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Synthesis of 5a-carba-hexopyranoses and hexopyranosylamines, as well as 5a,5a′-dicarbadisaccharides, from 3,8-dioxatricyclo[4.2.1.0^{2,4}]nonan-9-ol: glycosidase inhibitory activity of N-substituted 5a-carba-β-gluco- and β-galactopyranosylamines, and derivatives thereof

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Abstract—Since glycosidase and glycosyltransferase inhibitors, composed of carba-sugars, have recently attracted much attention, it is desirable to develop effective preparative routes for provision of new carba-sugar derivatives of potential biological interest. 1,2:3,6-Dianhydro-5a-carba-α-glucopyranose was here chosen for study of synthetic utility, and demonstrated to be a promising intermediate for supplying several carba-β-glycosylamines and N-linked dicarba-oligosaccharides. An N-linked 5a,5a′-dicarbalactose derivative obtained here was found to be a strong α-galactosidase inhibitor (IC_{50} 1.2 μM, green coffee beans).

1. Introduction

In recent years, glycosidase and glycosyltransferase inhibitors, of carba-glycosylamine[1] and N-linked carba-disaccharide types,[2] have attracted much attention, stimulating us to develop efficient preparative routes for different carba-sugars of biological interest. We here chose 1,2:3,6-dianhydro-5a-carba-α-DL-glucopyranose† (**2a**), (1*SR*,2*RS*,4*SR*,6*SR*,9*RS*)-3,8-dioxatricyclo[4.2.1.0^{2,4}]-nonan-9-ol, for examination of its potential as a synthetic intermediate with general application for further demands of glycobiology. Compound **2a** was first prepared[3] as a precursor for synthesis of β-validamine and its 6-amino-6-deoxy derivative, a branched-chain analogue of 2-deoxystreptamine. Recently, this compound was successfully utilized as an intermediate for synthesis of 5a-carba-sugars, especially fucose-type validamines.[4] The present communication describes a further investigation of the potential of **2a** as a key compound for several biologically interesting 5a-carba-sugars (Fig. 1).

Advantageous chemical features of **2a** are as follows: the 3,6-anhydro bridge plays a role both in protecting the 3- and 6-hydroxyl groups and in causing 5a-carba-α-glucopyranose to adopt the 1C conformation. The anhydro ring is easily opened by conventional acetolysis or bromination with HBr–AcOH. Furthermore, the 1,2-epoxide group is reactive toward common nucleophiles, being cleaved at C-1 with high regioselectivity. The 4-hydroxyl group of **2a** is readily oxidized to give rise to the ketone **4**, which can be reduced to regenerate **2a**. The 4-sulfonates **3f** and **3i** do not undergo nucleophilic displacement even with strong nucleophiles and also remain unchanged under acetolysis to open the 3,6-anhydro ring.

2. Results and discussion

2.1. Improved synthesis of 1,2:3,6-dianhydro-5a-carba-α-D-glucopyranose (2a)

Initially the dianhydride **2a** was prepared from 2,3,4-tri-*O*-acetyl-6-bromo-6-deoxy-5a-carba-β-glucopyranosyl

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† In this paper, the nomenclature of carba-sugar derivatives follows the IUPAC-IUB Recommendations 1996 (*Carbohydr. Res.* **1997**, *297*, 1).

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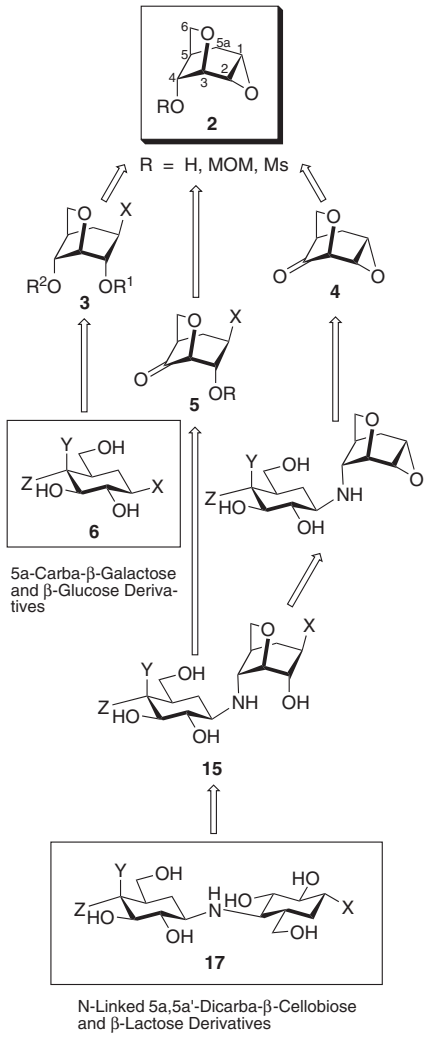
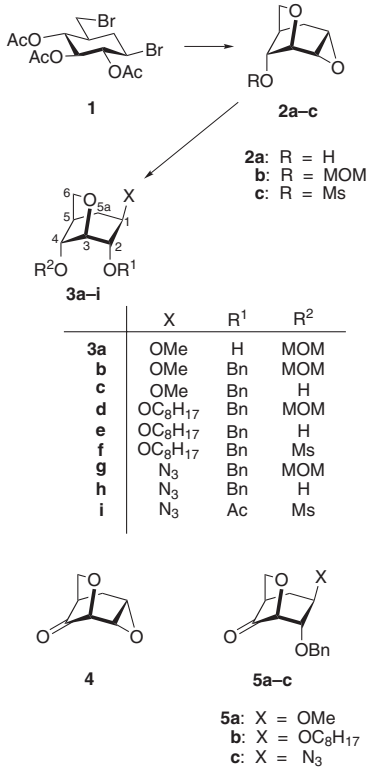


Figure 1. Possible synthetic routes to 5a-carba-β-galacto- and β-glucopyranose derivatives, and N-linked 5a,5a′-dicarbadisaccharides from 1,2:3,6-dianhydro-5a-carba-α-glucopyranose: X = NHR, OR, etc.; Y, Z = OH, NH_2, etc.



	X	R^1	R^2
3a	OMe	H	MOM
b	OMe	Bn	MOM
c	OMe	Bn	H
d	OC_8H_{17}	Bn	MOM
e	OC_8H_{17}	Bn	H
f	OC_8H_{17}	Bn	Ms
g	N_3	Bn	MOM
h	N_3	Bn	H
i	N_3	Ac	Ms

Scheme 1. Preparation of 1,2:3,6-dianhydro-5a-carba-α-glucopyranose and its transformation into synthetic intermediates.

bromide[5] (**1**) by treatment with an excess of methanolic sodium methoxide for 2 h at reflux temperature, and the major product **2a** was isolated as the acetate in 65% yield, accompanied by the methyl ether generated by cleavage of the 1,2-anhydro ring with a methoxide ion (Scheme 1). In this work, compound[6] **2a** was obtained directly as pure crystals in 89% by treatment of **1** with 3 molar equiv of solid sodium methoxide in methanol at 0–5 °C for 3 h. Compound **2a** was readily transformed into the protected derivatives: the methoxymethyl ether **2b** and mesylate **2c**.

2.2. Synthesis of 3,6-anhydro-5a-carba-β-glucopyranose derivatives

Treatment of **2b** with methanolic sodium methoxide (5 molar equiv) for 20 h at reflux temperature gave the methyl ether **3a** (75%), which was conventionally exposed to benzyl bromide–NaH in DMF (3 molar equiv) at room temperature to afford the benzyl ether[7] **3b** (95%). Subsequent removal of a methoxymethyl group of **3b** under the influence of THF and 12 M HCl at room temperature gave the 4-OH unprotected derivative **3c** (~100%). Similarly, the octyl ether was readily obtained from **2b** by treatment with a slight excess of sodium octoxide in octanol for 2 days at reflux temperature, and the product was isolated[8] as the benzyl ether **3d** (28% over-all yield), which was also converted into the 4-hydroxy compound **3e** (83%). Azidolysis of **2b** with sodium azide (3 molar equiv) in 80% aqueous DMF at 120 °C proceeded smoothly and the resulting sole azide was isolated as the benzyl ether **3g** (86% over-all yield), which was similarly converted into the 4-hydroxy compound **3h** (91%). Compounds **2a**, **3c**, **3e**, and **3h** were found to be oxidized with DMSO/Ac_2O to afford the respective ketones[9] **4** and **5a**–**c** in ~80% yields, which were used as acceptors for reductive amination with carba-glycosylamines, affording N-linked 5a,5a′-dicarbadisaccharides. When compound **2c** was treated with sodium azide (3 molar equiv) in DMF at 120 °C, this gave, after acetylation, the azido mesylate **3i** (64%), showing that the 4-mesyloxyl group is unreactive toward strong nucleophiles. Removal of the 3,6-anhydro bridges of **3f** and **3i** would be expected to provide useful precursors for the preparation of 5a-carba-β-galactopyranose derivatives.

2.3. Synthesis of alkyl 5a-carba-β-gluco- and β-galactopyranosides

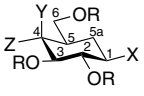
Conventional acetolysis of **3d** and **3f** with AcOH/Ac_2O/H_2SO_4 (40:20:1) at 80 °C gave carba-glucopyranoside derivatives **6a** (96%) and **6c** (81%), respectively.

O-Deacetylation of **6a** gave octyl 5a-carba-β-glucopyranoside[10] **6b** (84%). On the other hand, nucleophilic substitution of the 4-mesyloxyl group of **6c** with potassium acetate (5 molar equiv) readily proceeded in DMF in the presence of 18-crown-6 ether at 110 °C to give[8] a sole tetra-*O*-acetyl derivative **6d** (44%), which was O-deacetylated under Zemplén conditions to give octyl 5a-carba-β-galactopyranoside[10] **6e** (85%). In this reaction, formation of other products, initiated by neighboring participation of the 3-acetoxyl group, was not observed. The present synthesis significantly improved the preceding routes[10] to **6b** and **6e**, thus constituting a practical synthetic regimen for alkyl 5a-carba-galacto and glucopyranosides. Very recently some alkyl 5a-carba-glycopyranosides have actually been applied[11] as potent primers for biocombinatorial synthesis[12] (Scheme 2).

Acetolysis of compound **3i** produced[8,13] the mesylate **6f** (26%) and the acetate **6g** (5%). The latter appeared to be formed by further acetolysis of **6f** in situ. In fact, nucleophilic substitution of **6f** with sodium acetate in DMF gave **6g** (71%). Conventional O-deacetylation of **6g** followed by hydrogenolysis in ethanol in the presence of Raney nickel afforded, after purification over a column of Dowex-50W × 2 (H^+) resin with methanolic 5% ammonia, 5a-carba-β-galactopyranosylamine (**6h**, 85%), which was transformed into the *N*-acetyl derivative **6i** (~100%) (Scheme 3).

2.4. Synthesis of *N*-alkyl 3,6-anhydro-5a-carba-β-glucosylamines and derivatives thereof

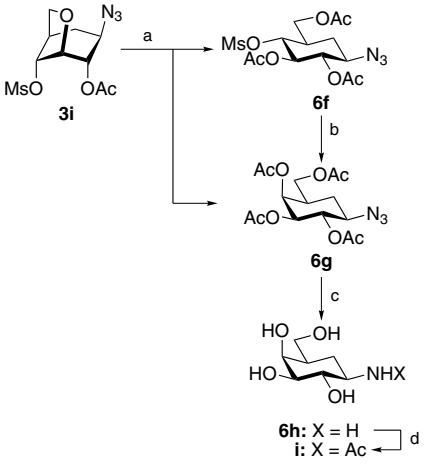
Direct nucleophilic cleavage of the 1,2-anhydro ring of **2a** with alkyl and phenylalkyl-amines was attempted in order to prepare N-substituted derivatives **7a–f**, from which corresponding 5a-carba-β-glucopyranosylamines might be obtainable (Scheme 4). Treatment with a molar equivalent of butylamine in 2-propanol in a sealed tube for 4 days at 120 °C resulted in preferential cleavage at C-1 to give, after purification by silica gel chromatography, *N*-butyl-3,6-anhydro-5a-carba-β-glucopyranosylamines[14] **7a** (78%). Similarly, by use of hexyl, octyl, decyl, dodecyl, benzyl, and 2-phenylethyl-amines, the corresponding N-substituted 3,6-anhydrides **7b–g** were synthesized in 98%, 97%, 38%,[8] 94%, 76%, and 83% yields, respectively.



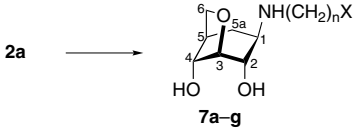
6a–i

	X	Y	Z	R
6a	OC_8H_{17}	H	OAc	Ac
b	OC_8H_{17}	H	OH	H
c	OC_8H_{17}	H	OMs	Ac
d	OC_8H_{17}	OAc	H	Ac
e	OC_8H_{17}	OH	H	H
f	N_3	H	OMs	Ac
g	N_3	OAc	H	Ac
h	NH_2	OH	H	H
i	NHAc	OH	H	H

Scheme 2. Synthesis of 5a-carba-β-galacto- and β-glucopyranose derivatives.

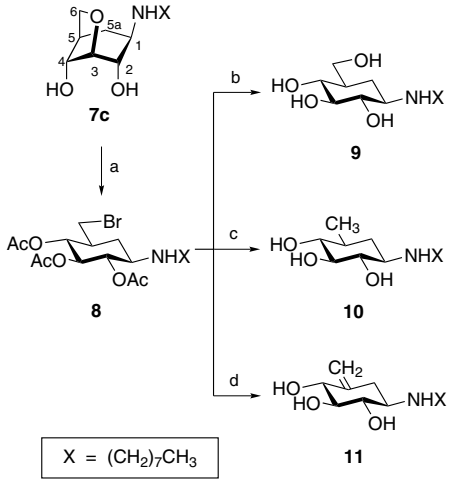


Scheme 3. Synthesis of 5a-carba-β-galactopyranosylamine and derivative. Reagents and conditions: (a) $AcOH/Ac_2O/H_2SO_4$ (40:20:1), 120 °C; (b) NaOAc, DMF, 110 °C; (c) NaOMe, MeOH; H_2, EtOH, Raney Ni; (d) Ac_2O, MeOH.



	n	X
7a	3	Me
b	5	Me
c	7	Me
d	9	Me
e	11	Me
f	1	Ph
g	2	Ph

Scheme 4. Structures of several N-substituted 3,6-anhydro-5a-carba-β-glucopyranosylamines.

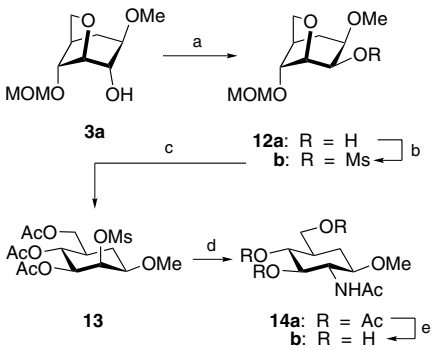


Scheme 5. Synthesis of some *N*-octyl-5a-carba-β-glucopyranosylamine derivatives. Reagents and conditions: (a) 30% HBr–AcOH, 85 °C; (b) Conventional acetolysis of **7c** or NaOAc, aq 80% 2-methoxyethanol, reflux; NaOMe, MeOH; (c) Bu_3SnH, AIBN, toluene; NaOMe, MeOH; (d) NaOAc, DMF, reflux; NaOMe, MeOH.

The *N*-octyl derivative **7c** was chosen, as an example, for possible further chemical transformation (Scheme 5). Thus, it was first acetylated and then treated with 30% HBr–AcOH at 85 °C, resulting in the opening of the 3,6-anhydro ring with a bromide ion to give the 6-bromo-6-deoxy derivative **8**, which was debrominated with tributyltin hydride in toluene in the presence of AIBN, followed by hydrolysis with 4 M hydrochloric acid, to afford *N*-octyl-6-deoxy-5a-carba-β-glucopyranosylamine **10** on acid resin chromatography with methanolic ammonia (25% over-all yield). Dehydrobromination of **8** was effected by treatment with sodium acetate (10 molar equiv) in DMF at reflux temperature to give the 6-deoxy-5-eno derivative **11** (~20% over-all yield). *N*-Octyl-5a-carba-β-galactopyranosylamine **9** was prepared in ~50% over-all yield by acetolysis of **7c** followed by hydrolysis with 4 M hydrochloric acid and purification over an acid resin column, in order to supply a sample for biological assays (Table 1) for enzyme-inhibitory activity to compare the three structurally related compounds **9**, **10**, and **11**. Alternatively, starting from the mesylate **2c**, a series of 5a-carba-β-galactopyranosylamine derivatives would be generated through amination and subsequent acetolysis, followed by 4-epimerization.

2.5. Synthesis of alkyl 2-acetamido-2-deoxy-5a-carba-β-glucopyranoside

Oxidation of **3a** with Ac_2O–DMSO and successive reduction with L-selectride gave preferentially the 2-epimer **12a** (59%), which was then transformed into the mesylate **12b** (91%). Acetolysis of **12b** gave methyl 3,4,6-tri-*O*-acetyl-2-*O*-mesyl-5a-carba-β-mannopyranoside (**13**, 82%). Similarly, methyl 5a-carba-β-mannopyranoside could be obtained from **12a**. Compound **13** was then subjected to azidolysis (NaN_3, 5 molar equiv) in DMF at 120 °C, giving a sole azide, which was similarly hydrogenolyzed in ethanol containing acetic anhydride, followed by acetylation, to give the penta-*N*,*O*-acetyl derivative[15] **14a** (52%), O-deacetylation of which afforded methyl 2-acetamido-2-deoxy-5a-carba-β-D-glucopyranoside **14b** (81%). This sequence could be generally utilized for the preparation of alkyl 5a-carba-β-mannosides and *N*-acetyl-5a-carba-β-glucosaminides (Scheme 6).

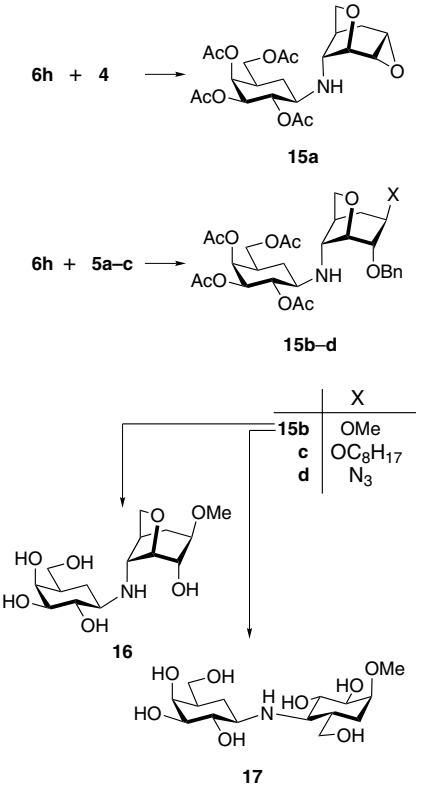


Scheme 6. Synthesis of methyl 2-acetamido-2-deoxy-5a-carba-β-glucopyranoside. Reagents and conditions: (a) Ac_2O, DMSO; L-selectride, THF; (b) MsCl, pyridine; (c) conventional acetolysis; (d) NaN_3, DMF, 120 °C; H_2, MeOH, Raney Ni, Ac_2O; (e) NaOMe, MeOH.

2.6. Synthesis of imino-linked 5a,5a′-dicarbalactose derivatives

Reductive amination of the ketones **4** and **5a**–**c** with 5a-carba-hexopyranosylamines has been demonstrated to proceed readily in stereoselective fashion, affording N-linked β(1→4)-5a,5a′-dicarbadisaccharide derivatives containing 3,6-anhydro-5a-carba-glucopyranose residues (Scheme 7).

5a-Carba-β-galactopyranosylamine **6h** was first converted into the hydrochloride under the influence of an equimolar amount of 1 M hydrochloric acid, and then subjected to reductive coupling with the ketone **4**. Thus, reaction of **4** (2 molar equiv) and the hydrochloride of **6h** was conducted in aqueous methanol in the presence of sodium cyanoborohydride (2 molar equiv) and anhydrous magnesium sulfate for 19 h at reflux temperature. The product could successfully be isolated as the tetra-*O*-acetyl derivative **15a** (47%). Similar coupling of **5a**–**c** with **6h** produced the respective 5a,5a′-dicarbadisaccharide derivatives **15b**–**d** in 60%, 41%, and 50% yields, respectively. O-Deacetylation of **15b** gave N-linked methyl 3,6-anhydro-5a,5a′-dicarba-β-D-lactoside[16] **16** (91%). Acetolysis of **15b** and subsequent deprotection would provide[17] 5a,5a′-dicarba-β-lactose **17**.



Scheme 7. Synthesis of some 5a,5a′-dicarbalactose derivatives.

Table 1. Inhibitory activity of some 5a-carba-hexopyranosylamine derivatives against three glycosidases

Compd	IC_{50} (M)		
	α-Galactosidase (green coffee beans)	β-Galactosidase (bovine liver)	β-Glucosidase (rat intestine)
6h	2.8	NI	130
6i	NI	NI	14
9	NI	10	NI
10	NI	18	NI
11	NI	30	NI
16	1.2	NI	NI

NI: No inhibition $<10^{-3}$ M.

2.7. Glycosidase inhibitory activity

Some of the new compounds synthesized underwent preliminary assay for enzyme-inhibitory activity against six glycosidases[18] (Table 1). Interestingly, 5a-carba-β-galactopyranosylamine (**6h**) was shown to be a good inhibitor of α-galactosidase rather than β-galactosidase, while its *N*-acetyl derivative **6i** exhibited moderate inhibition.[19] Seven *N*-alkyl and phenylalkyl-3,6-anhydro-5a-carba-β-glucopyranosylamines **7a**–**g** did not show any inhibitory activity against the six enzymes. In view of the structural relationship between substrates and enzyme inhibitors, *N*-octyl-β-gluopyranosylamine **9**, and its 6-deoxy and 6-deoxy-5-eno derivatives (**10** and **11**) can be considered to be model compounds for discussion regarding the hydrophobic nature of the region around substituents at C-5. The products are all moderate β-galactosidase inhibitors, being not α- nor β-glucosidase inhibitors, and substantial structural change around C-5 did not appreciably alter the activity.

Very interestingly, the N-linked dicarbalactose derivative **16** has been demonstrated to be a strong and specific α-galactosidase inhibitor (green coffee beans). As expected,[20] N-alkylation of **6h** much improved[21] the inhibitory potential toward α- and β-galactosidases, and β-glucosidase. However, its characteristic specificity as a α-galactosidase inhibitor completely disappeared. Hydrophobic spacer *N*-alkyl chains seemed to enhance its affinity for other enzymes, independent of specific recognition owing to structural mimicking dependent on the carba-galactopyranose residue. Therefore, in chemical modification of **6h**, the N-linked dicarbadisaccharide **16** might hopefully be a lead compound for development of specific α-galactosidase inhibitors of this kind.

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References and notes

1. Ogawa, S.; Kobayashi Matsunaga, Y.; Suzuki, Y. *Bioorg. Med. Chem.* **2002**, *10*, 1967; Matsuda, J.; Suzuki, O.; Oshima, M.; Yamamoto, Y.; Noguchi, A.; Takimoto, K.; Itoh, M.; Matsuzaki, Y.; Yasuda, Y.; Ogawa, S.; Sakata, Y.; Nanba, E.; Higaki, K.; Ogawa, Y.; Tominaga, L.; Ohno, K.; Iwasaki, H.; Watanabe, H.; Brandy, R. O.; Suzuki, Y. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 15912.
2. Okazaki, K.; Nishigaki, S.; Ishizuka, F.; Kajihara, Y.; Ogawa, S. *Org. Biomol. Chem.* **2003**, *1*, 2229.
3. Ogawa, S.; Oya, M.; Toyokuni, T.; Chida, N.; Suami, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1441.
4. Ogawa, S.; Mori, M.; Takeuchi, G.; Doi, F.; Watanabe, M.; Sakata, Y. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2811.
5. Ogawa, S.; Nakamoto, K.; Takahara, M.; Tanno, Y.; Chida, N.; Suami, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1174.
6. Compound **2a**: $[\alpha]_D^{20} - 68$ (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.62 (d, 1H, $J_{1,2} = 8.7$ Hz, H-1), 4.26 (dd, 1H, $J_{3,4} = 5.1$ Hz, $J_{2,3} = 8.3$ Hz, H-3), 4.20 (dd, 1H, $J_{3,4} = J_{4,5} = 5.1$ Hz, H-4), 4.15 (ddd, 1H, $J_{5a(exo),6exo} = 1.8$ Hz, $J_{5,6exo} = 5.4$ Hz, $J_{gem} = 8.8$ Hz, H-6*exo*), 3.83 (d, 1H, $J_{gem} = 8.8$ Hz, H-6*endo*), 3.41 (br s, 1H, H-2), 3.32–3.35 (m, 1H, H-1), 2.46–2.52 (m, 1H, H-5), 2.03–2.32 [m, 1H, H-5a(*exo*)], 1.99 [ddd, 1H, $J_{1,5a(endo)} = 2.0$ Hz, $J_{5,5a(endo)} = 4.2$ Hz, $J_{gem} = 16.1$ Hz, H-5a(*endo*)].
7. Compound **3b**: ^1H NMR (300 MHz, $CDCl_3$): δ 7.26–7.35 (m, 5H, Ph), 4.66 and 4.74 (ABq, each 1H, $J_{gem} = 6.7$ Hz, OCH_2), 4.64 (s, 2H, OCH_2), 4.20 (dd, 1H, $J_{3,4} = J_{4,5} = 4.9$ Hz, H-4), 4.11 (dd, 1H, $J_{2,3} = 2.0$ Hz, $J_{3,4} = 4.9$ Hz, H-3), 3.87 (ddd, 1H, $J_{5,6exo} = 3.2$ Hz, $J_{5a(exo),6exo} = 4.4$ Hz, $J_{gem} = 8.1$ Hz, H-6*exo*), 3.79 (d, 1H, $J_{gem} = 8.1$ Hz, H-6*endo*), 3.69 (ddd, 1H, $J_{1,2} = 3.7$ Hz, $J_{1,5a(endo)} = J_{1,5a(exo)} = 4.9$ Hz, H-1), 3.55 (ddd, 1H, $J_{2,3} = 2.0$ Hz, $J_{1,2} = 3.7$ Hz, H-2), 3.35, and 3.39 (2 s, each 3H, 2 × OMe), 2.50 [dddd, 1H, $J_{5a(exo),6exo} = 3.2$ Hz, $J_{1,5a(endo)} = 4.9$ Hz, $J_{5,5a(exo)} = 6.1$ Hz, $J_{gem} = 14.4$ Hz, H-5a(*exo*)], 2.50 (dddd, 1H, $J_{5,5a(endo)} = J_{5,6exo} = 4.4$ Hz, $J_{4,5} = 4.9$ Hz, $J_{5,5a(exo)} = 6.1$ Hz, H-5), 1.57 [ddd, 1H, $J_{5,5a(endo)} = 4.4$ Hz, $J_{1,5a(endo)} = 4.9$ Hz, $J_{gem} = 14.4$ Hz, H-5a(*endo*)].
8. The reaction conditions have not been optimized yet.
9. Compound **4**: ^1H NMR (300 MHz, $CDCl_3$) data for **4**; δ 4.32 (ddd, 1H, $J_{5a(eq),6exo} = 2.1$ Hz, $J_{5,6exo} = 4.9$ Hz, $J_{gem} = 8.5$ Hz, H-6*exo*), 4.18 (d, 1H, $J_{2,3} = 3.4$ Hz, H-3), 4.03 (d, 1H, $J_{gem} = 8.5$ Hz, H-6*endo*), 3.60 (dd, 1H, $J_{2,3} = 3.4$ Hz, $J_{1,2} = 3.7$ Hz, H-2), 3.27 (ddd, 1H, $J_{1,5a(endo)} = 1.2$ Hz, $J_{1,2} = 3.7$ Hz, $J_{1,5a(exo)} = 4.0$ Hz, H-1), 2.60 (ddd, 1H, $J_{5,5a(exo)} = 2.0$ Hz, $J_{5,6exo} = 4.9$ Hz, $J_{5,5a(endo)} = 6.8$ Hz, H-5), 2.44–2.48 [m, 1H, H-5a(*endo*)], 2.26 [ddd, 1H, $J_{5,5a(exo)} = 2.0$ Hz, $J_{1,5a(exo)} = 4.0$ Hz, $J_{gem} = 15.1$ Hz, H-5a(*exo*)]; for **5a**: δ 7.27–7.37 (m, 5H, Ph), 4.56 and 4.66 (ABq, each 1H, $J_{gem} = 11.8$ Hz, OCH_2), 4.37 (d, 1H, $J_{gem} = 7.8$ Hz, H-6*endo*), 4.15 (dd, 1H, $J_{2,3} = 4.9$ Hz, $J_{1,2} = 5.0$ Hz, H-2), 4.06 (ddd, 1H, $J_{5a(exo),6exo} = 2.9$ Hz, $J_{5,6exo} = J_{gem} = 7.8$ Hz, H-6*exo*), 3.95 (d, 1H, $J_{2,3} = 4.9$ Hz, H-3), 3.40 (ddd, 1H, $J_{1,5a(exo)} = 2.0$ Hz, $J_{1,5a(endo)} = 4.4$ Hz, $J_{1,2} = 5.0$ Hz, H-1), 3.38 (s, 3H, OMe), 2.49 (ddd, 1H, $J_{5,5a(endo)} = 3.4$ Hz, $J_{5,5a(exo)} = 3.7$ Hz, $J_{5,6exo} = 7.8$ Hz, H-5), 2.34–2.37 (m, 2H, H-5a,5a).
10. Ogawa, S.; Aoyama, H.; Sato, T. *Carbohydr. Res.* **2002**, *337*, 1979–1992.
11. Aoyama, H.; Ogawa, S.; Sato, T. In preparation.
12. (a) Miura, Y.; Arai, T.; Yamagata, T. *Carbohydr. Res.* **1996**, *289*, 193; (b) Miura, Y.; Yamagata, T. *Biochem. Biophys. Res. Commun.* **1997**, *241*, 698; (c) Nakajim, H.; Miura, Y.; Yamagata, T. *J. Biochem.* **1998**, *124*, 148; (d) Carmelita, M.; Kasuya, Z.; Wang, L. X.; Lee, Y. C.; Mitsuki, M.; Nakajima, H.; Miura, Y.; Sato, T.; Hatanaka, K.; Yamagata, S.; Yamagata, T. *Cabohydr. Res.* **2000**, *329*, 755–763.
13. Exhaustive acetolysis of **3i** is likely to give **6g** selectively; however, prolonged heating of intermediate **6f** and/or **6g**

under these conditions might cause substitution as well as elimination to give rise to aromatic compounds. Therefore, careful optimization should be worked out for the acetolysis.

14. Compound **7a**: ^{1}H NMR (300 MHz, MeOH): δ 4.25 (dd, 1H, $J_{4,5}$ = 4.8 Hz, $J_{3,4}$ = 5.1 Hz, H-4), 3.79 (dd, 1H, $J_{2,3}$ = 2.4 Hz, $J_{3,4}$ = 5.1 Hz, H-3), 3.77 (dd, 1H, $J_{5,6exo}$ = 2.2 Hz, J_{gem} = 8.3 Hz, H-6*exo*), 3.68 (d, 1H, J_{gem} = 8.3 Hz, H-6*endo*), 3.58 (br d, 1H, $J_{2,3}$ = 2.4 Hz, H-2), 2.85 (br dd, 1H, $J_{1,5a(endo)}$ = 3.7 Hz, $J_{1,5a(exo)}$ = 8.1 Hz, H-1), 2.54–2.59 (m, 2H, NHCH_2), 2.33 [ddd, 1H, $J_{5,5a(exo)}$ = 1.2 Hz, $J_{1,5a(exo)}$ = 8.1 Hz, J_{gem} = 14.6 Hz, H-5a(*exo*)], 2.17 (ddd, 1H, $J_{5,5a(exo)}$ = 1.2 Hz, $J_{5,6exo}$ = 2.2 Hz, $J_{4,5}$ = 4.8 Hz, H-5), 1.52 [br d, 1H, J_{gem} = 14.6 Hz, H-5a(*endo*)], 1.19–1.46 [m, 4H, (CH_2)$_2$CH$_3$], 0.85 (t, 3H, J = 7.2 Hz, CH_3).
15. Compound **14a**: $[\alpha]_D^{20}$ + 16 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.43 (d, 1H, $J_{2,NH}$ = 9.8 Hz, NH), 5.05 (dd, 1H, $J_{3,4}$ = 9.6 Hz, $J_{4,5}$ = 10.7 Hz, H-4), 4.93 (dd, 1H, $J_{3,4}$ = 9.6 Hz, $J_{2,3}$ = 10.5 Hz, H-3), 4.10 (dd, 1H, $J_{5,6b}$ = 3.7 Hz, J_{gem} = 11.2 Hz, H-6b), 4.05 (br d, 1H, $J_{2,NH}$ = 9.8 Hz, H-2), 3.97 (dd, 1H, $J_{5,6a}$ = 3.4 Hz, J_{gem} = 11.2 Hz, H-6a), 3.37 (s, 3H, OMe), 3.27 (ddd, 1H, $J_{1,5a(eq)}$ = 4.2 Hz, $J_{1,2}$ = 10.5 Hz, $J_{1,5a(ax)}$ = 11.2 Hz, H-1), 2.21 [ddd, 1H, $J_{5,5a(eq)}$ = 3.7 Hz, $J_{1,5a(eq)}$ = 4.2 Hz, J_{gem} = 13.2 Hz, H-5a(eq)], 1.97, 2.02, 2.07, and 2.08 (4 s, each 3H, 4 × Ac), 1.91 (br s, 1H, H-5), 1.50 [ddd, 1H, $J_{1,5a(ax)}$ = 11.2 Hz, $J_{5,5a(ax)}$ = 12.9 Hz, J_{gem} = 13.2 Hz, H-5a(ax)].
16. Compound **16**: $[\alpha]_D^{20}$ − 34 (*c* 0.15, MeOH); ^{1}H NMR (300 MHz, D_2O): δ 4.06 (br d, 1H, J_{gem} = 7.3 Hz, H-6*endo*), 4.03 (br s, 1H, H-2), 3.97 (br s, 1H, H-4′), 3.79–3.83 (m, 2H, H-3, H-6*exo*), 3.64 (br d, 1H, J_{gem} = 10.4 Hz, H-6b′), 3.52 (dd, 1H, $J_{5',6'a}$ = 2.7 Hz, J_{gem} = 10.4 Hz, H-6′), 3.46 (dd, 1H, $J_{2',3'}$ = 9.2 Hz, $J_{1',2'}$ = 9.5 Hz, H-2′), 3.33 (s, 1H, OMe), 3.30–3.36 (m, 3H, H-1, H-3′, H-4), 2.50 (ddd, 1H, $J_{1',5'eq}$ = 4.6 Hz, $J_{1',2'}$ = 9.5 Hz, $J_{1',5a'ax}$ = 11.8 Hz, H-1′), 2.38 (br dd, 1H, $J_{5,5a(endo)}$ = 3.5 Hz, $J_{5,5a(exo)}$ = 3.8 Hz, H-5), 2.20 [ddd, 1H, $J_{5,5a(endo)}$ = 3.5 Hz, $J_{1,5a(endo)}$ = 5.1 Hz, J_{gem} = 15.6 Hz, H-5a(*endo*)], 1.85 (ddd, $J_{5',5a'eq}$ = 2.9 Hz, $J_{1',5a'eq}$ = 4.6 Hz, J_{gem} = 12.5 Hz, H-5a′eq), 1.78 [br dd, 1H, $J_{5,5a(exo)}$ = 3.8 Hz, J_{gem} = 15.6 Hz, H-5a(*exo*)], 1.60 (dddd, 1H, $J_{5',6'a}$ = 2.7 Hz, $J_{5',5a'eq}$ = 2.9 Hz, $J_{4',5'}$ = 9.3 Hz, $J_{5',5a(ax)}$ = 12.0 Hz, H-5′), 1.32 (ddd, 1H, $J_{1',5a'ax}$ = 11.8 Hz, $J_{5',5a'ax}$ = 12.0 Hz, J_{gem} = 12.5 Hz, H-5a′ax).
17. Preliminary, when **15b** was subjected to the conventional acetolysis [$AcOH/Ac_2O/H_2SO_4$ (40:20:1), 80–95 °C], de-O-methylation was partly accompanied with opening of the anhydro ring and the benzyl ether group remained almost unaffected, contrary to the cases of **3d** and **3f**. Therefore, initial removal of the benzyl ether group by hydrogenolysis, followed by acetolysis, would be an effective route to furnish free N-linked dicarbadisaccharides. Furthermore, in order to get the 1-*O*-alkyl derivatives in acceptable yields, the acetolysis conditions should be optimized in each cases.
18. All compounds were assayed for activity against six glycosidases: α-galactosidase (green coffee beans), β-galactosidase (bovine liver), α-glucosidase (Baker's yeast), β-glucosidase (almond), α-fucosidase (bovine kidney), α-mannosidase (Jack beans). Biological assays were carried out in a standard manner by Drs. A. Takahashi and A. Tomoda (Hokko Chemical Industries, Co. Ltd, Toda, Atsugi, Japan).
19. Some *N*-alkyl derivatives of **6h** were synthesized for the purpose of comparing their activity with those of 6-deoxy congeners, the antipodes of α-fucopyranosylamine-type inhibitors. They have been shown to possess strong inhibitory activity against β-galactosidase and β-glucosidase, as well as α-galactosidase: Ogawa, S.; Fujieda, M.; Sakata, Y., in preparation.
20. With a series of *N*-alkyl-5a-carba-β-galactopyranosylamines, deoxylation at C-6 resulted in drastic change in potential and specificity of inhibitory activity: Ogawa, S.; Fujieda, S.; Sakata, Y.; Ishizaki, M.; Hisamatsu, S.; Okazaki, K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3461–3463.
21. Ogawa, S.; Ashiura, M.; Uchida, C.; Watanabe, S.; Yamazaki, C.; Yamagishi, K.; Inokuchi, J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 929; Ogawa, S.; Kobayashi, Y.; Kabayama, K.; Jimbo, M.; Inokuchi, J. *Bioorg. Med. Chem.* **1998**, *6*, 1955.