



## Tuneable regioselectivity during the mono-etherification of the 2,3-diol of a mannose derivative



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This paper is dedicated to the memory of the late Dr. John M. Webber, distinguished carbohydrate chemist and founding editor of Carbohydrate Research

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### ABSTRACT

The paper reports selective mono-etherification of the 2-, and 3-hydroxyl groups of methyl 4,6-*O*-isopropylidene- $\alpha$ -D-mannopyranoside using tin(II) chloride catalysed reactions of diaryldiazomethanes. By the use of different diazo compounds and the variation of the tin(II) chloride concentration the ether formation can be shifted from over 90% 3-selectivity to over 90% 2-selectivity.

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### 1. Introduction

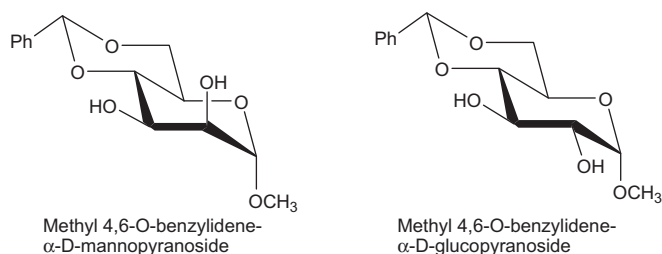
Many synthetic operations, both in oligosaccharide and general synthetic chemistry, require the selective protection of hydroxyl groups. This is particularly true for carbohydrate chemistry and general synthetic chemistry which uses carbohydrates and related compounds as chiral starting materials. Traditional acetal/ketal groups can give effective protection of hexoses and other monosaccharides, leaving from one to three free hydroxyl groups. These unprotected sites are then available for manipulations.<sup>1,2</sup> Compounds that are examples of this are the well-known 1,2:5,6-di-*O*-isopropylidene- $\alpha$ -D-glucofuranose or diacetoneglucose and 1,2-*O*-isopropylidene- $\alpha$ -D-glucofuranose or monacetoneglucose. Another well-established protection strategy starts from the easily available simple glycosides, methyl glycosides most commonly, followed by the 4,6-protection as an acetal or a ketal. This leaves the 2- and 3-hydroxyl groups free. Much work has been aimed at the selective protection of either of those two groups.<sup>3</sup> Interesting examples of this system are the methyl 4,6-*O*-benzylidene- $\alpha$ -D-mannopyranoside and the corresponding 4,6-*O*-isopropylidene.

These compounds contain a *cis* 2-axial-3-equatorial diol, whereas the equivalent *gluco* compounds are *trans eq-eq*. Preferential reaction of the sterically more accessible equatorial 3-OH for the manno compound is generally observed, although this varies greatly with reaction conditions. Thus, alkylations done under strongly basic conditions may prefer the more acidic 2-OH. The difference in reactivity is generally not so great as to be useful for either isomer on a preparative scale.<sup>4</sup> Very good regioselectivities of vicinal diols have, however, been achieved by forming stannylene acetals of these diols followed by alkylations or acylations.<sup>5–8</sup> Aritomi and Kawasaki's results during methylations of C- and O glycosides, that tin(II) chloride catalysed methylations with diazomethane gave a 3-OH methylation on the glucose moiety as well as a reaction of a phenolic OH present in the aglycone were of great interest. Other workers expanded this to include the use of tin(II) chloride to catalyse the reactions of aryl- or diaryldiazomethanes resulting in considerable regioselectivity.<sup>9–16</sup> The diaryldiazomethane methodology has the advantage over the stannylene acetal method that it is direct and does not require the separate step for the formation of the cyclic stannylene acetal.

Tin(II) chloride catalysed reactions of diaryldiazomethanes with methyl 4,6-*O*-benzylidene- $\alpha$ -D-mannopyranoside containing a *cis* vicinal 2-axial-3-equatorial diol gave almost exclusively 3-ether.

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**Figure 1.** Methyl 4,6-O-benzylidene- $\alpha$ -D-mannopyranoside and the gluco equivalent contain vicinal diol systems, *ax-eq* and *eq-eq* respectively.

This was explained by the greater steric accessibility of the equatorial OH (Fig. 1).<sup>17</sup>

The dihedral angle between the 2-C—O and the 3-C—O bonds is 60° for both mannopyranose and glucopyranose. It was therefore expected that the tin(II) chloride would catalyse reactions of the diazo compounds with methyl 4,6-O-benzylidene- $\alpha$ -D-glucopyranoside in a similar manner. Initially, this seemed not to be the case, but it was later found that the catalytic system was unstable at relatively high reagent concentrations with the *eq-eq* diol of the *gluco* compound. Tin(II) chloride catalysed reactions of diazodiphenylmethane with methyl 4,6-O-benzylidene- $\alpha$ -D-glucopyranoside at lower concentration were later performed and both the 2- and the 3-ether isolated in a ratio of 2:7 in about 90% overall yield.<sup>18</sup>

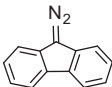
The 4,6-isopropylidene protection in combination with the diazodiarylmethyl ether protection is of interest since the isopropylidene is stable to hydrogenolysis, whereas both the diphenylmethyl ether and the 4,6-O-benzylidene groups can be removed with hydrogenolysis over palladium catalyst. It was therefore decided to repeat the benzhydrylation reactions on methyl 4,6-O-isopropylidene- $\alpha$ -D-mannopyranoside. The results from these reactions

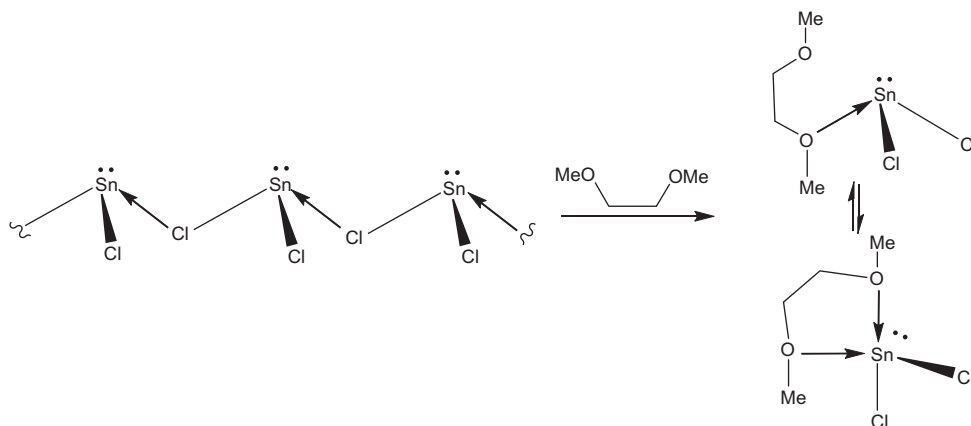
are summarized in Table 1 and, although isomers were not completely resolved, the results show a clear trend from a 3-O-selectivity in the case of diazo[bis(4-methoxyphenyl)]methane to an overriding 2-O-selectivity for diazofluorene.<sup>19</sup>

These reactions in the non-protic 1,2-dimethoxyethane solvent are different from the stannous chloride catalysed reactions of diazomethane with polyols in methanol which Shugar and co-workers claim to happen via the formation of 2-stanna-1,3-dioxolane involving the reaction of the methanol solvent with tin chloride.<sup>18,20</sup> Toman and collaborators have published a series of papers on tin(II) chloride catalysis of reactions of diazomethane and alkyl halides with polyols.<sup>21–24</sup> Their diazomethane reactions are also performed in methanol but the results are clearly consistent with cyclic complex formation involving the diol and tin chloride.<sup>25</sup> Anhydrous tin chloride is known to exist as a polymer chain where the tin atoms are linked through chlorine atoms by a covalent and a co-ordinate bond. With a donor solvent like methanol or 1,2-dimethoxyethane, used in the present work, the chain is dismantled forming co-ordinate bonds to the solvent.<sup>25,26</sup> For 1,2-dimethoxyethane as a solvent this could happen as illustrated in Figure 2.

Based on these observations and on general chemical principles a partial mechanism was proposed for the tin(II) chloride catalysed reactions of diaryldiazomethanes with diols. This is reproduced with minor modifications in Figure 3 with additional steps showing how an ether could be formed on one of the hydroxyl groups.<sup>27</sup> Tin(II) chloride dihydrate, which is normally formulated as SnCl<sub>2</sub>·2H<sub>2</sub>O has been shown to be [SnCl<sub>2</sub>(H<sub>2</sub>O)]·H<sub>2</sub>O containing the pyramidal SnCl<sub>2</sub>(H<sub>2</sub>O) structure (Sn—Cl, 259, Sn—O, 216 pm; mean bond angle 85°) and a separate more loosely bound H<sub>2</sub>O molecule.<sup>28</sup> A pyramidal structure such as 1 in Figure 3 must therefore be considered possible on mixing the tin(II) chloride with a diol in a non-protic solvent. Here a co-ordinate bond formed by a hydroxyl group's lone pair has replaced the ether co-ordinate bond.<sup>29</sup>

**Table 1**  
Results from the etherification of methyl 4,6-O-isopropylidene- $\alpha$ -D-mannopyranoside with diaryldiazomethanes/SnCl<sub>2</sub>

	3-Ether (%)	Unresolved (%)	2-Ether (%)	Total yield (%)
( <i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> ) <sub>2</sub> CN <sub>2</sub>	61	—	—	61
( <i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ) <sub>2</sub> CN <sub>2</sub>	60	24	8	92
( <i>p</i> -ClC <sub>6</sub> H <sub>4</sub> ) <sub>2</sub> CN <sub>2</sub>	40	12	42	94
(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CN <sub>2</sub>	39	20	38	97
	5	13	70	88



**Figure 2.** Depolymerisation of SnCl<sub>2</sub> chains by donor solvent.

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