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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-α-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.

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 acetel/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.[1,2] Compounds that are examples of this are the well-known 1,2:5, 6-di-*O*-isopropyliden-α-D-glucofuranose or diacetoneglucose and 1,2-*O*-isopropyliden-α-D-glucofuranose or monocetoneglucose. 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.[3] Interesting examples of this system are the methyl 4,6-*O*-benzylidene-α-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.[4] Very good regioselectivities of vicinal diols have, however, been achieved by forming stannylene acetals of these diols followed by alkylations or acylations.[5–8] 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 regioselectivety.[9–16] 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-α-D-mannopyranoside containing a *cis* vicinal 2-axial-3-equatorial diol gave almost exclusively 3-ether.

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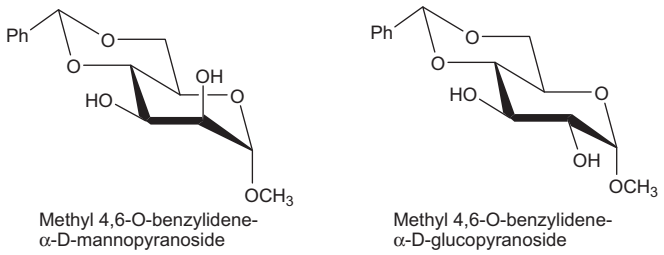


Figure 1. Methyl 4,6-O-benzylidene-α-D-mannopyranoside and the gluco equivalent contain vicinal diol systems, *ax–eq* and *eq–eq* respectively.

This was explained by the greater steric accessibility of the equatorial OH (Fig. 1).[17]

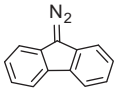
The dihedral angle between the 2-C—O and the 3-C—O bonds is 60° for both mannopyranose and glucopyranose. It was therefore expected that the tin(II) chloride would catalyse reactions of the diazo compounds with methyl 4,6-*O*-benzylidene-α-D-glucopyranoside in a similar manner. Initially, this seemed 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-α-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.[18]

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-α-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.[19]

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.[18,20] Toman and collaborators have published a series of papers on tin(II) chloride catalysis of reactions of diazomethane and alkyl halides with polyols.[21–24] Their diazomethane reactions are also performed in methanol but the results are clearly consistent with cyclic complex formation involving the diol and tin chloride.[25] 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.[25,26] 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.[27] Tin(II) chloride dihydrate, which is normally formulated as $SnCl_2 \cdot 2H_2O$ has been shown to be $[SnCl_2(H_2O)]\cdot H_2O$ containing the pyramidal $SnCl_2(H_2O)$ structure (Sn—Cl, 259, Sn-—O, 216 pm; mean bond angle 85°) and a separate more loosely bound H_2O molecule.[28] 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.[29]

Table 1
Results from the etherification of methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside with diaryldiazomethanes/$SnCl_2$

	3-Ether (%)	Unresolved (%)	2-Ether (%)	Total yield (%)
$(p\text{-}CH_3OC_6H_4)_2CN_2$	61	—	—	61
$(p\text{-}CH_3C_6H_4)_2CN_2$	60	24	8	92
$(p\text{-}ClC_6H_4)_2CN_2$	40	12	42	94
$(C_6H_5)_2CN_2$	39	20	38	97
	5	13	70	88

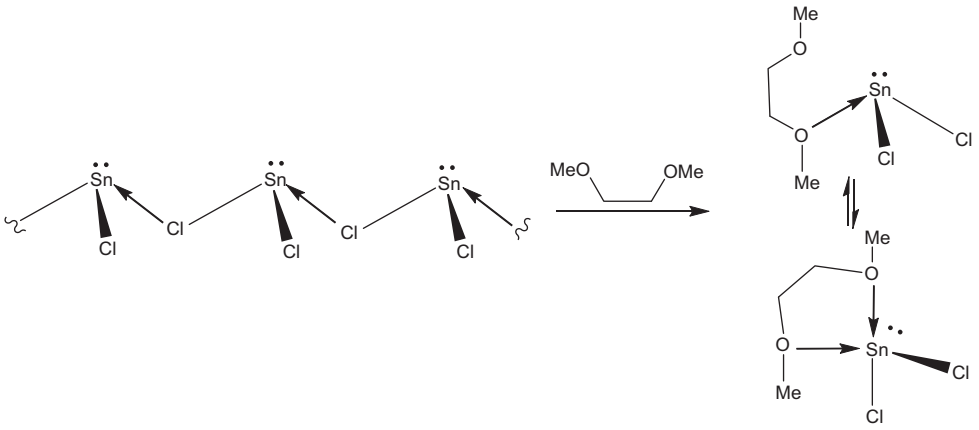


Figure 2. Depolymerisation of $SnCl_2$ chains by donor solvent.

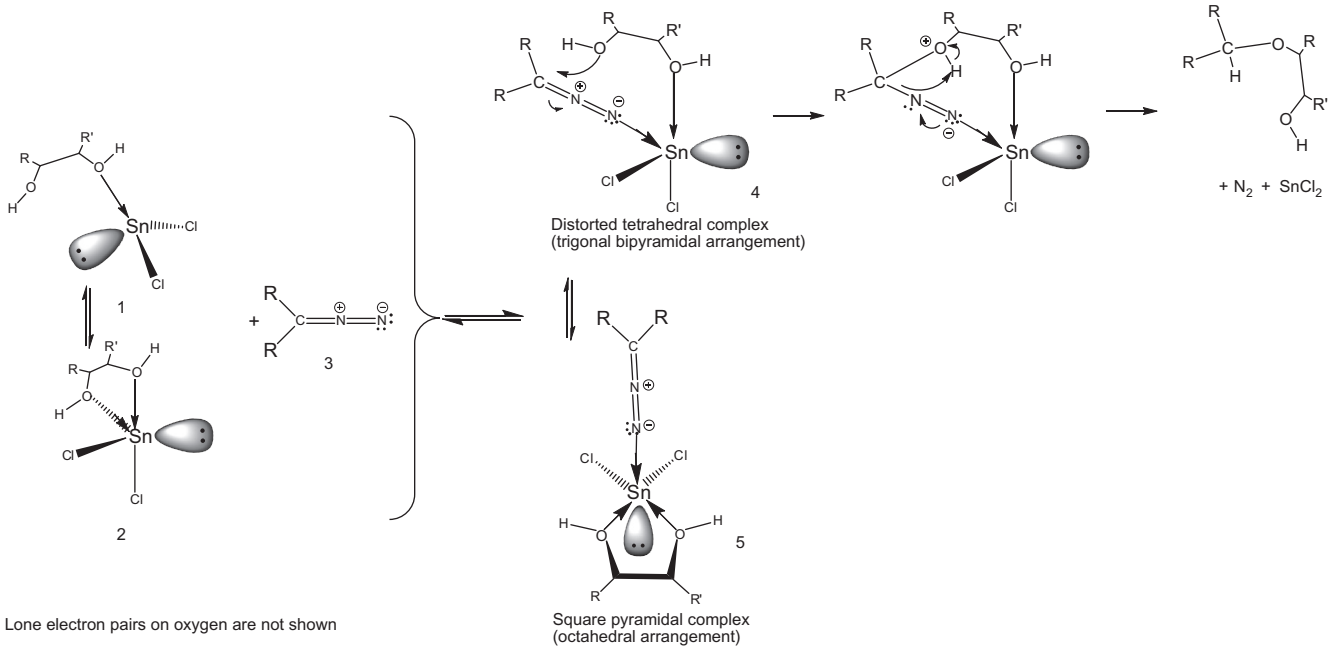


Figure 3. Suggested partial mechanism for the tin(II) chloride catalysed reaction.

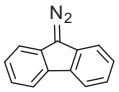
It is proposed that a diol would be more likely to form a second coordinate bond to the tin atom than another H_2O, which does not happen in the case of $[SnCl_2(H_2O)]\cdot H_2O$. If that were to happen the distorted tetrahedral structure 2 in Figure 3 would be formed, with the lone pair on tin in the equatorial position. The diazo compound's terminal nitrogen is a powerful ligand.[30] Complex formation of this ligand with 1 or 2 gives complexes 4 and 5. The free OH in complex 4 is well positioned to react with the diazo carbon giving an ether with release of molecular nitrogen happening before or concurrently. Since the 4,6-*O*-benylidene gives an overwhelming 3-selectivity the 2-OH must be the hydroxyl group, which complexes first with the tin(II) chloride leaving the 3-OH to react with the diazo carbon in 4. This could explain the almost exclusive 3-O-regioselectity in reactions with methyl 4,6-*O*-benzylidene-α-D-mannopyranoside. The formation of the square pyramidal complex 5 seems more likely to give a reaction of either hydroxyl group and a trend towards the more acidic hydroxyl group as the acid stability of the diazo compound increases would also result since increased reactivity with the diazo carbon by the more acidic OH results. This could explain what is happening during the reactions of the five diazo compounds with methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside. It seems reasonable to assume that the two mannose derivatives could show different ligand arrangements around the divalent tin but firm evidence showing that only the 4,6-*O*-isopropylidene forms the square pyramidal complex is not available.

2. Results and discussion

Following recent use of tin(II) bromide, instead of the chloride, as a catalyst in mono-etherification of diols a re-examination of some of these reactions has been undertaken.[31] It was observed that the tin(II) chloride catalyst used during this work was an order of magnitude more active than the sample used in the original study as observed by shorter reaction times.[17] More importantly, the relative amounts of the 3- and the 2-ethers formed from reactions with methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside were very different, giving a much higher 3-selectivity than observed previously. A plausible explanation for this seemed to be that the lower reaction rate observed earlier was due to a deteriorated sample of the catalyst and only a fraction of the material added was in fact tin(II) chloride. To test this hypothesis experiments were therefore conducted to ascertain whether lowering of the catalyst concentration resulted in a shift from high 3-OH selectivity to a significant or even overwhelming 2-OH reaction. The diazo compounds selected for this investigation were diazo[bis(4-methylphenyl)]methane, diazo[bis(4-chlorophenyl)] methane, diazodiphenylmethane, and diazofluorene. Experiments were conducted for each diazo compound using at least two different catalyst concentrations, 1.7 mM $SnCl_2$ (3.4 molar %) and 1/10 of this amount or 0.17 mM $SnCl_2$ (0.34 molar %). Up to four different catalyst concentrations were used. The results are shown in Table 2 and Figure 4. For convenience this series of reactions were done on a 0.5 millimolar scale, but the scaling up of these reactions to multigram amounts is easily done as was demonstrated in our original work.[17,19]

The results in Table 2 and Figure 4 show clearly a shift from 3-selectivity to 2-selectivity for this series of diazo compounds. This shift has been observed before and seems to follow the reactivity of the diazo compounds, that is to say that the most reactive, diazo[bis(4-methylphenyl)]methane, goes overwhelmingly for the 3-OH and the least reactive, diazofluorene, reacts preferentially with the 2-OH. Diazo[bis(4-chlorophenyl)]methane and diazomethane are intermediate in reactivity and also in selectivity. The 3-selectivity is rather higher for the dichloro compound even if its rate of reaction is only about a quarter of that for the parent diazodiphenylmethane pointing to a non-electronic component affecting selectivity as well. More interestingly and in accordance with the hypothesis, the results show a shift towards increased 2-selectivity on reduction of the tin(II) chloride concentration from 1.7 mM to 0.042 mM. This happens for all the diazo compounds. This agrees with the earlier proposed mechanism that is, with lower tin(II) chloride concentration the intramolecular shift from 1 to 2 in Figure 3 is expected to be relatively more likely to happen before the complexation with the diazo compound.

Table 2
Yields and 3-ether/2-ether ratios from reactions of selected diazo compounds with methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside using different concentrations of the tin(II) chloride catalyst

Diazo compound	[$SnCl_2$] = 1.7 mM		[$SnCl_2$] = 0.85 mM		[$SnCl_2$] = 0.17 mM		[$SnCl_2$] = 0.085 mM	
	3-Ether (%)	2-Ether (%)	3-Ether (%)	2-Ether (%)	3-Ether (%)	2-Ether (%)	3-Ether (%)	2-Ether (%)
(p-$CH_3C_6H_4)_2CN_2$	98	1.9			76	24		
Total yield (%)	87				60			
(p-$ClC_6H_4)_2CN_2$	81	19	52	48	40	60		
Total yield (%)	62		53		62			
$(C_6H_5)_2CN_2$	72	28			28	72		
Total yield (%)	86				76			
	40	60	14	86	10	90	6.0	94
Total yield (%)	75		85		91		84	

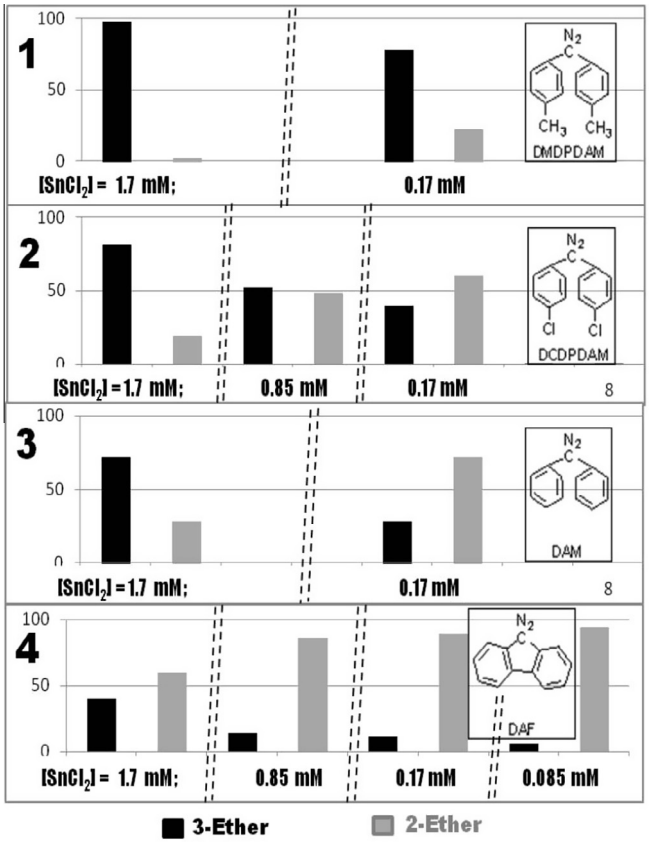


Figure 4. The relative yields of the 3- and the 2-ethers from the etherification reactions of methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside with diazo[bis(4-methylphenyl)]methane (1), diazo[bis(4-chlorophenyl)]methane (2), diazomethane (3) and diazofluorene (4) for varying concentrations of the $SnCl_2$ catalyst.

3. Conclusions

In conclusion it can be stated that these results as a whole in terms of regioselective 2-OH/3-OH protection using the two variables, that is the different diazo compounds and secondly the varying catalyst concentrations that the methodology represents a tuneable regioselectivity for the methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside system. Thus diazo[bis(4-methylphenyl)]methane with high concentration of catalyst (1.7 mM) gives 98% selectivity for the 3-OH. The most reactive diazo compound, diazo[bis(4-methoxyphenyl)]methane, was not included in this series, but earlier reactions for this compound gave no 2-ether.[15] Alternatively using the least reactive diazo compound, diazofluorene, and a low catalyst concentration (0.084 mM) resulted in a similar over-all yield of 87% but with a 6.0% 3-selectivity and 94% 2-selectivity. Investigation of other similar systems awaits future research.

4. Experimental section

The reactions of the diazo compounds with methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside were done on a half millimolar scale in dry 1,2-dimethoxyethane (10 mL). The products were identified by proton and carbon-13 NMR by comparison with previously characterized compounds.[15] Compounds were separated on columns of silica gel and weight. Where separations were not complete, amounts of 2- and 3-ethers in overlapping fractions were estimated by NMR integration of suitable peaks, usually the Ar_2-C*HO*– or the isopropylidene methyl peaks or from HPLC peak integrations.

4.1. General methods

Thin layer chromatography (TLC) was carried out on aluminium sheets coated with silica gel 60-F_{254} and detected using a spray of 0.2% w/v cerium(IV) sulphate and 5% ammonium molybdate in 2 M sulphuric acid with heating. ^1H and ^{13}C NMR spectra were run at 298 K on a Bruker AV400 instrument with Me_4Si as the external standard. Diaryldiazomethanes were prepared using published methods.[32] General reagents and the catalyst were from chemical suppliers and usually used without further purification. 1,2-Dimethoxyethane was distilled from and stored over sodium. Ethyl acetate and hexane were of HPLC grade and used as received. The HPLC instrument was Shimadzu Prominence with a reversed phase 150 × 4.6 mm SS Wakosil C18RS 3 mm column. The elution was isocratic with methanol/water 4:1 and detection was done with a UV detector at 254 nm.

4.2. Reaction of diazo[bis(4-methylphenyl)]methane with methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside ([$SnCl_2$] = 1.7 mM)

Methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside, 117 mg, 0.500 mmol, was dissolved in 1,2-dimethoxyethane (DME)/1.7 mM $SnCl_2$, 10 mL. The reaction mixture was cooled on an ice bath and diazo[bis(4-methylphenyl)]methane, 167 mg, 0.750 mmol, and the reaction allowed to go to completion in 45 min. The solvent was evaporated to dryness and the products purified on a column of silica gel eluting with hexane/ethyl acetate 9:1, 4:1 and finally 3:2. Methyl 4,6-*O*-isopropylidene-2-*O*-[di(4-methylphenyl)methyl]-α-D-mannopyranoside, 3.6 mg (H1-NMR: SP291012A), was isolated from the early fractions followed by an

unresolved mixture of the 2- and 3-ether, 80.8 mg (SP291012B; the faster 2-ether was in an insignificant amount according to NMR), and finally methyl 4,6-*O*-isopropylidene-3-*O*-[di(4-methylphenyl) methyl]-α-D-mannopyranoside, 101.1 mg (SP291012D). The total yield was 186 mg, 86.6%. The 3-ether/2-ether ratio is 98:2.0.

4.3. Reaction of diazo[bis(4-methylphenyl)]methane with methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside ([$SnCl_2$] = 0.17 mM)

Methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside, 117 mg, 0.500 mmol, was dissolved in 1,2-dimethoxyethane (DME)/ 0.17 mM $SnCl_2$, 10 mL. The reaction mixture was cooled on an ice bath and diazo[bis(4-methylphenyl)]methane, 167 mg, 0.750 mmol, and the reaction allowed to go to completion in 75 min. The solvent was evaporated to dryness and the products were purified on a column of silica gel eluting with hexane/ethyl acetate 9:1, 4:1 and finally 3:2. Methyl 4,6-*O*-isopropylidene-2-*O*-[di(4-methylphenyl)methyl]-α-D-mannopyranoside, 23.8 mg (SP291012A), was isolated from the early fractions followed by an unresolved mixture of the 2- and 3-ether, 33.4 mg (SP291012C), and finally methyl 4,6-*O*-isopropylidene-3-*O*-[di(4-methylphenyl)methyl]-α-D-mannopyranoside, 69.3 mg (SP291012D). The total yield was 127 mg, 59.0%. NMR analysis gave a 3-ether/2-ether ratio 76:24.

Methyl 4,6-*O*-isopropylidene-2-*O*-[di(4-methylphenyl)methyl]-α-D-mannopyranoside:

^{1}H NMR ($CDCl_3$): δ 1.37 & 1.48 (2 × 3H s, $C(CH_3)_2$), 2.02 (1H s, –OH), 2.25 & 2.26 (2 × 3H s, 2xAr-CH_3), 3.17 (3H, s, –OCH3), 3.50 (1H m, H-6A), 3.78 (4H m, H-2, H-3, H-5 & H-6B), 3.93 (1 H, t(apparent), $J_{H4–H3\ \&\ H4–H5}$ 9.4 Hz, H-4), 4.49 (1H s, H-1), 5.46 (1H s, Ar_2-CH), 7.05–7.18 (8 H, m, aromatic protons). ^{13}C NMR ($CDCl_3$): δ 19.35 & 29.27 ($C(CH_3)_2$), 20.96 (2xAr_2-CH_3), 54.83 (–OCH3), 62.44 (C-6), 64.03 (C-2), 69.22 (C-5), 72.32 (C-4), 72.42 (C-3) 84.20 (C-1), 99.80 (Ar_2-CHO–), 100.0 ($C(CH_3)_2$), 127.2, 129.1, 129.3, 137.4, 137.6, 138.8, 139.0 (aromatic C).

Methyl 4,6-*O*-isopropylidene-3-*O*-[di(4-methylphenyl)methyl]-α-D-mannopyranoside:

^{1}H NMR ($CDCl_3$): δ 1.49 & 1.55 (2 × 3H s, $C(CH_3)_2$), 2.37 & 2.39 (2 × 3H s, 2 × Ar-CH_3), 2.76 (1H s, –OH), 3.39 (3H, s, –OCH3), 3.64 (1H m, H-6A), 3.83 (1H dd, $J_{H3–H2}$ 3.53 Hz, $J_{H3–H4}$ 9.4 Hz, H-3), 3.89 (1H, m, H-5 & H-6B), 3.98 (1H dd, $J_{H2–H1}$ 1.26 Hz, $J_{H2–H3}$ 3.54 Hz, H-2), 4.20 (1H t(apparent), $J_{H4–H3}$ & $J_{H4–H5}$ 9.58 Hz, H-4), 4.74 (1H d, $J_{H1–H2}$ 1.26 Hz, H1), 5.34 (1H s, Ar_2-CH), 7.14–7.30 (8H, m, aromatic protons). ^{13}C NMR ($CDCl_3$): δ 19.57 & 29.40 ($C(CH_3)_2$), 21.22 (2 × Ar_2-CH_3), 54.81 (–OCH3), 62.54 (C-6), 64.06 (C-2), 70.32 (C-5), 71.68 (C-4), 74.49 (C-3), 82.88 (C-1), 99.68 ($C(CH_3)_2$), 101.0 (Ar_2-C HO–) 127.2, 129.1, 129.3, 137.4, 137.6, 138.8, 139.0 (aromatic C).

4.4. Reaction of diazodiphenylmethane with methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside ([$SnCl_2$] = 1.7 M)

Methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside, 117 mg, 0.500 mmol, was dissolved in 1,2-dimethoxyethane (DME), 10 mL, and tin(II) chloride, 3.2 mg, 0.017 mmol, was added followed by diazodiphenylmethane, 145 mg, 0.750 mmol. After 1 h reaction time the solution had a faint pink colour showing that it has gone virtually to completion. After complete disappearance of the pink colour some dry silica gel was added and the solvent evaporated to dryness and the products purified on a column of silica gel eluting with hexane/ethyl acetate 9:1, 4:1 and finally 3:2. Fractions 27–29 contained the minor component, methyl 2-*O*-diphenylmethyl-4,6-*O*-isopropylidene-α-D-mannopyranoside, 33 mg, 16% (SP030812B). Fractions 30–32 contained the major component, methyl 3-*O*-diphenylmethyl-4,6-*O*-isopropylidene-α-D-mannopyranoside and some minor component, 141 mg, 70%, giving a total yield of 86%. NMR showed fractions 30–32 to represent a 62% yield of the 3-ether and 8% yield of the 2-ether, based on the Ph_2C**H**– integration. The 3-ether/2-ether ratio is therefore 72%:28%.

4.5. Reaction of diazodiphenylmethane with methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside ([$SnCl_2$] = 0.17 M)

Tin(II) chloride solution: The tin(II) chloride solution was prepared by dissolving 3.2 mg, 0.017 mmol, of tin(II) chloride in 10 mL of 1,2-dimethoxyethane (DME); a 10× dilution was prepared by diluting 1.0 mL to a total volume of 10 mL.

Methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside, 117 mg, 0.500 mmol, was dissolved in DME, 9 mL and 1.0 mL of the tin(II) chloride solution, 0.32 mg, 0.0017 mmol, was added followed by diazodiphenylmethane, 145 mg, 0.750 mmol. After 4.5 h reaction time the solution had a pink colour showing that it was close to completion. The reaction was allowed to go to completion overnight. Some dry silica gel was added and the solvent evaporated to dryness and the products purified on a column of silica gel eluting with hexane/ethyl acetate 9:1 to 3:2. Fractions 12–13 contained the major component, methyl 2-*O*-diphenylmethyl-4,6-*O*-isopropylidene-α-D-mannopyranoside, 110 mg, 55% (SP030812B). Fractions 14–17 contained the minor component, methyl 3-*O*-diphenylmethyl-4,6-*O*-isopropylidene-α-D-mannopyranoside and a trace of the minor component, 42 mg, 21%, giving a total yield of 76%. The 3-ether/2-ether ratio is therefore 28%:72%.

Methyl 4,6-*O*-isopropylidene-2-*O*-diphenylmethyl-α-D-mannopyranoside:

^{1}H NMR ($CDCl_3$): δ 1.50 & 1.62 (2 × 3H s, $C(CH_3)_2$), 2.25 (1H d, $J_{OH–H3}$ 6.9 Hz, –OH), 3.29 (3H,s, –OCH3), 3.65 (1H m, H-6A), 3.94 (4H m, H-2, H-3, H-5 & H-6B), 4.09 (1H, t(apparent), $J_{H4–H3\ \&\ H4–H5}$ 9.5 Hz, H-4), 4.61 (1H s, H-1), 5.71 (1H s, Ph_2-CH), 7.31–7.438 (10H, m, aromatic protons). ^{13}C NMR ($CDCl_3$): δ 19.38 & 29.36 ($C(CH_3)_2$), 54.92 (–OCH3), 62.45(C-6), 64.33 (C-2), 69.34 (C-5), 72.29 (C-4), 77.46 (C-3) 84.49 (C-1), 99.97 ($C(CH_3)_2$), 100.0 (Ph_2-CHO–), 127.2–128.5 & 141.7 (aromatic C).

Methyl 4,6-*O*-isopropylidene-3-*O*-diphenylmethyl-α-D-mannopyranoside:

^{1}H NMR ($CDCl_3$): δ 1.35 & 1.48 (2 × 3H s, $C(CH_3)_2$), 2.62 (1H s, –OH), 3.24 (3H,s, –OCH3), 3.51 (1H m, H-6A), 3.71–3.79 (3H m, H-3, H-5 & H-6B), 3.87 (1H d, $J_{H2–H3}$, 2.65 Hz, H-2), 4.07 (1H, t(apparent), $J_{H4–H3\ \&\ H4–H5}$ 9.6 Hz, H-4), 4.62 (1H d, $J_{H1–H2}$ 1.0 Hz, H-1), 5.74 (1H s, Ph_2-CH), 7.16–7.27 (10H, m, aromatic protons). ^{13}C NMR ($CDCl_3$): δ 19.27 & 29.39 ($C(CH_3)_2$), 54.83 (–OCH3), 62.52 (C-6), 64.04 (C-2), 70.39 (C-4), 71.44 (C-5), 74.94 (C-3) 83.24 (C-1), 99.69 ($C(CH_3)_2$), 101.0 (Ph_2CHO–), 127.2–128.7 & 142.1, 142.4 (aromatic C).

4.6. Reaction of diazo[bis(4-chlorophenyl)]methane with methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside ([$SnCl_2$] = 1.7 mM)

Methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside, 117 mg, 0.500 mmol, was dissolved in 1,2-dimethoxyethane (DME), 10 mL, and tin(II) chloride, 3.2 mg, 0.017 mmol, was added followed by diazo[bis(4-chlorophenyl)]methane, 144 mg, 0.547 mmol. The reaction had gone to completion in less than 2 h. Some dry silica gel was added and the solvent evaporated to dryness and the products purified on a column of silica gel eluting with hexane/ethyl acetate 4:1–3:2. Fractions 13–14 contained the minor component, methyl 2-*O*-[di(4-chlorophenyl)methyl]-4,6-*O*-isopropylidene-α-D-mannopyranoside, 28 mg, 12%. Found: 491.1017 g/mol; $C_{23}H_{26}Cl_2O_6 \cdot Na^+$ requires 491.0999 g/mol. Fractions 15–18 contained the major component, methyl 3-*O*-[di(4-chlorophenyl)methyl]-4,6-*O*-isopropylidene-α-D-mannopyranoside, 120 mg, 50% (SP030812C), giving

a total yield of 62%. Found: 491.0992 g/mol; $C_{23}H_{26}Cl_2O_6{\cdot}Na^+$ requires 491.0999 g/mol. The 3-ether/2-ether ratio is 81:19.

4.7. Reaction of diazo[bis(4-chlorophenyl)]methane with methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside ([$SnCl_2$] = 0.85 mM)

Methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside, 117 mg, 0.500 mmol, was dissolved in 1,2-dimethoxyethane (DME), 10 mL, and tin(II) chloride, 1.6 mg, 0.0085 mmol, was added followed by diazo[bis(4-chlorophenyl)]methane, 196 mg, 0.745 mmol, and the reaction was allowed to go to completion overnight. Some dry silica gel was added and the solvent evaporated to dryness and the products purified on a column of silica gel eluting with hexane/ethyl acetate 9:1, then 4:1 and finally 3:1. Fractions 13–17 contained the minor component, methyl 2-*O*-[di(4-chlorophenyl)methyl]-4,6-*O*-isopropylidene-α-D-mannopyranoside, 54 mg contamin (SP291112A-2). Fractions 18-21 contained the major component, methyl 3-*O*-[di(4-chlorophenyl)methyl]-4,6-*O*-isopropylidene-α-D-mannopyranoside, and 6% of the minor component as judged by isopropylidene methyl proton integration, 70 mg (SP291112B-2). The 2-ether formed is therefore 54 + 4 = 58 mg, 25% and the 3-ether formed is 70−4 = 66 mg, 28%, giving a total yield of 53%. The 3-ether/2-ether ratio is 52:48.

4.8. Reaction of diazo[bis(4-chlorophenyl)]methane with methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside ([$SnCl_2$] = 0.17 M)

Tin(II) chloride solution: The tin(II) chloride solution was prepared by dissolving 3.2 mg, 0.017 mmol, of tin(II) chloride in 10 mL of 1,2-dimethoxyethane (DME) and making a 10× dilution by diluting 1.0 mL to a total volume of 10 mL.

Methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside, 117 mg, 0.500 mmol, was dissolved in DME, 9 mL and 1.0 mL of the tin(II) chloride solution (0.32 mg, 0.0017 mmol, of tin(II) chloride) was added followed by diazo[bis(4-chlorophenyl)]methane, 144 mg, 0.550 mmol. The reaction was left to go to completion overnight. Some dry silica gel was added and the solvent evaporated to dryness and the products purified on a column of silica gel eluting with hexane/ethyl acetate 4:1–3:2. Fractions 11–13 contained 95 mg of mono-ether consisting of 79 mg of the major component, methyl 2-*O*-[di(4-chlorophenyl)methyl]-4,6-*O*-isopropylidene-α-D-mannopyranoside, and 16 mg of the 3-ether, methyl 3-*O*-[di(4-chlorophenyl)methyl]-4,6-*O*-isopropylidene-α-D-mannopyranoside, as determined by the benzhydryl proton integration (SP030812D). Fractions 14–15 contained the minor 3-ether, 37 + 16 = 53 mg. Total yield is 132 mg, 62% and the 3-ether/2-ether ratio is 40:60.

Methyl 4,6-*O*-isopropylidene-2-*O*-[di(4-chlorophenyl)methyl]-α-D-mannopyranoside:

^{1}H NMR ($CDCl_3$): δ 1.36 & 1.47 (2 × 3H s, $C(CH_3)_2$), 2.06 (1H s, –OH), 3.18 (3H, s, –OCH3), 3.65 (1H m, H-6A), 3.7–3.9 (4H m, H-2, H-3, H-5 & H-6B), 3.93 (1H, t(apparent), $J_{H4-H3\ \&\ H4-H5}$ 9.6 Hz, H-4), 4.45 (1H d, J_{H1-H2} 1.26 Hz, H-1), 5.57 (1H s, Ar_2-CH), 7.15–7.27 (8H, m, aromatic protons). ^{13}C NMR ($CDCl_3$): δ 19.14 & 29.29 ($C(CH_3)_2$), 54.87 (–OCH3), 62.36 (C-6), 64.34 (C-2), 69.58 (C-5), 71.68 (C-4), 77.34 (C-3), 82.89 (C-1), 100.0 ($C(CH_3)_2$), 100.8 (Ar_2CHO–), 127.9–139.9 (aromatic C).

Methyl 4,6-*O*-isopropylidene-3-*O*-[di(4-chlorophenyl)methyl]-α-D-mannopyranoside:

^{1}H NMR ($CDCl_3$): δ 1.48 & 1.52 (2 × 3H s, $C(CH_3)_2$), 2.67 (1H s, –OH), 3.34 (3H, s, –OCH3), 3.62 (1H m, H-6A), 3.80 (1H dd, J_{H3-H2} 3.47 J_{H3-H4} 9.20 Hz, H-3), 3.84–3.90 (2H m, H-5 & H-6B), 3.97 (1H, d(apparent), J_{H2-H3} 3.31 Hz, H-2), 4.19 (1H, t(apparent), $J_{H4-H3\ \&\ H4-H5}$ 9.6 Hz, H-4), 4.74 (1H s, H-1), 5.80 (1H s, Ar_2-CH), 7.27–7.68 (8H, m, aromatic protons). ^{13}C NMR ($CDCl_3$): δ 18.92 & 29.329 ($C(CH_3)_2$), 54.87 (–OCH3), 62.44 (C-6), 64.01 (C-2), 70.17 (C-4), 71.54 (C-5), 75.08 (C-3), 81.93 (C-1), 99.78 ($C(CH_3)_2$), 100.92 (Ar_2CHO–), 128.7–128.9 (Ar C2/6 & C3/5), 133.5, 133.8 (Ar C4), 140.0, 140.4 (Ar C1).

4.9. Reaction of diazofluorene with methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside ([$SnCl_2$] = 1.7 mM)

Methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside, 117 mg, 0.500 mmol, was dissolved in 1,2-dimethoxyethane (DME), 10 mL, and tin(II) chloride, 3.2 mg, 0.017 mmol, was added followed by diazofluorene, 144 mg, 0.750 mmol. The reaction was left to go to completion overnight and then the products were separated on a column of silica gel eluting with hexane/ethyl acetate 9:1 to 7:3. Methyl 2-*O*-(9*H*-fluoren-9-yl)-4,6-*O*-isopropylidene-α-D-mannopyranoside was isolated from fractions 14–15, 72 mg, 36% (SP170812A_H1) and fractions 16–19 contained methyl 3-*O*-(9*H*-fluoren-9-yl)-4,6-*O*-isopropylidene-α-D-mannopyranoside and some of the 2-ether, 77 mg, 39%. NMR showed fractions 16–19 to be 30% 3-ether and 9% the 2-ether (SP170812B_H1). This gives a total yield of 75% and the 2-ether/3/ether ratio as 60:40.

4.10. Reaction of diazofluorene with methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside ([$SnCl_2$] = 0.85 mM)

Methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside, 117 mg, 0.500 mmol, was dissolved in 1,2-dimethoxyethane (DME), 10 mL, and tin(II) chloride, 1.6 mg, 0.0085 mmol, was added followed by diazofluorene, 144 mg, 0.750 mmol. The reaction was left to go to completion for two days and then the products were passed through a column of silica gel eluting with hexane/ethyl acetate 9:1–3:2. The unresolved mixture of methyl 2-*O*-(9*H*-fluoren-9-yl)-4,6-*O*-isopropylidene-α-D-mannopyranoside and methyl 3-O-(9*H*-fluoren-9-yl)-4,6-*O*-isopropylidene-α-D-mannopyranoside was isolated from fractions 17–26, 170 mg, 85% (SP301112B_2_H1). NMR (Fl = C***H***– peak) analysis showed this to be a 2-ether/3-ether mixture of 86:14.

4.11. Reaction of diazofluorene with methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside ([$SnCl_2$] = 0.17 mM)

Tin(II) chloride solution: The tin(II) chloride solution was prepared by dissolving 3.2 mg, 0.017 mmol, of tin(II) chloride in 10 mL of 1,2-dimethoxyethane (DME); a 10× dilution was prepared by diluting 1.0 mL to a total volume of 10 mL.

Methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside, 117 mg, 0.500 mmol, was dissolved in 1,2-dimethoxyethane (DME), 9.0 mL, and 1.0 mL of the diluted tin(II) chloride solution, 0.32 mg, 0.00017 mmol, was added followed by diazofluorene, 144 mg, 0.750 mmol. The reaction was left for three days to go to completion and then the products were passed through a column of silica gel eluting with hexane/ethyl acetate 9:1–7:3. Methyl 2-O-(9*H*-fluoren-9-yl)-4,6-O-isopropylidene-α-D-mannopyranoside was isolated from fractions 22-24, 153 mg, 77% (SP160812A_H1) and fractions 25-27 contained methyl 3-*O*-(9*H*-fluoren-9-yl)-4,6-*O*-isopropylidene-α-D-mannopyranoside and some of the 2-ether, 28 mg (SP160812B_H1). NMR (Fl = C***H***– peak) showed this to be 9% yield of the 3-ether and 5% yield of the 2-ether, giving a total yield of the 2-ether as 82% and the combined yield of 91%. The 2-ether/3-ether ratio is 90:10

4.12. Reaction of diazofluorene with methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside ([$SnCl_2$] = 0.085 mM)

Tin(II) chloride solution: The tin(II) chloride solution was prepared by dissolving 3.2 mg, 0.017 mmol, of tin(II) chloride in 10 mL of 1,2-dimethoxyethane (DME); a 20× dilution was prepared by diluting 0.5 mL to a total volume of 10 mL.

Methyl 4,6-*O*-isopropylidene-α-D-0.5 mL of the $SnCl_2$ solution was added followed by diazofluorene, 144 mg, 0.750 mmol, was then added. The reaction was left to go to completion over 24 h. The products were isolated off a column of silica gel, eluting with hexane/ethyl acetate 9:1–7:3. The early fractions contained pure methyl 2-*O*-(9*H*-fluoren-9-yl)-4,6-*O*-isopropylidene-α-D-mannopyranoside, 161.1 mg, followed by mixed fractions containing 18.5 mg. Reversed phase HPLC analysis (see Supplements) gave product 2, 3-ether, at 5.670 min, relative integration area: 12,472,228 or 72% and product 1,2-ether, at 7.701 min, relative integration area: 4,799,611 or 28%. Pure methyl 3-*O*-(9*H*-fluoren-9-yl)-4,6-*O*-isopropylidene-α-D-mannopyranoside, 6.9 mg was then obtained from the later fractions. Found: 421.1639 g/mol; $C_{23}H_{26}O_6{\cdot}Na^+$ requires 421.1622 g/mol. Total 2-ether produced was therefore: 161.1 + 13.4 = 174.5 mg and 3-ether: 5.1 + 6.9 = 12 mg, giving a total yield of mono-ethers as 186.5 mg, 93.6% and a 2-ether and 3-ether ratio of 94:6.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carres.2014.02.016.

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