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.

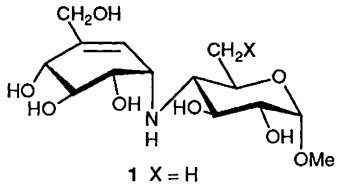
We report here a synthesis of (1*S*)-**3a** and (1*R*)-**3b**, which show very high inhibitory activity against α-glucosidase (Table 1), **3a** being substantially stronger than that of **1**.

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

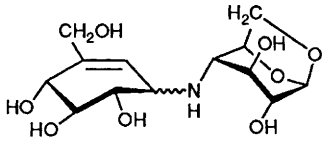
Table 1 Inhibitory activity (I%) against α-glucosidase[a]

	Concentration (μg ml^{-1})		
Compounds	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)

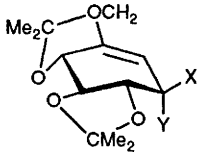
[a] Yeast α-glucosidase, *p*-nitrophenyl-α-D-glucopyranoside (0.66 mM), PBS (100 mM), pH 6.8; Numbers in parentheses denote IC_{50} (concentration required to cause 50% inhibition, μg ml^{-1}) values. [b] Totally synthesized by us.[3]



1 X = H
2 X = OH



3a, 3b: α–
4: β–



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

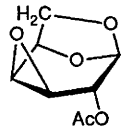


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Table 2 Inhibitory activity (I%) against α-mannosidase[a]

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

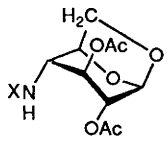
[a] Jack bean α-mannosidase, *p*-nitrophenyl-α-mannoside (20 mM), acetate buffer (100 mM), pH 4.5; Numbers in parentheses denote IC_{50} values.

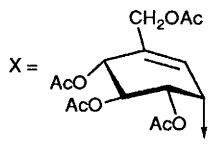
1: IC_{50} 1.07 × 10^{-9} M/ml). Consideration from the molecular models of **1** and **3a** indicated a marked difference of the spatial geometry between them in the vicinity of the nitrogen atom. In the latter, the *exo*-2′-hydroxy group and the pyranoid-oxygen atom exist in close proximity to the 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).

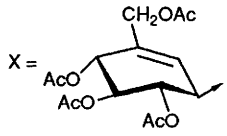
However, alteration of the hydroxymethylcyclohexenyl portion was carried out by replacement with 1-epivalienamine residue. Thus, coupling of the 4,7:5,6-di-*O*-isopropylidene derivative[7] **6** and **7** afforded, after conventional acetylation, the diacetate **9** (70%), which was *O*-deisopropylidenated 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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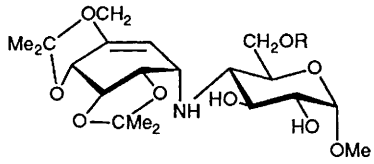
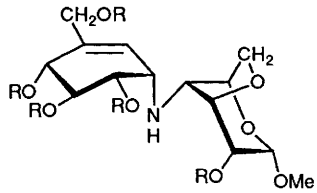


10 R = H
11 R = Ts



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.

We thank Dr S. Inouye and Dr T. Machinami (Meiji Seika Kaisha, Tokyo, Japan) for carrying out the biological assay.

Received, 15th June 1990; Com. 0/02695F

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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).