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Note

Synthesis of some analogues of methyl dehydro-oligobiosaminide (acarviosin)*

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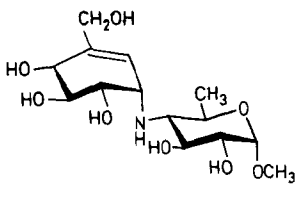
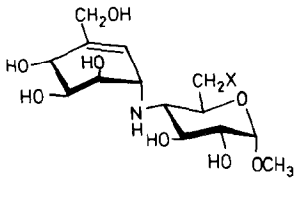
The title pseudo-disaccharide, methyl 4,6-dideoxy-4-{[(1*S*)-(1,4,6/5)-4,5,6-trihydroxy-3-hydroxymethyl-2-cyclohexen-1-yl]amino}-D-glucopyranoside, is an essential core unit of several pseudo-oligosaccharidic α-D-glucosidase inhibitors[2], which was initially obtained[3] as the methyl α-glycoside (**1**) by acid-catalysed methanolysis of oligostatin C. The reaction was considered to involve dehydration of the axial hydroxyl group originally located on the cyclohexane ring. Alternatively, **1** (designated as acarviosin) was isolated in a pure form[4], and was shown to be five times more potent an inhibitor than acarbose, whereas the β anomer exhibits only 5% activity[4].

We have been interested in the structure–activity relationship for this kind of inhibitor and have described[1] the synthesis of a core unit of oligostatins by condensation of the amino sugar with a protected (hydroxymethyl)cyclohexanediol epoxide. We now report a synthesis of some protected derivatives of the stereoisomers (**2–5**) of **1**.

Condensation of methyl 4-amino-4,6-dideoxy-α-D-glucopyranoside[5] (**6**) with DL-3,4-di-*O*-acetyl-1,2-anhydro-(1,2,3/4)-5-benzoyloxymethyl-5-cyclohexene-



1



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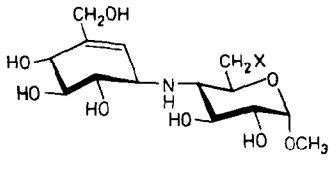
3 X = OH



4 X = H
5 X = OH

*Synthesis of Pseudo-oligosaccharidic Glycosidase Inhibitors, Part III. For Part II, see S. Ogawa, H. Sugizaki, Y. Iwasawa, and T. Suami, *Carbohydr. Res.*, 140 (1985) 325–331.
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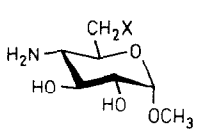
1,2,3,4-tetrol[6] (DL-**8**) in 2-propanol at 50° for 5 days, followed by acetylation and chromatography on silica gel, afforded the acetylated, diastereoisomeric pseudo-disaccharide derivatives **10** (46%), $[\alpha]_D$ +54° (chloroform), and **11** (31%), $[\alpha]_D$ +71° (chloroform). The structures of **10** and **11** were supported by elemental analyses and ^{1}H-n.m.r. data (three coupled signals due to H-4′,5′,6′). Nucleophilic attack at the epoxide ring clearly occurred at the allylic position. The $J_{H,H}$ values of the cyclohexene ring protons indicated that the conformations are not fixed. Furthermore, the small difference between the $[\alpha]_D$ values of **10** and **11** did not allow prediction of their absolute configurations by estimating the contribution of the cyclohexene moiety on the basis of an empirical rule for optical rotations of cyclitols[7]. The absolute structures were assigned following preparation of **10**, $[\alpha]_D$ +50° (chloroform), by the reaction of **6** with L-**8**[8].



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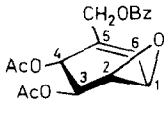
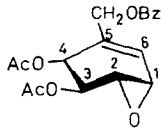
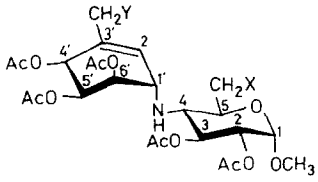
7 X = OH



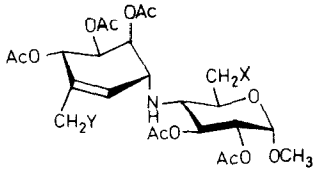
1L-(1,2,3/4)
L-8



1D-(1,2,4/3)
D-9



	X	Y
10	H	OBz
12	OAc	OAc

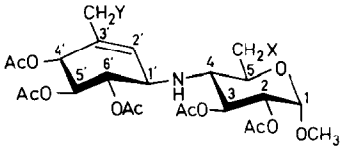


	X	Y
11	H	OBz
13	OAc	OAc

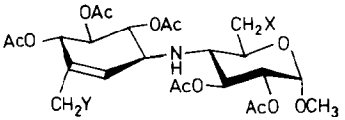
Similar reaction of methyl 4-amino-4-deoxy-α-D-glucopyranoside[9] (**7**) with DL-**8**, followed by acetylation, afforded an inseparable mixture of acetylated pseudo-disaccharide derivatives. Saponification of the mixture, chromatography of the resulting methyl glycosides on Dowex 1-X2 (HO^-) resin, and reacetylation gave the hepta-acetates **12** (10%), $[\alpha]_D$ +54° (chloroform), and **13** (7%), $[\alpha]_D$ +89° (chloroform). Their structures were assigned on the basis of elemental analyses, ^{1}H-n.m.r. spectra, and optical rotations.

The remaining stereoisomers of **1** were synthesised by coupling **6** (4 mol) with DL-3,4-di-*O*-acetyl-1,2-anhydro-(1,2,4/3)-5-benzoyloxymethyl-5-cyclohexene-1,2,3,4-tetrol[6] (DL-**9**) in *N*,*N*-dimethylformamide and 2-propanol at 50° for 5 days. Acetylation of the products, followed by chromatography, afforded the acetylated pseudo-disaccharide derivatives **14** (25%), $[\alpha]_D$ −0.5° (chloroform), and **15** (16%), $[\alpha]_D$ +104° (chloroform). The ^{1}H-n.m.r. spectra of **14** and **15** showed coupled

signals (J 8–10 Hz) due to H-4′,5′,6′, indicating that the epoxide ring had been cleaved at position 1. The contribution of the cyclohexene moieties to the optical rotations of **14** and **15** can be estimated[7]. The observed dextrorotation of **15** would be attributed to the cyclohexene moiety having the 1*S* configuration. This was confirmed by the reaction of **6** with D-**9**[8] which gave a single diastereoisomer (**14**), $[\alpha]_D$ −3° (chloroform).



	X	Y
14	H	OBz
16	OAc	OAc



	X	Y
15	H	OBz
17	OAc	OAc

Similarly, condensation of **7** with DL-**9**, followed by *O*-deacylation, gave a mixture of diastereoisomeric methyl 4-deoxy-4-{[(1,5/4,6)-4,5,6-trihydroxy-3-hydroxymethyl-2-cyclohexen-1-yl]amino}-α-D-glucopyranosides, which were isolated by chromatography on Dowex 1-X2 (HO^-) resin and characterised as the hepta-acetates **16** (26%), $[\alpha]_D$ +4° (chloroform), and **17** (31%), $[\alpha]_D$ +164° (chloroform). The structures were assigned by elemental analyses, ^{1}H-n.m.r. spectra, and optical rotations.

EXPERIMENTAL

General methods. — Melting points were determined with a Büchi 510 capillary melting-point apparatus and are uncorrected. Optical rotations were measured with a Hitachi HPL-225 instrument, unless otherwise stated, for solutions in chloroform. ^{1}H-N.m.r. spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si), using Varian EM-390 (90 MHz) and JEOL FX-200 (200 MHz) spectrometers. T.l.c. was performed on Silica Gel 60 F_{254} (Merck) and column chromatography on Wakogel C-300 (300 Mesh) (Wako Co.). Organic solutions were dried (Na_2SO_4) and concentrated at <50° under diminished pressure.

Methyl 2,3-di-O-acetyl-4,6-dideoxy-4-{[(1S)-(1,4/5,6)-4,5,6-triacetoxy-3-benzoyloxymethyl-2-cyclohexen-1-yl]amino}-α-D-glucopyranoside (**10**) *and its diastereoisomer* (**11**). — A mixture of **6**[1,5] (51 mg, 0.29 mmol) and DL-**8**[6] (100 mg, 0.29 mmol) in 2-propanol (3 mL) was heated in a sealed tube at 50° for 5 days and then concentrated, and the residue was treated with acetic anhydride (2 mL) and pyridine (2 mL) at room temperature overnight. T.l.c. (ethanol–toluene, 1:8) revealed the formation of two components (R_F 0.58 and 0.56). The products were isolated by column chromatography (2-butanone–toluene, 1:4). The first fraction contained **11** (46 mg, 31%), isolated as a syrup, $[\alpha]_D^{23}$ +71° (*c* 1). ^{1}H-N.m.r. data

(90 MHz): δ 8.15–8.05 (m, 2 H) and 7.67–7.36 (m, 3 H) (Ph), 5.90 (d, 1 H, $J_{1',2'}$ 3.8 Hz, H-2'), 5.72 (d, 1 H, $J_{4',5'}$ 6.8 Hz, H-4'), 5.40 (dd, 1 H, $J_{5',6'}$ 2.6 Hz, H-5'), 5.26 (bt, 1 H, $J_{2,3} = J_{3,4}$ = 9.8 Hz, H-3), 5.06 (dd, 1 H, $J_{1',6'}$ 4.5 Hz, H-6'), 4.82–4.74 (m, 4 H, H-1,2 and CH_2OBz), 3.37 (s, 3 H, OMe), 2.55 (t, 1 H, $J_{4,5}$ 9.8 Hz, H-4), 2.08–2.00 (m, 15 H, 5 OAc), 1.36 (d, 3 H, $J_{5,6}$ 6 Hz, CMe).

Anal. Calc. for $C_{31}H_{39}NO_{14}$: C, 57.31; H, 6.05; N, 2.16. Found: C, 57.30; H, 6.02; N, 2.16.

The second fraction contained **10** (70 mg, 46%), isolated as a syrup, $[\alpha]_D^{23}$ +54° (*c* 1.2). ^{1}H-N.m.r. data (200 MHz): δ 8.08–7.95 (d, 2 H) and 7.60–7.35 (m, 3 H) (Ph), 5.92 (d, 1 H, $J_{1',2'}$ 3.8 Hz, H-2'), 5.58 (d, 1 H, $J_{4',5'}$ 6 Hz, H-4'), 5.35 (dd, 1 H, $J_{5',6'}$ 2.5 Hz, H-5'), 5.28 (t, 1 H, $J_{2,3} = J_{3,4}$ = 10 Hz, H-3), 4.90 (dd, 1 H, $J_{1',6'}$ 6.4 Hz, H-6'), 4.80–4.70 (m, 4 H, H-1,2 and CH_2OBz), 3.68 (dq, 1 H, $J_{4,5}$ 10, $J_{5,6}$ 6.7 Hz, H-5), 3.58 (bdd, 1 H, H-1'), 3.37 (s, 3 H, OMe), 2.63 (t, 1 H, H-4), 2.09, 2.04, 2.02, and 2.00 (4 s, 3, 6, 3, and 3 H, 5 OAc), 1.33 (d, 3 H, CMe).

Anal. Found: C, 57.24; H, 6.02; N, 2.05.

A mixture of **6** (40 mg, 0.23 mmol) and L-**8**[8] (52 mg, 0.15 mmol) in 2-propanol (0.8 mL) was heated in a sealed tube at 55° for 5 days. The reaction mixture was processed and the product was purified as described above, to give **10** (76 mg, 77%) as a syrup, $[\alpha]_D^{25}$ +50° (*c* 1.3).

*Methyl 2,3-di-*O*-acetyl-4,6-dideoxy-4-{[(1*R*)-(1,5/4,6)-4,5,6-triacetoxy-4-benzoyloxymethyl-2-cyclohexen-1-yl]amino}-α-*D*-glucopyranoside* (**14**) *and its diastereoisomer* (**15**) — A mixture of **6** (57 mg, 0.32 mmol) and DL-**9**[6] (110 mg, 0.31 mmol) in *N*,*N*-dimethylformamide (1 mL) and 2-propanol (3 mL) was heated in a sealed tube at 50° for 5 days and then concentrated, and the residue was acetylated. The products were eluted from a column of silica gel with 2-butanone–toluene (1:4). The first fraction contained **14** (37 mg, 25%), isolated as a syrup, $[\alpha]_D^{27}$ −0.5° (*c* 1.4). ^{1}H-N.m.r. data (90 MHz): δ 8.15–8.00 (m, 2 H) and 7.66–7.48 (m, 3 H) (Ph), 5.98 (bs, 1 H, H-2'), 5.79 (bd, 1 H, $J_{4',5'}$ 7.5 Hz, H-4'), 5.24 (dd, 1 H, $J_{5',6'}$ 10 Hz, H-5'), 3.38 (s, 3 H, OMe), 2.46 (t, 1 H, $J_{3,4} = J_{4,5}$ = 10 Hz, H-4), 2.12–2.00 (m, 15 H, 5 OAc), 1.28 (d, 3 H, $J_{5,6}$ 6 Hz, CMe).

Anal. Calc. for $C_{31}H_{39}NO_{14}$: C, 57.31; H, 6.05; N, 2.16. Found: C, 57.11; H, 6.03; N, 2.34.

The second fraction contained **15** (24 mg, 16%), isolated as a syrup, $[\alpha]_D^{25}$ +104° (*c* 1.5). ^{1}H-N.m.r. data (200 MHz): δ 8.08–7.95 (m, 2 H) and 7.60–7.35 (m, 3 H) (Ph), 5.84 (s, 1 H, H-2'), 5.81 (d, 1 H, $J_{4',5'}$ 8 Hz, H-4'), 5.24 (dd, 1 H, $J_{5',6'}$ 11.3 Hz, H-5'), 5.22 (bt, 1 H, $J_{2,3} = J_{3,4}$ = 10 Hz, H-3), 4.96 (dd, 1 H, $J_{1',6'}$ 8 Hz, H-6'), 4.80–4.60 (m, 4 H, H-1,2 and CH_2OBz), 3.70 (bd, 1 H, H-1'), 3.56 (dq, 1 H, $J_{4,5}$ 10, $J_{5,6}$ 6.4 Hz, H-5), 3.35 (s, 3 H, OMe), 2.60 (t, 1 H, H-4), 2.12, 2.11, 2.08, 2.05, and 2.04 (5 s, 3, 3, 3, 3, and 3 H, 5 OAc), 1.33 (d, 3 H, CMe).

Anal. Found: C, 57.00; H, 6.01; N, 2.24.

A mixture of **6** (29 mg, 0.16 mmol) and D-**9**[8] (38 mg, 0.11 mmol) in 2-propanol (0.8 mL) was heated in a sealed tube at 55° for 5 days and then concentrated, and the residue was acetylated. The product was purified on a column of silica gel, to give **14** (37 mg, 52%) as a syrup, $[\alpha]_D^{25}$ −3° (*c* 1.4).

Methyl 2,3,6-tri-O-acetyl-4-deoxy-4-{[(1S)-(1,4/5,6)-4,5,6-triacetoxy-3-acetoxymethyl-2-cyclohexen-1-yl]amino}-α-D-glucopyranoside (**12**) *and its diastereoisomer* (**13**). — A mixture of **7**[1,9] (66 mg, 0.37 mmol) and DL-**8** (99 mg, 0.29 mmol) in *N,N*-dimethylformamide (1.5 mL) and 2-propanol (1.0 mL) was heated in a sealed tube at 60° for 7 days and then concentrated, and the residue was acetylated. T.l.c. (2-butanone–toluene, 1:3) revealed one major component (R_F 0.34) and a trace of DL-**8** (R_F 0.58). Column chromatography (2-butanone–toluene, 1:4) of the product gave a syrupy mixture (109 mg, 55%) of products. The mixture was then treated with methanolic M sodium methoxide (0.1 mL) in methanol (2 mL) at room temperature for 40 min. T.l.c. (chloroform–methanol, 1:1) then revealed a single component (R_F 0.41). The product was eluted from a short column of Amberlite IR-120B (H^+) resin, first with methanol and then with aqueous 3% ammonia, and the latter eluate was concentrated. The residue was washed with ethyl acetate, and eluted from a short column of Dowex 1-X2 (HO^-) resin with water to give two components: R_F 0.60 and 0.58 (t.l.c.; 1-butanol–pyridine–water, 12:8:5). The first fraction contained a syrup (7 mg) which was acetylated to give **13** (13 mg, 7%), isolated as a syrup, $[\alpha]_D^{20}$ +89° (*c* 0.6). ^{1}H-N.m.r. data (90 MHz): δ 5.72 (d, 1 H, $J_{1',2'}$ 3 Hz, H-2'), 5.62 (bd, 1 H, $J_{4',5'}$ 7 Hz, H-4'), 3.64 (bdd, 1 H, $J_{1',6'}$ 8 Hz, H-1'), 3.37 (s, 3 H, OMe), 2.95 (t, 1 H, $J_{3,4} = J_{4,5}$ = 10 Hz, H-4), 2.09, 2.06, and 2.01 (3 s, 9, 9, and 3 H, 7 OAc).

Anal. Calc. for $C_{28}H_{39}NO_{16}$: C, 52.09; H, 6.09; N, 2.17. Found: C, 51.91; H, 6.09; N, 2.04.

The second fraction contained a syrup (10 mg) which was acetylated to give **12** (19 mg, 10%) as a syrup, $[\alpha]_D^{20}$ +54° (*c* 0.9). ^{1}H-N.m.r. data (90 MHz): δ 5.82 (d, 1 H, $J_{1',2'}$ 3 Hz, H-2'), 5.50 (bd, 1 H, $J_{4',5'}$ 5.5 Hz, H-4'), 3.76 (bdd, 1 H, $J_{1',6'}$ 9 Hz, H-1'), 3.40 (s, 3 H, OMe), 3.02 (t, 1 H, $J_{3,4} = J_{4,5}$ = 10 Hz, H-4), 2.10, 2.06, and 2.05 (3 s, 3, 9, and 9 H, 7 OAc).

Anal. Found: C, 52.24; H, 6.04; N, 2.22.

Methyl 2,3,6-tri-O-acetyl-4-deoxy-4-{[(1R)-(1,5/4,6)-4,5,6-triacetoxy-3-acetoxymethyl-2-cyclohexen-1-yl]amino}-α-D-glucopyranoside (**16**) *and its diastereoisomer* (**17**). — A mixture of **7** (67 mg, 0.38 mmol) and DL-**9** (100 mg, 0.29 mmol) in *N,N*-dimethylformamide (1.7 mL) and 2-propanol (1.0 mL) was heated in a sealed tube at 60° for 7 days. The product was acetylated and purified by column chromatography to give a homogeneous mixture (146 mg) of two diastereoisomers. The compounds were *O*-deacetylated and then eluted from a column of Dowex 1-X2 (HO^-) resin with water. The first fraction (R_F 0.57; 1-butanol–pyridine–water, 12:8:5) contained methyl 4-deoxy-4-{[(1*S*)-(1,5/4,6)-4,5,6-trihydroxy-3-hydroxymethyl-2-cyclohexen-1-yl]amino}-α-D-glucopyranoside (30 mg), isolated as a syrup, $[\alpha]_D^{20}$ +140° (*c* 0.5, water). This compound was acetylated to give **17** (58 mg, 31% yield based on DL-**9** used), which was crystallised from ethanol to give needles (28 mg), m.p. 155–157°, $[\alpha]_D^{20}$ +164° (*c* 1.4). ^{1}H-N.m.r. data (90 MHz): δ 5.77 (bs, 1 H, H-2'), 5.69 (bd, 1 H, $J_{4',5'}$ 7.5 Hz, H-4'), 3.64 (bd, 1 H, $J_{1',6'}$ 9 Hz, H-1'), 3.37 (s, 3 H, OMe), 2.95 (t, 1 H, $J_{3,4} = J_{4,5}$ = 10 Hz, H-4), 2.12, 2.08, 2.04, 2.01, and 1.98 (5 s, 3, 6, 6, 3, and 3 H, 7 OAc).

Anal. Calc. for $C_{28}H_{39}NO_{16}$: C, 52.09; H, 6.09; N, 2.17. Found: C, 52.34; H, 6.21; N, 2.18.

The second fraction (R_F 0.54) gave the free base (25 mg) as a syrup, $[\alpha]_D^{20}$ +39° (*c* 0.9, water). This compound was characterised as the hepta-acetate **16** (48 mg, 26% based on DL-**9** used), m.p. 113–115° (from ethanol, needles), $[\alpha]_D^{20}$ +4° (*c* 0.7). ^{1}H-N.m.r. data (90 MHz): δ 5.84 (bs, 1 H, H-2′), 5.66 (bd, 1 H, $J_{4',5'}$ 7.5 Hz, H-4′), 3.67 (bd, 1 H, $J_{1',6'}$ 9 Hz, H-1′), 3.37 (s, 3 H, OMe), 2.76 (t, 1 H, $J_{3,4} = J_{4,5}$ = 10 Hz, H-4), 2.09, 2.07, 2.06, 2.04, 2.02, and 1.98 (6 s, 3, 3, 3, 6, 3, and 3 H, 7 OAc).

Anal. Found: C, 52.16; H, 6.13; N, 2.26.

ACKNOWLEDGMENT

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