

Silver Imidazolate-assisted Glycosidations. Part 4.*

Synthesis of β -D-Mannopyranosides

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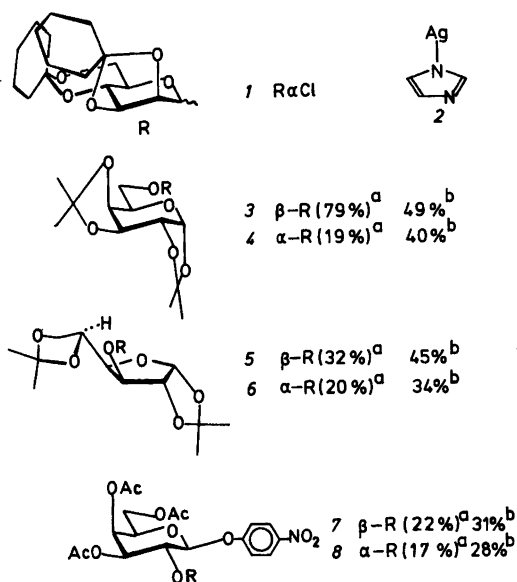
Silver imidazolate together with mercury(II) chloride in toluene is used in β -D-mannopyranoside synthesis with 2,3:4,6-di-*O*-cyclohexylidene- α -D-mannopyranosyl chloride as the glycosidating agent. Improvements are obtained in the glycosidation of alcohols with low reactivity.

Despite considerable efforts, the synthesis of β -D-mannopyranosides for aglycones of low reactivity remains a problem.^{1–9} In previous papers we have described a short route to β -D-mannopyranosides.^{7,8} This involves acetalization of D-mannose under kinetic control to give crystalline 2,3:4,6-di-*O*-cyclohexylidene- α -D-mannopyranose which is converted into the crystalline α -chloride **1**, in a total yield of 45%, without having to resort to chromatographic separations. Koenigs-Knorr glycosidations with **1** using silver carbonate as promotor in dichloromethane gave good yields of β -D-mannopyranosides in disaccharide synthesis when the linkage was formed to a sterically unhindered primary position. The yields and the stereospecificity were, however, much lower when the aglycone was a monosaccharide derivative with a free secondary hydroxyl group.

We now report the synthesis of β -D-mannopyranosides from 2,3:4,6-di-*O*-cyclohexylidene- α -D-mannopyranosyl chloride (**1**) using silver imidazolate¹⁰ and mercury(II) chloride as glycosidating promoters in toluene. The mannosyl chloride **1**, was chosen since this was tested with a range of glycosidation promoters in previous work.⁸ In pilot experiments, various metal halides were tested together with silver imidazolate using acetonitrile,

dichloromethane and toluene as solvents. Mercury(II) chloride, tin(II) chloride and zinc chloride promoted glycosidation; mercury(II) chloride in toluene gave the highest yield of disaccharides. Zinc chloride gave α -D-mannopyranosides only. No enhancement in rates or yields were obtained by adding tetrabutylammonium chloride.¹²

The results obtained in the glycosidations of three protected carbohydrates, with single free hydroxyl groups of widely differing reactivity, are



Scheme 1. a. Yields obtained in previous work using silver carbonate in dichloromethane. The molar ratio of **1** to aglycone was 4:1. b. Yields obtained in the present work. The molar ratio of **1** to aglycone was 1.5:1.

*Part 3 is Ref. 11.

shown in Scheme 1. The yields given in brackets are those previously obtained using silver carbonate in dichloromethane.⁸ The present glycosidating system gives somewhat improved yields of β -D-mannopyranosides in reactions at secondary positions of low reactivity (disaccharides 5 and 7). This is not due to increased stereospecificity, but rather to increased total yields of anomeric D-mannopyranosides. The reactivity of the present system permitted a lowering of the ratio of mannopyranosyl chloride 1 to alcohol from 4:1 to 1.5:1. In reactions at a primary position with good accessibility (disaccharide 3) the high stereospecificity previously observed using silver carbonate as promotor is lost.

EXPERIMENTAL

General methods were the same as those reported elsewhere.¹³ The identity of the disaccharides prepared with the appropriate reference materials was ascertained by ¹H and ¹³C NMR.

Typical glycosidation procedure. 6-O-[2,3:4,6-Di-O-cyclohexylidene-(α - and β -)-D-mannopyranosyl]-1,2:3,4-di-O-isopropylidene- α -D-galactopyranose (3, 4). A mixture of 1,2:3,4-di-O-isopropylidene- α -D-galactopyranose (402 mg, 1.54 mmol), 2,3:4,6-Di-O-cyclohexylidene- α -D-mannopyranosyl chloride^{7,8} (1, 810 mg, 2.26 mmol), silver imidazolite (2, 395 mg, 2.26 mmol) and mercury(II) chloride (1.670 g, 6.15 mmol) in toluene (15 ml) containing 4 Å molecular sieves was stirred at 60 °C in the dark for 5 days. The mixture was then diluted with toluene-ethyl acetate (1:1) containing triethylamine (2 ml), stirred for a few minutes, filtered through a silica gel pad, concentrated and the residue was subjected to silica gel column chromatography. An alternative work-up procedure has been described.¹¹ The β -linked disaccharide 3 was obtained, (440 mg, 49%) [α]_D²⁰ -82° (c, 2.0, chloroform), [Lit.^{7,8} [α]_D -82° (chloroform)], and also the α -linked disaccharide 4, (360 mg, 40%), [α]_D²⁰ -26° (c 1.0, chloroform), [Lit.⁸ [α]_D -30° (chloroform)].

3-O-(2,3:4,6-Di-O-cyclohexylidene-(α - and β -)-D-mannopyranosyl)-1,2:5,6-di-O-isopropylidene- α -D-glucopyranose (5, 6). After a reaction time of 5 days, using the above procedure, the β -linked disaccharide 5 was obtained (45%), [α]_D²⁰ -64° (c 6.0, chloroform), [Lit.⁸ [α]_D -68° (chloroform)] and also the α -linked disaccharide 6 (34%), [α]_D²⁰ +6° (c 3.5, chloroform), [Lit.⁸ [α]_D +3° (chloroform)].

p-Nitrophenyl 3,4,6-tri-O-acetyl-2-O-(2,3:4,6-di-O-cyclohexylidene-(α - and β -)-D-mannopyranosyl)- β -D-galactopyranoside (7, 8). After a reaction time of 34 days, using the above procedure, the β -linked disaccharide 7 was obtained (31%), [α]_D²⁰ -46°

(c 0.7, chloroform), [Lit.⁸ [α]_D -46° (chloroform)] and also the α -linked disaccharide 8 (28%), [α]_D²⁰ -6° (c, 0.5, chloroform), [Lit.⁸ [α]_D -3° (chloroform)].

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