ChemComm

Synthesis of 1,2-*trans C*-glycosyl compounds by reductive samariation of glycosyl iodides

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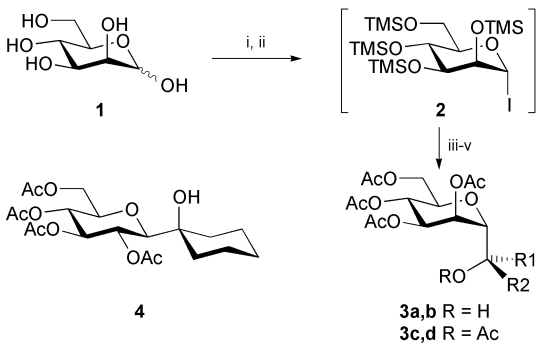
Received (in Liverpool, UK) 3rd August 2000, Accepted 16th October 2000
First published as an Advance Article on the web

Reductive samariation of per-*O*-trimethylsilyl or benzyl glycopyranosyl iodides in the presence of carbonyl compounds provides the corresponding 1,2-*trans*-*C*-glycosyl compounds in good yields.

Numerous synthetic methods have been developed for the preparation of *C*-glycosyl compounds, analogues of glycosides in which the interglycosidic oxygen atom has been replaced by a carbon atom.[1] Recent work in our laboratory has focused on a direct method for the synthesis of *C*-glycosyl compounds derived from neutral hexoses by the reductive samariation of anomeric 2-pyridyl sulfones in the presence of carbonyl compounds (Barbier procedure).[2] While the procedure is efficient with the manno series,[3] it is unsatisfactory with the gluco- or the galactopyranosyl series[2] because of too high a level of the competing β-elimination (an elimination–C–C bond formation ratio of approximately 1:1). We now report an unexpected solution to this problem starting from glycosyl iodides as efficient *C*-glycosyl donors in reductive samariation experiments. These glycosyl halides, first prepared by the reaction of glycosyl bromides with sodium iodide[4] and rarely used as electrophilic *O*-glycosyl donors,[5] can be prepared from methyl glycosides, glycosyl acetals and glycosyl acetates,[6] hemiacetals[7] or trimethylsilyl glycosides.[8] Either a rapid synthesis of structurally simple *C*-glycosyl compounds from commercial free sugars *via* the per-*O*-trimethylsilyl glycosyl iodides,[8] or a multi-step construction of more complex *C*-glycosyl compounds with the more practical per-*O*-benzyl iodides is possible.

Silylation of D-mannopyranose **1** and treatment of a DCM solution of the per-*O*-silylated derivative with iodotrimethylsilane (TMSI) according to the procedure of Uchiyama and Hindsgaul[8] provided anomeric iodide **2** which, after solvent removal, was successively treated with the carbonyl compound (2 equiv.) and a THF solution of SmI_2 (2.2 equiv.) at rt (Scheme 1 and Table 1). On completion of the reaction, indicated by the disappearance of the blue color of SmI_2 in approximately 1.5 h, the products were desilylated by addition of acidic MeOH and analyzed as their acetylated compounds. For the acetylation



Scheme 1 *Reagents and conditions*: i, TMSCl, Et_3N, DMF, 0 °C; ii, 1.1 equiv. of TMSI, CH_2Cl_2, 25 °C, 0.5 h; iii, 2 equiv. of carbonyl compound, 2.2 equiv. of SmI_2, THF, 25 °C, 1.5 h; iv, MeOH, 1 M HCl, (3:1, v/v), 25°C; v, Ac_2O, 2,6-lutidine, 25 °C.

Table 1 SmI_2-induced coupling of silylated glycopyranosyl iodides with carbonyl compounds[a]

Entry	Substrate	Conditions	*C*-Glycoside (yield)[b]
1	**1**	Cyclohexanone	**3a** (85%)
2	**1**	Pentan-3-one	**3b** (58%)
3	**1**	IsoButyraldehyde	**3c** (71%; 10:1[c])
4	**1**	*n*-Octanal	**3d** (72%; 4:1[c])
5	D-Glucose	Cyclohexanone	**4** (61%)[d]

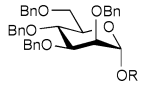
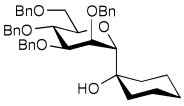
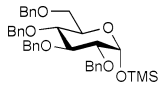
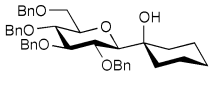
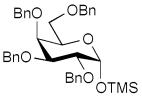
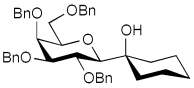
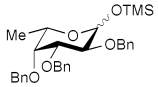
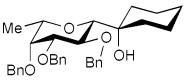
[a] See Scheme 1 for the reaction conditions. [b] Isolated yields from the free sugar after chromatography on silica gel. [c] Diastereomer ratio at the exocyclic asymmetric center. [d] The only other byproduct is the protonation product, 1,5-anhydro-2,3,4,6-tetra-*O*-acetyl-D-glucohexitol.

step, pyridine which suffered a samarium(III)-induced ring opening was replaced by 2,6-lutidine. This one-pot four-step procedure from the persilylated sugars (steps ii–v, Scheme 1) provided only the α-products **3a**–**d** as determined by ^{1}H-NMR analysis of the crude acetylated reaction mixtures, in yields of 58–85% from the commercial free sugar after silica gel column chromatography. The only identified byproduct was the 1,5-anhydromannohexitol (reprotonation product) in about 10%, presumably arising from traces of HI present in the starting glycosyl iodides. With the two aldehydes tested (entries 3 and 4, Table 1), a mixture of diastereomers were produced with selectivities (10:1 and 4:1, respectively) in line with the results previously obtained with anomeric 2-pyridyl sulfones.[2] D-Glucose provided *C*-glycosyl compound **4** by the same sequence of reactions (entry 5). Noteworthy is the absence of elimination products, particularly striking in the gluco series.

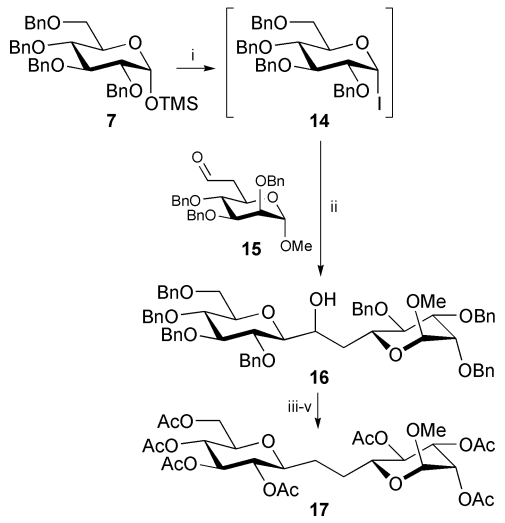
While this procedure is well suited for the rapid conversion of commercial sugars to simple 1,2-*trans*-*C*-glycopyranosyl compounds, more elaborated synthetic schemes would require protecting groups more stable than trimethylsilyl groups. We therefore tested the benzylated mannopyranosyl iodide available by TMSI treatment in DCM at rt of either the glycosyl acetate **5**[5] or the trimethylsilyl glycoside **6** (entries 1 and 2, Table 2). Reductive samariation as reported above in the presence of cyclohexanone provided comparable results. The same one-pot transformation (i, TMSI; ii, SmI_2, cyclohexanone) on the trimethylsilyl glycosides derived from glucose **7**, galactose **8** and fucose **9** also provided an unprecedented level of *C*-glycosylation for these series (72–75% yield), obviously to the detriment of the competing elimination reaction. For these three substrates, it was necessary to conduct the samariation step in the presence of one equiv. of 2,6-lutidine which greatly reduces the amount of the competing protonation leading to the 1,5-anhydro sugars. As usual, the 1,2-*trans* compounds were the only detectable *C*-glycosylation products, as indicated by the values of the H1–H2 coupling constants in the ^{1}H-NMR spectra (9.2 Hz for **11** and 9.3 Hz for **12** and **13** in a chair conformation of the pyranose ring). These results significantly differ from those obtained from anomeric 2-pyridyl sulfones.[2] Substitution of the 2-pyridyl sulfone group by an iodine atom in an otherwise identical structure resulted, under identical conditions, in an improvement of the *C*-glycosylation reaction at a synthetically

DOI: 10.1039/b006455f

Table 2 SmI_2-induced coupling of benzylated glycopyranosyl iodides with cyclohexanone

Entry	Free sugar	Carbonyl compound	*C*-Glycoside (yield)[a]
1	 **5** R = Ac	A[b]	 **10** (68%)
2	**6** R = TMS	A[b]	**10** (85%)
3	 **7**	B[c]	 **11** (72%)
4	**7**	C[d]	**11** (80%)
5	 **8** (α:β = 10:1)	B[c]	 **12** (74%)
6	 **9** (α:β = 2:1)	B[c]	 **13** (75%)

[a] Isolated yields from the trimethylsilyl glycoside after chromatography on silica gel. [b] Reaction conditions A: i, 1.1 equiv. of TMSI, CH_2Cl_2, 25°C, 0.5 h; ii, 2 equiv. of cyclohexanone, 2.2 equiv. of SmI_2, THF, 25°C, 0.25 h. [c] Reaction conditions B: see conditions A with 1 equiv. of 2,6-lutidine in step ii. [d] Reaction conditions C: see conditions A with 0.01 equiv. of NiI_2 at −10 °C in step ii.



Scheme 2 *Reagents and conditions*: i, 1.1 equiv. of TMSI, CH_2Cl_2, 25 °C, 0.5 h; ii, 1.1 equiv. of **15**, 2.2 equiv. of SmI_2, THF, 25 °C, 0.25 h, 66% from **7**; iii, 1.5 equiv. of NaH, CS_2, CH_3I, 25 °C, 3 h, 96%; iv, 1.5 equiv. of Bu_3SnH, cat. AIBN, toluene, 95 °C, 2.5 h, 89%; v, H_2, Pd/C, MeOH, Ac_2O, py, 94%.

useful level (72 *vs*. 39% yield in the gluco series) with a concomitant decrease in the elimination reaction. We also noticed a further improvement by incorporating catalytic amounts of NiI_2 with SmI_2,[9] and conducting the coupling reaction at −10 °C (80% of **11**, entry 4).

The utility of this new procedure has been demonstrated in a fast synthesis of the carbon-linked mimic of the D-glucopyranosyl(β1→6)-D-mannopyranoside dimer **17** (Scheme 2). Reductive samariation of iodide **14** in the presence of aldehyde **15**[10]† provided the β-*C*-dimer **16** in 66% yield. Only one isomer was detected at the exocyclic asymmetric center. Methyl xanthate formation and radical reduction furnished the methylene-linked dimer which was debenzylated and characterized as its per-*O*-acetyl derivative **17**.‡

In summary, we have shown that the silylated or benzylated glycopyranosyl iodides are useful *C*-glycosyl donors for the synthesis of 1,2-*trans* *C*-glycosyl compounds. Work is in progress to delineate a precise mechanism for the transformation.§

Notes and references

† Aldehyde **15** was prepared from methyl 2,3,4,6 tetra-*O*-benzyl-α-D-mannopyranoside in an overall yield of 54% by the following five-step sequence of reactions: i, Ac_2O, CF_3COOH, (4:1), 25 °C, 1 h; ii, MeONa, MeOH, 25 °C, 12 h; iii, 1.4 equiv. PPh_3, 4 equiv. I_2, imidazole, toluene, 70 °C, 1 h; iv, 1.4 equiv. Bu_4NCN, DMF, 0 to 25 °C, 3 h; v, 3 equiv. DIBAL-H, CH_2Cl_2,, −78 °C, 0.5 h.

‡ *Selected data* for **17**: $[\alpha]_D^{20}$ = + 22 (*c* = 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, atom numbering of a tridecopyranoside) δ = 5.29 (dd, 1H, *J* 9.8, 3.5, H-3), 5.26 (dd, 1H, *J* 3.5, 1.5, H-2), 5.18, 5.10, 5.04, 4.89 (4 t, 4H, *J* 9.5, H-4,9,10,11), 4.65 (d, 1H, *J* 1.5, H-1), 4.25 (d, 1H, *J* 12, 5.2, H-13), 4.10 (dd, 1H, *J* 12, 2.1, H-13′), 3.70 (ddd, 1H, *J* 10, 9.5, 2, H-12), 3.64 (ddd, 1H, *J* 10, 5, 2, H-5), 3.40 (ddd, 1H, H-8), 3.36 (s, 3H, OMe), 2.16, 2.11, 2.08, 2.06, 2.04, 2.02 and 2.00 (7 s, 21H, OAc), 1.9–1.8 and 1.5–1.4 (2 m, 4H, H-6,6′,7,7′); MS (ES): *m/z* = 671 [*M* + Na]; HR-MS (ES), calcd for $C_{28}H_{40}NaO_{17}$ [*M* + Na]: 671.2163, found: 671.2166.

§ We do not yet have a reasonable explanation for the significant differences between the behavior of anomeric iodides and anomeric 2-pyridyl sulfones. It is possible that there is a change in the electron transfer mechanism (inner *vs*. outer sphere ET) on going from anomeric 2-pyridyl sulfones to anomeric iodides inducing a change in the product distribution (C–C bond formation *vs*. elimination).

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