,10). The α-anomeric structure of **17** was derived from its $J_{1,2}$ value (3.5 Hz) of ^{1}H-NMR in comparison with the larger $J_{1,2}$ value (8.0 Hz) of the β-form **13**.

Removal of the protecting groups of β-D-glucoside (**13**) was performed by the three successive treatment with sodium methoxide (to cleave benzoyl groups), aqueous ammonia (to cleave the *N*,*N*-dimethylaminomethylene group), and DBU (to cleave the NPE group)[18] to furnish 6-hydroxymethylpterin β-D-glucopyranoside (**6b**) in 87% overall yield (Scheme 4).

Similarly, removal of the protecting groups of α-D-glucoside (**17**) was conducted by the following 4-step-procedures: cleavage of PMB by use of DDQ, followed by acetylation, afforded the 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl derivative (**18**), which was treated with aqueous ammonia and then with DBU, thus providing 6-hydroxymethylpterin α-D-glucopyranoside (**6a**) in 74% overall yield from **17**. Structures of **6a** and **6b** were unambiguously established as the corresponding pentaacetyl derivatives (**19a,b**) obtained by usual acetylation. Treatment of **19a** and **19b** with aqueous ammonia respectively regenerated **6a** and **6b** quantitatively. The precise ^{1}H- and ^{13}C-NMR parameters of **6a,b** are summarized in Table 2.



Scheme 4

Table 2. 600 MHz ^{1}H- and 151 MHz ^{13}C-NMR Spectral parameters for 6-hydroxymethylpterin α-D-glucoside (**6a**) and β-D-glucoside (**6b**) in DMSO-d_6 [a]

Com-Pound	Chemical shifts/δ (coupling constants/Hz)								
	Pterin moiety		Glycosyl moiety						
	H-7	CH_2-6 ($^{2}J_{H,H}$)	H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5}$)	H-5 ($J_{5,6a}$)	H^a-6 ($J_{6a,6b}$)	H^b-6 ($J_{5,6b}$)
6a	8.79	4.79, 4.61	4.82	3.24	3.48	3.08	3.42	3.59	3.45
		(13.1)	(3.7)	(9.8)	(9.6)	(9.6)	(1.0)	(11.3)	b
6b	8.81	4.93, 4.73	4.30	3.04	3.15	3.06	3.14	3.67	3.44
		(13.0)	(7.8)	(8.8)	(9.0)	(9.3)	(2.0)	(11.7)	(6.1)

	Pterin moiety							Glycosyl moiety					
	C-2	C-4	C-4a	C-6	C-7	C-8a	CH_2–C-6	C-1	C-2	C-3	C-4	C-5	C-6
6a	157.04	160.94	127.92	146.77	149.13	155.21	67.77	98.76	72.07	73.39	70.41	73.39	61.02
6b	156.91	162.10	128.04	147.43	149.60	154.68	69.38	102.92	73.72	76.73	70.28	77.29	61.33

[a] The assignments were made by D_2O exchange. [b] Uncertain because of overlapping with other signals.

The present work thus demonstrates an effective way for both selective α- and β-glycosylation of pterin derivatives. By employing these synthetic procedures, the first synthesis of 6-hydoxymethylpterin α- and β-D-glucoside (**6a,b**) was unequivocally achieved. Extension of this work including improvement of yield for glycosylation as well as applications of these findings in synthesizing other natural pterin glycosides is in progress.

EXPERIMENTAL

All reactions were monitored by TLC (Merck Silica gel 60 F_{254}) with an appropriate solvent system [(*A*) AcOEt, (*B*) 1:9 MeOH-$CHCl_3$, and (*C*) 5:3:1 2-PrOH-AcOEt-H_2O]. Column chromatography was performed with Daiso Silica Gel IR-60/210w. Components were detected by exposing the plates to UV light and/or 20% H_2SO_4-EtOH, with subsequent heating. The UV/Vis spectra were taken on a JASCO V-530 spectrophotometer. Optical rotations were measured with a JASCO P-1020 polarimeter. The NMR spectra were measured in $CDCl_3$ with Varian Unity Inova AS600 (600 MHz for ^{1}H, 151 MHz for ^{13}C) at 23 °C, unless otherwise stated. The solvent peak was used as an internal standard for chemical shifts: in $CDCl_3$, δ 7.26 for ^{1}H, 77.00 for ^{13}C; in DMSO-d_6, δ 2.50 for ^{1}H, 39.70 for ^{13}C. The assignments of ^{13}C signals were made with the aid of 2D C-H COSY measurements.

6-Hydroxymethylpterin (5a)[24] and 7-hydroxymethylpterin (5b).

A. With AcONa. The following modification of the literature procedures[16] was made. To a solution of 2,5,6-triamino-4-hydroxypyrimidine dihydrochloride (**8**) (800 mg, 3.74 mmol) and L-cystein hydrochloride monohydrate (657 mg, 3.74 mmol) dissolved in 4M aqueous sodium acetate (40 mL), was added a solution of dihydroxyacetone (1.01 g, 11.2 mmol) in water (10 mL). After stirring at rt for 2 h, air was introduced into the mixture at the same temperature for 24 h. The mixture was cooled at 0 °C and then the precipitates were collected by filtration and washed with cold water. The precipitates were suspended in hot water (30 mL) and then 1M aqueous NaOH was added dropwide. The mixture was treated with active charcoal and filtered. The filtrate was cooled to rt and then the pH was adjusted to 6.0 with 1M HCl. After cooling to 0 °C, the precipitates were collected by filtration, washed with cold water and methanol, and then dried under reduced pressure to give an 82:18 mixture (580 mg, 80%) of **5a** and **5b** as a yellow solid: R_f = 0 (*B*). ^{1}H NMR for **5a** (DMSO-d_6) δ 4.61 (2H, d, $J_{CH2,OH}$ = 5.7 Hz, CH_2-6), 5.56 (1H, t, OH), 6.90 (2H, br s, H_2N-2), 8.72 (1H, s, H-7), 11.44 (1H, br s, H-N(3)); ^{1}H NMR for **5b** (DMSO-d_6) δ 4.61 (2H, d, $J_{CH2,OH}$ = 5.9 Hz, CH_2-7), 5.66 (1H, t, OH), 6.90 (2H, br s, H_2N-2), 8.47 (1H, s, H-6), 11.44 (1H, br s, H-N(3)) .

B. With $NaHCO_3$. Compound **8** (200 mg, 0.934 mmol), L-systein hydrochloride monohydrate (164 mg, 0.934 mmol), and dihydroxyacetone (252 mg, 2.80 mmol) were dissolved in 1M aqueous sodium bicarbonate (10 mL). After stirring at rt for 2 h, the mixture was subjected to air-bubbling and the following same treatment described above, giving an 11:89 mixture (129 mg, 72%) of **5a** and **5b**.

6-Acetoxymethyl-N^2-(*N*,*N*-dimethylaminomethylene)pterin (9a)[25] and its 7-acetoxymethyl isomer (9b).

The 82:18 mixture of **5a**,**b** (580 mg, 3.00 mmol) was dissolved in dry DMF (15 mL) and then *N*,*N*-dimethylformamide dimethyl acetal (1.30 mL, 9.86 mmol) was added. The mixture was stirred at rt for 4 h and concentrated in vacuo. The residue was dissolved in dry pyridine (12 mL) and then acetic anhydride (4.00 mL, 42.3 mmol) was added at 0 °C. The mixture was stirred at rt for 12 h and then concentrated in vacuo. The residue was purified by column chromatography with 1:19 MeOH-$CHCl_3$ to give an inseparable mixture (82:18) of **9a**,**b** (668 mg, 77%) as a pale yellow solid [lit.,[25] 65% yield (**9a** from **5a**)]: R_f = 0.03 (*A*), 0.40 (*B*).

9a: ^{1}H-NMR δ 2.15 (1H, s, Ac), 3.18, 3.24 (3H each, 2s, Me_2N), 5.35 (2H, s, CH_2-6), 8.82 (1H, s, H-7), 8.98 (1H, s, CH=N-2), 9.62 (1H, br s, H-N(3)); ^{13}C-NMR δ 20.79 (CO*C*H_3), 35.52, 41.77 (2s, Me_2N), 64.82 (*C*H_2–C-6), 130.28 (C-4a), 147.19 (C-6), 149.46 (C-7), 156.09 (C-8a), 157.67 (C-2), 159.82 (NCH=N), 161.80 (C-4), 170.53 (*C*OCH_3).

9b: ^{1}H-NMR δ 2.17 (1H, s, Ac), 3.16, 3.22 (3H each, 2s, Me_2N), 5.29 (2H, s, CH_2-6), 8.56 (1H, s, H-6), 8.96 (1H, s, CH=N-2), 9.99 (1H, br s, H-N(3)); ^{13}C-NMR δ 20.74 (CO*C*H_3), 35.40, 41.65 (2s, Me_2N), 64.87 (*C*H_2–C-6), 130.72 (C-4a), 139.08 (C-6), 155.77 (C-8a), 156.72 (C-7), 157.93 (C-2), 159.82 (NCH=N), 162.01 (C-4), 170.34 (*C*OCH_3).

6-Acetoxymethyl-*N*^{2}-(*N*,*N*-dimethylaminomethylene)-3-[2-(4-nitrophenyl)ethyl]pterin (10a)[25] and its 7-acetoxymethyl isomer (10b).

To a solution of **9a**,**b** (668 mg, 2.30 mmol), 2-(*p*-nitrophenyl)ethanol (588 mg, 3.50 mmol) and triphenylphosphine (1.80 g, 6.86 mmol) in dry 1,4-dioxane (30 mL), was added DEAD (0.710 mL, 3.86 mmol). The mixture was stirred at rt for 12 h and then concentrated in vacuo. The residue was separated by column chromatography with 2:1 AcOEt-hexane to give **10a** (763 mg, 46% yield from **8**) and **10b** (167 mg, 10% yield).

10a: Pale yellow crystals; R_f = 0.09 (*A*), 0.71 (*B*); mp 212–213 °C (from AcOEt) (lit.,[25] 198–200 °C); ^{1}H-NMR δ 2.16 (1H, s, Ac), 3.16 [2H, t, ^3J = 7.6 Hz, C*H*$_2$$CH_2$–N(3)], 3.18, 3.23 (3H each, 2s, Me_2N), 4.61 [2H, t, CH_2–N(3)], 5.37 (2H, s, CH_2-6), 7.40, 8.12 (2H each, 2d, $J_{o,m}$ = 8.8 Hz, C_6H_4 of NPE), 8.82 (1H, s, H-7), 8.84 (1H, s, CH=N-2); ^{13}C-NMR δ 20.81 (CO*C*H_3), 34.08 (*C*$H_2$$CH_2$N), 35.48, 41.57 (2s, Me_2N), 43.71 (CH_2N), 64.90 (*C*H_2–C-6), 123.67 (C(*m*) of NPE), 129.11 (C-4a), 129.77 (C(*o*) of NPE), 146.61, 146.71 (2s, C(*ipso*, *p*) of NPE), 147.35 (C-6), 149.48 (C-7), 153.98 (C-8a), 157.85 (C-2), 159.26 (NCH=N), 161.84 (C-4), 170.54 (*C*OCH_3).

10b: Pale yellow crystals; R_f = 0.14 (*A*), 0.71 (*B*); mp 184–185 °C (from AcOEt); ^{1}H-NMR δ 2.20 (1H, s, Ac), 3.17 [2H, t, ^3J = 7.6 Hz, C*H*$_2$$CH_2$–N(3)], 3.18, 3.23 (3H each, 2s, Me_2N), 4.62 [2H, t, CH_2–N(3)], 5.32 (2H, s, CH_2-6), 7.40, 8.13 (2H each, 2d, $J_{o,m}$ = 8.8 Hz, C_6H_4 of NPE), 8.60 (1H, s, H-6), 8.85 (1H, s, CH=N-2); ^{13}C-NMR δ 20.77 (CO*C*H_3), 34.12 (*C*$H_2$$CH_2$N), 35.48, 41.57 (2s, Me_2N), 43.64 (CH_2N), 64.93 (*C*H_2–C-6), 123.68 (C(*m*) of NPE), 129.63 (C-4a), 129.74 (C(*o*) of NPE), 139.28 (C-6), 146.63, 146.73 (2s, C(*ipso*, *p*) of NPE), 153.65 (C-8a), 156.79 (C-2), 158.12 (C-7), 159.26 (NCH=N), 161.74 (C-4), 170.37 (*C*OCH_3). Anal. Calcd for $C_{20}H_{21}N_7O_5$: C, 54.67; H, 4.82. Found: C, 54.88; H, 4.99.

N^2-(*N*,*N*-Dimethylaminomethylene)- 6-hydroxymethyl-3-[2-(4-nitrophenyl)ethyl]pterin (11).

Compound **26a** (1.47 g, 3.36 mmol) was dissolved in dry MeOH (20 mL) and dry CH_2Cl_2 (20 mL) and then sodium methoxide (28% in MeOH, 0.16 mL, 0.84 mmol) was added at 0 °C. The mixture was stirred at rt for 2 h and neutralized with Amberlite IR-120(H^+). The resin was filtered off and the filtrate was evaporated in vacuo. The residue was recrystallized from $CHCl_3$ to give **27** as pale yellow solid. An additional amount of **27** was obtained from the mother liquor by column chromatographic purification: total yield 1.30 g (97%); R_f = 0.44 (*B*); mp 220–223 °C; ^{1}H-NMR δ 3.13 (1H, br s, HO), 3.17 [2H, t, ^3J = 7.6 Hz, C*H*$_2$CH$_2$–N(3)], 3.19, 3.24 (3H each, 2s, Me$_2$N), 4.62 [2H, t, CH$_2$–N(3)], 4.96 (2H, s, CH$_2$-6), 7.41, 8.14 (2H each, 2d, $J_{o,m}$ = 8.8 Hz, C$_6$H$_4$ of NPE), 8.85 (1H, s, H-7), 8.86 (1H, s, CH=N-2); ^{13}C-NMR δ 34.13 (*C*H$_2$CH$_2$N), 35.48, 41.57 (2s, Me$_2$N), 43.77 (CH$_2$N), 63.32 (*C*H$_2$–C-6), 123.72 (C(*m*) of NPE), 128.60 (C-4a), 129.80 (C(*o*) of NPE), 146.63, 146.76 (2s, C(*ipso*, *p*) of NPE), 151.41 (C-6), 148.76 (C-7), 153.86 (C-8a), 157.56 (C-2), 159.21 (NCH=N), 162.02 (C-4). Anal. Calcd for $C_{18}H_{19}N_7O_4$: C, 54.40; H, 4.82. Found: C, 54.19; H, 4.95.

N^2-(*N*,*N*-Dimethylaminomethylene)-3-[2-(4-nitrophenyl)ethyl]-6-[(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyloxy)methyl]pterin (13).

To a solution of **11** (25.6 mg, 0.0644 mmol), 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (**12**) (127 mg, 0.194 mmol) and TMU (0.008 mL, 0.064 mmol) in dry $CHCl_3$ (10 mL), was added silver triflate (33.0 mg, 0.13 mmol). The mixture was stirred at rt for 3 h in the dark and then refluxed for 3 h. The mixture was cooled to rt, diluted with $CHCl_3$, and filtered through Celite. The filtrate was washed with aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated in vacuo. The residue was separated by column chromatography with 2:1 AcOEt-hexane to give **13** (39.7 mg, 63%) and **11** (4.1 mg, 16% recovery).

13: Pale yellow crystals; mp 139–141 °C (from AcOEt); R_f = 0.24 (*A*), 0.68 (*B*); ^{1}H-NMR δ 3.15 [2H, t, ^3J = 7.6 Hz, C*H*$_2$CH$_2$-N(3)], 3.16, 3.21 (3H each, 2s, Me$_2$N), 4.20 (1H, ddd, $J_{4,5}$ = 9.9, $J_{5,6b}$ = 5.2, $J_{5,6a}$ = 3.1 Hz, H-5*), 4.46 (1H, dd, $J_{6a,6b}$ = 12.2 Hz, H^b-6*), 4.61 (1H, dd, H^a-6*), 4.59 [2H, t, CH$_2$-N(3)], 5.08 (1H, d, $J_{1,2}$ = 7.9 Hz, H-1*), 5.66 (dd, $J_{2,3}$ = 9.9 Hz, H-2*), 5.70 (1H, t, $J_{3,4}$ = 9.6 Hz, H-4*), 5.93 (1H, t, H-3*), 5.01, 5.21 (1H each, 2d, $^2J_{CH2}$ = 13.7 Hz, CH$_2$-6), 7.34, 8.12 (2H each, 2d, $J_{o,m}$ = 8.6 Hz, C$_6$H$_4$), 7.26-7.54 [12H, m, Bz(*m*,*p*)*], 7.82, 7.89, 7.92, 7.99 [2H each, 4dd, $J_{o,m}$ = 8.0, $J_{o,p}$ = 1.7 Hz, Bz(*o*)*], 8.81 (1H, s, CH=N-2), 8.84 (1H, s, H-7), *for glycosyl moiety. Anal. Calcd for $C_{52}H_{45}N_7O_{13}$: C, 63.99; H, 4.65. Found: C, 64.11; H, 4.71.

6-Benzoyloxy-*N*^{2}-(*N*,*N*-Dimethylaminomethylene)-3-[2-(4-nitrophenyl)ethyl]pterin (15).

To a solution of **11** (30.0 mg, 0.0755 mmol), **12** (230 mg, 0.349 mmol) and TMU (0.018 mL, 0.15 mmol) in dry $CHCl_3$ (12 mL), was added silver triflate (77.6 mg, 0.302 mmol). The mixture was stirred at rt for 3 h in the dark and then refluxed for 3 h. The mixture was worked up by use of the same procedures described above to give **13** (31.4 mg, 43%) and **15** (13.0 mg, 34%).

15: Pale yellow crystals; mp 208–210 °C (from AcOEt); R_f = 0.60 (*B*); ^{1}H-NMR δ 3.17 [2H, t, ^3J = 7.6 Hz, C*H*$_2$CH$_2$–N(3)], 3.18, 3.23 (3H each, 2s, Me$_2$N), 4.63 [2H, t, CH$_2$–N(3)], 5.64 (2H each, s, CH$_2$-6), 7.41, 8.13 (2H each, 2d, $J_{o,m}$ = 8.6 Hz, C$_6$H$_4$ of NPE), 7.45 [2H, t, $J_{o,m}$ = $J_{m,p}$ = 7.8 Hz, Bz(*m*)], 7.58 [1H, td, $J_{o,m}$ = 1.7 Hz, Bz(*p*)], 8.09 [2H, dd, Bz(*o*)], 8.85 (1H, s, CH=N-2), 8.94 (1H, s, H-7). Anal. Calcd for

$C_{25}H_{23}N_7O_5$: C, 59.87; H, 4.62. Found: C, 59.98; H, 4.79.

3,4,6-Tri-*O*-benzoyl-α-D-glucopyranose-1,2-{[*N*^{2}-(*N*,*N*-dimethylaminomethylene)-3-(4-nitrophenylethyl)pterin-6-yl]methyl}orthobenzoate (14).

To a solution of **11** (20.0 mg, 0.0503 mmol) and **12** (100 mg, 0.152 mmol) in $CHCl_3$(8.0 mL) were added tetraethylammonium bromide (21.0 mg, 0.116 mmol) and *N*-ethyldiisopropylamine (0.018 mL, 0.10 mmol). The mixture was then refluxed for 42 h. After cooling, the mixture was diluted with $CHCl_3$, washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with AcOEt to give **14** (45.8 mg, 93% yield) as a pale yellow syrup: R_f = 0.26 (*A*), 0.73 (*B*); ^{1}H-NMR δ 3.12 [2H, t, ^3J = 7.6 Hz, CH_2CH$_2$–N(3)], 3.15, 3.20 (3H each, 2s, Me$_2$N), 4.11 (1H, ddd, $J_{4,5}$ = 8.8, $J_{5,6b}$ = 5.1, $J_{5,6a}$ = 2.9 Hz, H-5*), 4.37 (1H, dd, $J_{6a,6b}$ = 12.1 Hz, H^b-6*), 4.52 (1H, dd, H^a-6*), 4.57 [2H, t, CH$_2$–N(3)], 4.69, 4.72 (1H each, 2d, $^2J_{CH2}$ = 13.3 Hz, CH$_2$-6), 4.90 (1H, ddd, $J_{1,2}$ = 5.1, $J_{2,3}$ = 3.2, $^4J_{2,4}$ = 1.2 Hz, H-2*), 5.49 (1H, dt, $J_{3,4}$ = 1.5 Hz, H-4*), 5.74 (1H, dd, H-3*), 6.13 (1H, d, H-1*), 7.26, 7.42, 7.425, 7.43 [2H each, 4t, $J_{o,m}$ = $J_{m,p}$ = 8.0 Hz, Ph(*m*)*], 7.36, 8.10 (2H each, 2d, $J_{o,m}$ = 8.6 Hz, C_6H_4 of NPE), 7.44, 7.48, 7.58, 7.59 [1H each, 4tt, $J_{o,p}$ = 1.7 Hz, Ph(*p*)*], 7.83, 7.925, 7.93, 8.06 [2H each, 4dd, Ph(*o*)*], 8.81 (1H, s, CH=N-2), 8.83 (1H, s, H-7), *for glycosyl moiety. Anal. Calcd for $C_{52}H_{45}N_7O_{13}$: C, 63.99; H, 4.65. Found: C, 64.18; H, 4.44.

***N*^{2}-(*N*,*N*-Dimethylaminomethylene)-3-[2-(4-nitrophenyl)ethyl]-6-{[4,6-di-*O*-acetyl-2,3-di-*O*-(4-methoxybenzyl)-α-D-glucopyranosyloxy]methyl}pterin (17).**

To a solution of **11** (30.0 mg, 0.0755 mmol) and **16** (127 mg, 0.224 mmol) in $CHCl_3$ (6.0 mL) was added tetraethylammonium bromide (28.0 mg, 0.155 mmol) and *N*-ethyldiisopropylamine (0.027 mL, 0.155 mmol). The mixture was refluxed for 24 h, diluted with $CHCl_3$, washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with AcOEt to give **17** (45.5 mg, 69% yield) as a pale yellow syrup: R_f = 0.07 (*A*), 0.80 (*B*); ^{1}H-NMR δ 1.94, 2.06 (3H each, 2s, AcO-4,6*), 3.19, 3.24 (3H each, 2s, Me$_2$N), 3.18 [2H, t, ^3J = 7.8 Hz, CH_2CH$_2$–N(3)], 3.62 (1H, dd, $J_{2,3}$ = 9.5, $J_{1,2}$ = 3.7 Hz, H-2*), 3.78, 3.79 (3H each, 2s, MeO*), 3.79 (1H, ddd, $J_{4,5}$ = 10.0, $J_{5,6a}$ = 5.6, $J_{5,6b}$ = 2.2 Hz, H-5*), 3.93 (1H, dd, $J_{6a,6b}$ = 12.7 Hz, H$_b$-6*), 3.94 (1H, t, $J_{3,4}$ = 9.3 Hz, H-3*), 4.22 (1H, dd, H$_a$-6*), 4.57, 4.72 (2H each, 2d, ^2J = 11.5 Hz, CH$_2$O-2 or 3*), 4.58, 4.80 (2H each, 2d, ^2J = 11.2 Hz, CH$_2$O-2 or 3*), 4.63 [2H, t, CH$_2$–N(3)], 4.82, 4.97 (1H each, 2d, $^2J_{CH2}$ = 13.7 Hz, CH$_2$-6), 4.85 (1H, d, H-1*), 5.00 (1H, dd, H-4*), 6.83, 6.85, 7.20, 7.25 (2H each, 4 d, $J_{o,m}$ = 8.6 Hz, C_6H_4 of PMB*), 7.41, 8.13 (2H each, 2d, $J_{o,m}$ = 8.7 Hz, C_6H_4 of NPE), 8.86 (1H, s, CH=N-2), 9.03 (1H, s, H-7), *for glycosyl moiety. Anal. Calcd for $C_{44}H_{49}N_7O_{13}$: C, 59.79; H, 5.59. Found: C, 59.55; H, 5.79.

***N*^{2}-(*N*,*N*-Dimethylaminomethylene)-3-[2-(4-nitrophenyl)ethyl]-6-[(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyloxy)methyl]pterin (18).**

To a solution of **17** (47.0 mg, 0.0532 mmol) in CH_2Cl_2 (4.0 ml) containing water (0.4 mL) was added DDQ (120 mg, 0.529 mmol). The mixture was stirred at rt for 2 h and then diluted with $CHCl_3$. The mixture was washed with aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated in vacuo. The residue was dissolved in dry pyridine (2.0 mL) and then acetic anhydride (0.25 mL, 2.66 mmol) was added at 0 °C. The mixture was stirred at rt for 12 h and then evaporated in vacuo. The residue was purified by column chromatography with AcOEt to give **18** (26.8 mg, 69% yield) as a pale yellow syrup: R_f = 0.06 (*A*), 0.71 (*B*); ^{1}H-NMR δ 2.02, 2.03, 2.09, 2.12 (3H each, 4s, AcO-2,3,4,6*), 3.17 [2H, t, ^3J = 7.7 Hz, CH_2CH$_2$–N(3)], 3.19, 3.24 (3H each, 2s, Me$_2$N), 4.13 (1H, ddd, $J_{4,5}$ = 10.3, $J_{5,6a}$ = 4.6, $J_{5,6b}$ = 2.2 Hz, H-5*), 4.08 (1H, dd, $J_{6a,6b}$ = 12.2 Hz, H^b-6*), 4.29 (1H, dd, H^a-6*), 4.62 [2H, t, CH$_2$–N(3)], 4.86, 5.03 (1H each, 2d, $^2J_{CH2}$ = 13.4 Hz, CH$_2$-6), 4.96 (1H, dd, $J_{1,2}$ = 3.9, $J_{2,3}$ = 10.3 Hz, H-2*), 5.09 (1H, t, $J_{3,4}$ = 9.5 Hz, H-4*), 5.21 (1H, d, H-1*), 5.54 (1H, t, H-3*), 7.40, 8.13 (2H each, 2d, $J_{o,m}$ = 8.7 Hz, C$_6$H$_4$ of NPE), 8.84 (1H, s, CH=N-2), 8.91 (1H, s, H-7), *for glycosyl moiety. Anal. Calcd for $C_{32}H_{37}N_7O_{13}$: C, 52.82; H, 5.13. Found: C, 52.69; H, 5.01.

6-[(α-D-Glucopyranosyloxy)methyl]pterin (6a).

A. From 18. Compound **18** (27.2 mg, 0.0374 mmol) was dissolved in MeOH (2.0 mL) and 28% aqueous ammonia solution (2.0 mL) was added. The mixture was stirred at rt for 12 h and then evaporated in vacuo. The residue was dissolved in DMF (2.0 mL) and then DBU (0.039 mL, 0.26 mmol) was added. The mixture was stirred at rt for 12 h, diluted with water (4.0 mL) and neutralized with Amberlite FPC3500(H$^+$). The resin was filtered off and the filtrate was evaporated in vacuo. The residue was washed with CHCl$_3$ and dried under reduced pressure to give **6a** (12.0 mg, 90%).

B. From 19a. Compound **19a** (18.2 mg, 0.0322 mmol) was dissolved in MeOH (1.0 mL) and 28% aqueous ammonia solution (1.0 mL) was added. The mixture was stirred at rt for 12 h and then evaporated in vacuo. The residue was washed with CHCl$_3$ and dried under reduced pressure to give **6a** (10.4 mg, 91% yield) as a pale yellow solid: mp 222–224 °C (dec.); R_f = 0.12 (*C*); $[\alpha]_D^{28}$ +47.1° (*c* 0.65, H$_2$O); UV (pH 7) λ_{max} 236 nm (log ε 3.95), 275 (4.01), 346 (3.65); ^{1}H and ^{13}C-NMR, see Table 2. Anal. Calcd for $C_{13}H_{17}N_5O_7$: C, 43.95; H, 4.82. Found: C, 44.09; H, 4.90.

N^2-Acetyl-6-[(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyloxy)methyl]pterin (19a).

Compound **6a** (12.0 mg, 0.0338 mmol) was dissolved in dry DMF (1.0 mL) and dry pyridine (2.0 mL) and then acetic anhydride (0.10 mL, 1.04 mmol) was added at 0 °C. The mixture was stirred at rt for 12 h and then evaporated in vacuo. The residue was purified by column chromatography with 1:99 MeOH-CHCl$_3$ to give **19a** (18.2 mg, 95%) as a pale yellow syrup: R_f = 0.60 (*B*); ^{1}H-NMR δ 2.02, 2.025, 2.09, 2.11 (3H each, 4s, AcO-2,3,4,6*), 2.49 (3H, s, AcN), 4.11 (1H, ddd, $J_{4,5}$ = 10.3, $J_{5,6a}$ = 4.4, $J_{5,6b}$ = 2.4 Hz, H-5*), 4.09 (1H, dd, $J_{6a,6b}$ = 12.0 Hz, H^b-6*), 4.28 (1H, dd, H^a-6*), 4.88, 5.07 (1H each, 2d, $^2J_{CH2}$ = 13.5 Hz, CH$_2$-6), 4.97 (1H, dd, $J_{2,3}$ = 10.3, $J_{1,2}$ = 3.9 Hz, H-2*), 5.10 (1H, t, $J_{3,4}$ = 9.5 Hz, H-4*), 5.25 (1H, d, H-1*), 5.53 (1H, t, H-3*), 9.00 (1H, s, H-7), 11.04 [1H, br s, H-N(3)], 12.75 (1H, br s, AcN*H*), *for glycosyl moiety. Anal. Calcd for $C_{23}H_{27}N_5O_{12}$: C, 48.85; H, 4.81. Found: C, 48.98; H, 4.99.

6-[(β-D-Glucopyranosyloxy)methyl]pterin (6b).

A. From 13. Compound **13** (32.0 mg, 0.0328 mmol) was dissolved in dry MeOH (1.0 mL) and dry CH$_2$Cl$_2$ (1.0 mL) and then sodium methoxide (28% in MeOH, 0.007 mL, 0.03 mmol) was added at 0 °C.

The mixture was stirred at rt for 2 h and neutralized with Amberlite IR-120(H^+). The resin was filtered off and the filtrate was evaporated in vacuo. The residue was dissolved in MeOH (2.0 mL) and then 28% aqueous ammonia solution (2.0 mL) was added. The mixture was stirred at rt for 12 h and evaporated in vacuo. The residue was dissolved in DMF (2.0 mL) and then DBU (0.029 mL, 0.20 mmol) was added. The mixture was stirred at rt for 18 h, diluted with water (4.0 mL), and neutralized with Amberlite FPC3500(H^+). The resin was filtered off and the filtrate was evaporated in vacuo. The residue was washed with $CHCl_3$ and dried under reduced pressure to give **6b** (10.1 mg, 87%).

B. From 19b. By use of same procedures for **6a** from **19a**, compound **6b** (15.1 mg, 0.0267 mmol) was converted into **6b** (8.7 mg, 92%) as a pale yellow solid: mp 238–240 °C (dec.); R_f = 0.12 (*C*); $[\alpha]_D^{28}$ –6.3° (*c* 0.12, H_2O); UV (pH 7) λ_{max} 237 nm (log ε 3.94), 276 (4.04), 347 (3.63); ^{1}H and ^{13}C-NMR, see Table 2. Anal. Calcd for $C_{13}H_{17}N_5O_7$: C, 43.95; H, 4.82. Found: C, 44.12; H, 4.70.

N^2-Acetyl-6-[(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)methyl]pterin (19b).

By use of same procedures for **19a** from **6a**, compound **6b** (10.1 mg, 0.0284 mmol) was converted into **19b** (15.1 mg, 94%): pale yellow syrup; R_f = 0.29 (*B*); ^{1}H-NMR δ 2.01, 2.03, 2.06, 2.07 (3H each, 4s, AcO-2,3,4,6*), 2.45 (3H, s, AcN), 3.73 (1H, ddd, $J_{4,5}$ = 10.0, $J_{5,6a}$ = 4.9, $J_{5,6b}$ = 2.2 Hz, H-5*), 4.10 (1H, dd, $J_{6a,6b}$ = 12.5 Hz, H^b-6*), 4.19 (1H, dd, H^a-6*), 4.71 (1H, d, $J_{1,2}$ = 7.8 Hz, H-1*), 5.00, 5.08 (1H each, 2d, $^2J_{CH2}$ = 14.0 Hz, CH_2-6), 5.10 (1H, t, $J_{3,4}$ = 9.3 Hz, H-4*), 5.12 (1H, dd, $J_{2,3}$ = 9.8 Hz, H-2*), 5.22 (1H, t, H-3*), 8.90 (1H, s, H-7), 10.68 [1H, br s, H-N(3)], 12.80 (1H, br s, AcN*H*), *for glycosyl moiety. Anal. Calcd for $C_{23}H_{27}N_5O_{12}$: C, 48.85; H, 4.81. Found: C, 49.04; H, 4.77.

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