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EFFICIENT TOTAL SYNTHESES OF NATURAL NEOPTERIN GLYCOSIDES: NEOPTERIN GLUCRONIDE AND SOLFAPTERIN

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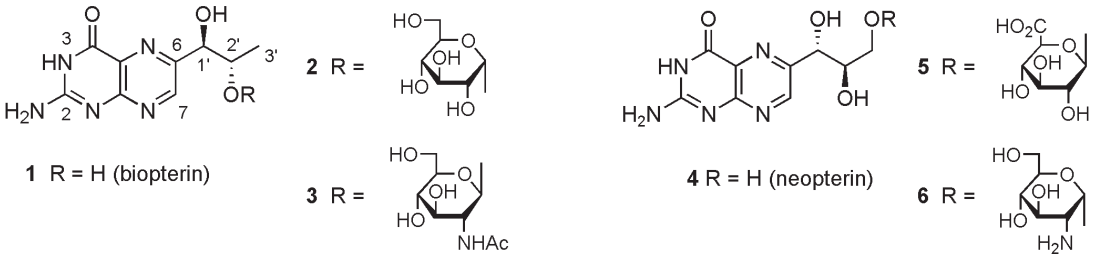
This paper is dedicated to Professor Masakatsu Shibasaki on cerebration of his 70th birthday.

Abstract – 1',2'-Di-*O*-acetyl-N^2-(*N*,*N*-dimethylaminomethylene)-3-[2-(4-nitrophenyl)ethyl]neopterin (**11a**) and its 1',2'-di-*O*-benzoyl analog (**11b**) were prepared from neopterin in 5 steps, respectively. Glycosylation of **11a** with methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranosyluronate bromide (**15b**) in the presence of silver triflate afforded the corresponding 3'-*O*-(β-D-glucopyranosyl)neopterin derivative (**18**) in 64% yield. The similar treatment of **11b** with 2-azido-3,4,6-tri-*O*-benzoyl-2-deoxy-α-D-glucopyranosyl bromide (**21b**) provided the corresponding 3'-*O*-(α-D-glucopyranosyl)neopterin derivative (**23a**) in 58% yield. The first syntheses of neopterin glucronide (**5**) and solfapterin (**6**) were achieved by successive removal of the protecting groups of **18** and **23a**, respectively.

INTRODUCTION

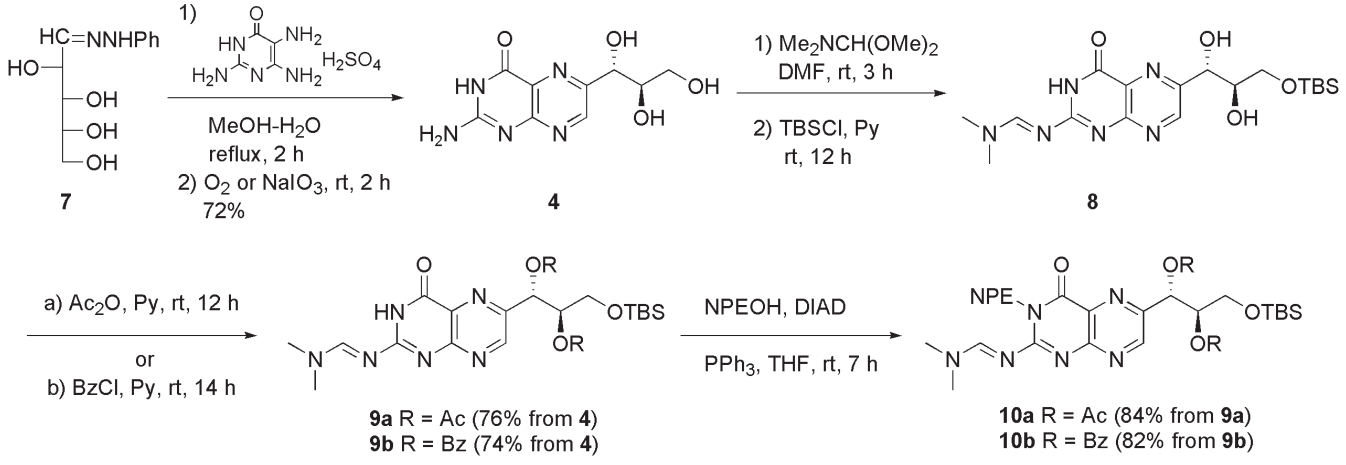
Pterin glycosides having various kinds of sugars attached to the side-chain at C–6 of the pteridine ring were found to be produced by certain prokaryotes such as cyanobacteria and anaerobic photosynthetic bacteria.[1] As representative examples for glycosides of biopterin (**1**), 2'-*O*-(α-D-glucopyranosyl)-biopterin (**2**) was isolated from cyanobacterium, *Anacystis nidulans*,[2] *Oscillatoria* sp.,[3] *Synechococcus* sp.,[4] and *Spirulina platensis*,[5] whereas its 2-acetamido-2-deoxy-β-D-glucopyranosyl analog (limipterin) (**3**) was isolated from a green sulfur photosynthetic bacterium, *Chlorobium limicola f. thiosulfatophilum* NCIB 8327.[6] As for glycosides of neopterin (**4**), 3'-*O*-(β-D-glucopyranosyluronic acid)neopterin (neopterin glucronide) (**5**) was isolated from *Azotobactor agilis*[7] and *Bacillus subtilis*,[8] whereas its

2-amino-2-deoxy-α-D-glucopyranosyl analog (solfapterin) (**6**) was isolated from thermophilic archaebacterium *Sulfolobus solfataricus*.[9] Various other glycosides consisting of different pterins and sugar moieties have also been found in nature.[10-12] However, the physiological functions of these pterin glycosides appear to have been little investigated[13,14] in contrast to the well-documented parent pterins: *e.g.*, biopterin (**1**) exhibits enzyme cofactor activity in aromatic amino acid hydroxylation[15] and nitric oxide synthesis[16] as the form of its tetrahydro derivative, while neopterin (**4**) has been shown to be a marker for the activation of cellular immunity or an inducer of apoptosis.[17] We have undertaken a synthetic exploration of various types of glycosides of biopterin and related pterins owing to a marked interest in their physiological functions and biological activities as well as the structural proof of those natural products.[18] We give herein a full account of efficient syntheses of neopterin glucronide (**5**) and solfapterin (**6**) as the first synthetic examples of natural neopterin glycosides.[19]



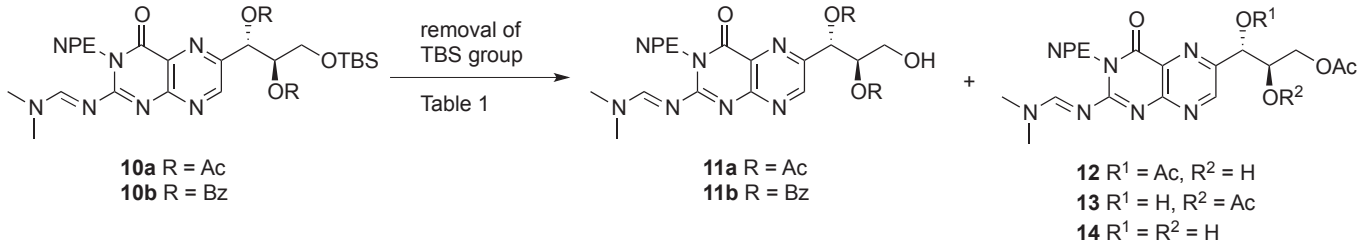
RESULTS AND DISCUSSION

The key precursors (**11a,b**), whose pyrimidine moiety and 1',2'-hydroxy groups of the side chain are appropriately protected, were prepared starting with neopterin (**4**) (available from D-arabinose phenylhydrazone (**7**) according to the reported procedures)[20] (Schemes 1,2). Namely, treatment of **4** with *N*,*N*-dimethylformamide dimethyl acetal in DMF, followed by the selective 3'-*O*-protection with



Scheme 1

tert-butyldimethylsilyl (TBS) group afforded **8**, which was then acetylated or benzoylated to give the N^2-(*N*,*N*-dimethylaminomethylene)neopterin derivatives (**9a,b**). The N-3 position of **9a,b** was protected with 2-(4-nitrophenyl)ethyl (NPE) group[21] by Mitsunobu reaction with 2-(4-nitrophenyl)ethanol in the presence of triphenylphosphine and diisopropyl azodicarboxylate (DIAD) to provide **10a,b**, respectively. Cleavage of 3'-*O*-TBS group of the 1',2'-di-*O*-acetylneopterin derivative (**10a**) with tetrabutylammonium fluoride resulted in the formation of the 1',3'-di-*O*- [**12** (47%)], 2',3'-di-*O*- [**13** (21%)], and 3'-*O*-acetate [**14** (13%)] instead of the desired 1',2'-di-*O*-acetate (**11a**) [Scheme 2, Table 1 (Entry 1)]. As production of **12–14** is likely to result from the 1'-*O*- and 2'-*O*-acetyl group migration by the action of 3'-alkoxide arising from the TBS cleavage, we employed acidic conditions for deprotection of 3'-*O*-TBS group of **10a**. Treatment of **10a** with trifluoroacetic acid (TFA) in dichloromethane exclusively provided the 1',3'-di-*O*-acetate (**12**), whereas hydrolysis of **10a** in 60% acetic acid predominantly gave the desired **11a** (84%), along with a minor amount of **12** (10%) (Entries 2,3). On the other hand, the same reaction of the 1',2'-di-*O*-benzoyl derivative (**10b**) in 60% acetic acid afforded only the desired product (**11b**) without the benzoyl migration (Entry 4).



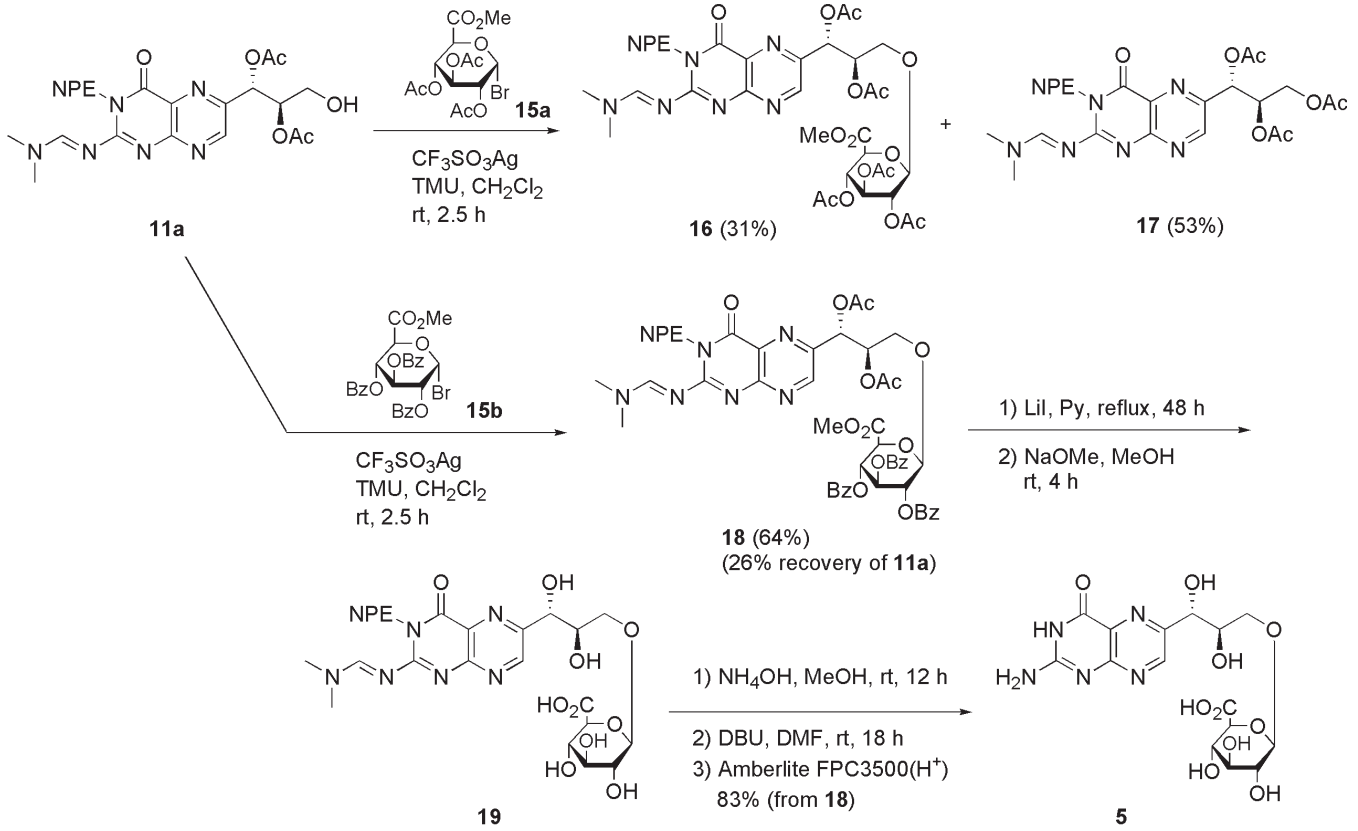
Scheme 2

Table 1. Cleavage of the 3'-*O*-TBS group of the neopterin derivatives (**10a,b**)

Entry	Substrates	Reagents, solvents	Temp, time	Products (yield)
1	**10a**	Bu_4NF, THF	rt, 30 min	**11a** (0%), **12** (47%), **13** (21%), **14** (13%)
2	**10a**	TFA, CH_2Cl_2	rt, 5 h	**11a** (2%), **12** (90%)
3	**10a**	3:1:1 AcOH-H_2O-THF	rt, 12 h	**11a** (84%), **12** (10%)
4	**10b**	3:1:1 AcOH-H_2O-THF	rt, 18 h	**11b** (95%)

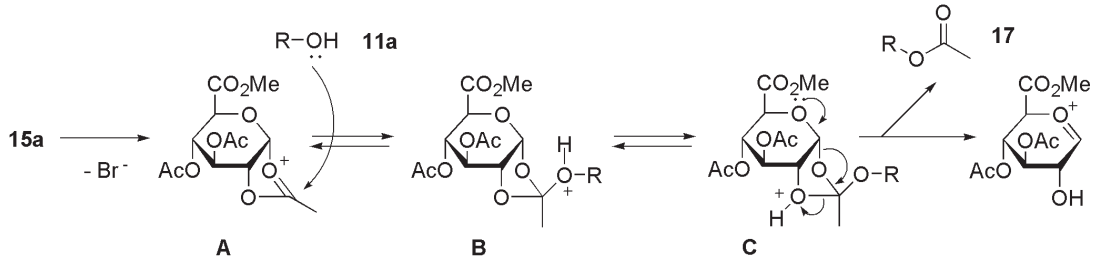
Glycosylation of **11a** with two glycosyl donors, such as methyl 2,3,4-tri-*O*-acetyl- (**15a**)[22] and 2,3,4-tri-*O*-benzoyl-α-D-glucopyranosyluronate bromide (**15b**),[23] was attempted (Scheme 3). Treatment of **11a** with 3.0 mol equiv. of **15a** in the presence of silver triflate (2.0 mol equiv.) and tetramethylurea (TMU) (1.0 mol equiv.) in dichloromethane at room temperature for 2.5 h brought about production of

the 1',2',3'-tri-*O*-acetylneopterin derivative (**17**) in 53% yield; the desired 3'-*O*-(β-D-glucopyranosyl-uronate)neopterin derivative (**16**) was obtained in a minor portion (31% yield).



Scheme 3

A plausible pathway for the formation of **17** from the glycosyl donor (**15a**) is illustrated in Scheme 4. Namely, the acyloxonium ion (**A**) derived from **15a** reacts with the glycosyl acceptor (**11a**) to give the 1,2-orthoacetate intermediate (**B**).[24,25] The subsequent orthoester cleavage via **C** would take place to afford the acetate (**17**).



Scheme 4

On the other hand, the similar treatment of **11a** with 3.0 mol equiv. of the 2,3,4-tri-*O*-benzoyl derivative (**15b**), provided the desired neopterin glycoside (**18**) in 64% yield, along with the recovery of **11a** (26%). Therefore the benzoyl analog (**15b**) seems to be a more suitable glycosyl donor for this work compared with the acetyl analog (**15a**). The precise ^{1}H-NMR parameters of **16** and **18** are summarized in Table 2 and their β-anomeric configurations were assigned by their $J_{1,2}$ values (7.3–7.9 Hz) (Table 2).

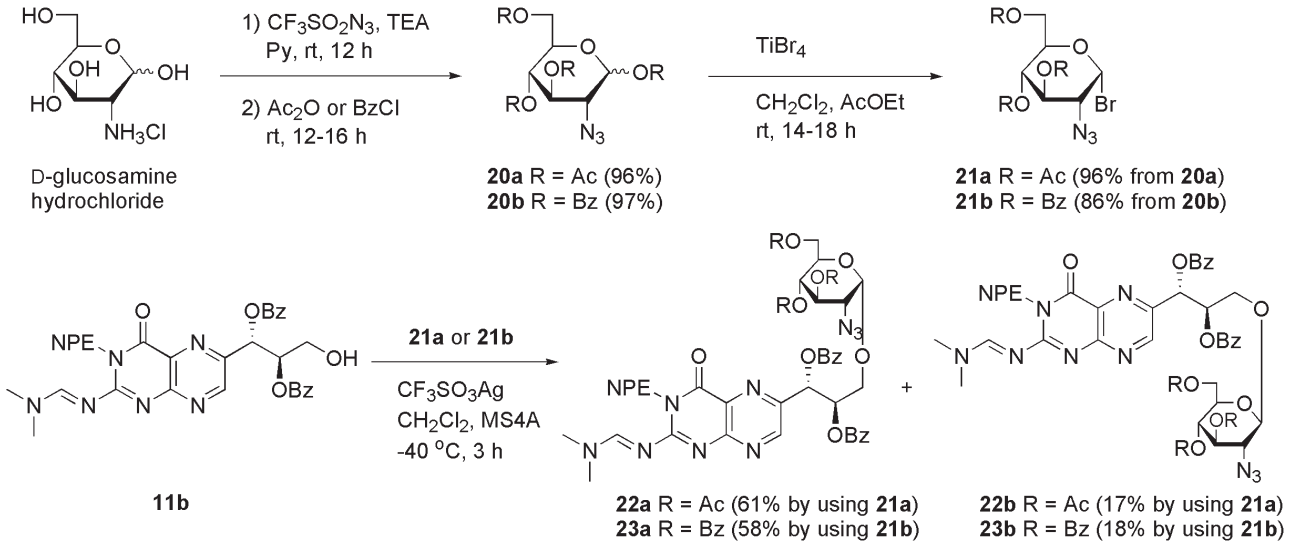
Removal of the protecting groups of the neopterin glycoside (**18**) was accomplished in the following manner. Attempted hydrolysis of all ester groups with aqueous sodium hydroxide resulted in the formation of an inseparable mixture of unidentified products, while selective cleavage of methyl ester of **18** with lithium iodide in refluxing pyridine,[26] followed by the action of sodium methoxide in methanol, afforded the 3'-*O*-(β-D-glucopyranosyluronic acid)neopterin derivative (**19**). Treatment of **19** with aqueous ammonia-methanol to remove the *N*,*N*-dimethylaminomethylene group and then with DBU in DMF to cleave the NPE group, followed by acidification using an acidic ion-exchange resin, furnished the target neopterin glucronide (**5**) in 83% (overall yield from **18**).

Table 2. 600 MHz ^{1}H-NMR Spectral parameters for neopterin glycosides (**16**, **18**, **5**)[a]

Com-Pound	Chemical shifts/δ (coupling constants/Hz)											
	Pterin moiety					Me_2NCH=N-2		NPE-N(3)				
	H-7	H-1' ($J_{1',2'}$)	H-2' ($J_{2',3'a}$)	H^a-3' ($J_{3'a,3'b}$)	H^b-3' ($J_{2',3'b}$)	Me_2N	CH=N	H(*o*) ($J_{o,m}$)	H(*m*)	$ArCH_2$ ($^3J_{H,H}$)	CH_2N ($^2J_{H,H}$)	Other signals
16	8.78	6.11 (5.3)	5.59 (3.2)	4.28 (11.7)	3.79 (6.5)	3.24 3.19	8.87	7.43 (8.6)	8.14	3.15 (7.7)	4.57, 4.55 (12.5)	2.15, 2.01 (Ac) [b]
18	8.73	6.12 (5.1)	5.59 (2.9)	4.38 (11.2)	3.83 (6.7)	3.28 3.21	8.94	7.43 (8.8)	8.13	3.16 (7.8)	4.58, 4.56 (12.6)	2.06, 1.77 (Ac)
5	8.87	5.01 (6.4)	4.22 (3.2)	4.09 (11.0)	3.79 (6.1)							
	Glycosyl moiety											
	H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5}$)	H-5	CO_2Me		Other Signals				
16	4.65 (7.9)	4.93 (9.1)	5.24 (9.4)	5.20 (9.4)	4.07	3.73		2.00, 1.995, 1.99 (Ac) [b]				
18	4.96 (7.3)	5.47 (9.0)	5.91 (9.3)	5.68 (9.3)	4.40	3.66		7.92, 7.90, 7.85 [Bz(*o*)], 7.50, 7.50, 7.44 [Bz(*p*)] 7.35, 7.34, 7.30 [Bz(*m*)]				
5	4.51 (8.1)	3.31 (9.0)	3.50 (9.1)	3.54 (9.5)	3.96							

[a] **16**, **18** in $CDCl_3$, **5** in D_2O. [b] The assignments may have to be interchanged.

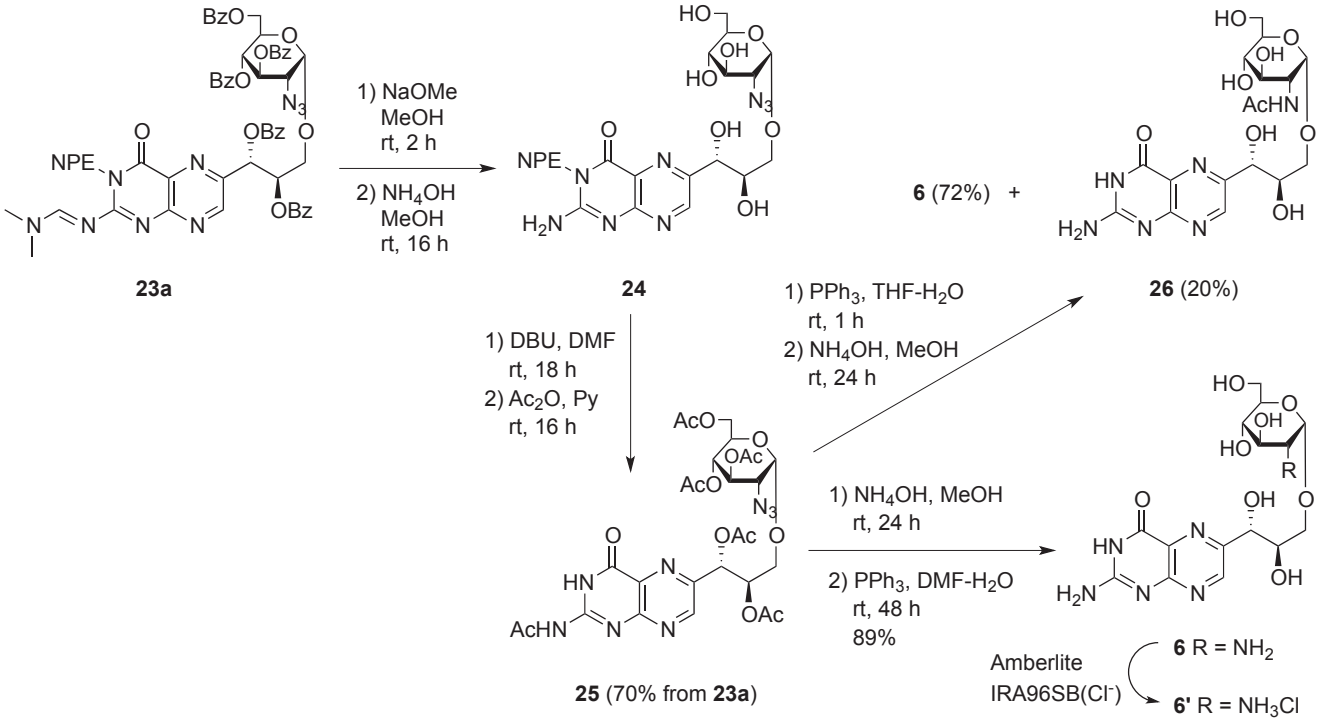
This successful synthesis of **5** led us to execute preparation of the other natural neopterin glycoside, solfapterin (**6**). The stereoselective formation of the β-glycosides (**16,18**) from **11a** was mainly caused by participation of the 2-*O*-acyloxy group of the glycosyl donors (**15a,b**) through the formation of an acyloxonium ion intermediate.[24] Accordingly, in order to avoid such a neighboring group participation in synthesis of the α-D-glucoside, solfapterin (**6**), we sought to introduce an azido group at C-2 of a glycosyl donor instead of a phthalimido group employed for preparation of limipterin (**3**).[18b] Thus, the glycosyl donors, tri-*O*-acetyl-2-azido-α-D-glucopyranosyl bromide (**21a**)[27] and its tri-*O*-benzoyl analog (**21b**) were prepared from D-glucosamine hydrochloride via the 2-azido-D-glucopyranose derivatives (**20a,b**) in three steps with a slight modification of the reported procedures[28] (Scheme 5).



Scheme 5

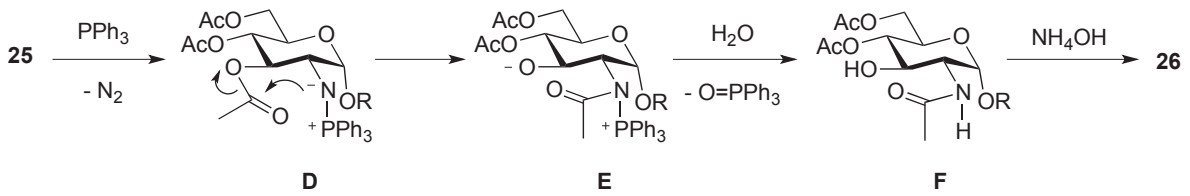
Glycosylation of the neopterin derivative (**11b**) with glycosyl donors (**21a,b**) was examined under various conditions. Treatment of **11b** with 3.0 mol equiv. of the acetate (**21a**) in the presence of silver triflate (2.0 mol equiv.) and TMU (1.0 mol equiv.) in dichloromethane at room temperature for 3 h resulted in the formation of an inseparable mixture (40:60) of the 3'-*O*-(α-D-glucopyranosyl)neopterin derivative (**22a**) and its β-anomer (**22b**) in 41% yield, along with the recovery of **11b** (48%), whereas the same reaction in the absence of TMU (to improve the reactivity) at –40 °C afforded an inseparable mixture (78:22) of **22a** and **22b** in 78% yield. Similarly, treatment of **11b** with the benzoyl analog (**21b**) in the presence of silver triflate at –40 °C afforded a 76:24 mixture of the neopterin glycosides (**23a,b**), which were then separated by column chromatography over silica gel into the desired α-D-glucopyranoside (**23a**) (58% yield) and the β-anomer (**23b**) (18%). The ^{1}H-NMR parameters of neopterin glycosides (**22a,b**, **23a,b**) are listed in Table 3.

Removal of the protecting groups of the neopterin α-D-glycoside (**23a**) was carried out by successive treatment of **23a** with sodium methoxide in methanol and then with aqueous ammonia-methanol, to give the 3-NPE-neopterin derivative (**24**) (Scheme 6). Removal of the NPE group of **24** with DBU in DMF, followed by acetylation for purification with column chromatography, provided the peracetylated drivative (**25**) in 70% (overall yield from **23a**).



Scheme 6

An attempt to reduce the azido group of **25** first by treatment with triphenylphosphine-water[29] and the following deacetylation with aqueous ammonia afforded an inseparable mixture of the desired solfapterin (**6**) and its 2-acetamido derivative (**26**). Production of **26** can be perceived as the result of the subtraction of the 3-*O*-acetyl group by the aza-ylide intermediate (**D**)[30] arising from **25** and the subsequent hydrolysis of **E** and ammonolysis of **F** (Scheme 7).



Scheme 7

Table 3. 600 MHz ^{1}H-NMR Spectral parameters for neopterin glycosides (**22a,b**, **23a,b**, **25**, **6**, **6'**)[a]

Com-Pound	Chemical shifts/δ (coupling constants/Hz)											
	Pterin moiety					Me_2NCH=N-2		NPE-N(3)				
	H-7	H-1' ($J_{1',2'}$)	H-2' ($J_{2',3'a}$)	H^a-3' ($J_{3'a,3'b}$)	H^b-3' ($J_{2',3'b}$)	Me_2N	CH=N	H(*o*) ($J_{o,m}$)	H(*m*)	$ArCH_2$ ($^3J_{H,H}$)	CH_2N ($^2J_{H,H}$)	Other signals
22a	8.98	6.68	6.15	4.17	4.14	3.22	8.83	7.40	8.13	3.14	4.58	8.09, 7.95 [Bz(*o*)]
		(5.9)	(5.3)	(11.4)	(4.1)	3.17		(8.5)		(7.8)	4.56	7.59, 7.54 [Bz(*p*)]
											(12.6)	7.45, 7.39 [Bz(*m*)]
22b	8.96	6.67	6.14	4.57	4.08	3.23	8.84	7.40	8.15	3.14	4.59	8.07, 7.95 [Bz(*o*)]
		(4.4)	(4.0)	(11.4)	(5.5)	3.18		(8.5)		(7.8)	4.57	7.59, 7.54 [Bz(*p*)]
											(12.5)	7.45, 7.41 [Bz(*m*)]
23a	9.05	6.81	6.24	4.38	4.19	3.20	8.83	7.35	8.11	3.12	4.55	8.09, 7.98 [Bz(*o*)]
		(6.2)	(4.1)	(11.4)	(3.8)	3.16		(8.5)		(7.8)	4.53	7.52, 7.51 [Bz(*p*)]
											(12.6)	7.38, 7.37 [Bz(*m*)][b]
23b	8.87	6.71	6.24	4.68	4.24	3.23	8.85	7.46	8.13	3.14	4.60	8.05, 7.97 [Bz(*o*)]
		(4.1)	(4.1)	(11.7)	(5.9)	3.18		(8.8)		(7.8)	4.58	7.58, 7.52 [Bz(*p*)]
											(12.5)	7.44, 7.38 [Bz(*m*)][c]
25	8.98	6.25	5.63	3.97	3.90	2.51 (AcN-2)		11.11 [H-N(3)]				2.18, 2.07 (Ac)[d]
		(4.7)	(5.0)	(11.4)	(4.7)	12.90 (NH-2)						
6	8.69	5.00	4.28	3.96	3.53							
		(6.5)	(5.0)	(10.6)	(4.4)							
6'	8.84	5.05	4.31	4.01	3.53							
		(6.8)	(4.9)	(10.6)	(4.4)							

	Glycosyl moiety							
	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 ($J_{5,6b}$)	Other Signals
22a	5.19	3.34	5.38	4.97	3.86	4.01	3.80	2.05, 2.00, 1.95 (Ac)
	(3.5)	(10.6)	(9.4)	(10.3)	(4.1)	(12.3)	(2.1)	
22b	4.55	3.45	4.97	4.97	3.75	4.21	4.07	2.04, 2.01, 1.98 (Ac)
	(8.2)	(10.0)	–	(10.2)	(4.4)	(12.3)	(2.0)	
23a	5.30	3.49	5.89	5.52	4.23	4.25	4.14	7.95, 7.94, 7.91 [Bz(*o*)], 7.495, 7.49, 7.48 [Bz(*p*)]
	(3.5)	(10.6)	(9.4)	(10.0)	(2.6)	(12.3)	(5.3)	7.36, 7.35, 7.30 [Bz(*m*)][b]
23b	4.98	3.75	5.57	5.49	4.23	4.55	4.35	7.93, 7.88, 7.82 [Bz(*o*)], 7.49, 7.47, 7.45 [Bz(*p*)]
	(7.9)	(10.3)	(9.4)	(10.0)	(3.2)	(12.0)	(5.6)	7.36, 7.29, 7.24 [Bz(*m*)][c]
25	5.01	3.29	5.09	4.98	3.95	4.27	4.05	2.05, 2.04, 2.01 (Ac)[d]
	(3.5)	(10.6)	(9.4)	(10.0)	(4.4)	(12.3)	(2.3)	
6	4.96	3.03	3.63	3.41	3.67	3.81	3.74	
	(3.5)	(10.3)	(9.4)	(9.7)	(2.1)	(12.3)	(5.0)	
6'	5.13	3.39	3.86	3.50	3.71	3.84	3.77	
	(3.5)	(10.6)	(9.4)	(9.7)	(2.1)	(12.3)	(5.3)	

[a] **22a,b**, **23a,b**, **25** in $CDCl_3$, **6**, **6'** in D_2O. [b–d] The assignments may have to be interchanged.

We thus performed conversion of **25** to **6** in the alternative sequence: removal of all acetyl groups of **25** with aqueous ammonia and the following reduction with triphenylphosphine-water afforded solfapterin (**6**) in 89% yield. Treatment of **6** with an ion-exchange resin Amberlite IRA96SB(Cl^-) furnished the corresponding hydrochloride (**6'**) of solfapterin. The precise parameters obtained on ^{1}H-NMR spectra of **6** and **6'** are summarized in Table 3. The spectral data of the synthetic solfapterin (**6**) were found to be essentially identical with those reported for natural product.[9]

The present work thus demonstrates the first syntheses of natural neopterin glycosides, neopterin glucronide (**5**) and solfapterin (**6**) by use of the key intermediates (**11a,b**). Extension of this work including applications of these findings in synthesizing other natural pterin glycosides and analogs is in progress.

EXPERIMENTAL

All reactions were monitored by TLC (Merck Silica gel 60 F_{254}) with an appropriate solvent system. Column chromatography was performed with Daiso Silica Gel IR-60/210w. Components were detected by exposing the plates to UV light and/or spraying them with 20% H_2SO_4-EtOH with subsequent heating. Optical rotations were measured with a JASCO P-1020 polarimeter. The ^{1}H NMR spectra were measured in $CDCl_3$ or D_2O with Varian NMR System 600 (600 MHz for ^{1}H, 151 Mz for ^{13}C) at 23 °C. Chemical shifts are reported as δ values relative to $CHCl_3$ (7.26 ppm in $CDCl_3$) and DOH (4.79 ppm in D_2O) as an internal standard for ^{1}H NMR, $CDCl_3$ (77.0 ppm in $CDCl_3$) and 1,4-dioxane (67.2 ppm in D_2O) as an internal standard for ^{13}C NMR. The assignments of ^{13}C signals were made with the aid of 2D HSQC measurements.

1',2'-Di-*O*-acetyl-3'-*O*-(*tert*-butyldimethylsilyl)-N^2-(*N,N*-dimethylaminomethylene)neopterin (9a).

To a solution of **4**[20] (1.11 g, 4.38 mmol) in DMF (15 mL) was added *N,N*-dimethylformamide dimethyl acetal (1.74 mL, 13.1 mmol). The mixture was stirred at rt for 3 h and concentrated in vacuo. The residue was dissolved in 5% MeOH-$CHCl_3$. The mixture was stirred at rt for 2 h and evaporated in vacuo. The residue was dissolved in dry pyridine (20 mL) and then *tert*-butyldimethylsilyl chloride (990 mg, 6.57 mmol) was added. The mixture was stirred at rt for 12 h (to give **8**) and then acetic anhydride (4.10 mL, 43.7 mmol) was added. The mixture was stirred at rt for 12 h, diluted with a small amount of cold water, and concentrated in vacuo. The residue was dissolved in $CHCl_3$, washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with 1:49 MeOH-$CHCl_3$ to give **9a** (1.69 g, 76% from **4**) as a yellow syrup: R_f = 0.48 (1:9 MeOH-$CHCl_3$); ^{1}H NMR ($CDCl_3$) δ –0.02, –0.01 (3H each, 2s, Me_2Si), 0.82 (9H, s, ^{t}Bu), 1.96, 2.13 (3H each, 2s, AcO-1',2'), 3.17, 3.23 (3H each, 2s, Me_2N), 3.78 (1H, dd, $J_{3'a,3'b}$ = 11.6, $J_{2',3'b}$ = 5.3 Hz, H^b-3'), 3.90 (1H, dd, $J_{2',3'b}$ = 3.7

Hz, H^a-3'), 5.45 (1H, td, $J_{1',2'}$ = 5.6 Hz, H-2'), 6.16 (1H, d, H-1'), 8.79 (1H, s, H-7), 8.97 (1H, s, NCH=N), 9.70 (1H, br s, H-N$_{(3)}$); ^{13}C NMR ($CDCl_3$) δ –5.60, –5.53 ($SiMe_2$), 18.12 ($\underline{C}Me_3$), 20.81, 20.85 ($CO\underline{C}H_3$), 25.65 ($C\underline{Me}_3$), 35.47, 41.71 (Me_2N), 61.03 (C-3'), 72.29 (C-1'), 74.26 (C-2'), 128.48 (C-4a), 147.86 (C-6), 149.55 (C-7), 156.13 (C-8a), 157.67 (C-2), 159.77 (NCH=N), 161.67 (C-4), 169.55, 169.76 ($\underline{C}OCH_3$). Anal. Calcd for $C_{22}H_{34}N_6O_6Si$: C, 52.16; H, 6.76; N, 16.59. Found: C, 52.09; H, 6.77; N, 16.69.

1',2'-Di-*O*-benzoyl-3'-*O*-(*tert*-butyldimethylsilyl)-N^2-(*N,N*-dimethylaminomethylene)neopterin (9b). The procedures similar to those for preparation of **9a** from **4** were employed. Thus, compound **4** (390 mg, 1.54 mmol) was converted into the intermediate **8**, which was then treated with benzoyl chloride (0.380 mL, 3.27 mmol) to give **9b** (721 mg, 74% yield from **4**) as a yellow foam: R_f = 0.55 (1:9 MeOH-$CHCl_3$); $[\alpha]_D^{23}$ –31.2° (*c* 1.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ –0.08, –0.03 (3H each, 2s, Me_2Si), 0.78 (9H, s, ^{t}Bu), 3.14, 3.21 (3H each, 2s, Me_2N), 3.98 (1H, dd, $J_{3'a,3'b}$ = 11.2, $J_{2',3'b}$ = 5.3 Hz, H^b-3'), 4.11 (1H, dd, $J_{2',3'a}$ = 4.4 Hz, H^a-3'), 5.93 (1H, td, $J_{1'2'}$ = 5.3 Hz, H-2'), 6.59 (1H, d, H-1'), 7.39, 7.43 (2H each, 2t, $J_{o,m} = J_{m,p}$ = 7.6 Hz, *m* of Bz), 7.52, 7.56 (1H each, 2tt, $J_{o,p}$ = 1.2 Hz, *p* of Bz), 7.95, 8.06 (2H each, dd, *o* of Bz), 8.95 (1H, s, H-7), 8.97 (1H, s, NCH=N), 9.55 (1H, br s, H-N$_{(3)}$); ^{13}C NMR ($CDCl_3$) δ = –5.60, –5.55 ($SiMe_2$), 18.08 ($\underline{C}Me_3$), 25.64 ($C\underline{Me}_3$), 35.45, 41.69 (Me_2N), 61.23 (C-3'), 73.31 (C-1'), 74.85 (C-2'), 128.43, 128.48 (*m* of Bz), 128.59 (C-4a), 129.27, 129.59 (*ipso* of Bz), 129.69, 129.89 (*o* of Bz), 133.13, 133.43 (*p* of Bz), 148.03 (C-6), 149.59 (C-7), 156.23 (C-8a), 157.66 (C-2), 159.75 (NCH=N), 161.58 (C-4), 165.17, 165.33 ($\underline{C}OPh$). Anal. Calcd for $C_{32}H_{38}N_6O_6Si$: C, 60.93; H, 6.07; N, 13.32. Found: C, 60.79; H, 6.16; N, 13.19.

1',2'-Di-*O*-acetyl-3'-*O*-(*tert*-butyldimethylsilyl)-N^2-(*N,N*-dimethylaminomethylene)-3-[2-(4-nitrophenyl)ethyl]neopterin (10a). To a solution of **9a** (314 mg, 0.620 mmol), 2-(*p*-nitrophenyl)ethanol (175 mg, 1.05 mmol) and triphenylphosphine (325 mg, 1.24 mmol) in dry THF (5.0 mL) was added DIAD (1.9 M in toluene, 0.60 mL, 1.14 mmol). The mixture was stirred at rt for 7 h and then concentrated in vacuo. The residue was purified by column chromatography with 2:1 AcOEt-hexane to give **10a** (342 mg, 84%) as a pale yellow syrup: R_f = 0.43 (AcOEt); $[\alpha]_D^{22}$ +48.0° (*c* 1.47, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.00, 0.03 (3H each, 2s, Me_2Si), 0.85 (9H, s, ^{t}Bu), 1.98, 2.15 (3H each, 2s, AcO-1',2'), 3.15 (2H, t, $^3J_{H,H}$ = 7.7 Hz, $C\underline{H}_2CH_2N$), 3.21, 3.29 (3H each, 2s, Me_2N), 3.81 (1H, dd, $J_{3'a,3'b}$ = 11.4, $J_{2',3'b}$ = 5.4 Hz, H^b-3'), 3.90 (1H, dd, $J_{2',3'b}$ = 3.9 Hz, H^a-3'), 4.57, 4.59 (2H, $^2J_{H,H}$ = 12.7 Hz, CH_2N), 5.47 (1H, ddd, $J_{1',2'}$ = 5.9 Hz, H-2'), 6.16 (1H, d, H-1'), 7.41 (2H, d, $J_{o,m}$ = 8.7 Hz, *o* of NPE), 8.14 (2H, d, *m* of NPE), 8.82 (H-7), 8.96 (1H, s, NCH=N); ^{13}C NMR ($CDCl_3$) δ = –5.57, –5.48 ($SiMe_2$), 18.15 ($\underline{C}Me_3$), 20.84, 20.87 ($CO\underline{C}H_3$), 25.68 ($C\underline{Me}_3$), 33.97

($\underline{C}H_2CH_2N$), 35.68, 41.85 (Me_2N), 43.92 (CH_2N), 61.02 (C-3') 72.30 (C-1'), 74.24 (C-2'), 123.76 (*m* of NPE), 128.48 (C-4a), 129.76 (*o* of NEP), 146.36, 146.80 (*ipso*, *p* of NPE), 148.83 (C-6), 149.59 (C-7), 156.10 (C-8a), 157.16 (C-2), 159.52 (NCH=N), 160.95 (C-4), 169.58, 169.75 ($\underline{C}OCH_3$). Anal. Calcd for $C_{30}H_{41}N_7O_8Si$: C, 54.95; H, 6.30; N, 14.95. Found: C, 54.79; H, 6.38; N, 14.78.

1',2'-Di-*O*-benzoyl-3'-*O*-(*tert*-butyldimethylsilyl)-N^2-(*N*,*N*-dimethylaminomethylene)-3-[2-(4-nitrophenyl)ethyl]neopterin (10b).

By use of the same procedures describe above, compound **9b** (233 mg, 0.369 mmol) was treated with 2-(*p*-nitrophenyl)ethanol (87.7 mg, 0.524 mmol), triphenylphosphine (196 mg, 0.747 mmol), and DIAD (1.9 M in toluene, 0.30 mL, 0.57 mmol) in dry THF (4.0 mL) to give **10b** (236 mg, 82%) as a pale yellow syrup: R_f = 0.55 (AcOEt); ^{1}H NMR ($CDCl_3$) δ –0.08, –0.02 (3H each, 2s, Me_2Si), 0.78 (9H, s, ^{t}Bu), 3.12 (2H, *t*, $^3J_{H,H}$ = 7.8 Hz, $C\underline{H}_2CH_2N$), 3.14, 3.18 (3H each, 2s, Me_2N), 4.00 (1H, dd, $J_{3'a,3'b}$ = 11.5, $J_{2',3'b}$ = 5.0 Hz, H^b-3'), 4.13 (1H, dd, $J_{2',3'a}$ = 4.4 Hz, H^a-3'), 4.57, 4.59 (1H each, $^2J_{H,H}$ = 12.8 Hz, CH_2N), 5.94 (1H, ddd, $J_{1',2'}$ = 5.6 Hz, H-2'), 6.60 (1H, d, H-1'), 7.38, 7.39 (2H each, 2t, $J_{o,m} = J_{m,p}$ = 7.8 Hz, *m* of Bz), 7.42 (2H, d, $J_{o,m}$ = 8.8 Hz, *o* of NPE), 7.53, 7.58 (1H each, 2tt, $J_{o,p}$ = 1.2 Hz, *p* of Bz), 7.95, 8.06 (2H each, dd, *o* of Bz), 8.12 (2H, d, *m* of NPE), 8.80 (1H, s, N-CH=N), 8.97 (1H, s, H-7); ^{13}C NMR ($CDCl_3$) δ –5.64, –5.57 ($SiMe_2$), 18.04 ($\underline{C}Me_3$), 25.61 ($C\underline{Me}_3$), 34.03 ($\underline{C}H_2CH_2N$), 35.38, 41.45 (Me_2N), 43.69 (CH_2N), 61.17 (C-3') 73.22 (C-1'), 74.86 (C-2'), 123.61 (*m* of NPE), 128.37, 128.45 (*m* of Bz), 129.12 (C-4a), 129.25, 129.58 (*ipso* of Bz), 129.64, 129.82 (*o* of Bz), 129.71 (*o* of NPE), 133.06, 133.37 (*p* of Bz), 146.64, 146.70 (*ipso*, *p* of NPE) 148.03 (C-6), 149.53 (C-7), 154.07 (C-8a), 157.79 (C-2), 159.13 (NCH=N), 161.48 (C-4), 165.15, 165.26 ($\underline{C}OPh$). Anal. Calcd for $C_{40}H_{45}N_7O_8Si$: C, 61.60; H, 5.82; N, 12.57. Found: C, 61.49; H, 5.91; N, 12.44.

1',2'-Di-*O*-acetyl-N^2-(*N*,*N*-dimethylaminomethylene)-3-[2-(4-nitrophenyl)ethyl]neopterin (11a) and its 1',3'-di-*O*-acetyl isomer (12).

Compound **10a** (121 mg, 0.184 mmol) was dissolved in a 3:1:1 AcOH-H_2O-THF solution (10 mL). The mixture was stirred at rt for 12 h and then concentrated in vacuo. The residue was separated by column chromatography with 1:19 MeOH-$CHCl_3$ to give **11a** (83.7 mg, 84%) and **12** (10.0 mg, 10%).

11a: Pale yellow syrup; R_f = 0.55 (1:9 MeOH-$CHCl_3$); $[\alpha]_D^{26}$ +87.0° (*c* 1.28, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.02, 2.18 (3H each, 2s, AcO-1',2'), 3.15 (2H, t, $^3J_{H,H}$ = 7.7 Hz, $C\underline{H}_2CH_2N$), 3.21, 3.28 (3H each, 2s, Me_2N), 3.24 (1H, br s, HO-3'), 3.80 (1H, dd, $J_{3'a,3'b}$ = 12.5, $J_{2',3a'}$ = 5.1 Hz, H^b-3'), 3.91 (1H, dd, $J_{2',3'b}$ = 5.3 Hz, H^a-3'), 4.56, 4.58 (1H each, 2dt, $^2J_{H,H}$ = 12.5 Hz, CH_2N), 5.49 (1H, td, $J_{1',2'}$ = 4.2 Hz, H-2'), 6.27 (1H, d, H-1'), 7.42 (2H, d, $J_{o,m}$ = 8.8 Hz, *o* of NPE), 8.14 (2H, d, *m* of NPE), 8.82 (1H, s, 7-H), 8.92 (1H, s, NCH=N); ^{13}C NMR ($CDCl_3$) δ 20.86, 20.89 ($CO\underline{C}H_3$), 33.98 ($\underline{C}H_2CH_2N$), 35.66, 41.80 (Me_2N), 43.94

(CH_2N), 60.69 (C-3') 72.95 (C-1'), 74.30 (C-2'), 123.77 (*m* of NPE), 128.19 (C-4a), 129.76 (*o* of NPE), 146.38, 146.80 (*ipso*, *p* of NPE) 147.63 (C-6), 149.49 (C-7), 153.24 (C-8a), 157.63 (C-2), 159.51 (NCH=N), 161.31 (C-4), 169.76, 170.08 ($\underline{C}OCH_3$). Anal. Calcd for $C_{24}H_{27}N_7O_8$: C, 53.23; H, 5.03; N, 18.11. Found: C, 53.09; H, 5.20; N, 18.01.

12: Pale yellow syrup; R_f = 0.50 (1:9 MeOH-$CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.09, 2.13 (3H each, 2s, AcO-1',3'), 3.14 (2H, t, $^3J_{H,H}$ = 7.5 Hz, $C\underline{H_2}CH_2N$), 3.20 (1H, s, HO-2'), 3.21, 3.29 (3H each, 2s, Me_2N), 4.29 (1H, dd, $J_{3'a,3'b}$ = 11.7, $J_{2',3'b}$ = 3.7 Hz, H^b-3'), 4.32 (1H, dd, $J_{2',3'a}$ = 5.4 Hz, H^a-3'), 4.55, 4.57 (2H, 2dt, $^2J_{H,H}$ = 12.5 Hz, CH_2N), 4.59 (1H, ddd, $J_{1',2'}$ = 7.1 Hz, H-2'), 5.97 (1H, d, H-1'), 7.41 (2H, d, $J_{o,m}$ = 8.8 Hz, *o* of NPE), 8.14 (2H, d, *m* of NPE), 8.86 (1H, s, H-7), 8.93 (1H, s, NCH=N); ^{13}C NMR ($CDCl_3$) δ 20.83, 20.88 ($CO\underline{C}H_3$), 33.91 ($\underline{C}H_2CH_2N$), 35.74, 41.91 (Me_2N), 44.00 (CH_2N), 64.77 (C-3') 70.40 (C-2'), 72.93 (C-1'), 123.78 (*m* of NPE), 128.24 (C-4a), 129.74 (*o* of NPE), 146.26, 146.81 (*ipso*, *p* of NPE) 149.20 (C-6), 150.48 (C-7), 152.63 (C-8a), 157.18 (C-2), 159.63 (NCH=N), 161.04 (C-4), 169.96, 171.18 ($\underline{C}OCH_3$). Anal. Calcd for $C_{24}H_{27}N_7O_8$: C, 53.23; H, 5.03; N, 18.11. Found: C, 53.11; H, 5.21; N, 18.25.

2',3'-Di-*O*-acetyl-N^2-(*N*,*N*-dimethylaminomethylene)-3-[2-(4-nitrophenyl)ethyl]neopterin (13) and its 3'- *O*-acetyl analog (14).

To a solution of **10a** (33.4 mg, 0.0509 mmol) in dry THF (0.4 mL) was added tetrabutylammonium fluoride (1.0 M THF solution, 0.065 mL, 0.065 mmol). The mixture was stirred at rt for 0.5 h and evaporated in vacuo. The residue was diluted with water and extracted with $CHCl_3$. The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by column chromatography with 1:19 MeOH-$CHCl_3$ to give a pale yellow syrup (22.1 mg) [R_f = 0.50–0.40 (1:9 MeOH-$CHCl_3$)], which consisted of **12** (47% yield), **13** (21%), and **14** (13%), the ratio being estimated by ^{1}H NMR.

13: ^{1}H NMR ($CDCl_3$) δ 1.99, 2.04 (3H each, 2s, AcO-2',3'), 3.14 (2H, t, $^3J_{H,H}$ = 7.5 Hz, $C\underline{H_2}CH_2N$), 3.20 (1H, s, HO-1'), 3.22, 3.29 (3H each, 2s, Me_2N), 4.27 (1H, dd, $J_{3'a,3'b}$ = 12.2, $J_{2',3'b}$ = 5.4 Hz, H^b-3'), 4.32 (1H, dd, $J_{2',3'a}$ = 2.9 Hz, H^a-3'), 4.56, 4.58 (2H, 2dt, $^2J_{H,H}$ = 12.5 Hz, CH_2N), 5.11 (1H, d, $J_{1',2'}$ = 7.1 Hz, H-1'), 5.19 (1H, ddd, H-2'), 7.41 (2H, d, $J_{o,m}$ = 8.8 Hz, *o* of NPE), 8.14 (2H, d, *m* of NPE), 8.87 (1H, s, H-7), 8.93 (1H, s, NCH=N).

14: ^{1}H NMR ($CDCl_3$) δ 2.09 (3H, 2s, AcO-3'), 3.16 (2H, t, $^3J_{H,H}$ = 7.5 Hz, $C\underline{H_2}CH_2N$), 3.22, 3.31 (3H each, 2s, Me_2N), 3.25–3.40 (2H, m, HO-1',2'), 4.12 (1H, ddd, $J_{1',2'}$ = 7.1, $J_{2',3'b}$ = 5.5, $J_{2',3'a}$ = 3.0 Hz, H-2'), 4.34 (1H, dd, $J_{3'a,3'b}$ = 12.2 Hz, H^b-3'), 4.40 (1H, dd, H^a-3'), 4.57, 4.59 (2H, 2dt, $^2J_{H,H}$ = 12.5 Hz, CH_2N), 4.90 (1H, d, H-1'), 5.19 (1H, ddd, H-2'), 7.41 (2H, d, $J_{o,m}$ = 8.6 Hz, *o* of NPE), 8.15 (2H, d, *m* of NPE), 8.96 (1H, s, NCH=N), 8.89 (1H, s, H-7).

1',2'-Di-*O*-benzoyl-N^2-(*N*,*N*-dimethylaminomethylene)-3-[2-(4-nitrophenyl)ethyl]neopterin (11b).
Compound **10b** (117 mg, 0.150 mmol) was dissolved in a 3:1:1 AcOH-H_2O-THF solution (2.0 mL). The mixture was stirred at rt for 18 h and then concentrated in vacuo. The residue was purified by column chromatography with AcOEt to give **11b** (94.9 mg, 95%) as a colorless syrup: R_f = 0.19 (AcOEt); $[\alpha]_D^{24}$ +2.3° (*c* 0.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.15 (2H, t, $^3J_{H,H}$ = 7.9 Hz, C$\underline{H_2}$CH_2N), 3.19, 3.24 (3H each, 2s, Me_2N), 3.65 (1H, br s, HO-3'), 4.01 (1H, dd, $J_{3'a,3'b}$ = 12.3, $J_{2',3'b}$ = 5.0 Hz, H^b-3'), 4.14 (1H, dd, $J_{2',3'a}$ = 5.6 Hz, H^a-3'), 4.57, 4.59 (1H each, 2dt, $^2J_{H,H}$ = 12.5 Hz, CH_2N), 5.93 (1H, td, $J_{1',2'}$ = 4.1 Hz, H-2'), 6.69 (1H, d, H-1'), 7.39, 7.44 (2H each, 2t, $J_{o,m} = J_{m,p}$ = 7.8 Hz, *m* of Bz), 7.41 (2H, d, $J_{o,m}$ = 8.8 Hz, *o* of NPE), 7.53, 7.58 (1H each, 2tt, $J_{o,p}$ = 1.2 Hz, *p* of Bz), 7.94, 8.06 (2H each, dd, *o* of Bz), 8.14 (2H, d, *m* of NPE), 8.85 (1H, s, N-CH=N), 8.97 (1H, s, H-7); ^{13}C NMR ($CDCl_3$) δ 34.07 ($\underline{C}H_2CH_2N$), 35.53, 41.63 (Me_2N), 43.89 (CH_2N), 60.98 (C-3') 73.86 (C-1'), 75.13 (C-2'), 123.74 (*m* of NPE), 128.50, 128.59 (*m* of Bz), 128.64 (C-4a), 129.02, 129.38 (*ipso* of Bz), 129.74, 129.97 (*o* of Bz), 129.77 (*o* of NPE), 133.35, 133.65 (*p* of Bz), 146.61, 146.77 (*ipso*, *p* of NPE) 147.34 (C-6), 149.46 (C-7), 154.21 (C-8a), 158.05 (C-2), 159.35 (NCH=N), 161.61 (C-4), 165.60, 165.33 ($\underline{C}$OPh). Anal. Calcd for $C_{34}H_{31}N_7O_8$: C, 61.35; H, 4.69; N, 14.73. Found: C, 61.49; H, 4.55; N, 14.56.

1',2'-Di-*O*-acetyl-N^2-(*N*,*N*-dimethylaminomethylene)-3'-*O*-(methyl 2,3,4-tri-*O*-acetyl-α-D-gluco-pyranosyluronate)-3-[2-(4-nitrophenyl)ethyl]neopterin (16) and 1',2',3'-tri-*O*-acetyl-N^2-(*N*,*N*-dimethylaminomethylene)-3-[2-(4-nitrophenyl)ethyl]neopterin (17).
To a solution of **11a** (34.1 mg, 0.0630 mmol), **15a**[22] (75.2 mg, 0.189 mmol), and TMU (0.007 mL, 0.063 mmol) in dry CH_2Cl_2 (1.5 mL) was added siver triflate (32.4 mg, 0.126 mmol). The mixture was stirred for 2.5 h in the dark, diluted with $CHCl_3$, and filtered. The filtrate was washed with aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated in vacuo. The residue was separated by column chromatography with 1:49 MeOH-$CHCl_3$ to give **16** (16.6 mg, 31%) and **17** (19.4 mg, 53%).
16: Pale yellow foam; R_f = 0.65 (1:9 MeOH-$CHCl_3$); ^{1}H-NMR ($CDCl_3$), see Table 2. Anal. Calcd for $C_{37}H_{43}N_7O_{17}$: C, 51.81; H, 5.05; N, 11.43. Found: C, 51.69; H, 5.20; N, 11.49.
17: Pale yellow syrup; R_f = 0.62 (1:9 MeOH-$CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.98, 2.03, 2.16 (3H each, 3s, AcO-1',2',3'), 3.15 (2H, t, $^3J_{H,H}$ = 7.7 Hz, C$\underline{H_2}$CH_2N), 3.19, 3.58 (3H each, 2s, Me_2N), 4.30 (1H, dd, $J_{3'a,3'b}$ = 12.2, $J_{2',3a'}$ = 5.9 Hz, H^b-3'), 4.43 (1H, dd, $J_{2',3'b}$ = 3.2 Hz, H^a-3'), 4.57, 4.59 (1H each, 2dt, $^2J_{H,H}$ = 12.5 Hz, CH_2N), 5.65 (1H, td, $J_{1',2'}$ = 6.1 Hz, H-2'), 6.17 (1H, d, H-1'), 7.41 (2H, d, $J_{o,m}$ = 8.8 Hz, *o* of NPE), 8.13 (2H, d, *m* of NPE), 8.80 (1H, s, H-7), 8.88 (1H, s, NCH=N); ^{13}C NMR ($CDCl_3$) δ 20.68, 20.72, 20.82 (CO$\underline{C}H_3$), 34.03 ($\underline{C}H_2CH_2N$), 35.57, 41.69 (Me_2N), 43.85 (CH_2N), 61.62 (C-3') 72.95 (C-2'), 74.30 (C-1'), 123.72 (*m* of NPE), 128.93 (C-4a), 129.76 (*o* of NPE), 146.52, 146.75 (*ipso*, *p* of NPE) 147.32 (C-6), 149.18 (C-7), 153.70 (C-8a), 157.79 (C-2), 159.39 (NCH=N), 161.30 (C-4), 169.52,

169.59, 170.48 (COCH$_3$). Anal. Calcd for $C_{22}H_{25}N_7O_7$: C, 52.90; H, 5.04; N, 19.63. Found: C, 53.01; H, 4.99; N, 19.52.

1',2'-Di-*O*-acetyl-N^2-(*N*,*N*-dimethylaminomethylene)-3'-*O*-(methyl 2,3,4-tri-*O*-benzoyl-α-D-gluco-pyranosyluronate)-3-[2-(4-nitrophenyl)ethyl]neopterin (18).

To a solution of **11a** (46.6 mg, 0.0861 mmol), **15b**[23] (151 mg, 0.259 mmol), and TMU (0.010 mL, 0.084 mmol) in dry CH_2Cl_2 (2.0 mL) was added siver triflate (44.3 mg, 0.172 mmol). The mixture was stirred for 2.5 h in the dark, diluted with $CHCl_3$, and filtered. The filtrate was washed with aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated in vacuo. The residue was separated by column chromatography with 1:49 MeOH-$CHCl_3$ to give **18** (57.5 mg, 64%) and **11a** (12.1 mg, 26% recovery).

18: Pale yellow foam; R_f = 0.55 (1:9 MeOH-$CHCl_3$), 0.18 (AcOEt); $[\alpha]_D^{26}$ +34.8° (*c* 3.49, $CHCl_3$); ^{1}H NMR ($CDCl_3$), see Table 2. Anal. Calcd for $C_{52}H_{49}N_7O_{17}$: C, 59.82; H, 4.73; N, 9.39. Found: C, 59.62; H, 4.91; N, 9.16.

3'-*O*-(β-D-Glucopyranosyluronic acid)neopterin (5).

To a solution of **18** (35.1mg, 0.0336 mmol) in dry pyridine (3.0 mL) was added anhydrous lithium iodide (48.4 mg, 0.361 mmol). The mixture was refluxed for 48 h and then concentrated in vacuo. The residue was dissolved in $CHCl_3$, washed with 1M hydrochloric acid and then water, dried ($NaSO_4$), and evaporated in vacuo. The residue was dissolved in dry MeOH (2.0 mL) and then sodium methoxide (28% in MeOH, 0.0013 mL, 0.052 mmol) was added. The mixture was stirred at rt for 4 h and neutralized with Amberlite IR120(H^+). The resin was filtered off and the filtrate was evaporated in vacuo to give **19** (20.6 mg) as a yellow syrup.

This syrup was dissolved in MeOH (2.0 mL) and then 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 dissolved in DMF (1.5 mL) and then DBU (0.034 mL, 0.23 mmol) was added. The mixture was stirred at rt for 18 h, diluted with water, and passed through a column of Amberlite FPC3500(H^+). The eluant was concentrated in vacuo. The residual solid was washed with $CHCl_3$ and dissolved in hot water. The solution was kept to stand at 0 °C overnight and the precipitate obtained by filtration was dried under reduced pressure to give **5** (12.0 mg, 83% from **18**) as an amorphous solid: R_f = 0 (1:9 MeOH-$CHCl_3$); $[\alpha]_D^{24}$ –1.88° (*c* 0.64, H_2O); ^{1}H NMR (D_2O), see Table 2; ^{13}C NMR (D_2O) δ 71.13 (C-3'), 71.89 (C-4*), 72.75 (C-1'), 73.30 (C-2'), 73.38 (C-2*), 75.08 (C-5*), 75.75 (C-3*), 103.29 (C-1*), 127.71 (C-4a), 149.49 (C-6), 150.07 (C-7), 153.00 (C-8a), 154.03 (C-2), 161.98 (C-4), 173.04 (C-6*), *for glycosyl moiety. Anal. Calcd for $C_{15}H_{19}N_5O_{10}$: C, 41.96; H, 4.46; N, 16.31. Found: C, 41.69; H, 4.68; N, 16.15.

2-Azido-1,3,4,6-tetra-*O*-benzoyl-2-deoxy-α,β-D-glucopyranoses (20b).

To a solution of sodium azide (667 mg, 10.1 mmol) in pyridine (10 mL) was added triflic anhydride (1.40 mL, 8.36 mmol) at 0 °C and the mixture was stirred for 2 h. The mixture containing triflic azide was added directly to a solution of D-glucosamine hydrochloride (1.50 g, 6.96 mmol), copper sulfate (38.1 mg, 0.0696 mmol) and TEA (1.85 mL, 13.9 mmol) in pyridine (8.0 mL) and water (6.0 mL) at 0 °C. The mixture was stirred at rt for 3 h and then evaporated in vacuo. The residue was dissolved in dry pyridine (10.0 mL) and then benzoyl chloride (8.0 mL) was added at 0 °C. The mixture was stirred at rt for 12 h. After adding water, the mixture was evaporated in vacuo and the residue was purified by column chromatography with 1:3 AcOEt-hexane to give an anomeric mixture (α:β = 41:59) of **20b** (4.19 g, 97%) as a colorless syrup: R_f = 0.44 (1:3 AcOEt-hexane); ^{1}H NMR ($CDCl_3$) for α-anomer δ 4.02 (1H, dd, $J_{2,3}$ = 10.6, $J_{1,2}$ = 3.7 Hz, H-2), 4.43 (1H, dd, $J_{6a,6b}$ = 12.5, $J_{5,6b}$ = 4.3 Hz, H^b-6), 4.51 (1H, ddd, $J_{4,5}$ = 10.0 Hz, H-5), 4.61 (1H, dd, $J_{5,6a}$ = 2.9 Hz, H^a-6), 5.74 (1H, t, $J_{3,4}$ = 9.8 Hz, H-4), 6.02 (1H, dd, H-3), 6.68 (1H, d, H-1), 7.35–7.55 (8H, m, *m* of Bz), 7.52–7.68 (4H, m, *p* of Bz), 7.89–8.20 (8H, m, *o* of Bz); ^{1}H NMR ($CDCl_3$) for β-anomer δ 4.13 (1H, dd, $J_{2,3}$ = 10.2, $J_{1,2}$ = 8.4 Hz, H-2), 4.29 (1H, ddd, $J_{4,5}$ = 9.8, $J_{5,6b}$ = 5.1, $J_{5,6a}$ = 2.8 Hz, H-5), 4.46 (1H, dd, $J_{6a,6b}$ = 12.7 Hz, H^b-6), 4.58 (1H, dd, H^a-6), 5.66–5.68 (2H, m, H-3,4), 6.04 (1H, d, H-1), 7.35–7.55 (8H, m, *m* of Bz), 7.52–7.68 (4H, m, *p* of Bz), 7.89–8.20 (8H, m, *o* of Bz).

2-Azido-3,4,6-tri-*O*-benzoyl-2-deoxy-α-D-glucopyranosyl bromide (21b).

To a solution of **20b** (1.00 g, 1.61 mmol) in CH_2Cl_2 (10.0 mL) and AcOEt (8.0 mL) was added titanium bromide (2.37 mg, 6.44 mmol) and the mixture was stirred at rt for 6 h. The mixture was diluted with $CHCl_3$, washed with cold water, saturated aqueous $NaHCO_3$, and then water. The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by recrystallization from AcOEt-hexane to give **21b** (801 mg, 86%) as colorless prisms: mp 142–143 °C (from AcOEt-hexane); R_f = 0.51 (1:3 AcOEt-hexane); $[\alpha]_D^{23}$ +109.5° (*c* 2.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.01 (1H, dd, $J_{2,3}$ = 10.0, $J_{1,2}$ = 3.8 Hz, H-2), 4.46 (1H, dd, $J_{6a,6b}$ = 12.6, $J_{5,6b}$ = 4.7 Hz, H^b-6), 4.64 (1H, dd, $J_{5,6a}$ = 2.6 Hz, H^a-6), 4.67 (1H, ddd, $J_{4,5}$ = 9.7 Hz, H-5), 5.69 (1H, t, $J_{3,4}$ = 10.0 Hz, H-4), 6.02 (1H, t, H-3), 6.55 (1H, d, H-1), 7.37, 7.38, 7.43 (2H each, 3t, $J_{o,m} = J_{m,p}$ = 7.8 Hz, *m* of Bz), 7.52, 7.525, 7.56 (1H each, 3tt, $J_{o,p}$ = 1.2 Hz, *p* of Bz), 7.93, 7.94, 8.03 (2H each, 3dd, *o* of Bz); ^{13}C NMR ($CDCl_3$) δ 61.85 (C-6), 62.90 (C-2), 68.34 (C-4), 71.57 (C-3), 72.91 (C-5), 87.69 (C-1), 128.36, 128.56, 129.40 (*ipso* of Bz), 128.43. 128.47, 128.48 (*m* of Bz), 129.77, 129.83, 129.93 (*o* of Bz), 133.26, 133.58, 133.68 (*p* of Bz), 165.16, 165.33, 165.92 (COPh). Anal. Calcd for $C_{27}H_{22}BrN_3O_7$: C, 55.87; H, 3.82; N, 7.24. Found: C, 55.90; H, 3.77; N, 7.05.

1',2'-Di-*O*-benzoyl-N^2-(*N*,*N*-dimethylaminomethylene)-3-[2-(4-nitrophenyl)ethyl]-3'-*O*-(3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-glucopyranosyl)neopterin (22a) and its β-anomer (22b).

A suspension of **11a** (253 mg, 0.380 mmol), silver triflate (292 mg, 1.14 mmol), and MS4A (700 mg) in dry CH_2Cl_2 (3.5 mL) was stirred at rt for 1 h in the dark and then a solution of **21a**[27] (450 mg, 1.14 mmol) in dry CH_2Cl_2 (2.0 mL) was added at –40 °C. After stirring at the same temp for 3 h, the mixture was diluted with $CHCl_3$ and filtered through celite. The filtrate was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with 1:1 AcOEt-hexane to give an inseparable mixture (290 mg), which consisted of **22a** (61% from **11b**) and **22b** (17%), the ratio being estimated by ^{1}H NMR: a pale yellow syrup; R_f = 0.45 (AcOEt), 0.51 (1:19 MeOH-$CHCl_3$); ^{1}H NMR ($CDCl_3$) see, Table 3. Anal. Calcd for $C_{46}H_{46}N_{10}O_{15}$: C, 56.44; H, 4.74; N, 14.31. Found: C, 56.28; H, 4.88; N, 14.25.

3'-*O*-(2-Azido-3,4,6-tri-*O*-benzoyl-2-deoxy-α-D-glucopyranosyl)-1',2'-di-*O*-benzoyl-N^2-(*N*,*N*-dimethylaminomethylene)-3-[2-(4-nitrophenyl)ethyl]neopterin (23a) and its β-anomer (23b).

A suspension of **11b** (153 mg, 0.230 mmol), silver triflate (177 mg, 0.689 mmol), and MS4A (380 mg) in dry CH_2Cl_2 (1.5 mL) was stirred at rt for 1 h in the dark and then a solution of **21b** (400 mg, 0.689 mmol) in dry CH_2Cl_2 (2.0 mL) was added at –40 °C. After stirring at same temperature for 3 h, the mixture was diluted with $CHCl_3$ and filtered through activated carbon. The filtrate was washed with saturated 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 **23a** (155 mg, 58% from **11b**) and **23b** (48.1 mg, 18%).

23a: Pale yellow prisms; mp 147–148 °C (from AcOEt-hexane); R_f = 0.61 (AcOEt), 0.36 (3:1 AcOEt-hexane); $[\alpha]_D^{26}$ +32.9° (*c* 1.44, $CHCl_3$); ^{1}H NMR ($CDCl_3$), see Table 3; ^{13}C NMR ($CDCl_3$) δ 34.04 ($\underline{CH_2}CH_2N$), 35.44, 41.54 (Me_2N), 43.80 (CH_2N), 61.35 (C-2*), 62.48 (C-6*), 66.43 (C-3'), 68.14 (C-5*), 69.21 (C-4*), 70.37 (C-3*), 72.54, 72.59 (C-1',2'), 98.49 (C-1*), 123.67 (*m* of NPE), 128.31, 128.35, 128.39, 128.53, 128.55 (*m* of Bz), 128.55, 128.70, 128.90, 129.01, 129.14, 129.52 (C-4a, *ipso* of Bz), 129.61, 129.71, 129.81, 129.84, 129.96, 129.96 (*o* of NPE, *o* of Bz), 133.08, 133.24, 133.42, 133.42 133.68 (*p* of Bz), 146.70, 146.76 (*ipso, p* of NPE), 147.24 (C-6), 149.96 (C-7), 154.36 (C-8a), 158.03 (C-2), 159.32 (NCH=N), 161.58 (C-4), 165.13, 165.19, 165.19, 165.35, 165.92 ($\underline{C}$OPh), *for glycosyl moiety. Anal. Calcd for $C_{61}H_{52}N_{10}O_{15}$: C, 62.88; H, 4.50; N, 12.02. Found: C, 62.71; H, 4.73; N, 12.20.

23b: Colorless syrup; R_f = 0.56 (AcOEt), 0.30 (3:1 AcOEt-hexane); $[\alpha]_D^{25}$ –15.6° (*c* 1.42, $CHCl_3$); ^{1}H NMR ($CDCl_3$), see Table 3; ^{13}C NMR ($CDCl_3$) δ 34.12 ($\underline{CH_2}CH_2N$), 35.49, 41.57 (Me_2N), 44.03 (CH_2N), 63.10 (C-6*), 64.23 (C-2*), 68.81 (C-3'), 69.66 (C-5*), 72.00 (C-4*), 72.64 (C-3*), 73.35, 73.41 (C-1',2'),

102.68 (C-1*), 123.74 (*m* of NPE), 128.21, 128.29, 128.36, 128.40, 128.57 (*m* of Bz), 128.73, 128.93, 128.99, 129.09, 129.41, 129.49 (C-4a, *ipso* of Bz), 129.58, 129.74, 129.78, 129.82, 129.87, 129.92 (*o* of NPE, *o* of Bz), 132.95, 133.22, 133.32, 133.32 133.58 (*p* of Bz), 146.74, 146.83 (*ipso, p* of NPE), 147.34 (C-6), 149.65 (C-7), 154.13 (C-8a), 158.00 (C-2), 159.31 (NCH=N), 161.61 (C-4), 165.21, 165.29, 165.45, 165.52, 165.94 (COPh), *for glycosyl moiety. Anal. Calcd for $C_{61}H_{52}N_{10}O_{15}$: C, 62.88; H, 4.50; N, 12.02. Found: C, 62.80; H, 4.66; N, 12.22.

Tri-*N*^{2}:1',2'-*O*-acetyl-3'-*O*-(3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-glucopyranosyl)neopterin (25). Compound **23a** (78.3 mg, 0.0672 mmol) was dissolved in dry 3:1 MeOH-$CHCl_3$ (1.80 mL) and sodium methoxide (28% in MeOH, 0.042 mL, 0.21 mmol) was added at 0 °C. The mixture was stirred at rt for 2 h and neutralized with Amberlite IR120(H^+). The resin was filtered off and the filtrate was evaporated in vacuo. The residue was dissolved in MeOH (1.50 mL) and then 28% aqueous ammonia solution (1.50 mL) was added. The mixture was stirred at rt for 16 h and evaporated in vacuo. The residual syrup of **24** was dissolved in DMF (2.0 mL) and then DBU (0.062 mL, 0.41 mmol) was added. The mixture was stirred at rt for 18 h, diluted with water (3.0 mL), and neutralized with Amberlite FPC3500(H^+). The resin was filtered off and the filtrate was evaporated in vacuo. The residue was dissolved in dry pyridine (2.0 mL) and then acetic anhydride (1.0 mL) was added at 0 °C. The mixture was stirred at rt for 16 h and evaporated in vacuo. The residue was purified by column chromatography with AcOEt to give **25** (32.5 mg, 70% from **23a**) as a colorless syrup: R_f = 0.42 (5:95 MeOH-$CHCl_3$), 0.30 (AcOEt); $[\alpha]_D^{26}$ +130.1° (*c* 3.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$), see Table 3; ^{13}C NMR ($CDCl_3$) δ 20.54, 20.61, 20.66, 20.71, 20.79 (OCO$\underline{C}H_3$), 25.04 (NHCO$\underline{C}H_3$), 60.70 (C-2*), 61.57 (C-6*), 65.79 (C-3'), 67.97 (C-5*), 68.12 (C-4*), 70.01 (C-3*), 71.74 (C-2'), 72.95 (C-1'), 97.96 (C-1*), 130.51 (C-4a), 149.41 (C-7), 149.69 (C-6), 154.59 (C-8a), 159.17 (C-2), 159.54 (C-4), 169.49, 169.62, 169.78, 169.78, 170.52 (O$\underline{C}OCH_3$), 173.82 (NH$\underline{C}OCH_3$), *for glycosyl moiety. Anal. Calcd for $C_{27}H_{32}N_8O_{14}$: C, 46.82; H, 4.66; N, 16.18. Found: C, 46.77; H, 4.80; N, 15.97.

3'-*O*-(2-Azido-2-deoxy-α-D-glucopyranosyl)neopterin (solfapterin) (6), its hydrochloride (6'), and 3'-*O*-(2-acetamido-2-deoxy-α-D-glucopyranosyl)neopterin (26).

A. Reduction and the following deacetylation. Compound **25** (16.2 mg, 0.0234 mmol) was dissolved in 4:1 THF-H_2O (1.00 mL) and then triphenylphosphine (12.7 mg, 0.0484 mmol) was added. The mixture was stirred at rt for 1 h and then evaporated in vacuo. The residue was dissolved in MeOH (0.40 mL) and 28% aqueous ammonia solution (0.60 mL) was added. The mixture was stirred at rt for 24 h and then evaporated in vacuo. The residue was dissolved in water and washed with $CHCl_3$. The aqueous layer was evaporated in vacuo to give a pale yellow syrup (9.1 mg), which consisted of **6** (72%

from **25**) and **26** (20%), the ratio being estimated by ^{1}H NMR: R_f = 0 (1:9 MeOH-$CHCl_3$).

26: ^{1}H NMR (D_2O) δ 1.99 (3H, s, AcN-2*), 3.44 (1H, t, $J_{3,4}$ = $J_{4,5}$ Hz, H-4*), 3.60–3.68 (3H, m, H-3*,5*, H^b-3'), 3.73 (1H, dd, $J_{6a,6b}$ = 12.3, $J_{5,6b}$ = 3.9 Hz, H^b-6*), 3.80 (1H, dd, $J_{5,6a}$ = 2.1 Hz, H^a-6*), 3.91 (1H, dd, $J_{2,3}$ = 10.8, $J_{1,2}$ = 3.7 Hz, H-2*), 3.94 (1H, dd, $J_{3'a,3'b}$ = 10.6, $J_{2',3'a}$ = 4.9 Hz, H^a-3'), 4.24 (1H, dt, $J_{1',2'}$ = 7.2, $J_{2',3'b}$ = 4.5 Hz, H-2'), 4.83 (1H, d, H-1*), 4.93 (1H, d, H-1'), 8.71 (1H, s, H-7), *for glycosyl moiety.

B. Deacetylation and the following reduction. Compound **25** (21.6 mg, 0.0312 mmol) was dissolved in MeOH (0.40 mL) and 28% aqueous ammonia solution (0.60 mL) was added. The mixture was stirred at rt for 24 h and then evaporated in vacuo. The residue was dissolved in 5:1 DMF-water (0.60 mL) and then triphenylphosphine (16.1 mg, 0.0621 mmol) was added. The mixture was stirred at rt for 48 h and concentrated in vacuo. The residue was dissolved in water and washed with $CHCl_3$. The aqueous layer was evaporated in vacuo to give **6** (11.5 mg, 89% from **25**) as a pale yellow powder: R_f = 0 (1:9 MeOH-$CHCl_3$); $[\alpha]_D^{23}$ +51.5° (*c* 0.43, H_2O); ^{1}H NMR (D_2O), see Table 3; ^{13}C NMR (D_2O) δ 52.57 (C-2*), 58.41 (C-6*), 66.04 (C-3'), 67.59 (C-4*), 69.95 (C-2'), 70.08 (C-3*), 70.21 (C-5*), 70.25 (C-1'), 95.43 (C-1*), 125.93 (C-4a), 146.24 (C-7), 147.50 (C-6), 153.37 (C-8a), 158.63 (C-2), 168.06 (C-4), *for glycosyl moiety.

Compound **6** (11.0 mg) was dissolved in water and passed through a column of Amberlite IRA96SB(Cl^-). The eluate was evaporated in vacuo to give solfapterin hydrochloride (**6'**) (11.4 mg) as pale yellow crystals: mp 207–208 °C (dec.) (from water-EtOH); $[\alpha]_D^{23}$ +77.5° (*c* 1.12, H_2O); ^{1}H NMR (D_2O), see Table 3; ^{13}C NMR (D_2O) δ 52.25 (C-2*), 58.35 (C-6*), 66.24 (C-3'), 67.51 (C-4*), 68.15 (C-3*), 69.92 (C-2'), 70.23 (C-5*), 70.47 (C-1'), 93.73 (C-1*), 125.73 (C-4a), 147.55 (C-7), 149.55 (C-6), 152.51 (C-8a), 162.56 (C-2), 174.99 (C-4), *for glycosyl moiety. Anal. Calcd for $C_{15}H_{23}ClN_6O_8$: C, 39.96; H, 6.14; N, 18.64. Found: C, 39.77; H, 6.28; N, 18.51.

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REFERENCES AND NOTES

1. T. Hanaya and H. Yamamoto, *IUBMB Life*, 2013, **65**, 330, and references cited therein.
2. H. S. Forrest, C. Van Baalen, and J. Myers, *Arch. Biochem. Biophys*., 1958, **78**, 95.
3. T. Matsunaga, J. G. Burgess, N. Yamada, K. Komatsu, S. Yoshida, and Y. Wachi, *Appl. Microbiol. Biotechnol*., 1993, **39**, 250.
4. Y. K. Choi, Y. K. Hwang, Y. H. Kang, and Y. S. Park, *Pteridines*, 2001, **12**, 121.
5. Y. Noguchi, A. Ishii, A. Matsushima, D. Haishi, K. Yasumuro, T. Moriguchi, T. Wada, Y. Kodera, M. Hiroto, H. Nishihara, M. Sekine, and Y. Inada, *Mar. Biotechnol*., 1999, **1**, 207.

6. K. W. Cha, W. Pfleiderer, and J. J. Yim, *Helv. Chim. Acta*, 1995, **78**, 600.
7. R. Suzuki and M. Goto, *J. Biochem*., 1968, **63**, 798.
8. K. Kobayashi and H. S. Forrest, *Comp. Biochem. Physiol.*, 1970, **33**, 201.
9. X. Lin and R. H. White, *J. Bacteriol*., 1988, **170**, 1396.
10. M. Ikawa, J. J. Sasner, J. F. Haney, and T. L. Foxall, *Phytochemistry*, 1995, **38**, 1229.
11. S.-H. Cho, J.-U. Na, H. Youn, C.-S. Hwang, C.-H. Lee, and S.-O. Kang, *Biochim. Biophys. Acta,* 1998, **1379**, 53.
12. H. W. Lee, C. H. Oh, A. Geyer, W. Pfleiderer, and Y. S. Park, *Biochim. Biophys. Acta*, 1999, **1410**, 61.
13. Y. Wachi, S. Yoshida, K. Komatsu, and T. Matsunaga, *Jpn. Patent*, 05,286,989, 1993 (*Chem. Abstr*., 1994, **120**, 161782t).
14. T. Saito, H. Ishikawa, Y. Hada, K. Fukui, Y. Kodera, A. Matsushima, and Y. Inada, *Dyes Pigments*, 2003, **56**, 203.
15. (a) S. Kaufman and E. E. Kaufman, '*Folates and Pterins*,' ed. by R. Blakley and S. J. Benkovic, John Wiley & Sons, New York, 1985, Vol. 2, pp. 251–352; (b) S. Kaufman and D. B. Fisher, '*Molecular Mechanisms of Oxygen Activation*,' ed. by O. Hayaishi, Academic Press, New York, 1974, pp. 285–369; (c) P. F. Fitzpatrick, *Annu. Rev. Biochem*., 1999, **68**, 355.
16. (a) N. S. Kwon, C. F. Nathan, and D. J. Stuehr, *J. Biol. Chem*., 1989, **264**, 20496; (b) M. A. Marletta, *Cell*, 1994, **78**, 927; (c) B. R. Crane, A. S. Arvai, D. K. Ghosh, C. Q. Wu, E. D. Getzoff, D. J. Stuehr, and J. A. Tainer, *Science*, 1998, **279**, 2121.
17. (a) H. Wachter, E. R. Werner, G. Reibnegger, D. Fuchs, and A. Hausen, *Pteridines*, 1989, **1**, 3; (b) A. Hausen, G. Reibnegger, B. Speck, and H. Wachter, *Transplantation*, 1984, **38**, 497; (c) G. Hoffman, S. Kenn, B. Wirleitner, C. Deetjen, S. Frede, M. Smolny, J. Rieder, D. Fuchs, G. Baier-Bitterlich, and W. Schobersberger, *Immunobiology*, 1998, **199**, 63.
18. (a) T. Hanaya, H. Baba, H. Toyota, and H. Yamamoto, *Tetrahedron*, 2009, **65**, 7989; (b) T. Hanaya, H. Baba, H. Toyota, and H. Yamamoto, *Tetrahedron*, 2008, **64**, 2090; (c) T. Hanaya, H. Baba, M. Kanemoto, and H. Yamamoto, *Heterocycles*, 2008, **76**, 635; (d) T. Hanaya, K. Ejiri, and H. Yamamoto, *Heterocycles*, 2012, **84**, 801; (e) T. Hanaya and H. Yamamoto, *Heterocycles*, 2012, **85**, 2375.
19. A part of the results concerning neopterin glucronide synthesis have been reported as a preliminary communication: T. Hanaya, T. Hattori, D. Takayama, and H. Yamamoto, *Pteridines*, 2010, **21**, 79.
20. R. Soyka and W. Pfleiderer, *Helv. Chim. Acta*, 1990, **73**, 808.
21. T. Hanaya, K. Torigoe, K. Soranaka, H. Yamamoto, Q. Yao, and W. Pfleiderer, *Pteridines*, 1995, **6**, 1.

22. G. N. Bollenback, J. W. Long, D. G. Benjamin, and J. A. Lindquist, *J. Am. Chem. Soc.*, 1955, **77**, 3310.
23. W. W. Zorbach and G. D. Valiaveedan, *J. Org. Chem*., 1964, **29**, 2462.
24. G. Wulff and G. Röhle, *Angew. Chem., Int. Ed. Engl*., 1974, **13**, 157, and references cited therein.
25. (a) J. Banoub and D. R. Bundle, *Can. J. Chem*., 1979, **57**, 2091; (b) T. Hanaya, H. Baba, K. Ejiri, and H. Yamamoto, *Heterocycles*, 2010, **80**, 1013.
26. F. Elsinger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, 1960, **43**, 113.
27. H. Paulsen, A. Richter, V. Sinnwell, and W. Stenzel, *Carbohydr. Res.*, 1978, **64**, 339.
28. R.-B. Yan, F. Yang, Y. Wu, L.-H. Zhang, and X.-S. Ye, *Tetrahedron Lett.*, 2005, **46**, 8993.
29. (a) J. D. M. Olsson and S. Oscarson, *Tetrahedron: Asymmetry*, 2009, **20**, 879; (b) M. B. Soellner, B. L. Nilsson, and R. T. Raines, *J. Am. Chem. Soc.*, 2006, **128**, 8820.
30. E. Saxon, J. I. Armstrong, and C. R. Bertozzi, *Org. Lett.*, 2000, **2**, 2141.