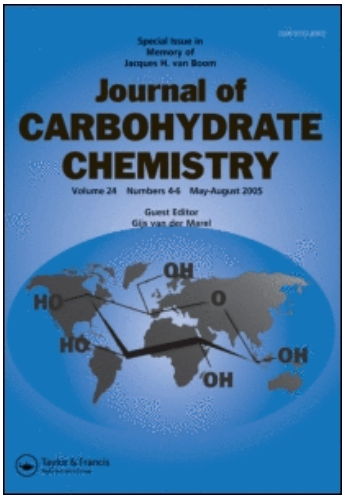

Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

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To cite this Article Wessel, Hans Peter and Minder, Rudolf(1998) 'The Synthesis of the 2- and 2'-Monodeoxygenated Analogues of β-Maltosyl-(1→4)-Trehalose', Journal of Carbohydrate Chemistry, 17: 4, 567 — 586
To link to this Article: DOI: 10.1080/07328309808002338
URL: http://dx.doi.org/10.1080/07328309808002338

J. CARBOHYDRATE CHEMISTRY, 17(4&5), 567-586 (1998)

THE SYNTHESIS OF THE 2- AND 2'-MONODEOXYGENATED ANALOGUES OF β-MALTOSYL-(1→4)-TREHALOSE[1]

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Final Form December 9, 1997

ABSTRACT

Two derivatives of β-maltosyl-(1→4)-trehalose monodeoxygenated at C-2 or C-2' have been synthesized in [2+2] block syntheses. *N*-Iodosuccinimide-mediated coupling of tetra-*O*-benzyl-glucose to tri-*O*-acetyl-D-glucal followed by *O*-acetylation furnished 3,4,6-tri-*O*-acetyl-2-deoxy-2-iodo-α-D-manno-pyranosyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (**7**), which was used as a starting material for both tetrasaccharides. For the preparation of the 2'-monodeoxygenated saccharide the deoxyiodo pyranose moiety of **7** was further elaborated by de-*O*-acetylation, *O*-benzylidenation, *O*-benzylation, and selective reductive opening of the benzylidene acetal to give glycosyl acceptor **10**. Glycosylation with hepta-*O*-acetylmaltosyl bromide and deprotection including removal of the iodo substituent afforded the 2'-deoxymaltosyl-(1→4)-trehalose **14**. On the other hand, the non-iodinated pyranose moiety of **7** was transformed to a glycosyl acceptor. The removal of the benzyl groups of **7** necessitated also the reduction of the iodo group at this early stage. The resulting 3,4,6-tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranosyl α-D-gluco-pyranoside was subjected to a similar reaction sequence as above to finally result in the 2-deoxymaltosyl-(1→4)-trehalose **22**.

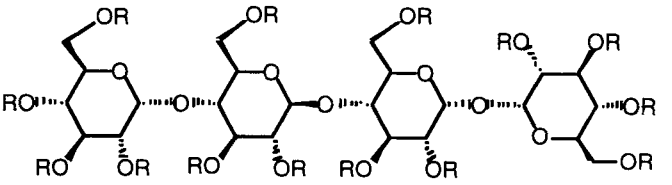
INTRODUCTION

The potent smooth muscle cell (SMC) proliferation inhibitor sulfated β-maltosyl-(1→4)-trehalose (**1**)[2] seems to mimic the action of heparan sulfate, an endogenous SMC growth regulator. In a program to investigate the relative importance of sulfate groups in the various positions of the sulfated tetrasaccharide **1**, we selectively removed single hydroxyl groups of the unprotected tetrasaccharide **2**. This approach has been outlined in more detail in earlier publications.[3,4]

Derivatives of **2** deoxygenated at the primary positions have been synthesized via the respective deoxyiodo compounds.[4] The syntheses of the tetrasaccharide analogues deoxygenated at secondary carbon atoms were achieved after Barton-McCombie deoxygenation[6] of the secondary hydroxyl groups. From these we have reported the preparation of the C-4- and C-4‴-deoxy derivatives,[7] the C-3″-deoxy derivative,[8] the C-3′- and C-3‴-deoxy derivatives,[9] and the C-2″-deoxy derivative.[10] While [2+2] block syntheses were favourably employed for those analogues, the glycosyl donor for the C-2‴-deoxy derivative was assembled in a phenylselenyl chloride mediated coupling reaction from monosaccharide precursors.[10] Here we report the syntheses of the 2- and 2′-deoxygenated analogues.

RESULTS AND DISCUSSION

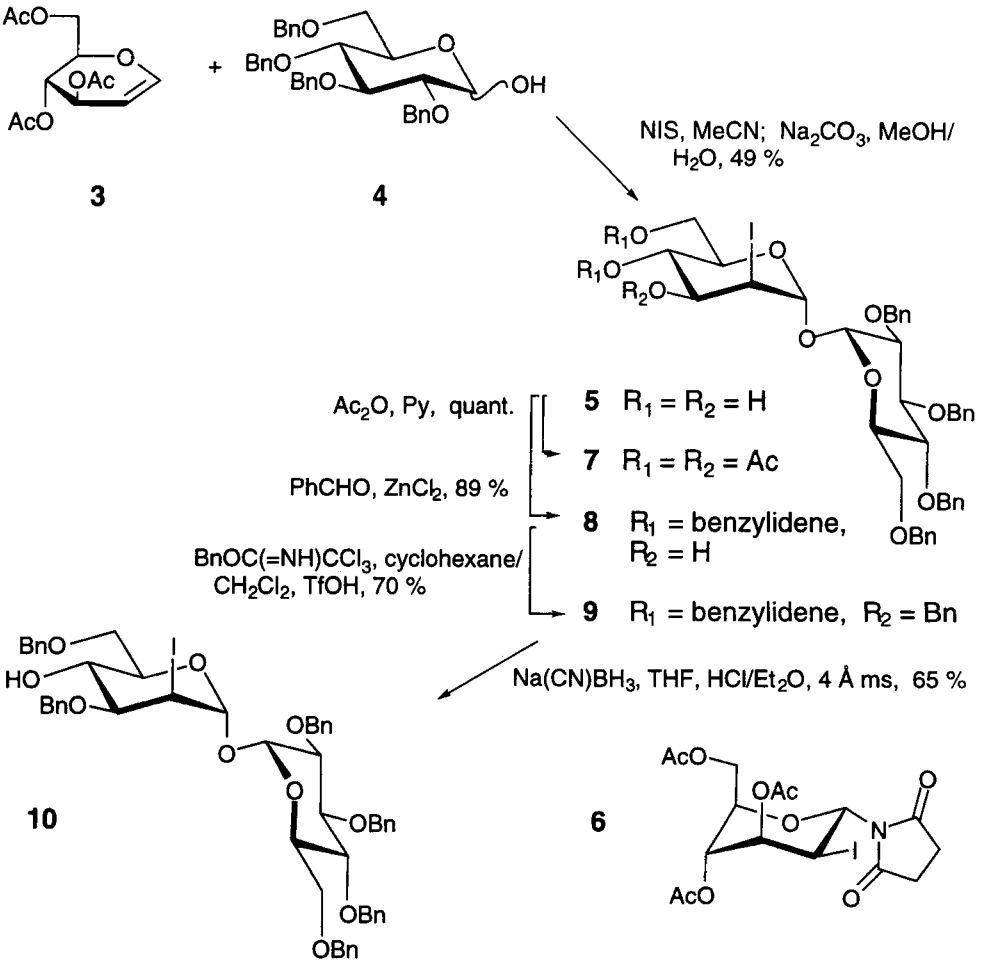
Apart from a low-yielding enzymatic synthesis of 2-deoxy-α,α-trehalose,[11] a preparation has been described starting from di-*O*-benzylidene trehalose and using mono-acylation to break the C_2-symmetry of the molecule.[12] This approach did not seem to be suitable to synthesize both the 2- and 2′-monodeoxygenated analogues of β-maltosyl-(1→4)-trehalose since the glucose moieties in the intermediates are not sufficiently differentiated to allow regioselective reactions leading to the two required glycosyl acceptors. Instead, we assembled the trehalose disaccharide from two differently protected monosaccharide units. Employing the well-established NIS



1 R = SO_3Na or H, DS ≈ 2.8[5]

2 R = H

Scheme 1



Scheme 2

procedure,[13,14] tri-*O*-acetyl-D-glucal **3** was reacted with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **4** to afford the expected α,α-linked disaccharide as the main product. To facilitate purification the disaccharide fraction was deacetylated to furnish crystalline **5** in 49 % yield. In addition, the succinimide **6** was obtained (25 %), a known by-product in NIS-mediated glycosylations.[15] For reference purposes and for use in the synthesis of the maltosyl trehalose analogue deoxygenated at C-2, disaccharide **5** was reacetylated to give **7** quantitatively.

Benzylidenation of **5** with zinc chloride in benzaldehyde afforded compound **8** in 89 % yield. The 3'-hydroxyl group was protected by benzylation with benzyl trichloroacetimidate[16,17] to furnish the fully protected **9** (70 %). The benzylidene ring was then opened selectively by reduction with sodium cyanoborohydride to arrive at the glycosyl acceptor **10** (68 %). These disaccharide structures were supported by their ^{1}H NMR spectra; data for the ring protons are summarized in Tables 1 and 2.

Koenigs-Knorr glycosylation of **10** with hepta-*O*-acetylmaltosyl bromide (**11**)[18] as glycosyl donor using the promoter silver triflate[19] and tetramethylurea furnished the tetrasaccharide **12** in a yield of 54 %. Standard deacetylation to give **13** (86 %) followed by two hydrogenolyses in solvents with increasing polarity led to the free tetrasaccharide **14** in moderate yield (34 %). Compound **14** constitutes the 2'-deoxygenated analogue of tetrasaccharide **2**.

For the synthesis of the tetrasaccharide deoxygenated at C-2 we employed the trehalose derivative **7**. While in the synthesis described above the iodinated glucose moiety had been further elaborated, we now redefined the molecule to make the glycosyl accepting hydroxyl group available at the non-iodinated glucose moiety of **7**. For this purpose the iodo substituent was removed by selective hydrogenolysis using 5 % palladium-on-charcoal to yield **15** (88 %). A second hydrogenolysis using 10 % palladium-on-charcoal and a longer reaction time removed the benzyl groups to furnish **16** in 67 % yield. The following reactions were carried out according to the same synthetic scheme as above. Benzylidenation of **16** with benzaldehyde and zinc chloride afforded **17** in 71 % yield, benzylation of the 2'- and 3'-hydroxyl groups with benzyl trichloroacetimidate led to **18** in moderate yield (52 %).

Table 1. ^{1}H NMR Chemical shifts and multiplicities for compounds **5** and **7** - **10**

Proton, multiplicity	**5**	**7**	**8**	**9**	**10**
H-1, d	5.15	5.21	5.14	5.12	5.24
H-2, dd	3.59	3.62	3.60	3.58	3.55
H-3, dd	3.96, ~t	4.02, ~t	3.98, ~t	3.68	3.89
H-4, dd	3.68	3.72, ~t	3.69, ~t	(2H)	
H-5, ddd	3.77	3.80	3.77	3.73	
H-6a, dd	3.72	3.75	3.73	3.89	
H-6b, dd	3.64	3.64	3.65	3.63	
H-1', br s	5.43	5.45	5.47	5.45	5.49
H-2', dd	4.40	4.53	4.48	4.39	4.36
H-3', dd	3.22, ddd	4.66	3.42	3.32	3.15
H-4', dd	3.85, ddd ~dt	5.37, ~t	3.97, ~t	4.16, ~t	4.01, ddd ~ t
H-5', ddd	3.65, br	4.27	4.25, ddd ~dt	4.27, ddd ~dt	4.19, ddd ~dt
H-6a', dd	3.95, ddd ~dt	4.01	4.12	4.14	
H-6b', dd	3.65, ddd	3.86	3.81, ~t	3.84, ~t	

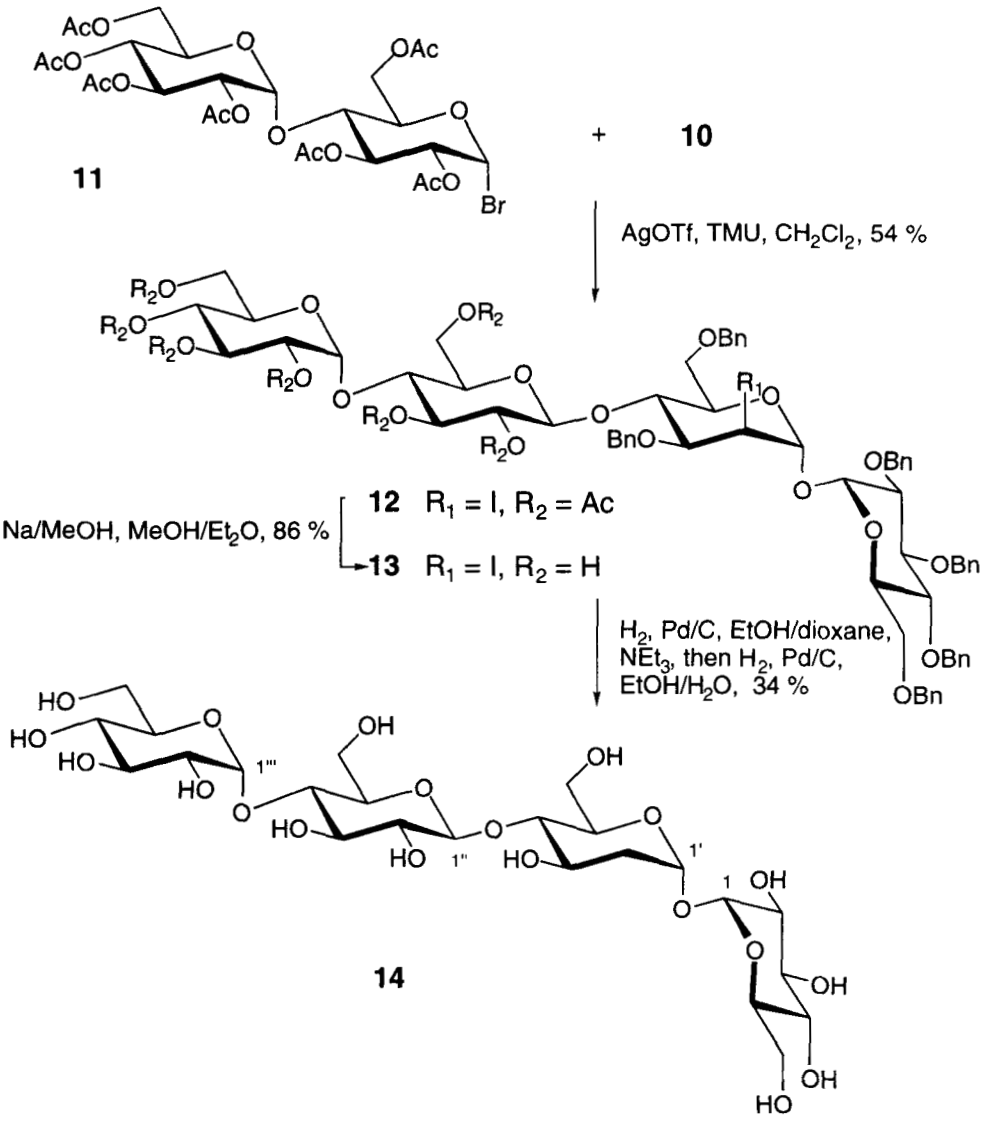
Table 2. ^{1}H NMR Coupling constants in Hz for compounds **5** and **7 - 10**

	5	**7**	**8**	**9**	**10**
$J_{1,2}$	3.7	3.6	3.5	3.6	3.6
$J_{2,3}$	9.7	9.8	9.7	9.8	9.6
$J_{3,4}$	9.0	8.7	9.3	-	8.4
$J_{4,5}$	10.0	10.0	10.0	10.0	
$J_{5,6a}$	3.0	3.5	~ 3	4.0	
$J_{5,6b}$	1.5	1.5	1.8	≤ 1.5	
$J_{6a,6b}$	11.0	11.0	~ 10	10.0	
$J_{1',2'}$	1.3	1.1	0.8	0.8	1.0
$J_{2',3'}$	4.4	4.0	4.6	4.4	4.0
$J_{3',4'}$	9.4	9.0	9.0	9.3	9.0
$J_{4',5'}$	10.0	9.2	9.5	9.5	9.5
$J_{5',6a'}$	4.3	2.3	4.9	4.7	Σ ($J_{5',6a'}$+ $J_{5',6b'}$) = 8.3
$J_{5',6b'}$	2.1	4.6	10.2	10.3	
$J_{6a',6b'}$	12.4	9.5	10.3	10.3	-

Regioselective reductive opening of the benzylidene ring with sodium cyanoborohydride gave the glycosyl acceptor **19** in good yield (88 %).

In a Koenigs-Knorr glycosylation reaction using silver triflate and tetramethylurea as activating system, hepta-*O*-acetylmaltosyl bromide **11** was coupled to glycosyl acceptor **19** to give the tetrasaccharide **20** in a yield of 78 %. Deblocking by transesterification (**21**, 61 %) followed by hydrogenolysis (97 %) furnished the β-maltosyl trehalose tetrasaccharide **22** deoxygenated at C-2.

The investigation of the antiproliferative activities of the highly sulfated derivatives of the deoxygenated tetrasaccharides **14** and **22** revealed that the



Scheme 3

Table 3. ^{1}H NMR Chemical shifts and multiplicities for compounds **15** - **19**

Proton, multiplicity	**15**	**16**	**17**	**18**	**19**
H-1, br d	5.26	5.26	5.29	5.25	5.26
H-2_{eq}, ddd~dd	2.20	2.25	2.28	2.27	2.23
H-2_{ax}, ddd~dt	1.89	1.89	1.95	1.92	1.89
H-3, ddd	5.39	5.37	5.38	5.41	5.41
H-4, dd	5.00, ~t	5.03, ~t	5.03, ~t	5.01, ~t	5.00, ~t
H-5, ddd	4.23	4.12	4.08	4.25	4.22
H-6a, dd	4.10	4.25	4.29	4.05	4.09
H-6b, dd	3.76	4.24	4.26	3.76	3.78
H-1', d	5.21	5.14	5.18	5.16	5.21
H-2', dd	3.61		3.74	3.62	3.58
H-3', dd	4.05, ~t		4.06, ~t	4.14, ~t	3.87, ~t
H-4', dd	3.69, ~t		3.51, ~t	3.65, ~t	3.68, ~t
H-5', ddd	3.79		3.82	3.89	3.75
H-6a', dd	3.72		4.26	4.26	3.69
H-6b', dd	3.62		3.72, ~t	3.72, ~t	3.65

removal of sulfates at C-2 and C-2′ had only little influence on activity,[3] and it was concluded that sulfation at these positions is not prerequisite for antiproliferative activity.

EXPERIMENTAL

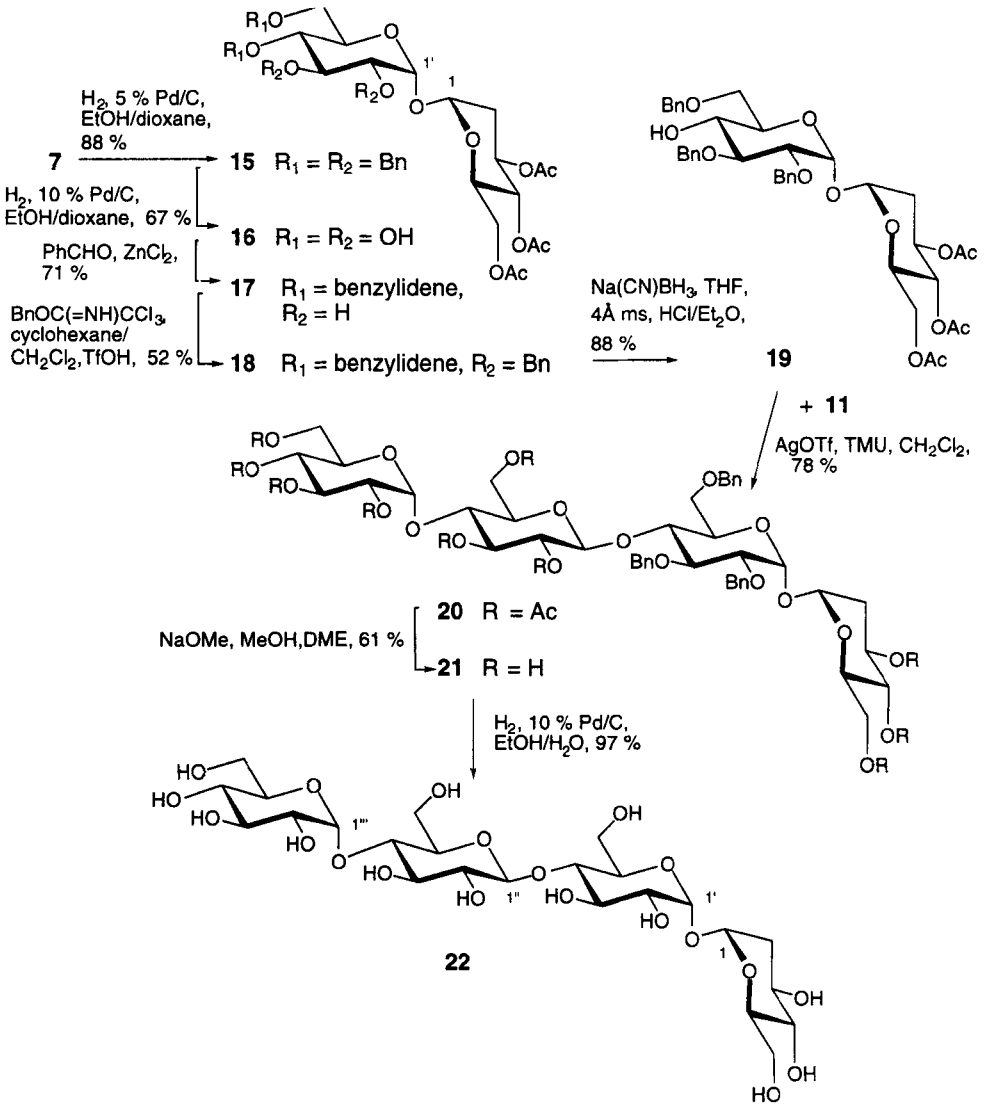
General Procedures. Experimental conditions were essentially as described before.[3] Specific rotations were measured at 20 °C. Mass spectra were

Table 4. ^{1}H NMR Coupling constants in Hz for compounds **15 - 19**

	15	**16**	**17**	**18**	**19**
$J_{1,2eq}$	≤ 1	≤ 1	≤ 1	≤ 1	≤ 1
$J_{1,2ax}$	3.0	~ 3	3.0	2.9	3.0
$J_{2eq,3}$	5.4	5.2	5.4	5.4	9.6
$J_{2ax,3}$	11.5	11.2	11.5	11.5	11.5
$J_{2eq,2ax}$	12.4	12.9	12.5	13.1	12.6
$J_{3,4}$	9.5	8.8	9.5	9.5	9.6
$J_{4,5}$	10.0	10.0	10.1	10.2	9.8
$J_{5,6a}$	4.0	4.0	4.0	3.7	4.0
$J_{5,6b}$	2.0	3.0	1.5	2.2	2.1
$J_{6a,6b}$	12.2	~ 11	~ 12.2	12.5	12.4
$J_{1',2'}$	3.6	3.0	3.9	3.8	3.5
$J_{2',3'}$	9.7		9.5	9.3	9.6
$J_{3',4'}$	8.8		8.5	9.3	8.8
$J_{4',5'}$	9.9		10.0	10.0	9.8
$J_{5',6a'}$	3.0		4.7	4.7	4.0
$J_{5',6b'}$	2.0		9.5	9.5	3.5
$J_{6a',6b'}$	10.4		10.0	10.0	~ 10

recorded on API III Sciex, Perkin Elmer (ionspray) or MS 902 (FAB) with data system DS 2050 (VG).

2-Deoxy-2-iodo-α-D-mannopyranosyl 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranoside (5). To a suspension of tri-*O*-acetyl-D-glucal (**3**, 54.4 g, 0.20 mol) and 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**4**, 75.0 g, 0.138 mol) in acetonitrile (1.5 L) was added *N*-iodosuccinimide (35.0 g, 0.155 mol) at 0 - 5 °C. The reaction mixture was stirred at rt for 3 d under argon, then concentrated. The



Scheme 4

residue was taken up in dichloromethane (1 L), washed twice with sodium thiosulfate soln (10 %, 500 mL), dried over magnesium sulfate, and evaporated. The residue was flash chromatographed on silica gel (1.5 kg) with ethyl acetate/ hexane/ dichloromethane 1:4:1 to obtain the crude target compound (96 g) as a syrup. Further elution with ethyl acetate/ hexane/ dichloromethane 5:5:2 afforded the by-product **6** (24.0 g, 25 %). The crude product was dissolved in methanol (1.92 L) and treated with a soln of sodium carbonate (50.0 g, 0.47 mol) in water (0.5 L). The reaction mixture was stirred at rt for 6 h, then concentrated. To the aqueous residue was carefully added water (1.0 L) under stirring to precipitate the compound. The precipitate was filtered, washed with water and dried. The solid was crystallized twice with acetone/ ether to furnish **5** (55.0 g, 49 %) as colourless crystals: mp 144-145 °C; $[\alpha]_D$ +98.8 ° (*c* 0.5, chloroform); MS (ionspray) *m/z* 830.1 (13 %, $[M + NH_4]^+$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36 - 7.25 (m, 18H, aromat), 7.15 - 7.12 (m, 2H, aromat), 4.97, 4.84 (2 d, 2H, J_{gem} = 11.0 Hz, CH_2Ph), 4.83, 4.48 (2 d, 2H, J_{gem} = 10.7 Hz, CH_2Ph), 4.74, 4.64 (2 d, 2H, J_{gem} = 11.8 Hz, CH_2Ph), 4.60, 4.47 (2 d, 2H, J_{gem} = 12.0 Hz, CH_2Ph), 2.79 (d, 1H, $J_{4',4'\text{-OH}}$ = 4.2 Hz, 4'-OH), 2.71 (d, 1H, $J_{3',3'\text{-OH}}$ = 6.6 Hz, 3'-OH), 1.97 (dd, 1H, $J_{6a',6'\text{-OH}}$ = 5.7 Hz, $J_{6b',6'\text{-OH}}$ = 6.3 Hz, 6'-OH).

Anal. Calcd for $C_{40}H_{45}IO_{10}$ (812.67): C, 59.12; H, 5.58; I, 15.62. Found: C, 59.36; H, 5.70; I, 15.35.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-iodo-α-D-mannopyranosyl 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranoside (**7**). To a soln of **7** (10.0 g, 12.3 mmol) in pyridine (50 mL) was added acetic anhydride (20 mL). The reaction mixture was stirred at rt for 17 h, then concentrated. The residue was treated with ice water and extracted with ethyl acetate. The organic phases were washed with 1N sulfuric acid, saturated sodium bicarbonate soln and brine, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel using ethyl acetate/ hexane 1:5 → 1:1 as eluent to give **7** (12.2 g, 100 %) as a syrup: $[\alpha]_D$ +71.3 ° (*c* 0.4, chloroform); MS (ionspray) *m/z* 956 (100 %, $[M + NH_4]^+$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36 - 7.25 (m, 18H, aromat), 7.17 - 7.14 (m, 2H, aromat), 4.97, 4.88 (2 d, 2H, J_{gem} = 11.0 Hz, CH_2Ph), 4.83, 4.50 (2

d, 2H, J_{gem} = 10.7 Hz, CH_2Ph), 4.79, 4.51 (2 d, 2H, J_{gem} = 12.0 Hz, CH_2Ph), 4.61, 4.48 (2 d, 2H, J_{gem} = 12.0 Hz, CH_2Ph), 2.09, 2.06, 2.01 (3 s, 9H, OAc).

Anal. Calcd for $C_{46}H_{51}IO_{13}$ (938.79): C, 58.85; H, 5.48; I, 13.52. Found: C, 59.36; H, 5.70; I, 13.12.

4,6-*O*-Benzylidene-2-deoxy-2-iodo-α-D-mannopyranosyl 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranoside (8). To a suspension of **5** (10.0 g, 12.3 mmol) in benzaldehyde (200 mL) was added zinc chloride (64.4 g, 470 mmol). The reaction mixture was stirred at rt for 2 h, then poured into a stirred mixture of ether (200 mL) and ice/ water (400 mL). The aqueous phase was extracted three times with diethyl ether. The extracts were washed with ice/water and brine, dried over magnesium sulfate, and concentrated. The residue was chromatographed on silica gel (1 kg) using ethyl acetate/ hexane 1:19 → 1:3 as eluent. Product fractions were concentrated to give **8** (9.91 g, 89 %) as a slightly coloured foam: $[\alpha]_D$ +76.0 ° (*c* 0.5, methanol); MS (ionspray) *m/z* 918.4 (30 %, $[M + NH_4]^+$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.48 - 7.46 (m, 2H, aromat), 7.39 - 7.27 (m, 21H, aromat), 7.15 - 7.13 (m, 2H, aromat), 5.58 (s, 1H, CHPh), 4.96, 4.84 (2 d, 2H, J_{gem} = 10.4 Hz, CH_2Ph), 4.84, 4.47 (2 d, 2H, J_{gem} = 10.5 Hz, CH_2Ph), 4.75, 4.68 (2 d, 2H, J_{gem} = 12.0 Hz, CH_2Ph), 4.61, 4.47 (2 d, 2H, J_{gem} = 12.0 Hz, CH_2Ph), 2.59 (d, 1H, $J_{3',3'\text{-OH}}$ = 4.4 Hz, 3'-OH).

Anal. Calcd for $C_{47}H_{49}IO_{10}$ (900.78): C, 62.67; H, 5.48; I, 14.09. Found: C, 62.75; H, 5.70; I, 13.89.

3-*O*-Benzyl-4,6-*O*-(*R*)-benzylidene-2-deoxy-2-iodo- α -D - mannopyranosyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (9). To a soln of **8** (10.2 g, 11.3 mmol) in dichloromethane (25 mL) and cyclohexane (250 mL) was added benzyl 2,2,2-trichloroacetimidate (5.2 g, 20.4 mmol) followed by triflic acid (0.5 mL) at rt. The reaction mixture was stirred for 3 h at rt, then neutralized by addition of triethylamine (2 mL) and poured into ice/water. The aqueous phase was extracted twice with ethyl acetate. The organic phases were washed with aq sodium bicarbonate soln and brine, dried over magnesium sulfate, and concentrated. The residue was chromatographed over silica gel using ethyl acetate/ hexane 1:9→1:3 as eluent to furnish **9** (7.84 g, 70 %) as a slightly

coloured syrup; $[\alpha]_D$ +52.2 ° (*c* 0.5, chloroform); MS (ionspray) *m/z* 1008.5 (6 %, $[M + NH_4]^+$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.50 - 7.47 (m, 2H, aromat), 7.39 - 7.14 (m, 28H, aromat), 5.62 (s, 1H, CHPh), 4.94, 4.82 (2 d, 2H, J_{gem} = 10.9 Hz, CH_2Ph), 4.85, 4.48 (2 d, 2H, J_{gem} = 10.5 Hz, CH_2Ph), 4.74, 4.71 (2 d, 2H, J_{gem} = 11.8 Hz, CH_2Ph), 4.72, 4.67 (2 d, 2H, J_{gem} = 11.8 Hz, CH_2Ph), 4.61, 4.48 (2 d, 2H, J_{gem} = 12.0 Hz, CH_2Ph).

Anal. Calcd for $C_{54}H_{55}IO_{10}$ (990.89): C, 65.45; H, 5.59; I, 12.61. Found: C, 65.75; H, 5.70; I, 12.15.

3,6-Di-*O*-benzyl-2-deoxy-2-iodo-α-D-mannopyranosyl 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranoside (**10**). To a soln of **9** (3.11 g, 3.14 mmol) in abs tetrahydrofuran (70 mL) were added pulverized 3Å molecular sieves (4.0 g) at 0 °C followed by sodium cyanoborohydride (2.7 g, 43 mmol) and a few crystals of methyl orange. The reaction mixture was stirred for 30 min, then hydrogen chloride in diethyl ether (30 mL of a 1.8 M soln, 54 mmol) was added dropwise over 1 h at 0 °C. After stirring for 2 h at this temperature, the orange-red reaction mixture was poured into sodium bicarbonate soln, and tetrahydrofuran was evaporated under reduced pressure. The aqueous residue was extracted four times with dichloromethane. The organic phases were washed with ice water and brine, dried over magnesium sulfate, and concentrated. The residue was chromatographed on silica gel (200 g) using ethyl acetate/ hexane 1:9 → 1:3 as eluent to give **10** (2.02 g, 65 %) as a colorless syrup: $[\alpha]_D$ +55.0 ° (*c* 0.5, chloroform); MS (ionspray) *m/z* 1010.3 (100 %, $[M + NH_4]^+$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.41 - 7.40 (m, 2H, aromat), 7.35 - 7.24 (m, 26H, aromat), 7.17 - 7.15 (m, 2H, aromat), 4.95, 4.83 (2 d, 2H, J_{gem} = 10.9 Hz, CH_2Ph), 4.70, 4.63 (2 d, 2H, J_{gem} = 12.0 Hz, CH_2Ph), 4.85, 4.68, 4.62, 4.60, 4.50, 4.49, 4.49, 4.46 (8 d, 8H, 4 CH_2Ph), 3. 76 - 3.64 (m, 6H), 2.46 (d, 1H, $J_{4',4'\text{-OH}}$ = 2.3 Hz, 4'-OH).

Anal. Calcd for $C_{54}H_{57}IO_{10}$ (992.90): C, 65.32; H, 5.79; I, 12.78. Found: C, 64.90; H, 5.68; I, 12.54.

***O*-(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl)- (1→4) -*O*-(2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl)-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-iodo-α-D-mannopyranosyl 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranoside** (**12**). To a soln of glycosyl

acceptor **10** (2.0 g, 2.01 mmol) and hepta-*O*-acetyl-α-maltosyl bromide[18] **11** (2.82 g, 4.03 mmol) in abs dichloromethane (20 mL) was added tetramethylurea (0.72 g, 6.05 mmol) and silver triflate (1.04 g, 4.04 mmol) at -5 °C. The reaction mixture was stirred at rt for 1 h and at reflux for 24 h, and then filtered through a pad of filter aid directly into an aq sodium bicarbonate soln. The filtrate and dichloromethane washings were combined and washed twice with aq sodium bicarbonate soln. The organic phases were dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel (60 g) using ethyl acetate/ hexane 1:3, 1:2 and 1:1 as eluents to furnish **12** (1.74 g, 54 %) as a colourless foam: $[\alpha]_D$ +79.0 ° (*c* 0.5, chloroform); MS (FAB) *m/z* 1649.4 (37%, $[M + K]^+$), 1633.3 (58%, $[M + Na]^+$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.42 - 7.14 (m, 30H, aromat), 5.44 (dd ~ br d, 1H, $J_{1',2'}$ = 1.5 Hz, H-1'), 5.35 (dd, 1H, $J_{1''',2'''}$ = 4.0 Hz, H-1'''), 5.33 (dd ~ t, 1H, $J_{3''',4'''}$ = 9.5 Hz, H-3'''), 5.16 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 5.10 (dd ~ t, 1H, $J_{4''',5'''}$ = 8.5 Hz, H-4'''), 5.01 (dd ~ t, 1H, H-3''), 4.99, 4.84 (2 d, 2H, J_{gem} = 10.9 Hz, CH_2Ph), 4.86, 4.77, 4.69, 4.64, 4.60, 4.59, 4.48, 4.46 (8 d, 8H, 4 CH_2Ph), 4.84 (dd, 1H, $J_{2''',3'''}$ = 10.5 Hz, H-2'''), 4.75 (dd ~ t, 1H, H-2''), 4.68 (s, 2H, CH_2Ph), 4.45 (d, 1H, H-1''), 2.08, 2.06, 2.031, 2.029, 2.01, 1.97, 1.80 (7 s, 21H, OAc).

Anal. Calcd for $C_{80}H_{91}IO_{27}$ (1611.44): C, 59.63; H, 5.69; I, 7.87. Found: C, 59.88; H, 5.80; I, 7.57.

***O*-α-D-Glucopyranosyl-(1→4)-β-D-glucopyranosyl- (1→4) -3,6-di-*O*-benzyl-2-deoxy-2-iodo-α-D-mannopyranosyl 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranoside (13).** To a soln of **12** (1.58 g, 0.98 mmol) in dimethoxyethane (3.2 mL) and methanol (16 mL) was added a soln of sodium methanolate (3.2 mL of 2.0 g Na/ 100 mL methanol) at rt. The reaction mixture was stirred for 5 h at rt, neutralized with Amberlite IR 120 (H^+), and filtered. After addition of a few drops of triethylamine, the filtrate and methanol washings were concentrated. The residue was chromatographed on silica gel using ethyl acetate/ methanol/ water 48:1:1 as eluent to obtain **13** (1.11 g, 86 %) as a colorless foam: $[\alpha]_D$ +87.2 ° (*c* 0.5, methanol); MS (FAB) *m/z* 1355.2 (60 % $[M + K]^+$); 1339.3 (74 %, $[M + Na]^+$); ^1H NMR ($CDCl_3$, trace D_2O; 400 MHz) δ 7.37 -

7.14 (m, 30H, aromat), 5.33 (dd ~ s, 1H, $J_{1',2'} \leq 1.5$ Hz, H-1'), 5.11 (d, 1H, H-1'''), 5.04 (d, 1H, H-1).

Anal. Calcd for $C_{66}H_{77}IO_{20}$ (1317.19): C, 60.18; H, 5.89; I, 9.63. Found: C, 60.39; H, 5.80; I, 9.43

***O*-α-D-Glucopyranosyl-(1→4)-β-D-glucopyranosyl - (1→4) - 2-deoxy-α-D-*arabino*-hexopyranosyl α-D-Glucopyranoside (14).** A soln of **13** (1.08 g, 0.82 mmol) in ethanol (27 mL) and dioxane (6 mL) was treated with hydrogen in the presence of 5% palladium on charcoal (1.08 g) at 1.1 bar and rt for 2 h. The reaction mixture was filtered over a pad of celite and washed with ethanol/ dioxane. After addition of a few drops of triethylamine the filtrate was concentrated. The residue was chromatographed on silica gel using ethyl acetate/ methanol/ water 95:3:2 as eluent to obtain mainly the deiodinated derivative. A soln of this product (0.86 g, 0.7 mmol) in ethanol (22 mL) and water (5 mL) was hydrogenolyzed in the presence of 10% palladium on charcoal (500 mg) at 1.1 bar and rt for 24 h. The reaction mixture was filtered over a pad of celite and washed with ethanol/ water 1:1. After addition of a few drops of triethylamine, the filtrate was concentrated. The residue was filtered through a column of RP-18 (70 g). The product fractions were concentrated, and the residue was lyophilized to obtain **14** (183 mg, 34 %) as an amorphous colourless powder: $[\alpha]_D$ +103.0 ° (*c* 0.1, water); MS (FAB) *m/z* 688,8 (42 %, $[M + K]^+$); 673.0 (85 %, $[M + Na]^+$); ^1H NMR (D_2O, 400 MHz) δ 5.42 (dd, 1H, $J_{1''',2'''} = 3.7$ Hz, H-1'''), 5.32 (dd ~ br d, 1H, $J_{1',2'ax} = 2.9$ Hz, H-1'), 5.15 (d, 1H, $J_{1,2} = 3.5$ Hz, H-1'), 4.55 (d, 1H, $J_{1'',2''} = 8.0$ Hz, H-1''), 2.26 (ddd ~ dd, 1H, H-2'eq), 1.78 (ddd ~ dt, 1H, H-2'ax).

Anal. Calcd for $C_{24}H_{42}O_{20}$ (650.60): C, 44.31; H, 6.51. Found: C, 44.21; H, 6.45.

3,4,6-Tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranosyl 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranoside (15). A soln of **7** (7.97 g, 8.50 mmol) in ethanol (200 mL) and dioxane (40 mL) was treated with hydrogen for 2 h in the presence of 5% palladium on charcoal (4.0 g) at 1.1 bar and rt. The reaction mixture was filtered over a pad of celite and washed with ethanol/ dioxane.

After addition of a few drops of triethylamine the filtrate was concentrated. The residue was chromatographed on silica gel using ethyl acetate/ hexane 3:7 as eluent to obtain **15** (6.07 g, 88 %) as a yellowish syrup: $[\alpha]_D$ +84.0 ° (*c* 0.5, chloroform); MS (ionspray) *m/z* 835.0 (18 %, $[M + Na]^+$); 830.4 (100 %, $[M + NH_4]^+$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.36 - 7.25 (m, 18H, aromat), 7.16 - 7.14 (m, 2H, aromat), 5.01, 4.88 (2 d, 2H, J_{gem} = 11.0 Hz, CH_2Ph), 4.84, 4.49 (2 d, 2H, J_{gem} = 10.8 Hz, CH_2Ph), 4.78, 4.66 (2 d, 2H, J_{gem} = 12.0 Hz, CH_2Ph), 4.60, 4.48 (2 d, 2H, J_{gem} = 12.0 Hz, CH_2Ph), 2.03, 2.02, 2.01 (3 s, 9H, OAc).

Anal. Calcd for $C_{46}H_{52}O_{13}$ (812.88): C, 67.97; H, 6.45. Found: C, 67.73; H, 6.66.

3,4,6-Tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranosyl α-D-Glucopyranoside (16). A soln of **15** (13.63 g, 16.8 mmol) in ethanol (340 mL) and dioxane (70 mL) was treated with hydrogen for 5 h in the presence of 10% palladium on charcoal (7.0 g) at 1.1 bar and rt. The reaction mixture was filtered over a pad of celite and washed with ethanol. After addition of a few drops of triethylamine, the filtrate was concentrated. The residue was chromatographed on silica gel (700 g) using ethyl acetate/ methanol/ water 92:5:3 as eluent to furnish **16** (5.04 g, 67 %) as a colourless foam: $[\alpha]_D$ +121.4 ° (*c* 0.5, methanol); MS (ionspray) *m/z* 451.1 (100 %, $[M - H]^+$); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.91-3.60 (m, 6H, H-2' - H-6'), 2.07, 2.04, 2.02 (3 s, 9H, OAc).

Anal. Calcd for $C_{18}H_{28}O_{13}$ (452.42): C, 47.79; H, 6.24. Found: C, 47.98; H, 6.08.

3,4,6-Tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranosyl 4,6-*O*-(*R*)-Benzylidene-α-D-glucopyranoside (17). To a suspension of **16** (3.0 g, 6.6 mmol) in benzaldehyde (60 mL) was added zinc chloride (17.0 g, 125 mmol). The reaction mixture was stirred at rt for 4 h, then poured into a stirred mixture of petroleum ether (100 mL) and ice/ water (400 mL). The aqueous phase was extracted three times with diethyl ether. The extracts were washed with ice water and brine, dried over magnesium sulfate, and concentrated. The residue was chromatographed on silica gel (350 g) using ethyl acetate/ hexane 1:1, 2:1, and pure ethyl acetate as eluents. Product fractions were concentrated to give **17** (2.91 g, 71 %) as a colourless foam: $[\alpha]_D$ +99.4 ° (*c* 0.5, chloroform);

MS (ionspray) *m/z* 563.2 (100 %, $[M + Na]^+$); 558.2 (45 %, $[M + NH_4]^+$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.51 - 7.49 (m, 2H, aromat), 7.40 - 7.37 (m, 3H, aromat), 5.53 (s, 1H, CHPh), 2.09, 2.03, 2.02 (3 s, 9H, OAc).

Anal. Calcd for $C_{25}H_{32}O_{13}$ (540.53): C, 55.55; H, 5.97; Found: C, 55.75; H, 5.70.

3,4,6-Tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranosyl 2,3-di-*O*-Benzyl-4,6-*O*-(*R*)-benzylidene-α-D-glucopyranoside (18). To a soln of **17** (2.55 g, 4.72 mmol) in dichloromethane (6 mL) and cyclohexane (30 mL) was added benzyl 2,2,2-trichloroacetimidate (4.08 g, 16.0 mmol) followed by triflic acid (10 drops) at rt. The reaction mixture was stirred 6 h at rt, then neutralized by adding a saturated aq sodium bicarbonate soln (100 mL), and the aq phase was extracted twice with ethyl acetate. The organic phases were washed with aq sodium bicarbonate soln and brine, dried over magnesium sulfate, and concentrated. The residue was chromatographed on silica gel (190 g) using ethyl acetate/ hexane 1:4, 1:3 and 1:2 as eluents to furnish **18** (1.78 g, 52.2 %) as a colourless foam: $[\alpha]_D$ +83.4 ° (*c* 0.5, chloroform); MS (FAB) *m/z* 759.1 (100 %, $[M + K]^+$); 743.0 (52 % $[M + Na]^+$); 721.0 (70 % $[M + H]^+$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.51 - 7.49 (m, 2H, aromat), 7.40 - 7.26 (m, 13H, aromat), 5.56 (s, 1H, CHPh), 4.99, 4.86 (2 d, 2H, J_{gem} = 11.0 Hz, CH_2Ph), 4.98, 4.66 (2 d, 2H, J_{gem} = 12.0 Hz, CH_2Ph), 2.04, 2.03, 2.01 (3 s, 9H, OAc).

Anal. Calcd for $C_{39}H_{44}O_{13}$ (720.78): C, 64.99; H, 6.15. Found: C, 64.75; H, 6.30.

3,4,6-Tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranosyl 2,3,6-Tri-*O*-benzyl-α-D-glucopyranoside (19). To a soln of **18** (1.70 g, 2.36 mmol) in abs tetrahydrofuran (40 mL) were added pulverized molecular sieves (3Å, 3.8 g) at 0 °C followed by sodium cyanoborohydride (1.81 g, 28.8 mmol) and a few crystals of methyl orange. The reaction mixture was stirred for 30 min, then hydrogen chloride in diethyl ether (24 mL of a 1.37 M soln, 33 mmol) was added dropwise over 1 h at 0 °C. After stirring for 2 h at 0 °C, the orange-red reaction mixture was poured into a sodium bicarbonate soln, and tetrahydrofuran was evaporated under reduced pressure. The aq residue was extracted four times with dichloromethane. The organic phases were washed

with ice water and brine, dried over magnesium sulfate, and concentrated. The residue was chromatographed on silica gel (80 g) using ethyl acetate/ hexane 1:4→1:1 as eluents to give **19** (1.51 g, 88 %) as a colorless foam: $[\alpha]_D$ +86.0 ° (*c* 0.2, chloroform); MS (ionspray) *m/z* 745.3 (48 %, $[M + Na]^+$), 740.4(100 %, $[M + NH_4]^+$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.39 - 7.26 (m, 15H, aromat), 5.02, 4.80 (2 d, 2H, J_{gem} = 11.0 Hz, CH_2Ph), 4.76, 4.66 (2 d, 2H, J_{gem} = 12.0 Hz, CH_2Ph), 4.58, 4.53 (2 d, 2H, J_{gem} = 12.0 Hz, CH_2Ph), 2.40 (br s, 1H, 4'-OH), 2.03 (s, 6H, OAc), 2.02 (s, 3H, OAc).

Anal. Calcd for $C_{39}H_{46}O_{13}$ (722.80): C, 64.81; H, 6.42. Found: C, 64.90; H, 6.68;

***O*-(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl)- (1→4) -*O*-(2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl 3,4,6-Tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranoside (20)**. To a soln of glycosyl acceptor **19** (0.40 g, 0.56 mmol) and acetobromomaltose **11** (0.97 g, 1.38 mmol) in abs dichloromethane (5 mL) was added tetramethylurea (0.25 g, 2.75 mmol) and silver triflate (0.36 g, 1.39 mmol) at -5 °C. The reaction mixture was stirred at rt for 4 h and at reflux for 4 h, and then filtered through a pad of filter aid directly into an aq sodium bicarbonate soln. The filtrate and the dichloromethane washings were combined and washed twice with aq sodium bicarbonate soln. The organic phases were dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel (60 g) using toluene/ ethyl acetate/ methanol 78:20:2, and 77:20:3 as eluents to furnish **20** (0.58 g, 78 %) as a colourless foam: $[\alpha]_D$ +93.6 ° (*c* 0.5, chloroform); MS (FAB) *m/z* 1379.2 (60%, $[M + K]^+$), 1363.3 (22%, $[M + Na]^+$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.44 - 7.16 (m, 15H, aromat), 5.39 (dd ~ t, 1H, ΣJ = 20.0 Hz, H-3'''), 5.33 (d, 1H, $J_{1''',2'''}$ = 3.8 Hz, H-1'''), 5.21 (br d, 1H, $J_{1,2ax}$ = 2.9 Hz, $J_{1,2eq} \leq 1$ Hz, H-1), 5.15 (d, 1H, $J_{1',2'}$ = 3.8 Hz, H-1'), 4.53 (d, 1H, $J_{1'',2''}$ = 8.0 Hz, H-1''), 2.23 (ddd ~ dd, 1H, $J_{2eq,3}$ = 5.0 Hz, $J_{2eq,2ax}$ = 12.4 Hz, H-2_{eq}), 2.12, 2.07, 2.04, 2.03, 2.02, 2.01, 2.00, 1.98, 1.97, 1.92 (10 s, 3H, OAc), 1.89 (ddd ~ dt, 1H, H-2_{ax}).

Anal. Calcd for $C_{65}H_{80}O_{30}$ (1341.36): C, 58.20; H, 6.01. Found: C, 58.02; H, 5.80.

***O*-α-D-Glucopyranosyl-(1→4)-*O*-β-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl 2-Deoxy-α-D-*arabino*-hexopyranoside (21).** To a soln of **20** (1.98 g, 1.44 mmol) in dimethoxyethane (3.2 mL) and methanol (16 mL) was added a soln of sodium methanolate (4.0 mL of 2.0 g Na/ 100 mL methanol) at rt. The reaction mixture was stirred for 2 h at rt, neutralized with Amberlite IR 120 (H^+), and filtered. After addition of a few drops of triethylamine, the filtrate and methanol washings were concentrated. The residue was chromatographed on silica gel using ethyl acetate/ methanol/ water 85:10:5 as eluent to obtain **21** (0.79 g, 61 %) as a colorless foam: $[\alpha]_D$ +126.0 ° (*c* 0.2, water); MS (ionspray) *m/z* 938.4 (96 %, $[M + NH_4]^+$); ^1H NMR (D_2O, 400 MHz) δ 7.47 - 7.42 (m, 15H, aromat), 5.32 (d, 1H, $J_{1''',2'''}$ = 3.6 Hz, H-1'''), 5.29 (br d, 1H, H-1), 5.28 (d, 1H, H-1'), 4.07 (d, 1H, $J_{1'',2''}$ = 8.0 Hz, H-1''), 2.20 (ddd ~ dd, 1H, H-2_{eq}), 1.78 (ddd ~ dt, 1H, H-2_{ax}).

Anal. Calcd for $C_{45}H_{60}O_{20}$ (920.97): C, 58.69; H, 6.57. Found: C, 58.89; H, 6.80.

***O*-α-D-Glucopyranosyl-(1→4)-*O*-β-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl 2-Deoxy-α-D-*arabino*-hexopyranoside (22).** A soln of **22** (0.73 g, 0.79 mmol) in ethanol (25 mL) and water (10 mL) was hydrogenated for 18 h in the presence of 10% palladium on charcoal (490 mg) at 1.1 bar and rt. The reaction mixture was filtered over a pad of celite and washed with ethanol/ water 1:1. After addition of a few drops of triethylamine, the filtrate was concentrated. The aqueous residue was lyophilized to obtain **22** (503 mg, 97 %) as an amorphous colorless powder: $[\alpha]_D$ +151.0 ° (*c* 0.2, water); MS (ionspray) *m/z* 673.4 (100 %, $[M + Na]^+$); ^1H NMR (D_2O, 400 MHz) δ 5.42 (d, 1H, $J_{1''',2'''}$ = 3.8 Hz, H-1'''), 5.30 (br d, 1H, $J_{1,2ax}$ = 2.9 Hz, $J_{1,2eq} \leq 1$ Hz, H-1), 5.15 (d, 1H, $J_{1',2'}$ = 3.8 Hz, H-1'), 4.54 (d, 1H, $J_{1'',2''}$ = 8.0 Hz, H-1''), 2.21 (ddd ~ dd, 1H, H-2_{eq}), 1.79 (ddd ~ dt, 1H, H-2_{ax}).

Anal. Calcd for $C_{24}H_{42}O_{20}$ (650.60): C, 44.31; H, 6.51. Found: C, 44.61; H, 6.35.

ACKNOWLEDGEMENTS

We wish to thank the following colleagues for the determination of physical data: Dr. W. Arnold (NMR), Mr. W. Meister (MS), and Mr. G. Nein (MA).

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