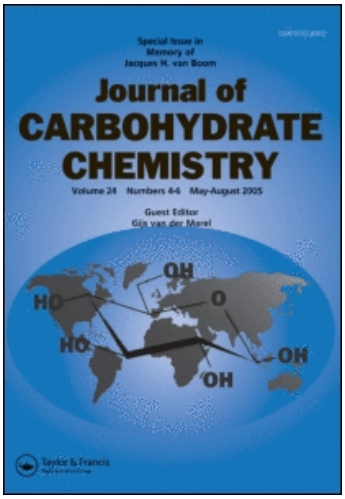

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THE SYNTHESIS OF THE 2''- AND 2'''-MONODEOXYGENATED ANALOGUES OF β-MALTOSYL-(1→4)-TREHALOSE

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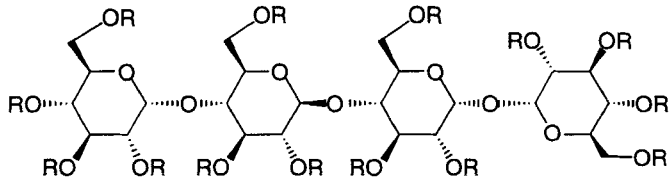
ABSTRACT

Two derivatives of β-maltosyl-(1→4)-trehalose monodeoxygenated at C-2'' or C-2''' have been synthesized in [2+2] block syntheses. *O*-(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-3,6-di-*O*-benzyl-1,2-di-*O*-acetyl-β-D-glucopyranose (**6**), prepared from the respective orthoester, was coupled to the glycosyl acceptor 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranosyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside. In the resulting tetrasaccharide **8**, the only ester group was removed and replaced by a xanthate which was reduced in a Barton-McCombie reaction to afford the 2''-deoxygenated tetrasaccharide **12**. For the synthesis of a 2'''-deoxygenated derivative, a maltose building block was assembled from two monosaccharides. The key building block was ethyl 2,3,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (**14**) which was used i) as a glycosyl acceptor in a phenylselenyl chloride mediated coupling reaction with tri-*O*-benzyl-glucal and ii) after the first coupling as a glycosyl donor to react with glycosyl acceptor **7** to give tetrasaccharide **18**. The phenylselenyl group was reduced with tributyltin hydride on the disaccharide level. Deprotection of **18** furnished the 2'''-deoxy-maltosyl-(1→4)-trehalose **20**.



1 R = SO_3Na or H, DS ≈ 2.8[4]

2 R = H

Scheme 1

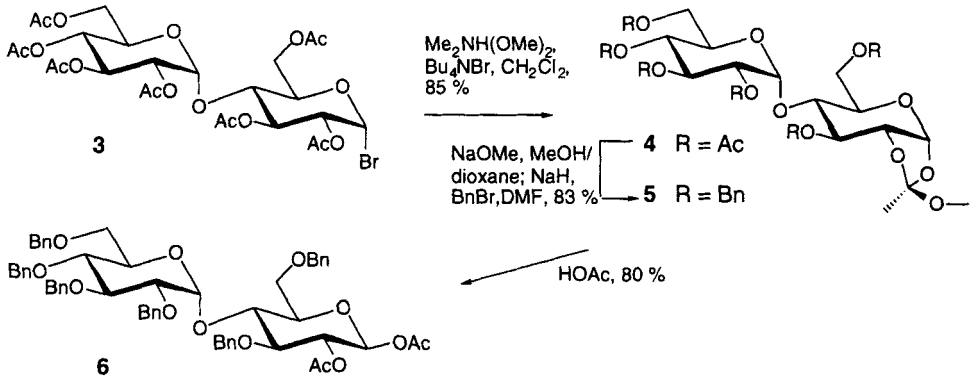
INTRODUCTION

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

Derivatives of **2** deoxygenated at the primary positions have been synthesized in block syntheses via the respective iodinated compounds.[3] The syntheses of the tetrasaccharide analogues deoxygenated at secondary carbon atoms were achieved after Barton-McCombie deoxygenation[5] of the secondary hydroxyl groups. From these we have reported the preparation of the C-4- and C-4‴-deoxy derivatives,[6] the C-3″-deoxy derivative,[7] and the C-3′- and C-3‴-deoxy derivatives.[8] In this report our syntheses of the 2″- and 2‴-deoxygenated analogues are detailed.

RESULTS AND DISCUSSION

All monodeoxygenated analogues of β-maltosyl-(1→4)-trehalose, as well as **2** itself, have been assembled in [2+2] block syntheses, which proved to be a



Scheme 2

practical approach since the maltose and trehalose building blocks are readily available. 2-Deoxymaltose has been synthesized enzymatically.[9] For the glycosylation reaction to prepare the 2''-deoxygenated β-maltosyl-(1→4)-trehalose, we foresaw an orthoester approach which allows glycosylation and activation or selective blocking at C-2 of the glycosyl donor at the same time[10,11] and should be applicable to a disaccharide. Starting with hepta-*O*-acetyl-maltosyl bromide **3**,[12] we have prepared the maltose orthoester **4**[13] using *N,N*-dimethylformamide dimethyl acetal and tetrabutylammonium bromide. Following the procedure of Banoub et al. [14] we obtained the pure *exo*-orthoester in 85 % yield after chromatography; the ^{1}H NMR spectroscopic data for the reducing end glycosyl moiety were in good agreement with the data for the glucose analogue.[15] *O*-Acetates of **4** were removed with sodium methanolate in methanol/ dioxane and replaced by benzyl protecting groups using sodium hydride in DMF and benzyl bromide to furnish the orthoester **5** in 83 % yield.

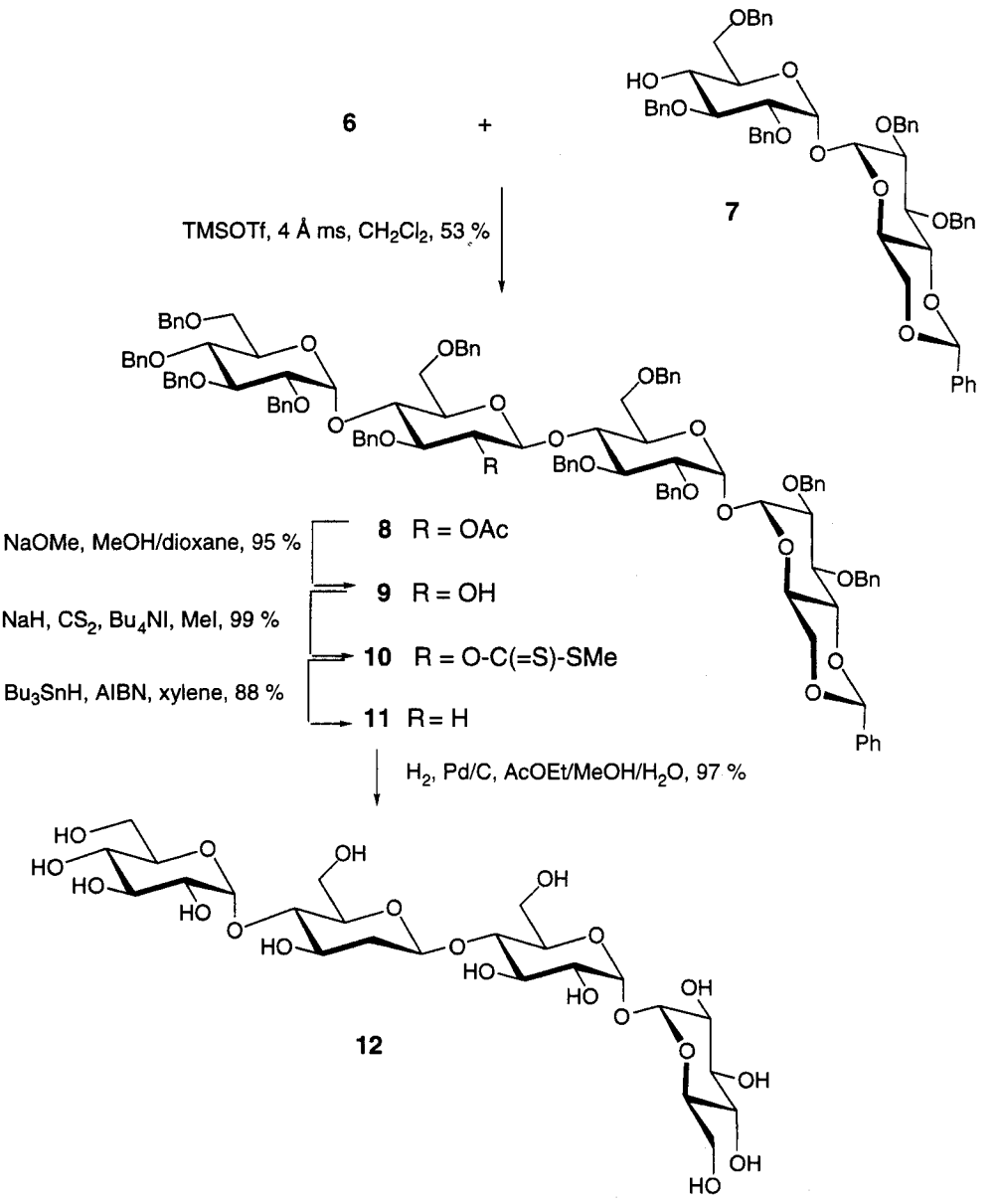
Next, we investigated the glycosylation reaction using trimethylsilyl triflate as promoter in absolute dichloromethane in the presence of 4 Å molecular sieves, the glycosyl acceptor of choice being the established trehalose derivative **7**.[3,16-21] In this reaction, the main products were the silylated glycosyl acceptor and the hydrolyzed orthoester (data not shown).

Therefore, the orthoester **5** was opened by glacial acetic acid to afford the anomeric β-acetate **6** selectively.[22] Reaction of this glycosyl donor with the trehalose glycosyl acceptor **7** using trimethylsilyl triflate as promoter in absolute dichloromethane as solvent gave, in the presence of 4 Å molecular sieves, the tetrasaccharide **8** in 53 % yield. The distinction by ^{1}H NMR spectroscopy of this saccharide from its isomeric orthoester was not straightforward since the acetate signal observed at high field (δ 1.60 ppm) might be attributed to an orthoester methyl signal (δ 1.68 ppm for **5** and δ 1.74 ppm for **4**) or to an acetate signal up-field shifted by interaction with the 3''-*O*-benzyl group (δ 1.68 ppm for the 2-*O*-acetate in **6**) or the 6'-*O*-benzyl group, usually observed in the range of δ 1.71 - 1.73 ppm.[3,6] When the 2''-*O*-acetate was cleaved after treatment with sodium methoxide in methanol/ dioxane to give **9** (95 %), the glycosidic structure of the tetrasaccharide was secured.

The now only available hydroxyl group at C-2'' was planned to be reduced in a Barton-McCombie reaction. Unexpectedly, no reaction was observed upon treatment of **9** with 1,1'-thiocarbonyldiimidazole under the usual reaction conditions, probably due to steric hindrance. Thus, a sterically less demanding xanthogenate was targeted. Treatment of **9** with sodium hydride and carbon disulfide in the presence of tetrabutylammonium iodide and methyl iodide furnished **10** in quantitative yield. Reduction with tributyltin hydride in refluxing xylene in the presence of azoisobutyronitrile (AIBN) as a radical starter afforded the monodeoxy tetrasaccharide **11** in 88 % yield. Carrying out the reaction in toluene as solvent led to a significantly lower yield.

Deprotection of **11** by hydrogenation under neutral reaction conditions in ethyl acetate/ methanol/ water gave in 97 % yield the free tetrasaccharide **12**. During the work-up of the reaction mixture, base had to be added to avoid partial degradation. Compound **12** constitutes the 2''-deoxygenated analogue of tetrasaccharide **2**.

For the synthesis of the tetrasaccharide deoxygenated at C-2''', a 2'-deoxygenated maltosyl donor was required. The preparation of the methyl

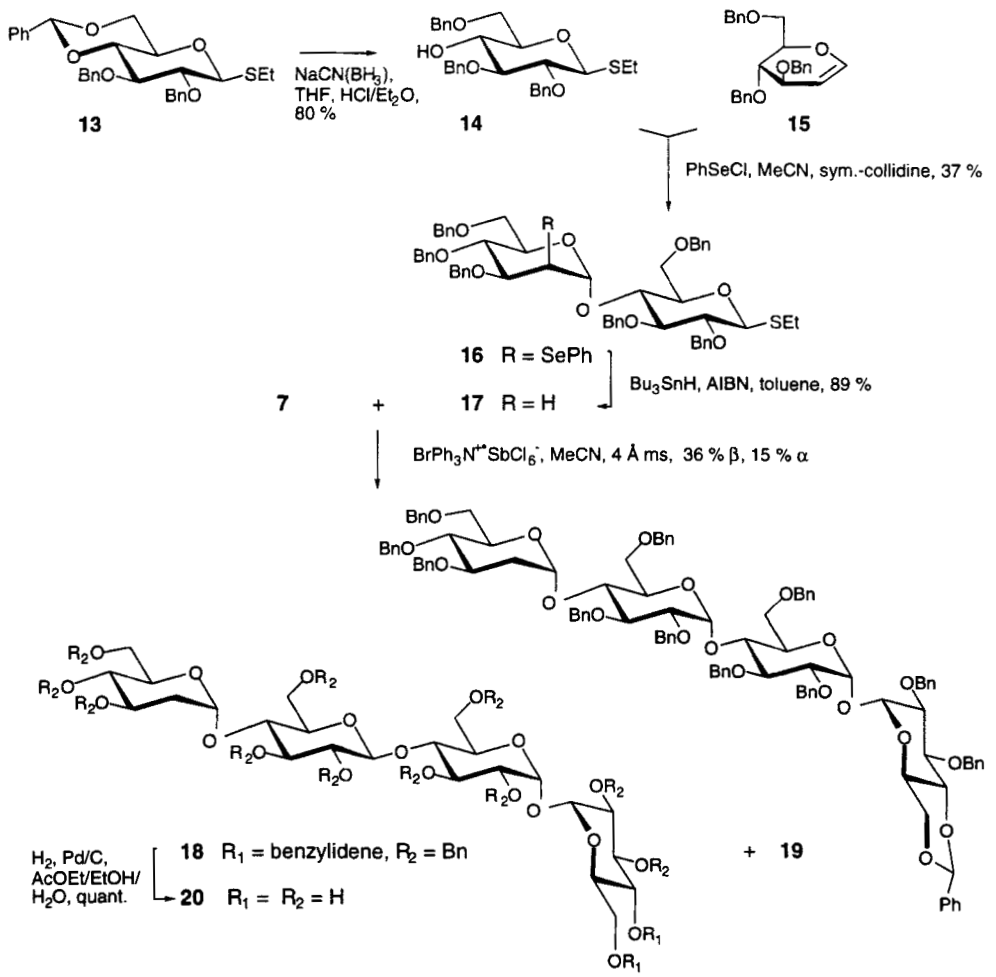


Scheme 3

glycoside of 2'-deoxy-maltose has been reported.[23] In this case it seemed indeed more appropriate to build up a maltose derivative from two monosaccharide units rather than to invest in a more complicated protective group scheme on the disaccharide level. For the preparation of 2-deoxyoligosaccharides a number of synthetic variants are at our disposal which have been competently reviewed.[24] Our choice in this case was the phenylselenyl procedure advocated by Sinaÿ and collaborators.[25] Whereas the thioglycoside **14**[26] served as a glycosyl acceptor it is at the same time latently activated at the anomeric center to function as a glycosyl donor. This hydroxyl compound was obtained from the benzylidenated precursor **13**[27] by treatment with sodium cyanoborohydride, and the reaction was advantageously carried out at low temperature (0 °C) to increase the yield of **14** to 80 %.

The glycosyl acceptor **14** was coupled with commercially available tri-*O*-benzyl-glucal **15** in the presence of phenylselenyl chloride to afford the 2'-phenylselenylated disaccharide **16** in 37 % yield after chromatography. Regarding the high activity of phenylselenyl triflate as glycosylation promoter of thioglycosides,[28] it is interesting to note that phenylselenyl chloride in this reaction did not interfere with the thioglycoside. The phenylselenyl group in **16** was then removed by reduction with tributyltin hydride in refluxing toluene in the presence of AIBN as a radical starter and furnished the deoxygenated disaccharide **17** in 89 % yield. Also under these reaction conditions the thioglycoside was not effected.

The thioglycoside **17** was activated employing the one-electron-transfer reagent tris(4-bromophenyl)ammoniumyl hexachloroantimonate[29] and was coupled to the trehalose glycosyl acceptor **7**. Acetonitrile was the solvent of choice to favor the formation of a β-D-glycosidic bond.[30,31] Furthermore, the glycosylation was carried out at low temperature which was reported to exert a favorable influence on the β/α-ratio.[29] Nevertheless, the ratio of tetrasaccharides **18/19** could not be increased above 7:3 with combined yields ranging from 52 - 58 %. With *N*-iodosuccinimide/ triflic acid as promoter[32] an even lower β/α-ratio of 3:2 was found, with the combined yields in the same range



Scheme 4

as above (data not shown). The desired tetrasaccharide **18** was deprotected by hydrogenation in the presence of palladium-on-charcoal to quantitatively yield the target tetrasaccharide **20**, the 2‴-deoxygenated analogue of **2**.

The investigation of the antiproliferative activities of the highly sulfated derivatives of the deoxygenated tetrasaccharides **12** and **20** revealed that the removal of sulfates at C-2″ and C-2‴ had no influence on activity[2] 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 recorded on API III Sciex, Perkin Elmer (ionspray) or MS 902 (FAB) with data system DS 2050 (VG).

***O*-(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl)-(1→4)-3,6-di-*O*-acetyl-1,2-*O*-[(S)-1-methoxyethylidene]-α-D-glucopyranose (4).** To a soln of hepta-*O*-acetyl-α-maltosyl bromide[12] (**3**, 5.02 g, 7.18 mmol) in dichloromethane (20 mL) was added tetrabutylammonium bromide (2.32 g, 7.2 mmol) and *N,N*-dimethylformamide dimethyl acetal (1.15 mL, 8.63 mmol), and the reaction mixture was heated to reflux for 16 h. The soln was diluted with dichloromethane and extracted with water. The organic phases were dried over sodium sulfate, concentrated, and purified by flash chromatography using toluene/ ethyl acetate 3:2 as eluent to furnish pure **4** (3.97 g, 85 %): mp 134 °C (dichloromethane/ hexane), lit.[13] 161 - 162 °C (MeOH, exo/endo ratio unknown); $[\alpha]_D$ +99 ° (*c* 0.3, chloroform), lit.[13] $[\alpha]_D$ +93.2 ° (*c* 0.7); MS (thermospray) *m/z* 668 ($[M + NH_4]^+$), 619 ($[M + H - CH_3OH]^+$); ^1H NMR ($CDCl_3$, 400 MHz; 1D TOCSY) δ 5.73 (d, 1H, $J_{1,2}$ = 5.4 Hz, H-1), 5.52 (d, 1H, $J_{1',2'}$ = 4.0 Hz, H-1'), 5.41 (dd ~ t, 1H, $J_{3',4'}$ = 9.5 Hz, H-3'), 5.06 (dd ~ t, 1H, $J_{4',5'}$ = 9.9 Hz, H-4'), 5.05 (dd ~ br d, 1H, H-3), 4.87 (dd, 1H, $J_{2',3'}$ = 10.3 Hz, H-2'), 4.33 (ddd, 1H, $J_{2,4}$ = 1.2 Hz, $J_{2,3}$ = 2.4 Hz, H-2), 4.30 (dd, 1H, $J_{5,6a}$ = 2.0 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6a), 4.24 (dd, 1H, $J_{5',6a'}$ = 4.4 Hz, $J_{6a',6b'}$ = 12.5 Hz, H-6a'), 4.20 (dd, 1H, H-6b), 4.07 (dd, 1H, 6-b'), 4.03 (ddd, 1H, H-5'), 3.89 (ddd, 1H, $J_{4,5}$ = 8.8 Hz, $J_{5,6b}$ = 5.6 Hz, H-5), 3.65 (ddd ~ br d, 1H, $J_{3,4} \approx 1$ Hz, H-4), 3.28 (s, 3H, OMe), 2.13, 2.11 (2 s, 6H, OAc), 2.09 (s, 6H, OAc), 2.04, 2.02 (2 s, 6H, OAc), 1.74 (s, 3H, Me).

***O*-(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-3,6-di-*O*-benzyl-1,2-*O*-[(S)-1-methoxyethylidene]-α-D-glucopyranose (5).** To a soln of **4** (3.725 g, 5.73 mmol) in methanol (10 mL) and dioxane (10 mL) was added a catalytic amount of sodium (few mgs). After 1 h the solvents were evaporated, and the crude residue was taken up in DMF (200 mL). At 0 °C, sodium hydride

(80 %, 2.06 g, 68.7 mmol) was added. The reaction mixture was stirred for 1 h at rt. Again at 0 °C, benzyl bromide (4.9 mL, 41.2 mmol) was added. After 16 h at rt, methanol was added at 0 °C, then the solvents were evaporated. The residue was partitioned between water and dichloromethane. Organic phases were died over sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography using ethyl acetate/ hexane 1:4 as eluent to afford pure **5** (4.47 g, 83 %): $[\alpha]_D$ +53 ° (*c* 0.4, chloroform); MS (FAB) *m/z* 977 ($[M + K]^+$), 961 ($[M + Na]^+$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (~d, 1H, aromat), 7.29 - 7.21 (m, 27H, aromat), 7.13 - 7.11 (m, 2H, aromat), 5.80 (d, 1H, $J_{1,2}$ = 5.3 Hz, H-1), 5.16 (d, 1H, $J_{1',2'}$ = 3.6 Hz, H-1'), 4.42 (ddd, 1H, $J_{2,4} \approx 1$ Hz, $J_{2,3}$ = 3.0 Hz, H-2), 3.96 (dd ~ t, 1H, $J_{3,4}$ = 3.6 Hz, H-3), 3.28 (s, 3H, OMe), 1.68 (s, 3H, Me).

Anal. Calcd for $C_{57}H_{62}O_{12}$ (939.11): C, 72.90; H, 6.65. Found: C, 73.12; H, 6.74.

***O*-(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)- (1→4) -3,6-di-*O*-benzyl-1,2-di-*O*-acetyl-β-D-glucopyranose** (**6**). A soln of **5** (1.521 g, 1.62 mmol) in glacial acetic acid was kept at rt for 1 h and concentrated. Residual acetic acid was co-evaporated with toluene. The residue was purified by flash chromatography using ethyl acetate/ hexane 1:3 as eluent to afford pure **6** (1.246 g, 80 %): $[\alpha]_D$ +43 ° (*c* 0.25, chloroform); MS (FAB) *m/z* 1005 ($[M + K]^+$), 989 ($[M + Na]^+$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 - 7.10 (m, 30H, aromat), 5.65 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1), 5.44 (d, 1H, $J_{1',2'}$ = 3.6 Hz, H-1'), 5.17 (dd, 1H, $J_{2,3}$ = 8.5 Hz, H-2), 2.07, 1.68 (2 s, 6H, OAc).

Anal. Calcd for $C_{58}H_{62}O_{13}$ (967.12): C, 72.03; H, 6.46. Found: C, 72.13; H, 6.78.

***O*-(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)- (1→4)-*O*-(2-*O*-acetyl-3,6-di-*O*-benzyl-β-D-glucopyranosyl) - (1→4) - 2,3,6-tri -*O*-benzyl -α-D-glucopyranosyl 4,6-*O*-(*R*)-benzylidene-2,3-di-*O*-benzyl-α-D-glucopyranoside** (**8**). To a soln of anomeric acetate **6** (966 mg, 1.0 mmol) and glycosyl acceptor **7** (878 mg, 1.0 mmol) in abs dichloromethane (10 mL) in the presence of powdered

molecular sieves (4 Å, ca. 1 g) was added trimethylsilyl triflate (270 µL, 1.5 mmol) at -30 °C. After 3 h triethylamine (1 mL) was added, and the reaction mixture was filtered over filter aid, which was washed with dichloromethane. The filtrates were washed with water, dried over sodium sulfate, and concentrated. The residue was purified by flash chromatography using ether/ hexane 1:1 as eluent. Product containing fractions were rechromatographed using dichloromethane/ 3 % → 5 % ethyl acetate as eluent to afford pure **8** (948 mg, 53 %): $[\alpha]_D$ +65 ° (*c* 0.5, chloroform); MS (FAB) *m/z* 1826 ([M + K]$^+$), 1810 ([M + Na]$^+$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.51 - 7.48 (m, 2H, aromat), 7.42 - 7.37 (m, 4H, aromat), 7.33 - 7.11 (m, 54H, aromat), 5.53 (s, 1H, CHPh), 5.45 (d, 1H, $J_{1''',2'''}$ = 3.6 Hz, H-1'''), 5.12, 5.10 (2 d 2H, $J_{1,2} \approx J_{1',2'} \approx$ 3.7 Hz, H-1, H-1'), 1.60 (s, 3H, OAc).

Anal. Calcd for $C_{110}H_{114}O_{22}$ (1788.10): C, 73.89; H, 6.43. Found: C, 73.86; H, 6.48.

O-(2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl)- (1→4) -O-(3,6-di-O-benzyl-β-D-glucopyranosyl)- (1→4) -2,3,6-tri-O-benzyl-α-D-glucopyranosyl 4,6-O-(R)-benzylidene-2,3-di-O-benzyl-α-D-glucopyranoside (**9**). To a soln of **8** (823 mg, 0.46 mmol) in methanol (10 mL) and dioxane (10 mL) was added a catalytic amount of sodium (few mgs). After 2 h the reaction mixture was neutralized by addition of acidic ion exchange resin (IR 120 H$^+$). The resin was filtered off and washed with methanol, and the filtrates were concentrated. The residue was purified by flash chromatography using toluene/ 8 % ethyl acetate as eluent to afford pure **9** (760 mg, 95 %): $[\alpha]_D$ +73 ° (*c* 0.3, chloroform); MS (FAB) *m/z* 1768 ([M + Na]$^+$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 - 7.49 (m, 2H, aromat), 7.41 - 7.37 (m, 4H, aromat), 7.34 - 7.13 (m, 52H, aromat), 7.10 - 7.03 (m, 2H, aromat), 5.63 (d, 1H, $J_{1''',2'''}$ = 3.7 Hz, H-1'''), 5.55 (s, 1H, CHPh), 5.12, 5.11 (2 d 2H, $J_{1,2} \approx J_{1',2'} \approx$ 3.8 Hz, H-1, H-1'), 4.53 (d, 1H, $J_{1'',2''}$ = 7.5 Hz, H-1''), 3.22 (d, 1H, $J_{2'',2''\text{-OH}}$ = 3.0 Hz, 2''-OH).

Anal. Calcd for $C_{108}H_{112}O_{21}$ (1746.06): C, 74.29; H, 6.47. Found: C, 74.59; H, 6.49.

O-(2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl)- (1→4) -O-[3,6-di-O-benzyl-2-O-(methylthio-thiocarbonyl)-β-D-glucopyranosyl]- (1→4) -2,3,6-tri-O-benzyl-α-D-glucopyranosyl 4,6-O-(R)-benzylidene-2,3-di-O-benzyl-α-D-glucopyranoside (10). To a soln of **9** (595 mg, 0.34 mmol) in abs tetrahydrofuran (10 mL) was added sodium hydride (80 %, 20 mg, 0.68 mmol) and tetrabutylammonium iodide (13 mg, 0.034 mmol). After stirring for 1 h, carbon disulfide (1 mL, 16.6 mmol) and methyl iodide (1 mL, 16.1 mmol) were added, and stirring was continued for 16 h at rt. Upon cooling to 0 °C, methanol was added, and the reaction mixture was concentrated. The residue was partitioned between water and dichloromethane, organic phases were dried over sodium sulfate and concentrated. This residue was purified by flash chromatography using toluene/ 8 % ethyl acetate as eluent to afford pure **10** (621 mg, 99 %): $[\alpha]_D$ +41 ° (*c* 0.3, chloroform); MS (FAB) *m/z* 1873 ([M + K]$^+$), 1856 ([M + Na]$^+$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 - 7.47 (m, 2H, aromat), 7.40 - 7.08 (m, 58H, aromat), 5.98 (dd ~ t, 1H, $J_{2'',3''}$ = 8.7 Hz, H-2''), 5.51 (s, 1H, CHPh), 5.48 (d, 1H, $J_{1''',2'''}$ = 3.5 Hz, H-1'''), 5.07, 5.03 (2 d 2H, $J_{1,2} \approx J_{1',2'} \approx$ 3.7 Hz, H-1, H-1'), 4.54 (d, 1H, $J_{1'',2''} \approx$ 8.0 Hz, H-1''), 2.30 (s, 3H, SMe).

Anal. Calcd for $C_{111}H_{114}S_2O_{21}$ (1836.23): C, 71.95; H, 6.26. Found: C, 72.35; H, 6.35.

O-(2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl)- (1→4) -O-[3,6-di-O-benzyl-2-deoxy-β-D-*arabino*-hexopyranosyl]-(1→4)-2,3,6-tri-O-benzyl-α-D-glucopyranosyl 4,6-O-(R)-benzylidene-2,3-di-O-benzyl-α-D-glucopyranoside (11). A soln of tributyltin hydride (0.75 mL, 2.8 mmol) in abs xylene (3 mL) was refluxed in the presence of a catalytic amount of AIBN for 20 min. Then a soln of **10** (496 mg, 0.27 mmol) in abs xylene (5 mL) was added dropwise via a syringe. After 2 h at reflux the reaction mixture was cooled and concentrated. The residue was purified by flash chromatography using toluene/ 8 % ethyl acetate as eluent. Residual tin compounds were removed by a second flash chromatography using ethyl acetate/ hexane 3:7 as eluent to afford pure **11** (409 mg, 88 %): $[\alpha]_D$ +64.5 ° (*c* 0.2, chloroform); MS (FAB) *m/z* 1768 ([M +

K]$^+$), 1752 ([M + Na]$^+$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 - 7.49 (m, 2H, aromat), 7.40 - 7.14 (m, 56H, aromat), 7.10 - 7.06 (m, 2H, aromat), 5.84 (d, 1H, $J_{1''',2'''}$ = 3.7 Hz, H-1'''), 5.55 (s, 1H, CHPh), 5.13, 5.11 (2 d 2H, $J_{1,2} = J_{1',2'}$ = 3.6 Hz, H-1, H-1'), 2.22 (ddd ~ dd, 1H, H-2''eq), 1.53 (ddd ~ q, 1H, H-2''ax).

Anal. Calcd for $C_{108}H_{112}O_{20}$ (1730.06): C, 74.98; H, 6.53. Found: C, 75.21; H, 6.62.

***O*-α-D-Glucopyranosyl- (1→4) -*O*-(2-deoxy-β-D-*arabino*-hexopyranosyl)-(1→4)-α-D-glucopyranosyl α-D-glucopyranoside (12).** A soln of **11** (175 mg, 0.10 mmol) in a mixture of ethyl acetate (6 mL), ethanol (3 mL) and water (1 mL) was hydrogenated in the presence of 10% palladium on charcoal (175 mg) at 1.1 bar and rt for 30 min. Triethylamine (3 mL) was added, and the reaction mixture was filtered over a pad of celite and washed with ethanol/ water 1:1. The filtrates were concentrated, and the residue was filtered through a column of Sephadex LH20 using ethanol/ water 1:1 as eluent. Product fractions were concentrated and lyophilized to obtain **12** (64 mg, 97 %) as an amorphous colourless powder: $[\alpha]_D$ +148 ° (*c* 0.3, water); MS (FAB) *m/z* 673 (100 %, [M + Na]$^+$); ^{1}H NMR (Me_2SO-d_6, 400 MHz) δ 5.02 (d, 1H, $J_{1''',2'''}$ = 3.6 Hz, H-1'''), 4.89. 4.86 (2 d 2H, $J_{1,2} = J_{1',2'}$= 3.4 Hz, H-1, H-1'), 4.62 (dd ~ br d, 1H, $J_{1'',2''ax}$ = 9.6 Hz, $J_{1'',2''eq} \leq$ 2 Hz, H-1''), 2.10 (ddd ~ dd, 1H, H-2''eq), 1.41 (ddd ~ q, 1H, H-2''ax).

Anal. Calcd for $C_{24}H_{42}O_{20}$ (650.58): C, 44.31; H, 6.51. Found: C, 44.21; H, 6.53.

Ethyl 2,3,6-Tri-*O*-benzyl-1-thio-β-D-glucopyranoside (14). To a soln of **13**[27] (3.06 g, 6.2 mmol) in abs tetrahydrofuran (40 mL) was added sodium cyanoborohydride (3.51 g, 55.9 mmol) in the presence of 4 Å powdered molecular sieves (ca. 0.5 g) and methyl orange as indicator. At 0 °C, a 1 M soln of HCl in ether was added dropwise. After 30 min, the reaction mixture was filtered, poured into ice/ sodium bicarbonate soln and extracted with first ether and then dichloromethane. The combined organic phases were dried over sodium sulfate, concentrated, and purified by flash chromatography

using toluene/ ethyl acetate 9:1 as eluent to afford pure **14** (2.46 g, 80 %) which was crystallized from ether/ hexane: mp 66 - 67 °C, lit.[26] 67 - 68 °C, lit.[27] 66 °C (from ethanol); $[\alpha]_D$ -34.5 ° (*c* 0.2, chloroform), lit.[27] $[\alpha]_D$ -38 ° (*c* 1, chloroform), lit.[26] $[\alpha]_D$ -32.3 ° (*c* 0.85, chloroform).

Ethyl *O*-(3,4,6-tri-*O*-benzyl-2-deoxy-2-phenylselenyl-α-D-mannopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (16). To a soln of glycosyl acceptor **14** (442 mg, 0.89 mmol) and glucal **15** (559 mg, 1.34 mmol) in abs acetonitrile (3 mL) was added phenylselenyl chloride (385 mg, 2.01 mmol) and sym-collidine (273 µL, 2.05 mmol) at 0 °C. After 4.5 h the reaction mixture was diluted with dichloromethane and washed with water. The organic phase was dried over sodium sulfate and concentrated. The residue was purified by flash chromatography using hexane/ ethyl acetate 9:1 as eluent to give crude **16** (609 mg) which was repurified by flash chromatography using toluene/ ethyl acetate 97:3 as eluent to furnish pure **16** (352 mg, 37 %): $[\alpha]_D$ +28 ° (*c* 0.3, chloroform); MS (FAB) *m/z* 1105 ($[M + K]^+$), 1089 ($[M + Na]^+$); ^1H NMR ($CDCl_3$, 400 MHz; 1D TOCSY) δ 7.42 - 7.40 (m ~ dd, 2H, aromat), 7.35 - 7.12 (m, 31H, aromat), 7.06 - 7.02 (m ~ t, 2H, aromat), 5.59 (d, 1H, $J_{1',2'}$ = 2.4 Hz, H-1'), 4.88, 4.69 (2 d, 2H, J_{gem} = 11.7 Hz, CH_2Ph), 4.83, 4.53 (2 d, 2H, J_{gem} = 10.1 Hz, CH_2Ph), 4.83, 4.48 (2 d, 2H, J_{gem} = 10.9 Hz, CH_2Ph), 4.61, 4.44 (2 d, 2H, J_{gem} = 12.2 Hz, CH_2Ph), 4.54, 4.44 (2 d, 2H, J_{gem} = 11.9 Hz, CH_2Ph), 4.41 (d, 1H, $J_{1,2}$ = 9.7 Hz, H-1), 4.32, 4.27 (2 d, 2H, J_{gem} = 11.2 Hz, CH_2Ph), 4.09 (m_c, 1H, $J_{3',4'} \approx$ 7.5 Hz, H-3'), 3.92 - 3.86 (m, 2H, H-4', H-5'), 3.81 (dd, 1H, $J_{5,6a}$ = 2.0 Hz, $J_{6a,6b}$ = 11.0 Hz, H-6a), 3.75 (dd ~ t, 1H, $J_{2',3'}$ = 4.5 Hz, H-2'), 3.75 (dd ~ t, 1H, $J_{4,5}$ = 8.9 Hz, H-4), 3.73 (dd, 1H, $J_{5,6b}$ = 5.4 Hz, H-6b), 3.66 (dd, 1H, $J_{5',6a'}$ = 4.0 Hz, $J_{6a',6b'}$ = 11.0 Hz, H-6a'), 3.57 (dd, 1H, $J_{5',6b'}$ = 1.0 Hz, 6-b'), 3.51 (dd ~ t, 1H, $J_{3,4}$ = 9.1 Hz, H-3), 3.39 (dd ~ t, 1H, $J_{2,3}$ = 8.5 Hz, H-2), 3.36 (ddd, 1H, H-5), 2.79, 2.77 (2 dq, 2H, J_{vic} = 7.4 Hz, J_{gem} = 12.6 Hz, SCH_2), 1.32 (t, 3H, Me).

Anal. Calcd for $C_{62}H_{66}O_9SSe$ (1066.22): C, 69.84; H, 6.24. Found: C, 69.82; H, 6.44.

Ethyl *O*-(3,4,6-tri-*O*-benzyl-2-deoxy-α-D-*arabino*-hexopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (17). To a soln of tributyltin

hydride (444 µL, 1.65 mmol) and a catalytic amount of AIBN in abs toluene (2 mL) was added dropwise a soln of **16** (352 mg, 0.33 mmol) in abs toluene (7 mL) and refluxed for 5 h. The reaction mixture was concentrated and purified by flash chromatography using toluene/ ethyl acetate 95:5 and hexane/ ethyl acetate 85:15 as eluent. Product fractions were crystallized from ethanol to give pure **17** (267 mg, 89 %): mp 89 - 90 °C; $[\alpha]_D$ +30 ° (*c* 0.25, chloroform); MS (FAB) *m/z* 933 ($[M + Na]^+$), 911 ($[M + H]^+$), 803 ($[M + H - BnOH]^+$; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35 - 7.15 (m, 30H, aromat), 5.43 (dd ~ br d, 1H, $J_{1',2'ax}$ = 3.0 Hz, $J_{1',2'eq} \leq$ 1.5 Hz, H-1'), 4.98, 4.64 (2 d, 2H, J_{gem} = 11.0 Hz, CH_2Ph), 4.91, 4.66 (2 d, 2H, J_{gem} = 10.0 Hz, CH_2Ph), 4.83, 4.47 (2 d, 2H, J_{gem} = 10.5 Hz, CH_2Ph), 4.57, 4.48 (2 d, 2H, J_{gem} = 12.0 Hz, CH_2Ph), 4.55, 4.42 (2 d, 2H, J_{gem} = 11.9 Hz, CH_2Ph), 4.54, 4.39 (2 d, 2H, J_{gem} = 12.2 Hz, CH_2Ph), 4.46 (d, 1H, $J_{1,2} \approx$ 8.5 Hz, H-1), 2.79, 2.76 (2 dq, 2H, J_{vic} = 7.6 Hz, J_{gem} = 12.6 Hz, SCH_2), 2.03 (ddd ~ dd, 1H, $J_{2'eq,2'ax}$ = 11.7 Hz, H-2'eq), 1.58 (ddd ~ dt, 1H, H-2'ax), 1.33 (t, 3H, Me).

Anal. Calcd for $C_{56}H_{62}O_9$ (911.17): C, 73.82; H, 6.86. Found: C, 73.67; H, 6.88.

***O*-(3,4,6-Tri-*O*-benzyl-2-deoxy-α-D-*arabino*-hexopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside** (**18**) and ***O*-(3,4,6-Tri-*O*-benzyl-2-deoxy-α-D-*arabino*-hexopyranosyl) - (1→4) - 2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside** (**19**). A soln of thioglycoside **17** (311 mg, 0.34 mmol) in abs acetonitrile (4 mL) containing 4 Å powdered molecular sieves (1.3 g) was stirred for 30 min. at rt. Then a soln of glycosyl acceptor **8** (250 mg, 0.28 mmol) in abs acetonitrile (4 mL) followed by a soln of tris(4-bromophenyl)ammoniumyl hexachloroantimonate (417 mg, 0.51 mmol) in abs acetonitrile (10 mL) were added dropwise at -25 °C. After 5 h at this temperature, triethylamine (1 mL) was added, and the reaction mixture was filtered over Celite and concentrated. The residue was flash chromatographed using toluene/ ethyl acetate 95:5 → 93:7 → 9:1 to obtain

crude **19** (164 mg) followed by crude **18** (386 mg). The crude α-D-linked product was purified by flash chromatography using hexane/ ethyl acetate 4:1 → 3:1 as eluent to give pure **19** (75 mg, 15 %). The crude β-D-linked product, being contaminated by some glycosyl acceptor, was treated with trimethylsilyl chloride (0.5 mL) in dichloromethane (10 mL) and triethylamine (1 mL). After 30 min the reaction mixture was concentrated. The residue was purified by flash chromatography using toluene/ ethyl acetate 93:7 and, in a second run, hexane/ ethyl acetate 4:1 → 3:1 as eluents to afford pure **18** (179 mg, 36 %).

Data of compound **18**: $[\alpha]_D$ +59.5 ° (*c* 0.25, chloroform); MS (FAB) *m/z* 1768 ([M + K]$^+$), 1752 ([M + Na]$^+$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.51 - 7.48 (m ~ dd, 2H, aromat), 7.39 - 7.14 (m, 58H, aromat), 5.52 (s, 1H, CHPh), 5.41 (dd ~ br d, 1H, $J_{1''',2'''ax}$ = 3.0 Hz, $J_{1''',2'''eq} \leq$ 1.5 Hz, H-1'''), 5.08, 5.07 (2 d ~ t, 2H, $J_{1,2} \approx J_{1',2'} \approx$ 4.0 Hz, H-1, H-1'), 4.38 (d, 1H, $J_{1'',2''} \approx$ 7.7 Hz, H-1''), 2.06 (ddd ~ dd, 1H, H-2'eq), 1.59 (ddd ~ dt, 1H, H-2'ax).

Anal. Calcd for $C_{108}H_{112}O_{20}$ (1730.06): C, 74.98; H, 6.53. Found: C, 74.88; H, 6.67.

Data of compound **19**: MS (FAB) *m/z* 1768 ([M + K]$^+$), 1752 ([M + Na]$^+$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 - 7.49 (m ~ dd, 2H, aromat), 7.42 - 7.38 (m, 5H, aromat), 7.28 - 7.13 (m, 53H, aromat), 5.58 (d, 1H, $J_{1'',2''}$ = 3.5 Hz, H-1''), 5.55 (s, 1H, CHPh), 5.45 (dd ~ br d, 1H, $J_{1''',2'''ax}$ = 3.0 Hz, $J_{1''',2'''eq} \leq$ 1.5 Hz, H-1'''), 5.20, 5.17 (2 d, 2H, $J_{1,2} = J_{1',2'}$ = 3.7 Hz, H-1, H-1'), 2.13 (ddd ~ dd, 1H, H-2'eq), 1.59 (ddd ~ dt, 1H, H-2'ax).

Anal. Calcd for $C_{108}H_{112}O_{20}$ (1730.06): C, 74.98; H, 6.53. Found: C, 74.80; H, 6.58.

***O*- (2-deoxy-α-D-*arabino*-hexopyranosyl)- (1→4) -*O*-β-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl α-D-Glucopyranoside (20)**. A soln of **18** (160 mg, 0.09 mmol) in ethyl acetate/ ethanol/water 6:3:1 (10 mL) was hydrogenated in the presence of 10 % palladium on charcoal (160 mg) at 1.1 bar for 30 min. Triethylamine (3 mL) was added, and the reaction mixture was filtered

through a pad of filter aid which was washed with ethanol/ water 1:1. The filtrates were concentrated and filtered over Sephadex LH 20 using ethanol/ water 4:1 as eluent to obtain pure **20** (60 mg) quantitatively as a colourless solid: $[\alpha]_D$ +155 ° (*c* 0.1, water); MS (FAB) *m/z* 689 ([M + K]$^+$), 673 ([M + Na]$^+$); ^{1}H NMR (D_2O, 400 MHz) δ 5.41 (dd ~ br d, 1H, H-1'''), 4.87, 4.85 (2 d, 2H, $J_{1,2} = J_{1',2'}$ = 3.7 Hz, H-1, H-1'), 4.27 (d, 1H, $J_{1'',2''}$ = 7.9 Hz, H-1''), 1.97 (ddd ~ dd, 1H, H-2'eq), 1.41 (ddd ~ dt, 1H, H-2'ax).

Anal. Calcd for $C_{24}H_{42}O_{20}$ (650.58): C, 44.31; H, 6.51. Found: C, 44.19; H, 6.54.

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