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SYNTHESIS OF A 4′-AMINO-4′,6′-DIDEOXYMALTOSE DERIVATIVE AS A SYNTHON OF AN α-D-GLUCOSIDASE INHIBITOR

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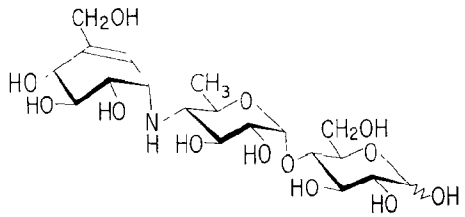
ABSTRACT

4′-Amino-1,6-anhydro-2,3,2′,3′-tetra-*O*-benzyl-4′,6′-dideoxy-β-maltose, required as a synthon for the preparation of an α-D-glucosidase inhibitor constituted of a basic pseudotrisaccharide, was prepared from 1,6-anhydromaltose (**2**). Two pathways were examined for introducing the amino function into **2** during that synthesis.

INTRODUCTION

In recent years, several complexes of α-D-glucosidase inhibitors with analogous pseudo-oligosaccharide structures, including acarbose and its homologs[1], amylostatins[2], and trestatins[3], have been isolated from the culture broth of *Actinomycetes* by various research groups. A unique pseudotrisaccharide (**1**) having an imino group as one internal linkage is the common, and essential, building block of these α-D-glucosidase inhibitors. Furthermore, **1** also has inhibitory activity against some α-D-glucosidases[4].

As part of a program on the synthesis of pseudo-oligosaccharides having biological activity, we chose **1** as a target, and achieved its synthesis[5]. We now describe the preparation of 4′-amino-1,6-anhydro-2,3,2′,3′-tetra-*O*-benzyl-4′,6′-dideoxy-β-maltose (**13**), required as one of the two synthons for the preparation of **1**.



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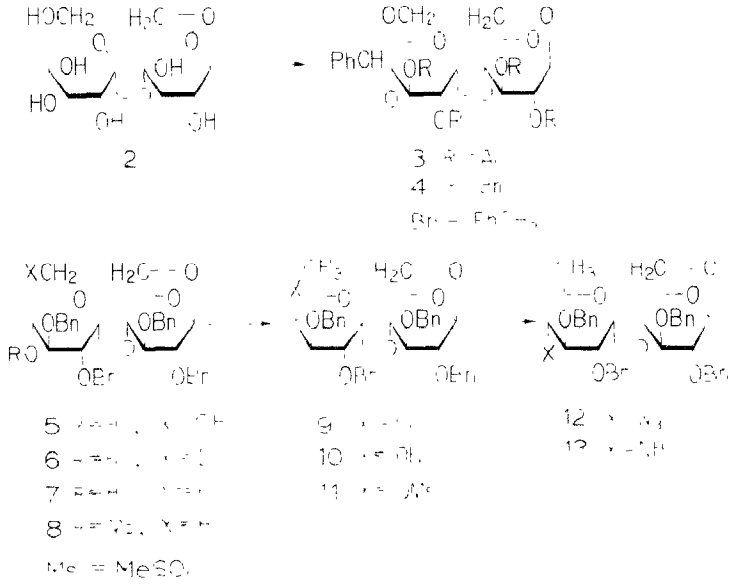
RESULTS AND DISCUSSION

The starting material, 1,6-anhydro-β-maltose (**2**), was readily accessible by our modified preparation-procedure[6]. Although benzylidenation of **2** had already been conducted with benzaldehyde and zinc chloride[7], we examined the applicability of another method, *i.e.*, the use of a combination[8] of α,α-dimethoxytoluene, *p*-toluenesulfonic acid, and *N*,*N*-dimethylformamide (DMF), which seemed to be a convenient system for the large-scale preparation of **5** without isolation of the intermediates (as described later). The reaction proceeded readily, and the product was isolated as the peracetate (**3**). Compound **3** was treated with sodium methoxide in methanol, and the product, with sodium hydride and benzyl bromide in *N*,*N*-dimethylformamide, to give 1,6-anhydro-2,3,2′,3′-tetra-*O*-benzyl-4′,6′-*O*-benzylidene-β-maltose (**4**) as crystals in almost quantitative yield. Removal of the benzylidene group of **4** with aqueous acetic acid gave syrupy **5**. The fact that the same solvent, *N*,*N*-dimethylformamide, was used for the benzylidenation and benzylation reactions prompted us to conduct continuous treatment by omitting the acetylation step for the large-scale preparation of **5**. Actually, **5** was prepared from **2** in an overall yield of 44% by this procedure, as shown in the Experimental part. Selective iodination of the primary hydroxyl group of **5** was achieved by employing triphenylphosphine and *N*-iodosuccinimide in *N*,*N*-dimethylformamide as the solvent[9], giving **6** as crystals in a yield of 74%. Compound **6** was reduced with lithium aluminum hydride, to give the crystalline 6′-deoxy derivative (**7**).

Two pathways were examined for the transformation of **7** into the corresponding 4′-azido-4′-deoxy derivative (**12**). In the first, the 4′-hydroxyl group of **7**



was directly replaced with chloride anion by treatment with sulfuryl chloride and imidazole[10], to give 1,6-anhydro-2,3-di-*O*-benzyl-4-*O*-(2,3-di-*O*-benzyl-4-chloro-4,6-dideoxy-α-D-galactopyranosyl)-β-D-glucopyranose (**9**), which underwent replacement of the chlorine with azide anion, to give **12**. Although this route comprised only two reaction steps, both required a rather long reaction-time, and the yields of the products (**9** and **12**) were not very high, *viz.*, 68 and 63%, respectively. The second route was rather circuitous, but each reaction step gave the respective product in moderately good yield. Compound **7** was methanesulfonylated in the usual way, to give **8**, which underwent replacement of the sulfonate by benzoate anion, and alkaline hydrolysis of the resulting benzoate gave 1,6-anhydro-2,3-di-*O*-benzyl-4-*O*-(2,3-di-*O*-benzyl-6-deoxy-α-D-galactopyranosyl)-β-D-glucopyranose (**10**). Methanesulfonylation of the hydroxyl group of **10** gave **11**, which was treated with azide anion to afford **12**. The overall yield of **12** from **7** was 52% by the second route, whereas it was only 43% by the first. Reduction of **12** with lithium aluminum hydride in ethyl ether as the solvent gave the expected 4′-amino-4′,6′-dideoxymaltose derivative (**13**) in good yield, and the **13** obtained was used[5] successfully for the synthesis of **1**.

EXPERIMENTAL

General. — Solutions were evaporated under diminished pressure; solvent extracts were dried with anhydrous sodium sulfate, or magnesium sulfate. Melting points are uncorrected. Optical rotations were measured with a Perkin–Elmer Model 241MC polarimeter. I.r. spectra were recorded with a Shimadzu IR-27 instrument, and n.m.r. spectra with a Jeol JNM FX-400 spectrometer, for solutions in deuteriochloroform containing tetramethylsilane as the internal standard.

2,3,2′,3′-Tetra-O-*acetyl-1,6-anhydro-4′,6′*-O-*benzylidene-β-maltose* (**3**). — A solution of dry **2** (1.0 g), α,α-dimethoxytoluene (520 mg), and *p*-toluenesulfonic acid monohydrate (1 mg) in DMF (5 mL) was evacuated, and rotated for 3 h at 60–70° in a rotary evaporator, several mL additional of DMF being added during the process. The mixture was cooled, pyridine (12 mL) and acetic anhydride (10 mL) were added, and the solution was kept overnight at room temperature, and evaporated; the residue was suspended in water, and extracted with ethyl acetate. The extract was successively washed with 3% aqueous sulfuric acid, aqueous sodium hydrogencarbonate, and water, dried, and evaporated to a syrup that was chromatographed on silica gel with 8:1 (v/v) benzene–ethyl acetate as the eluant, giving **3** (1.03 g, 58%); m.p. 207–209°, $[\alpha]_D^{21}$ +19° (*c* 1.2, chloroform); lit.[7] m.p. 215–216°, $[\alpha]_D^{24}$ +20° (*c* 1.01, chloroform).

Anal. Calc. for $C_{27}H_{32}O_{14}$: C, 55.86; H, 5.56. Found: C, 55.92; H, 5.55.

1,6-Anhydro-2,3,2′,3′-tetra-O-*benzyl-4′,6′*-O-*benzylidene-β-maltose* (**4**). — Methanolic sodium methoxide (0.42M; 5.8 mL) was added to a solution of **3** (7.0 g) in methanol (200 mL), and the mixture was stirred overnight at room temperature, and evaporated. The syrup obtained was dissolved in DMF (120 mL), sodium hydride

(2.2 g) was added, and the solution was stirred for 30 min at room temperature; benzyl bromide (19.3 mL) was added dropwise to the mixture cooled in an ice bath, and the resulting suspension was stirred for 3 h at room temperature. After addition of methanol (5 mL), the mixture was diluted with water, and extracted with ethyl ether. The extract was washed with water, dried, and evaporated to a syrup which was chromatographed on silica gel, with 8:1 (v/v) benzene–ethyl acetate as the eluant. Crystalline **4** (9.3 g, 99%) was obtained: m.p. 105.5–106°, $[\alpha]_D^{25}$ −27° (*c* 1.06, chloroform).

Anal. Calc. for $C_{47}H_{48}O_{10}$: C, 73.04; H, 6.26. Found: C, 73.21; H, 6.18.

1,6-Anhydro-2,3,2',3'-tetra-O-benzyl-β-maltose (**5**). — (*a*) *Preparation from* **4**. Water (42 mL) was added to a solution of **4** (9.28 g) in acetic acid (170 mL). The resulting solution was heated for 30 min at 97–98°, cooled, and evaporated to a syrup, which was chromatographed on silica gel with 97:3 (v/v) chloroform–methanol as the eluant, giving **5** (5.2 g, 63%): $[\alpha]_D^{20}$ +1.4° (*c* 0.8, chloroform); ν_{max}^{film} 3400 cm^{-1}.

Anal. Calc. for $C_{40}H_{44}O_{10}$: C, 70.16; H, 6.48. Found: C, 70.19; H, 6.50.

(*b*) *Large-scale preparation from* **2**, *omitting the acetylation step*. A solution of **2** (38 g), α,α-dimethoxytoluene (20 g), and *p*-toluenesulfonic acid monohydrate (300 mg) in DMF (300 mL) was evacuated to ~10 torr, rotated for 3 h at 70–80° in a rotary evaporator, diluted with more DMF (300 mL), and cooled. Sodium hydride (60%; 25 g) was added in portions to the solution, the mixture was stirred for 1 h at room temperature, and then cooled to below 5°. Benzyl bromide (110 mL) was added dropwise at 0°, and the mixture was stirred for 1 day at room temperature. After dropwise addition of methanol (50 mL), the mixture was diluted with dichloromethane (300 mL) and ethyl ether (1.5 L), washed with water, dried, and evaporated to a syrup. A solution of the syrup in 4:1 (v/v) acetic acid–water (300 mL) was heated for 1 h at 100–110°, cooled, and evaporated. After addition of toluene and evaporation, the residue was washed with hexane by decantation, and chromatographed on silica gel with 99:1→98:2 (v/v) chloroform–methanol as the eluant, giving **5** (35 g, 44% from **2**).

1,6-Anhydro-2,3,2',3'-tetra-O-benzyl-6'-deoxy-6'-iodo-β-maltose (**6**). Triphenylphosphine (5.69 g) was added to a solution of **5** (7.44 g) and *N*-iodosuccinimide (4.79 g) in DMF (370 mL) at 0°. The mixture was stirred for 3 h at 50°, methanol (2 mL) was added, and the solution was stirred for 1 h at room temperature, and evaporated to a syrup which was extracted with ethyl ether. The extract was washed with water, dried, and evaporated, to give a syrup which was chromatographed on silica gel with 97:3 (v/v) chloroform–methanol as the eluant. The isolated **6** crystallized from cyclohexane; yield 6.34 g (74%); m.p. 123–124.5°, $[\alpha]_D^{24}$ +3.3° (*c* 0.78, chloroform); ν_{max}^{KBr} 3400 cm^{-1}.

Anal. Calc. for $C_{40}H_{43}IO_9$: C, 60.46; H, 5.45; I, 15.97. Found: C, 60.46; H, 5.46; I, 16.07.

1,6-Anhydro-2,3,2',3'-tetra-O-benzyl-6'-deoxy-β-maltose (**7**). A solution of **6** (6.1 g) in dry oxolane (100 mL) was added dropwise below 5° to a suspension of lithium aluminum hydride (440 mg) in dry oxolane (300 mL), and the mixture was

stirred for 2 h at room temperature. After successive addition of ethyl acetate (10 mL) and methanol (10 mL), the mixture was diluted with a saturated solution of sodium potassium tartrate, and extracted with ethyl ether. The extract was washed with water, dried, and evaporated, giving crystalline, crude **7** which was chromatographed on silica gel with 4:1 (v/v) benzene–ethyl acetate. The isolated **7** was recrystallized from cyclohexane; yield 3.25 g (63%); m.p. 126–127°, $[\alpha]_D^{23}$ −2.2° (*c* 1.2, chloroform); ν_{max}^{KBr} 3450 cm^{-1}; δ 1.24 (d, 3 H, $J_{5',6'}$ 6.3 Hz, H-6′).

Anal. Calc. for $C_{40}H_{44}O_9$: C, 71.84; H, 6.63. Found: C, 71.85; H, 6.64.

In another preparation, the crude crystals were recrystallized from cyclohexane without purification by column chromatography, giving **7** in a yield of 80%.

*1,6-Anhydro-2,3,2′,3′-tetra-*O*-benzyl-6′-deoxy-4′-*O*-(methylsulfonyl)-β-maltose* (**8**). — Methanesulfonyl chloride (2 mL) was added dropwise at 0° to a stirred solution of **7** (5 g) in pyridine (20 mL) and dichloromethane (200 mL). The mixture was kept for 2 days at room temperature, diluted with water, and stirred for 1 h. After addition of more dichloromethane, the organic layer was separated, washed successively with 3% aqueous sulfuric acid and water, dried, and evaporated. The resulting syrup was chromatographed on silica gel with 19:1 (v/v) benzene–ethyl acetate as the eluant, giving **8** (5.2 g, 93%); $[\alpha]_D^{19}$ +11° (*c* 0.63, chloroform); δ 1.33 (d, 3 H, $J_{5',6'}$ 6.3 Hz, H-6′), 4.21 (t, 1 H, $J_{3',4'} = J_{4',5'} = 9.8$ Hz, H-4′), and 4.89 (d, 1 H, $J_{1',2'}$ 3.4 Hz, H-1′).

Anal. Calc. for $C_{41}H_{46}O_{11}S$: C, 65.93; H, 6.21; S, 4.29. Found: C, 65.75; H, 6.03; S, 4.32.

*1,6-Anhydro-2,3-di-*O*-benzyl-4-*O*-(2,3-di-*O*-benzyl-4-chloro-4,6-dideoxy-α-*D*-galactopyranosyl)-β-*D*-glucopyranose* (**9**). — Sulfuryl chloride (5 mL) was added dropwise below −40° to a solution of **7** (7.5 g) in DMF (100 mL), and the mixture was stirred for 1 h at −50°. Imidazole (7.63 g) was now added, and the mixture was kept for 3 days at room temperature with stirring, poured into ice–water, and extracted with ethyl ether. The extract was washed successively with 3% aqueous sulfuric acid and water, dried, and evaporated to dryness. Chromatography of the residual syrup on silica gel, with 2:1 (v/v) cyclohexane–ethyl ether as the eluant, gave **9** (5.2 g, 68%); $[\alpha]_D^{24}$ +33° (*c* 0.92, chloroform); δ 1.27 (d, 3 H, $J_{5',6'}$ 6.4 Hz, H-6′) and 4.27 (dd, 1 H, $J_{3',4'}$ 4, $J_{4',5'}$ 1.5 Hz, H-4′).

Anal. Calc. for $C_{40}H_{43}ClO_8$: C, 69.91; H, 6.31; Cl, 5.16. Found: C, 69.89; H, 6.30; Cl, 5.08.

*1,6-Anhydro-2,3-di-*O*-benzyl-4-*O*-(2,3-di-*O*-benzyl-6-deoxy-α-*D*-galactopyranosyl)-β-*D*-glucopyranose* (**10**). — Sodium benzoate (5 g) was added to a solution of **8** (10.2 g) in hexamethylphosphoric triamide (100 mL), and the mixture was stirred for 16 h at 120–130°, and then cooled to room temperature. Methanol (100 mL) and 2M aqueous sodium hydroxide (100 mL) were added, and the mixture was stirred overnight at room temperature, concentrated to half volume, diluted with water, and extracted with ethyl ether. The extract was washed successively with M hydrochloric acid, saturated aqueous sodium hydrogencarbonate, and water, dried, and evaporated, giving a syrup that was chromatographed on silica gel with 4:1 (v/v)

benzene–ethyl acetate as the eluant, to afford **10** (6.5 g, 71%), which was recrystallized from ethyl ether–hexane for analysis; m.p. 97–98°, $[\alpha]_D^{19}$ +12° (*c* 0.53, chloroform).

Anal. Calc. for $C_{40}H_{44}O_9$: C, 71.84; H, 6.63. Found: C, 71.53; H, 6.59.

1,6-Anhydro-2,3-di-O-benzyl-4-O-[2,3-di-O-benzyl-6-deoxy-4-O-(methylsulfonyl)-α-D-galactopyranosyl]-β-D-glucopyranose (**11**). — Methanesulfonyl chloride (4 mL) was added dropwise at 0° to a solution of **10** (5.9 g), triethylamine (4 mL), and 4-(dimethylamino)pyridine (0.5 g) in dichloromethane (200 mL). The mixture was stirred for 3 h at 0° and, after addition of water (5 mL), for a further 2 h at room temperature. The solution was diluted with ethyl ether, washed successively with 3% aqueous sulfuric acid, aqueous sodium hydrogencarbonate, and water, dried, and evaporated to a syrup that was chromatographed on silica gel with 19:1 (v/v) benzene–ethyl acetate as the eluant, giving **11** (6.2 g, 94%); $[\alpha]_D^{19}$ +28° (*c* 0.60, chloroform); δ 1.29 (d, 3 H, $J_{5',6'}$ 6.3 Hz, H-6'), 4.34 (broad q, 1 H, $J_{5',6'}$ 6.3 Hz, H-5'), 4.95 (d, 1 H, $J_{1',2'}$ 3.9 Hz, H-1'), and 4.97 (broad d, 1 H, $J_{3',4'}$ 3.8 Hz, H-4')

Anal. Calc. for $C_{41}H_{46}O_{11}S$: C, 65.93; H, 6.21; S, 4.29 Found: C, 66.02, H, 6.18; S, 4.23.

1,6-Anhydro-4'-azido-2,3,2',3'-tetra-O-benzyl-4',6'-dideoxy-β-maltose (**12**). — (*a*) *Preparation from* **9**. Sodium azide (1.08 g) was added to a solution of **9** (1.63 g) in hexamethylphosphoric triamide (30 mL), and the mixture was stirred for 3 days at 100–105°, cooled, and diluted with ethyl ether. The solution was washed several times with water, dried, and evaporated to a syrup that was chromatographed on silica gel with 15:1 (v/v) benzene–ethyl ether as the eluant, giving **12** (1.09 g, 66%): $[\alpha]_D^{25}$ +47° (*c* 0.68, chloroform); ν_{max}^{film} 2100 cm^{-1}; δ 1.27 (d, 3 H, $J_{5',6'}$ 6.3 Hz, H-6'), 3.10 (t, 1 H, $J_{3',4'} = J_{4',5'}$ = 9.8 Hz, H-4'), 4.87 (d, 1 H, $J_{1',2'}$ 3.9 Hz, H-1'), and 5.49 (broad s, 1 H, H-1).

Anal. Calc. for $C_{40}H_{43}N_3O_8$: C, 69.25; H, 6.32; N, 6.06. Found: C, 68.97; H, 6.32; N, 5.77.

(*b*) *Preparation from* **11**. Sodium azide (1.0 g) was added to a solution of **11** (5.8 g) in hexamethylphosphoric triamide (100 mL). The mixture was stirred for 10 h at 90–100°, and processed as described in (a), to give **12** (4.0 g, 83%).

4'-Amino-1,6-anhydro-2,3,2',3'-tetra-O-benzyl-4',6'-dideoxy-β-maltose (**13**). — Lithium aluminum hydride (1 g) was added in portions to a solution of **12** (1.2 g) in anhydrous ethyl ether (120 mL). The mixture was boiled under reflux for 10 h, cooled in an ice bath, and diluted with ethyl ether and a saturated aqueous solution of sodium potassium tartrate under vigorous stirring. The ethyl ether solution was washed with water, dried, and evaporated to a syrup that was chromatographed on silica gel with 99:1 (v/v) chloroform–methanol as the eluant, giving **13** (0.95 g, 84%); $[\alpha]_D^{19}$ +11° (*c* 0.38, chloroform); δ 1.22 (d, 3 H, $J_{5',6'}$ 6.3 Hz, H-6'), 2.49 (t, 1 H, $J_{3',4'} = J_{4',5'}$ = 9.8 Hz, H-4'), 3.52 (dd, 1 H, $J_{1',2'}$ 3.4, $J_{2',3'}$ 9.8 Hz, H-2'), 4.97 (d, 1 H, $J_{1',2'}$ 3.4 Hz, H-1'), and 5.49 (broad s, 1 H, H-1).

Anal. Calc. for $C_{40}H_{45}NO_8$: C, 71.94; H, 6.79; N, 2.10. Found: C, 71.83, H, 6.77; N, 2.07

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