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Note

Synthesis of [(1*S*)-(1,2,4/3,5)-2-amino-3,4-dihydroxy-5-(hydroxymethyl)-1-cyclohexyl] α-D-glucopyranoside*

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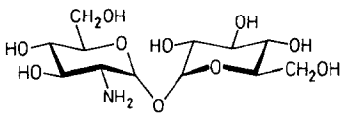
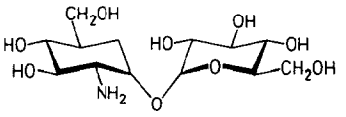
As part of a study of the elucidation of biochemical and biological properties of pseudo-sugars[1], replacement of the hexopyranosyl residues of biologically active disaccharides with structurally related pseudo-sugars has been investigated.

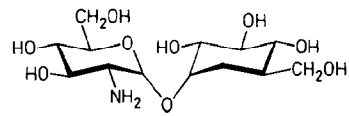
Trehalosamine[2] (**1**) is an aminoglycoside antibiotic[3] produced by *Streptomyces lavendulae*. It is an α,α-(1→1)-linked disaccharide composed of D-glucose and 2-amino-2-deoxy-D-glucose. Three related compounds, the 3-amino-3-deoxy[4]



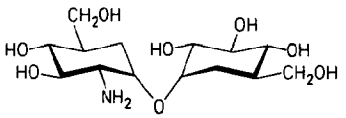
1
Trehalosamine



A



B



C

and 4-amino-4-deoxy isomers[5], and 2-amino-2-deoxy-α-D-glucopyranosyl α-D-mannopyranoside[6], have thus far been shown to possess antibacterial activity. The synthesis and biological activities of analogous disaccharides have been extensively studied by Baer and his co-workers[7–9].

Three types of pseudo-sugar analogues of trehalosamine may be considered:

*Synthesis of Pseudo-trehalosamine and Related Pseudo-disaccharides. Part I.
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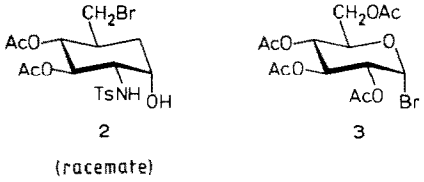
the pseudo-disaccharides consisting of (A) D-glucose and "pseudo-α-D-glucosamine", (B) "pseudo-α-D-glucose" and 2-amino-2-deoxy-D-glucose, and (C) "pseudo-α-D-glucose" and "pseudo-α-D-glucosamine". In this study, the α,β-(1→1)-linked isomer (type A) has been synthesized as a model compound by condensation of a protected "pseudo-α-DL-glucosamine" with an acylated glycosyl halide, followed by deprotection.

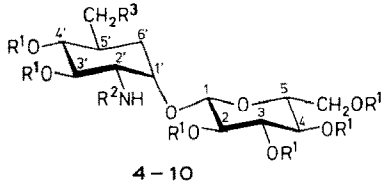
Condensation of (1*RS*)-3,4-di-*O*-acetyl-(1,2,4/3,5)-5-bromomethyl-2-(*p*-toluenesulfonamido)-1,3,4-cyclohexanetriol[10] (**2**) with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**3**) was performed in boiling benzene in the presence of mercury(II) cyanide for 2 days. The products were separated on a column of silica gel to give a homogeneous mixture of condensation products. Crystallization from ethanol afforded [(1*R*)-(1,2,4/3,5)-5-bromomethyl-3,4-dihydroxy-2-(*p*-toluenesulfonamido)-1-cyclohexyl] β-D-glucopyranoside hexaacetate (**11**), m.p. 200–201°, $[\alpha]_D$ −38° (chloroform), in 36% yield. The other diastereoisomer (**4**), $[\alpha]_D$ +55° (chloroform), was obtained in 31% yield as a crude syrup contaminated with a trace of **11**. The structures of **4** and **11** were assigned by elemental analyses and ^{1}H-n.m.r. spectra. The absolute structures were first deduced from their optical properties, as a dextrorotatory contribution of the cyclohexane moiety* of **4** to the optical rotation was predicted on the basis of an empirical rule[12] for the optical rotations of cyclitols. This conclusion was supported by subsequent degradation of



2

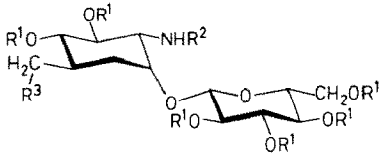
(racemate)

3



4 – 10

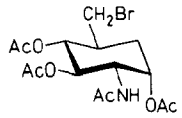
	R^1	R^2	R^3
4	Ac	Ts	Br
5	Ac	Ts	OAc
6	Ac	Ac	OAc
7	H	Ac	OH
8	Ac	Ts	H
9	Ac	Ac	H
10	Ac	Ts	N_3



11 – 16

	R^1	R^2	R^3
11	Ac	Ts	Br
12	Ac	Ts	OAc
13	Ac	Ac	OAc
14	H	Ac	OH
15	Ac	Ts	H
16	Ac	Ts	N_3

*This assumption may be based on the fact that the totally acetylated derivative of validamine, (1*S*)-(1,2,4/3,5)-2,3,4-trihydroxy-5-(hydroxymethyl)cyclohexylamine, possesses[11] $[\alpha]_D^{20}$ +62° ($CHCl_3$)



17

4 with hydrogen bromide in acetic acid, yielding (1*S*)-(+)-(1,2,4/3,5)-2-acetamido-5-bromomethyl-1,3,4-cyclohexanetriol triacetate (**17**), identical with an authentic sample[13].

Treatment of **4** with anhydrous sodium acetate in *N,N*-dimethylformamide (DMF) for 40 h at 80° afforded, after chromatography on silica gel, the pure hepta-acetate **5** in 80% yield. Similarly, **11** was converted quantitatively into the hepta-acetate **12**. Reductive *N*-detosylation of **5** and **12** with sodium in liquid ammonia afforded the free pseudo-disaccharides, which were isolated as the totally acetylated derivatives **6** and **13** in 59 and 46% yields, respectively. Compounds **6** and **13** were further characterized as their *N*-acetyl derivatives **7** and **14**.

Hydrogenolysis of **4** and **11** with Raney nickel T-4[14] in the presence of Amberlite IR-45 (HO^-) resin afforded the respective 7′-deoxy compounds **8** and **15** in good yield. Similar *N*-detosylation of **4** gave the totally acetylated derivative **9** in 42% yield.

Treatment of **4** and **11** with sodium azide in DMF for 5 h at 80° afforded the 7′-azido compounds **10** and **16**, respectively, in good yield.

EXPERIMENTAL

General methods. — Melting points were determined with a Büchi 510 capillary melting-point apparatus and are uncorrected. Optical rotations were measured with a Jasco DIP-4 polarimeter. ^{1}H-N.m.r. spectra were recorded at 90 MHz with a Varian EM-390 spectrometer for solutions in $CDCl_3$ with reference to Me_4Si as the internal standard. T.l.c. was performed on plates coated with Silica Gel 60 F-254 (E. Merck) and silica gel column-chromatography employed Wakogel C-300 (300 mesh, Wako Co.). Organic solutions were dried over anhydrous sodium sulfate and evaporated below 50° under diminished pressure.

*[(1S)-(1,2,4/3,5)-5-Bromomethyl-3,4-dihydroxy-2-(*p*-toluenesulfonamido)-1-cyclohexyl] β-*D*-glucopyranoside hexaacetate* (**4**) *and its (1*R*)diastereoisomer* (**11**). — A mixture of (1*RS*)-3,4-di-*O*-acetyl-(1,2,4/3,5)-5-bromomethyl-2-(*p*-toluenesulfonamido)-1,3,4-cyclohexanetriol[9] (**2**, 3.0 g, 6.3 mmol), 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**3**, 5.2 g, 12.7 mmol), mercury(II) cyanide (3.0 g), anhydrous calcium sulfate (5 g), and dry benzene (200 mL) was boiled under reflux fór 2 days. The cooled mixture was washed successively with aqueous sodium hydrogencarbonate and water, dried, and evaporated. The residue was crystallized from ethanol (50 mL) to give 1.7 g (33%) of **11** as prisms, m.p. 199–201°. The mother liquor was concentrated and eluted from a column of silica gel (200 g) with

1:4 butanone–toluene to give a homogeneous syrup, from which 0.15 g of **11** crystallized; total yield of **11** 36%. An analytical sample was prepared by recrystallization from ethanol; needles, m.p. 200–201°, $[\alpha]_D^{21}$ −38° (*c* 0.4, $CHCl_3$); ^{1}H-n.m.r., δ 7.60 and 7.17 (2 d, each 2 H, *J* 8 Hz, phenyl), 5.71 (d, 1 H, $J_{1,2}$ 5.5 Hz, H-1), 3.43–3.06 (m, 3 H, H-2, 6a, 6b), 2.35 (s, 3 H, tosyl Me), 2.05, 1.93, 1.75, and 1.49 (4 s, 9, 3, 3, and 3 H, 6 OAc).

Anal. Calc. for $C_{32}H_{42}NO_{16}SBr$: C, 47.53; H, 5.24; N, 1.73. Found: C, 47.58; H, 5.23; N, 1.66.

The mother liquor from **11** was evaporated to give 1.6 g (31%) of crude **4** as a syrup, $[\alpha]_D^{22}$ +55° (*c* 0.2, $CHCl_3$); ^{1}H-n.m.r., δ 7.62 and 7.20 (2 d, each 2 H, *J* 9 Hz, phenyl), 5.70 (d, 1 H, $J_{1,2}$ 5 Hz, H-1), 3.45–3.02 (m, 3 H, H-2′, H-6a,6b), 2.38 (s, 3 H, tosyl Me), 2.06, 1.97, 1.75, and 1.52 (4 s, 9, 3, 3, and 3 H, 6 OAc).

*[(1S)-(1,2,4/3,5)-3,4-Dihydroxy-5-hydroxymethyl-2-(*p*-toluenesulfonamido)-1-cyclohexyl] β-*D*-glucopyranoside heptaacetate* (**5**) *and its (1*R*)diastereoisomer* (**12**). — A mixture of the crude bromide **4** (200 mg, 2.5 mmol), anhydrous sodium acetate (81 mg, 10 mmol), and *N*,*N*-dimethylformamide (DMF) (10 mL) was stirred for 40 h at 80°. The mixture was concentrated and eluted from a column of silica gel with 1:2 butanone–toluene to give 160 mg (80%) of **5** as a homogeneous syrup, $[\alpha]_D^{20}$ +55° (*c* 1.2, $CHCl_3$); ^{1}H-n.m.r., δ 7.75 and 7.31 (2 d, each 2 H, *J* 8.5 Hz, phenyl), 5.71 (d, 1 H, $J_{1,2}$ 4.5 Hz, H-1), 3.35 (dt, 1 H, $J_{1',2'}$ 2.5, $J_{2',3'}$ 8.5, $J_{2',NH}$ 8.5 Hz, H-2′, changes to a doublet of doublets with 2.5 and 8.5 Hz on deuteration), 2.41 (s, 3 H, tosyl Me), 2.08, 2.02, 1.97, and 1.59 (4 s, 6, 9, 3, and 3 H, 7 OAc).

Anal. Calc. for $C_{34}H_{45}NO_{18}S$: C, 51.84; H, 5.76; N, 1.78; S, 4.07. Found: C, 51.56; H, 5.72; N, 1.59; S, 4.23.

Similarly, compound **11** (200 mg) was converted into **12** (0.20 g, 100%) as a syrup, $[\alpha]_D^{21}$ −39° (*c* 0.8, $CHCl_3$); ^{1}H-n.m.r., δ 7.72 and 7.27 (2 d, each 2 H, *J* 8.5 Hz, phenyl), 5.82 (d, 1 H, $J_{1,2}$ 5 Hz, H-1), 3.32 (dt, 1 H, $J_{1',2'}$ 3, $J_{2',3'}$ 9, $J_{2',NH}$ 9 Hz, H-2′, changes to a doublet of doublets with 3 and 9 Hz on deuteration), 2.40 (s, 3 H, tosyl Me), 2.07, 2.01, 1.96, 1.78, and 1.50 (5 s, 9, 3, 3, 3, and 3 H, 7 OAc).

Anal. Found: C, 51.56; H, 5.63; N, 1.75; S, 3.76.

*[(1S)-(1,2,4/3,5)-2-Acetamido-3,4-dihydroxy-5-hydroxymethyl-1-cyclohexyl] β-*D*-glucopyranoside heptaacetate* (**6**) *and its (1*R*)diastereoisomer* (**13**). — To liquid ammonia (20 mL) containing sodium (70 mg) was added a solution of **5** (86 mg, 0.11 mmol) in tetrahydrofuran (2 mL) and the mixture was stirred over a Dry Ice–acetone bath (*ca.* −70°) for 5 h. Ammonium chloride (0.1 g) was added to the mixture and ammonia was evaporated spontaneously at room temperature. The residue was treated with acetic anhydride (3 mL) and pyridine (3 mL) overnight at room temperature. The product was purified by elution from a column of silica gel with 1:1 butanone–toluene to give 34 mg (46%) of **6** as a syrup, $[\alpha]_D^{20}$ +43° (*c* 1.7, $CHCl_3$); ^{1}H-n.m.r., δ 5.95 (br d, 1 H, $J_{2',NH}$ 9 Hz, NH), 5.64 (d, 1 H, $J_{1,2}$ 6 Hz, H-1), 2.11, 2.07, 2.03, 2.00, 1.98, 1.93, and 1.83 (7 s, 3, 6, 3, 3, 3, 3, and 3 H, NAc and 7 OAc).

Anal. Calc. for $C_{29}H_{41}NO_{17}$: C, 51.55; H, 6.12; N, 2.07. Found: C, 51.28; H, 6.06; N, 2.16.

Similarly, compound **12** (118 mg) was converted into **13** (60 mg, 59%), obtained as a syrup, $[\alpha]_D^{20}$ −34° (*c* 1.0, $CHCl_3$); ^{1}H-n.m.r., δ 5.98 (br d, $J_{2',NH}$ 9 Hz, NH), 5.74 (d, 1 H, $J_{1,2}$ 5.3 Hz, H-1), 2.09, 2.03, 2.01, 1.94, and 1.74 (5 s, 6, 6, 6, 3, and 3 H, NAc and 7 OAc).

Anal. Found: C, 51.54; H, 5.98; N, 2.05.

*[(1S)-(1,2,4/3,5)-2-Acetamido-3,4-dihydroxy-5-hydroxymethyl-1-cyclohexyl] β-*D*-glucopyranoside* (**7**) *and its (1*R*)diastereoisomer* (**14**). — A mixture of **6** (31 mg, 0.045 mmol), M methanolic sodium methoxide (0.3 mL), and methanol (1 mL) was stirred for 2 h at room temperature. The mixture was treated with Dowex 50W X2 (H^+) resin (2 mL) and then evaporated to give 13 mg (78%) of **7** as an amorphous solid, $[\alpha]_D^{22}$ +39° (*c* 0.7, MeOH).

Anal. Calc. for $C_{15}H_{27}NO_{10} \cdot H_2O$: C, 45.11; H, 7.32; N, 3.51. Found: C, 44.96; H, 7.04; N, 3.21.

Similarly, compound **13** (34 mg, 0.05 mmol) was converted into **14** (18 mg, 94%), obtained as an amorphous solid, $[\alpha]_D^{21}$ −31° (*c* 0.4, MeOH).

Anal. Calc. for $C_{15}H_{27}NO_{10} \cdot 0.5\ H_2O$: C, 46.15; H, 7.23; N, 3.59. Found: C, 46.38; H, 7.24; N, 3.41.

Degradation of compound **4** *with hydrogen bromide in acetic acid.* — A mixture of **4** (100 mg, 1.3 mmol) and 20% hydrogen bromide in acetic acid (3 mL) was heated in a sealed tube for 20 h at 80°. The mixture was poured into ice–water, and then extracted with chloroform (20 mL). The organic layer was washed with water, dried, and evaporated. The residue was acetylated conventionally, and the product purified on a short column of alumina to give 48 mg (96%) of (1*S*)-(+)-(1,2,4/3,5)-2-acetamido-5-bromomethyl-1,3,4-cyclohexanetriol (**17**) as a syrup, $[\alpha]_D^{22}$ +42° (*c* 2.4, $CHCl_3$). The ^{1}H-n.m.r. spectrum was superposable on that of the racemic form[10] and the optical rotation was similar to that of an authentic sample[13] (syrup, $[\alpha]_D^{22}$ +65°).

*[(1S)-(1,2,4/3,5)-3,4-Dihydroxy-5-methyl-2-(*p*-toluenesulfonamido)-1-cyclohexyl] β-*D*-glucopyranoside hexaacetate* (**8**) *and its (1*R*)diastereoisomer* (**15**). — A solution of **4** (200 mg, 2.5 mmol) in ethyl acetate (15 mL) was hydrogenated overnight at room temperature in the presence of Raney nickel T-4[14] (*ca.* 0.5 mL) and Amberlite IR-45 (HO^-) resin (2 mL) at an initial hydrogen pressure of 3.4 kg · cm^{-2}. The catalyst and resin were filtered off and the filtrate was evaporated to a syrup that was eluted from a column of silica gel with 1:3 butanone–toluene to give 176 mg (98%) of **8** as a syrup, $[\alpha]_D^{19}$ +54° (*c* 1.0, $CHCl_3$); ^{1}H-n.m.r., δ 7.73 and 7.28 (2 d, each 2 H, *J* 8 Hz, phenyl), 5.74 (d, 1 H, $J_{1,2}$ 5.5 Hz, H-1), 3.34 (dt, 1 H, $J_{1',2'}$ 3.5, $J_{2',3'}$ 10, $J_{2',NH}$ 10 Hz, H-2', changes to a doublet of doublets with 3.5 and 10 Hz on deuteration), 2.41 (s, 3 H, tosyl Me), 2.11, 2.10, 1.99, 1.78, and 1.55 (5 s, 3, 6, 3, 3, and 3 H, 6 OAc), and 0.88 (d, 3 H, $J_{5,6}$ 6.5 Hz, CMe).

Anal. Calc. for $C_{32}H_{43}NO_{16}S$: C, 52.67; H, 5.94; N, 1.92; S, 4.39. Found: C, 52.91; H, 6.11; N, 1.98; S, 4.54.

Similarly, compound **11** (200 mg) was converted into **15** (177 mg, 98%); a syrup, $[\alpha]_D^{22}$ −33° (*c* 0.92, $CHCl_3$); ^{1}H-n.m.r., δ 7.57 and 7.11 (2 d, each 2 H, *J* 9

Hz, phenyl), 5.67 (d, 1 H, $J_{1,2}$ 5 Hz, H-1), 3.24 (dt, 1 H, $J_{1',2'}$ 3, $J_{2',3'}$ 10, $J_{2',NH}$ 10 Hz, H-2', changes to a doublet of doublets with 3 and 10 Hz on deuteration), 2.34 (s, 3 H, tosyl Me), 2.04, 1.90, 1.72, and 1.45 (4 s, 9, 3, 3, and 3 H, 6 OAc), and 0.86 (d, 3 H, $J_{5,6}$ 6.5 Hz, CMe).

Anal. Found: C, 52.42; H, 5.89; N, 2.07; S, 4.14.

[*(1S)-(1,2,4/3,5)-2-Acetamido-3,4-dihydroxy-5-methyl-1-cyclohexyl*] *β*-D-*glucopyranoside hexaacetate* (**9**). — Compound **4** (195 mg, 0.24 mmol) was *N*-detosylated as described for the preparation of **6** to give 62 mg (42%) of **9** as a syrup, $[\alpha]_D^{22}$ +46° (*c* 1.0, $CHCl_3$); ^{1}H-n.m.r., δ 5.95 (d, 1 H, $J_{2',NH}$ 8.3 Hz, NH), 5.69 (d, 1 H, $J_{1,2}$ 6 Hz, H-1), 2.13, 2.08, 2.04, 2.01, 1.94, and 1.74 (6 s, 3, 6, 3, 3, 3, and 3 H, NAc and 6 OAc), and 0.93 (d, 3 H, $J_{5,6}$ 6 Hz, CMe).

Anal. Calc. for $C_{27}H_{39}NO_{15}$: C, 52.51; H, 6.36; N, 2.27. Found: C, 52.31; H, 6.45; N, 2.07.

[*(1S)-(1,2,4/3,5)-5-Azidomethyl-3,4-dihydroxy-2-*(p-*toluenesulfonamido)-1-cyclohexyl*] *β*-D-*glucopyranoside hexaacetate* (**10**) *and its (1*R*)diastereoisomer* (**16**). — A mixture of **4** (200 mg, 2.5 mmol), sodium azide (48 mg, 7.4 mmol), and DMF (10 mL) was stirred for 5 h at 80°. The mixture was evaporated and the residue was eluted from a column of silica gel with 1:3 butanone–toluene to give 177 mg (93%) of **10** as a glass, $[\alpha]_D^{21}$ +55° (*c* 1.0, $CHCl_3$); ^{1}H-n.m.r., δ 7.72 and 7.25 (2 d, each 2 H, *J* 9 Hz, phenyl), 5.74 (d, 1 H, $J_{1,2}$ 5.5 Hz, H-1), 2.38 (s, 3 H, tosyl Me), 2.07, 1.97, 1.78, and 1.53 (4 s, 9, 3, 3, and 3 H, 6 OAc).

Anal. Calc. for $C_{32}H_{42}N_4O_{16}S$: C, 49.87; H, 5.49; N, 7.27; S, 4.16. Found: C, 49.66; H, 5.44; N, 7.28; S, 3.88.

Similarly, compound **11** (200 mg) was converted into **16** (176 mg, 92%) as thin needles, m.p. 172.5–173.5° (from C_2H_5OH), $[\alpha]_D^{21}$ −38° (*c* 1.0, $CHCl_3$); ^{1}H-n.m.r., δ 7.60 and 7.18 (2 d, each 2 H, *J* 8.5 Hz, phenyl), 5.70 (d, 1 H, $J_{1,2}$ 5.5 Hz, H-1), 2.37 (s, 3 H, tosyl Me), 2.07, 2.03, 1.92, 1.76, and 1.47 (5 s, 6, 3, 3, 3, and 3 H, 6 OAc).

Anal. Found: C, 49.61; H, 5.48; N, 7.02; S, 4.28.

ACKNOWLEDGMENTS

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