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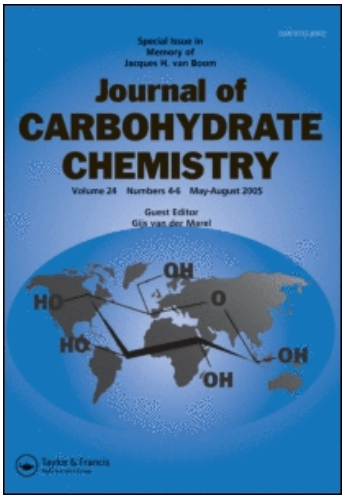

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SYNTHESIS OF UNSYMMETRICAL TREHALOSE ANALOGUES BY SILVER TRIFLUOROMETHANESULPHONATE PROMOTED GLYCOSYLATIONS

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ABSTRACT

The coupling of benzoylated glucosyl bromides with 2,3,4,6-tetra-*O*-benzylated *gluco, manno or galacto*-pyranoses promoted by silver triflate is described, and the compositions of the crude reaction mixtures, determined by ^{13}C NMR spectroscopy, are presented. Unsymmetrical trehalose derivatives can be synthesized by such couplings. However, the inherent formation of dimerization products of the reactants reduces the versatility of the reactions. The synthesis of α-D-glucopyranosyl α-L-glucopyranoside and α-D-glucopyranosyl ß-L-glucopyranoside is also described.

INTRODUCTION

α,α-Trehalose (α-D-glucopyranosyl α-D-glucopyranoside) is a naturally occurring, non-reducing disaccharide with significant biological functions. α,α-Trehalose stabilizes proteins, lipid membranes and other bio-molecules in so-called anhydrobiotic organisms, which can survive almost complete desiccation for long periods of time. The molecular basis for this phenomenon is, however, not yet known in detail.[1-4] The unique properties of α,α-trehalose may be investigated by comparison

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with synthetic analogues. During the course of this investigation, we have recently described the synthesis of α,α-trehalose 6-monophosphate and α,α-trehalose 6,6'-diphosphate.[5] The synthesis of trehaloses (glycopyranosyl glycopyranosides) comprised of two identical monosaccharide units (with or without identical anomeric configurations) has been described in the literature and such dimerizations can occur in high yields.[6-11] A large number of chemical transformations on α,α-trehalose itself have afforded both symmetrical[12-15] and unsymmetrical[12,16] analogues, but the methods used often employ several synthetic steps. Furthermore, Koenigs-Knorr type glycosylations leading to trehaloses have also been reported, but most of these syntheses generally gave lower yields.[11,13,14,17] The present work describes the syntheses of *O*-protected *unsymmetrical* trehalose analogues. We have thus examined the coupling of benzoylated glucosyl bromides with tetrabenzylated monosaccharides promoted by silver trifluoromethanesulphonate as a general method to prepare unsymmetrical trehalose analogues.

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RESULTS AND DISCUSSION

2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (**1**) was reacted with the three alcohols **2-4** in CH_2Cl_2 at -10 °C with silver trifluoromethanesulphonate as promotor. Glycosylation of 2,3,4,6-tetra-*O*-benzyl-D-glucose (**2**) gave a mixture of the α-D,ß-D-disaccharide **5** and ß-D,ß-D-disaccharide **6** in 55 % yield. Extensive use of silica gel chromatography afforded α-D,ß-D-disaccharide **5** in 25 % yield and the pure ß-D,ß-D-isomer **6** in 8 % yield. Compound **5** had the signals for the two anomeric carbons at δ 99.0 and 101.0, respectively, whereas the anomeric protons resonated at δ 5.09 (d, *J* 3.3 Hz) and 5.13 (d, *J* 8 Hz), respectively (Tables 1-2). For compound **6** the anomeric proton signals at δ 4.89 (d, *J* 7.6 Hz) and 5.33 (d, *J* 7.6 Hz) indicated a ß-D,ß-D-configurated compound (Table 2). The signals for the anomeric carbons were at δ 98.4 and 96.9, respectively.

Glycosylation of 2,3,4,6-tetra-*O*-benzyl-D-galactose (**3**) surprisingly afforded the α-D,α-D-configurated disaccharide **7** as 70 % of the crude product mixture, determined from an ^1H NMR spectrum. This product was purified by vacuum liquid chromatography (VLC) to give the pure compound **7** in 40 % yield. Similarly, glycosylation of

Table 1. ^{13}C NMR chemical shift data (δ, ppm) for protected trehalose derivatives.[a,b]

	5	6	7	8	10	11
C-1	98.97	98.38	94.79	94.14	94.53	98.13
C-1'	101.00	96.90	92.62	91.45	96.84	96.38
C-2	79.18	81.34	75.82	75.07	78.37	79.24
C-2'	71.86	71.78	71.75	70.67	73.41	71.96
C-3	81.58	84.28	78.88	79.29	81.20	81.95
C-3'	72.86	72.93	70.54	70.19	73.02	70.38
C-4	77.15	75.17	74.56	74.33	76.84	77.26
C-4'	69.49	69.68	68.76	69.58	69.55	69.03
C-5	71.54	73.45	69.86	72.59	70.90	72.49
C-5'	72.40	72.36	67.94	68.37	72.54	68.56
C-6	68.04	68.99	67.80	68.14	67.78	68.52
C-6'	63.17	63.05	62.22	62.91	63.16	62.66

a. Spectra were recorded at 125.76 MHz in $CDCl_3$ at 300 K. b. The primes (') refer to the benzoylated glucopyranosyl moieties.

2,3,4,6-tetra-*O*-benzyl-D-mannose (**4**) afforded the α-D,α-D-configurated disaccharide **8** in a crude yield of ca. 70 %. Purification by VLC afforded the pure compound **8** in 42 % yield. The α-D,α-D-configuration of **7** was suggested by the anomeric proton signals at δ 5.36 (d, *J* 3.4 Hz) and 5.66 (d, *J* 3.6 Hz), respectively, and by the anomeric carbon resonances at δ 94.8 and 92.6, respectively (Tables 1-2). Compound **8** had the anomeric proton signals at δ 5.19 (d, *J* 1.6 Hz) and 5.62 (d, *J* 3.8 Hz), respectively, and anomeric carbon signals at δ 94.1 and 91.5, all data indicating an α-D,α-D-configuration.

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Table 2. ^{1}H NMR chemical shifts (δ, ppm) and coupling constants (J, Hz) for protected trehalose derivatives.[a,b]

	5	6	7	8	10	11
H-1	5.09	4.89	5.36	5.19	5.33	5.85
H-1'	5.13	5.33	5.66	5.62	5.21	5.07
H-2	3.46	3.45	4.12	3.68	3.56	5.43
H-2'	5.66	5.67	5.42	5.51	5.77	3.57
H-3	3.96	3.68-3.43	4.24	4.03	3.84	6.33
H-3'	5.96	5.98	6.27	6.12	5.97	4.10
H-4	3.67	3.68-3.43	3.97-4.0	3.98	3.48-3.50	5.88
H-4'	5.71	5.78	5.76	5.69	5.76	3.72
H-5	4.08	3.68-3.43	3.97-4.0	3.63(m)	3.48-3.50	4.65
H-5'	4.19	4.20(m)	4.77(m)	4.20	4.24	4.23
H-6a	3.56	3.68-3.43	3.06	3.21	3.27	4.49
H-6'a	4.63	4.65	4.36	4.53	4.73	3.68
H-6b	3.66	3.68-3.43	3.38	3.29	3.16	4.70
H-6'b	4.48	4.54	4.10	4.39	4.57	3.84
benzyl	4.22-4.80	4.44-5.04	4.50-5.0	4.24-4.87	4.33-4.97	4.40-5.5
phenyl	7.0-8.05	7.15-8.03	7.05-8.09	7.08-8.10	6.90-8.03	6.98-8.2
$J_{1,2}$	3.3	7.6	3.4	1.6	4.0	4.6
$J_{1',2'}$	8.0	7.8	3.6	3.8	7.9	4.1
$J_{2,3}$	9.6	-	10.1	3.0	10.0	9.1
$J_{2',3'}$	9.8	8.7	10.2	10.3	10.0	9.1
$J_{3,4}$	9.4	-	2.4	9.3	-	9.1
$J_{3',4'}$	9.7	9.5	9.9	9.9	9.6	9.1
$J_{4,5}$	8.8	-	-	9.4	-	9.1
$J_{4',5'}$	9.7	9.6	9.9	9.9	10.0	9.1
$J_{5,6a}$	1.7	-	5.6	1.5	-	5.6
$J_{5',6'a}$	2.9	-	2.5	3.0	-	3.3
$J_{5,6b}$	-	-	8.6	4.3	3.0	-
$J_{5',6'b}$	5.2	-	4.1	5.2	5.3	-
$J_{6a,6b}$	10.6	-	8.6	11.1	10.5	11.7
$J_{6'a,6'b}$	12.1	-	12.4	12.1	12.2	11.1

a. Spectra were recorded at 500.14 MHz in $CDCl_3$ at 300 K. b. The primes (') refer to the benzoylated glucopyranosyl moieties.

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Table 3. ^{13}C NMR chemical shift data (δ, ppm) for deprotected trehalose derivatives.[a]

	13[b]	14	15[c]	16[c]	17[b]	18
C-1	101.05	99.94	94.11	95.77	95.70	101.30
C-1'	103.77		93.92	94.30	98.11	
C-2	72.24	73.43	68.73	70.81	71.56	72.46
C-2'	73.49		71.86	71.67	73.53	
C-3	73.92	76.86	70.07	71.04	72.97	74.11
C-3'	76.97		73.59	73.39	76.74	
C-4	70.20	70.30	69.79	67.50	70.12	70.12
C-4'	70.20		70.48	70.48	70.40	
C-5	73.61	76.52	72.12	74.04	73.47	73.53
C-5'	76.20		72.91	73.25	76.45	
C-6	61.23	61.44	62.00	61.32	61.19	61.22
C-6'	61.42		61.32	61.73	61.41	

a. Spectra were recorded at 125.76 MHz in D_2O at 300 K. b. The α-D-glucopyranosyl moiety is not primed. c. The α-D-glucopyranosyl moiety is primed.

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Glycosidation of 2,3,4,6-tetra-*O*-benzoyl-α-L-glucopyranosyl bromide (**9**) with the acceptor **2** afforded a mixture of 2,3,4,6-tetra-*O*-benzoyl-ß-L-glucopyranosyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (**10**) and the corresponding α-D,α-D-isomer **11**. The configurations were inferred from NMR spectroscopic data. Compound **10** had the two anomeric proton signals at δ 5.33 (d, *J* 4 Hz) and 5.21 (d, *J* 7.9 Hz), respectively. Furthermore, two doublets of doublets at δ 3.56 (*J* 4 Hz, 10 Hz) and 5.77 (*J* 7.9 Hz, 10 Hz), respectively, were seen. The anomeric carbons resonated at δ 94.5 and 98.1 ppm, respectively. Compound **11** had the signals for the two anomeric carbons at δ 98.1 and 96.4, respectively. However, the anomeric proton signals at δ 5.85 (d, *J* 4.6 Hz) and 5.07 (d, *J* 4.1 Hz), respectively, suggested an α-D,α-D-configurated compound. Separation by silica gel chromatography afforded the two compounds slightly contaminated with each other, in yields of about 25 % for **10** and

Table 4. ^{1}H NMR chemical shifts (δ, ppm) and coupling constants (J, Hz) for deprotected trehalose derivatives.[a]

	13[b]	14	15[c]	16[c]	17[b,d]	18
H-1	5.09	4.68	5.08	4.99	5.32	5.15
H-1'	4.51		5.07	5.05	4.67	
H-2	3.46	3.22	3.76	3.86	3.61	3.57
H-2'	3.27		3.51	3.49	3.52	
H-3	3.61	3.37	3.86	3.81	3.75	3.75
H-3'	3.35		3.70	3.61	3.51	
H-4	3.31	3.27	3.86	3.55	3.46	3.44
H-4'	3.74		3.31	3.30	3.41	
H-5	3.80	3.33	3.92	3.72	3.46	3.52-3.83[e]
H-5'	3.39		3.68	3.54	3.46	
H-6a	3.70	3.77	3.60	3.59	3.91	3.52-3.83[e]
H-6'a	3.35		3.62	3.61	3.84	
H-6b	3.62	3.59	3.60	3.73	3.73	3.52-3.83[e]
H-6'b	3.61		3.71	3.75	3.76	
$J_{1,2}$	2.7	8.0	4.0	-	4.0	3.8
$J_{1',2'}$	7.6		3.8	3.8	8.3	
$J_{2,3}$	-	8.7	-	-	9.8	10.1
$J_{2',3'}$	-		9.9	-	10.3	
$J_{3,4}$	-	9.2	-	-	-	9.1
$J_{3',4'}$	-		9.5	9.5	-	
$J_{4,5}$	-	9.4	-	-	-	9.1
$J_{4',5'}$	-		9.5	9.5	-	

a. Spectra were measured in D_2O at 300 K. b. The α-D-glucopyranosyl moiety is not primed. c. The α-D-glucopyranosyl moiety is primed. d. Assignments based on a double quantum filtered homonuclear correlated experiment. e. Higher order coupling pattern.

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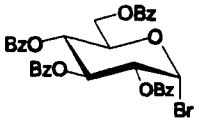

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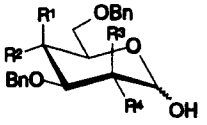
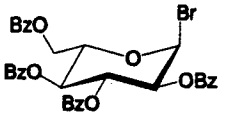


2 R^1, R^3 = H ; R^2, R^4 = OBn
3 R^1, R^4 = OBn ; R^2, R^3 = H
4 R^1, R^4 = H ; R^2, R^3 = OBn



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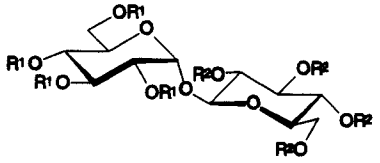
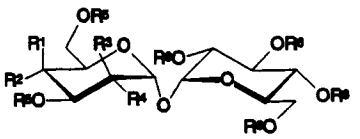
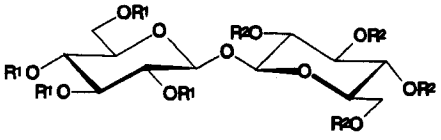


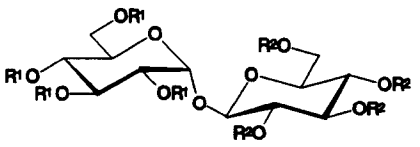
5 R^1 = Bn ; R^2 = Bz
13 R^1, R^2 = H



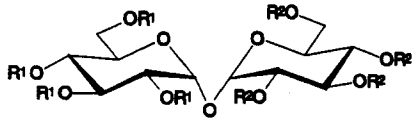
7 R^1, R^4 = OBn ; R^2, R^3 = H ; R^5 = Bn ; R^6 = Bz
8 R^1, R^4 = H ; R^2, R^3 = OBn ; R^5 = Bn ; R^6 = Bz
15 R^1, R^4 = OH ; R^2, R^3, R^5, R^6 = H
16 R^1, R^4, R^5, R^6 = H ; R^2, R^3 = OH



6 R^1 = Bn ; R^2 = Bz
14 R^1, R^2 = H



10 R^1 = Bn ; R^2 = Bz
17 R^1, R^2 = H
19 R^1, R^2 = Ac



11 R^1 = Bn ; R^2 = Bz
18 R^1, R^2 = H
20 R^1, R^2 = Ac

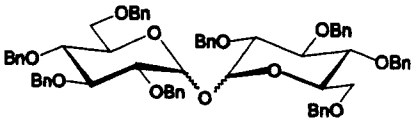


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Table 5. Composition of crude reaction mixtures determined by ^{13}C NMR spectroscopy (± 5 % accuracy).[a] The reactions were carried out in CH_2Cl_2 at -10 °C (2.5 h) using one equiv of glycosyl donor, one equiv of glycosyl acceptor, and one equiv of silver triflate as the promoter, followed by treatment with *N,N,N',N'*-tetramethylurea (TMU).

Synthesis D[b] A[c]	Products	Dimerization by-products A D	Hydrolysis by-products	Unreacted donor	Unreacted acceptor
Glc-Glc **1** **2**	1 % < α,α **5** 47 % α,β **6** 7 % β,β	4%α,α 19%α,β	6 %	8 %	7 %[e]
Glc-Glc **1** **2** 2 equivD[d]	11 % α,α **5** 41 % α,β **6** 9 % β,β	8%α,α 5%α,α 6%α,β 4%α,β	5 %	11 %	0 %
Glc-Glc 25 °C	**5** 17 % α,β	23%α,α 18%α,α 13%α,β	22 %	0 %	7 %
Glc-Gal **1** **3**	**7** 51 % α,α 7 % α,β	3%α,α 9%α,α 5%α,β 5%β,β	14 %	0 %	6 %
Glc-Man **1** **4**	**8** 68 % α,α	13%α,α	8 %	4 %	7 %
LGlc-Glc **9** **2**	**11** 27 % α,α **10** 35 % α,β	10%α,α 2%α,α 5%α,β	10 %	5 %	6 %

a. Figures denote percentage amount of the crude reaction mixtures as determined from the peak heights in the ^{13}C NMR spectra. b. D denotes glycosyl donor. c. A denotes glycosyl acceptor. d. 2 Equiv of **1** were used. e. In addition 2 % unidentified material.

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16 % for **11**. The compounds were further purified by deprotection, peracetylation and chromatography (*vide infra*). In addition a small amount of octa-*O*-benzyl-D-trehaloses **12** could be isolated (0.11 g 5 %), identified by their ^{13}C NMR data only.

In order to account for these by-products and to explain the rather poor yields in the reactions in general, the syntheses were repeated and the crude reaction mixtures were carefully examined by ^{13}C NMR spectroscopy (∓ 5% accuracy).[6,18] The results are presented in Table 5. Furthermore, in an attempt to improve the yields the glycosylation of **2** with **1** was repeated under two different conditions: [a)] at room temperature [b)] in a molar ratio of 2:1. The results are included in Table 5. Although the compositions of the mixtures are approximated from ^{13}C NMR spectra, it seems

evident that dimerization products of the acceptor are inherently formed during the reactions.[11] The formation of these by-products could be explained by protonation of an acceptor molecule with subsequent condensation with another acceptor molecule under the liberation of a water molecule. The liberated water could, in turn, account for the observed hydrolysis of the donor bromides under the otherwise rigorously dry conditions. This inherent formation of by-products under the strongly acidic glycosylation conditions severely limits the scope of these reactions, at least from a preparative point of view, due to the necessity of complicated and tedious purification procedures.

The predominant formation (Table 5) of the α-D,α-D-configurated compounds **7** and **8** is noteworthy, and might be due to mismatched interactions[19] between the donor **1** and the acceptors **3** (*galacto*) and **4** (*manno*), respectively, in the glycosylation reactions. The axial benzyl groups in the acceptors could be responsible for steric hindrance between donor and acceptor in the transition states, thus forcing the formation of the α-D,α-D-configurated products. Unusual stereochemical outcome in glycosylation reactions, due to double stereodifferentiation effects, have been observed previously.[19] The exclusive formation of α-D,ß-D- and ß-D,ß-D-configurated products in the case of the acceptor **2** (*gluco*) indicates, that the unexpected stereochemical outcomes above are not due to isomerization in the acidic reaction media.

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The synthesized trehalose analogues **5**,**6**,**7** and **8** were *O*-deprotected by treatment with sodium methoxide in methanol followed by catalytic hydrogenolysis (Pd/C), the overall yields being in the range of 80-90 %. The obtained disaccharides **13-16** were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy and their spectroscopic data were in agreement with data from the literature.[6,18,20]

Disaccharides **17** and **18** were obtained pure after acetylation, purification and deacetylation in overall yields of 43 % and 11 %, respectively (the two octaacetates of these, compounds **19** and **20** were fully characterized. Significant amounts of material were lost in the purification of these compounds, mostly due to complications in the chromatographic separations. In particular, octaacetate **20** proved very difficult to purify, and was obtained pure only after extensive use of silica gel chromatography, followed by crystallization. The ^{1}H and ^{13} C NMR spectroscopic data (Tables 3-4) for **17** and **18** were in agreement with those reported by Koto *et al.*[18] The optical rotation for the interesting *meso*-disaccharide **18** (α,α-D,L-trehalose) was, by measurement, 0°.

In conclusion, a thorough investigation of the coupling of some glycosyl bromides with tetra-*O*-benzylated monosaccharides has been described. Importantly, the crude reaction mixtures have been characterized by ^{13}C NMR spectroscopy. It has been shown that trehalose derivatives can be synthesized under strongly acidic conditions using AgOTf as the promotor. However, the inherent formation of dimerization by-products limits the scope of the reaction as an expedient method for obtaining larger amounts of unsymmetrical trehalose derivatives.

EXPERIMENTAL

General methods. Analytical grade solvents were dried over molecular sieves (pyridine was distilled from KOH and CH_2Cl_2 from P_2O_5). Petroleum ether was the 60-80 °C fraction. 2,3,4,6-Tetra-*O*-benzyl-D-glucose, 2,3,4,6-tetra-*O*-benzyl-D-galactose and 2,3,4,6-tetra-*O*-benzyl-D-mannose were purchased from Janssen. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter, TLC was performed on Merck coated aluminium foil plates F_{254}, vacuum liquid chromatography (VLC) was performed on silica Gel 60 H (E. Merck). ^1H and ^{13}C NMR spectra were recorded on a Bruker AM500 instrument. ^{13}C NMR spectra were recorded at 300 K in $CDCl_3$ relative to $CDCl_3$ (δ 77.0) or in D_2O with external reference 1,4-dioxane (δ 67.4). ^1H NMR spectra were recorded at 300 K in $CDCl_3$ relative to Me_4Si (δ 0.000), or in D_2O relative to acetone (δ 2.225). Assignment of ^1H NMR spectra was achieved by 2-D homonuclear correlation spectroscopy and of ^{13}C NMR spectra by 2-D heteronuclear correlation spectroscopy.

2,3,4,6-Tetra-*O*-benzoyl-ß-D-glucopyranosyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (5) and 2,3,4,6-tetra-*O*-benzoyl-ß-D-glucopyranosyl 2,3,4,6-tetra-*O*-benzyl-ß-D-glucopyranoside(6). 2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl bromide[21] (**1**, 2.0 g, 3.03 mmol g) was added to a mixture of 2,3,4,6-tetra-*O*-benzyl-D-glucose (**2**, 2.46 g, 3.03 mmol, α/ß ratio 5:1), silver trifluromethanesulphonate (0.79 g, 3.03 mmol), dry CH_2Cl_2 (20 mL) and molecular sieves (3 Å) at -40 °C under an argon atmosphere in the dark. The temperature was raised to -10 °C and the reaction was followed by TLC. After 3 h (the optimized reaction time) *N,N,N',N'*-tetramethyl-urea (0.42 mL, 3.03 mmol) was added and the temperature was slowly raised to 20 °C

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and stirred for 4 h at this temperature. The mixture was filtered through celite, washed with satd. $NaHCO_3$ (30 mL), water (50 mL), dried ($MgSO_4$) and concentrated to yield a syrup (4.37 g, 62 %), which was chromatographed several times (eluent pet. ether 8:EtOAc 2, then pet. ether 8:EtOAc 1.5:toluene 5) to yield the *title compound* **5** [0.84 g (25 %); mp 59-62 °C, $[\alpha]_D^{22}$ +22.3° (*c* 0.4, chloroform), Anal. Calcd for $C_{68}H_{62}O_{15}$: C 72.97; H 5.58. Found: C 73.01; H 5.57] and **6** [0.27 g (8 %); mp 52-56 °C $[\alpha]_D^{22}$ +5.2° (*c* 0.8, chloroform), Anal. Calcd for $C_{68}H_{62}O_{15}$: C 72.97; H 5.58. Found: C 73.10; H 5.69]. Both **5** and **6** were amorphous, colourless substances. ^1H NMR and ^{13}C NMR spectrocopy data are presented in Tables 1-2.

2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranoside (7). 2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (**1**, 1.22, 1.85 mmol g) was reacted with 2,3,4,6-tetra-*O*-benzyl-D-galactose (**3**, 1.0 g, 1.85 mmol, α/ß ratio 3:1) as described above, affording a syrupy, crude product mixture (2.16 g; ^1H NMR suggested 70 % disaccharide), which was chromatographed several times (eluents as above) to yield the syrupy *title compound* **7** in a pure form (0.83 g, 40 %), $[\alpha]_D^{22}$ +89.1° (*c* 0.9, chloroform). ^1H NMR and ^{13}C NMR spectroscopy data are presented in Tables 1-2.

Anal. Calcd for $C_{68}H_{62}O_{15}$: C 72.97; H 5.58. Found: C 73.75; H 5.83.

2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside (8). 2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (**1**, 1.22 g, 1.85 mmol) was added to a mixture of 2,3,4,6-tetra-*O*-benzyl-D-mannose (**4**, 1 g, 1.85 mmol, α/ß ratio 4:1), silver trifluoromethanesulphonate (0.48 g, 1.85 mmol), dry CH_2Cl_2 (20 mL) and molecular sieves (3 Å) at -40 °C under argon atmosphere in the dark. The glycosylation was performed and worked up as descibed above and the *title compound* **8** was obtained as a colourless syrup (1.46 g, 42 %) after silica gel chromatography, $[\alpha]_D^{22}$ +61.2° (*c* 1.9, chloroform). ^1H NMR and ^{13}C NMR spectroscopy data are presented in Tables 1-2.

Anal. Calcd for $C_{68}H_{62}O_{15}$: C 72.97; H 5.58. Found: C 73.71; H 5.84.

2,3,4,6-Tetra-*O*-benzoyl-ß-L-glucopyranosyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (10) and 2,3,4,6-tetra-*O*-benzoyl-α-L-glucopyranosyl α-D-glucopyranoside (11). 2,3,4,6-Tetra-*O*-benzoyl-α-L-glucopyranosyl bromide (**9**, 0.90 g, 1.36 mmol) was added to a stirred mixture of 2,3,4,6-tetra-*O*-benzyl-D-glucose (**2**, 0.74

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g, 1.36 mmol, α,ß ratio 5:1), silver trifluoromethanesulphonate (0.35 g, 1.36 mmol), dry CH_2Cl_2 (20 mL) and molecular sieves (3 Å) at -40 °C under argon atmosphere in the dark. The glycosylation was performed and worked up as described above to yield compound **10** as a white amorphous powder (0.55 g, 26 %), compound **11** as a syrup (0.24 g, 16 %), and a syrupy mixture of octa-*O*-benzyl-α,α- and α,ß-trehalose (**12**, 0.11 g, 5 %). Compounds **10** and **11** each contained ca. 10 % of the other isomer (10 % of **10** in **11**, and *vice versa*) according to ^{1}H NMR spectroscopy, but further purification by silica gel chromatography was unsuccesful. The compounds were transformed into their octaacetates **19** and **20**, which were purified and fully characterized (*vide infra*). ^{1}H NMR and ^{13}C NMR spectroscopy data for compound **10** and **11** are presented in Tables 1-2.

Anal. Calcd for $C_{68}H_{62}O_{15}$: C 72.97; H 5.58. Found: C 73.18; H 5.63.

α-D-Glucopyranosyl ß-D-glucopyranoside (13). A mixture of compound **5** (0.43 g, 0.38 mmol), dry MeOH (3 mL) and NaOMe in MeOH (1 M, 0.20 mL) was refluxed for 10 min. The mixture was cooled and deionized and neutralized with Amberlite IRC-50 (0.40 g). After filtration, MeOH (50 mL), acetic acid (5 mL) and palladium on charcoal (10 %, 0.43 g) was added and the mixture was hydrogenated at atmospheric pressure for 24 h, and was subsequently filtered through celite and the filtrate concentrated. The resulting syrup was dissolved in distiled water (20 mL) and washed with petroleum ether (20 mL). The aqueous solution was concentrated to a small volume (2 mL) and lyophilized to afford α,β-trehalose **13**,[13] pure by ^{1}H and ^{13} C NMR, as a white amorphous powder (0.12 g) in a overall 88 % yield, mp 55-57 °C, $[\alpha]_D^{22}$ +66° (*c* 1.1, water). ^{1}H NMR and ^{13}C NMR spectrocopy data are presented in Tables 3-4.

ß-D-Glucopyranosyl ß-D-glucopyranoside (14). Compound **6** (0.19 g, 0.17 mmol) was deprotected and worked up as above for compound **13** to afford ß,ß-trehalose[13] (**14**, 0.06 g), pure by ^{1}H and ^{13}C NMR, in a overall 100 % yield, mp 115-120 °C, $[\alpha]_D^{22}$ -18.3° (*c* 0.7, water). ^{1}H NMR and ^{13}C NMR spectrocopy data are presented in Tables 3-4.

α-D-Galactopyranosyl α-D-glucopyranoside (15). Compound **7** (0.55 g, 0.49 mmol) was deprotected and worked up as above to afford the title compound **15** (0.15 g), pure by ^{1}H and ^{13}C NMR, in 87 % overall yield, mp 65-70 °C, $[\alpha]_D^{22}$ +208°

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(*c* 0.9, water); lit.[12]: $[\alpha]_D$208°. ^{1}H NMR and ^{13}C NMR spectroscopic data are presented in Tables 3-4.

α-D-Glucopyranosyl α-D-mannopyranoside (16). Compound **8** (0.60 g, 0.53 mmol) was deprotected and worked up as above to afford the title compound **16** (0.17 g), pure by ^{1} H and ^{13}C NMR, in 92 % overall yield, mp 110-115 °C, $[\alpha]_D^{22}$ +111° (*c* 1, water); lit.[17]: mp 120-125 °C, $[\alpha]_D$ +110°. ^{1}H NMR and ^{13}C NMR spectroscopy data are presented in Tables 3-4 and agree with previously published data.[20]

α-D-Glucopyranosyl ß-L-glucopyranoside (17). Impure compound **10** (0.55 g) was deprotected as above to afford a brownish, amorphous material (0.14 g, 85 %). A mixture of this, pyridine (5 mL) and DMAP (0.02 g) was treated with acetic anhydride (1 mL) at 50 °C for 2 h. The mixture was cooled, poured into ice-water, extracted with CH_2Cl_2, washed with 1 % HCl, satd. $NaHCO_3$ and water, dried ($MgSO_4$) and concentrated to afford a syrup (0.26 g) which was subjected to silica gel chromatography (eluent: pet. ether-EtOAc 1:1). 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl 2,3,4,6-tetra-*O*-acetyl-ß-L-glucopyranoside (**19**) was obtained as a white, amorphous powder (0.14 g, 49 %); mp 68-70 °C, $[\alpha]_D^{22}$ +91.4° (*c* 0.9, chloroform); ^{13}C NMR($CDCl_3$) δ 96.73 (C-1'), 93.24 (C-1), 72.75 (C-3'), 72.12 (C-5'), 71.14 (C-2'), 69.86 (C-2), 69.49 (C-3), 68.33 (C-5), 68.25 (C-4), 68.07 (C-4') , 61.83 (C-6'), 61.64 (C-6) ppm; ^{1}H NMR ($CDCl_3$) δ 5.45 (d, *J* 3.8 Hz, 1 H, H-1), 5.41 (t, *J* 9.9 Hz, 1 H, H-3), 5.24 (t, *J* 9.3 Hz, 1 H, H-3'), 5.12 (t, *J* 9.3 Hz, 1 H, H-4'), 5.11 (dd, *J* 7.9 Hz, 9.3 Hz, 1 H, H-2'), 5.09 (t, *J* 9.7 Hz, 1 H, H-4), 4.89 (dd, *J* 3.8 Hz, 10.33 Hz, 1 H, H-2), 4.80 (d, *J* 7.9 Hz, 1 H, H-1'), 4.30 (m, 1 H, H-6a), 4.26 (m, 1 H, H-6'b), 4.16 (m, 1 H, H-6'a), 4.08 [dd, *J* 2.2 Hz, 12.3 Hz, 1 H, H-6b], 3.97 (ddd, *J* 2.3 Hz, 4.5 Hz, 10.3 Hz, 1 H, H-5), 3.75 (ddd, *J* 2.3 Hz, 5.4 Hz, 10.0 Hz, 1 H, H-5'), 2.20-2.07 (24 H, acetyl) ppm. Anal. Calcd for $C_{68}H_{62}O_{15}$: C 49.55; H 5.64. Found: C 49.08; H 5.70. Compound **19** (0.06 g, 0.09 mmol) was deprotected and worked up as above to afford the title compound **17** (0.03 g) 87 % yield, mp 128-132 °C, $[\alpha]_D^{22}$ +106° (*c* 0.5, water). ^{1}H NMR and ^{13}C NMR spectroscopy data for compound **17**[18] are presented in Tables 3-4.

α-D-Glucopyranosyl α-L-glucopyranoside (18). Impure compound **11** (0.24 g, mmol) was converted into its corresponding octaacetate **20** (syrup) as above

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for compound **19** in an overall yield of 11 % after extensive chromatographic purification. Crystallization from Et_2O-pet. ether gave crystalline material with mp 155-117 °C, $[\alpha]_D^{22}$ 0° (*c* 0.8, water); ^{13}C NMR($CDCl_3$) δ 94.56 (C-1), 70.89 (C-2), 69.72 (C-3), 68.69 (C-5), 67.90 (C-4), 61.59 (C-6) ppm; ^1H NMR ($CDCl_3$) δ 5.50 (t, *J* 9.8 Hz, 2 H, H-3), 5.32 (d, *J* 4.3 Hz, 2 H, H-1), 5.10 (t, *J* 9.8 Hz, 2 H, H-4), 4.89 (dd, *J* 4.3 Hz, 9.8 Hz, 2 H, H-2), 4.28 (dd, *J* 4.6 Hz, 13 Hz, 2 H, H-6a), 4.18 (m, 2 H, H-5), 4.15 (m, 2 H, H-6b), 2.13-2.08 (24 H, acetyl) ppm; $[M+H]^+$ 679. Compound **20** (0.007 g, 0.01 mmol) was deprotected and worked up as above for compound **19** to afford the title compound **18** (0.003 g) in 100 % yield, mp 279 °C (dec), $[\alpha]_D^{22}$ 0° (*c* 0.2, water). ^1H NMR and ^{13}C NMR spectroscopy data for compound **18**[18] are presented in Tables 3-4.

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