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Long Range Intramolecular Glycosidation

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Stereocontrolled synthesis of glycosides was achieved by intramolecular glycosidation of an aglycon tethered to the 4,5 and 6 position of a thioglycoside donor.

Intramolecular glycosidation has been studied by us and other groups[1] as a completely stereocontrolled method of obtaining 1,2-cis-glycosides. In all these studies the 2-OH of the glycosyl donor was used as a hinge for the aglycon. Use of other hydroxy groups in the glycosyl donor as hinges in this strategy would make it possible to stereoselectively synthesise other stereochemical patterns. It would be extremely useful both by widening the scope of the reaction and in protective group strategy (Fig. 1) as a free hydroxy group is obtained in the reaction and can be used as a possible new glycosidation site in oligosaccharide synthesis. One reservation against such "long range" intramolecular glycosidation was that aglycon delivery requires the formation

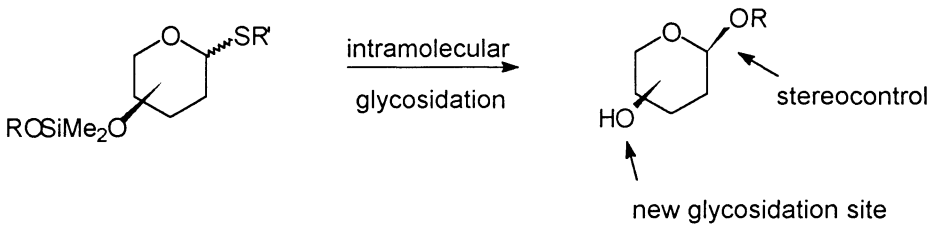

Fig. 1.

of large and probably unfavorable rings. However, the recent discovery that 8 membered disiloxanes were sometimes formed as byproducts in the silicon tethered intramolecular glycosidation[1g] encouraged us to investigate this strategy.

We decided to try intramolecular glycosidation from the 3,4 and 6 position of a thioglucoside as well as

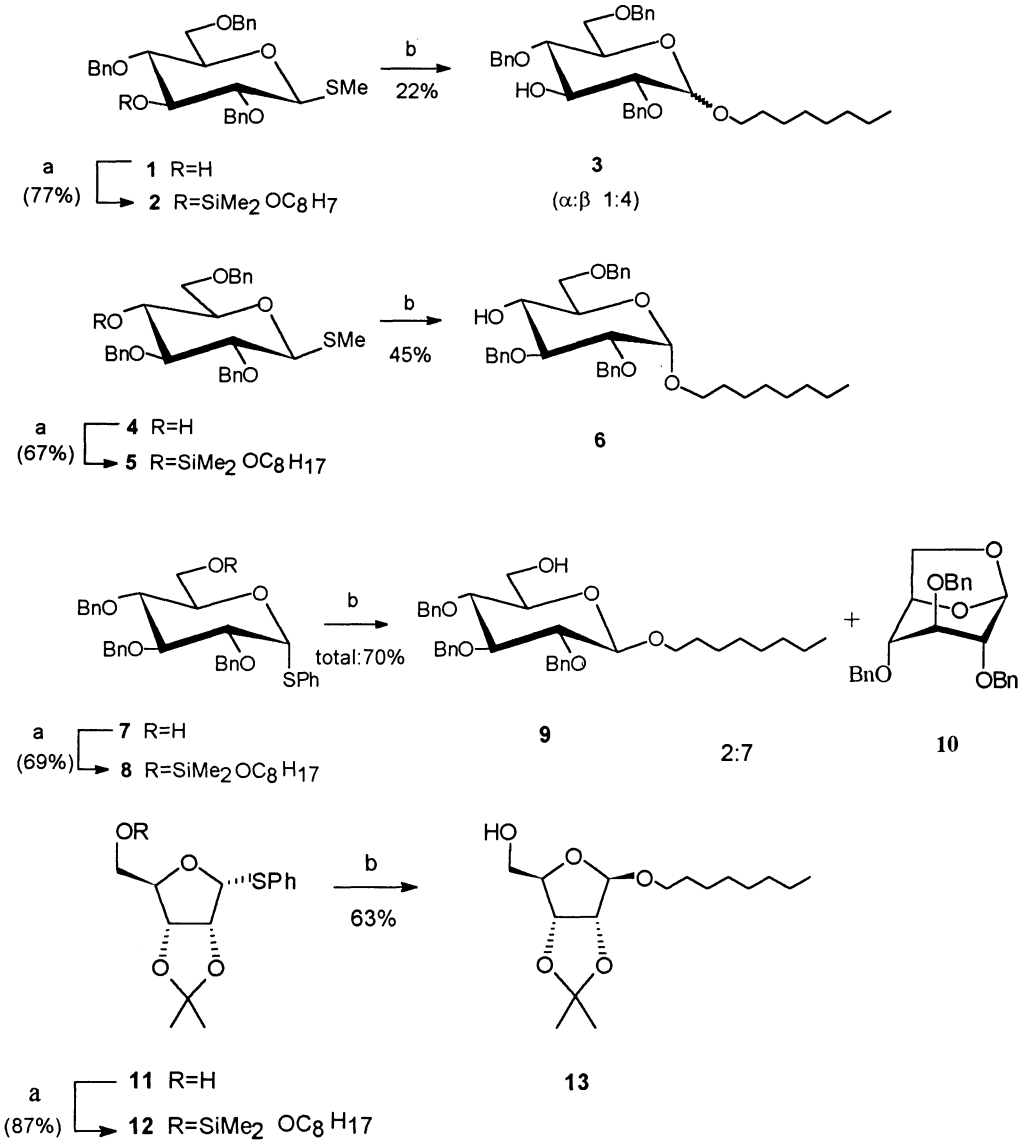

Fig. 2. a: $ClSiMe_2OC_8H_{17}$, THF, Pyridine; b: NIS, $MeNO_2$, 25 °C.

the 5 position of a thioriboside, using a dimethylsilylacetal as tether and 1-octanol as aglycon.

The results are shown in Fig. 2. The thioglycosides **1**[2], **4**[2], **7**[6] and **11**[7] were uneventfully converted to the octyloxysilyl ethers by reaction with octyloxydimethylsilyl chloride in pyridine/THF[1f] in 67-87% yield. Reaction of **2** with N-iodosuccinimide (NIS) in $MeNO_2$[1e] did give glycosides in 22% yield, but the reaction was not stereoselective as an α:β ratio of 1:4 was obtained. The preponderance of β-anomer indicated however that some intramolecular glycosidation was taking place. The reaction of the 4-*O*-(octyloxy)silylthioglucoside **5** with NIS was however completely stereoselective giving the α-glucoside **6** exclusively in 45% yield. Reaction of 6-*O*-(octyloxy)silylthioglucoside **8** was also completely stereoselective, the major product was, however, tribenzyl-levoglucosan **10** with the β-glucoside **9**[10] as minor product. 5-*O*-(Octyloxy)silylthioriboside **12** on the other hand exclusively gave the β-riboside **13**. Of the four cases studied intramolecular glycosidation of **2** goes through a 6-membered transition state while **5**, **8** and **12** goes through a 7-membered transition state. Judging from the fact that the three latter reactions were more stereoselective, a 7-membered transition state seems more favorable. This is probably partly because transannulation of a 6 membered ring unto a 6 membered ring is difficult, and partly an effect caused by the inclusion of the silicon atom in the ring. The Si-C and Si-O are approximetely 25% longer than the corresponding carbon bonds a fact that is known to favor the formation of larger rings.[11] It was remarkable that stereoselectivity was observed in the reaction of **2** and **5** since a conformational change was expected for intramolecular reaction to occur. The fact that stereocontrol is obtained by such long range aglycon delivery opens a new area of useful applications of intramolecular glycosidation. Further research will focus on improving yields and use in oligosaccharide synthesis.

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2) **1** and **4** were prepared by PBu_3/Me_2S_2 treatment[3] of 2,4,6-[4] and 2,3,6-tribenzylglucose.[5] Details will be published later.

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7) **11** ($[\alpha]_D^{20}$ + 132.8° (*c* 1.1, $CHCl_3$), ^1H, δ 5.70 (d, J 5 Hz, H-1), ^{13}C, δ 90.4 (C-1)) was prepared from 5-*O*-acetyl-2,3-isopropylidiene-D-ribono-1,4-lactone[8] in 3 steps: $((CH_3)_2CH(CH_3)CH)_2BH$ (3 equiv.), THF, 100%. PBu_3 (3 equiv.), Ph_2S_2 (3 equiv.), pyridine, 82%. NaOMe, MeOH, 94%. Configuration determined by NOESY.

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9) Data for new compounds (NMR in $CDCl_3$); **2**: $[\alpha]_D^{20}$ + 14.1° (*c* 0.7, CH_2Cl_2); ^1H, δ 4.35 (H-1, $J_{1,2}$ 9.5 Hz); ^{13}C, δ 85.0 (C-1). **3α**: ^1H, δ 4.75 (H-1, $J_{1,2}$ 3.5 Hz); ^{13}C, δ 96.2 (C-1). 3β: $[\alpha]_D^{20}$ +12.1° (*c* 2.2, CH_2Cl_2); ^1H, δ 4.35 (H-1, $J_{1,2}$ 8.0 Hz); ^{13}C, δ 103.1 (C-1). **5**: $[\alpha]_D^{20}$ + 27.1° (*c* 1.6, CH_2Cl_2); ^1H, δ 4.40 (H-1, $J_{1,2}$ 9.0 Hz); ^{13}C, δ 86.3 (C-1). **6**: $[\alpha]_D^{20}$ + 43°(*c* 1.6, CH_2Cl_2); ^1H, δ 4.75 (H-1, $J_{1,2}$ 3.5 Hz); ^{13}C, δ 96.7 (C-1). **8**: $[\alpha]_D^{20}$ + 140.0° (*c* 1.3, CH_2Cl_2); ^1H, δ 5.60 (H-1, $J_{1,2}$ 4.5 Hz); ^{13}C, δ 86.6 (C-1). **12**: $[\alpha]_D^{20}$ + 72.8° (*c* 1.1, $CHCl_3$); ^{13}C, 91.2 (C-1). **13**: $[\alpha]_D^{20}$ -46.2° (*c* 1.2, $CHCl_3$); ^1H, 5.09 (H-1, $J_{1,2} \sim 0$ Hz); ^{13}C, 108.6 (C-1).

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