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SYNTHESIS OF A COMMON STRUCTURAL UNIT OF THE ANTIBIOTIC OLIGOSTATINS

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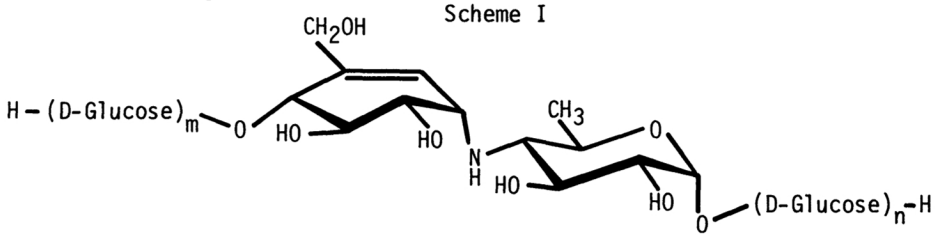
Methyl N-[(1S)-(1,2,4/3,5,6)-2,3,4,6-tetrahydroxy-5-(hydroxymethyl)cyclohexyl]-4-amino-4,6-dideoxy-α-D-glucopyranoside, a common structural unit of the antibiotic oligostatins, has been synthesized and characterized as the heptaacetate.

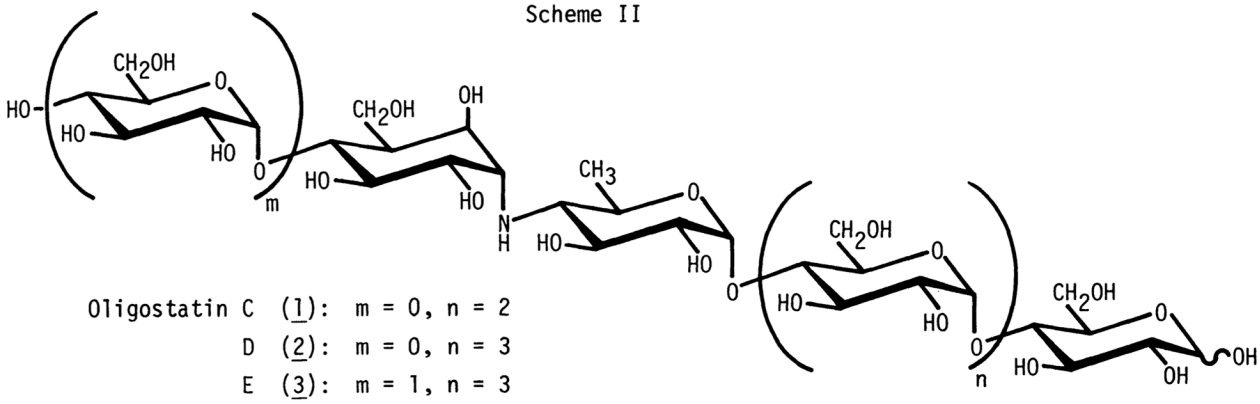
Recently, much interest has been focused on the pseudo-oligosaccharidic α-glucosidase inhibitors which contain the general structural formula shown in Scheme I.[1] The common structural unit is composed of 4-amino-4,6-dideoxy-D-glucopyranose and an unsaturated branched-chain cyclitol, which are bonded by way of an imino linkage.

Scheme I



The present report describes the first synthesis of such a kind of structural unit, a common portion of the antibiotic oligostatins C, D, and E (1–3), which are produced by Streptomyces myxogenes nov. sp. SF-1130 and exhibit not only antibacterial activity but also amylase inhibitory activity.[2a] The synthesis afforded several other pseudonitrogen disaccharides of biological interest.

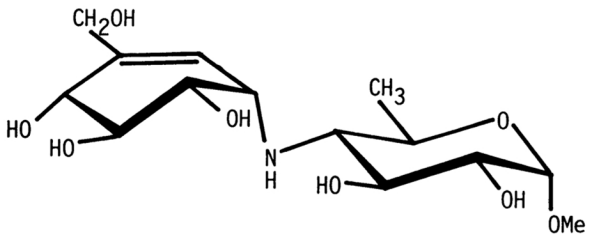
Scheme II



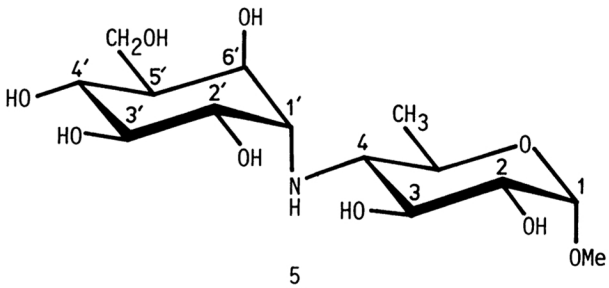
Oligostatin C (1): m = 0, n = 2
D (2): m = 0, n = 3
E (3): m = 1, n = 3

Methanolysis of 1 gave a crystalline methyl α-glycoside (methyl oligobiosaminide) (4).[2b] The formation of 4, instead of expected 5, was rationalized by assuming a β-elimination of the axially oriented hydroxyl group, originally present

Scheme III



Methyl oligobiosaminide (4)

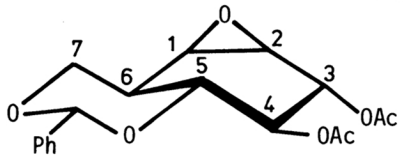


5

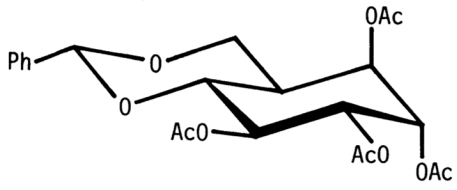
at C-6' in the cyclitol moiety, under acidic conditions. Therefore, it would be of interest to study synthesis and reactivity of 5 and its related compounds.

We have undertaken the reaction of DL-3,4-di-O-acetyl-1,2-anhydro-5,7-O-benzylidene-(1,2,4,6/3,5)-6-hydroxymethyl-1,2,3,4,5-cyclohexanepentol (6)[3] with methyl 4-amino-4-deoxy- (10) and 4-amino-4,6-dideoxy-α-D-glucopyranosides (12) to construct the pseudonitrogen disaccharide structures related to 5.

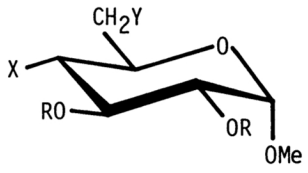
Scheme IV



6 (racemic)



7 (racemic)

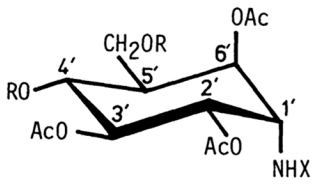


	R	X	Y
8	H	N_3	OH
9	H	N_3	Cl
10	H	NH_2	OH
11	H	NH_2	Cl
12	H	NH_2	H
13	Ac	NHAc	OAc
14	Ac	NHAc	H

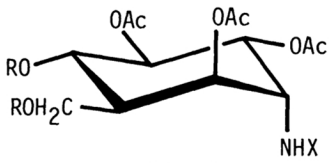
Catalytic hydrogenation of methyl 4-azido-4-deoxy-α-D-glucopyranoside (8)[4] in methanol in the presence of Raney nickel gave a crystalline amine 10 (57%): mp 163–165°C (lit.[4] mp 166–166.5°C).[5] Treatment of 8 with sulfonyl chloride in pyridine (-5°C, 2 h) gave selectively the corresponding 6-chloro-6-deoxy derivative 9 (63%): mp 144–145°C, $[\alpha]_D$ +240° (MeOH). Compound 9 was further characterized as the diacetate: ^{1}H NMR δ 2.07 (3H, s) and 2.10 (3H, s) (OAc), 3.41 (3H, s, OMe), 5.49 (1H, t, J = 9.5 Hz, H-4). A similar reduction of 9 gave the amine 11 (93%): mp 119–120.5°C, $[\alpha]_D$ +135° (H_2O). The preparation of 12 was simplified by direct hydrogenolysis of 9 with a large excess of Raney nickel in the presence of Amberlite IRA-45 (OH^-). Thus, 12 was obtained in 40% yield: mp 115–116°C, $[\alpha]_D$ +142° (H_2O) (lit.[6] mp 117–118°C, $[\alpha]_D$ +143.7°).

Condensation of a molar equiv. of 6 and 10 was first carried out in a small amount of 2-propanol in a sealed tube at 120°C for 117 h. Under these conditions, 10 was partly consumed by being converted into the corresponding acetamido derivative. The products were treated with acetic anhydride and pyridine at room temperature overnight. Disappearance of 6 and formation of five components were observed by TLC [ethanol–toluene (1:10)]. Fractionation of the products by using a silica gel column with 2-butanone–toluene (2:9) as an eluent gave in turn the cyclitol

Scheme V

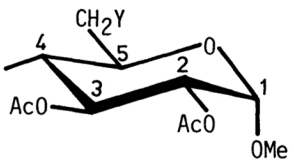


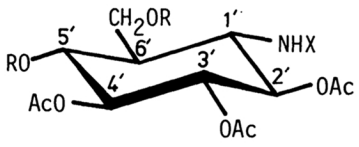
15a-d



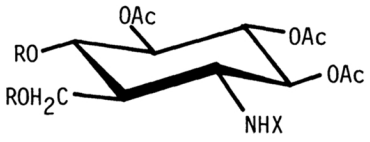
16a-d

X =





17a-d



18a-d

a: R, R = CHPh, Y = OAc

b: R = Ac, Y = OAc

c: R, R = CHPh, Y = H

d: R = Ac, Y = H

Table 1. Specific Rotations and Part of ^{1}H NMR Spectral Data[a)]

Compound	$[\alpha]_D^{23}$ (deg.)	Chemical shifts (δ)
15b[b)]	+101.3	2.95[c)] (1H, t, J = 10 Hz, H-4) 3.45 (1H, dd, J = 3.6 and 4 Hz, H-1')
15d[b)]	+101.0	2.58 (1H, t, J = 9.8 Hz, H-4) 3.46 (1H, t, J = 3.6 Hz, H-1')
16b	+35.2	2.82[c)] (1H, t, J = 10 Hz, H-4) 3.20 (1H, t, J = 3.4 Hz, H-1')
16d[b)]	+29.3	2.52 (1H, t, J = 9.5 Hz, H-4) 3.34 (1H, t, J = 3.6 Hz, H-1')
17b	+76.9	2.94 (2H, t, J = 9.5 Hz, H-1' and H-4)
17d	+71.4	2.58 (1H, t, J = 9.4 Hz, H-1')[d)] 3.05 (1H, t, J = 9.7 Hz, H-4)
18b	+64.5	2.95[c)] (2H, br t, J = 9 Hz, H-1' and H-4)
18d	+66.8	2.95 (1H, t, J = 9.7 Hz, H-1')[d)] 3.09 (1H, br t, J = 10.5 Hz, H-4)

a) Unless otherwise noted, the ^{1}H NMR spectra were measured at 90 MHz in chloroform-d after deuteration. The values given for coupling constants are of first-order. b) Measured at 200 MHz. c) Signal was shown, before deuteration, to be coupled with vicinal amine hydrogen (J = ca. 9–10 Hz). d) Assignment may be reversed.

tetraacetate 7 (40%), a mixture of amine hexaacetates 15a and 18a (25%), 17a (mp 201–202°C, $[\alpha]_D$ +81.9°, 7%), 16a ($[\alpha]_D$ +46.2°, 18%), and the peracetyl derivative 13 (52%) of 10. Compounds 16a and 17a were characterized by converting into the corresponding octaacetates 16b (96%) and 17b (95%), respectively, by treatment with 80% acetic acid (90°C, 90 min) followed by acetylation. A similar treatment of the mixture of 15a and 18a gave 15b and 18b, which were separable by chromatography on silica gel [2-butanone–toluene (1:3)]: 15b (16%) and 18b (7%). Four secondary amines theoretically obtainable were thus clearly isolated as the octaacetates. The structures were assigned as shown in Scheme V. The configurations of the branched-chain cyclitol parts were determined by the ^{1}H NMR signals due to the protons on carbon atoms bearing the imino linkages (Table I). The results were in consistent with the fact that the diastereomeric pair (15b and 16b) derived by a

diaxial opening of the epoxide ring, was obtained predominantly. The empirical rules on optical rotations of cyclohexanepolyols[7] suggested that the magnitude of the contributions of the cyclitol parts to the molar rotations were larger in 15b and 16b (chiro-configuration) than in 17b and 18b (scyllo-configuration). The rules also indicated that the cyclitol part of 15b, in which absolute S configuration at C-1' was assigned, would make a dextrorotatory contribution.[8] However, since there was only a small difference between the specific rotations of 17b and 18b, it was rather difficult to estimate convincingly which absolute configuration of the cyclitol parts made a larger contribution. Therefore, the structures of 17b and 18b may be reversed.

Condensation of 6 and 12 was similarly conducted in 2-propanol for 40 h. The products were acetylated and roughly separated by chromatography on silica gel. The peracetyl derivative 14 of 12, 6, and 7 were recovered in 34, 32, and 9% yields, respectively. A mixture (37%) of amine pentaacetates 15c, 17c, and 18c, and 16c ($[\alpha]_D$ +43.8°, 16%) were obtained. The mixture was treated with 80% acetic acid followed by acetylation and the resulting heptaacetates were separated by chromatography on silica gel [2-butanone–toluene (1:5)] to afford 15d, 17d, and 18d, in 15, 9, and 9% yields, respectively. Compound 16c was also characterized as 16d (92%). The structures of four secondary amine heptaacetates were assigned similarly (Scheme V). The structures of 17d and 18d may be reversed. Especially, the ^{1}H NMR spectra (200 MHz) of 15b, 15d, and 16d were almost completely interpreted by a first-order method, allowing to establish fully their assigned structures.

We are now attempting to convert 15d into 4 by elimination reaction. The present reaction sequence would provide a promising route for synthesis of homologous series of pseudo-oligosaccharidic α-glucosidase inhibitors.

References

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5) Optical rotations were determined on a Jasco DIP-4 polarimeter at 23°C, unless otherwise noted in chloroform. ^{1}H NMR spectra were measured on a Varian EM-390 (90 MHz) or a JEOL FX-200 (200 MHz) spectrometer in chloroform-d with reference to tetramethylsilane as an internal standard. The yields described in this paper are based on the starting materials used.

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8) It may be supported by the fact that 1S-(+)-hydroxyvalidamine, the branched-chain aminocyclitol whose absolute configuration is identical to that of the cyclitol part of 5, possesses $[\alpha]_D$ +80.7° (H_2O): S. Horii, T. Iwasa, E. Mizuta, and Y. Kameda, J. Antibiot., 24, 61 (1971).

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