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Efficient Stereocontrolled Glycosidation of Secondary Sugar Hydroxyls by Silicon Tethered Intramolecular Glycosidation

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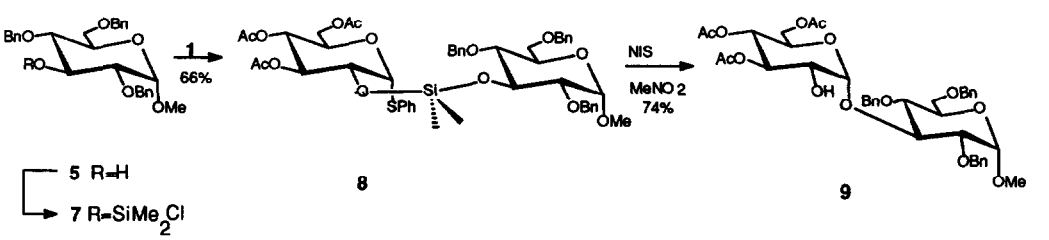
Abstract: Disaccharides containing 1,2-*cis* glycoside linkages were synthesized by an efficient stereocontrolled two step process involving a silicon tethering step, to a dimethylsilyl acetal followed by intramolecular glycosidation with N-iodosuccinimide in nitromethane.

INTRODUCTION

The chemical synthesis of glycosides is of considerable potential interest in connection with many biological[1] and medical[2] studies, since glycosides occur widespread in nature. Therefore, a tremendous amount of litterature on glycoside-synthesis exist,[3] and especially during the last decade a number of very efficient methods of forming glycosidic linkages have been developed.[4] The field is, however, still an area for specialists due to the high degree of unpredictability and lack of generality of the various methods. Contemporary intramolecular glycosidation methods,[5-10] can be seen as an effort to achieve predictability through stereocontrol and enhanced reactivity. Recently intramolecular glycosidations have been achieved by carrying out the reaction with the aglycon tethered to the 2-position of the glycosyl-donor by a carbon[5,6] or a silicon[7-10] linkage.The tethering process is somewhat cumbersome, however, requiring 2 steps. In this paper a one step procedure for preparing dimethylsilylene tethered disaccarides from the hydroxy-sugars is described, as well as an improved method of intramolecular glycosidation allowing the efficient stereocontrolled glycosidation of secondary sugar alcohols.[10]

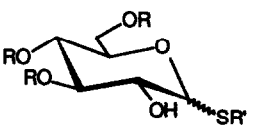
Scheme I

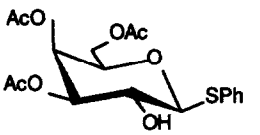


RESULTS AND DISCUSSION

It has previously been described that aliphatic alcohols and phenols can be α-glucosidated using a thioglucoside, a dimethylsilylacetal linker with N-iodosuccinimide (NIS)/trifluoromethanesulfonic acid (TfOH) as promoter.[8,9] As a continuation of this work it was decided to attempt to extend it to the synthesis of oligosaccharides. Thus, reaction of **5** (Scheme I) with excess dimethylsilyldichloride and triethylamine in dry ether allowed the isolation of the crude chlorodimethylsilyl ether **7**. The product contained several unidentified impurities, the formation of which it was not possible to avoid. Reaction of the thioglucoside **1**[8,9] with 3.6 equiv of **7** gave the dimethylsilyl acetal **8** in 66% yield. If a smaller excess of **7** was employed the yield decreased probably due to complications caused by the impurities in **7**. The identity of the product **8** was easily recognised by the two downfield peaks (-1.4, -1.8) in the ^{13}C NMR-spectrum from the diastereotopic methyl groups on the silylacetal.

Scheme II

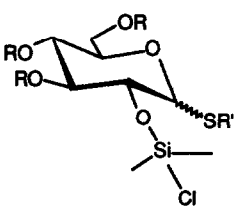




1 R=Ac, R'=Ph

2 R=Bn, R'=Et

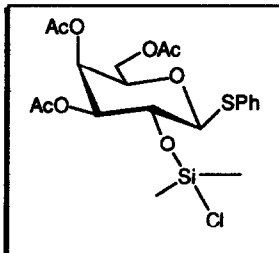
3



10 R=Ac, R'=Ph

11 R=Bn, R'=Et

α-Glucosyl donor

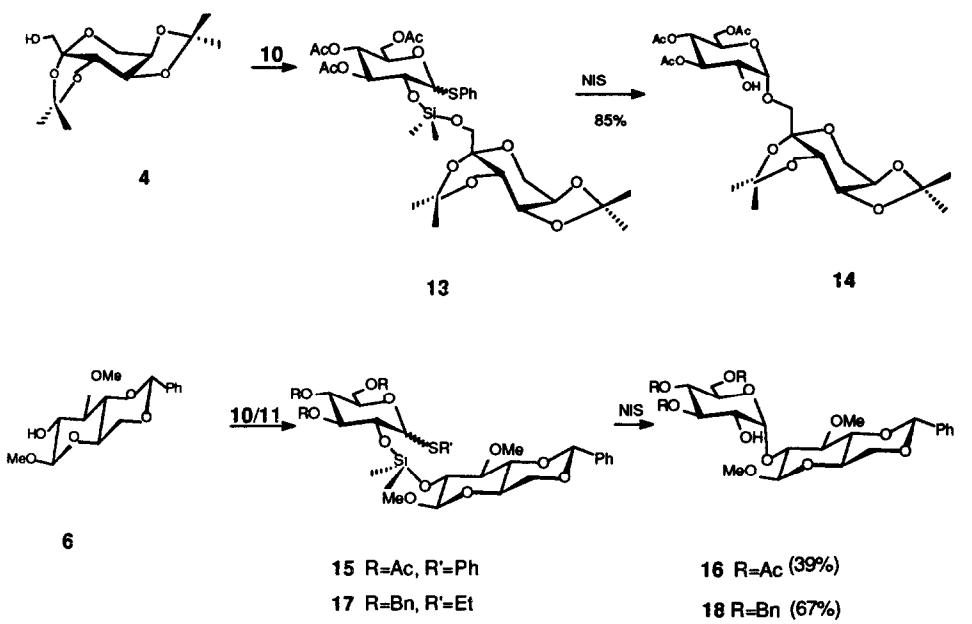


12

α-Galactosyl donor

Reaction of **8** with NIS and a catalytic amount of TfOH[4b,4c] according to the previous protocol[8,9] gave only 19% yield of α-glucoside **9**. In addition large amounts of **5** was isolated. Since NIS/TfOH had proved to be effective for the glycosidation of aliphatic alcohols regardless of steric hindrance, the low yield was probably not be caused by steric but by electronic effects, and could be due to the known reduced nucleophilicity of sugar hydroxy groups. Thus a slower intramolecular substitution could allow TfOH to cleave the silylene linkage faster than glycosidation could occur. If TfOH was omitted no activation of the thioglycoside occurred due to its "disarmed" nature. However by employing the dipolar, aprotic solvent $MeNO_2$ and increasing the temperature to 100°C **8** reacted with NIS alone to give the desired **9** in 74% yield. No β-glucoside was detected in the reaction product. At this point, improvement of the synthesis of the silylenelinkage seemed in order. The most generally applicable synthesis would be to convert thioglycoside donors **1-3** into the chlorodimethylsilyl ethers **10-12** (Scheme II). Aglycons could then be converted to glycosides simply by facile silylation with **10**, **11** or **12** followed by treatment with NIS. It was found that the unstable chlorodimethylsilyl ethers were handled much better when isolation was not attempted. Thus reaction

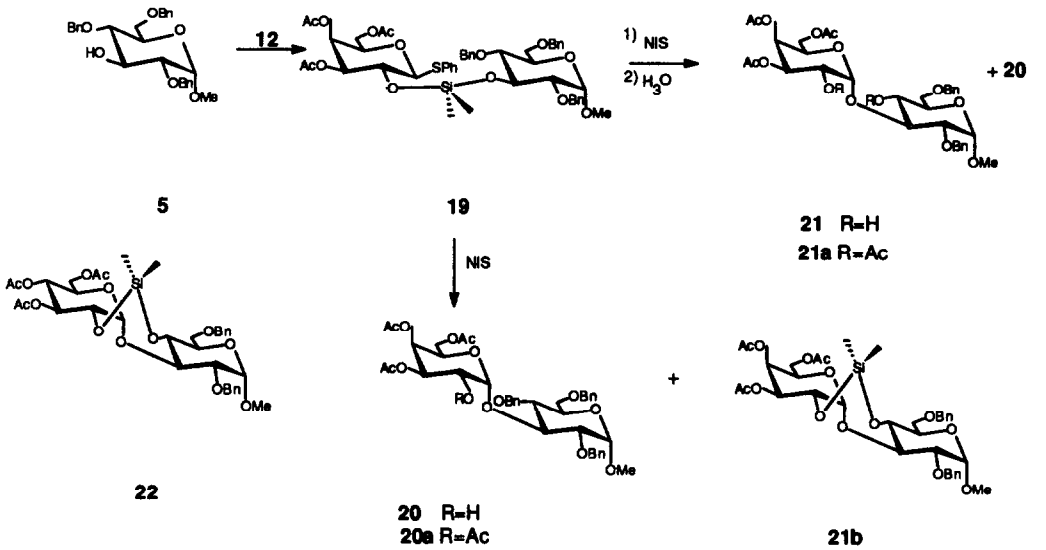
Scheme III



of **1** with 5 equiv. of Me_2SiCl_2 in pyridine/toluene followed by removal of excess Me_2SiCl_2 by distillation resulted in a solution of chlorosilyl ether **10** in pyridine/toluene. Alcohols could now easily be silylated with this solution (Scheme III). Thus reaction of the fructose-derivative **4**[12] with 1.5 equiv. of **10** gave the silylacetal **13** in 72% yield, while the glucose-derivative **6**[13] reacted with 1.6 equiv. of **10** to give silylacetal **15** in 76% yield. Treatment of **13** with NIS in $MeNO_2$ at 100°C for 1 h gave the α-glucoside **14** in 85% yield. Reaction of **15**

with NIS in $MeNO_2$ at 100º was slow and required 4 h to run to completion giving 39% of α-glucoside **16**. In neither of the two cases were any β-glucoside detected. In the latter case the crude reaction product was, despite the low yield, extremely pure so the loss of material was probably caused by over-oxidation during the long reaction time. Therefore, the glycosidation was repeated with the armed glycosyl donor **2**, which could be reacted under milder conditions. A solution of chlorosilyl ether **11** was prepared from **2**, Me_2SiCl_2 and pyridine, and **6** was silylated with 1.25 equiv. of this solution resulting in a 93% yield of the silylacetal **17**. Reaction of **17** with NIS (2.5 equiv.) in $MeNO_2$ at 25ºC for 4 h gave the α-glucoside **18** in 67% yield. The extension of the method to α-galactosidation was then attempted. Phenylthiogalactoside **3** was prepared in 56% yield from 3,4,6-tri-*O*-acetyl-β-D-galactosyl chloride[14] by substitution with potassium benzenethiolate, and converted to a solution of the chlorodimethylsilyl ether **12** by reaction with excess

Scheme IV

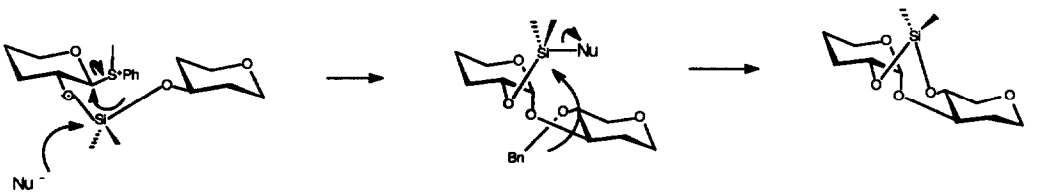


Me_2SiCl_2 and pyridine in toluene. Silylation of **5** with 1.5 equiv. of **12** gave the silylacetal **19** in 73% yield (Scheme IV). However, reaction of **19** with NIS (2.5 equiv.) in $MeNO_2$ for 1 2/3 h did not give one but two glycosides: the expected α-galactoside **20** and the 4-de-*O*-benzylated α-galactoside **21** in 32% and 49% yield, respectively. The structure of **21** was determined from the following facts: 1) It was an *O*-glycoside as seen from two ^{13}C NMR signals at 100.7 and 97.9 ppm. 2) It was an α-galactoside as seen from the ^1H NMR dublet at δ 5.35 having a coupling constant of 3.5 Hz. 3) Acetylation of **20** and **21** introduced one acetylgroup in **20** and two in **21** giving tetraacetate **20a** and pentaacetate **21a**, respectively. 4) The ^1H NMR spectrum of pentaacetate **21a** showed a double-dublet at low field (δ 5.05) with two large couplings (9.5 and 10.0 Hz) meaning that either OH-3 or OH-4 of **21** had been acetylated. 5) Irridiation of the triplet at δ 4.20 in the ^1H

NMR spectrum of **21a** converted the double dublets at 5.05 and 3.55 to dublets proving that OH-3 was the glycosylated hydroxy group.

The formation **21** was puzzling partly because no other debenzylated sugars were isolated and partly because debenzylation had not been observed in the reaction of **8** with NIS. Therefore the reaction of **19** was repeated, but the usual quenching with hydrochloric acid was avoided. In this case **20** and the tricyclic dimethylsilylene derivative **21b** was isolated in 31% and 46% yield respectively. Thus **21** was obviously formed from **21b** during work-up, and **21b** seemed the direct product of the debenzylation. To explain this, the mechanism outlined in Scheme V can be suggested. The intramolecular reaction must involve a nucleophilic substitution at silicon, probably by succinimide (Nu = $(CH_2CO)_2N^-$), since the formation of a positive charge on silicon is unlikely. Reaction between the silylsuccinimide and I_2 formed in the reaction, could be expected to lead to NIS and a silyl iodide known to be a debenzylation agent. Finally intramolecular debenzylation would lead to **21b**. Apparently the formation of the 8 membered ring was not unfavorable.

Scheme V



As a result of this mechanism, debenzylation should be a process occurring after the glycosidation. To investigate this, the reaction of **8** with NIS was reinvestigated. Reaction for 3 h in $MeNO_2$ at 100°C, followed by non-acidic work-up led to α-glucoside **9** (29%) and 4,3'-dimethylsilylene derivative **22** (22%, Scheme IV). So the debenzylation appeared to be general, but much slower in this case.

In conclusion, this paper describes an efficient protocol for stereocontrolled synthesis of α-glucosides or α-galactosides in oligossacharides by a two step intramolecular procedure: An improved method of preparing dimethylsilyl linked dissacharides allows easy synthesis of the precursors for intramolecular glycosidation which is efficiently carried out with NIS in $MeNO_2$. In difficult cases use of an "armed" glycosyl donor improves the yield.

EXPERIMENTAL

^{13}C-NMR spectra were recorded on a Bruker AC-250 instrument with D_2O as solvent using 1,4-dioxane as the internal reference (67.40 ppm). Melting points are uncorrected. Optical rotations were measured on a Perkin Elmer 141 polarimeter. Microanalyses were carried out by Leo Microanalytical Laboratory. Concentrations were performed on a rotary evaporator at a temperature below 40°C.

Ethylthio 3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (2). Ethylthio 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (3.1 g, 5.8 mmol), prepared from 3,4,6-tri-*O*-benzyl-1,2-*O*-(methoxyethylidene)-α-D-glucopyranose[15] using the analoguos procedure described for mannose[16], was dissolved in dry MeOH (40 ml), and Na (50 mg) in 10 ml MeOH was added. After stirring for 18 h the solution was neutralized by addition of excess Amberlite IR-120 cation-exchange resin (H^+), stirring until neutral, filtration and concentration to

give sirupy **2** (2.71 g, 95%). Crystallization from ether-pentane gave 2.07 g (72%). Mp: 61-62°C $[\alpha]_D^{20}$ -14.4° (c 1.0, CH_2Cl_2) ^{13}C NMR ($CDCl_3$): δ 137.9-138.4, 127.4-128.3 (Ar's), 85.9 (C-1), 85.9, 79.3, 77.3, 75.1, 74.9, 73.3, 73.1 (C-2-C-5, Bn's), 68.9 (C-6), 24.1 (CH_2S), 15.3 (Me). ^1H NMR ($CDCl_3$): δ 7.1-7.4 (m, 15H, Ar's), 4.8-5.0 (m, 3H, Bn's), 4.5-4.6 (m, 3H, Bn's), 4.3 (d, 1H, J_{12} = 9 Hz, H-1), 3.4-3.8 (m, 6H, H-2-H-6b), 2.70 (2 dq, 2H, CH_2S), 1.30 (t, 3H, J = 7.0 Hz, Me). Anal. Calc for $C_{29}H_{34}O_5S$: C, 70.42; H, 6.93. Found: C, 70.43; H, 6.85.

Phenylthio 3,4,6-tri-*O*-acetyl-β-D-galactopyranoside (**3**). A solution of K (153 mg, 3.9 mmol) in dry MeOH (5 ml) was prepared under Ar, and cooled to -78°C. Thiophenol (0.55 g, 5 mmol, 1.3 eq) was added, and after 10 min at this temperature 3,4,6-tri-*O*-acetyl-β-D-galactopyranosyl chloride[14] (1.16 g, 3.6 mmol) in MeOH (3 ml) was added. The mixture was allowed to reach 25°C, and then stirred for 6 h. Concentration, addition of EtOAc (50 ml), washing of the organic layer with $NaHCO_3$-solution (25 ml), drying and concentration left a sirup (1.37 g). Flash-chromatography (EtOAc-Pentane 1:2) gave **3** (803 mg, 56 %) as a faster moving product. Crystallization from ether gave mp. 117-119°C. $[\alpha]_D^{20}$ + 10.7° (*c* 1.3, CH_2Cl_2). ^{13}C NMR ($CDCl_3$): δ 132.8, 128.9, 128.3 (Ar), 88.7 (C-1), 74.4, 73.7, 67.3, 66.9 (C-2, C-3, C-4, C-5), 61.7 (C-6). 20.4-6 (3C, Ac's). ^1H NMR ($CDCl_3$) δ 7.6 (m, 2H, Ar), 7.3 (m, 3H, Ar). 5.4 (dd, 1H, J_{34} = 4.0 Hz, J_{45} = 1.0 Hz, H-4), 4.95 (dd, 1H, J_{23} = 9.5 Hz, H-3), 4.65 (d, 1H, J_{12} = 9.5 Hz, H-1), 4.2 (dd, 1H, $J_{6'6}$ = 11.5 Hz, J_{56} = 7.0 Hz, H-6), 4.1 (dd, 1H, $J_{56'}$ = 6.0 Hz, H-6'), 3.95 (ddd, 1H, H-5), 3.8 (t, 1H, H-2), 2.5 (bs, 1H, OH), 2.0-2.1 (3s, 9H, Ac's). Anal. Calc. for $C_{18}H_{22}O_8S$: C, 54.26; H, 5.57. Found: C, 53.97; H, 5.68.
Eluting the coloumn with EtOAc gave a slower moving product of methyl 3,4,6-tri-*O*-benzyl-α,β-D-glucopyranoside (246 mg).

Methyl 3-*O*-chlorodimethylsilyl-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (**7**). To methyl 2,4,6-tri-*O*-benzyl-α-D-glucopyranoside[11] (**5**, 4.64 g, 10 mmol) in dry ether (5 ml) under N_2 at 0°C was added dimethylsilyldichloride (2.41 ml, 258 g, 20 mmol) followed by Et_3N (1.39 ml, 1.01 g, 10 mmol). After stirring 10 min at 0°C, filtration and concentration of the filtrate left a sirupy residue of crude **7** (5.19 g, 93%). ^{13}C NMR ($CDCl_3$): δ 137.9-138.5 and 127.2-128.4 (Ar), 97.7 (C-1), 79.3, 77.9, 75.6, 74.7, 73.4, 73.3, 69.5 (C-2, C-3, C-4, C-5, 3 Bn), 54.8 (OMe), 2.9, 2.7 (Me_2Si).

Phenylthio 2-*O*-dimethyl-(1-*O*-methyl-2,4,6-tri-*O*-benzyl-α-D-glucopyranos-3-oxyl)-silyl-3,4,6-tri-*O*-acetyl-α-D-glucopyranoside (**8**). Phenylthio 3,4,6-tri-*O*-acetyl-α-D-glucopyranoside[9] (**1**, 100 mg, 0.25 mmol) dissolved in pyridine (0.5 ml) and THF (2 ml) was stirred under N_2. A solution of **7** (502 mg, 0.9 mmol, 3.6 eq.) in a small amount of THF (0.2 ml) was added. After stirring 2 h at 25°C ether (50 ml) was added, and the solution washed with water (10 ml) and 10% NaCl-solution (10 ml). Drying ($MgSO_2$), filtration and concentration gave a sirupy residue (553 mg). Flash-chromatography in EtOAc-pentane 1:10 followed by 1:6 followed by 1:4 gave the silyl acetal **8** (151 mg, 66%). $[\alpha]_D^{20}$ + 137.0° (*c* 0.4, CH_2Cl_2), ^{13} C NMR ($CDCl_3$): δ 170.3, 169.7, 169.7 (Ac's), 137.6-138.1 (Ar), 126.8-131.0 (Ar), 97.8 (C-1), 87.9 (C-1'), 79.7, 78.3, 74.6, 74.2, 73.3 (2C), 73.1, 70.3, 69.5, 68.6, 68.4, 67.9 (C-2 - C-6, C-2'-C-5', Bn's), 62.1 (C-6'), 54.8 (OMe), 20.5-20.7 (Ac's), -1.4, -1.8 (Me_2Si). ^1H NMR ($CDCl_3$): δ 7.2-7.5 (m, 20 H, Ar's), 5.8 (d, 1H, $J_{1'2'}$ = 5.5 Hz, H-1'), 5.3 (t, 1H, $J_{3'4'}$ = $J_{4'5'}$ =9.5 Hz, H-4'), 4.95 (dd, 1H, $J_{2'3'}$ =10 Hz, H-3'), 4.90 (d, 1H, Bn), 4.80 (d, 1H, Bn), 4.1-

4.7 (m, 9H), 4.0 (dd, 1H, $J_{6'a6'b}$ = 12.0 Hz, $J_{5'6'a}$ = 2.0 Hz, H-6a'), 3.3-3.7 (m, 4H), 3.35 (dd, 1H, H-2'), 3.3 (s, 3H, MeO), 2.0-2.1 (3s, 9H, Ac's), 0.25, 0.20 (2s, 6H, Me_2Si).
Anal. Calc. for $C_{48}H_{58}O_{14}SiS \times H_2O$: C, 61.52; H, 6.45. Found: C, 61.69; H, 6.37.

Methyl 3-*O*-(3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl)-2,4,6-tri-O-benzyl-α-D-glucopyranoside (**9**). To a solution of **8** (93 mg, 0.10 mmol) in $MeNO_2$ (5 ml) was added N-iodosuccinimide (75 mg, 3.3 eq), and the mixture was refluxed 1 h. Hydrochloric acid (25 ml, 1M) was added, and the water-layer was extracted with EtOAc (3 x 25 ml). The combined organic layers were washed with $NaHCO_3$ (10 ml, saturated) and $Na_2S_2O_3$-solutions (10 ml, 5%). Drying (Na_2SO_4) filtration and concentration gave a syrup (102 mg). Flash-chromatography in EtOAc-Pentane 1:4 followed by 1:2 followed by 1:1 gave the glycoside **9** (56 mg, 74%) as a clear syrup. $[\alpha]_D^{20}$ + 9.8° (c 1.1, CH_2Cl_2), ^{13}C NMR ($CDCl_3$): δ 171.1, 170.7, 169.5 (Ac's), 137.5, 127.6-128.5 (Ar), 98.4 (C-1'), 97.3 (C-1), 78.6, 77.9, 76.6, 74.1, 73.6, 73.5, 72.4, 71.1, 69.8, 68.1, 67.7, 67.5 (C-2 - C-6, C-2' - C-5', Bn's), 61.5 (C-6'), 55.0 (OMe), 20.6-20.8 (Ac's), ^1H NMR ($CDCl_3$): δ 7.1-7.4 (m, 15H, Ar's), 5.45 (d, 1H, $J_{1'2'}$= 3.5 Hz, H-1'), 5.25 (t, 1H, $J_{3'4'} = J_{4'5'}$ = 9.5 Hz, H-4'), 4.95 (t, 1H, $J_{2'3}$ = 10 Hz, H-3'), 4.8 (d, 1H, Bn), 4.75 (d, 1H, J_{12} = 3.5 Hz, H-1), 4.7 (d, 1H, Bn), 4.4 - 4.6 (m, 5H), 4.15 (m, 1H), 3.6 - 3.9 (m, 7H), 3.5 (dd, 1H, H-2'), 3.35 (s, 3H, OMe), 2.0-2.1 (3s, 9H, Ac's).
Anal. Calc. for $C_{40}H_{48}O_{14} \times H_2O$: C, 62.33; H, 6.54. Found: C. 62.23; H, 6.38.

Reagent 10 ("α-Glu"). To thioglucoside **1**[9] (2.33 g, 5.9 mmol) in dry toluene (40 ml) and dry pyridine (10 ml) under Ar was added dimethylsilyldichloride (3.5 ml, 3.78 g, 29 mmol, 5 eq), and the mixture was stirred for 1 h at 25°C. The apparatus was arranged for distillation and 10 ml was distilled off at which time the temperature at the top of the column had reached 105°C. The solution was cooled to 25°C and used as reagent **10** (40 ml, 0.15 M).

Reagent 11 ("armed α-Glu") To thioglucoside **2** (1.28 g, 2.6 mmol) in dry pyridine (5 ml) and dry toluene (20 ml) under Ar was added dimethylsilyldichloride (1.6 ml, 1.68 g, 13 mmol, 5 eq). After stirring 1 h at 25°C, the mixture was distilled carefully until the temperature reached 105-106°C (ca 15 ml). The solution in the distillation flask was cooled to 25°C and used as reagent **11** (11.6 ml, 0.22M).

Reagent 12 ("α-Gal"). To thiogalactoside **3** (719 mg, 1.8 mmol) in dry pyridine (3.5 ml) and dry toluene (15 ml) under Ar was added dimethylsilyldichloride (1.1 ml, 1.18 g, 9 mmol, 5 eq), and the mixture was stirred at 25°C for 1 h. Careful distillation until the temperature in the column reached 108°C (ca. 10 ml distilled) followed by cooling left a solution of reagent **12** (10 ml, 0.18 M).

Phenylthio 2-*O*-(2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranos-1-oxy)dimethylsilyl-3,4,6-tri-*O*-acetyl-α,β-D-glucopyranoside (**13**). 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose[12] (**4**, 0.50 g, 1.92 mmol) in pyridine (5 ml) was treated with reagent **10** (2.9 mmol **10** in 20 ml, 1.5 eq) and stirred under Ar at 25°C for 18 h. Ether (100 ml) was added, and the solution washed with H_2O (20 ml) and NaCl-solution (10%, 20 ml). The water layers were extracted with ether (10 ml), and the combined organic layers were dried (Na_2SO_2), filtered and concentrated to a syrup (1.99 g). Flash-chromatography in EtOAc-pentane 1:4 followed by 1:3 gave pure **13** (0.982 g, 72%, α/β 1:4). $[\alpha]_D^{20}$ + 9.5° (c 2.4, CH_2Cl_2). ^{13}C NMR ($CDCl_3$): 169.6-170.5 (Ac's), 127.7-

132.8 (Ar), 108.8, 108.2 ($Me_2\underline{C}$'s), 102.9 (C-2), 88.6 (C-1'), 75.4, 71.6, 71.0, 70.1, 69.2, 68.5 (6 C), 63.8, 62.3, 61.0 (C-1, C-6, C-6'), 26.5, 25.8, 25.5, 23.9 ($\underline{Me}_2C$'s), 20.5-20.9 (Ac's), -2.6, -2.9 (Me_2Si). ^1H NMR ($CDCl_3$): δ 7.5 (m, 2H, Ar), 7.3 (m, 3H, Ar), 5.1 (t, 1H, $J_{3'4'} = J_{4'5'} = 9.5$ Hz, H-4'), 4.95 (t, 1H, $J_{1'2'} = 9.5$ Hz, H-3'), 4.65 (d, 1H, $J_{1'2'} = 9.5$ Hz, H-1'), 4.55 (dd, 1H, $J_{23} = 8$ Hz, $J_{34} = 2.5$ Hz, H-4), 4.4 (d, 1H, H-3), 3.7-4.4 (m, 9H), 2.0-2.1 (3s, 9H, Ac's), 1.3-1.6 (4s, 12H), 0.25, 0.15 (2s, 6H, Me_2Si).
Anal. Calc. for $C_{32}H_{46}O_{14}SiS \times H_2O$: C, 52.44; H, 6.60. Found: C, 52.46; H, 6.41.

2,3:4,5-di-*O*-isopropylidene-1-*O*-(3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl)-β-D-fructopyranoside (**14**). To a solution of **13** (345 mg, 0.48 mmol) in $MeNO_2$ (15 ml) was added N-iodosuccinimide (272 mg, 1.2 mmol, 2.5 eq), and the mixture was refluxed for 1 h. Hydrochloric acid (1M, 50 ml) was added, and the mixture was extracted with EtOAc (5 x 25 ml). The combined organic layers were washed with saturated $NaHCO_3$-solution (10 ml) and $Na_2S_2O_3$-solution (10%, 10 ml), dryed ($MgSO_4$) and concentrated to a syrup (394 mg). Flash-chromatography in EtOAc-pentane 1:2 followed by 1:1 gave **14** as a clear syrup (224 mg, 85%). $[\alpha]_D^{20}$ + 66.3° (*c* 2.7; CH_2Cl_2). ^{13}C NMR ($CDCl_3$): δ 171.0, 170.5, 169.5 (Ac's), 109.0, 108.8 ($Me_2\underline{C}$'s), 101.7 (C-2), 98.1 (C-1'), 73.2, 70.8, 70.7, 70.0, 69.9, 69.1, 67.8, 67.7 (C-1, C-3 - C-5, C-1' - C-5'), 61.7, 61.1 (C-6, C-6'), 26.4, 25.8, 25.5, 23.9 ($\underline{Me}_2C$'s), 20.7, 20.6, 20.5 (Ac's), ^1H NMR ($CDCl_3$): δ 5.25 (t, 1H, $J_{3'4'} = J_{4'5'} = 9.5$ Hz, H-4'), 5.05 (t, 1H, $J_{2'3'} = 9.5$ Hz, H-3'), 5.00 (d, 1H, $J_{1'2'} = 3.5$ Hz, H-1'), 4.60 (dd, 1H, $J_{45} = 8.0$ Hz, $J_{34} = 2.5$ Hz, H-4), 4.40 (d, 1H, H-3), 4.25 (m, 2H), 4.10 (m, 2H), 3.95 (dd, 1H, $J_{6a6b} = 13.0$ Hz, $J_{56a} = 2.0$ Hz, H-6a), 3.90 (d, 1H, $J_{1a1b} = 10.5$ Hz, H-1a), 3.75 (dd, 1H, $J_{56b} = 0.5$ Hz, H-6b), 3.70 (dd, 1H, H-2'), 3.55 (d, 1H, H-1b), 2.0-2.1 (3s, 9H, Ac's), 1.3-1.55 (4s, 12 H, $\underline{Me}_2C$'s).
Anal. Calc. for $C_{24}H_{36}O_{14} \times 2\ H_2O$: C, 49.31; H, 6.90. Found: C, 49.57; H, 6.53.

Phenylthio 2-*O*-(4,6-*O*-benzylidene-1,3-di-*O*-methyl-β-D-glucopyranos-2-oxy)dimethylsilyl-3,4,6-tri-*O*-acetyl-α,β-D-glucopyranoside (**15**). A solution of methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-glucopyranoside[13] (**6**, 0.52 g, 1.76 mmol) in dry pyridine (5 ml) under Ar was treated with reagent **10** (20 ml, 2.9 mmol, 1.65 eq), and stirred for 18 h. Ether (100 ml) was added, and the organic layer washed with water (20 ml) and NaCl-solution (10%, 20 ml). The combined aqueous layers were extracted with ether (10 ml), and the combined organic layers dried (Na_2SO_4) and concentrated to a syrup (2.01 g). Flash-chromatography in EtOAc-pentane 1:4 followed by 1:3 gave pure **15** (1.00 g, 76%, α/β 1:3) as a clear syrup. $[\alpha]_D^{20}$ + 6.7 (*c* 1.4; CH_2Cl_2). ^{13}C NMR ($CDCl_3$): δ 171.0, 170.0, 169.6 (Ac's), 125.9-132.0 (Ar's), 104.6 (Ph-$\underline{CH}$), 101.0 (C-1), 88.8 (C-1'), 82.8, 81.7, 75.4, 75.2, 71.0, 68.7, 65.8 (7 C), 62.4, 60.9, 57.2 (C-6', MeO's), 20.5-21.1 (Ac's), -1.6, -1.7 (Me_2Si). ^1H NMR ($CDCl_3$): δ 7.2-7.6 (m, 10H, Ar's), 5.55 (s, 1H, PhC$\underline{H}$), 5.1 (t, 1H, $J_{3'4'} = J_{4'5'} = 9$ Hz, H-4'), 4.95 (t, 1H, $J_{2'3'} = 9.5$ Hz, H-3'), 4.65 (d, 1H, $J_{1'2'} = 9.5$ Hz, H-1'), 3.3-4.4 (m, 17 H), 2.0-2.1 (3s, 9H, Ac's), 0.2 (2s, 6H, Me_2Si). MS (CI, NH_3): m/z 768 ($M + NH_4^+$).

Methyl 4,6-*O*-benzylidene-3-*O*-methyl-2-*O*-(3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl)-β-D-glucopyranoside (**16**). To a solution of **15** (110 mg, 0.15 mmol) in $MeNO_2$ (5 ml) was added N-iodosuccinimide (83 mg, 0.37 mmol, 2.5 eq), and the mixture was refluxed for 4 h. Hydrochloric acid (1M, 25 ml) was added, and the mixture was extracted with EtOAc (3 x 25 ml). The combined organic layers were washed with $NaHCO_3$ (saturated, 10 ml) and $Na_2S_2O_3$ (10%, 10 ml). Drying ($MgSO_4$) and concentration left a syrupy residue, that was purified by Flash-chromatography in EtOAc-pentane 1:2 followed by 1:1 to give **16**

as a syrup (33 mg, 39%). $[\alpha]_D^{20}$ + 65.6° (*c* 1.1, CH_2Cl_2), ^{13}C NMR ($CDCl_3$): 169.5-171.0 (Ac's), 136.9, 125.8-129.5 (Ar), 104.0 (PhCH), 101.0 (C-1), 98.8 (C-1'), 81.6, 81.1, 78.6, 73.2, 70.8, 68.4, 67.8, 67.6, 65.7 (C-2 - C-6, C-2' -C-5'), 61.6, 60.5, 57.2 (C-6', OMe's), 20.5-20.7 (Ac's), ^1H NMR ($CDCl_3$): δ 7.4-7.5 (m, 5H, Ar), 5.55 (s, 1H, PhCH), 5.30 (d, 1H, $J_{1'2'}$ = 4.0 Hz, H-1'), 5.25 (t, 1H, $J_{3'4'} = J_{4'5'}$ = 9.5 Hz, H-4'), 5.05 (t, 1H, $J_{2'3'}$ = 9.5 Hz, H-3'), 4.45 (d, 1H, J_{12} = 7.5 Hz, H-1), 4.2-4.4 (m, 3H), 4.1 (m, 1H), 3.3-3.9 (m, 6H), 3.6, 3.55 (2s, 6H, OMe's), 2.0 (3s, 9H, Ac's). MS (CI, NH_3): m/z 602 ($M + NH_4^+$).

Ethylthio 2-*O*-(4,6-*O*-benzylidene-1,3-di-*O*-methyl-β-D-glucopyranos-2-oxy)dimethylsilyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (**17**). To a solution of methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-glucopyranoside[13] (0.40 g, 1.35 mmol) in pyridine (1 ml) was added reagent **11** (7.6 ml, 0.22M, 1.7 mmol, 1.25 eq) the mixture was stirred for 18 h at 25°C under Ar. Ether (50 ml) was added, and the solution was washed with water (10 ml) and NaCl-solution (10 ml, 10%). Drying (Na_2SO_2) and concentration left a syrup (1.52 g). Flash-chromatography in EtOAc-pentane 1:10 followed by 1:6 followed by 1:4 gave **17** as a colorless syrup (1.06 g, 93%). $[\alpha]_D^{20}$ -33.8° (*c* 4.5, CH_2Cl_2). ^{13}C NMR ($CDCl_3$): δ 137.0 - 138.7, 125.6 - 128.4 (Ar), 104.2 (PhCH), 100.5 (C-1), 86.7, 85.8, 85.7, 82.7, 81.0, 78.7, 74.7, 74.4, 73.6, 72.8, 68.5, 68.2, 65.2 (13 C), 60.5, 56.7 (OMe's), 24.1, 14.7 (SEt). Anal. Calc. for $C_{46}H_{58}O_{11}SiS \times H_2O$: C, 63.86; H, 6.99. Found: C, 63.81; H, 6.87.

Methyl 4,6-*O*-benzylidene-3-*O*-methyl-2-*O*-(3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl)-β-D-glucopyranoside (**18**). To a solution of **17** (583 mg, 0.69 mmol) in $MeNO_2$ (20 ml) under Ar was added N-iodosuccinimide (387 mg, 1.72 mmol, 2.5 eq), and the mixture was stirred for 4 h. Hydrochloric acid (1 ml, 1M) was added, and after 10 min. stirring CH_2Cl_2 (200 ml) was added. The organic layer was washed with HCl (50 ml, 1M), $NaHCO_3$-solution (50 ml, saturated) and $Na_2S_2O_3$-solution (50 ml, 10%), dried ($MgSO_4$) and concentrated. Flash-chromatography in EtOAc-pentane 1:4 followed by 1:2 gave **18** as a colorless syrup (337 mg, 67%). $[\alpha]_D^{20}$ + 40.1° (*c* 0.09, CH_2Cl_2). ^{13}C NMR ($CDCl_3$): δ 138.0-138.7, 125.9-128.9, 104.4 (PhCH), 101.1 (C-1), 99.5 (C-1'), 83.2, 81.8, 81.4, 78.7, 77.2, 75.1, 74.8, 73.4, 73.2, 70.9, 68.6, 68.3, 65.9 (C-2-C-6, C-2'-C-6', Bn's), 60.8, 57.2 (OMe's). ^1H NMR ($CDCl_3$): δ 7.1-7.6 (m, 20H, Ar), 5.55 (s, 1H, PhCH), 5.25 (bs, 1H, H-1'), 4.3-5.0 (m, 10H), 4.05 (m, 1H), 3.3-3.9 (m, 8H), 3.55, 3.50 (2s, 6H, OMe's). MS (CI, NH_3): m/z 746 ($M + NH_4^+$).

Phenylthio 2-*O*-dimethyl-(1-*O*-methyl-2,4,6-tri-*O*-benzyl-α-D-glucopyranos-3-oxy)silyl-3,4,6-tri-*O*-acetyl-β-D-galactopyranoside (**19**). To a solution of methyl 2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (559 mg, 1.2 mmol) in THF (2 ml) under Ar was added reagent **12** (10 ml, 1.8 mmol, 1.5 eq), and the mixture was stirred at 25°C for 18 h under Ar. Ether (100 ml) was added, and the solution was washed with water (20 ml) and NaCl-solution (20 ml, 10%). The combined aqueous layers were extracted with ether (10 ml), and the organic layers were dried (Na_2SO_4) and concentrated to a syrup (1.57 g). Flash chromatography in EtOAc-pentane 1:10 followed by 1:4 followed by 1:3 gave **19** as a colorless syrup (804 mg, 73%). $[\alpha]_D^{20}$ + 33.0° (*c* 1.9, CH_2Cl_2). ^{13}C NMR ($CDCl_3$): δ 170.0, 127.3-133.4 (Ar's), 97.8 (C-1), 88.6 (C-1'), 79.6, 78.1, 74.7, 74.4, 73.8, 73.3, 72.9, 69.5, 68.4, 68.2, 67.4, (11C), 61.6 (C-6'), 54.8 (OMe), 20.5-20.8 (Ac's), -1.7, -2.3 (Me_2Si). ^1H NMR ($CDCl_3$): δ 7.1-7.5 (m, 20H, Ar's), 5.35 (dd, 1H, $J_{3'4'}$ = 3.0 Hz, $J_{4'5}$ = 0.5 Hz, H-4'), 4.90 (d, 1H, J = 11.0 Hz, Bn), 4.75 (d, 1H, $J_{1'2'}$ = 9.5 Hz, H-1'), 4.70 (d, 1H, J_{12} = 3.5 Hz, H-1). 4.3-4.7 (m, 5H), 4.0-4.2

(m, 5H), 3.90 (t, 1H, J = 9.5 Hz), 3.5-3.7 (m, 4H), 3.45 (dd, 1H, J_{23} = 9.5 Hz, H-2), 3.30 (s, 3H, OMe), 2.05-2.1 (3s, 9H, Ac's), 0.3, 0.1 (Me_2Si). Anal. Calc. for $C_{48}H_{58}O_{14}SiS$ x H_2O: C, 61.52; H, 6.45. Found: C, 61.52; H, 6.35.

Methyl 3-*O*-(3,4,6-tri-*O*-acetyl-α-D-galactopyranosyl)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (**20**) and methyl 2,6-di-*O*-benzyl-3-*O*-(3,4,6-tri-*O*-acetyl-α-D-galactopyranosyl)-α-D-glucopyranoside (**21**). To a solution of **19** (185 mg, 0.20 mmol) in $MeNO_2$ (5 ml) under Ar was added N-iodosuccinimide (113 mg, 0.50 mmol, 2.5 eq). The mixture was refluxed for 1 h and 40 min., and after cooling to 25°C aqueous HCl (1 ml, 1M) was added. After stirring 10 min $NaHCO_3$-solution (25 ml, saturated) was added, and the mixture was extracted with EtOAc (3 x 25 ml). The combined organic layers were washed with $Na_2S_2O_3$-solution (10 ml, 10%), dried ($MgSO_4$) and concentrated to give a clear syrup (183 mg). Flash-chromatography in EtOAc-pentane 1:4 followed by 1:3 followed by 1:2 gave as a colorless syrup **20** (48 mg, 32%). Eluting with EtOAc gave **21** (66 mg, 49%) as a colorless syrup. Total yield: 81%. **20**: $[\alpha]_D^{20}$ + 106.4° (*c* 2.3, CH_2Cl_2), ^{13}C NMR ($CDCl_3$): δ 170.6, 170.4, 170.1 (Ac's), 137.6, 137.4, 127.6-128.3 (Ar), 98.9 (C-1'), 97.4 (C-1), 78.5, 78.2, 76.6, 74.2, 73.6, 72.7, 70.6, 69.7, 68.4, 68.0, 67.4, 66.7 (C-2 - C-6, C-2' - C-5', Bn's), 61.6 (C-6'), 55.0 (OMe), 20.5-20.7 (Ac's). ^1H NMR ($CDCl_3$): δ 7.1-7.4 (m, 15 H, Ar's), 5.50 (d, 1H, $J_{1'2'}$ = 4.0 Hz, H-1'), 5.30 (dd, 1H, $J_{3'4'}$ = 3.0 Hz, $J_{4'5'}$ = 1.0 Hz, H-4'), 5.15 (dd, 1H, $J_{2'3'}$ = 10.5 Hz, H-3'), 4.65 (d, 1H, J_{12} = 3.5 Hz, H-1), 4.4-4.8 (m, 7H), 4.15 (m, 1H), 4.05 (dd, 1H, J_{6a6b} = 11.0 Hz, J_{56a} = 6.0 Hz, H-6a), 3.85 (dd, 1H, J_{56b} = 7.0 Hz, H-6b), 3.6-4.0 (m, 5H), 3.50 (dd, 1H, J_{23} = 9.5 Hz, H-2), 3.30 (s, 3H, OMe), 1.95-2.1 (3s, 9H, Ac's). Anal. Calc. for $C_{40}H_{48}O_{14}$ x H_2O: C, 62.33; H, 6.54. Found: C, 61.84; H, 6.54.
21: ^{13}C NMR ($CDCl_3$): δ 170.3-5 (Ac's), 137.3-137.8, 127.6-128.4 (Ar's), 100.7 (C-1'), 97.9 (C-1), 81.4, 78.2, 73.6, 73.2, 70.7, 70.0, 68.8, 68.0, 67.8, 67.0 (10C), 61.5 (C-6'), 55.1 (OMe), 20.5-20.8 (Ac's). ^1H NMR ($CDCl_3$): δ 7.2-7.4 (m, 10H, Ar's), 5.40 (dd, 1H, $J_{3'4'}$ = 3.0 Hz, $J_{4'5'}$ = 1.0 Hz, H-4'), 5.35 (dd, 1H, $J_{1'2'}$ = 3.5 Hz, H-1'), 5.20 (dd, 1H, $J_{2'3'}$ = 10.5 Hz, H-3'), 4.4-4.9 (m, 5H), 4.50 (d, 1H, J_{12} = 3.5 Hz), 3.5-4.15 (m, 8H), 3.4 (dd, 1H, J_{23} = 9.5 Hz, H-2), 3.3 (s, 3H, OMe), 1.9-2.1 (3s, 9H, Ac's).
Acetylation of **20** (40 mg) with pyridine (0.5 ml) and acetic anhydride (0.2 ml) for 18 h at 25°C, followed by concentration med coconcentration with toluene gave tetraacetate **20a** (48 mg).
^1H NMR ($CDCl_3$): δ 7.0-7.4 (m, 15H, Ar's), 5.60 (d, 1H, $J_{1'2'}$ = 3.5 Hz, H-1'), 5.45 (dd, 1H, $J_{2'3'}$ = 11.0 Hz, $J_{3'4'}$ = 3.0 Hz, H-3'), 5.35 (dd, 1H, $J_{4'5'}$ = 1.0 Hz, H-4'), 5.30 (dd, 1H, H-2'), 4.75 (dt, 1H, $J_{5'6b'}$ = 7.0 Hz, $J_{5'6a'}$ = 6.0 Hz, H-5'), 4.65 (d, 1H, J_{12} = 3.5 Hz, H-1), 4.4-4.7 (m, 6H, Bn's), 4.15 (m, 1H, H-3), 4.05 (dd, 1H, $J_{6a'6b'}$ = 11.0 Hz, H-6a'), 3.80 (dd, 1H, H-6b'), 3.6-3.7 (m, 4H, H-4, H-5, H-6a, H-6b), 3.55 (dd, 1H, J_{23} = 9.5 Hz, H-2), 3.30 (s, 3H, OMe), 1.9-2.2 (4s, 12H, Ac's).

Acetylation of **21** (47 mg) in pyridine (0.5 ml) and acetic anhydride (0.2 ml) for 18 h at 25°C forllowed by concentration and coconcentration with toluene gave pentaacetate **21a** (45 mg). ^1H NMR ($CDCl_3$): δ 7.1-7.4 (m, 10H, Ar's), 5.35 (dd, 1H, $J_{2'3'}$ = 11.0 Hz, $J_{3'4'}$ = 3.5 Hz, H-3'), 5.30 (d, 1H, $J_{1'2'}$ = 3.5 Hz, H-1'), 5.25 (dd, 1H, $J_{4'5'}$ = 1.0 Hz, H-4'), 5.05 (dd, 1H, J_{45} = 10.0 Hz, J_{34} = 9.5 Hz, H-4), 5.0 (dd, 1H, H-2'), 4.65 (d, 1H, J_{12} = 3.5 Hz, H-1), 4.4-4.7 (m, 5H), 4.20 (t, 1H, J_{23} = 9.5 Hz, H-3), 3.95 (dd, 1H, $J_{6a'6b'}$ = 11.0 Hz, $J_{5'6a'}$ = 6.0 Hz, H-6a'), 3.75 (dd, 1H, $J_{5'6b'}$ = 7.0 Hz, H-6b'), 3.6-3.7 (m, 2H), 3.55 (dd, 1H, H-2), 3.4 (m, 1H), 3.3 (s, 3H, OMe), 1.9-2.1 (4s, 15H, Ac's). MS (CI, NH_3): m/z 764 ($M + NH_4^+$).

Methyl 2,6-di-*O*-benzyl-4,2'-di-*O*-dimethylsilylene-3-*O*-(3,4,6-tri-*O*-acetyl-α-D-galactopyranosyl-α-D-glucopyranoside (**21b**). Reaction of **19** (135 mg, 0.15 mmol), with N-iodosuccinimide (83 mg, 0.37 mmol, 2.5 eq) in $MeNO_2$ (4 ml) for 1½ h at 100°C as described above gave a solution to which CH_2Cl_2 (50 ml) was added. Washing with $NaHCO_3$-solution (10 ml, saturated) and $Na_2S_2O_3$-solution (10 ml, 10%), drying ($MgSO_4$) and concentration gave a syrup (154 mg). Flash-chromatography in EtOAc-pentane 1:4 followed by 1:2 followed by 1:1 gave first **21b** as a colorless syrup (49 mg, 46%) and as a slower moving product **20** (34 mg, 31%). **21b**: $[\alpha]_D^{20}$ + 66.4° (*c* 2.5, CH_2Cl_2). ^{13}C NMR ($CDCl_3$): δ 169.9-170.2 (Ac's), 138.0, 137.6, 132.1, 127.3-129.6 (Ar's), 102.2 (C-1'), 98.3 (C-1), 85.0, 77.4, 73.4, 73.3, 71.4, 70.0, 69.9, 68.7, 67.9, 67.7, 66.6 (C-2 - C6, C-2' - C-5', Bn's), 61.0 (C-6'), 55.0 (OMe), 20.3-20.5 (Ac's), -2.7, -3.0 (Me_2Si).

Methyl 2,6-di-*O*-benzyl-4,2'-di-*O*-dimethylsilylene-3-*O*-(3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl)-α-D-glucopyranoside (**22**). A solution of **8** (102 mg, 0.11 mol) and NIS (63 mg, 0.28 mmol, 2.5 eq.) in $MeNO_2$ (5 ml) was refluxed for 3 h. CH_2Cl_2 (50 ml) was added, and the solution washed with $NaHCO_3$-solution (10 ml, 10%), dryed over $MgSO_4$ and concentrated to a syrup (107 mg). Flash-chromatography in EtOAc-pentane 1:4 followed by 1:2 followed by 1:1 gave syrupy **22** as faster moving product (19 mg, 22%). As a slower moving product **9** was obtained (25 mg, 29%). **22**: ^{13}C NMR ($CDCl_3$): δ 127.5-128.5 (Ar's), 101.4 (C-1'), 98.3 (C-1), 84.9, 77.6, 73.6, 73.4, 73.0, 71.9, 71.7, 70.3, 68.1, 67.9 (10C), 61.7 (C-6'), 55.2 (OMe), 20.6-20.8 (Ac's), -2.7, -2.9 ($SiMe_2$). ^{1}H NMR ($CDCl_3$): δ 7.2-7.6 (m, 10H, Ar's), 5.35 (t, 1H, $J_{3'4'} = J_{4'5'} = 9.5$ Hz, H-4'), 5.30 (d, 1H, $J_{1'2'} = 4.0$ Hz, H-1'), 4.95 (t, 1H, $J_{2'3'} = 10.0$ Hz, H-3'), 4.75 (d, 1H, J = 12.0 Hz, Bn), 4.60 (d, 1H, $J_{12} = 3.5$ Hz, H-1), 4.55 (d, 1H, J = 12.0 Hz, Bn), 4.50 (s, 2H, Bn), 4.25 (dd, 1H, $J_{6a'6b'} = 12.5$ Hz, $J_{5'6'} = 3.5$ Hz, H-6a'), 4.10 (m, 1H, H-5'), 3.95 (dd, 1H, H-2'), 3.9 (t, 1H, $J_{34} = J_{45} = 9.0$ Hz, H-4), 3.8 (t, 1H, $J_{23} = 9.5$ Hz, H-3), 3.78 (dd, 1H, $J_{5'6b'} = 2.0$ Hz, H-6'b), 3.70 (dt, 1H, $J_{56a} = J_{56b} = 3.0$ Hz, H-5), 3.6 (d, 2H, J = 3.0 Hz, H-6a, H-6b), 3.5 (dd, 1H, H-2), 3.35 (s, 3H, OMe), 2.0 (3s, 9H, Ac's), 0.15, 0.10 (2s, 6H, Me_2Si).

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