Carbohydrate Research, 223 (1992) 279–286
Elsevier Science Publishers B.V., Amsterdam

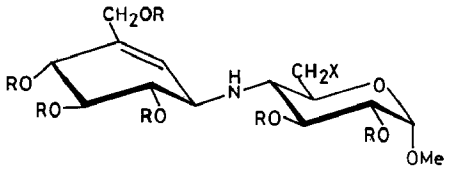
Note

Alternative synthesis and enzyme-inhibitory activity of methyl 1′-epiacarviosin and its 6-hydroxy analog*

Seiichiro Ogawa†, Chikara Uchida, and Yasushi Shibata
Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Kohoku-ku, Yokohama, 223 (Japan)

(Received June 26th, 1990; accepted for publication April 5th, 1991)

In connection with work already reported[2], methyl 1′-epiacarviosin (**1a**) and its 6-hydroxy analog (**2a**) have now been synthesized by reaction of the protected, enantiomerically pure 1′-epivalienamine, which is described for the first time, with the anhydro sugar derivative **10**, and their inhibitory activities against three enzymes were examined.

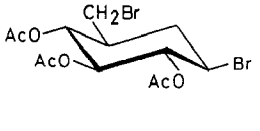


1a X = R = H
1b X = H; R = Ac
2a X = OH; R = H
2b X = OAc; R = Ac

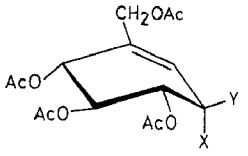
First, the amine synthon, di-*O*-isopropylidene-1-epivalienamine {(1*S*,2*R*,9*S*,10*S*)-9-amino-4,4,12,12-tetramethyl-3,5,11,13-tetraoxatricyclo[8.3.0.0.^{2,7}]tridec-7-ene, (**8**)} was synthesized from (1*R*)-(1,3/2,4,6)-1,2,3-tri-*O*-acetyl-4-bromo-6-bromomethyl-1,2,3-cyclohexanetetrol[3] (**3**), following the procedure[4] described for the preparation of the racemate. Treatment of **3** with 1,5-diazabicyclo[5.4.0]undec-5-ene in toluene afforded the conjugate diene, which was treated with bromine to the 1,4-addition product. Selective displacement of the primary bromide by acetate and successive treatment with sodium azide afforded a mixture (51% overall yield from **3**) of (1*S*)-(1,3/2,6)- (**4**) and (1,3,6/2)-4-acetoxymethyl-1,2,3-tri-*O*-acetyl-6-azido-4-cyclohexene-1,2,3-triol (**5**).

*Synthesis of Pseudo-oligosaccharidic Glycosidase Inhibitors, Part IX. For Part VIII, see ref. 1.
†To whom correspondence should be addressed.

0008-6215/92/$ 05.00

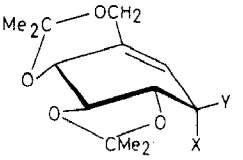


3



4 X = H; Y = N_3

5 X = N_3; Y = H

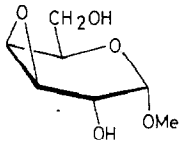


6 X = H; Y = N_3

7 X = N_3; Y = H

8 X = H; Y = NH_2

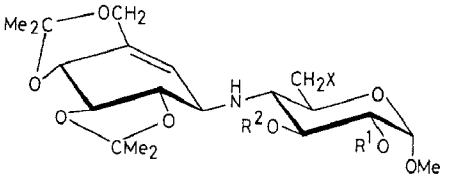
9 X = H; Y = NHAc



10

Zemplén *O*-deacetylation of the mixture, followed by isopropylidenation with 2-methoxypropene in *N,N*-dimethylformamide, gave, after chromatography, the *β*- (**6**) and *α*-azide[5] (**7**) as the di-*O*-isopropylidene derivatives in 61 and 26% yields, respectively. Compound **6** was reduced with hydrogen sulfide in aqueous pyridine to give the protected 1-epivalienamine (**8**, 97%), which was characterized as the *N*-acetyl derivative **9** by its ^{1}H-n.m.r. spectrum.

Coupling of the crude **8** with a slight excess of methyl 3,4-anhydro-*α*-D-galactopyranoside[6] (**10**) in 2-propanol for 45 h at 120° and successive acetylation of the products with acetic anhydride in pyridine afforded, after chromatography, the condensates **11** and **18** in 51 and 39% yields, respectively, based of **8**. They were characterized as the triacetates **12** and **19** on the basis of their ^{1}H.-n.m.r. spectra ($CDCl_3$), in which the signals due to the protons attached to the carbon atoms of the hexoside units bearing the imino bonds appeared as triplets (δ 2.93, J 10.3 Hz and δ 3.28, J 4 Hz, respectively), supporting the structures assigned.



11 R^1 = R^2 = H; X = OH

12 R^1 = R^2 = Ac; X = OAc

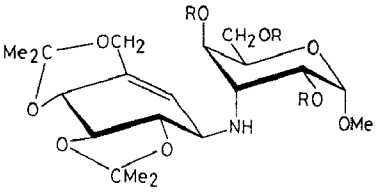
13 R^1 = R^2 = H; X = OTs

14 R^1 = Ts; R^2 = H; X = OTs

15 R^1 = R^2 = > CMe_2; X = OTs

16 R^1 = R^2 = > CMe_2; X = I

17 R^1 = R^2 = > CMe_2; X = H



18 R = H

19 R = Ac

Treatment of **11** with 1.7 molar equiv. of *p*-toluenesulfonyl chloride in pyridine at room temperature produced, after chromatography, the 6-tosylate **13** (~ 50%) and the 2,6-ditosylate **14** (~ 33%). After protection of **13** by conventional *O*-isopropylidenation (**13**→**15**, 36% overall yield from **11**), treatment of **15** with sodium iodide in *N,N*-dimethylformamide furnished the 6-iodide **16** (94%), deiodination of which with lithium triethylborohydride in tetrahydrofuran afforded the 6-deoxy compound **17** (91%).

O-Deisopropylidenation of **17** was effected by aqueous 70% acetic acid to afford the free carba-disaccharide **1a** (~ 100%). Compound **11** was similarly converted into **2a**. Compounds **1a** and **2a** were fully characterized as the totally acetylated derivatives **1b** and **2b** (ref. 2) respectively, based on the ^{1}H-n.m.r. spectra (Table I).

Biological assay. — Compounds **1a** and **2a** were tested for inhibitory activity against α- and β-D-glucosidase and α-D-mannosidase (see Table II). They were ~ 300

TABLE I

^{1}H-N.m.r. data (270 MHz, $CDCl_3$) of carba-disaccharide peracetates **1b** and **2b**

Proton	*Chemical shifts (δ)*		*Coupling constants (Hz)*		
	1b	**2b**		**1b**	**2b**
H-1	4.80 d	4.86 d	$J_{1,2}$	3.7	3.7
H-2	4.85 dd	4.88 dd	$J_{2,3}$	9.9	8.1
H-3	5.16 t	5.20 t	$J_{3,4}$	9.9	8.1
H-4	2.43 t	2.78 dt	$J_{4,5}$	9.9	8.1
H-5	3.56 dq	3.66 ddd	$J_{5,6}$	6.2	2.2
CH_3	1.27 d		$J_{5,6}$	–	5.1
H-6		4.52 dd	$J_{6,6}$	–	11.7
		4.13 dd	$J_{4,NH}$		3.2
H-1′	3.41 bd	3.28 bt	$J_{1',2'}$	~ 0	~ 0
H-2′	5.82 bs	5.85 bs	$J_{4',5'}$	7.4	7.7
H-4′	5.68 bd	5.67 bd	$J_{5',6'}$	10.6	10.6
H-5′	5.23 dd	5.20 dd	$J_{1',6'}$	8.4	8.6
H-6′	4.97 dd	4.96 dd	$J_{7',7'}$	12.8	13
H-7′	4.66 d	4.68 d	$J_{1',NH}$		8.6
H-7′	4.34 d	4.33 d			
NH		1.14 bdd			
OMe	3.36	3.37			
Ac	2.075[a]	2.11			
	2.07	2.09			
	2.06	2.08			
	2.04	2.076			
	2.01	2.06			
		2.03			
		2.00			

[a] Singlet for two methyl groups.

TABLE II

Inhibitory activity of carbo-disaccharides **1a** and **2a** against three enzymes

Compound	*Final concentration (μg mL^{-1})*							
	α-D-*Glucosidase*[a]			β-D-*Glucosidase*[b]		α-D-*Mannosidase*[c]		
	1000	*100*	*10*	*1000*	*10*	*1000*	*100*	*10*
1a	71.6[d]	40.9	11.9	32.7	7.1	89.2	71.4	20.9
2a	79.5	47.6	19.6	~0	0.6	86.0	55.2	10.3

[a] Yeast α-D-glucosidase, 0.66mM *p*-nitrophenyl α-D-glucopyranoside, 100mM PBS, pH 6.8. [b] Almond β-D-glucosidase, 0.33mM *p*-nitrophenyl β-D-glucopyranoside, 100mM acetate buffer, pH 5.0. [c] Jack bean α-D-mannosidase, 20mM *p*-nitrophenyl α-D-mannopyranoside, 100mM acetate buffer, pH 4.5. [d] Inhibition (*I*%).

times less active against α-D-glucosidase than the counterpart methyl acarviosin[7]. Interestingly, however, although methyl acarviosin has almost no inhibitory activity against α-D-mannosidase, the two compounds are potent inhibitors of α-D-mannosidase, being rather more effective than mannojirimycin hydrogensulfite adduct[8]. The configuration at C-1 of the cyclohexene moiety seems to play an important role for recognition and binding to the active center of the enzymes.

EXPERIMENTAL

General methods. — Melting points were determined with a MT capillary melting-point apparatus and uncorrected. Optical rotations were measured with a Jasco DIP-4 or DIP-370 polarimeter. ^{1}H-N.m.r. spectra were recorded for solution in $CDCl_3$ (internal Me_4Si) with Jeol JNM EX-90 (90 MHz) or Jeol JNM GSX-270 MHz) instruments. T.l.c was performed on silica gel 60 GF (Merck) with detection by charring with H_2SO_4. Column chromatography was conducted on Wakogel C-300 (300 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and evaporated at $<50°$ under diminished pressure.

(1S)-(1,3/2,6)- (**4**) *and (1S)-(1,3,6/2)-4-Acetoxymethyl-1,2,3-tri-*O*-acetyl-6-azido-4-cyclohexene-1,2,3-triol* (**5**). — (1*R*)-(1,3/2,4,6)-1,2,3-Tri-*O*-acetyl-4-bromo-6-bromomethylcyclohexane-1,2,3-triol[3] (**3**, 0.7 g, 1.63 mmol) was converted into a mixture (309 mg, 51%) of **4** and **5** as described in the preparation of the racemate[4].

Anal. Calc. for $C_{15}H_{19}N_3O_8$: C, 48.78; H, 5.19; N, 11.38. Found: C, 48.74; H, 5.10; N, 11.25.

*(1S,2R,9R,10S)- (***6***) and (1S,2R,9S,10S)-9-Azido-4,4,12,12-tetramethyl-3,5,11,13-tetraoxatricyclo[8.3.0.0^{2,7}]tridec-7-ene* (**7**). — A mixture of **4** and **5** (0.31 g, 0.84 mmol) was treated with methanolic M NaOMe (1 mL) in MeOH (8 mL) for 2 h at room temperature. The solution was neutralized with Amberlite IR-120B (H^+) resin and then the mixture was filtered and the filtrate evaporated to give a syrup (165 mg), to a solution of which in *N,N*-dimethylformamide (5.5 mL) were added 2,2-dimethoxypropane (2.1

mL) and *p*-toluenesulfonic acid monohydrate (43 mg, 0.25 mmol). After stirring for 16 h at room temperature, the mixture was neutralized with $NaHCO_3$ and then evaporated. Column chromatography (10 g) of the products with 1:35 butanone–toluene gave first compound **6** (142 mg, 61%) as a syrup; $[\alpha]_D^{26}$ −124° (*c* 1.4, $CHCl_3$); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 5.39 (bs, 1 H, H-8), 4.64 (bd, 1 H, $J_{1,2}$ 8 Hz, H-2), 4.53 and 4.18 (2 d, each 1 H, $J_{6,6}$ 14 Hz, H-6), 4.22 (bd, 1 H, $J_{9,10}$ 8.2 Hz, H-9), 3.75 (dd, 1 H, $J_{1,10}$ 9.8 Hz, H-1), 3.57 (dd, 1 H, H-10), 1.57, 1.48, and 1.43 (3 s, 3, 6, and 3 H, 2 CMe_2).

Anal. Calc. for $C_{13}H_{19}N_3O_4$: C, 55.51; H, 6.81; N, 14.94. Found: C, 55.23; H, 6.61; N, 14.74.

Eluted second was **7** (62 mg, 26%), isolated as a syrup; $[\alpha]_D^{21}$ +81° (*c* 0.9, $CHCl_3$). {lit.[5] $[\alpha]_D^{22}$ +91° (*c* 2.7, $CHCl_3$)}. The ^{1}H-n.m.r. spectral data accorded with those reported for an authentic sample.

(1S,2R,9S,10S)-9-Amino-4,4,12,12-tetramethyl-3,5,11,13-tetraoxatricyclo-[8.3.0.0^{2,7}]tridec-7-ene (**8**). — Compound **6** (1.41 g, 5.01 mmol) was treated with saturated H_2S in 50% aq. pyridine (10 mL) for 2 h at room temperature. Evaporation of the mixture gave a syrup containing sulfur, which was eluted from a column of silica gel (40 g) with toluene → 2:3 acetone-toluene to give crude **8** (1.25 g, 97%) as a syrup; $[\alpha]_D^{23}$ −90° (*c* 1, $CHCl_3$).

Compound **8** is very hydroscopic and did not give a satisfactory elementary analysis.

(1S,2R,9S,10S)-9-Acetamido-4,4,12,12-tetramethyl-3,5,11,13-tetraoxatricyclo-[8.3.0.0^{2,7}]tridec-7-ene (**9**). — Compound **8** (28 mg, 0.099 mmol) was acetylated with Ac_2O (0.3 mL) and pyridine (0.3 mL) and the mixture was evaporated. Column chromatography (1 g) of the products with 1:8 butanone–toluene gave **9** (26 mg, 88%) as a syrup; $[\alpha]_D^{23}$ −88° (*c* 1.3, $CHCl_3$); ^{1}H-n.m.r. (90 MHz, $CDCl_3$): δ 5.78 (bd, 1 H, $J_{9,NH}$ 7.8 Hz, NH), 5.49 (bs, 1 H, H-8), 4.83–4.58 (m, 2 H, H-2,9), 4.49 and 4.15 (2 d, each 1 H, $J_{6,6}$ 13.9 Hz, H-6), 3.81 (dd, 1 H, $J_{1,2}$ 7.9, $J_{1,10}$ 9 Hz, H-1), 3.56 (t, 1 H, $J_{9,10}$ 9 Hz, H-10), 2.10 (s, 3 H, NAc), 1.56, 1.47, and 1.43 (3 s, 3, 6, and 3 H, 2 CMe_2).

Anal. Calc. for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.33; H, 7.70; N, 4.45.

4′,7′:5′,6′-Di-O-isopropylidene derivative **11** *of methyl 4-deoxy-4-[(1R)-(1,5/4,6)-4,5,6-trihydroxy-3-hydroxymethyl-2-cyclohexenyl]amino-α-D-glucopyranoside and that* (**18**) *of methyl 3-deoxy-3-[(1R)-(1,5/4,6)-4,5,6-trihydroxy-3-hydroxymethyl-2-cyclohexenyl]amino-α-D-gulopyranoside.* — A mixture of the crude **8** (226 mg, 0.86 mmol), methyl 3,4-anhydro-α-D-galactopyranoside[6] (**10**, 182 mg, 1.04 mmol) and 2-propanol (1 mL) was heated in a sealed tube for 45 h at 120° and then evaporated. Column chromatography (25 g) of the products with 1:1 acetone–toluene gave, first, **18** (147 mg, 39% based on **8** used) as an amorphous powder. A portion (22 mg, 0.051 mmol) of **18** was acetylated with Ac_2O and pyridine to give the tri-*O*-acetyl derivative **19** (28 mg, 98%) as an amorphous powder; $[\alpha]_D^{22}$ +25° (*c* 1.2, $CHCl_3$); ^{1}H-n.m.r. (270 MHz, $CDCl_3$): δ 5.34 (bs, 1 H, H-2′), 5.08 (dd, 1 H, $J_{1,2}$ 3.7, $J_{2,3}$ 4 Hz, H-2), 4.98 (d, 1 H, $J_{3,4}$ 4, $J_{4,5}$ ~ 0 Hz, H-4), 4.87 (d, 1 H, H-1), 4.63 (bd, 1 H, $J_{4',5'}$ 8.1 Hz, H-4′), 4.51 and 4.16 (2 d, each 1 H, $J_{7',7'}$ 13.9 Hz, H-7′), 4.45–4.40 (m, 1 H, H-6), 4.16–4.05 (m, 2 H, H-5,6), 3.68 (dd, 1 H,

$J_{5',6'}$ 9.5 Hz, H-5'), 3.62 (d, $J_{1',6'}$ 8.1 Hz, H-1'), 3.43 (dd, 1 H, H-6'), 3.41 (s, 3 H, OMe), 3.28 (t, 1 H, H-3), 2.13, 2.11, and 2.06 (3 s, each 3 H, 3 Ac), 1.57, 1.443, 1.436, and 1.42 (4 s, each 3 H, 2 CMe_2).

Anal. Calc. for $C_{26}H_{39}NO_{12}$: C, 56.01; H, 7.05; N, 2.51. Found: C, 56.02; H, 6.99; N, 2.55.

Eluted second was **11** (194 mg, 51% based on **8** used), isolated as an amorphous powder, a portion (27 mg, 0.063 mmol) of which was acetylated conventionally to give **12** (34 mg, 97%) as an amorphous powder; $[\alpha]_D^{22}$ +62° (*c* 1.3, $CHCl_3$); ^{1}H-n.m.r. (270 MHz, $CDCl_3$): δ 5.26 (dd, 1 H, $J_{2,3}$ 12.3, $J_{3,4}$ 10.3 Hz, H-3), 5.17 (bs, 1 H, H-2'), 4.91 (dd, 1 H, $J_{1,2}$ 3.7 Hz, H-2), 4.89 (d, 1 H, H-1), 4.59 (dd, 1 H, $J_{5,6}$ 2, $J_{6,6}$ 11.7 Hz) and 4.26 (dd, 1 H, $J_{5,6}$ 6.6 Hz) (H-6), 4.57 (bd, 1 H, $J_{4',5'}$ 8.1 Hz, H-4'), 4.47 and 4.11 (2 d, each 1 H, $J_{7',7'}$ 13.9 Hz, H-7'), 3.73 (ddd, 1 H, $J_{4,5}$ 10.3 Hz, H-5), 3.64 (dd, 1 H, $J_{5',6'}$ 9.5 Hz, H-5'), 3.44 (bd, 1 H, $J_{1',6'}$ 8.8 Hz, H-1'), 3.38 (s, 3H, OMe), 2.93 (t, 1 H, H-4), 2.09 and 2.08 (2 s, 6 and 3 H, 3 Ac), 1.56, 1.461, 1.456, and 1.42 (4 s, each 3 H, 2 CMe_2).

Anal. Found: C, 56.01; H, 6.94; N, 2.56.

2,3;4',7':5',6'-Tri-O-isopropylidene derivative **15** *of methyl 4-deoxy-4-[(1R)-(1,5/4,6)-4,5,6-trihydroxy-3-hydroxymethyl-2-cyclohexenyl]amino-6-O-p-tolylsulfonyl-α-D-gluco-pyranoside.* — To a solution of compound **11** (168 mg, 0.39 mmol) in pyridine (5 mL) was added TsCl (42 mg, 0.22 mmol) at 0°. After stirring for 10 h at 0°, additional TsCl (84 mg, totally 0.66 mmol) was added to the mixture, which was stirred for a total of 37 h at the same temperature. After treatment with excess $NaHCO_3$, the mixture was evaporated, and the residue extracted with $CHCl_3$. Column chromatography (8 g) of the products with 2:3 acetone-toluene gave, first, the 4',7':5',6'-di-*O*-isopropylidene derivative **14** of methyl 4-deoxy-4-[(1*R*)-(1,5/4,6)-4,5,6-trihydroxy-3-hydroxymethyl-2-cyclohexenyl]amino-2,6-di-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside (95 mg, ~33%) as an amorphous powder, which was characterized by converting it into the syrupy acetate; ^{1}H-n.m.r. (270 MHz, $CDCl_3$): δ 7.77, 7.36, and 7.33 (3 d, 4, 2, and 2 H, *J* 8.1 Hz, 2 MeC_6H_4), 5.17 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.9 Hz, H-3), 5.07 (bs, 1 H, H-2'), 4.62 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1), 4.55 (bd, 1 H, $J_{4',5'}$ 8.1 Hz, H-4'), 4.50 (dd, 1 H, $J_{5,6}$ 2.2, $J_{6,6}$ 11 Hz) and 4.22 (dd, 1 H, $J_{5,6}$ 6.6 Hz) (H-6), 4.49–4.42 (m, 1 H) and 4.08 (d, 1 H, $J_{7',7'}$ 13.9 Hz) (H-7'), 4.44 (dd, 1 H, H-2), 3.68 (ddd, 1 H, $J_{4,5}$ 9.9 Hz, H-5), 3.57 (dd, 1 H, $J_{5',6'}$ 9.5 Hz, H-5'), 3.33 (bd, 1 H, $J_{1',6'}$ 8.8 Hz, H-1'), 3.23 (s, 3 H, OMe), 3.21 (dd, 1 H, H-6'), 2.75 (t, 1 H, H-4), 2.46 and 2.45 (2 s, each 3 H, 2 Ts Me), 1.91 (s, 3 H, Ac), 1.56, 1.42, 1.41, and 1.36 (4 s, each 3 H, 2 CMe_2).

Eluted second was the 4',7':5',6'-di-*O*-isopropylidene derivative **13** of methyl 4-deoxy-4-[(1*R*)-(1,5/4,6)-4,5,6-trihydroxy-3-hydroxymethyl-2-cyclohexenyl]amino-6-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside (113 mg, ~50%) as an amorphous powder, which was, without further purification, treated with 2-methoxypropene (0.28 mL, 1.98 mmol) in the presence of *p*-toluenesulfonic acid monohydrate (9 mg, 0.12 mmol) in *N,N*-dimethylformamide (4 mL) for 16 h at room temperature. The mixture was neutralized with $NaHCO_3$, filtered, and then the filtrate was evaporated. Column chromatography (5 g) of the products with 1:7 butanone–toluene gave **15** (18 mg, 36% based on **10**) as an amorphous powder; $[\alpha]_D^{23}$ + 58° (*c* 0.9, $CHCl_3$); ^{1}H-n.m.r. (270 MHz,

$CDCl_3$): δ 7.82 and 7.34 (2 d, each 2 H, MeC_6H_4), 5.39 (bs, 1 H, H-2'), 4.93 (d, 1 H, $J_{1,2}$ 2.9 Hz, H-1), 4.59 (bd, 1 H, $J_{4',5'}$ 7.9 Hz, H-4'), 4.52 and 4.16 (2 d, each 1 H, $J_{7',7'}$ 13.9 Hz, H-7'), 4.45 (dd, 1 H, $J_{5,6}$ 2.2, $J_{6,6}$ 10.6 Hz) and 4.37 (dd, 1 H, $J_{5,6}$ 5.1 Hz) (H-6), 3.75 (dd, 1 H, $J_{2,3}$ 9.5, $J_{3,4}$ 9.9 Hz, H-3), 3.63 (dd, 1 H, $J_{4',5'}$ 7.9, $J_{5',6'}$ 9.9 Hz, H-5'), 3.59 (bd, 1 H, $J_{1',6'}$ 9 Hz, H-1'), 3.46 (ddd, 1 H, $J_{4,5}$ 10.3 Hz, H-5), 3.42 (dd, 1 H, H-2), 3.41 (dd, 1 H, H-6'), 3.36 (s, 3 H, OMe), 2.96 (dd, 1 H, H-4), 2.45, (s, 3 H, Ts Me), 1.57, 1.43, and 1.41 (3 s, 3, 12, and 3 H, 3 CMe_2).

Anal. Calc. for $C_{30}H_{43}NO_{11}S$: C,57.59; H, 6.93; N, 2.24. Found: C,57.33; H, 6.58; N, 2.22.

2,3;4',7':5',6'-Tri-O-isopropylidene derivative **16** *of methyl 4,6-dideoxy-4-[(1R)-(1,5/4,6)-4,5,6-trihydroxy-3-hydroxymethyl-2-cyclohexenyl]amino-6-iodo-α-D-glucopyranoside.* — A mixture of **15** (17 mg, 0.027 mmol), NaI (9 mg, 0.06 mmol) and *N,N*-dimethylformamide (1 mL) was heated for 2.5 h at 100° and then evaporated. Column chromatography (1 g) of the residue with 1:8 butanone–toluene gave **16** (15 mg, 94%) as a syrup; $[\alpha]_D^{23}$ +64° (*c* 1.1, $CHCl_3$); ^{1}H-n.m.r. (270 MHz, $CDCl_3$): δ 5.44 (bs, 1 H, H-2'), 5.06 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1), 4.61 (bd, 1 H, $J_{4',5'}$ 8.1 Hz, H-4'), 4.52 and 4.16 (2 d, each 1 H, $J_{7',7'}$ 13.9 Hz, H-7'), 3.82 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, H-3), 3.75–3.68 (m, 1 H, H-1'), 3.72 (dd, 1 H, $J_{5',6'}$ 9.5 Hz, H-5'), 3.71 (dd, 1 H, $J_{5,6}$ 2.9, $J_{6,6}$ 10.6 Hz) and 3.58 (dd, 1 H, $J_{5,6}$ 5.7 Hz) (H-6), 3.52 (dd, 1 H, H-2), 3.47 (s, 3 H, OMe), 3.45 (dd, 1 H, $J_{1',6'}$ 9.2 Hz, H-6'), 3.14 (ddd, 1 H, $J_{4,5}$ 9.9 Hz, H-5), 2.87 (dd, 1 H, H-4), 1.57, 1.46, 1.45, 1.44, and 1.43 (5 s, 3, 6, 3, 3, and 3 H, 3 CMe_2).

Anal. Calc. for $C_{23}H_{36}INO_8$: C, 47.51; H, 6.24; N, 2.41. Found: C, 47.16; H, 6.42; N, 2.14.

2,3;4',7':5',6'-Tri-O-isopropylidene derivative **17** *of methyl 4,6-dideoxy-4-[(1R)-(1,5/4,6)-4,5,6-trihydroxy-3-hydroxymethyl-2-cyclohexenyl]amino-α-D-glucopyranoside.* — To a solution of **16** (45 mg, 0.077 mmol) in tetrahydrofuran (1.5 mL) was added M lithium triethylborohydride–tetrahydrofuran solution (1.2 mL, 1.2 mmol) at 0°. After stirring for 1 h at 0°, the reaction was quenched by adding MeOH (1 mL) and 35% hydrogen peroxide (1 mL). The mixture was diluted with $CHCl_3$ (25 mL), washed with water (25 mL, × 2) and then evaporated. Column chromatography (1 g) of the products with 1:5 butanone–toluene gave **17** (32 mg, 91%) as needles; m.p. 154–154.5° (from EtOH), $[\alpha]_D^{21}$ +63° (*c* 1.2, $CHCl_3$); ^{1}H-n.m.r. (270 MHz, $CDCl_3$): δ 5.47 (bs, 1 H, H-2'), 4,61 (d, 1 H, $J_{1,2}$ 2.9 Hz, H-1), 4.60 (bd, 1 H, $J_{4',5'}$ 8.1 Hz, H-4'), 4.52 and 4.14 (2 d, each 1 H, $J_{7',7'}$ 13.9 Hz, H-7'), 3.80 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, H-3), 3.71 (dd, 1 H, $J_{5',6'}$ 9.5 Hz, H-5'), 3.53 (dd, 1 H, H-2), 3.75–3.68 (m, 1 H, H-1'), 3.55–3.42 (m, 1 H, H-5), 3.45 (dd, 1 H, $J_{1',6'}$ 5.9 Hz, H-6'), 3.42 (s, 3 H, OMe), 2.73 (t, 1 H, $J_{4,5}$ 9.5 Hz, H-4), 1.57, 1.45, and 1.43 (3 s, 3, 9, and 6 H, 3 CMe_2), 1.36 (d, 3 H, $J_{5,6}$ 6.2 Hz, H-6).

Anal. Calc. for $C_{23}H_{37}NO_8$: C, 60.64; H, 8.19; N, 3.07. Found: C, 60.47; H, 8.01; N, 3.04.

Methyl 4,6-dideoxy-4-[(1R)-(1,5/4,6)-4,5,6-trihydroxy-3-hydroxymethyl-2-cyclohexenyl]amino-α-D-glucopyranoside (**1a**) *and its hexaacetate* **1b**. — Compound **17** (31 mg, 0.068 mmol) was heated in aq. 70% AcOH (1 mL) for 2 h at 60°. The mixture was evaporated to give a residue, which was eluted from a column of Amberlite IRA-400

(OH^-) resin with MeOH and the eluate was evaporated to give **1a** (23 mg, ~ 100%) as an amorphous powder; $[\alpha]_D^{24}$ + 32° (*c* 0.8, MeOH), which was directly subjected to biological assay.

Compound **1a** (16 mg, 0.048 mmol) was acetylated conventionally to give **1b** (24 mg, ~ 100%) as plates; m.p. 154–155° (from EtOH), $[\alpha]_D^{25}$ −11° (*c* 1.1, $CHCl_3$). ^{1}H-N.m.r. data are listed in Table I.

Anal. Calc. for $C_{26}H_{37}NO_{14}$: C, 53.15; H, 6.35; N, 2.38. Found: C, 52.93; H, 5.97; N, 2.40.

Methyl 4-deoxy-4-[(1R)-(1,5/4,6)-4,5,6-trihydroxy-3-hydroxymethyl-2-cyclohexenyl]amino-α-D-glucopyranoside (**2a**) *and its heptaacetate* **2b.** — Compound **11** (75 mg, 0.17 mmol) was *O*-deisopropylidenated as described in the preparation of **1a** to give **2a** (61 mg, ~ 100%) as an amorphous powder. $[\alpha]_D^{24}$ +37° (*c* 1.2, MeOH), which was directly subjected to biological assay.

Compound **2a** (24 mg, 0.068 mmol) was acetylated conventionally to give **2b** (46 mg, ~ 100%) as plates; m.p. 119–120° (from EtOH), $[\alpha]_D^{25}$ + 6° (*c* 1.2, $CHCl_3$) {lit.[2] m.p. 113–115° (from EtOH), $[\alpha]_D^{20}$ +4° (*c* 0.7, $CHCl_3$)}. ^{1}H-N.m.r. data are listed in Table I.

Anal. Calc. for $C_{28}H_{39}NO_{16}$: C, 52.09; H, 6.09; N, 2.17. Found: C, 51.95; H, 5.82; N, 2.30.

ACKNOWLEDGMENTS

We thank Mr. E. Hata for elemental analyses, and Drs. S. Inouye and T. Machinami (Meiji Seika Kaisha, Ltd., Yokohama) for carrying out bioassays. This work was supported, in part, by a grant of the Asahi Glass Foundation for contribution to industrial technology.

REFRENCES

1 Y. Shibata, Y. Kosuge, and S. Ogawa, *Carbohydr. Res.*, 199 (1990) 37–54.
2 S. Ogawa, K. Yasuda, T. Takagaki, Y. Iwasawa, and T. Suami, *Carbohydr. Res.*, 141 (1985) 329–334.
3 S. Ogawa, Y. Iwasawa, T. Nose, T. Suami, S. Ohba, M. Ito, and Y. Saito, *J. Chem. Soc., Perkin Trans. 1*, (1985) 903–906.
4 S. Ogawa, T. Toyokuni, and T. Suami, *Chem. Lett.*, (1980) 713–716; T. Toyokuni, S. Ogawa, and T. Suami, *Bull. Chem. Soc. Jpn.*, 56 (1983) 1161–1170.
5 S. Ogawa and Y. Shibata, *J. Chem. Soc., Chem. Commun.*, (1989) 605–606; Y. Shibata and S. Ogawa, *Carbohydr. Res.*, 189 (1989) 309–322.
6 J. G. Buchanan, *J. Chem. Soc.*, (1958) 2511–2517.
7 B. Junge, F.-R. Heiker, J. Kurz, L. Müller, D. D. Schmidt, and C. Wunsche, *Carbohydr. Res.*, 128 (1984) 235–268.
8 Y. Kodama, T. Tsuruoka, T. Niwa, and S. Inouye, *J. Antibiot.*, 38 (1985) 116–118; N. Chida, Y. Furuno, and S. Ogawa, *J. Chem. Soc., Chem. Commun.*, (1989) 1230–1231.