HETEROCYCLES, Vol. 70, 2006, pp. 355 – 365. © The Japan Institute of Heterocyclic Chemistry
Received, 1st September, 2006, Accepted, 5th October, 2006, Published online, 6th September, 2006. COM-06-S(W)33

SYNTHESIS OF 6- AND 7-(1,2,3-TRIHYDROXY-1,2-*O*-ISOPROPYL-IDENEPROPYL)PTERIDINES AND DEOXYGENATION OF THEIR 3'-HYDROXY GROUPS

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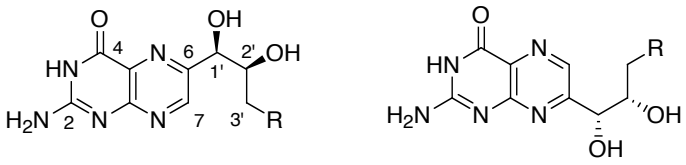
Abstract – Treatment of 3,4-*O*-isopropylidene-L-*threo*-pentos-2-ulose (**7**) with 5,6-diamino-1,3-dimethyluracil (**8**) afforded 1,3-dimethyl-6-[(1*R*,2*S*)-1,2,3-trihydroxy-1,2-*O*-isopropylidenepropyl]lumazine (**9a**) and its 7-substituted isomer (**9b**). Deoxygenation of 3'-hydroxy groups of **9a,b** was investigated in connection with a practical transformation of neopterin into biopterin.

INTRODUCTION

Various pteridines having a side-chain at C-6 or C-7 have been isolated from many living organisms.[1] Among them, L-biopterin (L-**1**) is the most abundant of the naturally occurring pteridines found in human urine[2] and plays an important role in hydroxylation of aromatic amino acids as a tetrahydro form.[3] In addition to L-**1**, D-neopterin (D-**2**), L-primapterin (L-**3**), and D-anapterin (D-**4**) have also been isolated from the urine of patients with hyperphenylalaninemia[4] (Figure 1).



1 R = H (biopterin) **3** R = H (primapterin)
2 R = OH (neopterin) **4** R = OH (anapterin)

Figure 1. Structures of representative, naturally occurring 6- and 7-substituted pteridines. Structures are illustrated in L-form.

Synthesis of pteridines having a 1,2,3-trihydroxypropyl group either at C-6 or C-7 has generally been accomplished in higher yields than those having a 1,2-dihydroxypropyl group. For example, L-neopterin (L-**2**) is prepared in 80% yield by the condensation of L-arabinose phenylhydrazone with 2,5,6-triamino-4-hydroxypyrimidine,[5] while L-biopterin (L-**1**) is obtained in 45% yield by the similar

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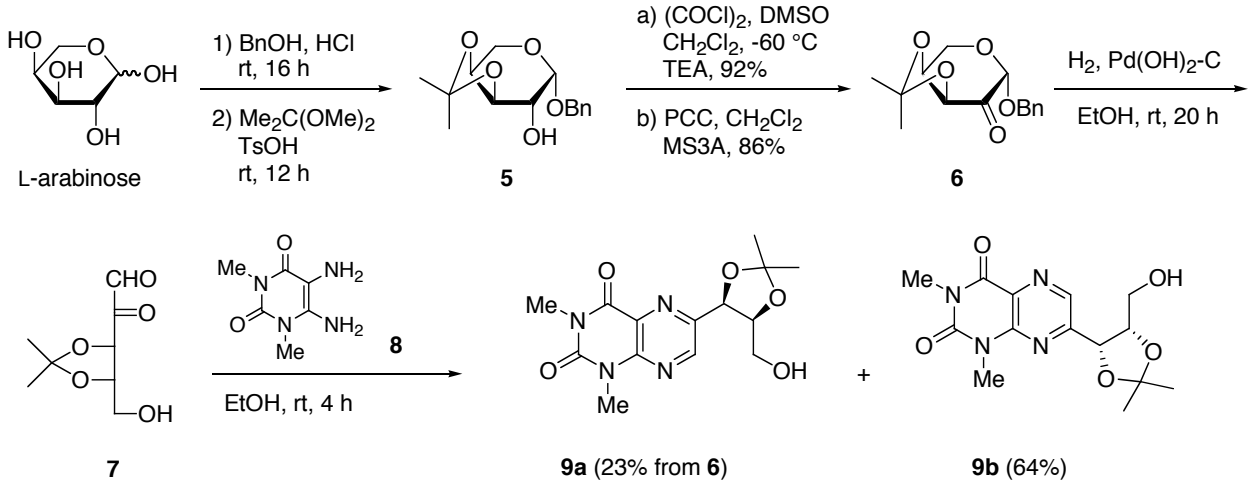
This paper is dedicated to Prof. Steven M. Weinreb on the occasion of his 65th birthday.

reaction of 5-deoxy-L-arabinose phenylhydrazone.[6] In addition, preparation of 5-deoxy-L-arabinose phenylhydrazone requires several, rather laborious steps. Therefore, the conversion of the 1,2,3-trihydroxypropyl group of such pteridines as **2** and **4** into the corresponding 1,2-dihydroxypropyl group is expected to offer an efficient synthetic procedure of pteridine derivatives (**1** and **3**). Although a few attempts were made to protect the two secondary hydroxy groups and the subsequent deoxygenation for the above purpose,[7–9] no successful result has been reported.

We describe herein our synthetic studies on the 6- and 7-(1,2,3-trihydroxy-1,2-*O*-isopropylidene-propyl)pteridines and some results on deoxygenation of the terminal hydroxy group in an attempt to explore a practical route for pteridine derivatives having 1,2-*O*-protected side chain by employing 1,3-dimethyllumazine as a model pteridine compound.

RESULTS AND DISCUSSION

The preparation of a 6-(1,2,3-trihydroxy-1,2-*O*-isopropylidenepropyl)pteridine derivative has been achieved[9] by the condensation of a 5,6-diaminopyrimidine derivative with D-arabinose phenylhydrazone and then the introduction of an isopropylidene group, followed by oxidation of the resulting 5,6,7,8-tetrahydropteridine intermediate. In the present study we undertook a novel alternative way for the preparaion of 6- and 7-(1,2,3-trihydroxy-1,2-*O*-isopropylidenepropyl)pteridines by using a common sugar moiety protected by an isopropylidene group for pteridine-ring formation, since benzyl β-L-*threo*-pentopyranosid-2-ulose (**6**)[10,11] turned out to be easily available from L-arabinose by glycosidation with benzyl alcohol and then acetalation with 2,2-dimethoxypropane, followed by oxidation of the resulting benzyl 3,4-di-*O*-isopropylidene-β-L-arabinopyranoside (**5**)[12] either with oxalyl chloride-DMSO (in 92%) or with pyridinium chlorochromate (PCC) (in 86%) (Scheme 1).



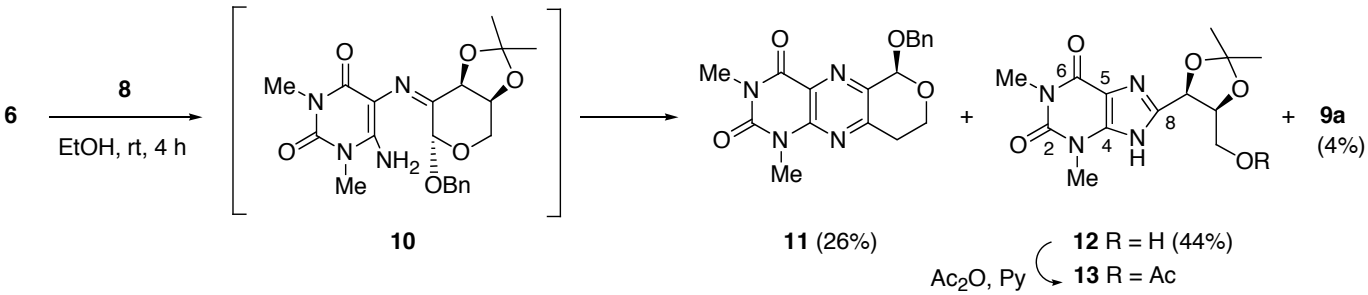
Scheme 1

The preferential preparation of C-6 and C-7 substituted pteridines was intended by altering the order of the subsequent step: either debenzylation of the sugar moiety or condensation with 5,6-diamino-1,3-dimethyluracil (**8**). These attempts are based on the selective pteridine-ring formation

by the combination of the 5-amino group of **8** having higher nucleophilicity and carbonyl carbons (C-1 *vs.* C-2) of the sugar moiety. Namely, debenzylation of the sugar intermediate (**6**) and the subsequent condensation with **8** were anticipated to result in the preferential formation of the 7-substituted pteridine, while condensation of **6** with **8** followed by debenzylation was presumed to afford the 6-substituted pteridine predominantly.

Thus, the 2-ulose (**6**) was hydrogenated in the presence of palladium hydroxide to give 3,4-*O*-isopropylidene-L-*threo*-pentos-2-ulose (**7**), which was condensed with 1.0 equiv of **8** to provide pteridine derivatives (**9a**,**b**). These products were separated by column chromatography over silica gel into the 6-substituted lumazine (**9a**) (23% overall yield from **6**) and the 7-substituted derivative (**9b**) (64%).

The structural assignment of **9a** and **9b** was achieved 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-alkylkylpteridines generally appear at a similar field, whereas C-7 signals of 7-alkyl derivatives shifts to a lower field (ca. 20 ppm) from those of C-6.[13] Therefore, the close values of **9a** (C-6: δ 149.85, C-7: δ 146.80) and the distant values of **9b** (C-6: δ 138.54, C-7: δ 158.27) indicate the 6-substituted lumazine for the former and the 7-substituted lumazine for the latter. These assignments are supported by the fact that H-7 signal (δ 8.89) of **9a** appears at a lower field than H-6 signal (δ 8.76) of **9b** due to conjugation with the 4-oxo group.[14,15] These characteristic tendency of NMR spectral data are also observed in those of derivatives of **9a** and **9b**.



Scheme 2

As an alternative route for preparation of **9a,b**, the benzyl pyranosid-2-ulose (**6**) was treated with **8** (Scheme 2). Prior to the following debenzylation, the resultant products were separated by column chromatography into three fractions, among which, however, no desired intermediate (**10**) was found. The ^{1}H-NMR spectrum of the first eluted product (**11**) indicated lack of isopropylidene group and existence of two adjacent methylenes, while its pteridine structure was derived from its ^{13}C-NMR spectral data. The molecular composition of **11** was confirmed by FAB-mass spectra, which gave the $(M+1)^{+}$ ions at *m/z* 355 corresponding to $C_{18}H_{19}N_4O_4$, and thus **11** was assigned to be (6*R*)-benzyloxy-8,9-dihydro-1,3-dimethyl-6*H*-pyrano[3,4-*g*]lumazine (26% yield from **6**). A possible pathway for the formation of **11** from the intermediate (**10**) is illustrated in Scheme 3. Namely, transformation of **10** into enamine and a subsequent release of acetone are likely to give the iminoketone, which would then be converted into the tricyclic compound (**11**) by intramolecular cyclization.

Table 1. 600 MHz ^{1}H-NMR spectral parameters for 6-substituted 1,3-dimethyllumazines (**9a,14a,16a**) and their 7-substituted congeners (**9b,14–18b**) in $CDCl_3$

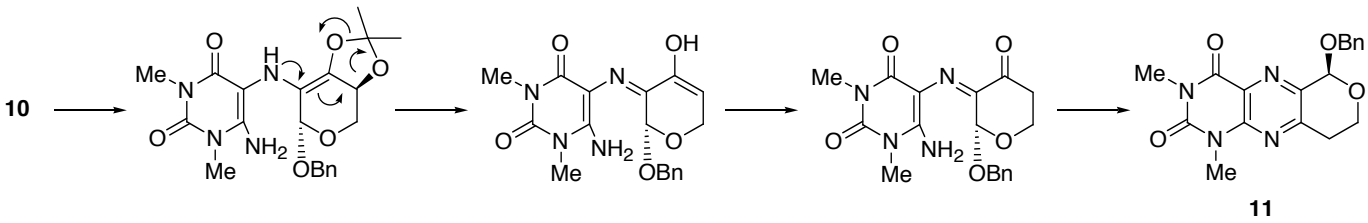
Com-pounds	Chemical Shifts / δ									Coupling Constants / Hz			
	Me-$N_{(1)}$,$N_{(3)}$	H-6	H-7	H-1'	H-2'	H^a-3'	H^b-3'	Me_2C	Others	$J_{1',2'}$	$J_{2',3'a}$	$J_{2',3'b}$	$J_{3a',3'b}$
9a	3.72, 3.53	-	8.89	5.53	4.70	3.47	3.39	1.68, 1.51	2.10[a]	7.6	4.9	4.2	12.2
9b	3.67, 3.53	8.76	-	5.39	4.71	3.53	3.40	1.70, 1.52	2.10[a]	7.8	3.9	5.1	12.0
14a	3.72, 3.54	-	8.85	5.60	4.82	3.91	3.63	1.69, 1.51	1.93[b]	7.6	3.7	6.6	12.0
14b	3.67, 3.54	8.76	-	5.42	4.80	4.09	3.71	1.70, 1.52	1.88[b]	7.6	3.4	6.1	12.0
15b	3.59, 3.56	8.68	-	5.42	4.80	3.95	3.84	1.58, 1.47	c	7.1	5.6	4.6	10.5
16a	3.71, 3.54	-	8.89	5.65	4.95	4.49	4.28	1.70, 1.52	2.44[d]	7.3	4.6	4.4	11.9
16b	3.67, 3.55	8.80	-	5.48	4.94	4.54	4.43	1.70, 1.54	2.41[d]	7.3	4.9	4.6	11.8
17b	3.70, 3.55	8.76	-	5.44	4.86	3.12	3.12	1.70, 1.52		7.1	6.1	6.1	-
18b	3.69, 3.55	8.74	-	5.30	4.78	0.90		1.69, 1.50		7.3	6.6		-

[a] HO-3'. [b] AcO-3'. [c] δ 2.40 (3H, s, CH_3-C_6), 7.23, 7.50 (2H each, 2d, J = 8.4 Hz, C_6H_4). [d] MeSC(=S)O-3'.

Table 2. 151 MHz ^{13}C-NMR spectral parameters for 6-substituted 1,3-dimethyllumazines (**9a,14a,16a**) and their 7-substituted congeners (**9b, 14–18b**) in $CDCl_3$

Com-pounds	Chemical Shifts / δ												
	C-2	C-4	C-4a	C-6	C-7	C-8a	Me-$N_{(1)}$,$N_{(3)}$	C-1'	C-2'	C-3'	*C*Me_2	C*Me*$_2$	Others
9a	159.92	150.51	125.42	149.85	146.80	147.30	29.40, 29.04	77.37	78.81	60.68	109.75	26.84, 24.37	
9b	159.90	150.58	126.65	138.54	158.27	146.81	29.23, 29.00	77.53	78.95	60.77	110.27	26.85, 24.57	
14a	159.78	150.44	126.04	148.70	146.32	147.51	29.43, 29.07	77.35	76.10	62.98	110.26	26.85, 24.49	a
14b	159.75	150.53	126.96	138.41	157.23	146.94	29.29, 29.06	77.43	76.45	62.49	110.85	26.87, 24.75	b
15b	159.71	150.45	127.04	138.07	155.99	146.83	29.19, 29.05	77.33	75.82	66.63	110.95	26.91, 24.83	c
16a	159.78	150.52	126.11	148.33	146.23	147.51	29.45, 29.08	77.41	75.94	70.67	110.43	26.95, 24.75	d
16b	159.77	150.58	127.07	138.27	156.72	146.95	29.35, 29.05	77.50	76.10	70.38	110.94	27.04, 24.91	e
17b	159.77	150.54	127.12	138.82	156.26	147.03	29.36, 29.07	78.38	78.27	30.05	110.83	27.16, 24.96	
18b	159.94	150.66	126.63	138.91	158.67	146.97	29.25, 29.01	79.47	74.68	16.74	109.80	27.16, 24.85	

[a] δ 170.24 (*C*OCH_3), 20.63 (CO*C*H_3). [b] δ 170.21 (*C*OCH_3), 20.59 (CO*C*H_3). [c] δ 145.19 [C(*ipso*) of Ts], 132.11 [C(*p*) of Ts], 129.69 [C(*o*) of Ts], 127.59 [C(*m*) of Ts], 21.60 (CH_3 of Ts). [d] δ 215.06 (C=S), 19.17 (SCH_3). [e] δ 215.29 (C=S), 19.27 (SCH_3).



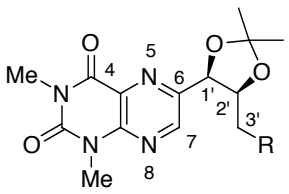
Scheme 3

From the second fraction, a minor amount of 6-substituted lumazine (**9a**) was obtained in 4%. The ^{1}H-NMR spectra of the third eluted product (**12**) indicated lack of benzyl group and the existence of isopropylidene group. For the structural assignment, **12** was acetylated with acetic anhydride-pyridine to give **13**. The ^{1}H-NMR spectra of **13** showed a terminal acetoxy group of the side chain but no aromatic proton, while its ^{13}C-NMR spectra indicated existence of five sp^2 carbons of the heterocycle besides a side chain and other substituents. In addition, the characteristic value (δ 106.50) of **13**, which was absent in pteridine derivatives, corresponded to a standard value of C-5 of xanthine derivatives.[16] These data show that **13** possesses the structure of 6-(3-*O*-acetyl-1,2,3-trihydroxy-1,2-*O*-isopropylidenepropyl)-1,3-dimethylxanthine. FAB-Mass spectrum of **13**, which gave the $(M+1)^+$ ions at *m/z* 353 corresponding to $C_{15}H_{21}N_4O_6$, supports this assignment. Although compound (**12**) is the main product of this reaction (44% yield), the mechanism of xanthine formation including cleavage of benzyl group and C-1 degradation is ambiguous at present stage. Thus the synthetic approach to 6-substituted pteridines through the condensation of **6** and **8** with subsequent debenzylation appears to be inappropriate but its limit of utility still remains to be further investigated.

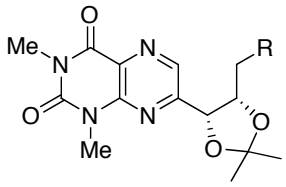
For the purpose of deoxygenation of 3'-hydroxy groups of 6- and 7-substituted lumazines (**9a,b**) we then examined their conversion into various derivatives: *i.e.* 3'-*O*-acetyl, tosyl, dithiocarbonyl, and 3'-bromo compounds (Table 3).

Acetylation of **9a,b** with acetic anhydride-pyridine afforded the corresponding 3'-*O*-acetyl derivatives (**14a,b**) in 92–94%. Treatment of **9b** with tosyl chloride-pyridine provided 3'-*O*-tosyl derivative (**15b**) in 73%, whereas the same treatment of **9a** gave no tosylated product. Dithiocarbonylation of **9a,b** with carbon disulfide and methyl iodide in the presence of sodium hydride afforded the corresponding 3'-*O*-[(methylthio)thiocarbonyl] derivatives (**16a,b**) in moderate yields. Bromination of **9b** with carbon tetrabromide and triphenylphosphine provided the 3'-bromo compound (**17b**) in 55% yield, while the same treatment of **9a** resulted in the formation of unidentified, decomposed compounds instead of the desired bromide (**17a**).

These results indicate that introduction of relatively strong leaving groups like tosyloxy and bromo groups at C-3' of 6-substituted pteridines can not be achieved easily. It is presumed for this reason that the resultant tosylate (**15a**) and bromide (**17a**) might immediately form pyrrole derivatives caused by intramolecular nucleophilic attack by N-5 at the activated C'-3. Similar pyrrolo-pteridine formation as the result of C-3' activation of neopterin side-chain has been reported.[8,17] In contrast, 7-substituted lumazines (**15b**, **17b**) are apparently more stable due to the lower nucleophilicity of N-8 compared with that of N-5 by the effect of the 4-oxo group.[15]



9a, 14–18a



9b, 14–18b

9 R = OH
14 R = OAc
15 R = OTs
16 R = OC(=S)SMe
17 R = Br
18 R = H

Table 3. Conversion of the terminal hydroxyl group of **9a,b**

Substrates	Reagents, Solvents	Temperature, Time	Products (Yield)
9a	Ac_2O, Py	rt, 12 h	**14a** (92%)
9b	Ac_2O, Py	rt, 12 h	**14b** (94%)
9a	TsCl, Py	rt, 12 h	**15a** (0%) [a]
9b	TsCl, Py	rt, 12 h	**15b** (73%)
9a	NaH, CS_2, MeI, THF	0 °C, 2 h	**16a** (67%)
9b	NaH, CS_2, MeI, THF	0 °C, 2 h	**16b** (80%)
9a	CBr_4, PPh_3, CH_2Cl_2	rt, 4 h	**17a** (0%) [a]
9b	CBr_4, PPh_3, CH_2Cl_2	rt, 4 h	**17b** (55%)
15b	$LiAlH_4$, THF	rt, 3 h	**18b** (0%) [a]
16a	Bu_3SnH, AIBN, toluene	110 °C, 8 h	**18a** (0%), **9a** (78%)
16b	Bu_3SnH, AIBN, toluene	110 °C, 8 h	**18b** (9%), **9b** (73%)
17b	Bu_3SnH, AIBN, toluene	110 °C, 6 h	**18b** (70%)

[a] Formation of an inseparable mixture of unidentified products.

Reduction of the side-chain terminus of **15b**, **16a,b**, and **17b** was then examined. Treatment of 3'-*O*-tosyl compound (**15b**) with lithium aluminum hydride resulted in the formation of an inseparable mixture of unidentified products. Attempted deoxygenation of 3'-*O*-dithiocarbonyl compound (**16b**) with tributyltin hydride led to the formation of a minor amount of the desired 3'-deoxy product (**18b**) besides a considerable amount of 3'-hydroxy compound (**9b**), while the same treatment of **16a** afforded only 3'-hydroxy compound (**9a**). However, reduction of 3'-bromo compound (**17b**) with tributyltin hydride turned out to be successful, affording 7-(1,2-dihydroxypropyl)pteridine derivative (**18b**) in 70% yield.

The present work demonstrates a convenient way for preparation of pteridine derivatives having 1,2,3-trihydroxy-1,2-*O*-isopropylidenepropyl group and transformation of their terminal hydroxy groups. Despite various attempts for deoxygenation of their 3'-hydroxy groups, the only procedure from 7-substituted pteridine derivatives via 3'-bromo intermediate was successful. Extension of this work including further investigation concerned with a selective preparation of 6-substituted pteridines and possible deoxygenarion of their 3'-hydroxy groups is in progress.

EXPERIMENTAL

All reactions were monitored by TLC (Merck silica gel 60F, 0.25 mm) with an appropriate solvent system [(*A*) 1:2, (*B*) 1:1, (*C*) 2:1 AcOEt–hexane, and (*D*) AcOEt]. 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% sulfuric acid–ethanol (with subsequent heating). Optical rotations were measured with a JASCO P-1020 polarimeter. The NMR spectra were measured in $CDCl_3$ with Varian Unity Inova AS600 (600 MHz for ^1H, 151 MHz for ^{13}C) spectrometer at 23 °C. Chemical shifts are reported as δ values relative to $CHCl_3$ (7.26 ppm as an internal standard for ^1H) and $CDCl_3$ (77.0 ppm as internal standard for ^{13}C). The assignments of ^{13}C signals were made with the aid of 2D C-H COSY measurements. The MS spectra were taken on a VG-70SE instrument and given in terms of *m/z* (relative intensity).

Benzyl 3,4-*O*-isopropylidene-β-L-*erythro*-pentopyranosid-2-ulose (6).[10,11]

A. Oxidation with oxalyl chloride-DMSO. The reported procedures[10] were employed with a slight modification. To a solution of oxalyl chloride (1.15 mL, 13.4 mmol) in dry CH_2Cl_2 (10 mL), a solution of DMSO (2.00 mL, 27.9 mmol) in dry CH_2Cl_2 (5.0 mL) at –60 °C was added under argon, and then a solution of **5**[12] (1.50 g, 5.35 mmol) in dry CH_2Cl_2 (5.0 mL) was slowly added. The mixture was stirred at –60 °C for 6 h, and then TEA (4.70 mL, 33.8 mmol) was added. The mixture was stirred at 0–10 °C for 20 min, diluted with $CHCl_3$ (20 mL), washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with 1:2 AcOEt-hexane to give **6** [1.37 g, 92% (lit.,[10] 93% yield)] as a colorless oil: R_f = 0.54–0.34 (*A*); ^1H NMR[18] δ = 1.39, 1.46 (3H each, 2s, Me_2C), 4.11 (1H, dd, $J_{5,5'}$ = 13.4, $J_{4,5'}$ = 0.7 Hz, H'-5), 4.30 (1H, dd, $J_{4,5}$ = 2.1 Hz, H-5), 4.53 (1H, ddd, $J_{3,4}$ = 5.6 Hz, H-4), 4.61, 4.80 (1H each, 2d, ^2J = 11.5 Hz, CH_2O-1), 4.70 (1H, d, H-3), 4.90 (1H, s, H-1), 7.33–7.38 (5H, m, Ph).

B. Oxidation with PCC. To a mixture of PCC (6.15 g, 28.6 mmol) and finely powdered MS3A (12 g) in dry CH_2Cl_2 (40 mL) was added a solution of **5** (4.01 g, 14.3 mmol) in dry CH_2Cl_2 (20 mL). The mixture was stirred at rt for 4 h and then 2-propanol (1.5 mL) was added. The mixture was stirred for 30 min, diluted with ether, and filtered. The filtrate was evaporated in vacuo and the residue was purified by column chromatography to give **6** [3.41 g, 86% (lit.,[11] 72% yield by use of pyridinium dichromate)].

1,3-Dimethyl-6-[(1*R*,2*S*)-1,2,3-trihydroxy-1,2-*O*-isopropylidenepropyl]lumazine (9a) and 1,3-dimethyl-7-[(1*R*,2*S*)-1,2,3-trihydroxy-1,2-*O*-isopropylidenepropyl]lumazine (9b).

Compound (**6**) (702 mg, 2.52 mmol) was dissolved in ethanol (15 mL) and hydrogenated in the presence of 20% $Pd(OH)_2$-C (380 mg, 0.50 mmol) at rt under an atmospheric pressure of H_2. After 15 h, the catalyst was filtered off and the filtrate was evaporated in vacuo to give 3,4-*O*-isopropylidene-L-*threo*-pentos-2-ulose (**7**) (480 mg) as a colorless syrup: R_f = 0.50–0.35 (*D*).

Compound (**7**) was dissolved in ethanol (10 mL) and added to a suspension of 5,6-diamino-1,3-dimethyluracil (**8**) (430 mg, 2.52 mmol) in ethanol (10 mL). The mixture was refluxed

for 4 h and then evaporated in vacuo. The residue was separated by column chromatography with 1:2 AcOEt-hexane to give **9a** and **9b**.

9a: Pale yellow syrup (183 mg, 23% from **6**); R_f = 0.35 (*D*); $[\alpha]_D^{26}$ –81.0° (*c* = 2.47, $CHCl_3$); ^1H and ^{13}C NMR, see Tables 1,2. *Anal*. Calcd for $C_{14}H_{18}N_4O_5$: C, 52.17; H, 5.63. Found: C, 52.26; H, 5.57.

9b: Pale yellow syrup (522 mg, 64% from **6**); R_f = 0.28 (*D*); $[\alpha]_D^{29}$ –102.2° (*c* = 1.17, $CHCl_3$); ^1H and ^{13}C NMR, see Tables 1,2. *Anal*. Calcd for $C_{14}H_{18}N_4O_5$: C, 52.17; H, 5.63. Found: C, 52.30; H, 5.61.

(6*R*)-Benzyloxy-8,9-dihydro-1,3-dimethyl-6*H*-pyrano[3,4-*g*]lumazine (11) and 1,3-dimethyl-8-[(1*R*,2*S*)-1,2,3-trihydroxy-1,2-*O*-isopropylidenepropyl]xanthine (12).

A mixture of **6** (117 mg, 0.420 mmol) and **8** (71.0 mg, 0.420 mmol) in ethanol (2 mL) was refluxed for 3 h and then evaporated in vacuo. The residue was separated by column chromatography with 1:1 AcOEt-hexane and then AcOEt, into three fractions A–C.

Fraction A [R_f = 0.63 (*C*)] gave **11** (38.3 mg, 26%) as yellow crystals: mp 154–155 °C (from AcOEt-hexane); $[\alpha]_D^{26}$ = +104.6° (*c* = 2.91, $CHCl_3$); ^1H NMR δ = 2.98 (1H, ddd, $J_{9,9'}$ = 18.3, $J_{8,9'}$ = 3.7, $J_{8',9'}$ = 1.0 Hz, H'-9), 3.30 (1H, $J_{8,9}$ = 12.5, $J_{8',9}$ = 7.1 Hz, H-9), 3.53 [3H, s, Me-N(3)], 3.68 [3H, s, Me-N(1)], 4.06 (1H, ddd, $J_{8,8'}$ = 11.7 Hz, H'-8), 4.44 (1H, ddd, H-8), 4.80, 4.91 (1H each, 2d, CH_2O-6), 5.92 (1H, s, H-6), 7.28 [1H, tt, $J_{m,p}$ = 7.3, $J_{o,p}$ = 1.5 Hz, Ph(*p*)], 7.34 [2H, td, $J_{o,m}$ = 7.6, $J_{o',m}$ = 1.5 Hz. Ph(*m*)], 7.41 [1H, dt, Ph(*o*)]; ^{13}C NMR δ = 29.00, 29.40 [Me-N(1),N(3)], 31.50 (C-9), 56.52 (*C*H_2Ph), 70.40 (C-8), 96.44 (C-6), 125.66 (C-4a), 127.88 [Ph(*p*)], 128.23 [Ph(*o*)], 128.44 [Ph(*m*)], 137.16 [Ph(*ipso*)], 144.38 (C-5a), 147.47 (C-10a), 150.63 (C-4), 155.20 (C-9a), 159.80 (C-2); FAB MS *m/z* 355 (M+1, 14), 307 (30), 289 (28), 247 (54), 176 (16), 154 (100), 136 (84). Found: *m/z* 355.1396. Calcd for $C_{18}H_{18}N_4O_4$: M+1, 355.1408.

Fraction B [R_f = 0.20 (*C*)] gave **9a** (5.6 mg, 4%).

Fraction C [R_f = 0.08 (*C*), 0.28 (*D*)] gave **12** (57.0 mg, 44%) as a pale yellow syrup; ^1H NMR δ = 1.48, 1.62 (3H each, 2s, Me_2C), 2.30 (1H, br s, HO-3'), 3.41, 3.57 [3H each, 2s, Me-N(1),N(3)], 3.50 (1H, dd, $J_{3'a,3'b}$ = 12.2, $J_{2',3'b}$ = 7.1 Hz, H^b-3'), 3.71 (1H, dd, $J_{2',3'a}$ = 4.4 Hz, H^a-3'), 4.67 (1H, td, $J_{1',2'}$ = 7.1 Hz, H-2'), 5.39 (1H, d, H-1'), 10.92 (1H, br s, NH); ^{13}C NMR δ = 20.64 (*M*eCO), 24.31, 26.81 (C*Me*$_2$), 28.33, 30.23 [Me-N(1),N(3)], 62.92 (C-3'), 73.66 (C-1'), 78.23 (C-2'), 106.41 (C-5), 110.63 (*C*Me_2), 148.30 (C-4), 150.86 (C-8), 151.42 (C-2), 154.88 (C-6). *Anal*. Calcd for $C_{13}H_{18}N_4O_5$: C, 50.32; H, 5.85. Found: C, 50.18; H, 5.93.

8-[(1*R*,2*S*)-3-*O*-Acetyl-1,2,3-trihydroxy-1,2-*O*-isopropylidenepropyl]-1,3-dimethylxanthine (13).

Compound (**12**) (36.5 mg, 0.118 mmol) was dissolved in dry pyridine (1.0 mL) and acetic anhydride (0.25 mL, 2.6 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 give **13** (39.0 mg, 94%) as a pale yellow syrup: R_f = 0.16 (*B*); $[\alpha]_D^{26}$ –2.77° (*c* = 2.30, $CHCl_3$); ^1H NMR δ = 1.48, 1.65 (3H each, 2s, Me_2C), 1.96 (3H, s, AcO-3'), 3.43, 3.58 [3H each, 2s, Me-N(1),N(3)], 3.81 (1H, dd, $J_{3'a,3'b}$ = 12.0, $J_{2',3'b}$ = 6.8 Hz, H^b-3'), 4.21 (1H, dd, $J_{2',3'a}$ = 3.7 Hz, H^a-3'), 4.74 (1H, ddd, $J_{1',2'}$ = 7.3 Hz, H-2'), 5.41 (1H, d, H-1'), 10.86 (1H, br s, NH); ^{13}C NMR δ = 20.64 (*M*eCO), 24.44, 26.90 (C*Me*$_2$), 28.34, 30.12

[Me-N(1),N(3)], 62.74 (C-3'), 72.85 (C-1'), 76.00 (C-2'), 106.50 (C-5), 110.84 (*C*Me$_2$), 148.76 (C-4), 149.65 (C-8), 151.52 (C-2), 155.00 (C-6), 170.33 (Me*C*O); FAB MS *m/z* 353 (M+1, 78), 311 (22), 289 (24), 176 (28), 154 (88), 136 (100). Found: *m/z* 353.1468. Calcd for $C_{15}H_{21}N_4O_6$: M+1, 353.1462.

6-[(1*R*,2*S*)-3-*O*-Acetyl-1,2,3-trihydroxy-1,2-*O*-isopropylidenepropyl]-1,3-dimethyllumazine (14a). Compound (**9a**) (47.2 mg, 0.146 mmol) was dissolved in dry pyridine (2.0 mL) and acetic anhydride (0.50 mL, 5.2 mmol) was added at 0 °C. The mixture was stirred at rt for 12 h, diluted with a small portion 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 2:1 AcOEt-hexane to give **14a** (50.1 mg, 94%) as colorless crystals: mp 92–94 °C (from AcOEt-hexane); R_f = 0.39 (*C*); $[\alpha]_D^{26}$ –129.9° (*c* = 2.66, $CHCl_3$); ^{1}H and ^{13}C NMR, see Tables 1,2; FAB MS *m/z* 365 (M + 1, 18), 323 (10), 307 (32), 289 (16), 265 (10), 176 (12), 154 (100), 136 (74). Found: *m/z* 365.1488. Calcd for $C_{16}H_{21}N_4O_6$: M+1, 365.1462.

7-[(1*R*,2*S*)-3-*O*-acetyl-1,2,3-trihydroxy-1,2-*O*-isopropylidenepropyl]-1,3-dimethyllumazine (14b). By use of the same procedures for **14a** from **9a**, compound (**9b**) (47.2 mg) was converted into **14b** (50.1 mg, 94%) as colorless crystals: mp 177–179 °C (from AcOEt-hexane); R_f = 0.31 (*C*); $[\alpha]_D^{26}$ –106.3° (*c* = 1.81, $CHCl_3$); ^{1}H and ^{13}C NMR, see Tables 1,2. *Anal*. Calcd for $C_{16}H_{20}N_4O_6$: C, 52.74; H, 5.53. Found: C, 52.88; H, 5.47.

1,3-Dimethyl-7-[(1*R*,2*S*)-1,2,3-trihydroxy-1,2-*O*-isopropylidene-3-*O*-tosylpropyl]lumazine (15b). Compound (**9b**) (100 mg, 0.310 mmol) was dissolved in dry pyridine (2.0 mL) and tosyl chloride (118 mg, 0.619 mmol) was added at 0 °C. 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 2:1 AcOEt-hexane to give **15b** (108 mg, 73%) as a colorless syrup: R_f = 0.24 (*B*); $[\alpha]_D^{26}$ –103.1° (*c* = 2.11, $CHCl_3$); ^{1}H and ^{13}C NMR, see Tables 1,2. *Anal*. Calcd for $C_{21}H_{24}N_4O_7S$: C, 52.93; H, 5.08. Found: C, 52.99; H, 4.99.

1,3-Dimethyl-6-{(1*R*,2*S*)-1,2,3-trihydroxy-1,2-*O*-isopropylidene-3-*O*-[(methylthio)thiocarbonyl]propyl}lumazine (16a). To a solution of **9a** (64.6 mg, 0.200 mmol) in dry THF (1.0 mL) was added sodium hydride (60% in mineral oil, 16 mg, 0.40 mmol) at 0 °C. After stirring for 30 min, carbon disulfide (0.048 mL, 0.81 mmol) was added at 0 °C. The mixture was stirred for 30 min and then methyl iodide (0.051 mmol, 0.81 mmol) was added at 0 °C. The mixture was stirred at same temperature for 2 h, diluted with saturated brine, and extracted with $CHCl_3$ three times. The combined organic layers were washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with 1:1 AcOEt-hexane to give **16a** (54.9 mg, 66%) as yellow crystals: mp 153–155 °C (from AcOEt-hexane); R_f = 0.50 (*B*); $[\alpha]_D^{29}$ –122.0° (*c* = 1.64, $CHCl_3$); ^{1}H and ^{13}C NMR, see Tables 1,2. *Anal*.

Calcd for $C_{16}H_{20}N_4O_5S_2$: C, 46.59; H, 4.89. Found: C, 46.71; H, 4.79.

1,3-Dimethyl-7-{(1*R*,2*S*)-1,2,3-trihydroxy-1,2-*O*-isopropylidene-3-*O*-[(methylthio)thiocarbonyl]propyl}lumazine (16b).

By use of the same procedures for **16a** from **9a**, compound (**9b**) (84.6 mg) was converted into **16b** (86.6 mg, 80%) as yellow crystals: mp 102–104 °C (from AcOEt-hexane); R_f = 0.45 (*B*); $[\alpha]_D^{29}$ –113.6° (*c* = 1.16, $CHCl_3$); ^1H and ^{13}C NMR, see Tables 1,2. *Anal*. Calcd for $C_{16}H_{20}N_4O_5S_2$: C, 46.59; H, 4.89. Found: C, 46.81; H, 4.80.

7-[(1*R*,2*R*)-3-Bromo-1,2-dihydroxy-1,2-*O*-isopropylidenepropyl]-1,3-dimethyllumazine (17b).

Compound (**9b**) (103 mg, 0.320 mmol) was dissolved in dry CH_2Cl_2 (2.0 mL) and then carbon tetrabromide (159 mg, 0.480 mmol) and triphenylphosphine (109 mg, 0.416 mmol) were added. The mixture was stirred at rt for 4 h and then diluted with $CHCl_3$. The mixture was washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with 1:1 AcOEt-hexane to give **17b** (68.0 mg, 55%) as colorless crystals: mp 116–118 °C (from AcOEt-hexane); R_f = 0.31 (*B*), 0.71 (*D*); $[\alpha]_D^{29}$ –65.5° (*c* = 1.03, $CHCl_3$); ^1H and ^{13}C NMR, see Tables 1,2. *Anal*. Calcd for $C_{14}H_{17}BrN_4O_4$: C, 43.65; H, 4.45. Found: C, 43.77; H, 4.32.

7-[(1*R*,2*S*)-1,2-dihydroxy-1,2-*O*-isopropylidenepropyl]-1,3-dimethyllumazine (18b).

A. From 17b. To a solution of **17b** (45.8 mg, 0.119 mmol) in dry toluene (1.0 mL) was added tributyltin hydride (0.070 mL, 0.260 mmol) and AIBN (4.0 mg, 0.024 mmol). The mixture was refluxed for 8 h and then evaporated in vacuo. The residue was purified by column chromatography with a gradient eluant of 1:1 AcOEt-hexane to AcOEt to give **18b** (25.6 mg, 70%) as a colorless syrup; R_f = 0.24 (*B*), 0.61 (*D*); ^1H and ^{13}C NMR, see Tables 1,2. *Anal*. Calcd for $C_{14}H_{18}N_4O_4$: C, 54.89; H, 5.92. Found: C, 54.75; H, 5.84.

B. From 16b. By use of the same procedures described above, **16b** (45.8 mg, 0.111 mmol) was treated with tributyltin hydride (0.066 mL, 0.245 mmol) and AIBN (4.0 mg, 0.024 mmol). The resulting mixture was separated by column chromatography to give **9b** (26.1 mg, 73%) and **18b** (3.0 mg, 9%).

ACKNOWLEDGEMENTS

We are grateful to the SC-NMR Laboratory of Okayama University for the NMR measurements.

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18. The complete parameters for **6** obtained in the present study are shown here, because the NMR data for this compound reported in Ref. 10 include insufficient assignments.