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SYNTHESIS OF PSEUDO-TREHALOSES: [(1,2,4/3,5)-2,3,4-TRIHYDROXY-5-HYDROXYMETHYL-1-CYCLOHEXYL] D-GLUCOPYRANOSIDES*

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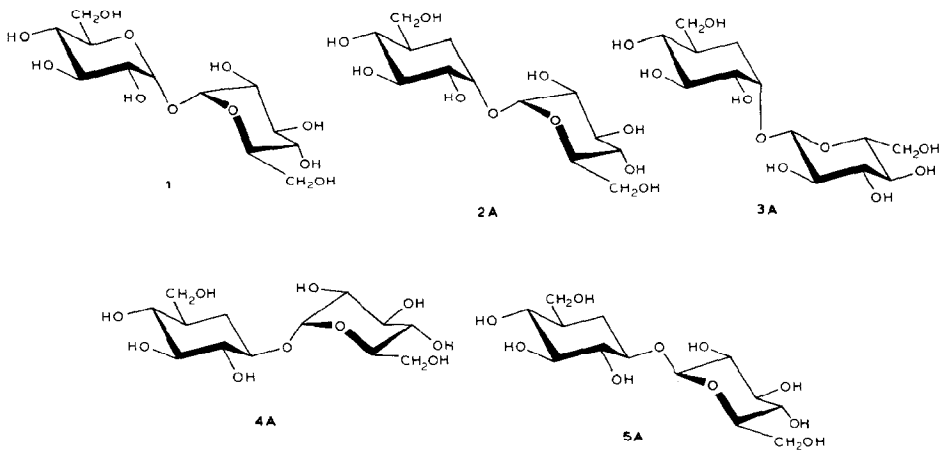
ABSTRACT

All the theoretically possible, four diastereoisomeric pairs, α,α (**2A** and **2B**), α,β (**3A** and **3B**), β,α (**4A** and **4B**), and β,β (**5A** and **5B**), of pseudo-trehalose, composed of D-glucopyranose and pseudo-D- or L-glucopyranose, have been synthesised by coupling of the appropriately protected pseudo-α- (**6**) and -β-DL-glucopyranoses (**9**) with D-glucopyranose derivatives (**10** and **11**) in the presence of trimethylsilyl trifluoromethanesulfonate. Elucidation of the structures and absolute configurations of the pseudo-disaccharides was based on the ^{1}H-n.m.r. spectra of their octa-acetates and the optical rotations. None of the pseudo-trehaloses inhibited trehalase.

INTRODUCTION

α,α-Trehalose (**1**) is widely distributed in the animal and plant kingdoms,



*Pseudo-sugars, Part XXIII. For Part XXII, see ref. 1.
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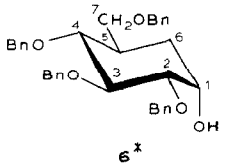
and plays an important role as an energy source as well as a carbohydrate reserve in insects[2]. Trehalase, a disaccharide hydrolase, cleaves **1** into two D-glucopyranose moieties, and systematic investigation[3] on its mechanism of action has been studied extensively.

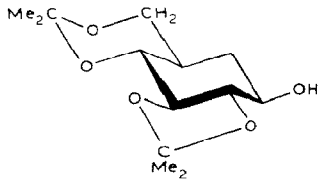
We are interested in the modification of naturally occurring disaccharides by replacement of one of the pyranose ring oxygens with a methylene group, which could affect their affinity for the corresponding hydrolase. In order to provide possible substrate analogues or inhibitors of trehalase, pseudo-α,α-trehalose (**2A**), [(1*S*)-(1,2,4/3,5)-2,3,4-trihydroxy-5-hydroxymethyl-1-cyclohexyl] α-D-glucopyranoside, a carbocyclic analogue of **1**, has been synthesised, together with all the possible diastereoisomers ($\alpha\alpha$, $\alpha\beta$, $\beta\alpha$, and $\beta\beta$) of pseudo-trehalose, which contain D-glucopyranose and pseudo-D- or L-glucopyranose.

RESULTS AND DISCUSSION

Pseudo-α,α- and -α,β-trehalose. — Condensation of equimolar amounts of 2,3,4,7-tetra-*O*-benzyl-pseudo-α-DL-glucopyranose[4] (**6**) and 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranose[5] (**10**) in dichloromethane in the presence of trimethylsilyl trifluoromethanesulfonate[6] and molecular sieve type 4A for 5 h at room temperature afforded, after column chromatography, the pseudo-disaccharide derivatives **12A** (34%), $[\alpha]_D$ +77° (chloroform), and **12B** (39%), $[\alpha]_D$ ~0° (chloroform). Hydrogenolysis of **12A** and **12B** in ethanol–acetic acid over Pd/C followed by treatment with acetic anhydride in pyridine gave the octa-acetates **13A** (87%), $[\alpha]_D$ +128° (chloroform), and **13B** (93%), $[\alpha]_D$ +59° (chloroform), respectively. The ^{1}H-n.m.r. spectra of **13A** and **13B** contained signals at δ 5.13 (d, *J* 3.9 Hz) and 5.31 (d, *J* 3.9 Hz), respectively, due to H-1′, supporting the presence of



6*



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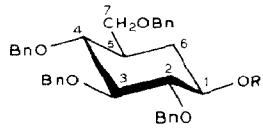
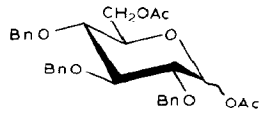


8 R = allyl
9 R = H



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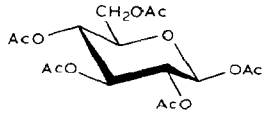

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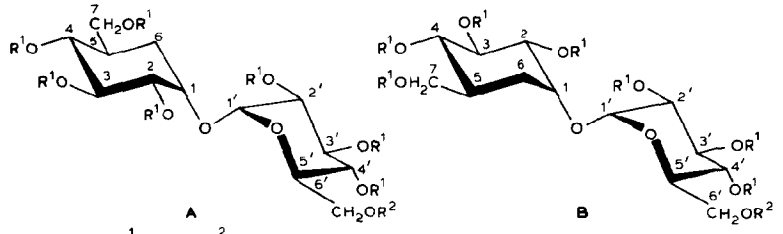
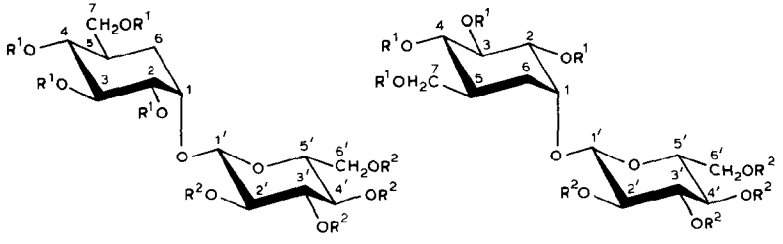
* The structures **6**–**9** depict the enantiomers corresponding to the D-series of normal hexopyranoses.



12 R^1 = Bn, R^2 = Ac
13 R^1 = R^2 = Ac



14 R^1 = Bn, R^2 = Ac
15 R^1 = R^2 = Ac

α-glucosidic linkages. Using the $[\alpha]_D$ value [+57° (chloroform)] of pseudo-α-D-glucopyranose penta-acetate[7], the absolute configurations of **13A** and **13B** are indicated by the difference of their optical rotations predicted on the basis of the contribution of the pseudo-sugar moieties.

Likewise, the β-glucosides of **6** were prepared by reaction of **10** with 1,2,3,4,6-penta-*O*-acetyl-D-glucopyranose[8] (**11**) for 3.5 h. Column chromatography then gave **14A** (30%) and **14B** (29%), which were *O*-debenzylated and then acetylated to give the octa-acetates **15A** (51%), $[\alpha]_D$ +15° (chloroform), and **15B** (87%), $[\alpha]_D$ −79° (chloroform), respectively. The low yields of **14A** and **14B** were due mainly to the difficulty in the separation. In the ^{1}H-n.m.r. spectra of **15A** and **15B**, signals for H-1′ appeared at δ 4.54 (d, J 7.8 Hz) and 4.48 (d, J 8.3 Hz), respectively, indicative of the β-glucosidic linkages. The absolute configurations were deduced from the optical rotations.

Pseudo-β,α- and -β,β-trehaloses. — In order to synthesise the isomers containing a pseudo-β-glucopyranose residue, 2,3,4,6-tetra-*O*-benzyl-pseudo-β-glucopyranose (**9**), was used as the aglycon, and prepared from the di-*O*-isopropylidene derivative[9] **7** by allylation and *O*-deisopropylidenation (→**8**, 98%) and then *O*-deallylation with selenium oxide (→**9**, 78%).

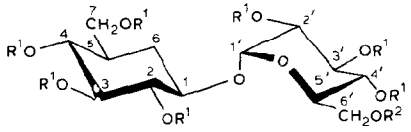
Condensation of **9** and **10**, as in the preparation of **12A** and **12B**, gave, after column chromatography, **16A** (27%) and **16B** (30%), which were converted into the respective octa-acetates **17A** (93%), $[\alpha]_D$ +94° (chloroform), and **17B** (96%), $[\alpha]_D$ +72° (chloroform).

TABLE I

FIRST-ORDER N.M.R. PARAMETERS OF PSEUDO-TREHALOSE OCTA-ACETATES[a]

Assignment	*Values for individual compounds*							
	13A	**13B**	**15A**	**15B**	**17A**	**17B**	**19A**	**19B**
Chemical shifts (δ)								
H-1	4.17bs	4.21bs	4.20bs	4.31bs	3.74ddd	3.87ddd	3.79ddd	3.78ddd
H-2	4.94dd	4.91dd	4.81dd	4.66dd	5.15t	5.16t		
H-3	5.46t	5.41t	5.26t	5.35bt				
H-4	5.01dd	5.03dd	4.99dd	4.95dd				
H-5	2.29m	2.45m	2.38m	2.15m				
H-6*a*	1.55ddd	1.72ddd		1.54ddd	1.47dt	1.74dt	1.47dt	1.65dt
H-6*e*	1.93dt	1.88dt		1.93dt				
H-7a	3.87dd	3.97dd	3.88dd	3.87dd	3.95dd	3.95dd	3.97dd	3.94dd
H-7b	4.12dd	4.18dd	4.15dd	4.10dd	4.08dd	4.11dd	4.07dd	4.09dd
H-1′	5.13d	5.31d	4.54d	4.48d	5.20d	5.28d	4.58d	4.65d
H-2′	4.86dd	4.83dd	5.02dd	5.01dd	4.83dd	4.78dd	4.88dd	4.94dd
H-3′	5.43t	5.47t	5.22t	5.20t	5.34t	5.41t	5.17t	5.14t
H-4′	5.07t	5.02t	5.05t	5.07t	5.05t	5.03t	5.08t	5.07t
H-5′	4.22ddd	3.98ddd	3.64ddd	3.65ddd	4.00ddd	4.05ddd	3.69ddd	3.67ddd
H-6′a	4.01dd	4.07dd	4.13dd	4.03dd	4.15dd	4.10dd	4.09dd	4.17dd
H-6′b	4.30dd	4.26dd	4.22dd	4.24dd	4.20dd	4.25dd	4.30dd	4.25dd
OAc[b]	2.08	2.17	2.15	2.10	2.11(2)	2.10	2.09	2.10
	2.07	2.08	2.09	2.05	2.08(2)	2.09	2.07	2.07
	2.064(2)	2.07	2.08	2.04(2)	2.07(2)	2.043	2.04	2.06
	2.062(2)	2.06	2.05	2.03(3)	2.068(2)	2.04	2.02(3)	2.03
	2.03	2.05(2)	2.03(2)	2.00		2.02	2.00	2.02(2)
	2.02	2.02	2.028			2.01(2)	1.99	2.00
		1.99	1.98			1.98		1.98
Coupling constants (Hz)								
$J_{1,2}$	3.2	2.7	2.9	3.2	9.8	9.3	8.8	9.3
$J_{2,3}$	10	10	10	10.3	9.8	9.3		
$J_{3,4}$	10	10	10	9.3				
$J_{4,5}$	11.5	11	11.5	11				
$J_{5,6a}$	13.2	13		12.9	13.5	13.5	13.2	13.5
$J_{5,6e}$	3.9	3.9		3.4				
$J_{5,7a}$	5.1	3	2.9	3.4	3.2	3.2	3.4	3.4
$J_{5,7b}$	3.4	4	4.4	5.1	5.1	4.9	5.1	4.4
$J_{6a,1}$	1.7	2		1.2	11.5	11.7	11.7	11.7
$J_{6e,1}$	3.9	3.9		3.4	4.6	4.9	4.9	4.9
$J_{6,6}$	15.1	14.7		14.7	13.5	13.5	13.2	13.5
$J_{7,7}$	11.2	11	11.2	11.7	11.5	11.2	11.2	11.2
$J_{1',2'}$	3.9	3.9	7.8	8.3	3.9	3.9	7.3	7.8
$J_{2',3'}$	10.3	10	9.8	9.3	10	10.3	9.3	9.3
$J_{3',4'}$	10.3	10	9.8	9.3	10	10.3	9.3	9.3
$J_{4',5'}$	10.3	10	9.8	9.3	10	10.3	10	9.8
$J_{5',6'a}$	2	2.4	2.4	2.4	2.4	2.4	2.4	2.4
$J_{5',6'b}$	4.4	4.9	4.9	5.4	3.9	4.9	4.9	4.6
$J_{6',6'}$	12.2	12.2	12.2	12.5	12.7	12.1	12.5	12.2

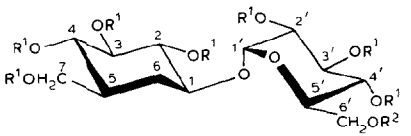
[a]Measured on solutions in $CDCl_3$ at 400 MHz. [b]Values in parenthesis show the number of acetoxyl groups.



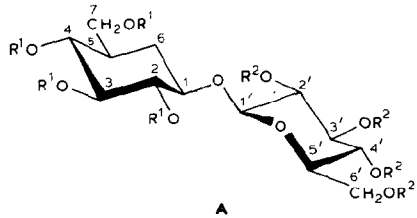
A

16 R^1 = Bn, R^2 = Ac

17 R^1 = R^2 = Ac



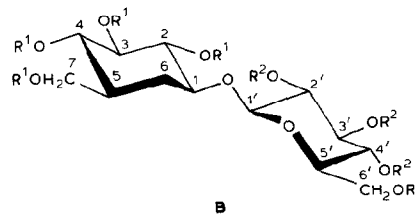
B



A

18 R^1 = Bn, R^2 = Ac

19 R^1 = R^2 = Ac



B

Likewise, the condensation of **9** and **11** gave the crystalline products **18A** (25%) and **18B** (33%), which were then converted into the respective octa-acetates **19A** (89%), $[\alpha]_D$ −16° (chloroform), and **19B** (98%), $[\alpha]_D$ −34° (chloroform).

The structures of **17A, 17B, 19A,** and **19B** were assigned on the basis of the ^{1}H-n.m.r. data in Table I. The difference of the $[\alpha]_D$ values for each pair of the diastereoisomers was smaller than those for the pseudo-α-glucopyranose analogues. Since the $[\alpha]_D$ value of pseudo-β-D-glucopyranose penta-acetate[10] is only $[\alpha]_D$ +14° (chloroform), the absolute configurations are assigned tentatively.

Biological assays. — Treatment of the octa-acetates **13A,B, 15A,B, 17A,B,** and **19A,B** with methanolic sodium methoxide provided the respective pseudo-disaccharides **2A,B, 3A,B, 4A,B,** and **5A,B,** in almost quantitative yield, none of which inhibited the trehalase prepared from the midgut homogenate of the silkworm.

EXPERIMENTAL

General methods. — Melting points were determined with a MEL-TEMP capillary melting-point apparatus and are uncorrected. Unless otherwise noted, ^{1}H-n.m.r. spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si) with Varian EM-390 (90 MHz) and Jeol JNM-GX FT (400 MHz) spectrometers. T.l.c. was performed on Wakogel B-10 (Wako Co., Osaka, Japan) with detection by charring with 10% sulfuric acid. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated at <50° under diminished pressure.

[(1S)-(1,2,4/3,5)-2,3,4-Tribenzyloxy-5-benzyloxymethyl-1-cyclohexyl] 6-O-acetyl-2,3,4-tri-O-benzyl-α-D-glucopyranoside (**12A**) *and its (1R)-diastereoisomer*

(**12B**). — To a mixture of DL-(1,2,4/3,5)-2,3,4-tri-*O*-benzyl-5-benzyloxymethyl-1,2,3,4-cyclohexanetetrol[4] (**6**; 115 mg, 0.21 mmol), 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranose (**10**; 119 mg, 0.22 mmol), and powdered molecular sieve type 4A (300 mg) in dichloromethane (2 mL) was added trimethylsilyl trifluoromethanesulfonate (49 μL, 0.25 mmol) at room temperature under argon. The mixture was stirred vigorously for 5 h at room temperature, then filtered through Celite, washed with saturated aqueous sodium hydrogencarbonate and water, and dried. Evaporation of the solvent gave a residue, column chromatography (chloroform–ethyl acetate–hexane, 2:1:10) of which gave, first, syrupy **12B** (84 mg, 39%), R_F 0.77 (chloroform–ethyl acetate, 20:1), $[\alpha]_D^{24}$ ~0° (*c* 0.8, chloroform). ^{1}H-N.m.r. data (90 MHz): δ 7.30 (s, 35 H, 7 Ph), 5.50 (d, 1 H, $J_{1,2}$ 3 Hz, H-1), and 1.98 (s, 3 H, OAc).

Anal. Calc. for $C_{64}H_{68}O_{11}$: C, 75.87; H, 6.67. Found: C, 75.85; H, 6.85.

Further elution gave syrupy **12A** (74 mg, 34%), R_F 0.66, $[\alpha]_D^{24}$ +77° (*c* 0.5, chloroform). ^{1}H-N.m.r. data (90 MHz): δ 7.27 (s, 35 H, 7 Ph) and 1.90 (s, 3 H, OAc).

Anal. Found: C, 75.96; H, 6.91.

[(1S)-(1,2,4/3,5)-2,3,4-Triacetoxy-5-acetoxymethyl-1-cyclohexyl] 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside (**13A**). — A mixture of **12A** (74 mg, 0.07 mmol) and 10% Pd/C (30 mg) in ethanol (7 mL) and acetic acid (1 mL) was hydrogenated in a Parr apparatus with an initial H_2 pressure of 50 p.s.i. overnight at room temperature. The catalyst was removed, the filtrate was concentrated, and the residue was treated with pyridine (1 mL) and acetic anhydride (1 mL) for 15 h at room temperature. The mixture was concentrated, the residue was extracted with dichloromethane, and the extract was dried and concentrated. Column chromatography (ethyl acetate–hexane, 1:8) of the syrupy residue gave syrupy **13A** (43 mg, 87%), R_F 0.33 (chloroform–ethyl acetate, 2:1), $[\alpha]_D^{27}$ +128° (*c* 1.2, chloroform). The ^{1}H-n.m.r. data (400 MHz) are given in Table I.

Anal. Calc. for $C_{29}H_{40}O_{18}$: C, 51.48; H, 5.96. Found: C, 51.37; H, 5.69.

[(1R)-(1,2,4/3,5)-2,3,4-Triacetoxy-5-acetoxymethyl-1-cyclohexyl] 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside (**13B**). — Treatment of **12B** (84 mg, 0.08 mmol), as described for **12A**, gave syrupy **13B** (52 mg, 93%), R_F 0.39 (chloroform–ethyl acetate, 2:1), $[\alpha]_D^{27}$ +59° (*c* 1.8, chloroform). The ^{1}H-n.m.r. data (400 MHz) are given in Table I.

Anal. Calc. for $C_{29}H_{40}O_{18}$: C, 51.48; H, 5.96. Found: C, 52.01; H, 5.85.

[(1S)-(1,2,4/3,5)-2,3,4-Tribenzyloxy-5-benzyloxymethyl-1-cyclohexyl] 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**14A**) *and its (1R)-diastereoisomer* (**14B**). — To a mixture of **6** (426 mg, 0.79 mmol), 1,2,3,4,6-penta-*O*-acetyl-D-glucopyranose (**11**; 319 mg, 0.81 mmol), and powdered molecular sieve type 4A (300 mg) in dichloromethane (6 mL) was added trimethylsilyl trifluoromethanesulfonate (0.20 mL, 1.20 mmol) at room temperature under argon. After stirring for 3.5 h at room temperature, the mixture was processed as described for the preparation of **12A** and **12B**. Column chromatography (ethyl acetate–hexane, 1:3) of the product gave, first,

syrupy **14A** (208 mg, 30%), R_F 0.46 (ethyl acetate–hexane, 1:1), $[\alpha]_D^{21}$ +16° (*c* 1.1, chloroform). ^{1}H-N.m.r. data (90 MHz): δ 7.30–7.27 (m, 20 H, 4 Ph), 2.00, 1.98, and 1.87 (3 s, 12 H, 4 OAc).

Anal. Calc. for $C_{49}H_{56}O_{14}$: C, 67.35; H, 6.46. Found: C, 67.61; H, 6.34.

Eluted second was **14B** (138 mg, 20%), m.p. 158–160.5° (from chloroform–hexane), R_F 0.39, $[\alpha]_D^{21}$ −52° (*c* 0.5, chloroform). ^{1}H-N.m.r. data (90 MHz): δ 7.30 (s, 20 H, 4 Ph), 2.00 and 1.97 (2 s, 12 H, 4 OAc).

Anal. Found: C, 67.77; H, 6.52.

*[(1S)-(1,2,4/3,5)-2,3,4-Triacetoxy-5-acetoxymethyl-1-cyclohexyl] 2,3,4,6-tetra-O-acetyl-β-*D*-glucopyranoside* (**15A**). — Treatment of **14A** (199 mg, 0.20 mmol), as described for **12A**, gave syrupy **15A** (79 mg, 51%), R_F 0.32 (chloroform–ethyl acetate, 2:1), $[\alpha]_D^{27}$ +15° (*c* 1.25, chloroform). The ^{1}H-n.m.r. data (400 MHz) are given in Table I.

Anal. Calc. for $C_{29}H_{40}O_{18}$: C, 51.48; H, 5.96. Found: C, 51.67; H, 5.75.

*[(1R)-(1,2,4/3,5)-2,3,4-Triacetoxy-5-acetoxymethyl-1-cyclohexyl] 2,3,4,6-tetra-O-acetyl-β-*D*-glucopyranoside* (**15B**). — Treatment of **14B** (144 mg, 0.14 mmol), as described for **12A**, gave syrupy **15B** (97 mg, 87%), R_F 0.26 (chloroform–ethyl acetate, 2:1), $[\alpha]_D^{27}$ −79° (*c* 1.1, chloroform). The ^{1}H-n.m.r. data (400 MHz) are given in Table I.

Anal. Calc. for $C_{29}H_{40}O_{18}$: C, 51.48; H, 5.96. Found: C, 51.08; H, 5.86.

DL-*(1,3,5/2,4)-2,3,4-Tri-O-benzyl-5-benzyloxymethyl-1,2,3,4-cyclohexanetetrol* (**9**). — (1*SR*,2*RS*,7*RS*,9*RS*,10*RS*)-4,4,12,12-Tetramethyl-3,5,11,13-tetraoxatricyclo[8.3.0.0^{2,7}]tridecan-9-ol[9] (**7**; 1.0 g, 3.9 mmol) was treated with allyl bromide (0.64 mL, 7.74 mmol) and sodium hydride (60% in oil, 308 mg, 7.70 mmol) in *N,N*-dimethylformamide (19 mL) for 3 h at room temperature. The reaction was quenched by adding a few drops of methanol, the mixture was concentrated, the residue was extracted with dichloromethane, and the extract was dried and concentrated. A solution of the residue in ethanol (10 mL) and M hydrochloric acid (10 mL) was stirred for 1 h at room temperature and then concentrated, and the residue was dried *in vacuo*. The resulting solid (1.15 g) was treated with benzyl bromide (2.79 mL, 23.5 mmol) and sodium hydride (60% in oil, 1.29 g, 32.3 mmol) in *N,N*-dimethylformamide (18 mL) overnight at room temperature. A few drops of methanol were added to the mixture, which was then concentrated. The residue was extracted with dichloromethane, and the extract was dried and concentrated. Column chromatography (ethyl acetate–hexane, 1:12) of the residue afforded the allyl ether **8** (2.19 g, 98%) as a syrup. ^{1}H-N.m.r. data (90 MHz): δ 7.33–7.30 (m, 20 H, 4 Ph), 6.17–5.73 (m, 1 H, $CH_2CH{=}CH_2$), 5.47–5.07 (m, 2 H, $CH_2{-}CH{=}CH_2$), and 4.23–4.10 (d, 2 H, *J* 6 Hz, $CH_2CH{=}CH_2$).

Acetic acid (0.33 mL, 5.76 mmol) was added to a solution of crude **8** (2.15 g, 3.80 mmol) in 1,4-dioxane (40 mL) in the presence of selenium(IV) oxide (633 mg, 5.70 mmol). The mixture was stirred and heated under reflux for 30 min, then filtered, and concentrated. Column chromatography (ethyl acetate–hexane, 1:8) of the residue gave **9** (1.60 g, 78%), as an amorphous solid. ^{1}H-N.m.r. data (90 MHz): δ 7.32 (s, 20 H, 4 Ph) and 2.23 (s, 1 H, OH).

Anal. Calc. for $C_{35}H_{38}O_5$: C, 78.04; H, 7.11. Found: C, 78.12; H, 7.14.

[*(1R)-(1,3,5/2,4)-2,3,4-Tribenzyloxy-5-benzyloxymethyl-1-cyclohexyl*] *6-O-acetyl-2,3,4-tri-O-benzyl-α-D-glucopyranoside* (**16A**) *and its (1S)-diastereoisomer* (**16B**). — To a mixture of **9** (558 mg, 1.04 mmol), **10** (560 mg, 1.05 mmol), and powdered molecular sieve type 4A (500 mg) in dichloromethane (10 mL) was added trimethylsilyl trifluoromethanesulfonate (0.24 mL, 1.24 mmol) at room temperature under argon. After stirring for 6 h at room temperature, the mixture was treated as described for the preparation of **12A** and **12B**. Column chromatography (ethyl acetate–hexane, 1:6) of the product gave, first, syrupy **16B** (311 mg, 30%), R_F 0.59 (ethyl acetate–hexane, 1:2), $[\alpha]_D^{24}$ +34.5° (*c* 0.6, chloroform). ^{1}H-N.m.r. data (90 MHz): δ 7.26–7.15 (m, 35 H, 7 Ph) and 1.90 (s, 3 H, OAc).

Anal. Calc. for $C_{64}H_{68}O_{11}$: C, 75.87; H, 6.76. Found: C, 76.04; H, 6.79.

Further elution gave a mixture of **16A** and **16B** (120 mg) and pure syrupy **16A** (287 mg, 27%), R_F 0.52, $[\alpha]_D^{24}$ +13° (*c* 0.7, chloroform). ^{1}H-N.m.r. data (90 MHz): δ 7.30–7.13 (m, 35 H, 7 Ph) and 1.97 (s, 3 H, OAc).

Anal. Found: C, 75.72; H, 6.76.

[*(1R)-(1,3,5/2,4)-2,3,4-Triacetoxy-5-acetoxymethyl-1-cyclohexyl*] *2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside* (**17A**). — Compound **16A** (296 mg, 0.29 mmol) was treated as described for the preparation of **13A**, to afford syrupy **17A** (183 mg, 93%), R_F 0.33 (ethyl acetate–hexane, 1:2), $[\alpha]_D^{29}$ +94° (*c* 1.4, chloroform). The ^{1}H-n.m.r. data (400 MHz) are given in Table I.

Anal. Calc. for $C_{29}H_{40}O_{18}$: C, 51.48; H, 5.96. Found: C, 51.08; H, 5.86.

[*(1S)-(1,3,5/2,4)-2,3,4-Triacetoxy-5-acetoxymethyl-1-cyclohexyl*] *2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside* (**17B**). — Compound **16B** (270 mg, 0.27 mmol) was treated as described for the preparation of **13B**, to give syrupy **17B** (172 mg, 96%), R_F 0.39 (chloroform–ethyl acetate, 2:1), $[\alpha]_D^{29}$ +72° (*c* 1.3, chloroform). The ^{1}H-n.m.r. data (400 MHz) are given in Table I.

Anal. Calc. for $C_{29}H_{40}O_{18}$: C, 51.48; H, 5.96. Found: C, 50.92; H, 5.80.

[*(1R)-(1,3,5/2,4)-2,3,4-Tribenzyloxy-5-benzyloxymethyl-1-cyclohexyl*] *2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside* (**18A**) *and its (1S)-diastereoisomer* (**18B**). — To a mixture of **9** (370 mg, 0.69 mmol), **11** (269 mg, 0.69 mmol), and powdered molecular sieve type 4A (300 mg) in dichloromethane (6 mL) was added trimethylsilyl trifluoromethanesulfonate (0.20 mL, 1.03 mmol) at room temperature under argon. After stirring for 2.5 h at room temperature, the mixture was worked-up as described for the preparation of **12A** and **12B**. Column chromatography (ethyl acetate–hexane, 1:3) of the product gave, first, **18B** (196 mg, 33%), R_F 0.73 (ethyl acetate–hexane, 1:3), m.p. 108–109° (from chloroform–light petroleum), $[\alpha]_D^{22}$ −60° (*c* 0.85, chloroform). ^{1}H-N.m.r. data (90 MHz): δ 7.33, 7.30, 7.27, 7.23 (4 s, 20 H, 4 Ph), 2.03, 2.00, 1.97, and 1.80 (4 s, 12 H, 4 OAc).

Anal. Calc. for $C_{49}H_{56}O_{14}$: C, 67.35; H, 6.46. Found: C, 67.77; H, 6.47.

Eluted second was **18A** (148 mg, 25%), R_F 0.65 (ethyl acetate–hexane, 1:1), m.p. 161–162° (from chloroform–light petroleum), $[\alpha]_D^{22}$ −0.7° (*c* 1, chloroform).

^{1}H-N.m.r. data (90 MHz): δ 7.28–7.23 (m, 20 H, 4 Ph) and 2.00–1.97 (m, 12 H, 4 OAc).

Anal. Found: C, 67.70; H, 6.45.

*[(1R)-(1,3,5/2,4)-2,3,4-Triacetoxy-5-acetoxymethyl-1-cyclohexyl] 2,3,4,6-tetra-O-acetyl-β-*D*-glucopyranoside* (**19A**). — Treatment of **18A** (131 mg, 0.15 mmol), as described for the preparation of **13B**, gave syrupy **19A** (91 mg, 89%), R_F 0.32 (chloroform–ethyl acetate, 2:1), $[\alpha]_D^{29}$ −16° (*c* 1.2, chloroform). The ^{1}H-n.m.r. data (400 MHz) are given in Table I.

Anal. Calc. for $C_{29}H_{40}O_{18}$: C, 51.48; H, 5.96. Found: C, 51.07; H, 5.85.

*[(1S)-(1,3,5/2,4)-2,3,4-Triacetoxy-5-acetoxymethyl-1-cyclohexyl] 2,3,4,6-tetra-O-acetyl-β-*D*-glucopyranoside* (**19B**). — Treatment of **19A** (184 mg, 0.21 mmol), as described for the preparation of **13A**, gave syrupy **19B** (140 mg, 98%), R_F 0.35 (chloroform–ethyl acetate, 2:1), $[\alpha]_D^{27}$ −34° (*c* 1.1, chloroform). The ^{1}H-n.m.r. data (400 MHz) are given in Table I.

Anal. Calc. for $C_{29}H_{40}O_{18}$: C, 51.48; H, 5.96. Found: C, 51.27; H, 5.78.

Preparation of pseudo-trehaloses. — The octa-acetate (**13A**, 74 mg) was treated with methanolic M sodium methoxide (0.4 mL) in methanol (4 mL) overnight at room temperature. The mixture was neutralised with an acidic resin and concentrated to give syrupy **2A** (37 mg, 100%), $[\alpha]_D^{24}$ +55° (*c* 0.6, water).

Similarly, **13B, 15A, 15B, 17A, 17B, 19A,** and **19B** were converted into the respective pseudo-disaccharides **2B**, $[\alpha]_D^{24}$ +4 ±2° (*c* 0.6, water); **3A**, $[\alpha]_D^{22}$ +27° (*c* 0.3, methanol); **3B**, $[\alpha]_D^{22}$ −86° (*c* 0.7, water); **4A**, $[\alpha]_D^{24}$ +89° (*c* 0.7, water); **4B**, $[\alpha]_D^{22}$ +66° (*c* 0.6, water); **5A**, $[\alpha]_D^{22}$ −44° (*c* 0.6, methanol); **5B**, $[\alpha]_D^{22}$ −16° (*c* 0.3, methanol). These pseudo-disaccharides were subjected directly to the biological assay.

Biological assay. — None of the eight stereoisomers of pseudo-trehalose inhibited the hydrolysis of trehalose by the trehalase prepared from the midgut homogenate of the last instar larvae of the silkworm.

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REFERENCES

1 S. Ogawa, M. Uemura, and T. Fujita, *Carbohydr. Res.*, 177 (1988) 213–221.
2 G. C. Birch, *Adv. Carbohydr. Chem.*, 18 (1963) 201–225.
3 A. D. Elbein, *Adv. Carbohydr. Chem. Biochem.*, 30 (1974) 227–256; K. Bock, J. Defaye, H. Driques, and E. Bar-Guilloux, *Eur. J. Biochem.*, 131 (1983) 595–600, and references cited therein.

4 S. OGAWA AND Y. SHIBATA, *Carbohydr. Res.*, 176 (1988) 309–315.
5 G. ZEMPLÉN, Z. CSUROS, AND S. J. ANGYAL, *Chem. Ber.*, 70 (1973) 228–231; S. A. HOLICK, S.-H. L. CHIU, AND L. ANDERSON, *Carbohydr. Res.*, 50 (1976) 215–225.
6 T. OGAWA, K. BEPPU, AND S. NAKABAYASHI, *Carbohydr. Res.*, 93 (1981) c6–c9.
7 S. OGAWA, K. NAKAMURA, AND T. TAKAGAKI, *Bull. Chem. Soc. Jpn.*, 59 (1986) 2956–2958.
8 M. L. WOLFROM AND A. THOMPSON, *Methods Carbohydr. Chem.*, 2 (1963) 212.
9 S. OGAWA, Y. TSUKIBOSHI, Y. IWASAWA, AND T. SUAMI, *Carbohydr. Res.*, 136 (1985) 77–89.
10 S. OGAWA, Y. IWASAWA, T. NOSE, T. SUAMI, S. OHBA, M. ITO, AND Y. SAITO, *J. Chem. Soc., Perkin Trans. 1*, (1985) 903–906.