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Efficient total syntheses of natural pterin glycosides: limipterin and tepidopterin

Tadashi Hanaya [a,*], Hiroki Baba [a], Hiroki Toyota [a], Hiroshi Yamamoto [b]

[a] *Department of Chemistry, Faculty of Science, Okayama University, Tsushima-naka, Okayama 700-8530, Japan*
[b] *School of Pharmacy, Shujitsu University, Okayama 703-8516, Japan*

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Abstract

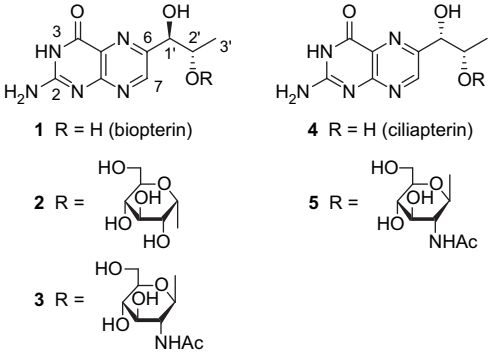
The key, versatile precursors N^2-(*N*,*N*-dimethylaminomethylene)-1′-*O*-(4-methoxybenzyl)-3-[2-(4-nitrophenyl)ethyl]biopterin (**29a**) and its ciliapterin analog (**29b**) were prepared, respectively, from D-xylose (in 14 steps) and L-xylose (in 11 steps). Treatment of **29a** and **29b** with 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl bromide in the presence of silver triflate and tetramethylurea, followed by removal of the protecting groups, led to the first selective syntheses of limipterin (**3**) and tepidopterin (**5**), respectively.

Keywords: Pteridine; Pterin glycoside; Glycosylation; Protecting group

1. 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. As representative examples for glycosides of biopterin (**1**), 2′-*O*-(α-D-glucopyranosyl)-biopterin (**2**) was isolated from cyanobacterium, *Anacystis nidulans*,[1] *Synechococcus* sp.,[2] and *Spirulina platensis*,[3] whereas limipterin [2′-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)biopterin] (**3**) was isolated from a green sulfur photosynthetic bacterium, *Chlorobium limicola f. thiosulfatophilum* NCIB 8327.[4] However, their physiological function[5] has remained obscure, in contrast to the detailed study on that of the parent biopterin, e.g., **1** exhibits enzyme cofactor activity in aromatic amino acid hydroxylation[6] and nitric oxide synthesis[7] in the form of its tetrahydro derivative.

Various other glycosides consisting of different pterins and sugar moieties have also been found in nature, although some of them have remained unclear about the glycosylated position of the pterin moiety and the anomeric structure of the glycoside.[8] Tepidopterin (**5**) was isolated from a green sulfur photosynthetic bacterium *Chlorobium tepidum* and was characterized as the 2′-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl) derivative of ciliapterin[9] (L-*threo*-biopterin) (**4**).[10] The L-*threo* structure of **4** appears somewhat peculiar in view of the tendency that biopterin derivatives having an L-*erythro* form are common among natural pterin glycosides, and thus identifying the enzyme from *C. tepidum* and elucidating the biosynthetic pathway of **4** have been attempted.[11]



Despite a considerable interest from the viewpoint of their biological activities and functions as well as structural proof,

* Corresponding author. Fax: +81 86 251 7853.
E-mail address: hanaya@cc.okayama-u.ac.jp (T. Hanaya).

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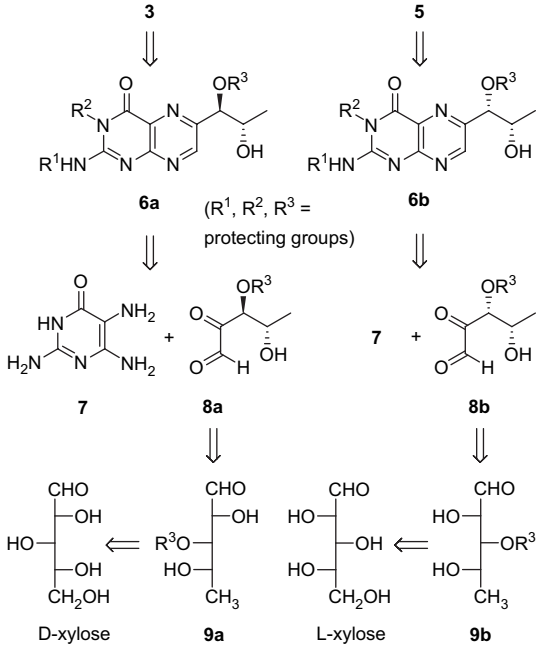


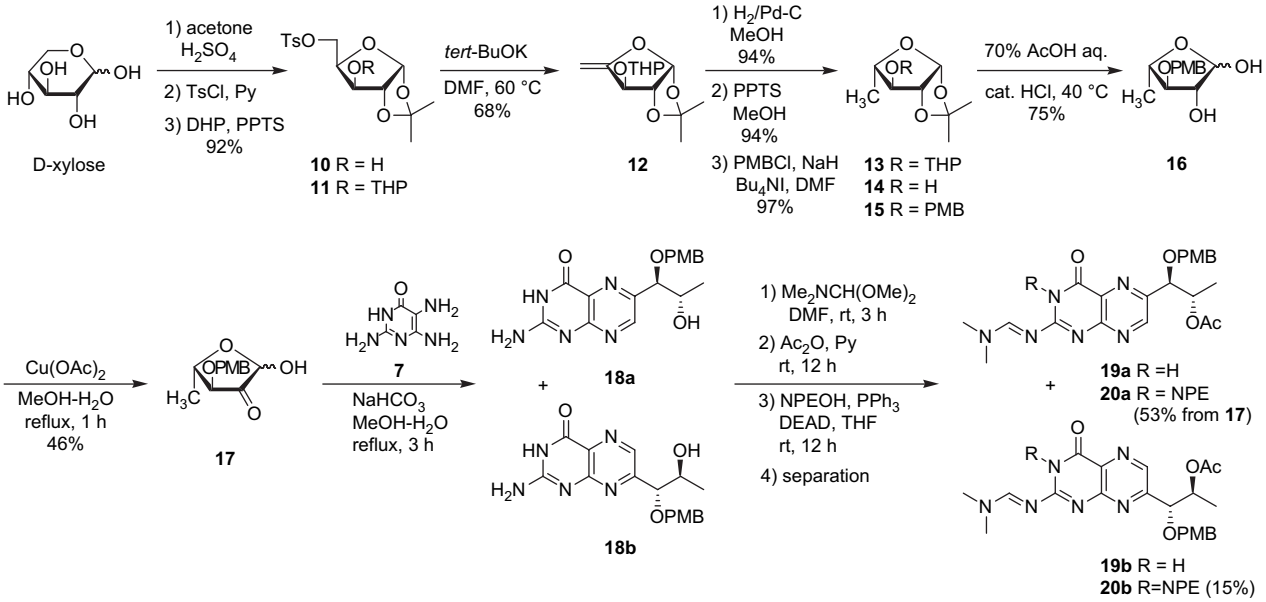
Scheme 1.

attempts at preparation of pterin glycosides have so far scarcely been made. We reported in a previous paper[12] that the glycosylation of a biopterin derivative whose two hydroxy groups were unprotected did not afford the 2′-*O*-(D-glucopyranosyl)biopterin with high regioselectivity, yielding an appreciable amount of 1′-*O*- and 1′,2′-di-*O*-(D-glucopyranosyl) derivatives as well. These facts prompted us to develop a more efficient synthetic protocol for pterin 2′-*O*-glycosides and to prove the proposed structures of the reported natural products. We give herein a full account of the first, efficient syntheses of limipterin (**3**) and tepidopterin (**5**) by glycosylation of appropriately protected biopterin and ciliapterin derivatives.[13,14]

2. Results and discussion

A retrosynthetic analysis outlined in Scheme 1 suggests that the biopterin and ciliapterin derivatives (**6a** and **6b**) can be perceived as the key precursors for **3** and **5**, respectively, to achieve selective 2′-O-glycosylation, if the pyrimidine ring moiety and 1′-hydroxy group of the side chain are suitably protected. The pteridine ring formation of **6a** would be obtained by condensation of 2,5,6-triamino-4-hydroxypyrimidine (**7**) with the L-*erythro*-pentos-2-ulose (**8a**), which would be derived from the 3-*O*-protected 5-deoxy-L-arabinose (**9a**). Compound **9a** would be available from D-xylose by inversion of C-4 configuration and deoxygenation of C-5. Similarly, compound **6b** would be obtainable from the L-*threo*-pentos-2-ulose (**8b**), which would be derived from L-xylose via the 3-*O*-protected 5-deoxy-L-xylose (**9b**). Taking into consideration the available conditions to remove the protecting groups of the glycosides derived from **6a** and **6b**, we employed *p*-methoxybenzyl (PMB) group for protection of 1′-hydroxy, *N*,*N*-dimethylaminomethylene group for 2-amino, and 2-(4-nitrophenyl)ethyl (NPE) group for N(3) of the ring.[13]

1,2-*O*-Isopropylidene-5-*O*-tosyl-α-D-xylofuranose (**10**) (available from D-xylose in 2 steps) served as the starting material for preparation of 5-deoxy-3-*O*-PMB-L-*erythro*-pentos-2-ulose (**17**), the key intermediate for the 1′-*O*-PMB-biopterin derivative (Scheme 2). Treatment of **10** with 3,4-dihydro-2*H*-pyran (DHP) in the presence of pyridinium *p*-toluenesulfonate (PPTS) afforded the 3-*O*-THP derivative (**11**)[15] (in 92% yield), which was then converted into the 5-deoxy-4-enofuranose (**12**) by the action of potassium *tert*-butoxide in DMF in 68% yield. Hydrogenation of **12** having the E_4 conformation[16] proceeded from the less hindered upper side of the ring, exclusively affording the 5-deoxy-L-arabinofuranose derivative (**13**). The 3-*O*-THP group of **13** was then cleaved with PPTS in methanol to provide **14**. Treatment of **14** with *p*-methoxybenzyl chloride and sodium hydride in DMF gave the 3-*O*-PMB derivative



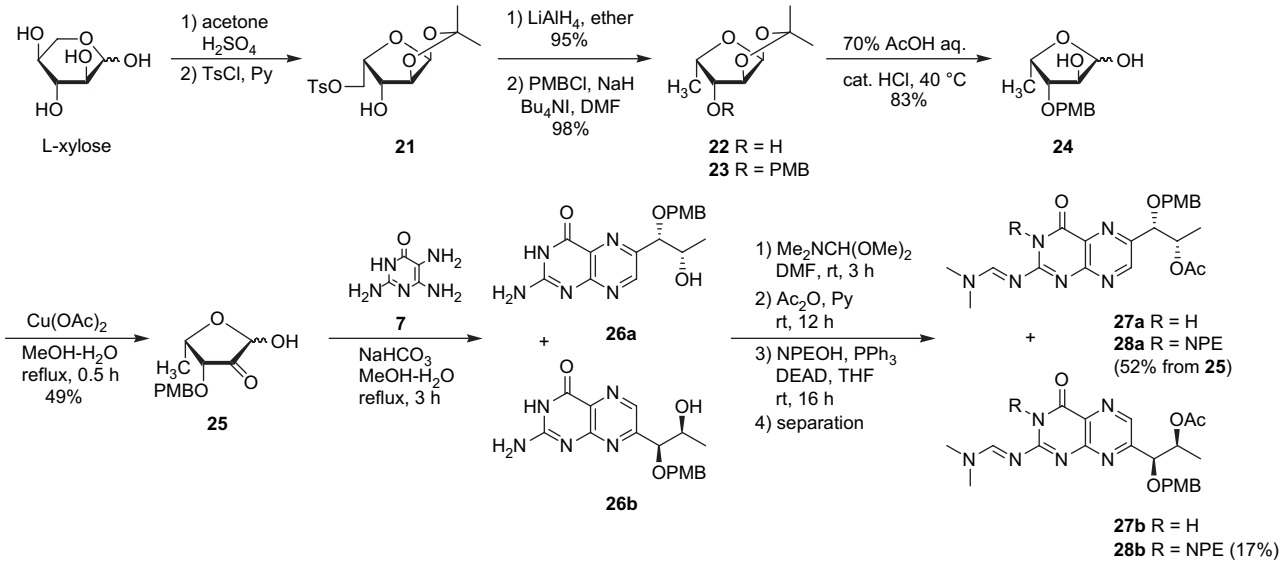
Scheme 2.

(**15**), which afforded 5-deoxy-3-*O*-PMB-L-arabinose (**16**) by hydrolysis in 70% acetic acid containing a catalytic amount of hydrochloric acid. The selective oxidation of 2-hydroxy group of **16** with cupric acetate[17] provided the L-*erythro*-pentos-2-ulose derivative (**17**).

The pteridine ring formation of **17** with monosulfate of 2,5,6-triamino-4-hydroxypyrimidine (**7**) under neutral conditions afforded an inseparable mixture (24:76) of the C-6 substituted pterin (biopterin) (**18a**) and its C-7 substituted isomer (7-biopterin)[9] (**18b**), whereas the same condensation in an aqueous sodium bicarbonate solution resulted in a predominant formation of the desired **18a** in a ratio of 78:22.[18] The difference in the major products (6- vs 7-substituted pterins) under these conditions could be explained in terms of the combination of higher electrophilicity of the C-2 carbonyl carbon (than that of the hemiacetal C-1) of **17** and basicity of the relevant two amino groups (5- and 6-) of pyrimidine **7**; under the basic conditions (pH 9–10), the most nucleophilic 5-amino group of **7** would attack the C-2 carbonyl of **17** and the subsequent pteridine ring formation would predominantly afford the 6-substituted isomer **18a**, while under the neutral conditions an attack of the 6-amino group of **7** (owing to the protonation of the 5-amino group) to the ketone **17** would preferentially take place to yield the 7-substituted isomer **18b**. These products **18a**,**b** were separated and characterized after having been converted into the fully protected derivatives (**20a**,**b**) by the following three steps: treatment of the mixture (78:22) of **18a**,**b** with *N*,*N*-dimethylformamide dimethyl acetal in DMF, followed by acetylation of a hydroxy group, afforded 2′-*O*-acetyl-N^2-(*N*,*N*-dimethylaminomethylene)-1′-*O*-PMB derivatives (**19a**,**b**), whose N(3) position was then protected with NPE group by Mitsunobu reaction with 2-(4-nitrophenyl)ethanol in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD) to give **20a** and **20b**. These products were then separated by column chromatography over silica gel into the desired biopterin derivative (**20a**, 53% overall yield from **17**) and the 7-biopterin derivative (**20b**, 15%).

On the other hand, the preparation of ciliapterin derivatives was started with 1,2-*O*-isopropylidene-5-*O*-tosyl-α-L-xylofuranose (**21**), which was easily prepared from L-xylose (Scheme 3). Reduction of **21** with lithium aluminum hydride in ether afforded the 5-deoxy derivative (**22**)[19] (in 95% yield), which was then converted into 5-deoxy-3-*O*-PMB-L-*threo*-pentos-2-ulose (**25**) via the 3-*O*-PMB derivatives (**23**, **24**) by employing the same procedures as those for **17** from **14**. The condensation of **25** with sulfate of **7** was carried out in an aqueous sodium bicarbonate solution to give an inseparable mixture (75:25) of the 6-substituted pterin (ciliapterin) derivative (**26a**) and its 7-substituted isomer (7-ciliapterin)[9] (**26b**). These products were, as in the cases of **20a**,**b** from **18a**,**b**, converted into the corresponding 2′-*O*-acetyl-N^2-(*N*,*N*-dimethylaminomethylene)-3-NPE-1′-*O*-PMB derivatives (**28a**,**b**) via **27a**,**b**. Purification of the crude products on a silica gel column provided the desired ciliapterin derivative (**28a**) (52% overall yield from **25**) and the 7-ciliapterin derivative (**28b**) (17%).

The structural assignment of the 6-substituted pterins (**20a**, **28a**) and their 7-substituted isomers (**20b**, **28b**) was made primarily on the basis of their ^{1}H and ^{13}C NMR spectral data (Tables 1 and 2). The signals of C-6 and C-7 of 6-alkylpterins generally appear at a similar field, whereas C-7 signals of 7-alkyl derivatives shift to a lower field (ca. 20 ppm) from those of C-6.[20] Thus, the close values of **20a** (C-6: δ 150.71, C-7: δ 149.88) and the distant values of **20b** (C-6: δ 140.92, C-7: δ 159.98) indicate the 6-substituted pterin for the former and the 7-substituted pterin for the latter. Similarly, the 6-substituted pterin **28a** and the 7-substituted pterin **28b** were derived from the corresponding values of **28a** (C-6: δ 151.14, C-7: δ 149.35) and **28b** (C-6: δ 140.24, C-7: δ 160.50). These assignments are supported by the fact that H-7 signals (δ 8.96) of **20a** and **28a** appear at a lower field than those of H-6 of **20b** (δ 8.78) and **28b** (δ 8.77) because



Scheme 3.

Table 1
^{1}H NMR (600 MHz) spectral parameters for 6-substituted pterins (**20a**, **28a**) and their 7-substituted isomers (**20b**, **28b**) in $CDCl_3$

Compound	Chemical shifts/δ (coupling constants/Hz)																	
	Pterin moiety					$Me_2NCH{=}N$-2		NPE-N(3)				PMBO-1′						
	H-6	H-7	H-1′ ($J_{1',2'}$)	H-2′ ($J_{2',3'}$)	H$_3$-3′	Me_2N	CH=N	H(o) ($J_{o,m}$)	H(m)	CH_2CH_2N ($^3J_{H,H}$)	CH_2N ($^2J_{H,H}$)	H(o) ($J_{o,m}$)	H(m)	CH_2O ($^2J_{H,H}$)	MeO	AcO-2′		
20a	—	8.96	4.77 (4.4)	5.36 (6.6)	1.23	3.24, 3.19	8.89	7.41 (8.7)	8.13	3.17 (7.6)	4.61, 4.59 (12.5)	7.22 (8.7)	6.84	4.51, 4.48 (11.5)	3.79	1.96		
20b	8.78	—	4.66 (4.2)	5.37 (6.6)	1.22	3.23, 3.18	8.86	7.42 (8.6)	8.14	3.18 (7.7)	4.62	7.21 (8.6)	6.84	4.55, 4.46 (11.7)	3.79	1.97		
28a	—	8.96	4.78 (3.9)	5.20 (6.6)	1.28	3.24, 3.19	8.87	7.42 (8.7)	8.14	3.17 (7.6)	4.61, 4.595 (12.2)	7.22 (8.7)	6.84	4.57, 4.37 (11.7)	3.79	1.96		
28b	8.77	—	4.60 (3.7)	5.24 (6.6)	1.28	3.22, 3.18	8.86	7.42 (8.5)	8.13	3.17 (7.7)	4.605	7.21 (8.7)	6.83	4.61, 4.34 (11.5)	3.78	1.92		

of the lower electron density of C-7 than that of C-6 due to the conjugation with the 4-oxo group.[21]

Methanolysis of 2′-*O*-acetyl-1′-*O*-PMB-biopterin and ciliapterin derivatives (**20a** and **28a**) in the presence of sodium methoxide provided their 1′-*O*-PMB derivatives (**29a** and **29b**), respectively (Scheme 4). These compounds are versatile precursors for the 2′-O-monoglycosylation. Thus, glycosylation of **29a** and **29b** was accomplished by the condensation with 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl bromide[22] in the presence of silver triflate and tetramethylurea (TMU) in dichloromethane at room temperature for 3 h, affording the 2′-*O*-(β-D-glucopyranosyl)biopterin derivative (**30a**, 82%) and the ciliapterin derivative (**30b**, 92%), respectively. The anomeric configurations of these products were assigned on the evidence of their $J_{1,2}$ values (8.5 Hz).

Removal of the protecting groups of **30a** and **30b** was conducted as follows. First, cleavage of the PMB group of **30a** and **30b** was performed by use of DDQ to afford **31a** (87%) and **31b** (89%), respectively. These were treated with methylamine to remove the phthaloyl, *N*,*N*-dimethylaminomethylene, and acetyl groups and were then acetylated with acetic anhydride in pyridine to give the fully-acetylated derivatives **32a** (91%) and **32b** (85%), respectively. Treatment of **32a** with aqueous ammonia (to cleave acetyl groups except for 2-acetamido of the sugar moiety) and then with DBU (to cleave the NPE group) furnished limipterin (**3**) in 94% overall yield, while the similar treatment of **32b** afforded tepidopterin (**5**) in 85% yield. The spectral data of the synthetic compounds **3** and **5** were found to be essentially identical with those reported for the natural product (Table 3).[4,10,23]

3. Conclusion

The present work demonstrates a novel effective way for preparation of the pterin 2′-*O*-glycosides via N^2-(*N*,*N*-dimethylaminomethylene)-1′-*O*-PMB-3-NPE-pterin derivatives (**29a** and **29b**). By employing this synthetic strategy for representative natural pterin glycosides, the first efficient, total syntheses of limipterin (**3**) and tepidopterin (**5**) were achieved. The 1′-*O*-PMB-biopterin compound (**29a**) derived from D-xylose and its ciliapterin analog (**29b**) derived from L-xylose are thus regarded as highly useful precursors for other pterin glycosides having various types of sugar moiety.

4. Experimental

4.1. General procedures

All reactions were monitored by TLC (Merck Silica gel 60 F_{254}) with an appropriate solvent system [(*A*) 1:4, (*B*) 1:2, (*C*) 1:1 AcOEt–hexane, (*D*) AcOEt, (*E*) 1:9 MeOH–$CHCl_3$, and (*F*) 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

Table 2
^{13}C NMR (151 MHz) spectral parameters for 6-substituted pterins (**20a**, **28a**) and their 7-substituted isomers (**20b**, **28b**) in $CDCl_3$

Compound	Chemical shifts/δ												
	C-2	C-4	C-4a	C-6	C-7	C-8a	C-1′	C-2′	C-3′	NCH=N	Me_2N	$COCH_3$	$COCH_3$
20a	157.55	161.83	128.36	150.71	149.88	153.63	82.21	71.76	15.92	159.31	41.61, 35.51	170.04	21.10
20b	157.88	161.83	129.29	140.92	159.98	153.17	82.26	71.94	15.61	159.24	41.55, 35.51	169.96	21.11
28a	157.56	161.78	128.90	151.14	149.35	153.90	82.05	72.11	16.43	159.24	41.60, 35.49	170.15	21.01
28b	157.83	161.79	129.35	140.24	160.50	153.44	82.33	71.92	16.61	159.19	41.52, 35.49	170.10	20.96

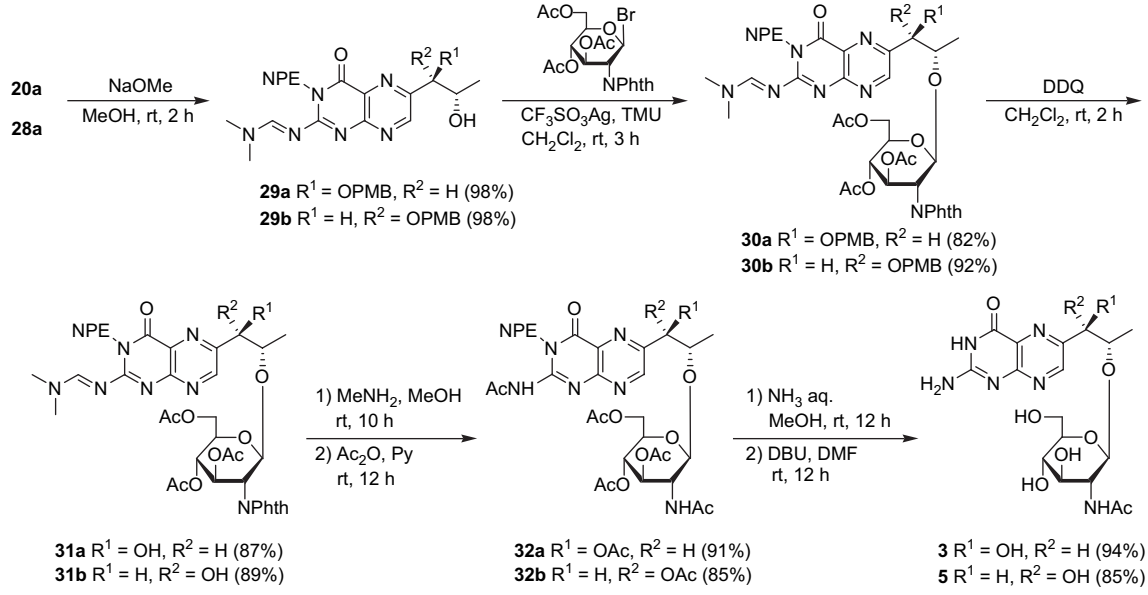
Compound	Chemical shifts/δ											
	NPE–N(3)						PMBO–1′					
	C(*ipso*)[a]	C(*o*)	C(*m*)	C(*p*)[a]	CH_2CH_2N	CH_2N	C(*ipso*)	C(*o*)	C(*m*)	C(*p*)	CH_2O	MeO
20a	146.63	129.78	123.71	146.78	34.13	43.26	129.40	129.52	113.84	159.37	71.81	55.26
20b	146.66	129.79	123.70	146.78	34.15	43.71	129.16	129.64	113.86	159.43	71.98	55.26
28a	146.66	129.79	123.70	146.73	34.11	43.75	129.11	129.78	113.82	159.43	72.09	55.25
28b	146.63	129.76	123.67	146.70	34.10	43.66	128.72	130.01	113.82	159.48	71.94	55.22

[a] The assignments may have to be interchanged.

polarimeter in $CHCl_3$. The NMR spectra were measured in $CDCl_3$ with Varian Unity Inova AS600 (600 MHz for ^1H, 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 ^1H, 77.00 for ^{13}C; in DMSO-d_6, δ 2.50 for ^1H, 39.70 for ^{13}C. The assignments of ^{13}C signals were made with the aid of 2D C–H COSY measurements.

*4.2. 1,2-O-Isopropylidene-3-O-(tetrahydropyran-2-yl)-5-O-tosyl-α-D-xylofuranose (**11**)*[15]

A solution of **10** (1.88 g, 5.46 mmol) and DHP (2.30 g, 27.4 mmol) in dry CH_2Cl_2 (20 mL) containing PPTS (140 mg, 0.557 mmol) was stirred at rt for 4 h. The solution was diluted with $CHCl_3$, washed once with saturated brine, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with a gradient eluent of 1:4 to 1:2 AcOEt–hexane to give **11** (2.15 g, 92%) as colorless crystals; mp 91–93 °C (lit.[15] mp 93–94 °C, 68% yield by use of DHP–TsOH); R_f=0.43, 0.39 [(*B*), two diastereomers with respect to the THP group]. ^1H NMR for the faster-eluting diastereomer δ 1.285, 1.435 (3H each, 2s, CMe_2), 1.40–1.75 (6H, m, $(CH_2)_3$), 2.445 (3H, s, CH_3C_6–S), 3.51, 3.88 (1H each, 2 m, CH_2O–C–O-3), 4.12 (1H, dd, $J_{5,5}$=9.5, $J_{4,5'}$=5.6 Hz, H′-5), 4.12 (1H, d, $J_{3,4}$=3.2, $J_{2,3}$=0 Hz, H-3), 4.26 (1H, dd, $J_{4,5}$=7.3 Hz, H-5), 4.34 (1H, ddd, H-4), 4.52 (1H, m, CH–O-3), 4.73 (1H, d, $J_{1,2}$=3.4 Hz, H-2), 5.84 (1H, d, H-1), 7.35, 7.79 (2H each, 2d, $J_{o,m}$=8.3 Hz, C_6H_4–S). ^1H NMR for the slower-eluting diastereomer: δ 1.29, 1.44 (3H each, 2s, CMe_2), 1.40–1.75 (6H, m, $(CH_2)_3$), 2.45 (3H, s, CH_3C_6–S), 3.51, 3.74 (1H each, 2 m, CH_2O–C–O-3), 4.21 (1H, dd, $J_{5,5}$=10.0, $J_{4,5'}$=6.1 Hz, H′-5), 4.30 (1H, d, $J_{3,4}$=3.4, $J_{2,3}$=0 Hz, H-3), 4.38 (1H, ddd, $J_{4,5}$=5.1 Hz, H-4), 4.415 (1H, dd, H-5), 4.775 (1H, d, $J_{1,2}$=3.7 Hz, H-2), 4.70 (1H, m, CH–O-3), 5.845 (1H, d, H-1), 7.34, 7.81 (2H each, 2d, $J_{o,m}$=8.3 Hz, C_6H_4–S).



Scheme 4.

Table 3
^{1}H NMR (600 MHz) spectral parameters for limipterin (**3**) and tepidopterin (**4**) in DMSO-d_6[a]

Compound	Chemical shifts/δ (coupling constants/Hz)																
	Pterin moiety							Glycosyl moiety[b]									
	H-7	H-1′ ($J_{1',2'}$)	H-2′ ($J_{2',3'}$)	H$_3$-3′	H$_2$N-2	H-N(3)	HO-1′ ($J_{1',OH}$)	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 ($J_{5,6b}$)	H^b-6 ($J_{6a,6b}$)	Ac	NH-2 ($J_{2,NH}$)
3	8.66	4.53 (4.9)	4.07 (6.4)	1.10	7.31	10.12	5.50 (5.2)	4.42 (8.6)	3.33 (9.9)	3.22 (8.8)	3.02 (9.4)	3.06 (1.4)	3.68 (5.9)	3.43 (12.3)	1.70	7.54 (8.8)
3[c]	8.76	4.65 (6.2)	4.18 (6.2)	1.21	[d]	[d]	[d]	4.53 (8.4)	3.45 (9.3)	3.33 (8.9)	3.12 (9.3)	3.17 (1.0)	3.78 (5.8)	3.53 (12.5)	1.81	[d]
4	8.65	4.59 (4.4)	4.01 (6.4)	1.12	6.99	11.55	5.31 (5.3)	4.32 (8.3)	3.32 (9.9)	3.20 (8.6)	3.02 (9.5)	3.05 (2.0)	3.67 (6.1)	3.42 (11.7)	1.71	7.42 (8.8)

[a] The solvent peak (δ 2.50) was used as an internal standard and the assignments were made with the aid of D_2O exchange and 2D C–H COSY measurements.
[b] δ 4.25–5.05 (m, HO-3,4,6).
[c] Data of natural product (Ref. 4). Chemical shifts were reported relative to TMS (δ 0) as an external standard.
[d] Not reported.

*4.3. 5-Deoxy-1,2-O-isopropylidene-3-O-(tetrahydropyran-2-yl)-β-L-threo-pent-4-enofuranose (**12**)*

To a solution of **11** (200 mg, 0.467 mmol) in dry DMF (4.0 mL) was added potassium *tert*-butoxide (200 mg, 1.78 mmol) at rt. The mixture was stirred at 60 °C for 8 h. After cooling, the mixture was diluted with aqueous NH_4Cl and extracted with $CHCl_3$ several times. The combined organic layer was washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with 1:4 AcOEt–hexane to give **12** (81.0 mg, 68%) as a colorless syrup; R_f=0.50, 0.46 [(*A*), two diastereomers with respect to the THP]. ^{1}H NMR for the faster-eluting diastereomer δ 1.385, 1.47 (3H each, 2s, CMe_2), 1.52–1.80 (6H, m, $(CH_2)_3$), 3.55, 3.83 (1H each, 2 m, CH_2O–C–O-3), 4.24 (1H, d, $J_{5E,5Z}$=1.7 Hz, H(*E*)-5), 4.56 (1H, s, $J_{2,3}$=0 Hz, H-3), 4.60 (1H, d, H(*Z*)-5), 4.605 (1H, d, $J_{1,2}$=3.2 Hz, H-2), 4.87 (1H, m, CH–O-3), 6.06 (1H, d, H-1); ^{1}H NMR for the slower-eluting diastereomer δ 1.38, 1.465 (3H each, 2s, CMe_2), 1.48–1.80 (6H, m, $(CH_2)_3$), 3.53, 3.88 (1H each, 2 m, CH_2O–C–O-3), 4.29 (1H, d, $J_{5E,5Z}$=1.7 Hz, H(*E*)-5), 4.53 (1H, d, $J_{1,2}$=3.4, $J_{2,3}$=0 Hz, H-2), 4.595 (1H, s, H-3), 4.60 (1H, d, H(*Z*)-5), 4.82 (1H, m, CH–O-3), 6.055 (1H, d, H-1). Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.79; H, 7.98.

*4.4. 5-Deoxy-1,2-O-isopropylidene-3-O-(tetrahydropyran-2-yl)-β-L-arabinofuranose (**13**)*

Compound **12** (545 mg, 2.13 mmol) dissolved in MeOH (15 mL) was hydrogenated in the presence of 10% Pd–C (400 mg, 0.38 mmol) at rt under an atmospheric pressure of H_2. After 8 h, the catalyst was filtered off and the filtrate was evaporated in vacuo. The residue was purified by column chromatography with 1:4 AcOEt–hexane to give **13** (516 mg, 94%) as a colorless syrup; R_f=0.45 (*A*). ^{1}H NMR (54:46* diastereomeric mixture with respect to the THP) δ 1.33, 1,335*, 1.54*, 1.545 (6H, 4s, CMe_2), 1.405, 1.42* (3H, 2d, $J_{4,5}$=6.8, 6.6* Hz, H-5), 1.50–1.82, 1.50–1.82* (6H, m, $(CH_2)_3$), 3.54, 3.54*, 3.82*, 3.89 (1H each, 3 m, CH_2O–C–O-3), 4.01, 4.04* (1H, 2dd, $J_{3,4}$=2.7, 3.7*, $J_{2,3}$=1.0, 1.0*, H-3), 4.14, 4.145* (1H, 2qd, H-4), 4.52*, 4.70 (1H, 2dd, $J_{1,2}$=4.1, 4.1* Hz, H-2), 4.67, 4.75* (1H, m, CH–O-3), 5.83*, 5.85 (1H, 2d, H-1). Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.29; H, 8.71.

*4.5. 5-Deoxy-1,2-O-isopropylidene-β-L-arabinofuranose (**14**)*

A solution of **13** (516 mg, 2.00 mmol) dissolved in MeOH (20 mL) containing PPTS (110 mg, 0.44 mmol) was refluxed for 1 h. After cooling, the mixture was evaporated in vacuo. The residue was purified by column chromatography with 1:2 AcOEt–hexane to give **14** (329 mg, 94%) as colorless prisms; mp 78–79 °C (from AcOEt–hexane); $[\alpha]_D^{18}$ −15.2 (*c* 1.86); R_f=0.07 (*A*), 0.19 (*B*); ^{1}H NMR δ 1.33, 1.54 (3H each, 2s, CMe_2), 1.42 (3H, d, $J_{4,5}$=6.8 Hz, H-5), 1.87 (1H, br s, HO-3), 4.07 (1H, dd, $J_{3,4}$=2.7, $J_{2,3}$=0.8 Hz, H-3), 4.09 (1H, qdd, $J_{2,4}$=0.8 Hz, H-4), 4.53 (1H, dt, $J_{1,2}$=4.1 Hz, H-2), 5.89 (1H, d, H-1); ^{13}C NMR δ 19.76 (C-5), 26.23, 26.85 (Me_2C), 80.02 (C-4), 83.63 (C-3),

87.51 (C-2), 105.51 (C-1), 112.61 (Me_2C). Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.02; H, 8.19.

4.6. 5-Deoxy-1,2-O-isopropylidene-3-O-(4-methoxybenzyl)-β-L-arabinofuranose (15)

Compound **14** (289 mg, 1.66 mmol), *p*-methoxybenzyl chloride (0.450 mL, 3.30 mmol), and tetrabutylammonium iodide (180 mg, 0.49 mmol) were dissolved in DMF (10 mL) and with stirring, sodium hydride (60% in mineral oil, 130 mg, 3.25 mmol) was added at 0 °C under argon. The mixture was stirred at rt for 2 h, diluted with saturated NH_4Cl (5 mL), and evaporated 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 1:4 AcOEt–hexane to give **15** (474 mg, 97%) as a colorless syrup. $[\alpha]_D^{21}$ −26.1 (*c* 1.28); R_f=0.35 (*A*), 0.58 (*B*). ^{1}H NMR δ 1.35, 1.54 (3H each, 2s, CMe_2), 1.37 (3H, d, $J_{4,5}$=6.6 Hz, H-5), 3.73 (1H, dd, $J_{3,4}$=3.9, $J_{2,3}$=1.2 Hz, H-3), 3.81 (3H, s, MeO), 4.12 (1H, qd, H-4), 4.48, 4.57 (1H each, 2d, J=11.5 Hz, CH_2O-3), 4.62 (1H, dd, $J_{1,2}$=4.2 Hz, H-2), 5.83 (1H, d, H-1), 6.88, 7.26 (2H each, 2d, $J_{o,m}$=8.7 Hz, C_6H_4); ^{13}C NMR δ 19.96 (C-5), 26.56, 27.20 (Me_2C), 55.26 (MeO), 71.49 (CH_2O), 80.32 (C-4), 85.63 (C-3), 86.89 (C-2), 105.33 (C-1), 112.89 (Me_2C), 113.87 (C(*m*) of PMB), 129.39 (C(*ipso*) of PMB), 129.40 (C(*o*) of PMB), 159.37 (C(*p*) of PMB). Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.38; H, 7.39.

4.7. 5-Deoxy-3-O-(4-methoxybenzyl)-α,β-L-arabinofuranoses (16)

A solution of **15** (200 mg, 0.679 mmol) in 70% AcOH (10 mL) containing 0.1 M HCl (0.50 mL) was heated at 40 °C for 12 h. After addition of pyridine (0.20 mL), the mixture was evaporated in vacuo. The residue was purified by column chromatography to give an inseparable anomeric mixture (α/β=39:61) of **16** (129 mg, 75%) as a colorless syrup; R_f=0.15 (*C*), 0.54 (*D*). ^{1}H NMR for α-anomer δ 1.32 (3H, d, $J_{4,5}$=6.4 Hz, H_3-5), 1.88, 3.30 (1H each, 2br s, HO-1,2), 3.57 (1H, ddd, $J_{3,4}$=3.9, $J_{2,3}$=2.0, $J_{1,3}$=1.0 Hz, H-3), 3.81 (3H, s, MeO), 4.19 (1H, d, $J_{1,2}$=0 Hz, H-2), 4.34 (1H, qd, H-4), 4.55, 4.56 (1H each, 2d, ^2J=11.5 Hz, CH_2O-3), 5.23 (1H, br d, H-1), 6.89, 7.25 (2H each, 2d, $J_{o,m}$=8.7 Hz, C_6H_4); ^{1}H NMR for β-anomer δ 1.35 (3H, d, $J_{4,5}$=6.6 Hz, H_3-5), 2.54, 3.48 (1H each, 2br s, HO-1,2), 3.67 (1H, dd, $J_{3,4}$=6.0, $J_{2,3}$=5.2 Hz, H-3), 3.81 (3H, s, MeO), 3.95 (1H, quint, H-4), 4.16 (1H, dd, $J_{1,2}$=4.4 Hz, H-2), 4.57, 4.68 (1H each, 2d, ^2J=11.5 Hz, CH_2O-3), 5.29 (1H, d, H-1), 6.88, 7.28 (2H, d, $J_{o,m}$=8.7 Hz, C_6H_4). Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.41; H, 7.13. Found: C, 61.26; H, 7.02.

4.8. 5-Deoxy-3-O-(4-methoxybenzyl)-α,β-L-erythro-pentos-2-uloses (17)

Compound **16** (242 mg, 0.952 mmol) was dissolved in MeOH (6 mL) and water (3 mL). The solution was refluxed and then cupric acetate hydrate (1.02 g, 5.03 mmol) was added. The mixture was refluxed for 1 h and then precipitates were filtered off and washed with ethyl acetate. The filtrate was concentrated in vacuo and the residue was separated by column chromatography with 1:2 AcOEt–hexane to give **17** (110 mg, 46% yield) as a colorless syrup; R_f=0.24–0.33 (*C*); from the slower-eluting fraction, compound **16** (58.2 mg, 23%) was recovered.

4.9. 2′-O-Acetyl-N^2-(N,N-dimethylaminomethylene)-1′-O-(4-methoxybenzyl)biopterin (19a) and its 7-biopterin isomer (19b)

Compound **17** (395 mg, 1.57 mmol) was dissolved in MeOH (11 mL), and a solution of 2,5,6-triamino-4-hydroxypyrimidine sulfate (450 mg, 1.88 mmol) and $NaHCO_3$ (263 mg, 3.13 mmol) dissolved in water (9 mL) was added. The mixture was refluxed for 3.5 h and then evaporated in vacuo. The residue was dissolved in DMF and sodium sulfate was filtered off. The filtrate was concentrated in vacuo to give a mixture of 1′-*O*-(4-methoxybenzyl)biopterin (**18a**) and 1′-*O*-(4-methoxybenzyl)-7-biopterin (**18b**); R_f=0.15 (*E*).

The mixture of **18a**,**b** was dissolved in dry DMF (8 mL) and then *N*,*N*-dimethylformamide dimethyl acetal (0.50 mL, 3.75 mmol) was added. The mixture was stirred at rt for 3 h and concentrated in vacuo. The residue was dissolved in dry pyridine (15 mL) and acetic anhydride (6.0 mL, 63 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 (78:22) of the biopterin derivative (**19a**) and its 7-biopterin isomer (**19b**) (554 mg, 78% yield from **17**) as a pale yellow foam; R_f=0.45 (*E*). ^{1}H NMR for **19a** δ 1.23 (3H, d, $J_{2',3'}$=6.4 Hz, H_3-3′), 1.96 (3H, s, AcO-2′), 3.19, 3.25 (3H each, 2s, Me_2N), 3.79 (3H, s, MeO), 4.47, 4.50 (1H each, 2d, ^2J=11.6 Hz, CH_2O-1′), 4.75 (1H, d, $J_{1',2'}$=4.5 Hz, H-1′), 5.35 (1H, qd, H-2′), 6.84, 7.21 (2H each, 2d, $J_{o,m}$=8.7 Hz, C_6H_4), 8.97 (1H, s, H-7), 9.00 (1H, s, CH=N-2); ^{1}H NMR for **19b** δ 1.22 (3H, d, $J_{2',3'}$=6.4 Hz, H_3-3′), 1.97 (3H, s, AcO-2′), 3.19, 3.24 (3H each, 2s, Me_2N), 3.79 (3H, s, MeO), 4.45, 4.54 (1H each, 2d, ^2J=11.6 Hz, CH_2O-1′), 4.64 (1H, d, $J_{1',2'}$=4.2 Hz, H-1′), 5.35 (1H, qd, H-2′), 6.84, 7.21 (2H each, 2d, $J_{o,m}$=8.7 Hz, C_6H_4), 8.76 (1H, s, H-6), 9.00 (1H, s, CH=N-2).

4.10. 2′-O-Acetyl-N^2-(N,N-dimethylaminomethylene)-1′-O-(4-methoxybenzyl)-3-[2-(4-nitrophenyl)ethyl]biopterin (20a) and its 7-biopterin isomer (20b)

To a solution of **19a**,**b** (554 mg, 1.22 mmol), 2-(*p*-nitrophenyl)ethanol (285 mg, 1.70 mmol) and triphenylphosphine (630 mg, 2.41 mmol) in dry THF (20 mL), was added DEAD (0.390 mL, 2.12 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 **20a** (502 mg, 53% yield from **17**) and **20b** (142 mg, 15% yield).

Compound **20a**: Pale yellow solid; R_f=0.25 (*D*); $[\alpha]_D^{29}$ −60.6 (*c* 1.22). ^{1}H and ^{13}C NMR, see Tables 1 and 2. Anal. Calcd for $C_{30}H_{33}N_7O_7$: C, 59.69; H, 5.51. Found: C, 59.51; H, 5.60.

Compound **20b**: Pale yellow solid; R_f=0.35 (*D*); $[\alpha]_D^{29}$ −22.8 (*c* 1.14). ^{1}H and ^{13}C NMR, see Tables 1 and 2. Anal. Calcd for $C_{30}H_{33}N_7O_7$: C, 59.69; H, 5.51. Found: C, 59.48; H, 5.69.

4.11. 5-Deoxy-1,2-O-isopropylidene-α-L-xylofuranose (22)[18]

The following modification of the literature procedures[17] was made. To a solution of **21** (947 mg, 2.75 mmol) in dry ether (15 mL), lithium aluminum hydride (210 mg, 5.55 mmol) was added at 0 °C under argon. The mixture was stirred at rt for 6 h, and then water was added. The precipitates were filtered off and washed with $CHCl_3$. The filtrate was washed with aqueous NaCl, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with 1:2 AcOEt–hexane to give **22** (455 mg, 95%) as colorless needles; mp 68–69 °C (from 1:1 AcOEt–hexane) (lit.[18] mp 70–72 °C, 79% yield); R_f=0.42 (*C*).

4.12. 5-Deoxy-1,2-O-isopropylidene-3-O-(4-methoxybenzyl)-α-L-xylofuranose (23)

By use of same procedures as described for **15** from **14**, compound **22** (455 mg, 2.61 mmol) was treated with *p*-methoxybenzyl chloride (0.71 mL, 5.2 mmol), tetrabutylammonium iodide (290 mg, 0.79 mmol), and sodium hydride (60% in mineral oil, 207 mg, 5.2 mmol) in DMF (15 mL) to give **23** (751 mg, 98%) as a colorless syrup; R_f=0.34 (*A*), 0.58 (*B*); $[\alpha]_D^{28}$ +50.9 (*c* 1.26). ^{1}H NMR δ 1.29 (3H, d, $J_{4,5}$= 6.6 Hz, H-5), 1.31, 1.48 (3H each, 2s, CMe_2), 3.70 (1H, d, $J_{3,4}$=3.2 Hz, $J_{2,3}$=0 Hz, H-3), 3.81 (3H, s, MeO), 4.30 (1H, qd, H-4), 4.44, 4.63 (1H each, 2d, *J*=12.0 Hz, CH_2O-3), 4.60 (1H, dd, $J_{1,2}$=3.9 Hz, H-2), 5.89 (1H, d, H-1), 6.87, 7.25 (2H each, 2d, $J_{o,m}$=8.8 Hz, C_6H_4); ^{13}C NMR δ 13.27 (C-5), 26.16, 26.24 (Me_2C), 55.27 (MeO), 71.42 (CH_2O), 76.13 (C-4), 82.29 (C-3), 82.79 (C-2), 104.73 (C-1), 111.16 (Me_2C), 113.81 (C(*m*) of PMB), 129.25 (C(*o*) of PMB), 129.73 (C(*ipso*) of PMB), 159.31 (C(*p*) of PMB). Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.38; H, 7.39.

4.13. 5-Deoxy-3-O-(4-methoxybenzyl)-α,β-L-xylofuranoses (24)

By use of same procedures as described for **16** from **15**, compound **23** (138 mg, 0.469 mmol) was treated with 70% AcOH (5.0 mL) containing 0.1 M HCl (0.25 mL) to give an inseparable anomeric mixture (α/β=69:31) of **24** (98.6 mg, 83%) as colorless solid; R_f=0.15 (*C*). ^{1}H NMR for α-anomer δ 1.24 (3H, d, $J_{4,5}$=6.4 Hz, H_3-5), 2.25 (2H, br s, HO-1,2), 3.80 (1H, ddd, $J_{3,4}$=4.9, $J_{2,3}$=2.9 Hz, H-3), 3.80 (3H, s, MeO), 4.20 (1H, dd, $J_{1,2}$=4.4 Hz, H-2), 4.41 (1H, qd, H-4), 4.49, 4.62 (1H each, 2d, ^2J=11.7 Hz, CH_2O-3), 5.45 (1H, d, H-1), 6.88, 7.26 (2H each, 2d, $J_{o,m}$=8.8 Hz, C_6H_4); ^{1}H NMR for β-anomer δ 1.36 (3H, d, $J_{4,5}$=6.6 Hz, H_3-5), 2.25 (2H, br s, HO-1,2), 3.73 (1H, dd, $J_{3,4}$=3.9, $J_{2,3}$=1.0 Hz, H-3), 3.81 (3H, s, MeO), 4.24 (1H, d, $J_{1,2}$=0 Hz, H-2), 4.39 (1H, qd, H-4), 4.50, 4.61 (1H each, 2d, ^2J=11.5 Hz, CH_2O-3), 5.06 (1H, s, H-1), 6.89, 7.25 (2H, d, $J_{o,m}$=8.8 Hz, C_6H_4). Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.41; H, 7.13. Found: C, 61.30; H, 6.98.

4.14. 5-Deoxy-3-O-(4-methoxybenzyl)-L-threo-pentos-2-ulose (25)

By use of same procedures as described for **17** from **16**, compound **24** (361 mg, 1.42 mmol) was treated with cupric acetate hydrate (1.14 g, 5.71 mmol) in MeOH (10 mL) and water (5 mL). The products were separated by column chromatography to give **25** (177 mg, 49% yield) as a colorless syrup; R_f=0.33–0.24 (*C*); from the slower-eluting fraction, compound **24** (95.0 mg, 26%) was recovered.

4.15. 2′-O-Acetyl-N^2-(N,N-dimethylaminomethylene)-1′-O-(4-methoxybenzyl)ciliapterin (27a) and its 7-ciliapterin isomer (27b)

Compound **25** (174 mg, 0.690 mmol) was dissolved in MeOH (10 mL), and then a solution of 2,5,6-triamino-4-hydroxypyrimidine sulfate (306 mg, 1.28 mmol) and $NaHCO_3$ (358 mg, 4.26 mmol) dissolved in water (10 mL) was added. The mixture was refluxed for 3 h and then evaporated in vacuo. The residue was dissolved in DMF and sodium sulfate was filtered off. The filtrate was concentrated in vacuo to give a mixture of 1′-*O*-(4-methoxybenzyl)ciliapterin (**26a**) and its 7-ciliapterin isomer (**26b**); R_f=0.17 (*E*).

The mixture of **26a**,**b** was dissolved in dry DMF (8 mL) and *N*,*N*-dimethylformamide dimethyl acetal (0.34 mL, 2.56 mmol) was added. The mixture was stirred at rt for 3 h and concentrated in vacuo. The residue was dissolved in dry pyridine (8 mL) and acetic anhydride (4.0 mL, 42.6 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 (75:25) of **27a** and **27b** (257 mg, 82% from **25**) as a pale yellow foam; R_f=0.44 (*E*). ^{1}H NMR for **27a** δ 1.27 (3H, d, $J_{2',3'}$=6.6 Hz, H_3-3′), 1.95 (3H, s, AcO-2′), 3.24, 3.31 (3H each, 2s, Me_2N), 3.79 (3H, s, MeO), 4.37, 4.58 (1H each, 2d, ^2J=11.7 Hz, CH_2O-1′), 4.77 (1H, d, $J_{1',2'}$=3.7 Hz, H-1′), 5.19 (1H, qd, H-2′), 6.84, 7.21 (2H each, 2d, $J_{o,m}$=8.8 Hz, C_6H_4), 8.97 (1H, s, H-7), 9.11 (1H, s, CH=N-2); ^{1}H NMR for **27b** δ 1.28 (3H, d, $J_{2',3'}$=6.6 Hz, H_3-3′), 1.93 (3H, s, AcO-2′), 3.23, 3.27 (3H each, 2s, Me_2N), 3.79 (3H, s, MeO), 4.36, 4.62 (1H each, 2d, ^2J=11.7 Hz, CH_2O-1′), 4.60 (1H, d, $J_{1',2'}$=3.5 Hz, H-1′), 5.24 (1H, qd, H-2′), 6.84, 7.21 (2H each, 2d, $J_{o,m}$=8.8 Hz, C_6H_4), 8.77 (1H, s, H-6), 9.03 (1H, s, CH=N-2).

4.16. 2′-O-Acetyl-N^2-(N,N-dimethylaminomethylene)-1′-O-(4-methoxybenzyl)-3-[2-(4-nitrophenyl)ethyl]ciliapterin (28a) and its 7-ciliapterin isomer (28b)

The above mixture of **27a**,**b** (257 mg, 0.605 mmol) was dissolved in dry THF (10 mL) and then 2-(*p*-

nitrophenyl)ethanol (143 mg, 0.850 mmol), triphenylphosphine (474 mg, 1.81 mmol), and DEAD (1.95 mL, 1.06 mmol) were added. The mixture was stirred at rt for 16 h and then concentrated in vacuo. The residue was separated by column chromatography with 1:1 AcOEt–hexane to give **28a** (216 mg, 52% yield from **25**) and **28b** (72.0 mg, 17% yield).

4.16.1. Compound *28a*

Pale yellow solid; R_f=0.18 (*D*); $[\alpha]_D^{28}$ +28.9 (*c* 1.91). ^{1}H and ^{13}C NMR, see Tables 1 and 2. Anal. Calcd for $C_{30}H_{33}N_7O_7$: C, 59.69; H, 5.51. Found: C, 59.51; H, 5.60.

4.16.2. Compound *28b*

Pale yellow solid; R_f=0.30 (*D*); $[\alpha]_D^{28}$ +44.2 (*c* 1.74). ^{1}H and ^{13}C NMR, see Tables 1 and 2. Anal. Calcd for $C_{30}H_{33}N_7O_7$: C, 59.69; H, 5.51. Found: C, 59.39; H, 5.68.

4.17. N^2-(N,N-Dimethylaminomethylene)-1′-O-(4-methoxybenzyl)-3-[2-(4-nitrophenyl)ethyl]biopterin (*29a*)

Compound **20a** (272 mg, 0.451 mmol) was dissolved in dry MeOH (6.0 mL) and then NaOMe (28% in MeOH, 0.040 mL, 0.21 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 purified by column chromatography with 1:49 MeOH–$CHCl_3$ to give **29a** (249 mg, 98%) as a pale yellow syrup; R_f=0.60 (*E*); $[\alpha]_D^{29}$ −48.8 (*c* 1.10); UV (MeOH) λ_{max} 225 nm (log ε 4.32), 279 (4.34), 309 (4.45), 353 (4.02); ^{1}H NMR δ 1.12 (3H, d, $J_{2',3'}$=6.6 Hz, H_3-3′), 2.94 (3H, s, HO-2′), 3.17 (2H, t, ^3J=7.8 Hz, CH_2CH_2–N(3)), 3.19, 3.25 (3H each, 2s, Me_2N), 3.80 (3H, s, MeO), 4.26 (1H, qd, $J_{1',2'}$=4.4 Hz, H-2′), 4.46, 4.49 (1H each, 2d, ^2J=11.2 Hz, CH_2O-1′), 4.60, 4.615 (1H each, 2dt, ^2J=12.7 Hz, CH_2–N(3)), 4.70 (1H, d, H-1′), 6.86, 7.23 (2H each, 2d, $J_{o,m}$=8.7 Hz, C_6H_4 of PMB), 7.42, 8.14 (2H each, 2d, $J_{o,m}$=8.7 Hz, C_6H_4 of NPE), 8.88 (1H, s, CH=N-2), 8.98 (1H, s, H-7); ^{13}C NMR δ 18.28 (C-3′), 34.15 (CH_2CH_2N), 35.49, 41.60 (Me_2N), 43.81 (CH_2N), 55.27 (MeO), 69.79 (C-2′), 71.95 (CH_2O-1′), 84.19 (C-1′), 113.92 (C(*m*) of PMB), 123.72 (C(*m*) of NPE), 128.52 (C-4a), 129.44 (C(*ipso*) of PMB), 129.66 (C(*o*) of PMB), 129.78 (C(*o*) of NPE), 146.66, 146.78 (C(*ipso*, *m*) of NPE), 149.88 (C-7), 151.10 (C-6), 153.67 (C-8a), 157.47 (C-2), 159.31 (NCH=N), 159.46 (C(*p*) of PMB), 161.94 (C-4). Anal. Calcd for $C_{28}H_{31}N_7O_6$: C, 59.88; H, 5.56. Found: C, 59.72; H, 5.72.

4.18. N^2-(N,N-Dimethylaminomethylene)-1′-O-(4-methoxybenzyl)-3-[2-(4-nitrophenyl)ethyl]ciliapterin (*29b*)

By use of the same procedures as described above, compound **28a** (1.05 g, 1.74 mmol) was treated with NaOMe (28% in MeOH, 0.17 mL, 0.87 mmol) in dry MeOH (20 mL) to give **29b** (963 mg, 98%) as pale yellow crystals; mp 174–176 °C; R_f=0.66 (*E*); $[\alpha]_D^{28}$ +62.1 (*c* 1.35); UV (MeOH) λ_{max} 226 nm (log ε 4.35), 280 (4.38), 309 (4.50), 355 (4.06); ^{1}H NMR δ 1.17 (3H, d, $J_{2',3'}$=6.4 Hz, H_3-3′), 2.78 (3H, s, HO-2′), 3.16 (2H, t, ^3J=7.7 Hz, CH_2CH_2–N(3)), 3.19, 3.24 (3H each, 2s, Me_2N), 3.78 (3H, s, MeO), 4.04 (1H, qd, $J_{1',2'}$=5.6 Hz, H-2′), 4.41, 4.47 (1H each, 2d, ^2J=11.2 Hz, CH_2O-1′), 4.59, 4.61 (1H each, 2dt, ^2J=12.5 Hz, CH_2–N(3)), 4.57 (1H, d, H-1′), 6.84, 7.21 (2H each, 2d, $J_{o,m}$=8.7 Hz, C_6H_4 of PMB), 7.40, 8.13 (2H each, 2d, $J_{o,m}$=8.7 Hz, C_6H_4 of NPE), 8.88 (1H, s, CH=N-2), 8.92 (1H, s, H-7); ^{13}C NMR δ 18.87 (C-3′), 34.07 (CH_2CH_2N), 35.49, 41.61 (Me_2N), 43.77 (CH_2N), 55.22 (MeO), 70.36 (C-2′), 72.03 (CH_2O-1′), 84.74 (C-1′), 113.86 (C(*m*) of PMB), 123.68 (C(*m*) of NPE), 129.94 (C-4a), 129.18 (C(*ipso*) of PMB), 129.74 (C(*o*) of PMB), 129.78 (C(*o*) of NPE), 146.57, 146.70 (C(*ipso*, *m*) of NPE), 149.24 (C-7), 151.79 (C-6), 153.54 (C-8a), 157.41 (C-2), 159.26 (NCH=N), 159.45 (C(*p*) of PMB), 161.76 (C-4). Anal. Calcd for $C_{28}H_{31}N_7O_6$: C, 59.88; H, 5.56. Found: C, 59.96; H, 5.69.

4.19. N^2-(N,N-Dimethylaminomethylene)-1′-O-(4-methoxybenzyl)-3-[2-(4-nitrophenyl)ethyl]-2′-O-(3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)biopterin (*30a*)

To a solution of **29a** (46.4 mg, 0.0826 mmol), 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl bromide (150 mg, 0.302 mmol), and TMU (0.010 mL, 0.083 mmol) in dry CH_2Cl_2 (2.0 mL) was added silver triflate (56.0 mg, 0.212 mmol). The mixture was stirred at rt for 2.5 h in the dark, 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 purified by column chromatography with 1:49 MeOH–$CHCl_3$ to give **30a** (66.2 mg, 82%) as a pale yellow foam; R_f=0.20 (*D*), 0.58 (*E*). ^{1}H NMR δ 1.16 (3H, d, $J_{2',3'}$=6.7 Hz, H_3-3′), 1.85, 2.02, 2.08 (3H each, 3s, AcO-3,4,6*), 3.15 (2H, t, ^3J=7.6 Hz, CH_2CH_2–N(3)), 3.18, 3.24 (3H each, 2s, Me_2N), 3.77 (3H, s, MeO), 3.85, 3.98 (1H each, 2d, ^2J=11.9 Hz, CH_2O-1′), 3.91 (1H, ddd, $J_{4,5}$=10.1, $J_{5,6a}$=5.2, $J_{5,6b}$=2.5 Hz, H-5*), 4.14 (1H, dd, $J_{6a,6b}$=12.2 Hz, H^b-6*), 4.21 (1H, qd, $J_{1',2'}$=4.0 Hz, H-2′), 4.29 (1H, dd, H^a-6*), 4.33 (dd, $J_{2,3}$=10.7, $J_{1,2}$=8.5 Hz, H-2*), 4.57, 4.59 (1H each, 2dt, ^2J=12.2 Hz, CH_2–N(3)), 4.45 (1H, d, H-1′), 5.11 (1H, dd, $J_{3,4}$=8.9 Hz, H-4*), 5.54 (1H, d, H-1*), 5.82 (1H, dd, H-3*), 6.71, 6.89 (2H each, 2d, $J_{o,m}$=8.7 Hz, C_6H_4 of PMB), 7.41, 8.13 (2H each, 2d, $J_{o,m}$=8.6 Hz, C_6H_4 of NPE), 7.61, 7.76 (2H each, 2 m, Phth*), 8.54 (1H, s, H-7), 8.84 (1H, s, CH=N-2), *for glycosyl moiety. Anal. Calcd for $C_{48}H_{50}N_8O_{15}$: C, 58.89; H, 5.15. Found: C, 58.98; H, 5.29.

4.20. N^2-(N,N-Dimethylaminomethylene)-1′-O-(4-methoxybenzyl)-3-[2-(4-nitrophenyl)ethyl]-2′-O-(3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)ciliapterin (*30b*)

By use of the same procedures as described above, compound **29b** (30.0 mg, 0.0534 mmol) was glycosylated with 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl bromide (80.0 mg, 0.160 mmol) in dry CH_2Cl_2 (2.0 mL) in the presence

of silver triflate (28.0 mg, 0.106 mmol) and TMU (0.006 mL, 0.054 mmol) giving **30b** (48.2 mg, 92%) as a pale yellow foam; R_f=0.18 (*D*), 0.60 (*E*). ^{1}H NMR δ 1.18 (3H, d, $J_{2',3'}$=6.4 Hz, H_3-3′), 1.80, 1.99, 2.10 (3H each, 3s, AcO-3,4,6*), 3.15 (2H, t, ^3J=7.3 Hz, CH_2CH_2−N(3)), 3.23, 3.30 (3H each, 2s, Me_2N), 3.76 (3H, s, MeO), 4.12, 4.25 (1H each, 2d, ^2J=11.5 Hz, CH_2O-1′), 3.78 (1H, ddd, $J_{4,5}$=10.0, $J_{5,6a}$=4.9, $J_{5,6b}$=2.4 Hz, H-5*), 4.14 (1H, dd, $J_{6a,6b}$=12.2 Hz, H^b-6*), 4.25 (1H, qd, $J_{1',2'}$=4.9 Hz, H-2′), 4.29 (1H, dd, H^a-6*), 4.26 (dd, $J_{2,3}$=10.5, $J_{1,2}$=8.5 Hz, H-2*), 4.56 (2H, t, CH_2−N(3)), 4.45 (1H, d, H-1′), 5.09 (1H, dd, $J_{3,4}$=9.0 Hz, H-4*), 5.40 (1H, d, H-1*), 5.62 (1H, dd, H-3*), 6.74, 7.03 (2H each, 2d, $J_{o,m}$=8.2 Hz, C_6H_4 of PMB), 7.42, 8.16 (2H each, 2d, $J_{o,m}$=8.5 Hz, C_6H_4 of NPE), 7.63, 7.74 (2H each, 2 m, Phth*), 8.63 (1H, s, H-7), 8.92 (1H, s, CH=N-2), *for glycosyl moiety. Anal. Calcd for $C_{48}H_{50}N_8O_{15}$: C, 58.89; H, 5.15. Found: C, 58.78; H, 5.06.

*4.21. N^2-(N,N-Dimethylaminomethylene)-3-[2-(4-nitrophenyl)ethyl]-2′-O-(3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)biopterin (**31a**)*

To a solution of **30a** (25.2 mg, 0.0257 mmol) in CH_2Cl_2 (1.0 mL) containing water (0.05 mL) was added DDQ (17.5 mg, 0.0772 mmol). The mixture was stirred at rt for 2 h and then diluted with saturated NaCl. The mixture was extracted with $CHCl_3$ three times. The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column chromatography with 1:49 MeOH−$CHCl_3$ to give **31a** (19.2 mg, 87%) as pale yellow crystals; mp 166−167 °C; R_f=0.50 (*E*). ^{1}H NMR δ 1.22 (3H, d, $J_{2',3'}$=6.4 Hz, H_3-3′), 1.82, 2.02, 2.11 (3H each, 3s, AcO-3,4,6*), 3.14 (2H, t, ^3J=7.6 Hz, CH_2CH_2−N(3)), 3.20, 3.26 (3H each, 2s, Me_2N), 3.91 (1H, ddd, $J_{4,5}$=10.1, $J_{5,6a}$=5.2, $J_{5,6b}$=2.4 Hz, H-5*), 4.17 (1H, dd, $J_{6a,6b}$=12.0 Hz, H^b-6*), 4.26 (1H, qd, $J_{1',2'}$=5.2 Hz, H-2′), 4.28 (1H, dd, H^a-6*), 4.29 (dd, $J_{2,3}$=10.7, $J_{1,2}$=8.6 Hz, H-2*), 4.31 (1H, br s, HO-1′), 4.55 (2H, t, CH_2−N(3)), 4.80 (1H, d, H-1′), 5.13 (1H, dd, $J_{3,4}$=9.2 Hz, H-4*), 5.53 (1H, d, H-1*), 5.70 (1H, dd, H-3*), 7.41, 8.14 (2H each, 2d, $J_{o,m}$=8.7 Hz, C_6H_4 of NPE), 7.65, 7.76 (2H each, 2 m, Phth*), 8.67 (1H, s, H-7), 8.83 (1H, s, CH=N-2), *for glycosyl moiety. Anal. Calcd for $C_{40}H_{42}N_8O_{14}$: C, 55.94; H, 4.93. Found: C, 56.02; H, 5.01.

*4.22. N^2-(N,N-Dimethylaminomethylene)-3-[2-(4-nitrophenyl)ethyl]-2′-O-(3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)ciliapterin (**31b**)*

By use of the same procedures as described above, compound **30b** (23.3 mg, 0.0238 mmol) was treated with DDQ (32.0 mg, 0.141 mmol) in CH_2Cl_2 (1.0 mL) containing water (0.05 mL) to give **31b** (18.1 mg, 89%) as a pale yellow foam; R_f=0.52 (*E*). ^{1}H NMR δ 1.28 (3H, d, $J_{2',3'}$=6.4 Hz, H_3-3′), 1.80, 2.01, 2.11 (3H each, 3s, AcO-3,4,6*), 3.16, 3.18 (1H each, 2dt, ^2J=12.7, ^3J=7.6 Hz, CH_2CH_2−N(3)), 3.23, 3.31 (3H each, 2s, Me_2N), 3.30 (1H, br s, HO-1′), 3.88 (1H, ddd, $J_{4,5}$=10.3, $J_{5,6a}$=5.4, $J_{5,6b}$=2.5 Hz, H-5*), 4.18 (1H, dd, $J_{6a,6b}$=12.2 Hz, H^b-6*), 4.25 (dd, $J_{2,3}$=10.7, $J_{1,2}$=8.3 Hz, H-2*), 4.28 (1H, dd, H^a-6*), 4.47 (1H, qd, $J_{1',2'}$=3.9 Hz, H-2′), 4.59 (2H, t, CH_2−N(3)), 4.65 (1H, d, H-1′), 5.10 (1H, dd, $J_{3,4}$=9.0 Hz, H-4*), 5.41 (1H, d, H-1*), 5.69 (1H, dd, H-3*), 7.42, 8.14 (2H each, 2d, $J_{o,m}$=8.7 Hz, C_6H_4 of NPE), 7.67, 7.73 (2H each, 2 m, Phth*), 8.64 (1H, s, H-7), 8.96 (1H, s, CH=N-2), *for glycosyl moiety. Anal. Calcd for $C_{40}H_{42}N_8O_{14}$: C, 55.94; H, 4.93. Found: C, 56.11; H, 4.99.

*4.23. 2′-O-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-di-N^2:1′-O-acetyl-3-[2-(4-nitrophenyl)ethyl]biopterin (**32a**)*

Compound **31a** (80.0 mg, 0.0928 mmol) was dissolved in MeOH (2.0 mL) and 40% methanolic methylamine (1.5 mL) was added. The mixture was stirred at rt for 12 h and evaporated in vacuo. The residue was dissolved in pyridine (2.0 mL) and then acetic anhydride (0.8 mL, 8.8 mmol) was added at 0 °C. The mixture was stirred at rt for 12 h and evaporated in vacuo. The residue was purified by column chromatography with 1:2 AcOEt−hexane (to remove impurities) and then 1:49 MeOH−$CHCl_3$ as an eluent to give **32a** (67.8 mg, 91%) as pale yellow crystals; mp 142−144 °C (from AcOEt−hexane); R_f=0.55 (*E*). ^{1}H NMR δ 1.26 (3H, d, $J_{2',3'}$=6.4 Hz, H_3-3′), 1.86, 2.02, 2.02, 2.08, 2.16 (3H each, 5s, *Ac*NH-2*, AcO-3,4,6*, AcO-1′), 2.34 (3H, s, *Ac*NH-2), 3.17 (2H, t, ^3J=7.6 Hz, CH_2CH_2−N(3)), 3.72 (1H, ddd, $J_{4,5}$=10.0, $J_{5,6a}$=5.5, $J_{5,6b}$=2.4 Hz, H-5*), 3.72 (dt, $J_{2,3}$=10.6, $J_{1,2}$=$J_{2,NH}$=8.5 Hz, H-2*), 4.13 (1H, dd, $J_{6a,6b}$=12.2 Hz, H^b-6*), 4.22 (1H, dd, H^a-6*), 4.43, 4.55 (1H each, 2dt, ^2J=12.4 Hz, CH_2−N(3)), 4.44 (1H, qd, $J_{1',2'}$=5.2 Hz, H-2′), 4.82 (1H, d, H-1*), 5.00 (1H, dd, $J_{3,4}$=9.4 Hz, H-4*), 5.27 (1H, t, H-3*), 5.83 (1H, br d, NH-2*), 5.91 (1H, d, H-1′), 7.50, 8.19 (2H each, 2d, $J_{o,m}$=8.8 Hz, C_6H_4 of NPE), 8.70 (1H, s, H-7), 13.90 (1H, br s, NH-2), *for glycosyl moiety. Anal. Calcd for $C_{35}H_{41}N_7O_{15}$: C, 52.56; H, 5.17. Found: C, 52.39; H, 5.29.

*4.24. 2′-O-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-di-N^2:1′-O-acetyl-3-[2-(4-nitrophenyl)ethyl]ciliapterin (**32b**)*

By use of the same procedures as described above, compound **31b** (48.0 mg, 0.0559 mmol) gave **32b** (38.0 mg, 85%) as a pale yellow foam; R_f=0.54 (*E*). ^{1}H NMR δ 1.29 (3H, d, $J_{2',3'}$=6.6 Hz, H_3-3′), 1.82, 2.00, 2.01, 2.08, 2.22 (3H each, 5s, *Ac*NH-2*, AcO-3,4,6*, AcO-1′), 2.35 (3H, s, *Ac*NH-2), 3.17, 3.19 (1H each, 2dt, ^2J=12.7, ^3J=7.7 Hz, CH_2CH_2−N(3)), 3.64 (1H, ddd, $J_{4,5}$=10.0, $J_{5,6a}$=5.4, $J_{5,6b}$=2.4 Hz, H-5*), 3.61 (dt, $J_{2,3}$=10.7, $J_{2,NH}$=8.5, $J_{1,2}$=8.3 Hz, H-2*), 4.11 (1H, dd, $J_{6a,6b}$=12.2 Hz, H^b-6*), 4.19 (1H, dd, H^a-6*), 4.56 (2H, t, CH_2−N(3)), 4.40 (1H, qd, $J_{1',2'}$=3.4 Hz, H-2′), 4.73 (1H, d, H-1*), 4.98 (1H, dd, $J_{3,4}$=9.3 Hz, H-4*), 5.29 (1H, dd, H-3*), 5.82 (1H, br d, NH-2*), 5.91 (1H, d, H-1′), 7.52, 8.20 (2H each, 2d, $J_{o,m}$=8.7 Hz, C_6H_4 of NPE), 8.63 (1H, s, H-7), 13.55 (1H, br s, NH-2), *for glycosyl moiety. Anal. Calcd for $C_{35}H_{41}N_7O_{15}$: C, 52.56; H, 5.17. Found: C, 52.42; H, 5.11.

4.25. 2′-O-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-biopterin (limipterin) (3)

Compound **32a** (64.0 mg, 0.0880 mmol) was dissolved in MeOH (8.0 mL) and 28% aqueous ammonia solution (3.0 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 DBU (0.10 mL, 0.64 mmol) was added. The mixture was stirred at rt for 12 h, diluted with water (4.0 mL), and neutralized with Amberlite IRC50(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 **3** (36.3 mg, 94%) as pale yellow solid; R_f=0.28 (*F*). ^{1}H NMR, see Table 3; ^{13}C NMR (DMSO-d_6) δ 18.00 (C-3′), 23.25 ($COCH_3$), 55.87 (C-2*), 61.36 (C-6*), 70.93 (C-4*), 74.55 (C-3*), 745.37 (C-1′), 77.06 (C-5*), 78.10 (C-2′), 101.88 (C-1*), 127.48 (C-4a), 149.06 (C-7), 150.52 (C-6), 153.93 (C-8a), 156.58 (C-2), 161.88 (C-4), 169.37 ($COCH_3$), *for glycosyl moiety. Anal. Calcd for $C_{17}H_{24}N_6O_8$: C, 46.36; H, 5.49. Found: C, 46.19; H, 5.68.

4.26. 2′-O-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-ciliapterin (tepidopterin) (5)

By use of the same procedures as described above, compound **32b** (34.0 mg, 0.0425 mol) gave **5** (15.9 mg, 85%) as pale yellow solid; R_f=0.30 (*F*). ^{1}H NMR, see Table 3; ^{13}C NMR (DMSO-d_6) δ 18.20 (C-3′), 23.31 ($COCH_3$), 56.07 (C-2*), 61.32 (C-6*), 70.83 (C-4*), 74.62 (C-3*), 74.82 (C-1′), 77.02 (C-5*), 78.43 (C-2′), 101.88 (C-1*), 127.63 (C-4a), 149.12 (C-7), 150.72 (C-6), 153.91 (C-8a), 156.82 (C-2), 161.27 (C-4), 169.58 ($COCH_3$), *for glycosyl moiety. Anal. Calcd for $C_{17}H_{24}N_6O_8$: C, 46.36; H, 5.49. Found: C, 46.21; H, 5.58.

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References and notes

1. Forrest, H. S.; Van Baalen, C.; Myers, J. *Arch. Biochem. Biophys.* **1958**, *78*, 95.
2. Choi, Y. K.; Hwang, Y. K.; Kang, Y. H.; Park, Y. S. *Pteridines* **2001**, *12*, 121.
3. Noguchi, Y.; Ishii, A.; Matsushima, A.; Haishi, D.; Yasumuro, K.; Moriguchi, T.; Wada, T.; Kodera, Y.; Hiroto, M.; Nishihara, H.; Sekine, M.; Inada, Y. *Mar. Biotechnol.* **1999**, *1*, 207.
4. Cha, K. W.; Pfleiderer, W.; Yim, J. J. *Helv. Chim. Acta* **1995**, *78*, 600.
5. Some inhibitory activities against tyrosinase were reported for biopterin D-glucoside (**2**): Wachi, Y.; Yoshida, S.; Komatsu, K.; Matsunaga, T. Jpn. Patent 05,286,989, 1993; *Chem. Abstr.* **1994**, *120*, 161782t.
6. (a) Kaufman, S.; Fisher, D. B. *Molecular Mechanisms of Oxygen Activation*; Hayaishi, O., Ed.; Academic: New York, NY, 1974; pp 285–369; (b) Kaufman, S.; Kaufman, E. E. *Folates and Pterins*; Blakley, R., Benkovic, S. J., Eds.; Wiley and Sons: New York, NY, 1985; Vol. 2, pp 251–352.
7. (a) Kwon, N. S.; Nathan, C. F.; Stuehr, D. J. *J. Biol. Chem.* **1989**, *264*, 20496; (b) Marletta, M. A. *Cell* **1994**, *78*, 927.
8. (a) Hatfield, D. L.; Van Baalen, C.; Forrest, H. S. *Plant Physiol.* **1961**, *36*, 240; (b) Lin, X.; White, R. H. *J. Bacteriol.* **1988**, *170*, 1396; (c) Lee, H. W.; Oh, C. H.; Geyer, A.; Pfleiderer, W.; Park, Y. S. *Biochim. Biophys. Acta* **1999**, *1410*, 61; (d) Ikawa, M.; Sasner, J. J.; Haney, J. F.; Foxall, T. L. *Phytochemistry* **1995**, *38*, 1229.
9. Trivial names of natural pteridines are used according to the pteridine nomenclature recommended by the International Society of Pteridinology: Ferre, J.; Jocobson, K. B.; Pfleiderer, W. *Pteridines* **1990**, *2*, 129.
10. Cho, S.-H.; Na, J.-U.; Youn, H.; Hwang, C.-S.; Lee, C.-H.; Kang, S.-O. *Biochim. Biophys. Acta* **1998**, *1379*, 53.
11. Supangat, S.; Seo, K. H.; Choi, Y. K.; Park, Y. S.; Son, D.; Han, C.; Lee, K. H. *J. Biol. Chem.* **2006**, *281*, 2249.
12. Hanaya, T.; Soranaka, K.; Harada, K.; Yamaguchi, H.; Suzuki, R.; Endo, Y.; Yamamoto, H.; Pfleiderer, W. *Heterocycles* **2006**, *67*, 299.
13. (a) Hanaya, T.; Torigoe, K.; Soranaka, K.; Yamamoto, H.; Yao, Q.; Pfleiderer, W. *Pteridines* **1995**, *6*, 1; (b) Hanaya, T.; Toyota, H.; Yamamoto, H. *Synlett* **2006**, 2075.
14. A part of the results concerning tepidopterin synthesis have been reported as a preliminary communication: Hanaya, T.; Baba, H.; Yamamoto, H. *Carbohydr. Res.* **2007**, *342*, 2159.
15. Kiss, J.; D'Souza, R.; Taschner, P. *Helv. Chim. Acta* **1975**, *58*, 311.
16. Hall, L. D.; Black, S. A.; Slessor, K. N.; Tracey, A. S. *Can. J. Chem.* **1972**, *50*, 1912.
17. (a) Weinstock, J. U.S. Patent 3,505,329, 1970; *Chem. Abstr.* **1970**, *72*, 132787h; (b) Taylor, E. C.; Jacobi, P. A. *J. Am. Chem. Soc.* **1976**, *98*, 2301.
18. The ratio of **18a**,**b** (**26a**,**b**) was determined by ^{1}H NMR spectra (based particularly on the H-1′, 6, 7 signals) after having been converted into 2′-*O*-acetyl-N^2-(*N*,*N*-dimethylaminomethylene) derivatives **19a**,**b** (**27a**,**b**).
19. Jones, N. A.; Nepogodiev, S. A.; MacDonald, C. J.; Hughes, D. L.; Field, R. A. *J. Org. Chem.* **2005**, *70*, 8556.
20. (a) Geerts, J. P.; Nagel, A.; Van der Plas, H. C. *Org. Magn. Reson.* **1976**, *8*, 606; (b) Hanaya, T.; Takayama, D.; Yamamoto, H. *Heterocycles* **2006**, *70*, 355.
21. (a) Ewers, U.; Günther, H.; Jaenicke, L. *Chem. Ber.* **1974**, *107*, 3275; (b) Tobias, S.; Günther, H.; Pfleiderer, W. *Chem. Ber.* **1985**, *118*, 354.
22. Farkas, J.; Ledvina, M.; Brokes, J.; Jezek, J.; Zajicek, J.; Zaoral, M. *Carbohydr. Res.* **1987**, *163*, 63.
23. The complete assignments of **3** and **5** have been established by the present work; some ambiguous parameters were included in the previous reports for the natural compounds. Although ^{1}H and ^{13}C NMR charts for the natural **5** are shown in Ref. 10 without the assigned parameters, we have found that the parameters of the synthetic **5** completely agree with the NMR charts of the natural **5**.