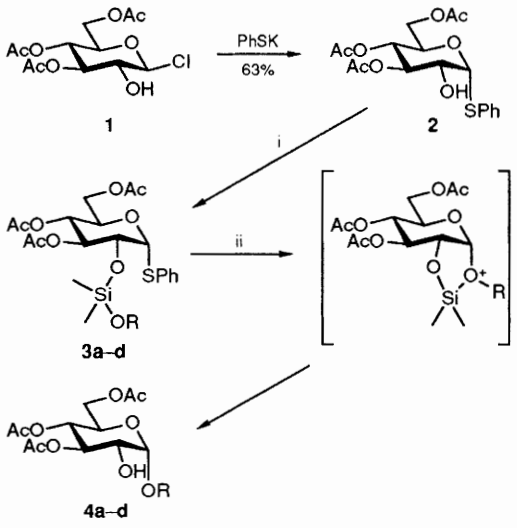
Stereocontrolled Synthesis of α-Glucosides by Intramolecular Glycosidation

Mikael Bols

Department of Organic Chemistry, The Technical University of Denmark, Building 201, DK-2800 Lyngby, Denmark

α-Glucosides are prepared by connecting phenylthio 3,4,6-tri-*O*-acetyl-α-D-glucopyranoside and an alcohol or a phenol with a dimethylsilylene bridge followed by iodonium ion catalysed intramolecular glycosidation.

Efficient synthesis of glycosides remains an important problem in organic chemistry. Though many excellent improvements of the glycosidation reaction have been developed in recent years[1–3] no method exists, which 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 these two problems. Recently Barresi and Hindsgaul described the synthesis of β-mannosides through intramolecular glycosidation of a thiomannoside, bonded to the aglycone in



Scheme 1 *Reagents and conditions*: i, $ROSiMe_2Cl$ (2 equiv.), pyridine, tetrahydrofuran, 2 h, 25 °C; ii, NIS (2.5 equiv.), TfOH (0.2 equiv.), CH_2Cl_2, 10 min, 25 °C

Table 1 Yields (%), after chromatography, of **3**(i) and **4**(ii)

	R	i	ii
a	n-Octyl	75	59
b	Cyclohexyl	74	62
c	*tert*-Butyl	76	61
d	Phenyl	54[a]	72

[a] **3d** was unstable during chromatography resulting in the lower yield.

the 2-position *via* a ketal.[4] Substituting the ketal linkage with a silylene group,[5] could improve this method, since silylenes of monofunctional alcohols can be prepared readily.[6,7] This paper reports on the stereocontrolled synthesis of α-glucosides by intramolecular glycosidation of a phenylthio glucoside having an alkoxydimethylsilyl group in the 2-position.

3,4,6-Tri-*O*-acetyl-β-D-glucopyranosyl chloride **1**, available from 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose in two steps,[8] was converted to crystalline phenylthio 3,4,6-tri-*O*-acetyl-α-D-glucopyranoside **2**† by reaction with potassium benzenethiolate in 63% yield. Thioglucoside **2** was reacted with either $C_8H_{17}OSiMe_2Cl$,[9] $C_6H_{11}OSiMe_2Cl$,[10] Bu^{t}O-$SiMe_2Cl$[11] or $PhOSiMe_2Cl$[12] in pyridine to give silylenes **3a–d**† in the yields given in Table 1. The alkoxychlorodimethylsilanes could readily be prepared from the alcohols with Me_2SiCl_2 and Et_3N.[13] Treatment‡ of the dimethylsilylenes **3a–d** with *N*-iodosuccinimide (NIS) and a catalytic amount of trifluoromethanesulfonic acid resulted in instantaneous reaction, and the α-glucosides **4a–d**† were isolated as the only products (Table 1). No β-glucosides were observed in the reactions. The reaction probably occurs by initial formation of a carbonium ion at C-1, cyclisation to a five-membered ring (Scheme 1), collapse to an α-glucoside leaving an unstable silylene derivative at C-2, which is lost during work-up.

It is interesting to observe that the yield of this glycosidation is virtually the same for primary, secondary and tertiary alcohols totally unlike intermolecular glycosidations. Thus this method may be useful for synthesis of α-glucosides in those cases where the alcohol is unreactive.

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† *Relevant data* for new compounds: **2**: m.p. 128–131 °C, $[\alpha]_D^{20}$ + 252 (*c* 0.7, CH_2Cl_2), NMR ($CDCl_3$), ^{13}C: δ 90.5 (C-1), ^1H: δ 5.65 (d, *J* 6.0 Hz, H-1); **3a**: $[\alpha]_D^{20}$ + 137 (*c* 0.2, CH_2Cl_2), NMR ($CDCl_3$), ^{13}C: δ 88.3 (C-1), ^1H: δ 5.66 (d, *J* 5.5 Hz, H-1); **3b** $[\alpha]_D^{20}$ + 148 (*c* 0.2, CH_2Cl_2), NMR ($CDCl_3$), ^{13}C: δ 88.4 (C-1), ^1H: δ 5.67 (d, *J* 5.5 Hz, H-1); **3c**: $[\alpha]_D^{20}$ + 180 (*c* 1,2, CH_2Cl_2); NMR ($CDCl_3$), ^{13}C: δ 88.5 (C-1), ^1H: δ 5.69 (d, *J* 5.5 Hz, H-1); **3d**: $[\alpha]_D^{20}$ + 112 (*c* 0.5, CH_2Cl_2); NMR ($CDCl_3$), ^{13}C: δ 88.1 (C-1), ^1H: 5.58 (d, *J* 5.5 Hz, H-1); **4a**: $[\alpha]_D^{20}$ + 116 (*c* 0.2, CH_2Cl_2), ^{13}C: δ 98.0 (C-1), ^1H: δ 4.92 (d, *J* 4.0 Hz, H-1); **4b**: $[\alpha]_D^{20}$ + 132 (*c* 0.4, CH_2Cl_2), ^{13}C: δ 96.8 (C-1), ^1H δ 5.06 (d, *J* 4.0 Hz, H-1); **4c** $[\alpha]_D^{20}$ + 134 (*c* 0.4, CH_2Cl_2), ^{13}C: δ 92.7 (C-1), ^1H: δ 5.20 (d, *J* 4.0 Hz, H-1), **4d**: $[\alpha]_D^{20}$ + 170 (*c* 0.5, CH_2Cl_2), ^{13}C: δ 96.8 (C-1), ^1H: δ 5.62 (d, *J* 4.0 Hz, H-1).

‡ *Typical preparative procedure:* to a solution of the silylene derivative **3a–d** (0.1 mmol) and NIS (56 mg, 0.25 mmol) in CH_2Cl_2 (5 ml) was added trifluoromethanesulfonic acid (TfOH) (2 μl, 3.4 mg, 0.02 mmol). After 10 min at 25 °C, EtOAc (50 ml) was added and the organic layer washed with $NaHCO_3$ and $Na_2S_2O_3$ solutions (10 ml each). Drying, concentration and flash-chromatography (EtOAc–pentane 1 : 2) gave products **4a–d** in the yields indicated.