Synthesis of Potent α-Glucosidase Inhibitors: Methyl Acarviosin Analogue composed of 1,6-Anhydro-β-D-glucopyranose Residue

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Compound **3a** has been shown to possess stronger inhibitory activity against α-glucosidase than methyl acarviosin **1**.

Methyl acarviosin[1] **1**, which is a core structure of acarbose and related pseudo-oligosaccharidic α-amylase inhibitors,[2] possesses a strong inhibitory activity against some glycoside hydrolases. We have so far synthesized[3] several analogous compounds of **1** in order to elucidate the structure and inhibitory-activity relationship of this kind of inhibitor. A recent attempt to invert the conformation ($^4C_1 \rightarrow {}^1C_4$) of its sugar moiety by replacement of the methyl 4-amino-4,6-dideoxy-α-D-glucopyranoside residue with 4-amino-1,6-anhydro-4-deoxy-β-D-glucopyranose led to the discovery of a new type of potent pseudo-disaccharidic inhibitor of biological interest.

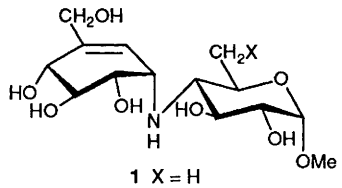
We report here a synthesis of (1*S*)-**3a** and (1*R*)-**3b**, which show very high inhibitory activity against α-glucosidase (Table 1), **3a** being substantially stronger than that of **1**.

Coupling of the 4,7:5,6-di-*O*-isopropylidene-(±)-valienamine[4] **5** and 2-*O*-acetyl-1,6:3,4-dianhydro-β-D-galactopyranose[5] **7** in propan-2-ol at 120 °C afforded, after *O*-deisopropylidenation with aqueous acetic acid, conventional acetylation and chromatography on a column of silica gel, the diastereoisomeric, protected pseudo-disaccharides **8a** {50%, $[\alpha]_D^{22}$ +5° ($CHCl_3$)} and **8b** {48%, $[\alpha]_D^{22}$ −39° ($CHCl_3$)}. Compounds **8a** and **8b** were characterized by the ^1H NMR spectra. *O*-Deacetylation of **8a** and **8b** with methanolic sodium methoxide afforded free pseudo-disaccharides **3a** {$[\alpha]_D^{24}$ +26° (MeOH)} and **3b** {$[\alpha]_D^{24}$ −84° (MeOH)} quantitatively, the configurations of which were assigned on the basis of the optical rotations.[6] Compound **3a** showed IC_{50} 5.6×10^{-10} M/ml for α-glucosidase (*cf.* compound

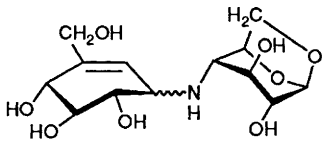
Table 1 Inhibitory activity (I%) against α-glucosidase[a]

Compounds	Concentration (μg ml^{-1})		
	1000	100	10
1[b]	—	93.9	87.7 (0.36)
2[b]	96.2	94.2	80.0 (1.4)
3a	96.8	95.9	91.6 (0.18)
3b	95.1	84.8	58.2 (6.5)
4	28.5	2.6	2.7
13	96.5	91.8	83.6 (1.45)

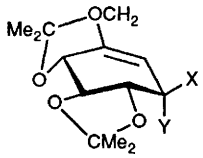
[a] Yeast α-glucosidase, *p*-nitrophenyl-α-D-glucopyranoside (0.66 mM), PBS (100 mM), pH 6.8; Numbers in parentheses denote IC_{50} (concentration required to cause 50% inhibition, μg ml^{-1}) values. [b] Totally synthesized by us.[3]



1 X = H
2 X = OH



3a, 3b: α–
4: β–



5 X = H, Y = NH_2 (racemate)
6 X = NH_2, Y = H

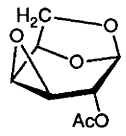


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Table 2 Inhibitory activity (I%) against α-mannosidase[a]

	Concentration (μg ml^{-1})		
Compounds	1000	100	10
3a	16.5	3.0	0
4	93.3	86.7	43.2 (~12)
13	15.5	0	0

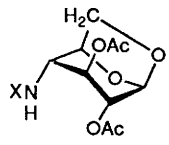
[a] Jack bean α-mannosidase, *p*-nitrophenyl-α-mannoside (20 mM), acetate buffer (100 mM), pH 4.5; Numbers in parentheses denote IC_{50} values.

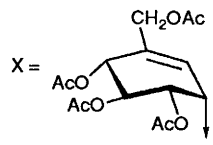
1: IC_{50} 1.07 × 10^{-9} M/ml). Consideration from the molecular models of **1** and **3a** indicated a marked difference of the spatial geometry between them in the vicinity of the nitrogen atom. In the latter, the *exo*-2′-hydroxy group and the pyranoid-oxygen atom exist in close proximity to the NH group. This situation might play a role in increasing any inhibitory activity through enhancement of its binding to the active centre of the enzyme.

Therefore, the structurally related 3,6-anhydro derivative **13** of methyl oligobiosaminide **2** was prepared as follows: Selective *p*-toluenesulphonylation of the 6-hydroxy group of the protected derivative[3] **10** (**10** → **11**), treatment with methanolic sodium methoxide at 50 °C (**11** → **12**), and *O*-deacetylation (**12** → **13**). Compound **13** {35% overall yield from **10**, $[\alpha]_D^{22}$ +59° ($CHCl_3$)} which resembles **3a** in the structure of the sugar moiety exhibited also very high inhibitory activity (IC_{50} 4.7 × 10^{-9} M/ml).

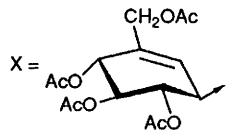
However, alteration of the hydroxymethylcyclohexenyl portion was carried out by replacement with 1-epivalienamine residue. Thus, coupling of the 4,7:5,6-di-*O*-isopropylidene derivative[7] **6** and **7** afforded, after conventional acetylation, the diacetate **9** (70%), which was *O*-deisopropylidenated and *O*-deacetylated to give the free pseudo-disaccharide **4** {90%, $[\alpha]_D^{28}$ −97° (MeOH)}. Interestingly, **4** possesses considerable inhibitory activity (IC_{50} ~3.7 × 10^{-8} M/ml) against α-mannosidase[8] and very weak activity against α-glucosidase (listed in Tables 1 and 2).

The presence of the 1,6-anhydro-β-D-glucopyranose residues seems to be essential for the appearance as well as the





8a,8b



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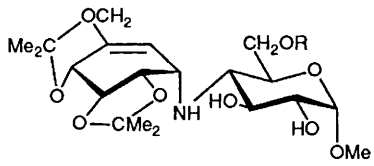
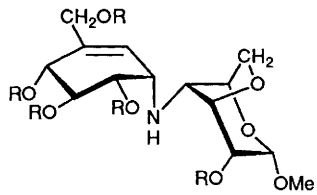


10 R = H
11 R = Ts



12 R = Ac
13 R = H

enhancement of their inhibitory activity against enzymes. Modification of the cyclohexenyl portions of **3a** and **13**, therefore, becomes of interest, and is now under way.

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6 Differentiation of **8a** and **8b** was made on the basis of the empirical rule of superposition of rotatory contributions by the cyclohexene parts, using a positive value of the specific rotation of (1*S*)-penta-*N*,*O*-acetylvalienamine {$[\alpha]_D^{23}$ +30.2° ($CHCl_3$); Y. Kameda and S. Horii, *J. Chem. Soc., Chem. Commun.*, 1972, 746}.
7 Since reliable data are not yet available to predict the configuration of each diastereoisomer formed by coupling of racemic 1-epivalienamine derivative **6** with **7**, the optically active **6** {$[\alpha]_D^{23}$ −90° ($CHCl_3$)} prepared by an 11-step reaction from (2*S*)-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid was used here; S. Ogawa, C. Uchida and Y. Shibata, *Carbohydr. Res.*, submitted for publication.
8 Methyl 1-epiacarviosin possesses IC_{50} 8.2 × 10^{-8} M/ml against α-mannosidase (unpublished results, S. Ogawa, C. Uchida and Y. Shibata) (*cf.* mannojirimycin hydrogen sulphite adduct: IC_{50} 3.5 × 10^{-5} M/ml).