Application of Intramolecular Glycosidation to the Stereocontrolled Synthesis of Disaccharides containing α-Gluco and α-Galacto Linkages

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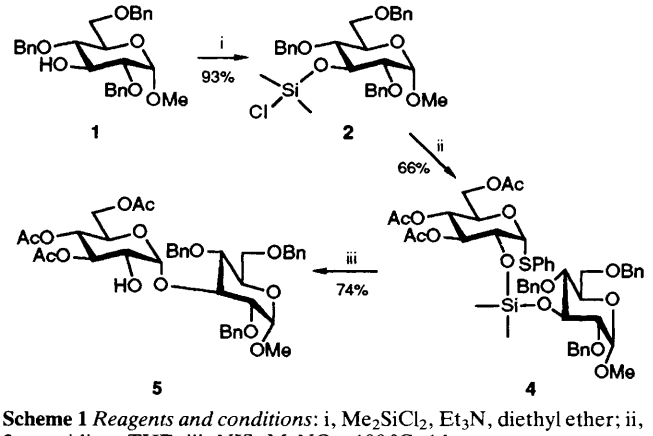
Disaccharides containing α-glucose and α-galactose linkages are stereospecifically synthesized from primary and secondary sugar hydroxy groups and a 2-hydroxythioglycoside *via* intramolecular glycosidation of a dimethylsilyl tethered intermediate.

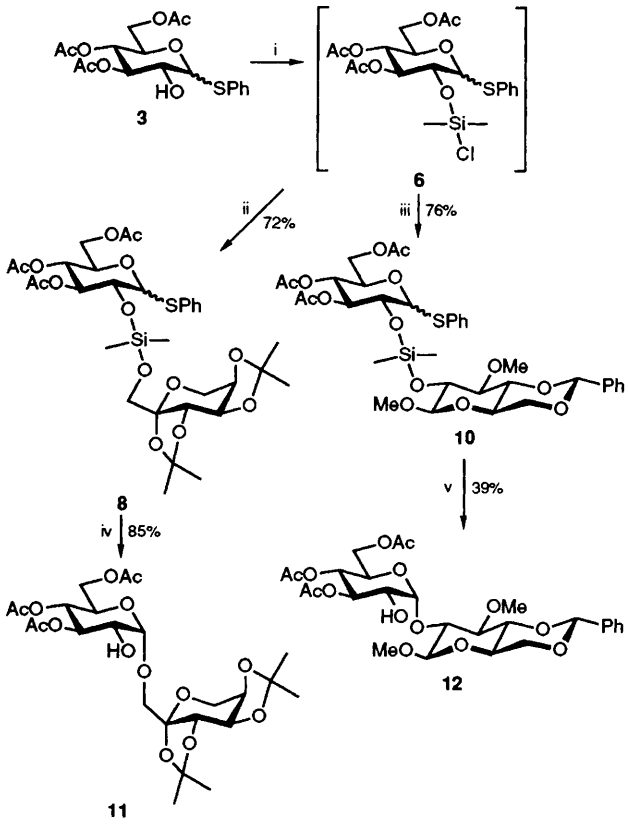
Improving the glycosidation reaction has recently been explored,[1–6] but still no method exists that is not critically dependent on the sugar or the alcohol structure. In many cases the reactions suffer from either low reactivity or lack of stereoselectivity. Intramolecular glycosidation could solve both problems. Recently, the stereocontrolled synthesis of β-mannosides by intramolecular glycosidation of a thiomannoside, bonded to the aglycone in the 2-position *via* a ketal has been described.[7,8] Subsequently, intramolecular glycosidation of thioglycosides linked in the 2-position to the aglycon with a dimethylsilylene linkage, has been successfully applied in the stereocontrolled synthesis of β-mannosides[9] and α-glucosides.[10,11] In neither of these cases were the other anomeric glycosides formed. While the silylene linkage is more readily prepared than the ketalic linkage it has so far not been successfully applied to the glycosidation of the weakly nucleophilic secondary sugar hydroxy groups. Furthermore, known methods for preparing silylene-tethered sugar derivatives either proceed in rather modest yields[12] or require a large excess of one sugar component.[9] Continuing previous work[10,11] this communication reports intramolecular α-glucosidation and α-galactosidation of primary and secondary sugar hydroxy groups, and also an easy and effective method of preparing unsymmetric dimethylsilyl acetals of sugar derivatives.



Scheme 1 *Reagents and conditions*: i, Me_2SiCl_2, Et_3N, diethyl ether; ii, **3a**, pyridine, THF; iii, NIS, $MeNO_2$, 100 °C, 1 h

Reaction of methyl 2,4,6-tri-*O*-benzyl-α-D-glucopyranoside **1**,[13] with Me_2SiCl_2 (2 equiv.) and Et_3N (1 equiv.) in diethyl ether gave essentially **2**† in 93% yield (Scheme 1). Silylation of phenylthio-3,4,6-tri-*O*-acetyl-α-D-glucopyranoside **3a**[10,11] with 3 equiv. of **2** in pyridine gave the dimethylsilylacetal **4** in 66% yield. Reaction of **4** with *N*-iodosuccinimide (NIS) and a catalytic amount of trifluoromethanesulfonic acid (TfOH), according to the previously published procedure,[10,11] led to a disappointing 19% yield of the α-glucoside **5**. In addition, the aglycone **1** was isolated. Because it was previously found that

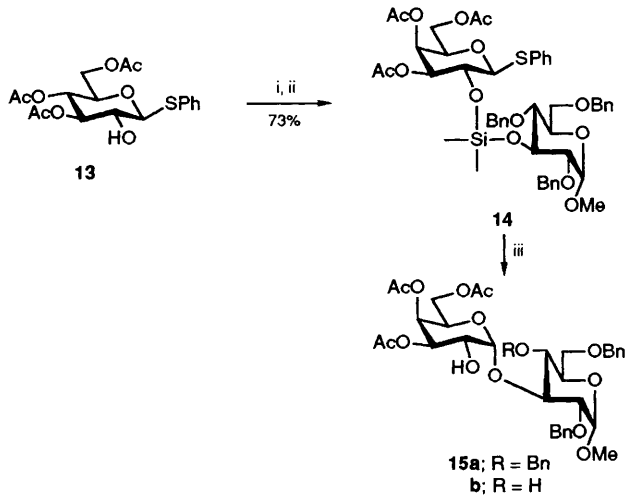
† *Selected data* for new compounds. **2**: ^{13}C NMR ($CDCl_3$): δ 2.9, 2.7 (Me_2SiCl). **4**: $[\alpha]_D^{20}$ +137.0 (*c* 0.4, CH_2Cl_2); NMR ($CDCl_3$), ^{13}C: δ 97.8 (C-1), 87.9 (C-1′), ^1H: δ 5.80 (d, *J* 5.5 Hz, H-1′). **5**: $[\alpha]_D^{20}$ +9.8 (*c* 1.1, CH_2Cl_2), NMR ($CDCl_3$), ^{13}C: δ 98.4 (C-1′), 97.3 (C-1), ^1H: δ 5.46 (d, *J* 3.5 Hz, H-1′), 4.74 (d, *J* 3.5 Hz, H-1). **8**: α/β 1:4, $[\alpha]_D^{20}$ +9.5 (*c* 2.4, CH_2Cl_2), NMR ($CDCl_3$, β-anomer), ^{13}C: δ 102.9 (C-2), 88.6 (C1′), ^1H: δ 4.65 (d, *J* 9.5 Hz, H-1′). **10**: α/β 1:3 $[\alpha]_D^{20}$ + 6.7 (*c* 1.4, CH_2Cl_2), NMR ($CDCl_3$, β-anomer), ^{13}C: δ 101.0 (C-1), 88.8 (C-1′), ^1H: δ 4.65 (d, *J* 10.0 Hz, H-1′), 4.30 (d, *J* 7.5 Hz, H-1). **11**: $[\alpha]_D^{20}$ +66.3 (*c* 2.7, CH_2Cl_2), NMR ($CDCl_3$), ^{13}C: δ 101.7 (C-2), 98.1 (C-1′), ^1H: δ 5.00 (d, *J* 3.5 Hz, H-1′). **12**: $[\alpha]_D^{20}$ + 65.6 (*c* 1.1, CH_2Cl_2), NMR ($CDCl_3$), ^{13}C: δ 101.1 (C-1), 99.0 (C-1′), ^1H: δ 5.30 (d, *J* 3.5 Hz, H-1′), 4.45 (d, *J* 7.5 Hz, H-1). **13**: $[\alpha]_D^{20}$ + 10.7 (*c* 1.3, CH_2Cl_2), NMR ($CDCl_3$), ^{13}C: δ 88.7 (C-1), ^1H δ 4.65 (d, *J* 9.5 Hz, H-1). **14**: $[\alpha]_D^{20}$ +33.0 (*c* 1.9, CH_2Cl_2), NMR ($CDCl_3$), ^{13}C: δ 97.8 (C-1), 88.6 (C-1′), ^1H: δ 4.75 (d, *J* 9.5 Hz, H-1′), 4.70 (d, *J* 3.5 Hz, H-1). **15a**: $[\alpha]_D^{20}$ +106.4 (*c* 2.3, CH_2Cl_2), NMR ($CDCl_3$), ^{13}C: δ 98.9 (C-1′), 97.4 (C-1), ^1H: δ 5.50 (d, *J* 4.0 Hz, H-1′), 4.65 (d, *J* 3.5 Hz, H-1). **15b**: NMR ($CDCl_3$), ^{13}C: δ 100.7 (C-1′), 97.9 (C-1), ^1H: δ 5.35 (d, *J* 3.5 Hz, H-1′), 4.50 (d, *J* 3.5 Hz, H-1′).



Scheme 2 *Reagents and conditions*: i, Me_2SiCl_2, pyridine, PhMe; ii, **7**, iii, **9**; iv, NIS, $MeNO_2$, 100 °C, 1 h; v, NIS, $MeNO_2$, 100 °C, 4 h

the glycosidation was independent of steric hindrance,[10,11] the unsatisfactory result was probably due to the low nucleophilicity of the secondary sugar alcohol, caused by the many electron-withdrawing substituents, making the glycosidation slower than acid-catalysed cleavage of the silyl acetal. After further experiments it was found that TfOH could be omitted when changing solvent to refluxing nitromethane, thus increasing the yield of **5** to 74%. No β-glucoside was detected.

To improve the synthesis of the silyl acetal derivatives a one-step procedure was attempted (Scheme 2). Reaction of **3** with Me_2SiCl_2 (5 equiv.) and pyridine in toluene followed by removal of the excess of Me_2SiCl_2 by distillation, resulted in a solution of **6** in pyridine–toluene. Treatment of 2,3:4,5-di-isopropylidene-β-D-fructopyranoside **7**[14] with 1.5 equiv. of this solution gave 72% of the dimethylsilyl acetal **8**.‡ Similarly, treatment of methyl 4,6-benzylidene-3-*O*-methyl-β-D-glucopyranoside **9**[15] with 1.6 equiv. of the solution of **6** gave 76% of dimethylsilyl acetal **10**. Intramolecular glycosidation of **8** with NIS in $MeNO_2$ at 100 °C for 1 h gave the α-glucoside **11** in 85% yield.§ Similarly reaction of **10** with NIS in $MeNO_2$ for 4 h gave α-glucoside **12** in 39% yield. The modest yield was possibly due to instability of the protection groups under the prolonged reaction time required. In neither case were β-glucosides detected.



Scheme 3 *Reagents and conditions*: i, Me_2SiCl_2, pyridine, PhMe; ii, **1**; iii, NIS, $MeNO_2$, 100 °C, 1.5 h

Finally an α-galactosidation was carried out (Scheme 3). Thiogalactoside **13** was obtained from 3,4,6-tri-*O*-acetyl-β-D-galactopyranosyl chloride[16] by substitution with potassium benzenethiolate in 56% yield. Treatment of **13** with Me_2SiCl_2 and pyridine in toluene and removal of the excess of Me_2SiCl_2 by distillation gave a solution of 2-*O*-chlorodimethylsilyl-galactoside which by subsequent reaction with **1** in a 1.5:1 ratio gave the dimethylsilyl acetal **14** in 73% yield. Intramolecular glycosidation with NIS in $MeNO_2$ at 100 °C for 1.5 h gave 2 products: The expected α-galactoside **15a** was obtained in 32% yield, but in addition another α-galactoside **15b** that had lost a benzyl group was obtained in 49% yield. After acetylation of **15b**, proton decoupling experiments of the pentaacetate thus obtained showed **15b** to be a 3-*O*-glycoside that had been debenzylated in the 4-position. Thus, the combined yield of 3-*O*-α-galactosides in the reaction was 81%. The debenzylation of **15a** to **15b** was particularly puzzling since it did not occur in the case of the α-glucoside **5**.

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‡ Typical silylation procedure: thioglucoside **3** (1.1 g, 2.9 mmol) was dissolved in PhMe (50 ml) and pyridine (5 ml) under argon and Me_2SiCl_2 (1.75 ml, 1.89 g, 14.5 mmol, 5 equiv.) were added. After stirring for 1 h at 25 °C the mixture was distilled until the temperature of the distillate was 110 °C. After cooling to 25 °C **7** (0.50 g, 1.92 mmol) was added, and the mixture was stirred 18 h. Addition of diethyl ether (100 ml), washing with H_2O (20 ml), saturated NaCl (20 ml), drying, concentration and flash-chromatography in EtOAc–pentane 1:4 followed by 1:3 gave the silyl acetal **8** (0.98 g, 72%).

§ Typical glycosidation procedure: dimethylsilyl acetal **8** (345 mg, 0.48 mmol), $MeNO_2$ (15 ml) and NIS (272 mg, 1.2 mmol, 2.5 equiv.) were refluxed for 1 h. Addition of HCl (50 ml, 1 mol dm^{-3}), extraction with EtOAc (5 × 25 ml), washing with $NaHCO_3$ (10 ml), $Na_2S_2O_3$ (10 ml) and drying, concentration and flash-chromatography in EtOAc–pentane 1:2 followed by 1:1 gave disaccharide **11** (224 mg, 85%).

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