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# SYNTHESIS OF AMYLOSTATIN (XG), α-GLUCOSIDASE INHIBITOR WITH BASIC PSEUDOTRISACCHARIDE STRUCTURE

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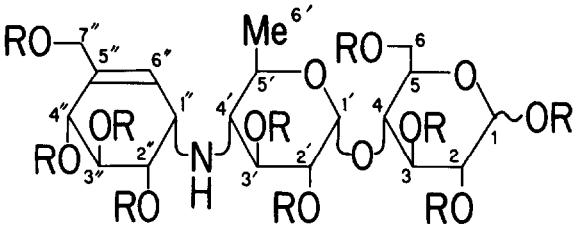
Summary: The basic pseudotrisaccharide (1) constituting the common and essential building block of several α-glucosidase inhibitors of microbial origin was synthesized by coupling two synthons: the chiral cyclohexyl halide (11) and the 4'-amino-4'-deoxy-disaccharide (14).

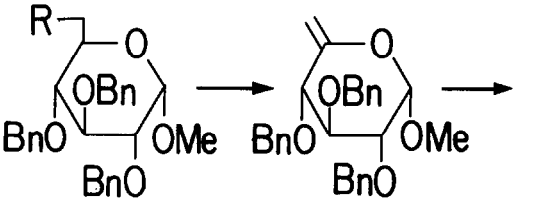
In recent years, several complexes of the α-glucosidase inhibitors with analogous pseudo-oligosaccharide structures have been isolated from culture broth of Actinomycetes by various research groups. They are acarbose and its homologs[1], amylostatins[2], trestatins[3], and so on[4].

This communication describes the synthesis of the peracetate (2) of a pseudotrisaccharide, O-4,6-dideoxy-4-[1D-(1,2,4/3)-2,3,4-trihydroxy-5-hydroxymethyl-5-cyclohexenyl]amino-α-D-gluco-pyranosyl-(1→4)-D-glucopyranose (1) that is the common and essential building block of the above α-glucosidase inhibitors. Compound 1 was also detected in the culture filtrate of the amylostatins-producing microorganism, designated as amylostatin (XG), and found to have the inhibitory activity against some α-glucosidases[2]. Since basic hydrolysis of 2 gave 1[5], this paper constitutes the first synthesis of 1.

The synthesis of 2 comprizes two important stages; i.e., the preparation of the chiral cyclohexenyl bromide (11) and the coupling of 11 with the other synthon, 4'-amino-4'-deoxy-disaccharide (14). Methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside (3)[6] was converted into the corresponding 6-mesylate (4)[7], mp. 73.5-74°; $[\alpha]_D^{24}$ +27° (c 0.86, $CHCl_3$). The mesyloxy group of 4 was substituted with an iodo anion in the usual way, giving 5, mp. 68-69°; $[\alpha]_D^{22}$ +30° (c 0.44, $CHCl_3$). When a solution of 5 in tetrahydrofuran was refluxed with six equimolar DBU and the raw product was chromatographed[8] with benzene-ethyl acetate (97:3) as the eluant, the 6-deoxy-5-enohexopyranoside (6), mp. 57-58°; $[\alpha]_D^{15}$ +18° (c 0.5, $CHCl_3$); $\nu_{max}^{film}$ $cm^{-1}$: 1650 (C=C), was obtained in 79% yield. Transformation of 6 to the cyclohexane derivative relied upon the Ferrier reaction[9], which was found to proceed quite smoothly with this benzylated sugar. Thus, 6 was refluxed for 90 min. in aqueous acetone with one equimolar mercuric chloride and the raw product was chromatographed with benzene-cyclohexane-methanol (50:50:1), giving 2L-(2,4,5/3)-2,3,4-tribenzyloxy-5-hydroxycyclohexanone (7), mp. 113-114°; $[\alpha]_D^{15}$ -51° (c 0.5, $CHCl_3$); $\nu_{max}^{film}$ $cm^{-1}$: 3400 (OH), 1720 (C=O); $\delta$[10] (acetone-$d_6$, 100 MHz) ppm: 2.46 (1H, dd, $J_{5,6a}$ 3.5 Hz, $J_{6a,6b}$ 15 Hz, H-6a), 2.78 (1H, dd, $J_{5,6b}$ 3.0 Hz, H-6b), in 84% yield. The compound 7 underwent ready β elimination on treatment with mesyl chloride in pyridine, giving the enone (8), mp. 60-61.5°; $[\alpha]_D^{25}$ +74° (c 0.65, $CHCl_3$); $\nu_{max}^{film}$ $cm^{-1}$: 1685 (C=O); $\delta$ ($CDCl_3$, 400 MHz) ppm: 6.03 (1H, dd, $J_{4,5}$ 1.8 Hz, $J_{5,6}$ 10.0 Hz, H-5), 6.80 (1H, d, H-6), in 91% yield. The Wittig reaction between 8 and methylenetriphenylphosphorane[11] proceeded in ether at room temperature to give a key inter-

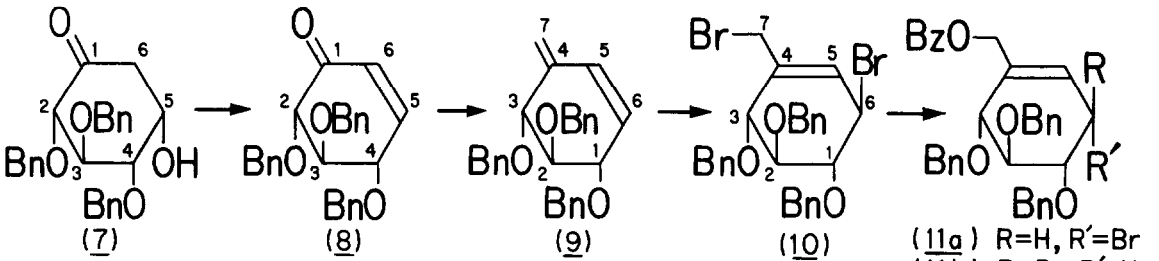


(1) R = H
(2) R = Ac



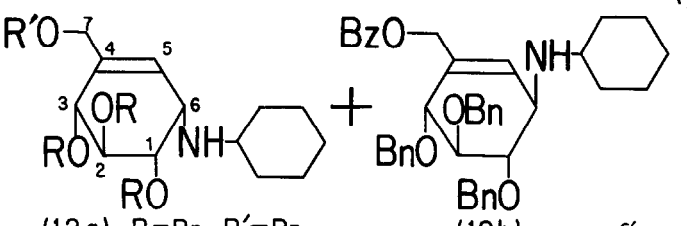
(3) R = OH
(4) R = OMs
(5) R = I

(6)



(7) (8) (9) (10)

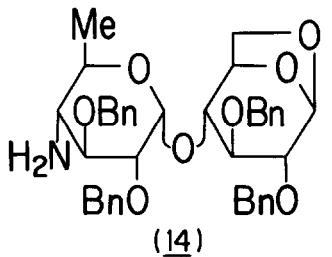
(11a) R=H, R′=Br
(11b) R=Br, R′=H



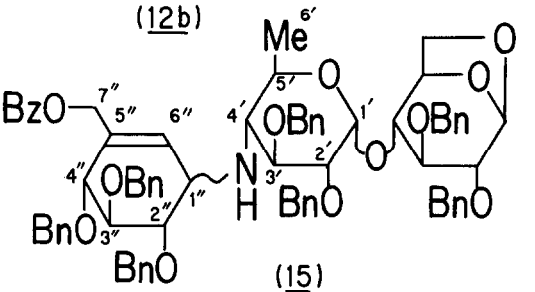
(12a) R=Bn, R′=Bz
(13) R=R′=H

(12b)

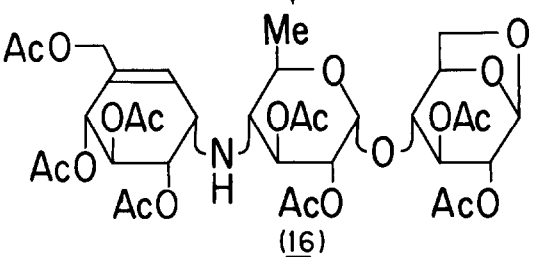
11a,b



(14)



(15)



(16)

mediate, 1D-(1,3/2)-1,2,3-tri-O-benzyl-4-methylene-5-cyclohexen-1,2,3-triol (9), mp. 54-55°; $[\alpha]_D^{15}$ +28° (c 1.03, $CHCl_3$); δ ($CDCl_3$, 100 MHz) ppm: 5.03 and 5.30 (1H x 2, bs, C=$CH_2$), 5.63 (1H, bd, $J_{5,6}$ 11.5 Hz, H-6), 6.10 (1H, d, H-5), in 77% yield. Ogawa et al.[12] reported 1,4-addition of bromine to an exocyclic diene system[13] similar to that of 9 and the utilization of the resulting dibromides for the preparation of racemic epivalidoxylamine A[14]. We examined the application of this procedure for the synthesis of 2 and found several novel features. Bromination of 9 in dichloromethane with one equimolar bromine proceeded smoothly without any influence on the benzyl groups, giving essentially the sole product with 1D-(1,3/2,6)-configuration (10), mp. 130-131°; $[\alpha]_D^{15}$ -151° (c 0.30, $CHCl_3$); δ ($CDCl_3$, 400 MHz) ppm: 3.83 (1H, d, $J_{7a,7b}$ 10.0 Hz, H-7a), 4.39 (1H, bd, H-7b), 4.70 (1H, dq, $J_{1,6}$ 8.0 Hz, $J_{3,6}$ 5.8 Hz, $J_{6,7b}$ 2.7 Hz, H-6), 5.95 (1H, bs, H-5), in 84% yield. Selective substitution of the primary bromide of 10 in DMF at room temperature with one equimolar benzoate anion accompanied partial epimerization of the secondary bromide, giving 1D-(1,3,6/2)-4-benzoyloxymethyl-6-bromo-1,2,3-tri-O-benzyl-4-cyclohexene-1,2,3-triol (11a), $[\alpha]_D^{24}$ +59° (c 0.75, $CHCl_3$); $\nu_{max}^{film}$ $cm^{-1}$: 1715 (C=O); δ ($CDCl_3$, 400 MHz) ppm: 3.55 (1H, dd, $J_{1,2}$ 10.0 Hz, $J_{1,6}$ 4.0 Hz, H-1), 6.05 (1H, d, $J_{5,6}$ 6.0 Hz, H-5), and the corresponding 1D-(1,3/2,6)-isomer (11b), $[\alpha]_D^{25}$ -55° (c 0.54, $CHCl_3$); $\nu_{max}^{film}$ $cm^{-1}$: 1715 (C=O); δ ($CDCl_3$, 400 MHz) ppm: 3.80 (1H, t, $J_{1,2}=J_{1,6}$ 10 Hz, H-1), 5.97 (1H, s, H-5), in the total yield of 63%[15].

For the next coupling reaction, the mixture of 11a and 11b was used because there was a rapid equilibration between them under the reaction conditions employed. Cyclohexylamine was first employed as a model nucleophile for testing. The mixture, 11a,b and cyclohexylamine completely resisted coupling each other under the conditions (diisopropylamine, DMF, room temperature) successfully employed for the synthesis of epivalidoxylamine A[14]. This was probably due to the benzyloxy group in 11a,b as a neiboring group nonparticipating in the substitution reaction. After further unsuccessful attempts, we finally succeeded in the coupling by keeping both reactants in DMSO at room temperature in the presence of NaI, obtaining 12a, $[\alpha]_D^{15}$ +31° (c 0.53, $CHCl_3$); δ ($CDCl_3$, 400 MHz) ppm: 3.63 (1H, m, H-6), 5.98 (1H, d, $J_{5,6}$ 3.4 Hz, H-5), and 12b, $[\alpha]_D^{15}$ -74° (c 0.48, $CHCl_3$); δ ($CDCl_3$, 400 MHz) ppm: 3.49 (1H, d, $J_{1,6}$ 9.8 Hz, H-6), 5.79 (1H, s, H-5), in the yield of 30% and 28% respectively. Deprotection of 12a on successive treatments with sodium methylate and with sodium in liquid ammonia gave 13, $[\alpha]_D^{23}$ +19° (c 0.43, $H_2O$); δ ($D_2O$, 400 MHz) ppm: 5.87 (1H, d, $J_{5,6}$ 3.5 Hz, J-5), in 70% yield.

An attempt to couple 11a,b with the other synthon, 4'-amino-1,6-anhydro-2,2',3,3'-tetra-O-benzyl-4',6'-dideoxy-β-maltose (14)[16], $[a]_D^{19}$ +11° (c 0.38, $CHCl_3$), was carried out according to the results of the above model reaction. The reaction proceeded rather slowly, giving a few unidentified products in addition to the coupled compound (15). Thus, a mixture of 11a,b, 14, and NaI in the molar ratio of 1:6:1.5 was stirred for three days in DMSO under the nitrogen atomosphere. Separation of the products by column chromatography with benzene-cyclohexane-ethyl acetate (10:10:3) gave 15 as a diastereomeric mixture in 13% yield from 11 and 90% of the unchanged 14. For the structural elucidation, one of the diastereomers with the desired configuration was isolated from a small amount of 15 by preparative thin layer chromatography; δ ($CDCl_3$, 400 MHz) ppm: 1.23 (3H, d, $J_{5',6'}$ 5.9 Hz, H-6'), 4.03 (1H, t, $J_{1",2"}=J_{1",6"}$ 3.4 Hz,

H-1"), 6.00 (1H, d, H-6"). The mixture, 15 was treated with sodium in liquid ammonia for deprotection. After desalting with ion exchange resins, the resulting product was acetylated with acetic anhydride and pyridine[17] and chromatographed with benzene-ethyl acetate (3:2), giving the compound with the desired configuration (16), δ ($CDCl_3$, 400 MHz) ppm: 6.00 (1H, bd, $J_{1",6"}$ 5.3 Hz, H-6"), and its 1"-epimer in 43% and 36% yields respectively. Acetolysis of 16 was performed at room temperature with acetic anhydride, acetic acid, and conc. $H_2SO_4$ (300:300:7 v/v) and the product was chromatographed with benzene-ethyl acetate (1:1) to give 2, m/z 843.2750 [$(M-CH_3COOH)^+$, calcd. for $C_{37}H_{49}NO_{21}$: 843.2793]; δ ($CDCl_3$, 400 MHz) ppm: 1.19 (3H, d, $J_{5',6'}$ 4.9 Hz, H-6'), 3.72 (1H, m, H-1"), 4.38 (1H, d, $J_{7a",7b"}$ 13.2 Hz, H-7a"), 4.45 (1H, d, H-7b"), 4.93 (1H, dd, $J_{2",3"}$ 10.2 Hz, $J_{1",2"}$ 4.4 Hz, H-2"), 5.26 (1H, d, $J_{1',2'}$ 3.9 Hz, H-1'), 5.60 (1H, dd, $J_{3",4"}$ 6.8 Hz, H-3"), 5.73 (trace, d, $J_{1,2}$ 8.3 Hz, H-1 of β-anomer), 5.96 (1H, bd, $J_{1",6"}$ 5.2 Hz, H-6"), 6.24 (1H, d, $J_{1,2}$ 3.9 Hz, H-1 of α-animer). The nmr spectrum indicating that acetolysis of 16 predominantly gave the α-anomer of 2 was identical with that of the authentic specimen derived from natural 1[5] except their anomeric ratios.

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13) The racemic compound of the tri-O-acetate corresponding to 9.

14) S. Ogawa, T. Toyokuni, and T. Suami, Chem. Lett., 947 (1981).

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16) N. Sakairi, H. Murakami, and H. Kuzuhara, Carbohydr. Res., submitted for publication.

17) The amino linkage was not acetylated. For a similar example, see S. Omoto, J. Ito, H. Ogino, K. Iwamatsu, N. Nishizawa, and S. Inouye, The Journal of Antibiotics, 34, 1429 (1981).


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