Háskólinn á Akureyri

Regioselective mono-etherification of vicinal diols using tin(II) halide catalysts and diazo compounds

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June 2015

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Master thesis for 90 credit M.Sc. in Biotechnology

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Útdráttur

Staðvendnir (regioselective) varnarhópar eru þýðingarmiklir í efnafræði kolhydrata. Sú rannsókn sem fjallað er um í þessari ritgerð tók fyrir not tin(II) klóríð og tin(II) brómíð hvata við einalkylerun hliðlægra díóla í 4,6-asetal vörðum mannósíðum og glúkósíði með fimm mismunandi diazo efnasamböndum, þ.e. diazo[*bis*(4-methoxyphenyl)]methane, diazo[*bis*(4-methylphenyl)]methan, diazodiphenylmethane, diazo[*bis*(4-chlorophenyl)]methane og diazofluorene.

Frumathugun var einnig gerð á notkun Magtrieve^{TM} (chromium(IV) oxide) sem vistvæns og endurnýtanlegs oxunarmiðils við myndun diazoefnasambanda úr tilheyrandi hydrasónum. Tilraunir sem miðuðu að því að hámarka heimtur úr þessum oxunarhvörfum sýndu að 15 móljafngildi af Magtrieve^{TM} nægði til þess að mynda diazo efnasamböndin á tveimur klukkustundum eða minna. Þegar þessar tilraunir voru gerðar á meira magni hvarfefna kom í ljós að heimtur voru sambærilegar við ‘mercury(II) oxide‘ oxunaraðferðina. Til þess að sýna fram á notagildi aðferðarinnar voru tvær tilraunir framkvæmdar þar sem diazoefnasambandið var myndað með MagtrieveTM aðferðinni og það síðan tekið beint og án einangrunar í hvarf við methyl 4,6-*O*-benzylidene-α-D-mannopyranoside. Þessi hvörf gáfu góðar heimtur og góða staðvendni fyrir 3-OH hópinn.

Síðan voru framkvæmd hvörf sem báru saman tin(II) klóríð og tin(II) brómíð hvötun í hvörfum við methyl 4,6-*O*-benzylidene- og 4,6-*O*-isopropylidene-α-D-mannopyranoside. Flest diazoefnasamböndin sem tekin voru fyrir gáfu eingöngu 3-OH staðvendni í hvörfum við 4,6-benzylidene kerfið. Diazodiphenylmethane gaf einnig fyrst og fremst 3-*O*-eterinn, en smávegis af 2-*O*-eternum var einnig einangrað í því tilfelli. Tin(II) halíð hvötuð hvörf diazoefnasambandanna við 4,6-*O*-isopropylidene mannokerfið gáfu hins vegar bæði 2-*O*- og 3-*O*-etera þar sem 3-eterinn var þó í meira magni í flestum tilfellum. Áhugaverð undantekning frá þessu eru hvörf diazofluorene en í því tilfelli var 2-*O*-eterinn í meira magni. Rannsóknir á hvörfum við methyl 4,6-*O*-

benzylidene-α-D-glucopyranoside voru erfiðar þar sem hvatakerfið er óstöðugt í þessu tilfelli. Heimtur voru þó ásættanlegar og 3-*O*-eterinn myndaðist í meira magni.

Athugun var loks gerð á áhrifum styrks tin(II) klóríðs á staðvendni hvarfa diazoefnasambandanna við methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside. Þessi rannsókn sýndi að hár styrkur hvatans jók myndun 3-*O*-etersins en við minnkandi styrk hvatans jókst myndun 2-*O*-etersins. Diazofluorene er sérstaklega áhugavert, en þetta efnasamband gaf hlutfallslega yfir 90% staðvendni fyrir 2-OH hópinn.

Abstract

Regioselective protecting group strategies are of great importance in carbohydrate chemistry. This investigation examined the use of tin(II) chloride and tin(II) bromide as catalysts for mono-alkylation of the vicinal diol systems of 4,6-acetal protected mannosides and glucosides using five diazo compounds, namely diazo[*bis*(4-methoxyphenyl)]methane, diazo[*bis*(4-methylphenyl)]methane, diazodiphenylmethane, diazo[*bis*(4-chlorophenyl)]methane og diazofluorene.

Preliminary work assessed the use of Magtrieve™ (chromium(IV) oxide) as a 'green' and recyclable reagent for the preparation of diazo compounds from the corresponding hydrazones. Optimization experiments demonstrated that 15 molar equivalence of Magtrieve™ was sufficient to oxidize hydrazones to the corresponding diazo compounds in two hours or less. Preparative-scale syntheses of the five diazo compounds resulted in good overall yields comparable to mercury(II) oxide-based oxidations. Two proof of concept reactions using the in situ preparation of diazo compounds followed by tin(II) chloride-catalyzed reactions with methyl 4,6-*O*-benzylidene-α-D-mannopyranoside showed good yields and high regioselectivity for the 3-OH.

Subsequent work examined the regioselectivity patterns of tin(II) chloride and tin(II) bromide-catalyzed reactions with methyl 4,6-*O*-benzylidene- and 4,6-*O*-isopropylidene-α-D-mannopyranoside. Most of the diazo compounds investigated yielded exclusively the 3-*O* ether in the case of the 4,6-benzylidene system, with the exception of diazodiphenylmethane which gave predominantly the 3-*O*-ether with traces of the 2-*O*-ether formed, in good overall yield. Tin(II) halide-catalyzed reactions between diazo compounds and the 4,6-*O*-isopropylidene manno system gave a mixture of the 2-*O*- and the 3-*O*-ether with the 3-*O*-ether being the dominant product in most cases. A noteworthy exception includes reactions involving diazofluorene in which the 2-*O*-ether was the dominant product.

Investigations into these reactions with methyl 4,6-*O*-benzylidene-α-D-glucopyranoside were problematic due to the instability of the catalyst system. Overall yields were acceptable with the 3-*O*-ether being the main product in all cases.

Finally, the role of tin(II) chloride concentration on the regioselectivity patterns of reactions of diazo compounds with methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside was investigated. With the diaryl diazo compounds explored, a general trend emerged in which high catalyst concentration favored alkylation at the 3-OH position while lower catalyst concentrations gave more of the corresponding 2-*O*-ether. In the case of diazofluorene, the relative selectivity at low catalyst concentration is over 90% for the 2-OH position.

Table of Contents

List of Figures

List of Tables

Acknowledgements

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Abbreviations

Ac - Acetyl
All - Allyl
b.p. – Boiling point
Bn - Benzyl
Bu – Butyl
Bz – Benzoyl
DCC - *N*,*N*'-Dicyclohexylcarbodiimide
DMAP - *p*-(dimethyl)aminopyradadine
DME – 1,2-dimethoxyethane
DMSO – Dimethylsulfoxide
EDA – Ethyl diazoacetate
EDG – Electron donating group
eq – Equivalence
EWG – Electron withdrawing group
HPLC – High performance liquid chromatography
Hz – Hertz
Lev – Levulinate
m.p. – Melting point
Me – Methyl
Mes – Mesylate
MOM - Methoxymethyl
N – Nucleophilicity
ND – Not determined
nm = Nanometers
NMR – Nuclear Magnetic resonance
PCL – *Pseudomonas cepacia* lipase
PFL – *Pseudomona fluorescens* lipase
PG – Protecting group
Piv – Pivolate
PTC – Phase transfer catalyst
R_f – Retardation factor

p-TsOH – *para*-Toluene sulfonic acid
TBDMS - *t*-Bu di-me silyl
TBDPS - *t*-Bu di-phenyl silyl
TEA – Trimethyl amine
TIPDS – 1,3-(1,1,3,3-tetraisopropyl-disiloxanylidene)
TLC – Thin layer chromatography
TMS - Trimethylsilyl
Tos – Toslyate
Trt - Trityl
UV – Ultra violet
vic – Vicinal

1 Research objectives

Carbohydrates are ubiquitous in nature and have diverse roles in biological systems; carbohydrates are involved in energy metabolism, cell-to-cell interactions, in cell signaling and adhesion, as well as the immune response and acting as structural supports (Fukuda, 1994; Osborn, 2003; Taylor & Drickamer, 2011). The structure of carbohydrates is more complex than other biomolecules due to the presence of multiple stereocenters which allows for connectivity in either the alpha or beta position, linkage variations (*O*-, *N*-, S-) and branching, in addition to other modifications (Fukuda, 1994). As such, the synthesis of specific carbohydrates requires efficient protecting group strategies.

The regioselective protection of hydroxyl groups is often complicated by similar reactivities among secondary hydroxyl groups. Finding highly efficient and regioselective protecting groups remains an ongoing challenge in carbohydrate chemistry. The introduction of a protecting group must not only be done selectively, but it must also be performed under sufficiently mild conditions as to avoid the modification or migration of other protecting groups already in place.

The aim of this work was to use tin(II) chloride and tin(II) bromide for the regioselective introduction of diarylmethyl protecting groups on partially protected monosaccharides using diazo compounds as alkyl donors. The key purposes of this work are as follows:

- Examination of "green" preparation of diazo compounds using chromium(IV) oxide (Magrieve^{TM}) for the further

preparation of one-pot regioselective protections of partially protected monosaccharides (**Manuscript I**).

- Investigation of the use of this tin(II) halide-catalyzed regioselective introduction of diarylmethyl protecting groups on partially protected monosaccharides on a preparative scale (**Manuscript II and III**).
- Investigation of the role of catalyst concentration in observed regioselectivity in hopes of tuning the regioselectivity of the reaction for either selective 2-OH or 3-OH protections (**Manuscript IV**).

2 The chemistry of diazo compounds

The first work on diazo compounds stemmed from their discovery in 1858 by Johann Peter Griess with the treatment of aromatic amino acids with nitrous acid (Cain, 1908; Zollinger, 1994). While initial work on diazo chemistry was limited to aromatic amines, the chemistry of the aliphatic diazo compounds was later established by Curtius (1883) with the advent of ethyl diazoacetate and von Pechmann's exploration of diazomethane (1894; 1895). Early interest in diazo compounds was due to their use in the preparation of azo dyes. In the decades since, the utility of diazo compounds as organic synthons has given rise to diverse applications in organic synthesis and other uses (Maas, 2009; Zollinger, 1994, 1995). By the middle of the 20th Century, the usefulness of diazo compounds in conjunction with transition metals to guide highly regioselective and enantioselective reactions had received tremendous attention (Davies & Beckwith, 2003).

The general structures of diazo compounds and other closely related functional groups are given in Figure 1. This chapter will focus exclusively on the chemistry of aliphatic diazo compounds.

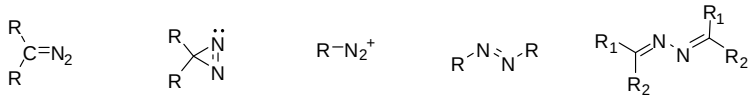


Figure 1 – Functional groups bearing two covalently bonded nitrogens; left to right, diazo compounds, diazirines, diazonium salts, azo compounds, and azines

The diazo functional group is of great utility for the construction of carbon backbones in synthetic organic chemistry due to its high reactivity. Notably, diazomethane has proven to be a highly effective

methylating agent (Wuts & Greene, 2007; Zollinger, 1995) while diaryl diazo compounds present a convenient method for introducing the diarylmethyl protecting group to a hydroxyl group (Petursson, 2008).

2.1 General properties, structure, and hazards

Diazo compounds have the general formula R_2CN_2 of which the simplest is diazomethane, where R=H. The nature of the diazo group (C_α-N_1-N_2) is linear relative to the carbon atom and the diazo group has a dipole moment of 1.4D; the linearity of the diazo group has been confirmed by X-ray crystallographic studies (Tulip, Corfield, & Ibers, 1978). Diazo compounds exist as resonance hybrids as is evidenced by the C_α-N bond lengths of 1.32 Å and the N-N bond lengths of 1.139Å (Smith & March, 2007; Zollinger, 1995). The relatively short N-N and C-N bonds is evidence of a double bond character which supports the linearity of the diazo group.

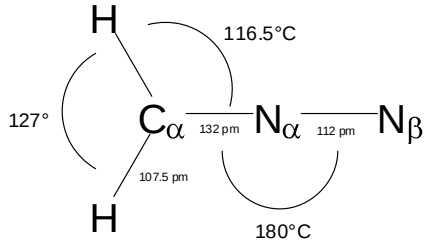


Figure 2 - The structure of diazomethane (modified from Zollinger, 1995)

Diazo compounds can exist as 1,2- and 1,3-dipolar ylides; several resonance structures for diazo compounds can be drawn as generalized in Figure 3; Figure 3b and 3c show the two most stable resonance forms where the charge separation is limited.

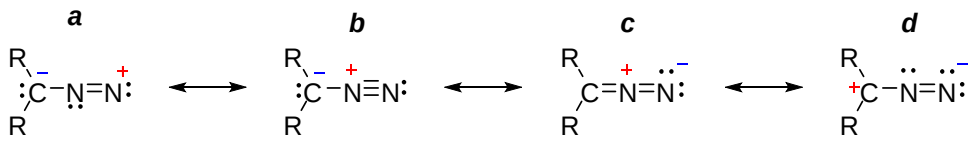


Figure 3 - Resonance structures of diazo compounds

The physical properties of diazo compounds are diverse and highly dependent upon the substituents attached to the α carbon. Due to the presence of delocalized aromatic electrons, diazo compounds are typically yellow to red or purple in color and have distinctive spectral properties with characteristic absorption maximas in the visible and UV portion of the spectrum. The diazo group itself also has a distinctive absorption pattern in the infrared portion of the spectrum (with a strong peak at 1950 and 2300 cm^{-1}) due to the stretching of the nitrogen-nitrogen triple bond.

Diazomethane is a gas at room temperature (b.p. -23°C). Low molecular weight diazo compounds are inconvenient to handle due to their low melting points. Diazodiphenylmethane has a melting point of approximately 29°C after recrystallization, making it awkward to handle while substituted diazodiphenylmethane compounds have higher melting points (>100°C) and are nicely crystalline at ambient temperatures, making them convenient to handle (Petursson, 2013).

The hazards associated with diazo compounds include their propensity for decomposition, the potential for explosion, and their toxicity. Simple aliphatic diazo compounds are highly unstable due to their interaction with light, heat, and in some cases, shocks. The stability of diazo compounds can be modified by altering the electronics with the inclusions of conjugating systems or electron withdrawing substituents attached to the α-carbon (Section 2.3.2; Zollinger, 1994). This is evident by examining the relative stability of chlorodiazomethane which is less stable than diazomethane, whereas diazo groups stabilized via resonance stabilization, such diazodiphenyl methane, are comparatively stable. Diazo compounds in which the diazo group is on a secondary or a tertiary carbon with one or two

phenyl rings attached are more stable due to resonance stabilization and can be isolated and stored for extended periods of time at low temperatures (Beyer & Walter, 1997).

Diazo compounds decompose upon exposure to acids, heat, and UV light. Simple alkyldiazo compounds, such as diazomethane, can degenerate explosively due to the evolution of nitrogen and hydrocarbon gasses and thus must be handled with extreme care (Maas, 2009; Otera, 2003). Ethyl diazoacetate (EDA) does not detonate but is shock and thermally sensitive (Clark, et al., 2002; Clark, Shah, Peterson, Patelis, Kersten, Heemskerk, et al., 2002). Diazomethane is notoriously unstable, reacting with ground glass joints, presenting a hazard upon spontaneous crystallization, reacting with light, and even sharp glass edges (Arndt, 1935; McKay, 1970; Moore & Reed, 1961). Other simple diazoalkanes are similarly unstable while more highly substituted diazo compounds, such as EDA and (trimethylsilyl)diazomethane, are sufficiently stable to be commercially available[1]. Trimethylsilydiazomethane also has the advantage of being non-toxic (Otera, 2003).

The cytotoxic nature of many alkyldiazo compounds is due to their ability to act as alkyl donors which can cause the alkylation of biomolecules such as DNA with diazomethane being a potent carcinogen (Schoental, 1960). Not surprisingly, numerous other diazo compounds, as well as *N*-nitrosodialkylamines, which are converted *in vivo* to diazoalkanes, are recognized as active carcinogens thus necessitating that they be handled with care (Mizrahi & Emmelot, 1962; Schoental, 1960).

Despite the inherent hazards associated with some diazo species, several procedures exist for their use on an industrial scale. Large-scale processes have been reported with nearly two moles of diazomethane present in the reaction vessel at a given time (Maas, 2009 and references therein). For example, EDA has been successfully used by Monsanto for the synthesis of β-keto esters (Clark, et. al, 2001; Clark,

[1] Sigma-Aldrich

Shah, & Peterson, 2002) and in other large-scale processes with *in situ* generation of the diazo species.

2.2 Preparation of diazo compounds

The following section will focus on general methods for the preparation of diazo compounds with emphasis on diazofluorene, diazodiphenylmethane, and related derivatives. Numerous routes to the preparation of diazo compounds have been described in the literature are partially summarized in Figure 4; a more exhaustive overview of these methodologies can be found in (Maas, 2009) and the references therein. *N*-nitroso and mercury(II) oxide-based oxidations are the most common methods for the preparation of diazo compounds. Zollinger's comprehensive review on diazo chemistry (1994, 1995) and references therein, provides a more comprehensive listing of preparative methodologies.

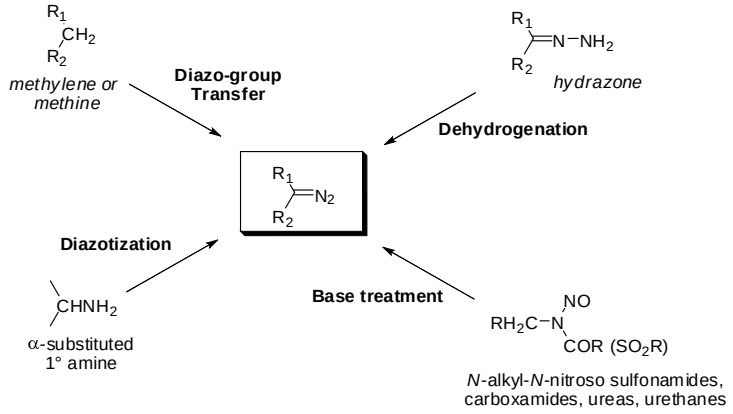


Figure 4 - Selected synthetic routes for the preparation of diazocompounds (modified from Maas, 2009)

The preparation of diazo compounds is often hampered by the degradation of the target molecule (as evidenced by the evolution of nitrogen), by formation of reaction side-products such as azines via azo

coupling reactions, and by product loss during recrystallization. Additionally, many of the methods for generating diazo compounds suffer from the use of hazardous materials, such as heavy metals.

Historically, diazomethane has been prepared by the base hydrolysis of *N*-methyl nitrosamide or from *N*-nitroso-*N*-methylurea. However, more contemporary techniques use more stable precursors such as the Aldrich Diazald® reagent (*N*-methyl-*N*-nitroso-*p*-toluenesulfonamide) or *N*-methyl-*N*'-nitro-*N*-nitroguanidine (Moore & Reed, 1961). Commercially available apparatus for the preparation of 300 mmol of Diazald are routinely used in the generation of diazomethane.

Diazotization reactions present a route to diazo compounds through the oxidation of primary or secondary amines with a strong oxidizing agent such as sodium nitrite. EDA can be readily prepared in this manner from ethyl ester of glycine using sodium nitrite (Figure 5).

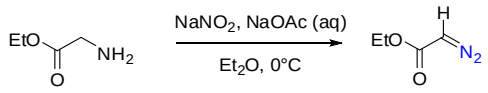


Figure 5 - Synthesis of ethyl diazoacetate by diazotization

Another route to diazo compounds includes diazo group transfer reactions in which an azide, such as tosyl azide, undergoes a coupling with a reactive carbon nucleophile to yield the corresponding diazo compound. This method is employed to prepare cyclic α-diazoketones, which cannot be prepared using other methods. (Beyer & Walter, 1997; Carey & Sundberg, 2001b)

Higher diazo compounds can be prepared by the oxidation of the corresponding hydrozones. The preparation of diphenyldiazomethane and related derivatives has been reported from the precursor hydrazone using mercury(II) oxide (Smith & Howard, 1944), silver(I) oxide, chromium(IV) oxide which is licensed by Merck under the trade name Magtrieve™ (Ko & Kim, 1999), manganese dioxide, and lead(IV) acetate. A particularly noteworthy recent development is the use of

Swern oxidation using oxalyl chloride in dimethyl sulfoxide (DMSO) and triethylamine (TEA) at -78°C as described by Javed & Brewer (2007). They reported good yields by both gas evolution and the esterification of diazodiphenylmethane with yields of at least 88%.

Current lines of investigation have focused on the "green" and *in situ* preparation of diazo compounds (Maas, 2009; Morandi, 2012; Schnaars, 2013). As a reagent for the *in situ* generation of diazodiphenylmethane, Magtreive™ (chromium(IV) oxide) is considerably less toxic than mercury(II) and lead(IV) oxides and has the added feature of being magnetic and can thus be reused by regenerating spent reagent at 300-350°C in air (Ko & Kim, 1999).

Low molecular weight diazo compounds can be recovered by distillation or direct use after preparation. The recovery of diazodiphenylmethane and its derivatives has been reported from simple recrystallization from petroleum ether or diethyl ether (Miller, 1959; Smith & Howard, 1944). High product recoveries have also been reported through simple filtration of reaction products through basic alumina (Javed & Brewer, 2008).

2.3 Diazo compounds and their carbenes

The decomposition of diazo compounds is highly thermodynamically favorable (negative ΔG values) and leads to the generation of highly reactive carbene species. The principles dictating the reactivity of diazo compounds and their carbenes are covered in Section 2.3.2. Diazo compounds also react with transition metals to generate metal-complexes as discussed in Section 2.3.3.

Under neutral conditions, diazo compounds undergo dediazoniation upon heating or photolysis into a highly reactive carbene and molecular nitrogen as shown in Figure 6 (Beyer & Walter, 1997; Carey & Sundberg, 2001b). The formation of the carbene is thermodynamically favorable due to the formation of highly stable

gaseous dinitrogen. The resultant carbene is a neutral species in which the carbon atom is divalent, possessing a sextet of electrons which includes a lone pair of electrons and a vacant *p* orbital (Beyer & Walter, 1997).

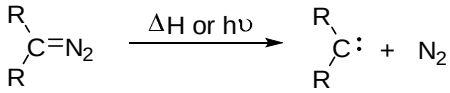


Figure 6 – Generation of carbenes via thermal decomposition or photolysis

The reactivity of carbenes produced by the degradation of diazo compounds is a consequence of their electronic state; singlet carbenes with a vacant *p* orbital have reactivity similar to that of other electrophiles while triplet carbenes resemble the reactivity of free radicals (Figure 7). The primary product of carbene generation is typically the singlet carbene, which usually reacts before the triplet carbene can form, although the energy gap between singlet and triplet carbenes is very small (36 kJ/mol) and favors the triplet state (Beyer & Walter, 1997; Zollinger, 1995). Singlet and triplet carbenes can rapidly interconvert with rate constants approaching diffusion limits (Closs & Rabinow, 1976).

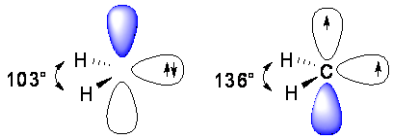


Figure 7 - Singlet versus triplet carbenes (modified from Carey & Sundberg, 2001a)

The energy gap between the carbene's singlet and triplet states directly correlates to the electron releasing ability (ρ = +) of the substituents attached to the α-carbon, which ultimately stabilizes the singlet state more than the corresponding triplet state (Figure 8; Baird & Taylor, 1978). Thus, the substituents attached to the α-carbon determine the reactivity and selectivity of the resultant carbene. As demonstrated in Figure 8, electron-donating substituents can stabilize a carbene by filling the vacant *p* orbital.

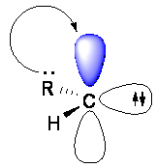


Figure 8 - Stabilization of singlet carbene with an electron-releasing substituent on the α-carbon

The photodegradation of carbenes leads to the formation of an excited diazo compound which results in one of three fates (as summarized in Figure 9): decomposition into an excited carbene or direct reaction with an electron rich substrate. The formed carbenes interconvert between the singlet and triplet states. Triplet sensitizing agents, such as benzophenone, can lead to the direct formation of a triplet carbene (Zollinger, 1995; pg 317).

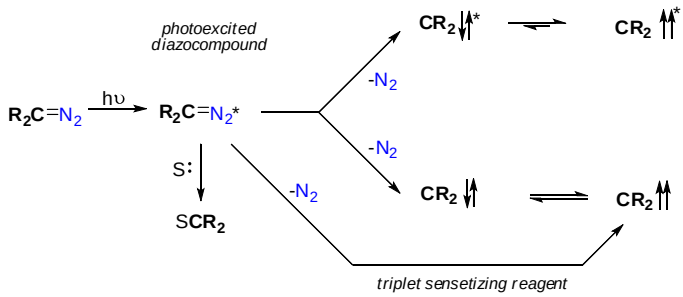


Figure 9 - Photosensitization of diazo compounds (modified from Zollinger, 1995)

The generation of carbenes from diazodiphenylmethane (diphenylcarbene) and diazofluroene (fluorenylidene) has been intensively studied (Closs & Rabinow, 1976; Eisenthal et al., 1980, 1985; Jones & Rettig, 1965). Singlet carbenes typically react before they have a chance to decay into a triplet carbene; the rate of singlet reactions typically approaches the rate of diffusion (Zollinger, 1995). The fluorenylidene is a special case due to the rapid interconversion of the singlet and triplet states. Studies of diphenyldiazomethane and diazofluorene have determined that the triplet state is the predominant species upon photolysis (Platz, 2002).

Figure 10 – Interconversion of singlet (left) and triplet (right) carbenes

Singlet carbenes participate in pericyclic reactions where they participate as either electrophiles (if an unfilled *p* orbital is present) or nucleophiles and tend to demonstrate a degree of selectivity. Triplet carbenes behave like diradicals and participate in reactions in two-steps as compared to reacting in a concerted fashion as do singlet carbenes. As such, singlet and triplet carbenes differ in their reactivity as illustrated for fluorenylidene in Figure 11.

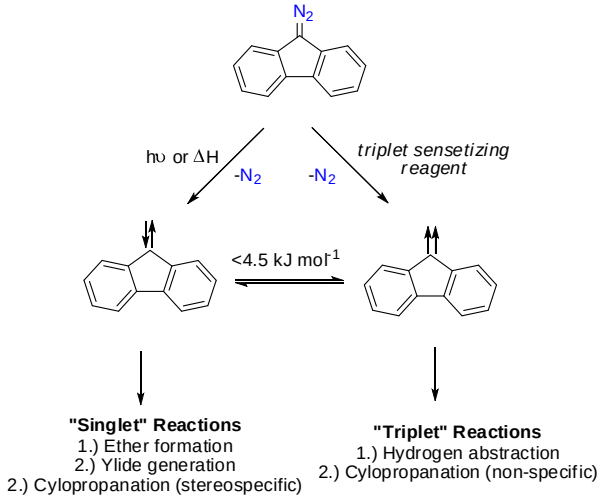


Figure 11 - Singlet and Triplet reactions of fluorlyidene (Zollinger, 1995)

Due to these two modes of reactivity, reactions of singlet methylene are stereospecific whereas those of triplet methylene are stereoselective. This difference in reaction selectivity can be used to probe the nature of a carbene. Studies of diazodiphenylmethyl and diazofluorene have indicated that the persistent carbenes (diphenylcarbene and fluorenylidene) predominately exist as triplet carbenes (Platz, 2002 and references therein).

2.4 Philicity and relative reactivity of diazo compounds

The nature of the diazo group is ambipathic (Bug, Hartnagel, Schlierf, & Mayr, 2003); diazo compounds can perform as either nucleophiles or electrophiles depending on the specifics of the reaction conditions (Cowell & Ledwith, 1970). The C_α typically has an electrophilic character due to a vacant *p* orbital whereas the N has a nucleophilic character although this is highly dependent upon the nature of the groups attached to the C_α.

Initial NMR studies (Ledwith & Friedrich, 1964) of diazomethane demonstrated that the C_α (methylene) has a strong carbanionic character as evidenced by strong shielding of the two attached protons (δ 6.92 ppm). Subsequent NMR studies of higher diazoalkanes have confirmed that the C_α is shielded and the presence of electron withdrawing groups favors resonance structures with a formal carbanion whereas the presence of electron donating groups favor the forms with a positive formal charge on the C_α (Cowell & Ledwith, 1970). Notably, diazofluorene tends to have a carbanion favoring resonance structure (Cowell & Ledwith, 1970).

Early studies based upon the reactivity of diazo compounds in inert solvents determined the following relative reactivity Figure 12.

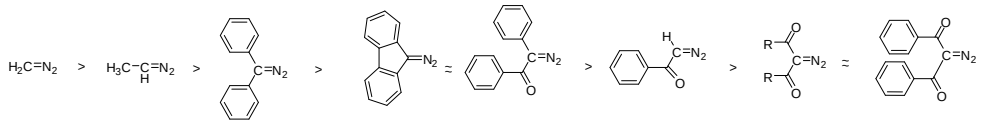


Figure 12 - Relative reactivity of aliphatic diazo compounds (Zollinger, 1995)

Studies examining the relative reactivity of diazo compounds with benzhydryl cations as reference electrophiles have determined that the nucleophilicity of diazo compounds as is summarized in Figure 13

(Bug et al., 2003). The importance of substitutions on the alpha carbon atom become readily apparent as the nucleophilicity of the diazo compounds examined by Bug, et al (2003) span ten orders of magnitude. Interestingly, while diazomethane is highly nucleophilic, diazodiphenylmethane is only one order of magnitude less nucleophilic than diazomethane while diazodiphenylmethane and ethyl diazomethane are 6 and 7 orders of magnitude less nucleophilic, respectively. This illustrates the role of electron donating substituents and the stabilizing effect of ring systems for trapping delocalized electrons of the associated phenyl groups attached to C_{α}.

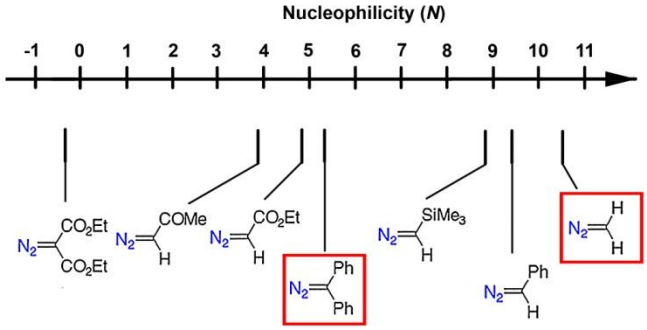


Figure 13 - Nucleophilicity (*N*) of selected diazo compounds on a logarithmic scale (modified from Bug et al., 2003)

Thus, the role of resonance stabilization and inductive electron withdrawing functional groups is readily apparent. The differences between diazomethane (*N*= 10.5), diazophenylmethane (*N*= 9.4), diazodiphenylmethane (*N*= 5.3), and ethyl diazoacetate (*N*= -0.4) highlighting the role of resonance stabilization as well as electron effects; the influence of strongly electron withdrawing groups on EDA is noteworthy. The large difference between diazophenylmethane and diazodiphenylmethane could be due to steric shielding of the diazo group (Bug, 2003) but also due to the additional electron withdrawing nature of the second phenyl group.

The philicity of carbenes can range from having a nucleophilic to electrophilic character depending upon the nature of the substitutions attached to the α-carbon. Fine tuning of the reactivity of diazodiphenylmethane can be accomplished with the addition of electron withdrawing (acceptor) or electron donating groups (donor). While a few studies have quantitatively examined diazodiphenylmethane derivatives, it is clear from the work of Petursson & Webber (1982) that the reactivity of diaryldiazo compounds with hydroxyl groups is as follows:

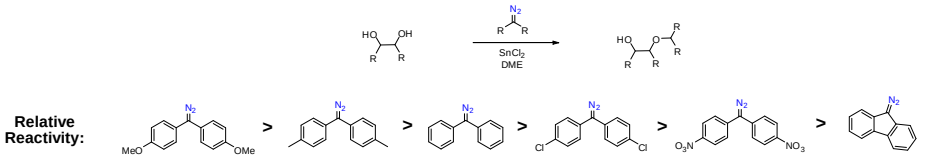


Figure 14 - Relative reactivity of substituted diazodiarylmethane compounds based on reactivity towards hydroxyl groups in *vic* diol systems

The increased relative reactivity of diazo[*bis*(4-methoxylphenyl)]methane and diazo[*bis*(4-methylphenyl)]methane can be explained in the context of the Hammett substituent constants (Table 1); both the methyl and methoxy groups have an electron releasing nature thus helping to stabilizing the electron deficient C_α and thus making them more reactive. Conversely, diazo[*bis*(4-chlorophenyl)]methane and diazo[*bis*(4-nitrophenyl)]methane derivatives have an electron withdrawing character making the C_α less reactive. As the methyl groups of $(p\text{-}CH_3Ph)_2CN_2$ are electron releasing, we would expect that it is *more* nucleophilic than diazodiphenylmethane whereas $(p\text{-}ClPh)_2CN_2$ is less nucleophilic as the electrons are pulled away from C_α. By comparison, ethyl diazoacetate's strong electron withdrawing substituents increase its stability decreasing its reactivity.

Table 1 - Hammett substituent constants for benzene derivatives (Hammett, 1937); positive ρ indicates EWG is favored by a reaction, negative ρ indicates EDG is favored by a reaction

	Effect (ρ)	
Substituent	*Para*	*Meta*
None	0.000	0.000
Methoxy	-0.268	+0.115
Methyl	-0.170	-0.069
Fluoro	+0.062	+0.337
Chloro	+0.227	+0.373
Nitro	+0.778	+0.710

2.4.1 Metal-carbene complexes

The degradation of diazo compounds into nitrogen and reactive carbenes in the presence of transition metals has been known since the early 20th century (Zollinger, 1995). As a result of the copper salt-catalyzed decomposition of diazoketons, Yates (1952) postulated that a transition metal catalyst's interaction with diazo compounds leads to the formation of a stabilized metal carbocation (a "carbenoid") rather than a free carbene or activated diazo compound. The complexation of a metal and a diazo compound to form a reactive carbenoid is generalized in Figure 15. The complexation of carbenes with metals dramatically alters their selectivity towards reactive substrates.

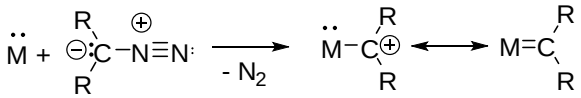


Figure 15 - Formation of electrophilic metal-carbene complexes (Carey & Sundberg, 2001a)

In the decades since, carbenes capable of forming metal-stabilized complexes, hence forth referred to as carbenoids, have been the subject of much attention (Figure 16). As such, carbenoids have not been isolated or conclusively identified (Doyle, McKervey, & Ye, 1998; Doyle, 1986a). However, their existence is supported by indirect evidence such as the following:

- Evolution of N_2 from diazo compounds at lower temperatures than thermolysis
- Chirality transfer
- Reaction selectivity (regio- and stereo-)
- Carbene dimer formation

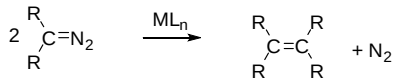


Figure 16 - Metal-catalyzed dimer formation from a diazo compound

Carbenoids have been noted to form with main group metals, such as Group 14 (formerly group IV) metals including tin, silicon, germanium, and lead (Rubina & Gevorgyan, 2004; Seyferth, 1970) but also lithium (Pearlman, Putt, & Fleming, 2006), as well as transition metals including rhodium, palladium, and molybdenum (Doyle, 1986b). The literature mostly discusses carbenoids in the context of those involving transition metals; for instance carbenoids of rhodium have been extensively investigated (Davies & Antoulinakis, 2001; Li, Parr, & Davies, 2012). Tin-containing carbenes and carbenoids have likely received little attention as they often give poor yields in cyclopropanation reactions as shown in Figure 17 (Rubina & Gevorgyan, 2004) whereas rhodium carbenoids consistently give good results. It has also been noted that tin(II) halides rarely interact with alkenes but have reacted with activated alkynes under specific conditions (Zuckerman, 2009).

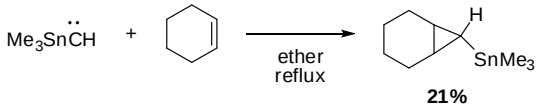


Figure 17 - Insertion of a tin carbenoid into an alkene in poor yield

Metal-carbene complexes are generally divided into two categories: Fischer's carbenes and "Schrock" carbenes. Fischer-type carbenes involve low oxidation state metals with π-accepting auxiliary ligands as well as substituents attached to the C_α capable of donating π electrons. Conversely, Schrock-type carbenes involve early transition metals, non-π-accepting auxiliary ligands, and substitutions on the C_α that do not donate π electrons. It is noteworthy that carbenes attached to a metal atom tend to be in the singlet state rather than the triplet state (Huheey, Keiter, & Keiter, 1993). The discussion herein will focus on Fisher-type carbenes.

Figure 18 - Fisher carbenoids (left) and Schrock carbenoids (right)

Diazo compounds interact with metals by forming an end-on complex as shown in Figure 19. Orbital overlap between the metal and the lone pair on the terminal nitrogen results in delocalization (d_π-p_π*) or "back donation". Typically, strong back donation gives N_2-metal complexes a nucleophilic character.

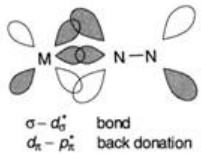


Figure 19 - Orbital overlap between end-on metal-N_2 complexes (Zollinger, 1995)

The cycle between diazo compounds and transition metals was first postulated by Doyle, (1986a, 1986b). The formation of carbenes can be catalyzed by transition metals leading to the formation of a carbene-metal complex also referred to as a carbenoid, thus bypassing the formation of a proper carbene. The catalytic cycle is summarized in Figure 20. The interaction of an electrophilic transition metal with the nucleophilic C_α of the diazo compound leads to an intermediate which degenerates into N_2 and a carbenoid which then reacts with an electron-rich substrate. Following the reaction with the substrate, the metal catalyst is regenerated and can undergo addition reaction cycles.

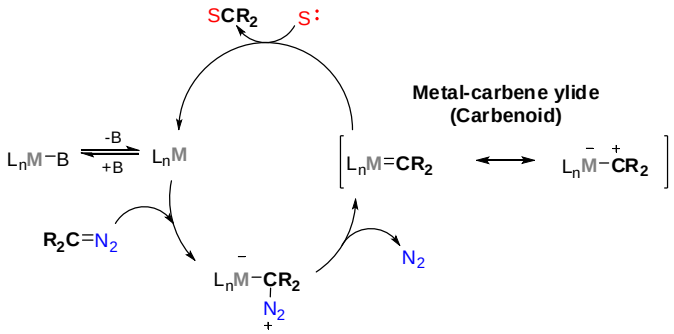


Figure 20 - Catalytic cycling of metal-carbene complexes during reactions with electron-rich substrates (modified from Zollinger, 1995)

Carbenoids can be broadly classified based upon the electron donating or withdrawing nature of their substituents as summarized in Figure 21. As with the reactivity of carbenes, a carbenoid's reactivity and selectivity is highly dependent upon the nature of the substituents attached to the C_α, although they are less reactive than free carbenes. Additionally, the co-ligands attached to the metal atom as well as the electron density of the metal are of great importance in determining the stability and reactivity of the resultant carbenoid; electron rich transition metals with low oxidation states tend to form more stable complexes (Zollinger, 1995). Donor/Acceptor-carbenoids have been broadly utilized in the context of natural products synthesis particularly in the context of cycloadditions as reviewed in (Davies & Denton, 2009).

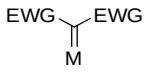
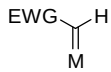
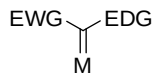
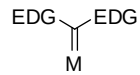
	Carbenoid Species			
	Acceptor/acceptor	Acceptor	Donor/acceptor	Donor/donor*
				
Relative selectivity	Intermediate	Least	Very High	Not reported
Relative stability	Low	Intermediate	High	Not reported
Electrophilicity	Very High	High	Intermediate	Not reported
Reactivity	Very High	High	Intermediate	Not reported

Figure 21 – Classification and selectivity of carbenoids (modified from Davies & Denton, 2009); common EWGs include CO_2R, COR, NO_2, etc.; common EDGs include vinyl, aryl, heteroaryl

The selectivity of metal-carbene complexes is highly influenced by steric factors of the substituents attached to the α-carbon and the electronics of the donor diazo compound but also steric factors of organic substituents attached to the metal in addition to the specific transition metal being used (Michael P. Doyle, 1986b). It has been suggested that the combination of donor and acceptor groups give the resultant carbenoid sufficient electrophilicity and stability to allow selective reactions to occur (Davies & Beckwith, 2003) although these reactions are limited to studies involving alkenes as substrates.

Interestingly, carbenoids complexed with two substituents bearing electron donating groups, such as diaryldiazomethane derivatives, have not been included in this classification scheme.

Given the various parameters that can be controlled, the reactivity of a carbenoid species can be fine-tuned to meet the needs of an individual synthesis. The selection of transition metals also affects the selectivity of carbenoids has been extensively studied in cyclopropanation reactions (Zollinger, 1995, pg 358-361).

2.4.2 Reactions involving diazo compounds

The utility of diazo compounds in synthetic organic chemistry is highly diverse as they can be used for the formation of C-C bonds and insertions into C-H, Si-H, N-H, and O-H bond. Additionally, diazo compounds react with transition metals forming carbene-metal complexes, which often demonstrate unique and highly selective reactivities upon subsequent interactions with electron-rich substrates. Diazomethane and diazodiphenylmethane can be used to transform carboxylic acids into the corresponding esters (Otera, 2003 and references therein).

As carbene precursors, they can be used to introduce alkyl groups to double bonds or nucleophiles and can be used for the generation of cyclopropanes (Carey & Sundberg, 2001a). The use of diazo compounds and carbenoids for insertions into C-H bonds has received extensive attention in recent years (review: (Davies & Antoulinakis, 2001; Davies, 2002; Davies & Beckwith, 2003; Davies & Manning, 2008; Doyle, Duffy, Ratnikov, & Zhou, 2010). C-C bond forming reactions such as the conversion of α-diazo ketones into ketenes or the so-called "Wolff Rearrangement" (reviews: (Kirmse, 2002) among others (Li et al., 2012). Stereoselective insertions into C-C bonds using rhodium catalysts with donor/acceptor carbenoids and chiral allyl alcohols has also been reported (Li et al., 2012).

Insertion into Hydroxyl groups

While diazo species can react with a variety of functionalities, only the reactions involving hydroxyl groups will be considered in detail herein.

Diazo compounds and carbenoids are also capable of insertions into O-H bonds (Chamni et al., 2011). The reactivity of hydroxyl groups in such insertion reactions is directly correlated to their acidity with some alcohols only reacting in the presence of a catalyst (Smith & March, 2007). Chiral copper carbenoids involving diazoesters have been used

for the asymmetric synthesis of α-hydroxyesters (Zhu, Chen, & Zhou, 2008). In the presence of water, diazo compounds react to give the corresponding alcohol or phenol (Beyer & Walter, 1997).

Under neutral conditions, diazo compounds decompose into a highly reactive carbene and molecular nitrogen in the presence of heat or by photolysis as given in Figure 22 (Carey & Sundberg, 2001b).

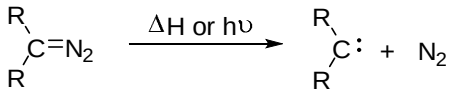
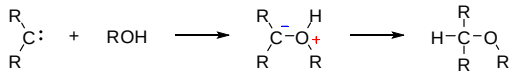


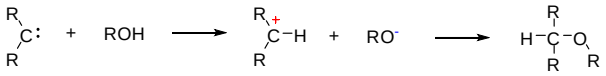
Figure 22 - Thermal or photolysis of a diazo comound yielding the corresponding carbene and the evolution of molecular nitrogen

Subsequently, the generated carbene will react with a hydroxyl group to yield the corresponding ether. There are three potential mechanisms by which the carbene can then react with a hydroxyl group Figure 23: 1) formation of a ylide and subsequent rearrangement, 2) proton abstraction followed by nucleophilic attack, or 3) direct insertion.

1) *Ylide formation followed by rearrangement to an ether*



2) *Proton abstraction forms carbonium ion intermediate followed by nucleophilic attack*



3) *Direct insertion*

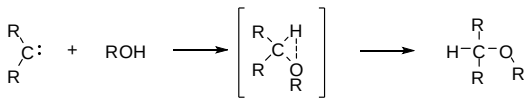


Figure 23 - Potential reaction mechanisms for insertion of diazo compounds into hydroxyl groups under non-acidic conditions (Petursson, 1979; pg 22)

Uncatalyzed reactions of diazodiarylmethanes can be used to introduce benzhydryl groups into O-H bonds by refluxing the diazo compound in an aromatic nonpolar solvent (Best et al., 2008). Diphenyldiazomethane can be used to transform carboxylic acids into benzhydryl esters. By heating in the presence of alcohols diaryl diazo compounds decompose into a reactive carbene, which reacts unselectively with hydroxyl groups (Petursson & Webber, 1982; S. Petursson, 1979). In the case of diols and one equivalence of a diazo compound, a mixture of mono- and di-ethers is obtained.

The use of metals as catalysts for the insertion of diazo compounds into O-H bonds has been investigated. This is covered in more detail in Section 3.2.3.

Potential Side Reactions

Diazo compounds, such as diphenyldiazomethane, are capable of forming azines and dimer products (such as tetraphenylethane in the case of diazodiphenylmethane) during both thermal and photolytic decomposition. Azine formation occurs though the formation of a carbene which then attacks a second diazo molecule liberating molecular nitrogen. The formation of the azines seems to be preferred except under some circumstances involving photolysis where tetraphenylethane is the predominant product (Petursson, 1979). Additionally, carbenes generated by diazo compounds may react with molecular oxygen to give the corresponding ketone or abstract a proton from the solvent.

3 Protecting group strategy for carbohydrates

Protecting groups (PGs) are often a necessity during multistep synthetic operations to prevent non-target functional groups from reacting. This is particularly a challenge in the context of carbohydrate chemistry where multiple nucleophilic and mildly acidic hydroxyl groups can be found in close proximity making differentiation between them difficult (Robertson & Stafford, 2003). Thus, synthetic operations involving carbohydrates necessitate the use of protecting groups due to the presence of three or more hydroxyl groups many of which often have similar reactivities. Hence, the regioselective manipulation of carbohydrate hydroxyls requires careful manipulation of the subtle differences in reactivity. General reviews covering specific PGs and strategies as well as several specifically considering carbohydrates include (Boons, 2000; Codée, Ali, Overkleeft, & van der Marel, 2011; Kadereit, Reinhard, Waldmann, & Herbert, 2002; Liptak, Borbas, & Bajza, 2007; Moitessier, Englebienne, & Chapleur, 2005; Oscarson, 2006; Petursson, 1997; Robertson, 2003; Wuts & Greene, 2007).

In order to be efficacious, the introduction of a protecting group should readily meet the following general conditions:

- High chemo- and regioselectivity
- High yield for both introduction and removal
- Avoidance of the formation of new stereocenters or diastereomers
- Introduction and removal performed under mild conditions
- Protecting group should be stable under conditions used in subsequent steps
- Protecting group should have no (or minimal) additional functionality
- It should be selectively removable in the presence of other protecting groups

Orthogonal protecting group strategies often rely upon an assortment of protecting group chemistries that can be selectively manipulated under different reaction conditions; these conditions should be chosen with either a high specificity for a given PG, as illustrated in Figure 24, or conditions capable of removing multiple or all PGs (Schelhaas & Waldmann, 1996). Many classical PG strategies employ orthogonal protecting groups with a combination of base, acid, hydrogenolysis, fluoride, and redox sensitive groups. A particularly illustrative example being the use of Seeberger's landmark multi-gram automated preparation of oligosaccharides (Plante, Palmacci, & Seeberger, 2003). The experimental part of this work included the preparation of several oligosaccharides; an example of this is shown in Figure 25.

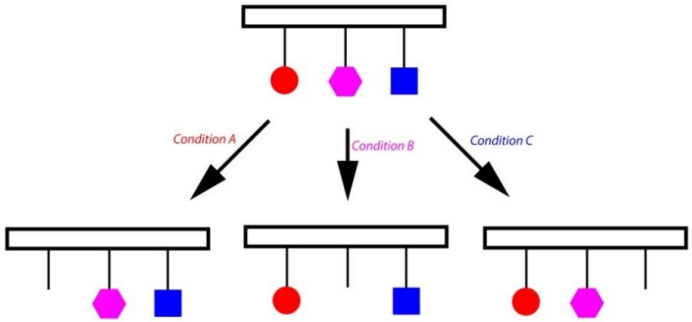


Figure 24 - Orthogonal stability as a protecting group strategy (modified from Schelhaas & Waldmann, 1996)

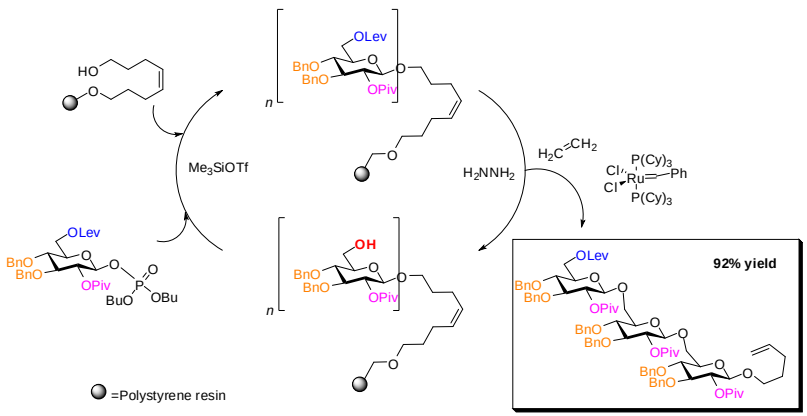


Figure 25 -Seeberger's (et al., 2003) automated synthesis of a β-(1-6)-*O* triglucoside using orthogonal, one-pot automated synthesis

An alternative to orthogonal strategies is to use a modulated liability protecting group strategy in which the PGs used are sensitive to a single set of conditions but vary in the extent to which they react under those conditions thus facilitating selective removal; the use of this PG strategy is reviewed in Schelhaas & Waldman, (1996).

PG strategies are often divided into partial versus complete protection as well as permanent and temporary; temporary protecting groups transiently mask a functionality whereas permanent protecting groups are intended to survive many synthetic steps. Additionally, so-called "participating permanent protecting groups" can be used to alter the reactivity of the molecule and affect the stereochemical result of a reaction. PGs can be used to tune the reactivity of monosaccharides with the use of "arming" (electron donating) and "disarming" (electron withdrawing) groups and the choice of protecting groups can often influence the stereoselectivity of glycosidic bond formation (Fraser-Reid & Lopez, 2011; Huang & Wang, 2007; Ye & Wong, 2000). 2-*O*-participating groups are particularly important in influencing stereochemical control in glycosylations due to their proximity to the anomeric carbon (Huang & Wang, 2007; Oscarson, 2006).

Beyond blocking functional groups, PGs can be used to confer additional features to a molecule. Protecting groups can aid structure elucidation or be used to introduce synthetically useful functionalities to the synthon such as the enhancement of crystallinity or traceability via UV absorption or fluorescence (Ellervik, 2003) or by the introduction of a purification handle as has been done with fluorous protecting groups (Gladysz, Curran, & Horvath, 2004).

A common criticism of many protecting group strategies is that multistep synthesis inevitably results in a decrease in yield with each subsequent reaction and a decrease in the atom economy[2]. Protecting group free strategies, as with reviews and noteworthy advances are

[2] Defined by Trost (1995) as $atom\ economy = 100\% \cdot \frac{molar\ mass\ of\ desired\ products\ achieved}{molar\ mass\ of\ all\ reactants}$

covered in the references and citations therein (Baran, 2007; Unsworth, 2013; Young, 2009), as well as enzymatic methods (reviews: (Drauz & Waldmann, 2002; Faber, 2011; Kadereit et al., 2002; Nair, Tang, Eriksen, & Zhao, 2010; Whitesides & Wong, 1985; Wong & Whitesides, 1994), are available although no method is universally appropriate. Thus, there is a sustained need for new protecting group strategies with orthogonal stability that can be rapidly introduced with a high degree of selectivity and ease of purification.

This chapter will focus on well-established and commonly used protecting groups as well as techniques for introducing protecting groups with high regioselectivity. A special emphasis will be placed on the regioselective protection of 2- and 3-hydroxyl groups of 4,6-acetal protected monosaccharides, particularly the use of diphenylmethyl and related protecting groups.

3.1 Reactivity of carbohydrate hydroxyl groups

Monosaccharides in their pyranose or furanose form contain multiple hydroxyl groups of similar but varying reactivity. Generally, the reactivity of free hydroxyl groups is as described in the figure below. More acidic hydroxyl groups are generally more reactive and behave as nucleophiles.

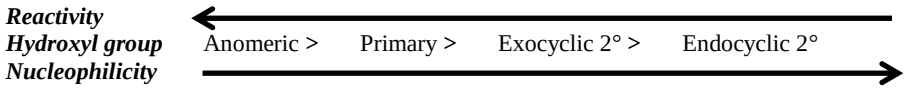


Figure 26 - General reactivity of hydroxyl groups in pyranose and furanose monosaccharides (Stick, 2001)

The factors affecting the reactivity of individual hydroxyl groups include steric factors, stereoconfiguration, for example axial or equatorial orientation, electronic factors, and the ability to form

intramolecular hydrogen bonds (Miljkovic, 2009). The most important overall consideration in determining hydroxyl group reactivity is the specific conditions being used (Robertson & Stafford, 2003).

A number of generalizations regarding the reactivity of specific hydroxyl groups can be made. The anomeric hydroxyl group, which is a hemialdehyde, is the most reactive and can be selectively manipulated under acidic conditions followed in reactivity by primary hydroxyl groups which can be selectively protected under basic conditions (Robertson & Stafford, 2003). The selective protection of the anomeric center is considered Oscarson's (2006) review of the use of PGs in carbohydrate chemistry. As such, the hydroxyl group at the anomeric center cannot be directly compared to other hydroxyls present. Among secondary hydroxyl groups, exocyclic hydroxyls are generally more reactive than endocyclic hydroxyls. Furthermore, equatorial hydroxyls tend to react more quickly than axial hydroxyls; this can be taken advantage of by forming 1,6-anhydrosugars (Robertson & Stafford, 2003).

The stereochemistry of the anomeric hydroxyl can alter the selectivity of the etherification and esterification of the 2-OH (Kondo, 1975) as illustrated in Figure 27.

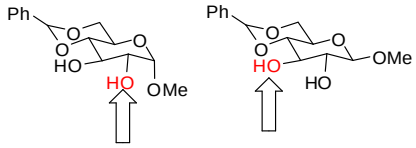


Figure 27 - Preferred reactive hydroxyl during benzoylation for α or β anomer of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside

Intramolecular hydrogen bonding networks within a monosaccharide are also of great importance in determining the reactivity of a hydroxyl group and subsequently the selectivity of a given reaction. It has been noted that intramolecular hydrogen bond networks can stabilize or disrupt reactions as protons of hydroxyl groups are linked more strongly (Sadekov, Minkin, & Lutskii, 1970).

An illustrative example of this is the greater reactivity of the 2-OH of α-glucopyranoside over the β-anomer towards acylation; this is attributed to the activating effect of the anomeric oxygen due to hydrogen bonding which is *cis* oriented in the case of the α-anomer and trans in the case of the β-anomer (Miljkovic, 2009).

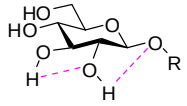


Figure 28 - Internal hydrogen bond network of β-glucopyranoside proposed by Yoshida and colleagues

While differences among the reactivity of secondary hydroxyl groups exist, carrying out regioselective reactions remains an on-going challenge in carbohydrate chemistry.

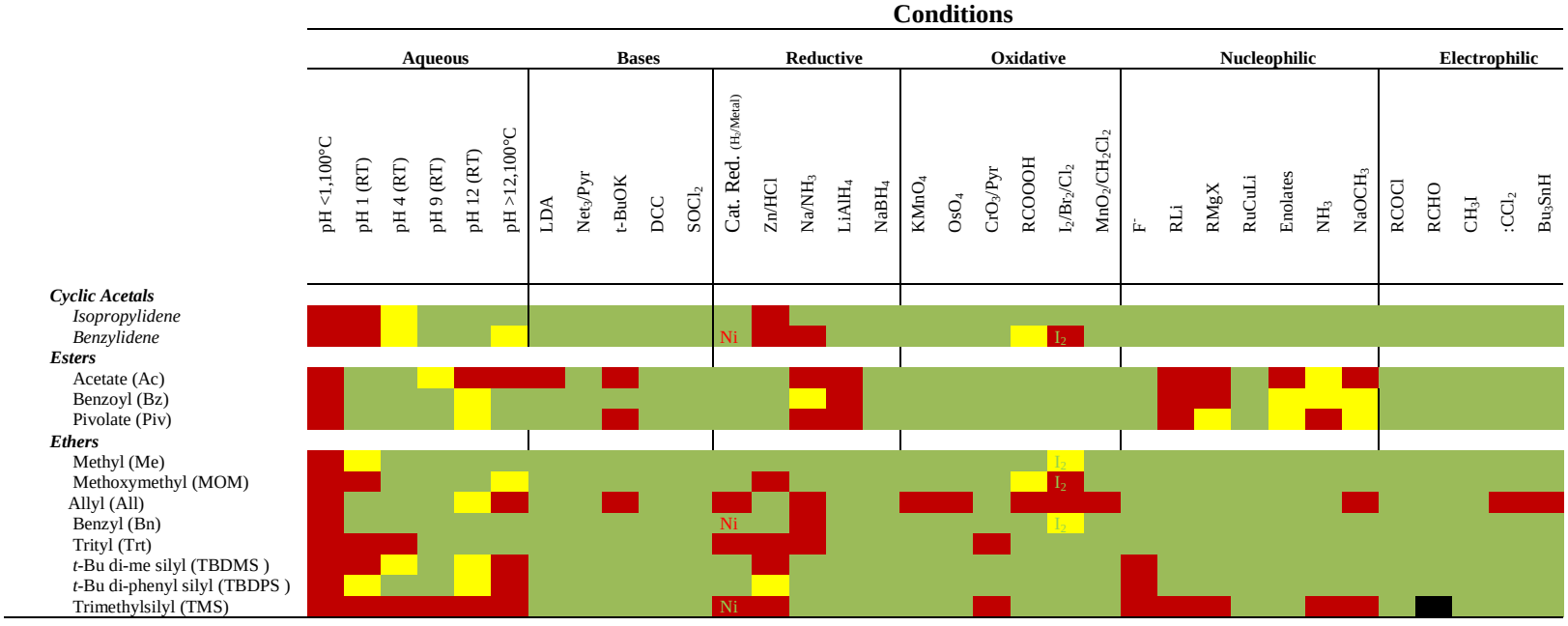
3.2 Regioselective introduction and modification of protecting groups

A central problem in carbohydrate chemistry is the selective protection and deprotection of hydroxyl groups (Faber, 2011; pg 99). While selectivity can be achieved for primary hydroxyl groups, differentiation between secondary hydroxyl groups is more challenging. The following sections will focus upon temporary and permanent protecting groups that can be introduced regioselectively or groups that can be manipulated yielding regioselective protections. The number of potential diol and hydroxyl protecting groups is extensive and the following will not be an exhaustive discussion. Rather, emphasis will be placed on the most common protecting groups and strategies offering high regioselectivity.

Commonly used protecting groups include cyclic acetals for the protection of 1,2- and 1,3-diol systems (Section 3.2.1), esters (Section 3.2.2), and ethers (Section 3.2.2). The stability of some representative protecting groups used in orthogonal strategies under commonly used

reaction conditions are covered in subsequent sections and are presented in Table 2.

Table 2 – Selected stability features of commonly used hydroxyl protecting groups (data from Wuts & Greene, 2007); Green indicates that PG is stable, yellow indicates PG is moderately stable; red indicates PG is unstable; black indicates no data values given



3.2.1 Cyclic acetals

Cyclic acetals are useful protecting groups for diol systems within a monosaccharide. Their ease of formation is paralleled by their ease of removal making them particularly useful for temporary protection. Acetals are generally introduced via direct condensation or directly with a ketone under acidic conditions. Typically, the ketone will react preferentially with anomeric and primary hydroxyl groups. Cyclic acetals are useful as they simultaneously protect two hydroxyl groups and can, in some cases, be selectively manipulated by manipulating steric and electronic conditions and by taking advantage of kinetic products or thermodynamic control. Acetal protection of the 4 and 6-OH positions can often influence the reactivity of the 2 and 3 OHs of pyranoses (Oscarson, 2006).

Isopropylidene acetal

Isopropylidenes can be introduced to unprotected 1,2- or 1,3-diols of carbohydrates using acetone in the presence of a Lewis acid and acetone or 3-pentanone. While 3-pentanone is historically popular, contemporary methods utilize 2,2-methoxypropane-based procedures (Miljkovic, 2009; Wuts & Greene, 2007). The formation of 1,2-diols is generally favored over 1,3- and 1,4-systems with the thermodynamically more stable product prevailing making the protection of cis vicinal diols particularly facile. Isopropylidene formation proceeds through a hemi-acetal intermediate allowing some degree of kinetic control. The formation of the 4,6-isopropylidene derivative of methyl mannopyranoside can be accomplished using 2,2-dimethoxypropane under kinetic control although the product rearranges to the more thermodynamically stable 2,3-isopropylidene (Evans, 1977).

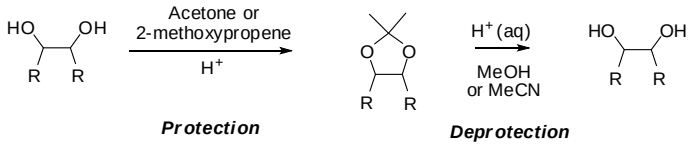


Figure 29 - Introduction and removal of isopropylidene acetal

Secondary hydroxyls react preferentially with the formation of 1,2-acetals although acetals involving primary hydroxyls can be formed if the other available secondary OH groups are in a trans configuration (Wuts & Greene, 2007). Isopropylidenes are unstable under acidic conditions although selective manipulations of isopropylidene acetals can be achieved in some cases. A serious disadvantage of isoproplyidenes is their propensity to migrate (Miljkovic, 2009). Furthermore, the use of kinetic control to introduce 4,6-isopropylidenes to pyranosides is notoriously difficult. It often produces irreproducible results due to the 2,3-isopropylidene, the di-isopropylidene being the more thermodynamically stable products.

Benzylidene acetal

Methyl hexopyranosides selectively form 4,6-benzylidenes in the presence of benzaldehyde or benzylidene dimethylacetal under acid conditions (Figure 30). The protection of 1,3-diol systems is generally preferred over 1,2- systems due to the formation of a six-membered ring. Removal can be achieved under acidic conditions although catalytic reduction using H_2/Pd-C is often preferable.

Selective 4,6-*O* monobenzylidations have been reported in good yields using α,α-dimethoxytoluene and *p*-TsOH in pyridine for most common hexoses (Patroni, Stick, Skelton, & White, 1988).

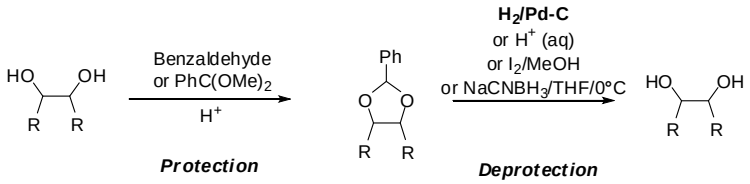


Figure 30 - Introduction and removal of benzylidene for a diol system

Benzylidenes are less prone to migration than isopropylidenes. Additionally, 4,6-*O*-benzylidene derivatives of pyranosides can undergo selective reductive ring cleavage giving either the 4-*O*- or 6-*O*-benzyl ethers as the product with the selectivity being highly dependent upon the nature of the substituent at the 3-OH position; sterically bulky substituents generally favor formation of the corresponding 4-*O*-benzoyl upon reduction (Miljkovic, 2009). Reductions of 4,6-*O*-benzylidenes with DiBAL or $LiAlH_4/AlCl_3$ selectively liberate the 6-OH group while reductions using $NaBH_3CN/HCl$ demonstrate regio-preference for liberating the 4-OH (Boons, 2000). The selective cleavage of O-benzylidene acetals to benzyl ethers is reviewed in Garegg (1996) and the references therein.

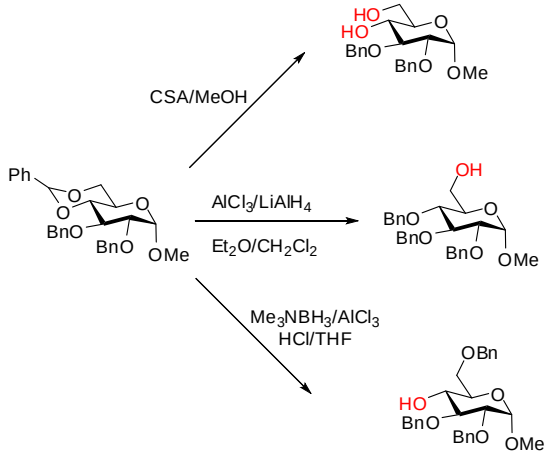


Figure 31 – Removal and selective opening of benzylidene acetals

A major disadvantage of the selective ring opening of the 4,6-benzylidene yielding the 4-*O*-benzyl ether is that the conditions are not

compatible with ester protecting groups although the 6-*O*-benzyl ether can be formed under less disruptive conditions.

TIPDS acetal

One of the more commonly used silyl acetals is the 1,3-(1,1,3,3-tetraisopropyl-disiloxanylidine) acetal (TIPDS). The TIPDS group is readily introduced using the dichloride under basic conditions. As with other silyl ethers, the TIPDS is liable in the presence of fluoride. (Oscarson, 2006)

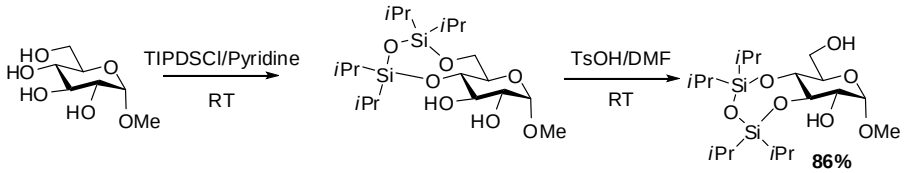


Figure 32 - Introduction and migration of TIPDS acetal (modified from Liptak, Borbas, & Bajza, 2007)

Stannylene acetals

Stannylene acetals are useful protection groups for substrates bearing *cis*- or *trans*-diols. First used in the mid-1970s, the use of stannylene intermediates in carbohydrate synthesis for the protection of diols has become wide spread as they can undergo highly regioselective acylations and alkylations (Grindley, 1994). While frequently utilized as intermediates, stannylene acetals can be readily isolated although they are frequently used without isolation. Stannylation of a diol increases the nucleophilicity of one of the hydroxyl groups making selective manipulations possible (Boons, 2000). A number of reviews that cover the selective introduction and modification of stannylene acetals are available (David & Hanessian, 1985; David, 1996; Grindley, 1994, 2008; Grindley, 1998; Hodosi & Kovac, 1997; Martinex-Bernhardt, Castro, Godjoian, & Gutierrez, 1998).

Reactions for the preparation of stannylenes are performed by refluxing the diol-bearing substrate in the presence of R_2SnO in toluene/methanol with water removal using a Dean-Stark apparatus. More recently, it has been found that forgoing the aforementioned water removal can be skipped if the procedure is followed by careful water evaporation with the addition of methanol prior to subsequent steps (Simas, Pais, & da Silva, 2003). The introduction of a di-butylstannylene acetal to diols is rapid and can be done under very mild conditions as summarized in Figure 33 (Grindley, 2008). Alternately, microwave-based procedures have become more popular in recent years.

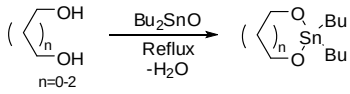


Figure 33 - Introduction of dibutylstannylene acetal (Grindley, 2008)

The introduction of stannylenes is often regioselective with a preferences for primary hydroxyl groups and with a preference for hydroxyl groups in the equatorial position (Simas et al., 2003). Stannylenes of cis diol systems form more quickly than trans diols (Grindley, 1998) Subsequent reactions of stannylene acetals are useful for the monoalkylation of hydroxyl groups as the reactive stannylene will rapidly react with electrophiles to give monosubstituted products with high regioselectivity, in good yield, and under mild conditions (Grindley, 1994). It is noteworthy that the 2,3-stannylene acetal is readily introduced in the presence of 4,6-*O*-benzylidene for hexopyranosides which opens the possibility of regioselective ring openings (Grindley, 2008).

Generally, substitutions of di-butylstannylenes prefer substitutions of the equatorial position when the configuration of the vicinal diol includes both and axial and equatorial partner (Liptak et al., 2007).

As stannylenes increase the nucleophilicity of the oxygen atoms with which they react, subsequent treatments with electrophilic reagents such as acyl, silyl, and alkyl halides, present a convenient

route to the regioselective introduction of the corresponding PGs. Both silyl ethers and esters are readily introduced in this manner under ambient conditions in a short period of time whereas reactions with alkylating reagents frequently require refluxing over longer periods (Oscarson, 2006). The use of di-butylstannylene intermediates can also furnish highly regioselective mono-acylations of a vicinal diol pair in a one-pot synthesis; an example of the regioselective benzoylation at the 3-OH position (Otera, 2003).

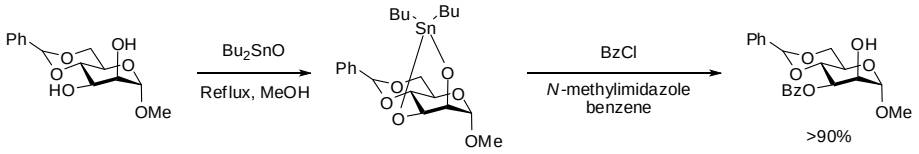


Figure 34 - Use of a stannylene for the monoacylation of a vicinal diol

Alternately, the 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-glucopyranoside reacts with benzoyl chloride (BzCl) in 1,4-dioxane to give the corresponding 2-*O*-benzoyl ester in 90% yield (Miljkovic, 2009 and references therein). Unprotected methyl α-D-galctopyranosides can be selectively protected at the 6-OH or 3-OH position as shown in the figure below by utilizing a stannylene intermediate (Oscarson, 2006).

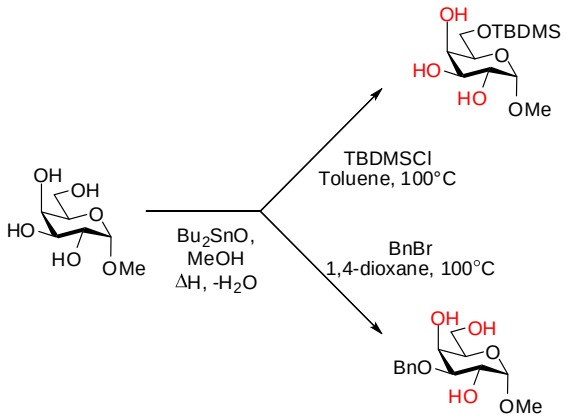


Figure 35 – Example of stannylene intermediates in highly selective protections of unprotected galactopyranosides (Oscarson, 2006)

Regioselective benzoylations are also possible after stannylene protection as reviewed in (Zhang & Wong, 2002).

One of the drawbacks to using stannylene acetals is the need for a molar equivalent of a tin derivative; alkyl tin derivatives present an environmental hazard due to their toxicity (Bulten & Meinema, 1991). Additionally, migration of the stannylene group can occur under increased temperature (Zhang & Wong, 2002).

3.2.2 Esters

Esterification is routinely used for the protection of a monosaccharide's primary and secondary hydroxyl groups. Esters are conveniently introduced using either the corresponding acyl chloride, diacyl anhydride, acid or by lipase-catalyzed acylations (Bornscheuer & Kazlauskas, 2006b; Otera, 2003). Acyl protecting groups are typically readily introduced and removed from target molecules in high yields and under reasonably mild conditions. The structures of commonly used acyl groups are presented in the figure below.

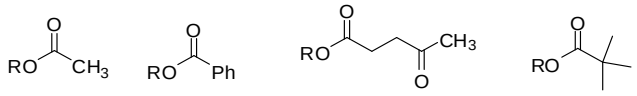


Figure 36 - Commonly used ester protecting groups; left to right: acetate (Ac), benzoyl (Bz), levulinate (Lev), pivolate (Piv)

One of the main drawbacks to using acyl groups is their ability to migrate, depending on solvent, pH, configuration, and reactivity of other OH groups (Miljkovic, 2009). The migration of acyl groups can be used to achieve selective protection under specific conditions (Chittenden & Buchanan, 1969). Ester PGs are particularly prone to migration under basic conditions which are often used to introduce ether PGs.

Esters typically decrease the reactivity of a molecule and are frequently used as disarming groups in oligosaccharide synthesis (Huang & Wang, 2007).

Acetates

Acetates are generally formed by the reaction of one or more equivalence of acetic anhydride or acetyl chloride in pyridine using *p*-(dimethyl)aminopyridine (DMAP) as a catalyst. Acetates are easily removed under Zemplén conditions (catalytic quantities of sodium in methanol). As with other acyl groups, acetyl esters are prone to migration under basic conditions.

While there have been studies to determine the relative reactivity of partially protected hexopyranoses and regioselective operations using stannylenes do exist, the regioselective introductions of acetyl groups is not as high as with more sterically bulky esters such as the benzoyl and pivaloyl protecting groups (Boons, 2000; Miljkovic, 2009).

A notable exception, beyond the scope, of this work is the use of lipases and lipases and esterases for the introduction of acetyl (and other acyl) protection protection with varying degrees of selectivity. Lipases exhibit varying degrees of degrees of catalytic promiscuity depending on the nature of the substrate, acyl substrate, acyl donor, and active site. Numerous lipases are commercially commercially available. Illustrative examples of 2-*O* and 3-*O* protections with a protections with a high degree of discrimination between the two free hydroxyls hydroxyls of 4,6-*O*-benzylidene protected glucopyranosides have been reported reported using vinyl chloride as an acyl donor in DMF as summarized in (in (

Table 3); other regioselective applications in carbohydrate chemistry are extensively reviewed in the following references (Bornscheuer & Kazlauskas, 2006a; Faber, 2011; Kadereit et al., 2002; Whitesides & Wong, 1985; Wong & Whitesides, 1994).

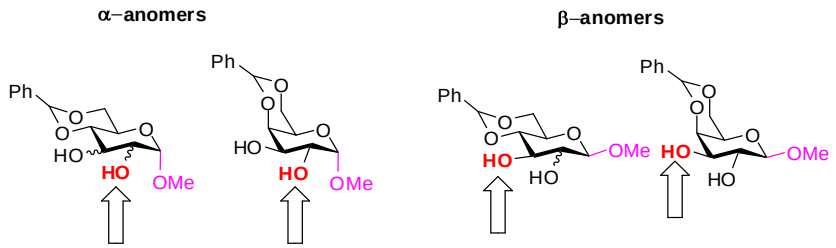


Figure 37 - Regioselectivity of *Pseudomans cepacia* (PCL) and *Pseudomonas fluorescens* lipase (PFL*)*-catalyzed acetylation of α and β anomers of methyl 4,6-*O*-benzylidene pyranosides (Bornscheuer & Kazlauskas, 2006b)

Benzoates

Benzoyl (Bz) esters are a commonly used protecting group that is easily introduced using benzoyl chloride. Benzoates are less prone to migration than acetates under basic conditions. Introduction of benzoyl groups to primary hydroxyls can be accomplished using benzoyl cyanide or by using one molar equivalence of the corresponding chloride (Liptak et al., 2007). Among the common hexopyranoses, the reactivity of the secondary hydroxyl to benzoyl chloride groups are as follows: benzoyl chloride selectivity for methyl α-D-glucopyranoside and galactopyranoside is 2-OH>3-OH>4-OH; alternately, the relative preference for benzoylation of methyl α-D-mannoyranoside is 3-OH>2-OH>4-OH (Miljkovic, 2009).

Selective protection of the 2-OH of 4,6-*O*-isopropyliden-α-D-galactopyranoside is possible by using benzoyl cyanide as the acylating agent (Gu, Yang, Du, & Kong, 2001). Other methods for selective introductions can be obtained using stannylene acetal intermediates as previously discussed (Section 3.2.1).

Benzoyl esters can be easily removed by hydrolysis under basic conditions or by the Zemplén deacetylation method using catalytic quantities of sodium methoxide or ammonia in methanol. Benzoyl groups can also be converted to benzyl ethers under reductive

conditions. One of the major drawbacks to the use of benzoyl groups for hydroxyl protection is that the group tends to migrate under basic conditions.

Pivaloates

As with other acyl groups, pivolate (Piv, trimethylacetyl) esters can be introduced to primary or secondary hydroxyl groups using the corresponding chloride, anhydride or vinyl derivatives in good yields (Brito-Arias, 2007). Due to their steric bulk, selective procedures for their introduction to primary hydroxyl groups have been described (Oscarson, 2006).

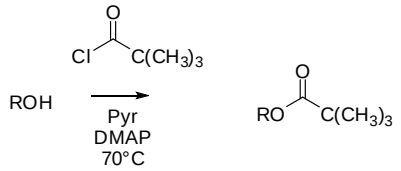


Figure 38 – Introduction of pivolate protection

As with other esters, Piv protection is often base labile; this group is readily cleaved by Bu_4NOH at ambient temperatures (Wuts & Greene, 2007). The utility of Piv in oligosaccharide synthesis is noteworthy. When used as 2-OH protection on glycosyl donors, they decrease the formation of orthoester side products (Oscarson, 2006).

Sulfonates (mesylate, tosylate)

The use of sulfonates for hydroxyl group protection and leaving groups is almost exclusively limited to oligosaccharide synthesis; the use of tosylate esters, for instance, are of their utility for the protection of the 2-OH which allows easy access to 1,2-*cis* glycosides (Wuts & Greene, 2007). The introduction of the tosylate and mesylate esters to a hydroxyl group is readily accomplished in the presence of corresponding chloride; excellent selectivity for primary hydroxyl groups in the presence of secondary OH groups can be obtained with triflate derivatives (Wuts & Greene, 2007). Introduction can usually be

done in high yield and removal is accomplished using metals or metal hydrides.

Figure 39 - Sulfonate esters; mesylate (Mes, left) and tosylate (Tos, right)

The use of phase-transfer catalysts (PTC) can allow for the selective position of the more acidic 2-OH in 4,6-acetal derivatives of pyranosides (Liptak et al., 2007).

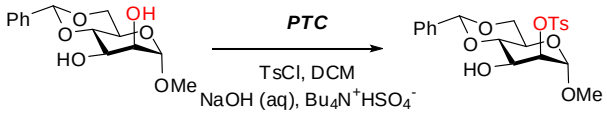


Figure 40 - Regioselective tosylation with phase-transfer conditions

Table 3 – Selected regioselective esterifications of 4,6-acetal-protected monosaccharides using common protecting groups; dominant product is bold.

Substrate	PG	2:3 ratio	**Product Distribution** (%) 2-*O*-	3-*O*-	2,3-*O*-di	Reaction Conditions	Reference
Me 4,6-*O*-α-D-glucopyranoside							
	Ac	1:0	**82**	-	18	Substrate/$HgCl_2$/NaH1:1:2; THF, AcCl, RT	Eby, et al., 1984
	Ac	1:5.3	15	**80**	5	Substrate/$CuCl_2$/NaH1:1:2; THF, AcCl, RT	Eby, et al., 1984
	Ac	1:0	**100**	-	0	PCL or PFL, vinyl acetate, DMF	Riva, 1996
	Ac	1:0	**68**	0	16	CH_3SO_2Cl, Pyr	Jeanloz, 1957
	Ac	1:14	3	**42**	26	Ac_2O, Pyr	Jeanloz, 1957
	Ac	1:0	16	0	**23**	AcCl, Pyr	Jeanloz, 1957
	Bz	4:1	24	6	**35**	PhCOCl, Pyr	Jeanloz, 1957
	Bz	1:0	**62**	-	-	BzCN, MeCN, TEA	Abbas, 1975
	Bz	22.5:1	**90**	4	2	1-(benzoyloxy)benzotriazole,DCM,RT	Kim, 1985
	Bz	1:0	**87**	0	13	Substrate/$HgCl_2$/NaH1:1:2; THF, BzCl, RT	Eby et al., 1984
	Bz	1:0	**41**	-	25	Bu_2SnO; BzCl, benzene	Holzapfel, et al., 1984
	Bz	1:0	**82**	-	-	Bu_2SnO; BzCl, benzene	Holzapfel et al., 1984
	Bz	1:0	**93**	-	-	Bu_2SnO; BzCl, benzene	David & Thieffry, 1979
	Bz	18:1	**72**	4	4	BzCl, PTC	Szeja, 1983
	Bz	4.7:1	**52**	11		BzCl, PTC, NaI	Szeja, 1983
	Bz	1:1.9	13	**25**	9	$(PhCO)_2O$	Jeanloz , 1957
	Mes	1:0	**40**	0	6	Mes_2O, Pyr	Jeanloz, 1957
	Tos	1:1.3	21	**28**	4	TsCl, Pyr	Stirm, 1966
	Tos	1:0	**80-85**	0	15	Ts_2O, Pyr	Jeanloz, 1957
Me 4,6-*O*-β-D-glucopyranoside							
	Ac	1:15.7	6	**94**	0	PCL or PFL, vinyl acetate, DMF	Riva, 1996
	Tos	~1:4	2-5	8	**40**	TsCl, pyr, 4°C, 6 days	Guthrie, 1970
	Mes	1:2.8	6	17	**41**	MsCl, 4°C overnight	Guthrie et al., 1970

(Cont'd)

Table 3 - (Continued) – Selected regioselective esterifications of 4,6-acetal-protected monosaccharides using common protecting groups

Substrate	PG	2:3 ratio	Product Distribution (%) 2-*O*-	3-*O*-	2,3-*O*-di	Reaction Conditions	Reference
Me 4,6-*O*-benzenylidene-α-D mannopyranoside							
	Ac	32.3:1	**97**	3	0	PCL or PFL, vinyl acetate, DMF	Riva, 1996
	Bz	2.3:1	-	-	-	BzCN, MeCN, TEA	Carey, 1979
	Bz	0:1	0	>**90**	-	Bu_2SnO, MeOH; BzCl, *N*-methylimidizole, benzene	Holzapfel et al., 1984; Otera, 2003
	Bz	1:0	**~80**	-	-	Bu_2SnO, MeOH; BzCl, benzene	Holzapfel et al., 1984
	Ts	1:0	**95**	0	0	PTC; TsCl, DCM, NaOH (aq), Bu_4NHSO_4	Liptak et al., 2007
	Ts	1:0	**35.9**		4.3	TsCl, pyr, 0°C, 24 hr	Buchanan & Schwarz, 1962
Me 4,6-*O*-benzylidene-β-D mannopyranoside							
	Ac	1:49	2	**98**	0	PCL or PFL, vinyl acetate, DMF	Riva, 1996
4,6-*O*-ethylidene-α-D mannopyranoside	Ts	0:1	-	**59.2**	--	TsCl, -0-5°C, 3 day	Aspinal & Zweifel, 1957
Methyl 4,6-*O*-di-benzyl-α-D mannopyranoside							
	Ac	7:1	**77**	11	4	Substrate/$HgCl_2$/NaH1:1:2; THF, AcCl, RT	Eby et al., 1984
	Ac	1:65	10	**65**	0	Substrate/$CuCl_2$/NaH1:1:2; THF, AcCl, RT	Eby et al., 1984
	Bz	2.4:1	**50**	21	29	Substrate/$HgCl_2$/NaH1:1:2; THF, BzCl, RT	Eby et al., 1984
	Bz	1:3	25	**75**	0	Substrate/$CuCl_2$/NaH1:1:2; THF, BzCl, RT	Eby et al., 1984

3.2.3 Ethers

Ether PGs are among the most widely used PGs for hydroxyl groups; they are favored over other classes of protecting groups, such as esters, for their stability. Generally, ethers are more stable under both acidic and basic conditions than esters and are less prone to migration. However, the stability of ethers also limits their applicability as temporary protecting groups as conditions (Lewis acids and a displacing nucleophile) that remove ethers can also cause the cleavage of other protecting groups. Selective removal methods for ether PGs are reviewed in Weissman & Zewge (2005).

In the context of oligosaccharide synthesis, ethers are generally used as "arming" groups which are electron donating in nature (Huang & Wang, 2007). Generally, the most widely used ethers are typically either alkyl or benzyl-type ethers. Most ethers are introduced under highly basic conditions which is problematic due to the migration of acyl groups although benzhydryl ethers can be introduced under mild conditions that do not favor acyl group migration. Procedures for the introduction of ethers under neutral conditions using silver(I) oxide or stannyl ethers and acetals can also be employed.

Ether protecting groups can be generally divided into allyl ethers and and bulkier benzyl-type ethers which also include benzhydryl and trityl ethers. ethers. The use of metal chelates of diols for the selective activation of specific specific hydroxyl groups has been shown to result in interesting regioselective regioselective protections in the presence of alkylating agents as illustrated by illustrated by Avela, et al. (1971) used copper(II) chelates and stannylene stannylene intermediates. Selections relevant for the regioselective protection of protection of 4,6-acetals are summarized in

Table 4.

Methyl ethers

Methyl (Me) ethers are a commonly used protecting group favored for their overall stability. Numerous methodologies for the introduction of the methyl group to hydroxyls have been developed although facile and rapid methodologies based upon the Williamson synthesis, typically using a methyl donor such as dimethylsulfate/NaOH/Bu_4NI or methyl iodide in the presence of KOH (Robertson, 2003; Wuts & Greene, 2007), are the most common. Alternately, diazomethane can be used (Chittenden, 1973; Neeman, Caserio, Roberts, & Johnson, 1959). These methods do not generally show a high degree of discrimination between hydroxyl groups.

While the use of diazomethane is effective, large excesses of the reagent are required and the reaction is non-selective. An accidental discovery by (Aritomi & Kawasaki, 1970) involving methanol "aged" in a tin canister revealed changes in selectivity during methylation using diazomethane. Subsequent work revealed various transition metal salts during methylation altered diazomethane's regioselectivity on vicinal diol substrates using tin(II) chloride dihydrate showing regioselective methylations at the 3-OH on methyl 4,6-*O*-benzylidene α-D-glucopyranoside (Aritomi & Kawasaki, 1970). Very high regioselectivity has been achieved using diazomethane and tin(II) chloride for the mono-methylation of 4,6-protected monosaccharides and other partially protected monosaccharides bearing unprotected vicinal diols (Aritomi & Kawasaki, 1970; Chittenden, 1975, 1979).

The work of Eby and Avela on copper chelates of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside showed that mono-methylations using diazomethane were possible. This work resulted in mixtures of the corresponding 2- and 3-methyl ethers with the 3-ether being the dominant product in good overall yields with no formation of the corresponding di-ether (Avela & Holmbom, 1971; Eby et al., 1984).

Methoxy methyl ethers

Methoxymethyl (MOM-OR) ethers are another common ether PG. Introduction is typically facilitated with a methoxymethyl halide in the presence of NaH using NaI as a catalyst. Selective protections of diol systems have been reported using Bu_2SnO and MOMCl in the presence of Bu_4Li in good yields (David, 1981). Recently, the popularity of this PG has decreased due to concerns over the carcinogenicity of MOM-Cl.

Allyl (All) ethers

As with many other ethers, allyl ethers are introduced using the corresponding bromide and an alkoxide, barium oxide/barium hydroxide, or silver(I) oxide(Boons, 2000). The utility of allyl ethers stems from their broad stability under both acidic and basic conditions and facile two-step removal as shown in Figure 41.

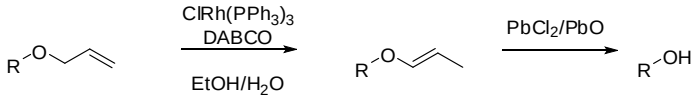


Figure 41 - Two-step removal of allyl ethers

Regioselective introductions of allyl ethers into 4,6-*O*-benzylidene glucospyranosides can be accomplished using stannylene intermediates (Alpe & Oscarson, 2002).

Benzyl (Bn) ethers

The protection of hydroxyl groups with benzyl ethers (Bn) is one of the most the most commonly used protecting groups in carbohydrate chemistry. Like Like methyl ethers, benzyl groups are often introduced using a Williamson Williamson reaction (Carey & Sundberg, 2001b). Numerous procedures for the procedures for the introduction of benzyl ethers under anionic, neutral, and and mildly acidic conditions have been described in the literature although these although these methods rarely offer any degree of regioselectivity without the without the use of either phase-transfer conditions or a transition metal catalyst catalyst (Boons, 2000). Selected regioselective benzylations are summarized in summarized in

Table 4.

Phase transfer conditions (PTC) under basic conditions have been noted to lead to highly regioselective benzylations of partially protected monosaccharides with primary hydroxyls being preferred over secondary hydroxyls (Boons, 2000). A particularly striking example is that of methyl 4,6-*O*-di-benzyl-α-D-mannopyranoside which can be selectively benzylated at the 2-OH position in good yield, as shown in Figure 42.This nicely complements Bu_2SnO procedures as well as selective benzhydrylation procedures using tin(II) catalysts that typically prefer the 3-OH position.

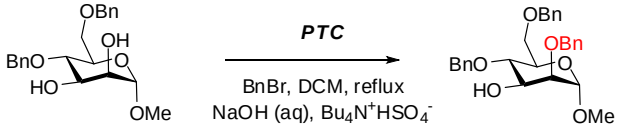


Figure 42 - Selective benzylation of the 2-OH using phase-transfer conditions (modified from Oscarson, 2006)

Selective benzylation of the 4,6-benzylidene pyranosides has given conflicting results in the literature with respect to the reactivity differences of the 2-OH and 3-OH. Studies purporting to use the same conditions results in different regioselectivity patterns. Another

substantial drawback of the reported selective benzylation procedures are substantial formation of the di-ether. Interestingly, the use of tin(II) chloride has been reported to give monobenzyl ethers of methyl α-L-rhamnopyranoside (Toman, Rosik, & Zikmund, 1982).

As with selective methylation of methyl 4,6-*O*-benzyidene pyranosides, regioselective benzylation has been reported using copper(II) and mercury(II) chelates (Eby et al., 1984 and references therein).

Benzyl ethers are generally introduced under basic conditions and can be selectively removed using reductive hydrogenolysis, Lewis acid hydrolysis, or under oxidative conditions (Wuts & Greene, 2007). Catalytic hydrogenolysis methodologies are the most commonly employed method of removal due to their quantitative yields and relatively mild conditions (Boons, 2000). Lewis acids such as $SnCl_4$ or $TiCl_4$ can be used as selective acetolysis agents which preferentially remove the most acid-liable benzyl group, typically on a primary hydroxyl, and replace it with the corresponding acetate (Boons, 2000).

Stannyl Ethers

O-Stannyl ethers are useful synthetic intermediates for the selective protection of hydroxyl groups. Of particular note is the use of *bis*(tributyltin) oxide; introduction is performed by refluxing the substrate in the presence of the tin reagent in methanol (Grindley, 2008; Grindley, 1998). The resultant stannous ether will react regiospecifically with benzoyl chloride in the absence of other reagents to yield the corresponding mono-benzoate (David & Hanessian, 1985). Selective alkylations are also possible but typically proceed more slowly.

It has been noted that the formation of a covalent bond between Sn and O-atoms enhances the nucleophilicity of the oxygen allowing selective manipulations in subsequent reactions with electrophilic reagents, although steric factors may also be involved (David &

Hanessian, 1985). One of the major drawbacks to using stannyl ethers such as tribuyltin oxide is the need for stoichiometric quantities of the reagent and the deleterious effects of organotin compounds in the environment (Bulten & Meinema, 1991).

Some interesting selectivity has been observed. For instance, the α anomer of 4,6-*O*-benzylidene D-glucopyranoside gives a higher selectivity for the 3-OH position than the β-anomer (Cruzado, Bernabe, & Martin-Lomas, 1989). Additionally, trialkylstannylenes can be used for the selective introduction of alkyl groups (Ogawa, Takahashi, & Matsui, 1982). A comprehensive review of stannyl ethers can be found in (Grindley, 1998).

Silyl ethers

Pioneering work by E.J. Corey introduced silicon derivatives as protecting groups for carbohydrate hydroxyls. Fluoride-liable silyl ethers have gained tremendous popularity on orthogonal protection strategies. The wide-spread utilization of silyl ethers stems from the modulating the steric bulk and electronic nature of the substituents attached to the silicon thus modifying the ease of introduction and removal. Sterically bulky silyl ethers generally react with primary hydroxyl groups over secondary hydroxyls and are resistant to a wide range or reaction conditions making them popular as both permanent and temporary PGs. Silyl ethers are readily deprotected in the presence of fluoride and can also be removed under acidic conditions.

Commonly used silyl ethers include trimethylsilane (TMS), *tert*-butyl-dimethyl silyl (TBDMS), and *tert*-butyl diphenyl silyl (TBDPS). These common silyl ethers are shown in Figure 43.

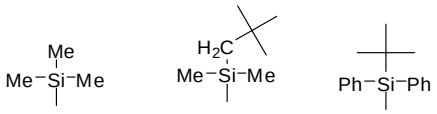


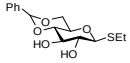
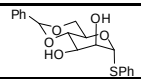
Figure 43 - Commonly used silyl ethers; left to right: trimethyl silyl (TMS), *tert*-butyl-dimethyl silyl (TBDMS), and *tert*-butyl diphenyl silyl (TBDPS)

Silyl ethers, particularly TBDMS, are prone to migration in protic solvent systems as well as under basic conditions (Wuts & Greene, 2007); this can be used to deliberately migrate silyl groups although this phenomenon is more frequently problematic during synthetic operations. It is noteworthy that bulky silyl ethers tend to migrate to axial hydroxyl groups in sterically crowded environments (Wuts & Greene, 2007).

The acid/base stability; TMS is generally regarded as being too liable to be of utility in carbohydrate synthesis (Liptak et al., 2007). TBDPS is a popular alternative for primary hydroxyl groups that, like trityl ethers, has a large steric footprint but can be introduced under milder conditions, and have better stability.

TBDMS and TBDPS ethers are mostly commonly used in carbohydrate chemistry due to their stability. As with other acetals and ketals, silyl ethers can be manipulated under specific conditions and be used for the selective mono-alkylation or mono-esterification (Wuts & Greene, 2007). TBDMS ethers are commonly used for the protection of primary and secondary hydroxyls in carbohydrate chemistry whereas TBDPS ethers are used for their ability to be selectively introduced to a primary hydroxyl group in the presence of secondary hydroxyls (Brito-Arias, 2007; Oscarson, 2006). To the authors knowledge, the selective introduction of silyl ether protecting groups onto 4,6-acetal protected pyranosides has not been reported in the literature.

Table 4 – Selected regioselective alkylations of 4,6-acetal-protected monosaccharides using common protecting groups; bold indicates dominant product

Substrate	PG	2:3 ratio	Product Distribution (%) 2-*O*-	3-*O*-	2,3-*O*-di	Reaction Conditions	Reference
Me 4,6-*O*-benzylidene-α-D-glucopyranoside							
	All	1.4:1	19	**77**	0	Allyl iodide, Cu, DME	Eby et al., 1984
	Bn	1.4:1	18	**74**	0	Sub/$CuCl_2$/NaH1:2:1; DME, BnI, reflux, 24 hr	Eby et al., 1984
	Me	1:3.3	20	**66**	0	Cu(II) chelate (1:2:1) MeI, THF, RT	Eby et al., 1984
	Me	1:3.8	19	**73**	0	Cu(II) chelate (sub/NaH/$CuCl_2$ 1:2:1 mol ratio), MeI, THF, RT	Avela & Holmbom, 1971
	Me	1:4.9	16	**78**	0	Cu(II) chelate (sub/NaH/$CuCl_2$ 1:2:1 mol ratio), MeI, THF, RT	Avela & Holmbom, 1971
	Me	1:24.3	4	**97**	Trace	MeN_2, MeOH,$SnCl_2$ (2 mM)	Aritomi, 1970
	Me	0:1	0	**93**	Trace	Diazomethane, $SnCl_2$ (2 mM)	Aritomi & Kawasaki, 1970
	All	0:1	NR	**68**	NR	1) Bu_2SnO, MeOH, reflux; 2) AllBr, CsF, DMF	Alpe & Oscarson, 2002
	Bn	0:1	NR	**65**	NR	1) Bu_2SnO; 2) BnBr, CsF, DMF, 100°C	Oscarson, 2006
Me 4,6-*O*-benzylidene-α-D-mannopyranoside							
	All	1:4.2	19	**81**	0	Allyl iodide, Cu, DMF	Eby et al., 1984
	All	1:4	20	**80**	0	Allyl iodide, Cu, THF	Eby et al., 1984
	Bn	2.9:1	**55**	19	10	AgO, DMF, BnBr	Kondo, et al., 1983
	Bn	1:4.1	16	**66**	10	BaO, DMF, BnBr	Kondo et al., 1983
	Bn	0:1	**36**	-	-		Boren, 1972
	Bn	1:0	-	**66**	20		Srivastava, 1977
	Bn	1:0	**80**	0	-	1) Bu_2SnO; 2) BnBr, DMF, 100°C	Oscarson, 2006
	Me	1.6:1	34	**53**	trace	Diazomethane, $SnCl_2$ (2 mM)	Aritomi & Kawasaki, 1970
	Bn	1:0	**75**	0	0	PTC, $TBAHSO_4$, CH_2Cl_2, BnBr	Freedman & Dubois, 1975

Triphenylmethyl (Trt)

Triphenylmethyl, also commonly called trityl (Tr or Trt), ethers are mainly used for the protection of primary hydroxyl groups in the presence of other unprotected hydroxyl groups using a triphenylmethyl halide under basic conditions. While secondary hydroxyls can be protected, the steric bulk of the trityl group makes this unfavorable. The trityl group is easily removed in the presence of dilute acid in good yields. The ease with which the trityl group can be removed can be problematic in the course of additional steps.

Benzhydryl (diphenylmethyl), 9-fluorenyl ethers, and related derivatives

The use of diphenylmethyl (DPM), also referred to as a benzhydryl, ethers as protecting groups has not received wide usage in carbohydrate chemistry although the DPM residue has been reported to be of medicinal value (Hayashu, 1997). To date, means for their introduction is limited to niche uses in the selective protection of carbohydrates or small vicinal diols (S Petursson & Jonsdottir, 2012; Pétursson, 2001). DPM and four of its derivatives as well as the 9-fluorenyl ether are described in Figure 44.

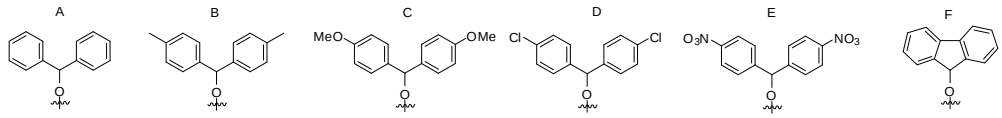


Figure 44 - Structures of selected ethers of diarylmethane derivatives and fluorenyl ether; A – diphenylmethyl, B – di(4-methylphenyl)methyl, C – di(4-methoxyphenyl)methyl, D – di(4-chlorophenyl)methyl, E – di(4-nitrophenyl)methyl, F – fluorenyl

John Webber and co-workers explored the use of diazodiphenylmethane for the introduction of the benzhydryl group into carbohydrates, Sigþór Pétursson and Webber expanded this work to include various other symmetrical diaryldiazomethanes. They reported the use of tin(II) chloride as a catalyst for the regioselective

mono-alkylations of vicinal diols (Jackson, Jones, Petursson, & Webber, 1982; Petursson & Webber, 1982; Petursson, 2008).

Although less widely used than benzyl and trityl protecting groups, benzhydryl ethers can be used to protect hydroxyl groups in good yields. Additionally, benzhydryl ethers as protecting groups can be introduced under mild conditions. Benzhydryl ethers, being secondary ethers, are not as acid labile as tertiary ethers, such as trityl groups and not prone to migration as is the case with some acyl protecting groups. Diphenylmethyl and substituted diphenyl groups can be introduced under mild or acidic conditions and removed with simple hydrogenation over Pd-C (Wuts & Greene, 2007). Work by Paredes & Perez (1998) has also demonstrated that diphenylmethyl ethers can be introduced using catalytic quantities of *p*-TsOH and by refluxing in benzene with a Dean-Stark apparatus. Under acidic conditions, both primary and secondary hydroxyl groups will react with benzhydrol to yield the corresponding ether (Liptak et al., 2007). Benzhydryl ethers can also be prepared by refluxing with tri-diphenylmethyl phosphates (Lapatsanis, 1978).

The *di*(4-nitrophenyl)methyl group can be cleaved in the presence of allyl, benzyl, silyl, trityl, and ketal protecting groups (Just, Wang, & Chan, 1988) although the stability of many other diphenylmethyl derivatives have not been reported. A more comprehensive overviews of the introduction and removal of benzhydryl and fluorenyl ethers can be found in Petursson's (2013) review of benzhydryl ethers.

Work by Pale *et al.* has demonstrated the use of transition metal halides as Lewis acid catalysts to introduce benzhydryl derivatives to primary and secondary hydroxyl groups using the corresponding alcohol of the benzhydryl. Early work used benzhydrol in the presence of palladium(II) chloride and was found to protect primary and secondary alcohols under mild conditions using 0.1 molar equivalence of the $PdCl_2$ catalyst; under conditions where both primary and secondary hydroxyls were present, the primary alcohol was protected selectively (Bikard et al., 2007). Subsequent work demonstrated that

$PdCl_2(MeCN)_2$ is a more efficient catalyst with similar chemoselectivity and yields under milder conditions (20 °C) (Bikard et al., 2008).

Later work demonstrated that $PdCl_2(MeCN)_2$ could be used to introduce a *di*(4-methoxyphenyl)methyl group at ambient temperatures and good yields for primary and secondary hydroxyl groups (Bikard et al., 2008). Further work demonstrated the use of copper(II) bromide as a greener alternative to palladium salts (Mezaache et al., 2009). The use of $CuBr_2$ was further developed and for the replacement of silyl ethers with *di*(4-methoxyphenyl)methyl via *trans*-protection (Specklin et al., 2011).

Benzhydryl (diarylmethyl) ethers can be introduced using diazo compounds under mild conditions; non-selectively via thermolysis or selectively to vicinal diols using tin(II) chloride (Petursson & Webber, 1982; Petursson, 1979). The use of thermolysis in an excess of the diazo derivative in the presence of a 4,6-acetal of a methyl pyranoside leads to a mixture of the corresponding 2-*O*, 3-*O*, and 2,3-*O*-di ethers. The mechanism by which the benzhydryl group via the decomposition of the diazo compound into a reactive carbene is introduced to a hydroxyl group is summarized in Figure 45.

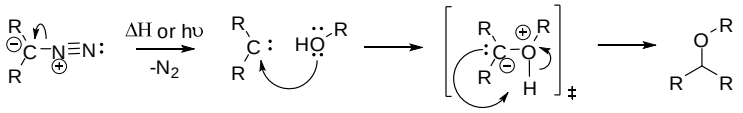


Figure 45 - Mechanism of ether formation from a corresponding diarylmethyl diazo compound via thermolysis

The uncatalyzed reaction of diazodiphenylmethane with 1,2-*O*-isopropyliden-α-D-glucofuranose gives a complex mixture of products while as while as do 4,6-acetals of mannopyranosides (Petursson, 1979). Alternately, the Alternately, the use of tin(II) halides to catalyze the formation of diarylmethyl diarylmethyl ethers gives only the corresponding mono-ether. The reactivity of reactivity of the parent diazo compound influences the regioselectivity of the of the alkylation when tin(II) chloride is used as a catalyst as summarized in

Table 5. It has been observed that highly reactive diaryldiazo compounds, notably diazo–[*bis*(4-methylpheny)methane] and diazo-[*bis*(4-methoxyphenyl)methane], tend to be more selective for the 3-OH than diazo-*bis*(phenyl)-, *bis*(4-chlorophenyl)-, and *bis*(4-nitrophenyl)methane and diazofluorene when used in combinations with tin(II) halide catalysts. Interestingly, diazofluorene has a higher propensity to reacting with the 2-OH. Recently, tin(II) bromide has also been used to catalyze the reactions of vicinal diols with diazo compounds for simple diol systems (Petursson, 2009).

The mechanism by which tin(II) chloride interacts with diols and diazo compounds is still unclear. Smith (1976) suggested a tin(II)-sugar intermediate. Later work by Alfondi and coworkers (1982) involving ^{1}H-, ^{13}C-, and ^{119}Sn-NMR suggested that tin(II) chloride dissolved in deuterated acetone is coordinated by the solvent which is then displaced by vicinal hydroxyl groups in the C-2 and C-3 position of the sugar (in this case *O*-methyl-a-L-rhamnopyranoside). Further work by Blunden et. al (1984) disputed the $SnCl_2$-vicinal diol hypothesis instead showing that the interaction between the $SnCl_2$ and methanol/acetone system was preferential as was the case with the aprotic solvent systems such as *N*,*N*-DMF and DMSO.

Pétursson (2001) suggested that tin(II) halide-catalyzed alkylations involving diazo compounds proceed through a tin(II) halide-diol complex as shown in Figure 46. The interaction of the tin(II) halide with a vicinal diol system leads to the formation of a trigonal bipyramidal complex with the N_2-end of the diazo compound.

Recent work has shown the influence of catalyst concentration on the regioselectivity during tin(II) chloride catalyzed mono-etherification of methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside by diaryldiazomethanes (Petursson, Scully, & Jonsdottir, 2014).

Pétursson et al. have proposed a more detailed mechanism as shown in Figure 46.

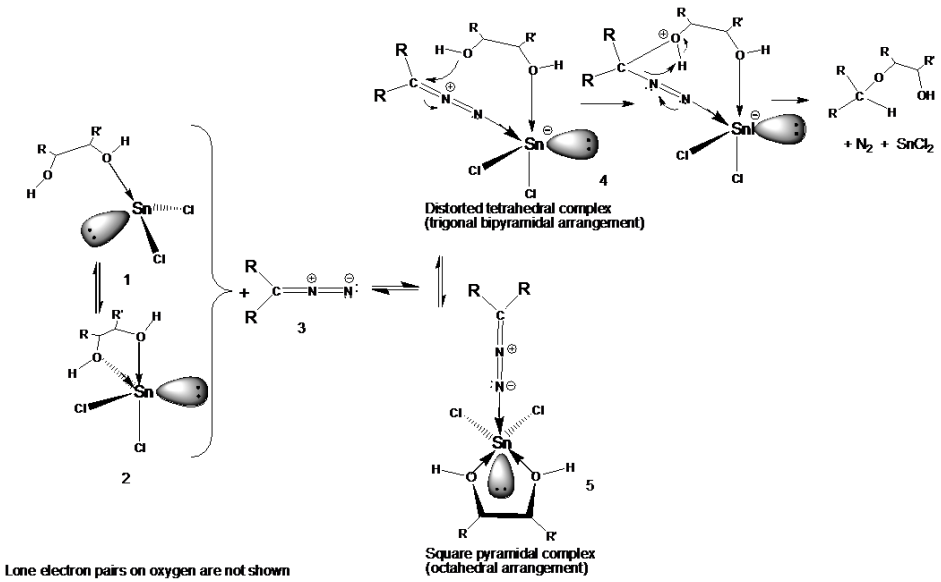
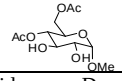


Figure 46 - Proposed mechanism of tin(II) halide catalyzed reactions of diarylmethyl diazo compounds with vicinal diol systems (Petursson, Scully, & Jonsdottir, 2014; Manuscript IV)

Table 5 – Regioselective protection of 4,6-acetal-protected monosaccharides using benzhydryl ethers

Substrate	Protecting Group	2:3 ratio	Product Distribution (%) 2-*O*-	3-*O*-	2,3-*O*-di	Reaction Conditions	Reference
Me 4,6-*O*- benzylidene-α-D glucopyranoside	Diphenylmethyl	1:3.5	19.6	69.1	0	Ph_2N_2, DME, $SnCl_2$ (3.11 mM)	Pétursson, 2001
	Diphenylmethyl	1.8:1	25	14	ND	Ph_2N_2, $PdCl_2(MeCN)_2$, DCE, 60°C 24 h	Bikard et al., 2008
Me 4,6-benzylidene- α -D-mannopyranoside							
	Diphenylmethyl	1:11.7	6	70	0	Ph_2N_2, DME, $SnCl_2$ (20 mM)	Petursson & Webber, 1982
	Di(methylphenyl)methyl	0:1	0	80	0	(p-$CH_3Ph)_2CN_2$, DME, $SnCl_2$ (20 mM), 3°	Petursson & Webber, 1982
	Fluorenyl	0:1	0	65	0	Diazofluorene, DME, $SnCl_2$ (20 mM)	Petursson & Webber, 1982
Me 4,6-isopropylidene-α-D-mannopyranoside	Diphenylmethyl	1:1.01	38	38.5	0	Ph_2N_2, DME, $SnCl_2$ (5 mM)	Petursson & Webber, 1982
	Di(methylphenyl)methyl	1:7.5	8	60	0	(p-$CH_3Ph)_2CN_2$, DME, $SnCl_2$ (5 mM)3°C	Petursson & Webber, 1982
	Di(chlorophenyl)methyl	1.04:1	41.5	40	0	(p-$ClPh)_2CN_2$, DME, $SnCl_2$ (5 mM)	Petursson & Webber, 1982
	Di(methoxyphenyl)methyl	0:1	0	61	0	(p-$CH_3OPh)_2CN_2$, DME, $SnCl_2$ (5 mM), -10°C	Petursson & Webber, 1982
	Fluorenyl	6.4:1	76.5	11.9	0	Diazofluorene, DME, $SnCl_2$ (5 mM)	Petursson & Webber, 1982

4 Results

4.1 Preparation of diazo compounds using Magtrieve™

The synthesis of five diazo compounds by oxidation of the parent hydrazone using various molar equivalence The data presented in this section is presented in **Manuscript I**.

Optimization of Magtrieve™-based oxidations of diaryl hydrazones to diazo compounds

Optimization experiments using different loadings of CrO_2 showed that less than 6 molar equivalence yielded an incomplete conversion of the hydrazone substrate to the corresponding diazo compound. 10, 15, and 20 equivalence yielded rapid oxidation of the hydrazone. Kinetic plots are given in Appendix B.

Table 6 – Reaction times of the synthesis of five diaryl diazo compounds using various molar equivalence of Magtrieve^{TM} (CrO_2); all reaction times were determined by experiments performed in triplicate. ND – not determined

	Reaction time (min)						
	molar equivalence of Magtrieve^{TM} (CrO_2)						
Diazo Compound	**0.75**	**1.5**	**3**	**6**	**10**	**15**	**20**
Ph_2CN_2	>270	>270	270	240	180	90	45
(*p*-$CH_3Ph)_2CN_2$	>240	>240	240	150	120	15	30
(*p*-$CH_3OPh)_2CN_2$	>480	>480	480	420	120	60	45
(*p*-$ClPh)_2CN_2$	ND	ND	ND	ND	90	60	60
Diazofluorene	>270	>270	270	240	120	120	120

The use of 15 molar equivalence of Magtrieve^{TM} gave reasonable reaction times and was selected for use in subsequent work.

Preparative scale synthesis of diazo compounds using Magtrieve^{TM}

Small preparative-scale reactions (5 mmol) yielded the corresponding diazo compound in acceptable yields The overall yields and reaction times for the preparation of diazo compounds from their corresponding hydrazones is summarized in Table 7.

Table 7 - Yields and reaction times for the preparation of five diazo compounds from the corresponding hydrazone using 15 molar equivalence of CrO_2. Values represent the average of triplicates ± standard deviation.

Diazo compound	**Isolated Yield** (%)	**m.p.** (°C)	**Reaction time** (min)
1 Ph_2CN_2	95.1 ± 1.54	29-31	90
2 (*p*-$CH_3C_6H_4)_2CN_2$	81.9 ± 1.98	105	30
3 (*p*-$CH_3OC_6H_4)_2CN_2$	68.9 ± 2.23	110	60
4 (*p*-$ClC_6H_4)_2CN_2$	61.0 ± 1.92	108	60
5 Diazofluorene	90.3 ± 1.58	153	120

One-pot synthesis of a mono-ether from a 4,6-acetal protected monosaccharide

MagtrieveTM was used for the one-pot preparation of the 3-*O*-ether of methyl 4,6-benzylidene-α-D-mannopyranoside, as shown in Figure 47, in good yield.

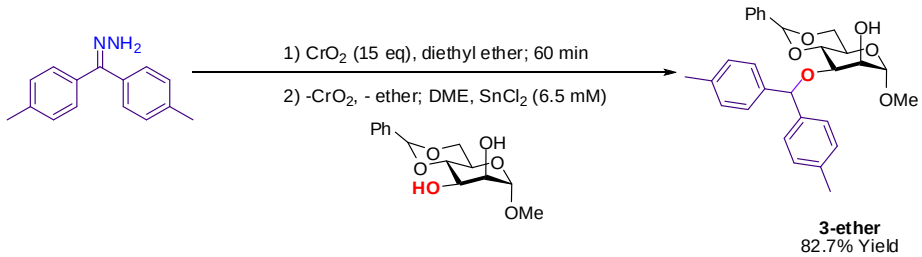


Figure 47 – One-pot synthesis of methyl 3-*O*-(*bis*(4-methylphenyl)methyl)-4,6-*O*-benzylidene-α-D-mannopyranoside using Magtrieve^{TM}

4.2 Tin(II) halide-catalyzed reactions of partially protected carbohydrates containing vicinal diols

The contents of the following sections are described in **Mansucripts II** (manno derivatives) and **Manuscript III** (gluco derivatives). Summary chromatographs for each series of reactions are presented in Appendix D.

4.2.1 Methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside

Reactions (Figure 48) between the five diazo compounds and methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside using tin(II) chloride or tin(II) bromide yielded a mixture of the corresponding 2-*O*- and 3-*O*- ethers with the 3-ether being the predominant

product except in the case of diazofluorene as the alkyl donor in which case the 2-*O* ether was the dominant product. The yields and reaction times are summarized in Table 8.

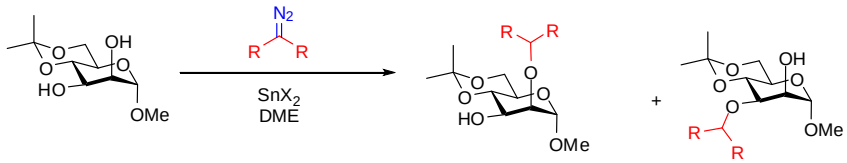


Figure 48 – Tin(II) halide-catalyzed reaction of methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside with a diazo compound

Differences in regioselectivity between the use of tin(II) chloride and tin(II) bromide while using the five diazo compounds as an alkylating agent for methyl 4,6-isopropyliden-α-D-methyl mannopyranoside are displayed in Figure 49A ($SnCl_2$) and Figure 49B ($SnBr_2$). The overall yields were good in all cases (greater than 85% of the theoretical yield) with the exception of the reactions involving diazo *bis*(4-methoxyphenyl)methane; in both cases yields of the resultant ether were less than 60%.

Table 8 - Reaction times and yields of mono-etherifications of methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside catalyzed by $SnCl_2$ or $SnBr_2$

Diazo Compound	$SnCl_2$			$SnBr_2$		
	Overall Yield (%)	**2:3 ratio**	**Time** (hrs)	**Overall Yield** (%)	**2:3 ratio**	**Time** (hrs)
Diazo *bis*(4-methoxyphenyl)methane	56.1	0:1	<3 min	38.6	0:1	< 2 min
Diazo *bis*(4-methylphenyl)methane	88.2	1:34.2	0.33	88.2	0:1	2 min
Diazodiphenylmethane	94.9	1:26.1	2.4	97.7	1:5.6	1.2
Diazo *bis*(4-chlorophenyl)methane	98.5	1:43.8	6	91.3	1:3.4	3
Diazofluorene	89.6	1.4:1	72	74.7	3.8:1	72

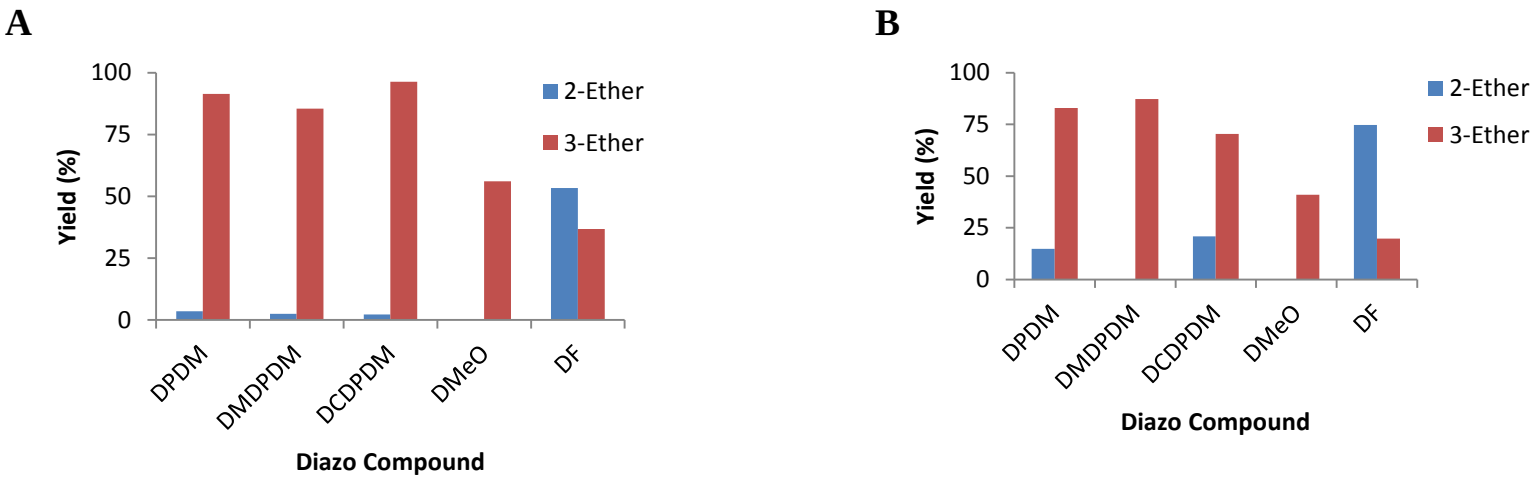


Figure 49 - Regioselectivity and yields between reactions of diazo compounds and methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside using $SnCl_2$ **(A)** or $SnBr_2$ **(B)** catalysts

4.2.2 Methyl 4,6-*O*-benzylidene-α-D-mannopyranoside

Reactions between the five diazo compounds and methyl 4,6-*O*-benzylidene-α-D-mannopyranoside using tin(II) chloride or tin(II) bromide yielded the corresponding 3-ether in all cases (Figure 50). The yields and reaction times are summarized in Table 9.

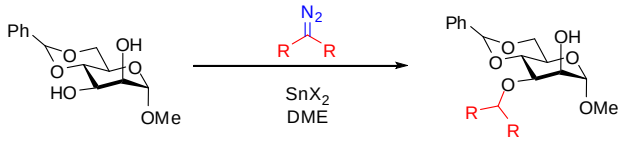


Figure 50 - Tin(II) halide-catalyzed reaction of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside with a diazo compound

Table 9 - Reaction times and yields of mono-etherifications of methyl 4,6-*O*-benzylidene α-D-mannopyranoside with $SnCl_2$ and $SnBr_2$

	$SnCl_2$			**$SnBr_2$**		
Diazo Compound	**Overall Yield (%)**	**2:3**	**Time** (hrs)	**Overall Yield (%)**	**2:3**	**Time** (hrs)
Diazodiphenylmethane	81.7	0:1	72	73.7	0:1	46
Diazo *bis*(4-methylphenyl)methane	79.8	0:1	26	92.4	0:1	21
Diazo *bis*(4-chlorophenyl)methane	73.1	0:1	56	67.1	0:1	53
Diazo *bis*(4-methoxyphenyl)methane	58.2	0:1	<0.25	61.0	0:1	<0.25
Diazofluorene	67.3	0:1	66*	56.3	0:1	67*

4.2.3 Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside

Reactions (Figure 51) between the five diazo compounds and methyl 4,6-*O*-benzylidene-α-D-glucopyranoside using tin(II) chloride or tin(II) bromide yielded the corresponding 3-ether in all cases. The yields and reaction times are summarized in Table 10.

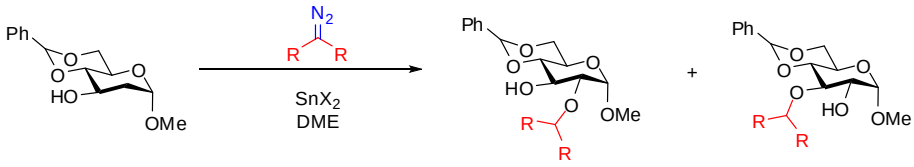


Figure 51 – Tin(II) halide-catalyzed reaction of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside with a diazo compound

Table 10 - Reaction times and yields of mono-etherifications of methyl 4,6-*O*-benzylidene α-D-glucopyranoside with $SnCl_2$ and $SnBr_2$

	$SnCl_2$			$SnBr_2$		
Diazo Compound	**Yield** (%)	**2:3**	**Time** (hrs)	**Yield** (%)	**2:3**	**Time** (hrs)
Diazo *bis*(4-methoxyphenyl)methane	44.8	0:1	4[d]	49.4	0:1	3[d]
Diazo *bis*(4-methylphenyl)methane	49.3	0:1	0.25[a]	55.8%	0:1	0.25[b]
Diazodiphenylmethane	94.0%	0.34	48	98.1%	0.28	46 h*
Diazo *bis*(4-chlorophenyl)methane	89.2%	0:1	56*	85.1%	0:1	53**[c]
Diazofluorene	ND	ND	>168*[e]	ND	ND	>168*[e]

*catalyst fell out of solution, additional SnX_2 added, [a] additional 1 eq of diazo compound added, [b] additional 1.5 eq of diazo compound added, [c] additional 2.5 eq of diazo compound added, [d] additional 5 eq of diazo compound added, [e] greater than 10 additional equivalence required; ND – Not determined

4.3 The effect of catalyst concentration on regioselectivity of $SnCl_2$-catalyzed reactions with diazo compounds

Reactions involving tin(II) chloride catalyzed mono-etherification demonstrated results that diverged from the 2-*O*- and 3-*O*-ether selectivities previously reported by (Petursson & Webber, 1982). Thus, the reactions, shown in Figure 52, of methyl 4,6-*O*-α-D-mannopyranoside with the five diazo compounds described in the previous sections were repeated. The results are summarized in Table 11.

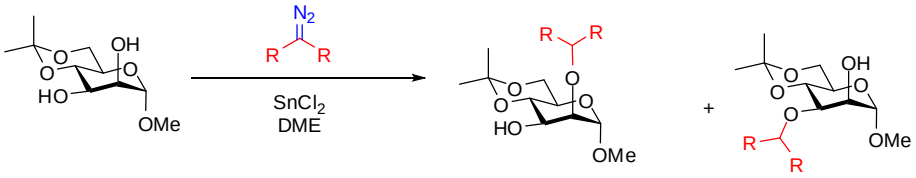


Figure 52 - Tin(II) chloride-catalyzed reaction of methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside with a diazo compound

Due to the difference of the results presented in Table 11 with results previously reported by (Petursson & Webber, 1982). The effect of catalyst concentration was examined as presented in Figure 53.

Table 11 – Mono-etherification of methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside with diaryldiazomethanes using $SnCl_2$ (1.7 mM) as a catalyst

		Product Distribution		
Diazo compound	**Total yield** (%)	**2-ether** (%)	**Unresolved** (%)	**3-ether** (%)
Diazo *bis*(4-methoxyphenyl)methane	61	0	0	61
Diazo *bis*(4-methylphenyl)methane	92	8	24	60
Diazodiphenylmethane	94	42	12	40
Diazo *bis*(4-chlorophenyl)methane	97	38	20	39
Diazofluorene	88	70	13	5

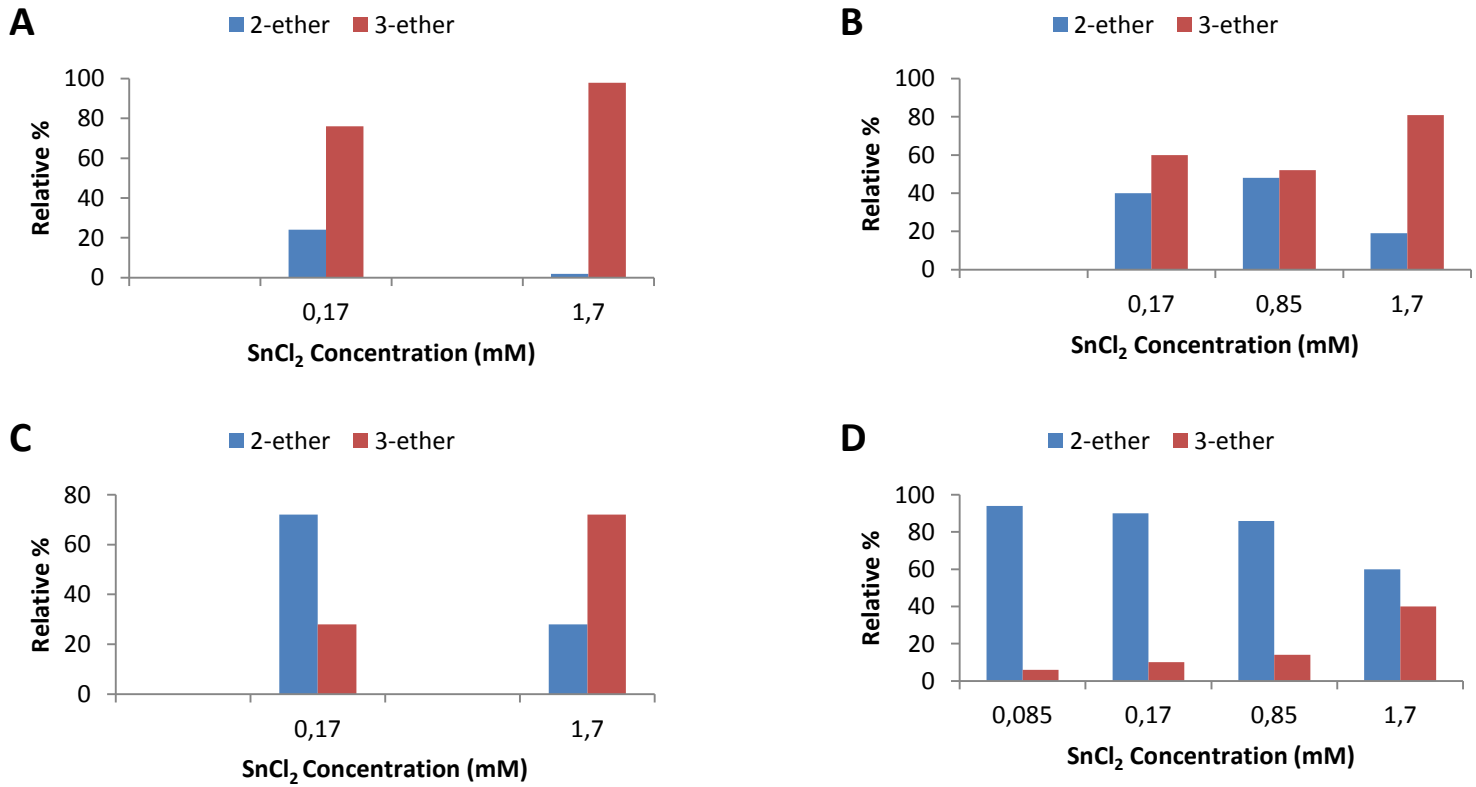


Figure 53 – Effect of tin(II) chloride concentration on reactions between methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside and diazo [*bis*-(methylphenyl)methane] (A), diazo [*bis*-(chlorophenyl)methane] (B), diazo diphenylmethane (C), diazofluorene (D).

5 Discussion

In 1982, Pétursson and Webber published a paper in *Carbohydrate Research*, which reported an interesting and varied regioselectivity during tin(II) chloride catalyzed reactions of diaryl diazo compounds with methyl 4,6-*O*-benzylidene- and isopropylidene-α-D-mannopyranosides. The reason for the selectivity, which showed mainly preferential reactions of the equatorial 3-OH, but shifted towards the axial 2-OH for the less reactive diazo compounds was not clear at that time. It was therefore decided to have a closer look at these reactions and to include tin(II) bromide as a catalyst, which has since also been shown to be a catalyst for these reaction.

During the course of this study, the observed yields for the tin(II) halide-catalzyed introduction of diarylmethyl protection showed higher regioselectivities for the 2,3-diol pair of the 4,6-acetal manno system than other methods methods reported. Furthermore, it transpired that catalyst concentration was a factor in the varied selectivity. These results were pursued further and the results were published recently (Petursson et al., 2014). Reactions of methyl 4,6-*O*-benzylidene- and isopropylidene-α-D-glucopyranosides, which since the original work have also been shown to react, were also investigated.

The preparation of the diazo compounds using mainly mercury(II) oxide is environmentally undesirable and has probably hampered the wider use of these methods. The use of the recyclable chromium(IV) oxide (*Magtrieve*^{TM}) as an oxidant for the preparation of diazo compounds from the corresponding hydrazones was therefore investigated and successfully optimized as described in draft Manuscript I.

5.1 Preparation of diazo compounds using Magtrieve™

The yields from these procedures were generally comparable to other methods such as the mercury(II) oxide or silver(I) oxide methods previously reported in the literature. While the utilization of mercury(II) oxide for the generation of diazo compounds from the corresponding hydrazones gives good yields, it necessitates the removal of Hg_2^{2+} and unreacted mercury(II) oxide by filtration with reaction times in excess of four hours.

The use of Magtrieve™ in large excess to generate diazo compounds from their corresponding hydrazones was first reported by Ko and Kim (1999) and subsequently used in the one-pot protection of carboxylic acids. Unlike Ko and Kim's work in which the CrO_2-mediated oxidation was carried out in dichloromethane, all reactions were carried out in diethyl ether. Ko and Kim reported that the oxidation of benzophenone hydrazone was complete in 15 minutes whereas the oxidations in this study required a longer period of time. This could be due to the solvent system used or the rate of agitation which was not reported by Ko and Kim.

The methods developed here present a facile, rapid, and more environmentally friendly method for generating diazo compounds as the use of heavy metal oxides (mercury(II) oxide, silver(I) oxide) is avoided. Magtrieve™ was routinely recovered and regenerated by heating in an oven at 325-350°C with no effect on performance of the reagent. The utilization of chromium(IV) oxide (Magtrieve™) allows the use of large excesses of the oxidizing agent which can then be recovered using a magnet and regenerated in the presence of oxygen at elevated temperatures. Additionally, chromium(II) oxide is inherently safer than mercury reagents which pose significant health and environmental hazards and require special disposal techniques.

As Magtrieve™ retains its magnetic character after the oxidation of the outer layer (Lee & Donald, 1997), this presents the possibility of a one-pot generation of partially-protected carbohydrates once the reagent has been retrieved. This had the advantage of not having to isolate or otherwise handle diazo compounds, which are potent carcinogens. This was demonstrated with the 3-*O* mono-alkylation methyl 4,6-*O*-benzylidene-α-D-mannopyranoside in good yields although a 2 equivalence excess of the starting hydrazone was used. This methodology could likely be extended to other vicinal diol systems or compounds with only one free OH (such as γ- and δ- sugar lactones) under mild conditions via thermolysis of the generated diazo compound after removal of the Magtrieve™.

5.2 Tin(II) halide-catalyzed reactions of partially protected carbohydrates containing vicinal diols

In this work, the tin(II) chloride-catalyzed mono-etherifications using diazo compounds, which had previously been investigated by Petursson (1979, 1982, 2003), were compared to tin(II) bromide catalysis. Three substrates, methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside (**Manuscript II**), methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (**Manuscript II**), and 4,6-*O*-benzylidene-α-D-glucopyranoside (**Manuscript III**), were treated with diaryl diazo compounds in the presence of catalytic quantities of tin(II) chloride or tin(II) bromide. A summary of these reactions is given in Figure 54.

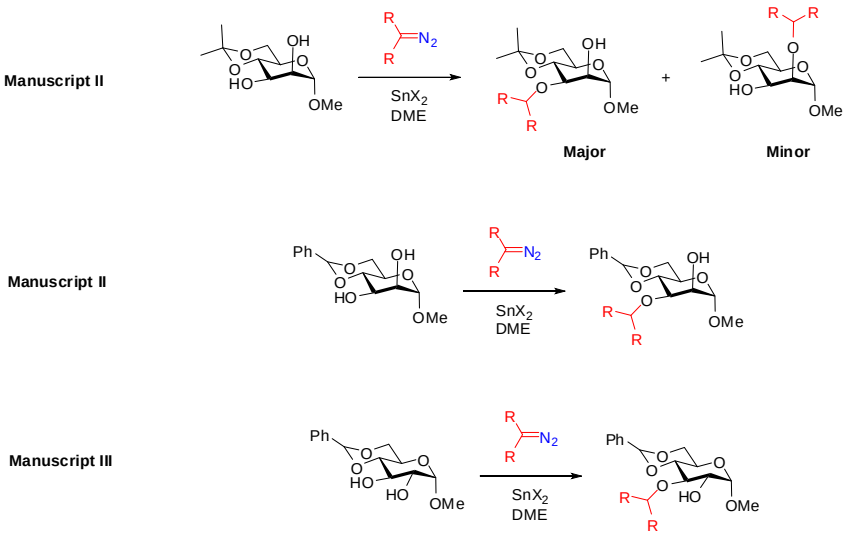


Figure 54 - Reactions examined with 4,6-acetal protected hexopyranosides

It should be noted that the data presented in **Manuscript III** is preliminary and that this manuscript is in a very early stage. Additional experiments are needed due to problems encountered with the stability of the *trans* diol system; as such, this work is included due to the strikingly different behavior of the gluco systems over similar partially protected manno systems. A noticeable difference in catalyst stability

and much longer reaction times was observed and large excesses of the diazo compound was often required. This will be discussed in more detail in subsequent sections.

Initial attempts involved the use of catalyst concentrations of approximately 6.5 mM of tin(II) halide in the reactions of 4,6-*O*-isopropylidene-α-D-mannopyranoside. It became readily apparent that the reactions proceeded much more rapidly than previously reported and, more interestingly, the distribution of end products differed from those originally reported (Petursson & Webber, 1982). It was posited by Scully and Petursson that the explanation was due to deteriorated catalysts so the influence of catalyst concentration was investigated as reported in and discussed in the Section 5.4 and **Manuscript IV** (Petursson et al., 2014).

Experiments involving tin(II) halide catalyzed reactions of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (Figure 55) typically gave good yields and exclusivity for reactions at the 3-OH position. An exception to this were reactions involving diazo diphenylmethane which gave a small quantity of the corresponding 2-*O*-ether. The complete regioselectivity of most of these reactions is superior to many of the regioselective alkylations reported in Table 1.

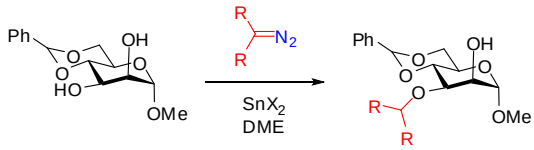


Figure 55 - Tin(II) halide catalyzed reactions of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside with diazo compounds

Tin(II) halide-catalyzed reactions involving 4,6-*O*-isopropylidene-α-D-mannopyranoside (Figure 56) gave good overall yields for both catalyst systems used but a mixture of the corresponding 2-*O* and 3-*O*-ethers. A notable exception was the reaction involving diazo *bis*(4-methoxyphenyl)methane which gave consistently poor yields and separations hampered by side products but excellent selectivity for the 3-OH. In most cases, the 3-ether was the dominant product with the

exception of the tin(II) bromide-catalyzed reaction of 4,6-isopropylidene which gave predominately the 2-*O*-ether when diazofluorene was used as the alkylating reagent. Generally, the reactions using tin(II) chloride exhibited a higher degree of regioselectivity than tin(II) bromide which gave a higher relative yield of the 2-*O*-ether.

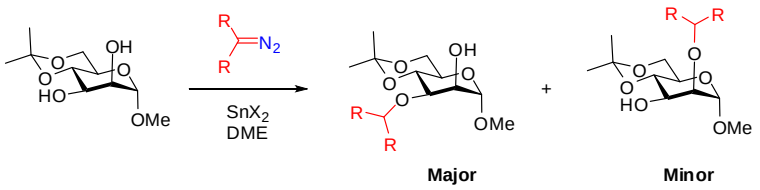


Figure 56 - Tin(II) halide-catalyzed reactions of 4,6-*O*-isopropylidene-α-D-mannopyranoside with diazo compounds

It should be noted that due to the speed of the reactions conducted with methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside, a lower concentration of catalyst (1.7 mM) was used so that the reactions could be monitored by HPLC. The reactions involving the 4,6-benzylidene derivatives were performed using 6.5 mM of catalyst as originally intended. The discussion for these three substrates (methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside, methyl 4,6-*O*-benzylidene-α-D-mannopyranoside, and methyl 4,6-*O*-benzylidene-α-D-glucopyranoside) will be divided into three parts: an examination of the regioselectivity patterns of individual diol substrates (Section 5.3.1), the diazo compounds (5.3.2), and the catalysts (5.3.3).

As previously mentioned, the distribution of end products observed in the reactions with methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside differed from the results originally reported by Petursson and Webber (1982). Reactions in the current work with methyl 4,6-*O*-benzylidene-α-D-mannopyranoside using tin(II) chloride and tin(II) bromide went to completion much more rapidly and had a higher propensity for the formation of the corresponding 3-monoether. A notable example of this is the reaction of diazo [*bis*-(4-chlorophenyl)methane] for which Petursson reported a roughly 50-50 distribution of the resultant mono-ethers. Here, a much higher

selectivity for alkylation at the 3-OH position was observed. Additionally, Petursson's reaction with diazofluorene gave 70% of the 2-ether, 13% of an unresolved mixture (composition not reported), and only 5.4% of the corresponding 3-ether. A notable difference between this work and that reported by Petursson and Webber (1982) is the difference in catalyst concentration (5 mM) whereas the work reported here uses 1.7 mM. Indeed, subsequent work has revealed that the concentration of the tin halide catalyst plays a role in the end product ratios (Petursson et al., 2014; **Manuscript IV**). This paper proposes a mechanism to explain the varying selectivities.

When viewed in the context of other work using ethers and esters as protecting groups (summarized in Table 2 and

Table 3) that offer the selective protection of the vicinal diol pair of 4,6-acetal protected monosaccharides, this work offers greatly improved regioselectivities. While not all of the alkylating agents used in this work may be universally appropriate for synthetic work, the dimethyl derivative stands out as offering a combination of rapid reaction times under ambient conditions, good overall yields and very good selectivity for the 3-OH. In the context of other regioselective protections involving 4,6-acetals of mannopyranosides, this work offers much milder reaction conditions with higher regioselectivities allowing access to a 2-OH free monosaccharide. Conversely, reactions involving diazofluorene using $SnBr_2$ as a catalyst offer a convenient route to 3-OH free 4,6-acetals. Outside of reactions performed under phase-transfer conditions or some reactions involving stannylene intermediates, this work stands out as a unique instance of 2-OH selectivity for these a partially protected mannopyranoside. Regioselective esterifications of the 4,6-acetal-2,3-stannylene derivatives of hexopyranosides can be used to generate 2-*O*-esters (Miljkovic, 2009).

It is worth noting that the synthesis of methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside was not without problems. While its synthesis has been reported in the literature, problems involving the reproducibility of the results have been reported. The formation of the 2,3-isopropylidene and the di-2,3-*O*-,4,6-O-isopropylidene products are more thermodynamically favorable. Chromatographic separation of the 2,3-*O*-isoproplyidene from the desired 4,6-*O* product was not without problems. Ultimately, trityl chloride was employed to remove the 2,3-isopropylidene by reacting with the free primary hydroxyl group allowing the facile separation of the desired 4,6-product chromatographically.

5.2.1 Factors for regioselective mono-alkylations of partially protected pyranosides

In the course of this work, three different vicinal diol systems were examined: two 4,6-acetal protected mannosides and methyl 4,6-*O*-benzylidene-α-D-glucopyranoside. Generally, these tin(II) halide catalyzed reactions show that the more reactive diazo compounds have a greater preference for reacting with the 3-OH position in these 4,6-acetal protected systems. The differences in reactivity and the distribution of end products can potentially be explored in the context of steric and electronic factors. Additionally, disruption of the internal hydrogen bond network may also explain reactivity differences between these substrates.

Methyl 4,6-O-isopropylidene and 4,6-O-benzylidene-α-D-mannopyranoside

In mannopyranoside systems, the general order of reactivity for the free hydroxyl group is 3-OH>2-OH (Miljkovic, 2009). The vicinal diol pair of the manno system is in the *cis* configuration and the dihydral angle between the two hydroxyls is 60°. The Newman projection for this system is shown in Figure 57.

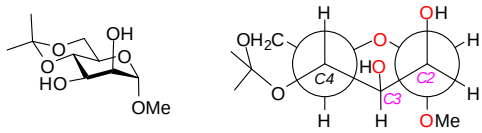


Figure 57 - Newman projection for methyl 4,6-O-isopropylidene-α-D mannopyranoside system (modified from Miljkovic, 2009)

From an electronic perspective, it would be anticipated that the two methyl groups of the isopropylidene maybe more electron releasing than the benzylidene. However, this is not supported by the greater propensity of the 2-*O*-ether formed. Furthermore, it is unlikely that significant electronic effects from the methyl groups of the isopropylidene would have an influence over that many bond lengths. Thus, it is more likely that the greater accessibility of the free hydroxyl groups in the isopropylidene system is the reason for the difference in regioselectivity patterns.

The 2-OH is generally regarded as being more acidic due to its proximity to the anomeric center and in an aprotic solvent the corresponding anion increases the reactivity of the 3-OH particularly in the manno system as shown in Figure 58. Interestingly, it is known that the 2-OHs in the axial position are less acidic than those in the equatorial position as is the case with glucose as explained by the intramolecular hydrogen bond network as shown in Figure 58 (Zhang et al., 2015).

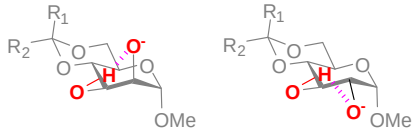


Figure 58 - Hydrogen bonding of alkoxide in manno (left) and gluco systems (right) (modified from Zhang, Li, Lindström, & Mischnick, 2015)

The above may explain the greater relative reactivity of the 3-OH in the manno system which is generally regarded as being more sterically accessible. Furthermore, the 4,6-*O*-isopropylidene has less steric bulk than the benzylidene and thus may allow more avenues of attack for the tin(II) halide catalyst, diaryl diazo compound, or other reactive

intermediate species. This may explain the mixture of end products obtained which in most cases was a mixture of the 3-*O* and 2-*O* ether with the 3-*O* ether being the dominant end product in all cases except when diazofluorene was used. The much shorter reaction times of the 4,6-*O*-isopropylidene over the 4,6-*O*-benzylidene support this notion.

Interestingly, the reactions involving methyl 4,6-*O*-benzylidene-α-D-mannopyranoside yielded only the corresponding 3-ether in good overall yield with the exception of diazodiphenyl methane reactions which yielded small quantities of the 2-ether and diazo *bis*(4-methoxypheny)methane which gave poor yields but excellent selectivity for the 3-OH position. Reaction times were generally between 24 and 72 hours with the exception of diazo *bis*(4-methoxypheny)methane whose reaction time was less than 15 minutes.

The Newman projection for this system is shown in Figure 59. The dihedral angle between the 2-OH and the 3-OH is 60°.

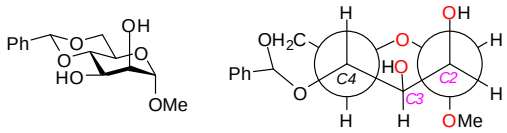


Figure 59 – Newman projection for methyl 4,6-O-benzylidene-α-D mannopyranoside system (modified from Miljkovic, 2009)

The long reaction times and selectivity could be explained by the greater steric footprint of the benzylidene group which could hinder the attack of the alkyl donor, particularly at the less accessible 2-OH.

Methyl 4,6-O-benzylidene-α-D-glucopyranoside

Unlike the mannopyranoside system, the vicinal diol pair of methyl 4,6-*O*-benzylidene-α-D glucopyranoside shown in Figure 60 is in a *trans* configuration although the dihedryl angle is also 60° (Petursson, 2003).

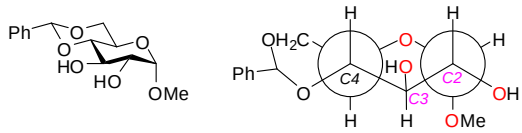


Figure 60 - Newman projection for methyl 4,6-*O*-benzylidene-α-D glucopyranoside system (modified from Miljkovic, 2009)

In the work described in Manuscript III, reactions of the faster reacting diazo compound yielded the corresponding 3-ether although diazodiphenylmethane did yield a considerable amount of the 2-ether. In the case of both tin(II) halide catalyzed etherifications using diazo compounds, the 3-OH reacted preferentially albeit more slowly than the corresponding 4,6-benzylidene mannopyranoside.

These reactions were more problematic than the manno system as the catalyst fell out of solution repeatedly requiring the addition of additional tin(II) halide. This is consistent with previous reports by (2001). Petursson suggested that the *trans* vicinal diol system is unstable and involved in destroying the catalyst (Pétursson, 2001).

5.2.2 Tin(II) halide-catalyzed alkylations using specific diazo compounds

Of the five diazo compounds investigated, diazo *bis*(4-methylphenyl)methane, diazo *bis*(4-methoxyphenyl)methane, and diazofluorene stand out as being of interest due to their high regioselectivities.

Diazo bis(4-methylphenyl)methane

Diazo *bis*(4-methylphenyl)methane (Figure 61)consistently gave highly regioselective reactions with a preference for the 3-OH position and short reaction times. Overall, this diazo compound is a promising reagent for rapidly introducing a PG with a high degree of selectivity.

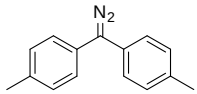


Figure 61 - The structure of diazo-[*bis*-(methylphenyl)methane]

Diazo bis(4-methoxyphenyl)methane

The reactions involving diazo *bis*(4-methoxyphenyl)methane Figure 62 demonstrated high regioselectivities for the 3-OH position and short reaction times (often less than 15 minutes). However, the reaction gave consistently poor yields although no other sugar products could be identified in the reaction mixture. Unfortunately, all reactions with this compound required a large excess of the diazo compound and also formed side-products that complicated the subsequent separation of the 3-*O*-ether. Petursson (1979) tentatively identified two of the reaction side products as 1,1:2,2-tetra-(4-methoxyphenyl)-ethane and the the corresponding azine.

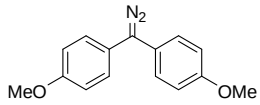


Figure 62 - The structure of diazo-[*bis*-(methoxyphenyl)methane]

The two co-products eluting just before and after (R_f=0.23 and 0.14 in hexane/ethyl acetate 4:1, respectively) the desired product (R_f=0.18) complicated the separation of the protected sugar due to the amount present in the reaction mixture and retention times on silica gel that immediately preceded and followed the products. No solvent system adequately resolved the impurities from the target compound and crystallization of either the impurities or the product were largely unsuccessful.

In this work, one of the side-products co-eluted slightly ahead of the desired 3-ether product while the other co-eluted just after; attempts to modify the solvent system during chromatographic separations were largely unsuccessful. Furthermore, cooling the

reaction mixture did not avert (or even minimize) the formation of these co-products and thus adding additional title diazo compound was necessitated.

Diazofluorene

The increase propensity of diazofluorene (Figure 63) to form the 2-ether in the case of methyl 4,6-*O*-isopropylidene-α-D mannopyranoside is difficult to explain. It is notable that the reaction of diazofluorene took, in all cases, longer than the reactions with diaryl diazo compounds. A potential explanation for this could be the increased stability of the carbanionic character due to the increased delocalization of the fluorenyl system.

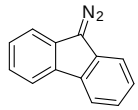


Figure 63 - The structure of diazofluorene

5.2.3 Tin(II) chloride versus tin(II) bromide

Differences in regioselectivity and reaction times were observed. Generally, reaction times for experiments involving $SnBr_2$ were shorter than when $SnCl_2$ was used as a catalyst. In the cases of the methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside, the differences between the regioselectivity of $SnCl_2$ and $SnBr_2$ are more difficult to explain. Generally, the use of $SnBr_2$ resulted in the production of more of the corresponding 2-*O*-ether

In the reactions involving methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside, a difference in the regioselectivity of the $SnCl_2$ and $SnBr_2$ was observed. The tin(II) bromide catalyzed reactions demonstrated much greater formation of the 2-*O*-ether. A potential explanation of this is that the Sn atom of tin(II) bromide is less electrophilic than that of tin(II) chloride due to the bromine atoms being less electron withdrawing as described in Figure 64. As such, tin(II) bromide may not mask the more nucleophilic 2-OH as effectively leaving it more susceptible to attack by the tin(II) halide-diazo complex.

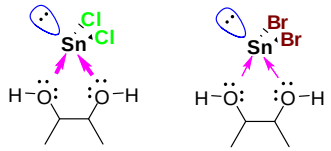


Figure 64 - Proposed relative interaction of tin(II) chloride and tin(II) bromide with a vicinal diol hydroxyl pair

As such, neither tin(II) halide catalyst stands out as superior to the other; instead, each may have its niche uses.

5.3 The effect of catalyst concentration on regioselectivity of $SnCl_2$-catalyzed reactions with diazo compounds

The work presented in **Manuscript IV** demonstrates the effect of $SnCl_2$ catalyst concentration on the regioselectivity of reactions between diazo compounds and methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside. As previously mentioned, initial experiments with this vicinal diol substrate greatly differed in terms of their shorter reaction times and increased regioselectivities as compared to the work originally performed by Petursson (Petursson & Webber, 1982; Petursson, 1979).

Experiments varying in catalyst concentrations with diaryldiazo compounds revealed the general trend that high catalyst concentrations favor substitution at the 3-OH position while low catalyst concentrations result in a preference for the 2-OH position. While the use of diazo-[*bis*-(4-methyphenyl)diazomethane] always resulted in the corresponding 3-O ether being the dominant product, lower catalyst concentrations did increase the amount of the 2-ether formed. For both diazodiphenylmethane and diazo-[*bis*-(4-chlorophenyl)methane)], the 2-ether became the dominant product at low catalyst concentrations.

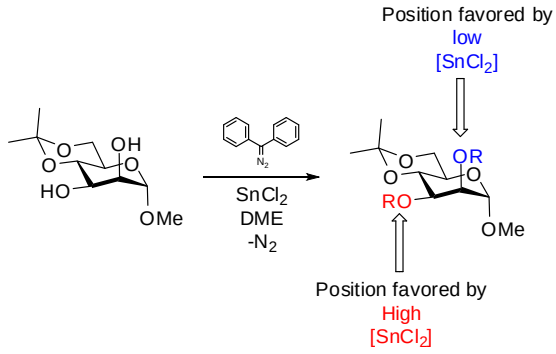


Figure 65 - Catalyst concentration-dependent change in regioselectivity of etherification of methyl-4,6-*O*-isopropylidene-α-D-mannopyranoside with diphenyldiazomethane

Interestingly, reactions involving the $SnCl_2$-catalyzed etherifications using diazofluorene demonstrated this trend with high catalyst concentrations still generally favoring the 2-OH position and while low concentrations strongly favored the 2-OH position. With further experimentation, lower catalysts concentrations could lead to complete 2-OH selectivity. In light of the work with tin(II) bromide presented in Manuscript II, even higher 2-OH selectivities could be achieved by changing catalysts.

The mechanism proposed in **Manuscript IV** only partially explains the observed regioselectivity. A potential explanation of this phenomenon is that high concentration of tin(II) chloride seems to favor regioselective reactions as tin(II) chloride coordinates with diols and masks the more acidic hydroxyl groups. The author would like to suggest that the concentration-dependent selectivity be explained as follows:

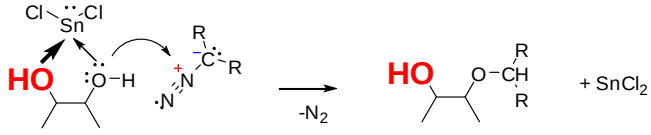


Figure 66 - Proposed $SnCl_2$-masking of the more acidic hydroxyl at high catalyst concentrations

The above scenario would explain the observed 3-OH selectivity of diphenyldiazomethane and related derivatives as the 2-OH of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside) is more acidic and thus it would be expected that an electron deficient metal atom would coordinate more strongly at that hydroxyl.

5.4 Future directions

Optimization of reaction conditions

The use of 1.5 molar equivalence of the diazo compound in many cases was excessive as evidenced by TLC and HPLC examinations of reactions. Several reactions using diol systems (propane-1,2-diol, propane-1,3-diol, and methyl 4,6-*O*-benzylidene-α-D-mannopyranoside) have been shown to react with 1.1 eq of diazo diphenylmethane and diazo-(*bis*-[4-methylphenyl]methane) and give quantitative yields (Scully, Unpublished data).

As highlighted in **Manuscript IV**, fine-tuning of catalyst concentration makes it possible to maximize the 2- and 3-OH selectivity. An investigation of the influence of tin(II) bromide's concentration is also forthcoming. As evidenced by the limited stability of the tin(II) halide catalyst system in the reactions of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside described in **Manuscript III**, additional work finding a catalyst concentration that does not result in rapid deterioration of the catalyst is needed.

The *in situ* generation of diazo compounds also warrants further attention. As demonstrated in **Manuscript I**, the use of a recyclable and easily retrieved oxidizing agent greatly reduces the hassle of isolating and storing diazo compounds.

Other diol substrates

Other partially protected carbohydrates bearing vicinal diol systems, such as galactose, L-rhamnose, and L-fucose (Figure 67), warrant investigation as these building blocks are also of great synthetic value in carbohydrate chemistry.

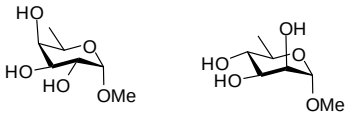


Figure 67 – The structures of L-fucose (left) and L-rhamnose (right)

Other pyranosides bearing only a protected 6-OH with 2-, 3-, and 4-OHs free (Figure 68) may also make interesting targ**e**ts for selective protection. Of particular interest would be the selective protection of a *cis*-diol system in the presence of a trans-diol system.

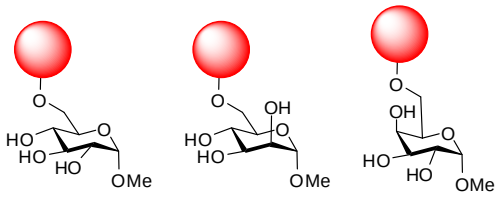


Figure 68 - 6-OH protected gluco, manno, and galacto systems

Another interesting series of substrates are 1,2-*O*-isopropylidene-3-*O*-benzoyl-glucofuranose and 1,2-*O*-isopropylidene-6-*O*-benzoyl-glucofuranose (Figure 69). Methanolic reaction systems using $SnCl_2$ have reported selective alkylations of the 5-OH of these systems (Petursson, 1979 and references therein). Reactions in DME may offer routes to different selectivity using the same pool of reagents.

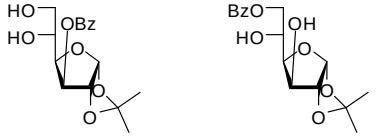


Figure 69 - Sturtures of 1,2-*O*-isopropylidene-3-*O*-benzoyl-glucofuranose and 1,2-*O*-isopropylidene-6-*O*-benzoyl-glucofuranose

Beyond this, the reactivities of tin(II) halide-catalyzed etherifications should also be investigated for both the α and β-anomers. Furthermore, chemoselective protections of carbohydrates bearing other hetero atoms should be addressed, such as thiol derivatives, that are often used to block the anomeric center and sugars bearing amines which are ubiquitous in nature.

Stability and Deprotection Studies of diphenylmethyl protecting groups

Comprehensive studies of the stability of diphenylmethyl ethers and related derivatives needs to be conducted to have a full grasp of the utility of these PGs in the context of orthogonal protecting group strategies. While some limited work has been done (such as removal of diphenylmethyl ethers using catalytic hydrogenloysis), more studies in line with the broader stability under a range of conditions used in synthetic operations (such as those presented in Table 2) need to be undertaken so that the utility of diphenylmethyl protection can be realized.

Other catalysts and diazo compounds

Other metal halides or metals bearing other ligands may be useful catalysts for the introduction of diazo compounds into O-H bonds. Palladium, copper, and Rhodium halides as well as indium(III) bromide has also been reported to regioselectively protect 4,6-acetal protected mannosides with a high selectivity for the 3-OH position when diazo diphenylmethane is used (Best, 2015).

To the author's knowledge, the only diazo compounds used for the tin(II) halide protection of hydroxyl groups are diazomethane, diazodiphenylmethane and related derivatives, and diazofluorene. The reactivities of other easily accessible diazo compounds, such as EDA, warrants investigation.

The 2-OH selectivity of diazofluorene warrants that other 12-π-electron systems be investigated. Other polyaromatic diazo compounds, such as those shown in Figure 70, might demonstrate interesting selectivity on the basis of increased carbene (or carbenoid) stabilization by the higher pi electron systems or increased steric bulk. Potential candidates from easily accessible substrates might include anthyl and benzahydryl derivatives which can easily be prepared from the corresponding hydrazone (Scully, unpublished data). Azulene-

derived ester protecting groups have been noted to be selective for the 3-OH position of 4,6-benzylidene glucoside and galactoside (Timmer, Stocker, Northcote, & Burkett, 2009). The use of diazo azulene might prove to be interesting in terms of its selectivity during tin(II) halide catalyzed reactions.

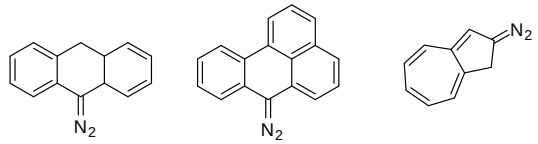


Figure 70 - Potential polyaromatic diazo compounds for further investigations

6 Conclusions

Carbohydrate chemistry demands highly efficient protecting groups that can be introduced with a high degree of regioselective control under mild conditions. As such, diazo compounds are high utility synthons for introducing protecting groups to hydroxyls. However, the deleterious nature of the preparation of diazo compounds and their high reactivity poses a number of risks to their use. The first part of this focuses on a more environmentally friendly route to the preparation of diazo compounds using Magtrieve™ (chromium(IV) oxide). This work demonstrates the usefulness of Magtreive™ for the *in situ* preparation of diazo compounds for the highly regioselective one-pot protection of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside using tin(II) chloride as a catalyst in good yield.

Experiments investigating the application of tin(II) halide catalysts for the introduction of mono-ether protection to vicinal diols of partially protected monosaccharides using five diaryl diazo compounds was also investigated. In the case of 4,6-acetal protected mannopyranoside derivatives, the introduction of benzhydryl derivatives with a high degree of regioselectivity was demonstrated, particularly in the cases of diazo-[*bis*-(4-methylphenyl)methane] and diazo-[*bis*-(4-methoxyphenyl)methane]. Tin(II) halide-catalyzed methyl 4,6-*O*-benzylidene-α-D-glucopyranoside was also investigate but these reactions were problematic due to problems with catalyst's stability.

The primary conclusions of this work are that

- The generation of diazo compounds using Magtrieve™ (chromium(IV) oxide) present a rapid, facile, and inherently "greener" approach than the utilization of mercury(II) oxide. The use of Magtrieve™ is also well suited to the *in situ* preparation of diazo compounds for tin(II)-halide catalyzed reactions.

- Tin(II) halide-mediated introduction of benzhydryl protecting groups is highly efficient, facile, and highly regioselective with good overall yields (typically > 80%) in the *cis* vicinal diol systems examined. These methods are more problematic for *trans* systems.

- While the use of diazo-[*bis*-(4-methoxyphenyl)methane] to introduce protecting group is extremely fast and highly regioselective, it comes at the expense of ease of separation, requiring a large excess of the diazo compound, and results in low yields (<70%).

- Patterns of regioselectivity are influence by choice of tin(II) halide catalyst, the catalyst concentration, diazo compound, and the positioning of the substrate's vicinal diol pair.

7 Experimental

7.1 General methods

All reagents were commercially obtained from Sigma-Aldrich and used without further purification unless otherwise noted. Dimethoxyethane (DME) was refluxed over sodium for 2 hours prior to distillation; dried DME was stored over sodium in an air-tight container. Anhydrous *N*,*N*-DMF was purchased from Sigma. Anhydrous methanol and dichloromethane were prepared by drying over oven-dried 3Å molecular sieves for 6 hours followed by distillation; the distillate was stored over 3Å molecular sieves in an air-tight container.

Preparative chromatography was performed using silica gel (60Å, 230-400 mesh) obtained from Sigma-Aldrich; column dimension were 2.2x20 cm unless otherwise noted. Thin-layer chromatography was performed on Silica gel TLC cards with a fluorescent indicator were obtained from Fluka; TLC plates were visualized using a UV lamp (λ254) and sprayed with molybdenum-cerium sulfate solution and visualized by heating.

^{1}H and ^{13}C NMR Spectrum were obtained using a Bruker AV400 Nuclear Magnetic Resonance spectrometer using $CDCl_3$ using trimethylsilane (TMS) as an internal standard. All melting points were obtained using a Thiel tube and are uncorrected. UV-Visible spectra were obtained on a Perkin-Elmer Lambda 25 UV-Visible Spectrophotometer using a quartz cell with a pathlength of 1 cm.

Reaction vessels were oven dried at 105°C for at least one hour and stored in a desiccator prior to use. All reactions were performed at

room temperature (22-25°C) unless otherwise noted and wrapped with aluminum foil to exclude light.

High-Performance Liquid Chromatograph (HPLC)

The samples were run on a Shimadzu UFLC using two 20-AD solvent pumps and a 20-A UV-VIS Detector at 254 nm, with a DGU-20A_3 online degasser and a Rheodyne manual sample injector equipped with a 20 µL loop. Separation was achieved using a reverse phase column (Supleco, 150 mm x 4.6 mm, 3 µm) with a guard column (Supelco, 20mm x 4.0, 3 µm) mm C18 guard cartridge. Mobile phase was rigorously degassed (sonic bath, 1 hour) prior to use and was delivered at a flow rate of 1 mL per minute composed of un-buffered 20% water and 80% methanol.

10 µL of reaction sample was diluted with 240 µL of mobile phase prior to injection. Retention times of analytes were verified using characterized products from relevant separations.

Determination of Extinction Coefficients for Diazo Compounds

10 mM solution of the diazo compound was prepared in DME. The spectrum was scanned using a Perkin-Elmer Lambda 25 UV-Visible spectrophotometer in a 1 mL quartz cuvette with a pathlength of 1 cm from 190 nm to 1100 nm. The extinction coefficients were calculated according to Beer-Lambert's law. Results are summarized in **Appendix A.**

7.2 Preparation of diol substrates and diazo compounds

7.2.1 Diazo compounds

Diphenyldiazomethane 13.2942 g (66.7 mmol) of benzophenone hydrazone was dissolved in 200 mL of diethyl ether; 15 g of anhydrous $MgSO_4$ and 36.08 g (166.5 mmol, 2.5 eq.) of HgO. 5 mL of a saturated KOH/Ethanol solution was added at 15:00. The vessel was wrapped in aluminum foil to exclude light. The reaction was followed by TLC (4:1 Hexane/Ethyl acetate). The reaction was left at room temperature until 23:00 at which point it was transferred to the refrigerator (0-4°C). The TLC (4:1 hexane/ethyl acetate). After12 hours, the material was passed through two pieces of Whatman #1 filter paper by gravity and collected in a 500 mL round bottom flask. The solvent was removed on the rotary evaporator at ~30°C and negative pressure (~-0.8 bar) until a solid formed. The residue was re-dissolved in approximately 20 mL of hexane and filtered into a 100 mL Erlenmeyer flask; the filter paper was rinsed with additional hexane until the filtrate was clear (~30 ml). The material was chilled to -40°C. The solid crystals where then vacuum filtered using Whatman #1 filter paper and the retained crystals were rinsed with ~10 mL of cold hexane. The material was dried under vacuum for 30 minutes then stored at -40°C. 10.2280 g of product was isolated (90% yield); m.p. = 29-31°C.

Diazofluorene -10.1522 g (52.2 mmol) of fluorenone hydrazone was added to a 1L Erlenmeyer flask containing 650 mL of diethyl ether and 7.01 g of anhydrous $MgSO_4$. 12.6481 g (54.6 mmol, 1.05 eq.) of Ag_2O was added at 13:30; the vessel was wrapped in aluminum foil to excluded light and magnetically stirred until TLC examination (4:1 hexane/EtOAc) showed that all of the starting material had reacted. At 16:00 TLC indicated that the starting material had diminished; the reaction mixture was filtered on Whatman #1 filter paper by gravity;

the filter cake was rinsed with a few mL of diethyl ether until the filtrate was clear. The filtrate was placed on the rotary evaporator at ~35°C until solid material began to form in the flask. At this point the flask was transferred to an ice bath then to the -40°C freezer overnight. The ether/product solution was vacuum filtered over Whatman #1 filter paper and rinsed with ~5 mL of cold ether. The resultant product a reddish-orange, needle-like crystal; the product was dried in a vacuum desiccator for 1 hour. 5.62 g of material was recovered (60 % yield); m.p. = 153°C.

4,4'dimethylbenzophenone hydrazone - 30.0078 g (142.7 mmol) of 4,4'dimethylbenzophenone was added to a 500 mL round bottom flask with 150 mL of *n*-BuOH. 19.5 mL (400 mmol) of 98% hydrazine hydrate was added. The solution was refluxed with air condenser overnight starting at 14:00. The reaction was followed by TLC using a 4:1 hexane/ethyl acetate eluent system. After 24 hours, the solvent was removed using a rotary evaporator at 55°C and under -1 bar of pressure; the temperature was slowly increased to ~70°C. The product was re-dissolved in ~140 mL of hot methanol and activated carbon was added. The material was filtered with Whatman#1 filter paper and celite by vacuum filtration. The methanol/product solution was cooled to room temperature; crystals formed quickly and the mixture was transferred to the refrigerator (0-4°C) overnight. The light pink crystals were isolated with Whatman#1 filter paper and dried in a desiccator under low pressure until a constant mass was reached. TLC examination indicated that no product was present in the mother liquor. 27.8 grams of product was recovered (86.8% yield).

Diazo[*bis*-(4-methylphenyl)]methane)- 200 mL of diethyl ether and 20 g of anhydrous $MgSO_4$ was added to a 500 mL Erlenmeyer flask; 14.8023 g (66.0 mmol) of 4,4'dimethylbenzophenone hydrazone was added to the flask followed by 30 g of mercuric oxide (138.5 mmol, 2.1 eq.) and 5 mL of saturated KOH in ethanol at 13:40. The reaction was monitored by TLC (4:1 hexane/ethyl acetate). After 2.5 hours, TLC indicated that most of the starting material had reacted. The solvent was removed on the rotary evaporator at room temperature and

under negative pressure until solid crystals started to form. The material was placed in the refrigerator overnight. The purple crystals were isolated on a Büchner funnel using Whatman#1 filter paper and rinsed with 50 mL of cold ether. The crystals were dried in a desiccator under vacuum. 8.0144 g (54.6% yield) of the title compound was isolated. The mother liquor was re-crystallized and yielded another 4 grams of material (total yield 81.9%); m.p. = 105°C.

Diazo-[*bis*-(4-methoxyphenyl)]methane)- 48.4100 g (200 mmol) was placed in a 500 mL round bottom flask; and 200 mL of *n*-BuOH was added followed by 21 mL (433 mmol) of hydrazine hydrate. The mixture was refluxed using an air condenser for 24 h and followed by TLC (4:1 Hexane/EtOAc). The n-butanol was removed on the rotary evaporator by slowly increasing the temperature from ~55°C to 85°C under negative pressure until a constant volume was reached. The resultant syrup was re-dissolved in 60 mL of methanol; the solvent was removed again on the rotary evaporator to drive off any remaining n-butanol. 60 mL of methanol was added to the mixture and heated until all of the material dissolved. The solution was allowed to cool to room temperature before being transferred to the refrigerator overnight. The resultant yellow crystals were vacuum filtered over Whatman #1 filter paper and rinsed several times with methanol. The isolated crystals were allowed to dry in a vacuum desiccator. 47.81 grams (93.3% yield) of 4,4'dimethoxybenzophenone hydrazone was recovered; m.p. = 110°C.

Preparation of 4,4'-dichlorobenzophenone hydrazone 101.0 g of 4,4'dichlorobenzophenone was dissolved in 300 mL of methanol and refluxed over decolorizing carbon for 6 hours. The solution was quickly filtered through Whatman#1 filter paper and collected in a 500 mL round bottom flask; the solvent was removed using a rotary evaporator (50°C, reduced pressure) and material was re-crystallized from ethyl acetate. The resultant crystals were dried under vacuum yielding 93.109 g (92.2% recovered). 40.0 g of the decolored and re-crystalized hydrazone was dissolved in 400 mL of n-butanol; 20 mL of hydrazine was added and the solution was refluxed for 24 hours. The

solvent was removed on the rotary evaporator (50°C, reduced pressure); the product was crystallized from methanol and isolated using filter paper yielding 27.413 g (65.1% yield).

Diazo-[*bis*-(4-chlorophenyl)]methane)- 17.5 g (66 mmol) of the starting hydrazone was dissolved in 200 mL of diethyl ether with 15 g of $MgSO_4$ and 35.737 g of mercuric oxide (165 mmol, 2.5 eq) followed by 5 mL of a saturated KOH/ethanol solution. The reaction was monitored by TLC (4:1 hexane/ethyl acetate). After 2 hours, the starting material had been consumer and the reaction mixture was filtered through two pieces of Whatman #1 filter paper into a 500 mL round bottom flask. The solvent was removed (35°C, reduced pressure) and the product was crystallized from hexane yielding 13.62 g (78.4%); m.p. = 29-31°C; m.p. = 108°C.

Dimethoxydiphenlydiazomethane 20.6 grams (80.4 mmol) of 4,4'dimethoxybenzophenone hydrazone was added to a pre-dried 1 L Erlenmeyer flask and dissolved in 700 mL of diethyl ether; 42 grams of anhydrous $MgSO_4$ followed by 60 grams (277 mmol) of mercuric oxide. The reaction mixture was stirred for 5.5 hours and monitored by TLC (4:1 Hexane/EtOAc). Light was excluded from the reaction vessel using aluminum foil. The reaction mixture was filter through double Whatman #1 filter paper by gravity; the material retained by the filter paper was carefully rinsed with diethyl ether. The filtrate was filtered a second time to remove mercury that passed through the filter. The dark purple solution was transferred to a large round bottom flask; the solvent was removed on a rotary evaporator at ~30°C until dry. The resultant solid was re-dissolved in 200 mL of diethyl ether and quickly heated to a gentle boil. The solution was allowed to cool to room temperature before being transferred to an ice bath. The crystals were isolated by vacuum filtration using Whatman #1 filter paper; the product was rinsed with three 15 mL portions of cold diethyl ether. 15.5 grams of Dimethoxydiazomethane was recovered (85.2% yield). An additional 1.9 grams of crude crystals were also recovered.

7.2.2 Carbohydrate building blocks

Methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside from methyl α-D-mannopyranoside - 5 grams of methyl α-D-mannopyranoside was quickly dissolved in 80 mL of DMF and cooled to 0°C in an ice bath; 4.8 mL of 2-methoxypropene and 20 mg of *para*-Toluene sulfonic acid mono-hydrate was added. The reaction mixture was stirred for approximately 12 hours at which time examination by TLC (EtOAc) indicated that all of the starting material has reacted. The reaction was quenched with 0.5 g of sodium carbonate and stirred for ~30 minutes. The mixture was filtered through Whatman #1 filter paper by vacuum into a round bottom flask.

The DMF was removed the under high vacuum at approximately 40°C using a rotary evaporator. Several fractions (~10 mL) of xylene were added to drive off the DMF. The resulting syrup was re-dissolved in ~50 mL of distilled water and partitioned three times with 50 mL of dichloromethane; the dichloromethane fractions were re-extracted with water. The aqueous fractions were pooled and the water removed on the rotary evaporator 40°C and under high vacuum The resultant syrup was redissolved in ethyl acetate and passed through a column (40 x 300 mm) packed with a silica gel/EtOAc slurry. Fractions were collected as 25 mL fractions and the separation was followed by TLC and fractions containing the product were pooled and evaporated. The resulting solid was re-crystallized by dissolving the material in dichloromethane.

Methyl 4,6-*O*-benzylidene-α-D-mannopyranoside - Methyl α-D-mannose-pyranoside, 20.0684 g (100 mmol) of methyl α-D-mannopyranoside was quickly dissolved in 100 mL of 98-100% formic acid and 100 mL (981 mmol, ~10 eq.) of benzaldehyde in a 500 mL Erlenmeyer flask; the mixture was stirred magnetically at room temperature for 5 minutes. The mixture was quickly poured into a 3 L Erlenmeyer flask containing 800 mL of distilled water, 275 g of K_2CO_3 and 800 mL of hexane. The aqueous layer was removed using a separation funnel and re-extracted with several potions of hexane; the

combined organic layers was filtered through Whatman #1 filter paper. The separation was followed by TLC using ethyl acetate as an eluent. The crude material isolated on the filter paper was crystallized twice from chloroform and benzene. The crystals were vacuum filtered over Whatman #1 filter paper to give 5.8937 g (19.9% yield) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$, ppm 4.79 (d, J = 1.19 Hz, 1H), 4.10 (dd, J = 9.37, 3.54 Hz, 1H), 4.06 (dd, J = 3.54, 1.37 Hz, 1H), 3.98-3.89 (m, 1H), 3.88 (q, J = 2.22, 2.02, 2.02 Hz, 1H), 3.87-3.83 (m, 1H), 3.44 (s, 1H), 2.92-2.61 (m, 1H), 5.61 (s, 1H), 7.61-7.47 (m, 1H), 7.42 (dd sext., J = 6.47, 6.47, 6.47, 6.47, 6.47, 3.82, 1.82 Hz, 1H), 4.36-4.29 (m, 1H).

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9 List of Manuscripts

Manuscript I

Preparation of diaryldiazocompounds and diazofluorene with Magtrieve™ and their use for regioselective protection of partially protected sugars

(To be submitted to *Carbohydrate Research*)

Manuscript II

Regioselective mono-alkyations of the vicinal diol group of partially-protected mannopyranosides using diaryldiazoalkanes and tin(II) halides

(To be submitted to *Carbohydrate Research*)

Manuscript III

Regioselective mono-alkylation of methyl 4,6-*O*-α-D-glucopyranoside using tin(II) halides

(To be submitted *Carbohydrate Research*)

Manuscript IV

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

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I

Manuscript I – Preparation of diaryldiazocompounds and diazofluorene with Magtrieve™ and their use for regioselective protection of partially protected sugars

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Keywords: chromium dioxide, one-pot, diazo-(*bis*[4-methyphenyl]methane)

Abstract

Numerous methods for the preparation of diazo compounds have been reported many of which pose significant health and environmental hazards. The use of Magtrieve™ for the preparation of diaryldiazomethanes presents a "green" route to their synthesis. In this paper the preparation of five diaryldiazomethanes are described and a procedure for the facile one-pot 3-*O*-ether protection of the 4,6-benzylidene acetals of two pyranosides is reported.

Introduction

Diaryl diazo compounds such as diazodiphenylmethane and its symmetrical derivatives are useful synthons for the introduction of diarylmethyl groups to carboxylic acids or alcohols to give the corresponding ester or ether, respectively (Petursson, 2008; Wuts & Greene, 2007). While numerous routes to the preparation of diaryldiazomethanes via the dehydrogenation of the corresponding hydrazone have been reported in the literature (Maas, 2009), many of these methods require the use of heavy metal salts such as

mercury(II) oxide, lead(IV) acetate, and silver oxide. Beyond the obvious environmental drawbacks to using these methods, the isolation of diazo compounds can be problematic due to their decomposition and the loss of product during manipulation. Furthermore, diazo compounds present a significant hazard due to the risk of explosive decomposition of low molecular diazo compounds and their ability to alkylate DNA. The recent preparation of diazo compounds including diazodiphenylmethane using activated DMSO offering a greener alternative to heavy metal-based oxidations has been reported (Javed & Brewer, 2008; Javed & Brewer, 2007).

Chromium(IV) oxide (Magtrieve™) is a ferromagnetic oxidizing agent; it has been demonstrated to readily oxidize benzophenone hydrazone to diphenyldiazomethane for the *in situ* protection of carboxylic acids (Ko & Kim, 1999). The workup of Magtrieve™-based syntheses is facile as only the outer surface of the heterogeneous CrO_2 is reduced meaning that the spent reagent can easily be retained with a magnet (Lee & Donald, 1997). Chromium(IV) oxide-based preparations have obvious environmental advantages and can be easily retrieved and reused after re-oxidation at 300-350°C in the presence of oxygen in air atmosphere.

Derivatives of diphenyldiazomethane have shown utility in synthetic operations requiring the selective protection of vicinal diols or single hydroxyl groups (Best et al., 2008; Petursson & Jonsdottir, 2012; Petursson, Scully, & Jonsdottir, 2014; Petursson & Webber, 1982; Petursson, 1979, 2009, 2013; Pétursson, 2001). The use of diazo compounds for the protection of hydroxyl groups can be accomplished under mild conditions and is particularly convenient as the reaction can be followed colorimetrically. Despite the high regioselectivities observed, these methods have not caught on. This is likely due to perceived hazards associated with handling diazo compounds.

Herein, the optimization and synthesis of selected diaryldiazomethanes is reported using Magtrieve™ and diazodiphenylmethane and diazo-*bis*(4-methylphenyl)methane are then used for the rapid one-pot preparation of the 3-*O*-ether of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside and methyl 4,6-*O*-benzylidene-α-D-mannopyranoside.

Results and Discussion

Optimization of chromium(IV) oxide preparation of seven diazo compounds

Five diazo compounds (**Figure 1**) were oxidized in the presence of 0.75 to 20 equivalence of chromium(IV) oxide. Reaction mixtures were followed spectroscopically until absorbance was constant or started to decrease; reaction times at various molar equivalence of CrO_2 are as summarized in **Table 1** (**and Appendix B**).

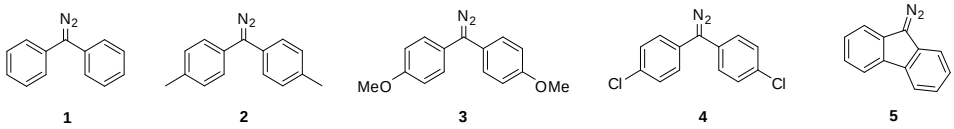

Figure 1 – Five diaryl diazo compounds prepared in this work; 1 – diazodiphenylmethane; 2 – diazo-(*bis*-[4-methylphenyl]methane)]; 3 - diazo-(*bis*-[4-methoxyphenyl]methane)]; diazo-(*bis*-[4-chlorophenyl]methane)]; 5 – diazofluorene

The use of 15 and 20 equivalence of CrO_2 resulted in the shortest reaction times between 30 and 60 minutes. The use of 6 (or less) equivalence of CrO_2 resulted in low yields as calculated from extinction coefficients of individual diazo compounds and protracted reaction times. 15 and 20 eq resulted in reasonable reaction times and high reaction rate.

Table 1 – Time needed to reach A_{max} for the oxidation of 0.1 mmol of diaryl hydrazones to their corresponding diazo compounds using different molar equivalence of Magtrieve™ (CrO_2).

	Reaction time (min)						
	CrO_2 molar equivalence						
Diazo Compound	0.75	1.5	3	6	10	15	20
1 Ph_2CN_2	>270	>270	270	240	180	90	45
2 (*p*-$CH_3C_6H_4)_2CN_2$	>240	>240	240	150	120	15	30
3 (*p*-$CH_3OC_6H_4)_2CN_2$	>480	>480	480	420	120	60	45
4 (*p*-$ClC_6H_4)_2CN_2$	ND	ND	ND	240	90	60	60
5 Diazofluorene	>270	>270	270	240	120	120	120

After the oxidations were complete, the Magtrieve™ was retained using a strong magnet; the retention of the Magtrieve™ completely eliminated the need for filtration. A Magtrieve™ was washed with diethyl ether, and dried in an oven at 325°C for several hours and re-used for subsequent oxidations.

Preparative-scale synthesis of Diazo compounds using Magtrieve™

Based on the previous experiments, 15 molar equivalence of CrO_2 was selected for preparative scale synthesis of diazo compounds from the corresponding hydrazone. Yields, reaction times (on the basis of the disappearance of the parent hydrazone by TLC examination), and melting points of the resultant products are summarized in Table 2.

Table 2 – Yields and reaction times for the preparation of five diazo compounds from the corresponding hydrazone using 15 molar equivalence of CrO_2. Values represent the average of triplicates ± standard deviation.

Diazo compound	Isolated Yield (%)	m.p. (°C)	Reaction time (min)
1 Ph_2CN_2	95.1 ± 1.54	29-31	90
2 (p-$CH_3C_6H_4)_2CN_2$	81.9 ± 1.98	105	30
3 (p-$CH_3OC_6H_4)_2CN_2$	68.9 ± 2.23	110	60
4 (p-$ClC_6H_4)_2CN_2$	61.0 ± 1.92	108	60
5 Diazofluorene	90.3 ± 1.58	153	120

After the addition of CrO_2, the characteristic colors of the diazo compounds developed rapidly. The yields of the diazo compounds were similar to those reported for the mercury(II) oxide oxidations of hydrazones (Petursson, 1979 and references therein).

One-pot mono-etherfication of methyl 4,6-O-benzylidene α-D-mannopyranoside with dimethyldiphenyldiazomethane

Here the 3-*O*-ether of methyl 4,6-*O*-benzylidene α -D-mannopyranoside was prepared in good yield (82.7%) using the *in situ* generation of diazo-[*bis*(4-methylphenyl)methane] using $SnCl_2$ as a catalyst after the removal of Magrieve™. This one-pot protection demonstrates the utility of Magrieve™ for the facile generation and immediate use of a diazo compound without the need for a workup involving removing heavy metals such as mercury(II) oxide.

Conclusion

Magtrieve™ (CrO_2) presents a greener, more efficient, and facile route to the preparation of diaryl diazo compounds as well as diazofluorene than oxidations using heavy metal oxides. The *in situ* preparation of diazo compounds allows the synthesis of partially

protected monosaccharides in one pot thus avoiding the isolation of unstable and potentially hazardous alkylating agents.

Experimental

General methods

All reagents were obtained from Sigma Aldrich. Glassware was oven dried prior to use dimethoxyethane (DME) was distilled from and stored over sodium. Chromium(IV) oxide was washed with ether and regenerated in a muffle furnace at 325°C for at least 4 hours. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker AV400. Hydrazones were prepared according to conventional methods. Recovered Magtrieve™ was routinely washed with dichloromethane and dried in a muffle furnace at 325°C prior re-use. Magtrieve reaction vessels were shaken on an orbital shaker at 150 rpm.

Optimization of CrO_2 Oxidation of Hydrazones

The hydrazone, 0.5 mmol, was precision weighed into a 100 mL Erlenmeyer flask and dissolved in diethyl ether, 25 mL. Chromium(IV) oxide (Magtrieve^{TM}), 0.75 to 20 eq, was added at time zero. Reaction mixtures were shaken at 150 rpm. Reactions monitored by periodically withdrawing a sample and measuring the absorbance at the diazo compound's A_{max} using a Shimadzu UV-1800 UV-Vis spectrophotometer in a quartz cuvette with a pathlength of 1 cm. All experiments were performed in triplicate.

Preparative Scale CrO_2 Oxidation of Hydrazones

The hydrazone, 5 mmol, was dissolved in diethyl ether, 50 mL. Magtrieve™, 6.29925 g, 75 mmol, 15 eq, was added and the reaction mixture was shaken at 150 rpm. Reactions were followed by TLC (4:1 hexane/ethyl acetate). At the end of the reaction the Magtrieve™ was removed with a magnet and the diethyl ether was removed at 30°C on a rotatory evaporator. Diazo compounds were dissolved in diethyl ether, 10 mL, and cooled to -20°C. Crystals were isolated by vacuum filtration using Whatman #1 filter paper, with the exception of diazodiphenylmethane which was isolated as a red oil, and dried *in vacuo* for at least 1 hour. Melting points matched those of authentic compounds. Reported yields are the average of triplicate preparations.

Methyl 4,6-*O*-benzylidene-3-*O*-[di(*p*-methylphenyl)methyl]-α-D-mannopyranoside –

4,4'Dimethylbenzophenone hydrazone, 1.12 g, 5.00 mmol was placed in a round bottom flask containing Magtrieve™ , 6.33 g, 75.0 mmol and shaken at 150 rpm for 90 minutes. The Magtrieve™ was removed with a glass-covered magnetic rod and the ether was removed on a rotary evaporator at 30°C. DME, 50 mL, was added followed by methyl 4,6-*O*-benzylidene-α-D-mannopyranoside, 0.706 g, 2.50 mmol and tin(II) chloride, 62.5 mg, 0.30 mmol. After ~24 hours, the reaction mixture was light yellow. The DME was removed on a rotary evaporator at 45°C and the resultant mixture was chromatographed on a column of silica gel (4.4x25 cm) eluting with 4:1 hexane/ethyl acetate. The title compound, 0.985 g, 82.7% was isolated. ^{1}H NMR (400 MHz, *CDCl*$_3$ δ ppm 1.36 (s, 3H, C$\underline{H}_3$), 1.41 (s, 3H C$\underline{H}_3$), 2.67 (s, broad, 1H, 2-OH), 3.22 (s, 3H, OC$\underline{H}_3$), 3.51 (m, 1H, H-6A), 3.73-3.78 (m, 3H, H-3, H-5, H-6B), 3.88

(dd, *J* = 3.55, 1.37 Hz, 1H, H-2), 3.94 (t, 1H, *J*=9.41, H-4) 4.09 (m, 1H, 4-H), 4.63 (d, *J* = 1.30 Hz, 1H, H-1), 5.75 (s, 1H, C<u>H</u>Ph_2), 7.13-7.37 (m, 10H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 19.26, (CH_3), 29.38, (CH_3), 54.84, (OCH_3), 62.50, (C3), 63.91, (C5), 71.61, (C4), 74.91, (C6), 83.22, (C1), 99.69, (CPh_2), 100.01, ($C(CH_3)_2$), 127.18, 127.41, 127.475, 127.91, 128.16, 128.665, (C_{Ar}).

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II

Manuscript II - Regioselective mono-alkyations of the vicinal diol group of partially-protected mannopyranosides using diaryldiazoalkanes and tin(II) halides

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Abstract

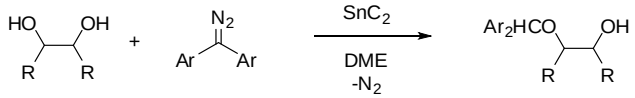
The use of tin(II) chloride and tin(II) bromide catalyzed reactions of methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside and methyl 4,6-*O*-benzylidene-α-D-mannopyranoside was investigated using several diaryldiazo compounds as alkyl donors. Regioselective protection of the 3-OH position was observed in the case of both $SnCl_2$ and $SnBr_2$-catalyzed reactions of methyl 4,6-*O*-benzylidene α-D-mannopyranoside with all five diazo compounds investigated. Reactions involving methyl 4,6-*O*-ispropylidene α-D-mannopyranoside yielded a mixture of the corresponding 2- and 3-*O* ether products with the 3-*O*-ether being the major product. A noteworthy exception is when diazofluorene was used then the 2-*O*-ether was the dominant product and when $SnBr_2$ was used the reaction gave a 94.5% of which 79.1% was the 2-ether. Generally, the $SnBr_2$-catalyzed reactions showing slightly higher 2-ether yields and the $SnCl_2$ catalyzed reactions and were also faster.

1 Introduction

Procedures for the highly regioselective protection of partially protected carbohydrates is of tremendous importance. The use of acetal or ketal groups for 4,6-protection of methyl glycosides leaves the 2- and 3-hydroxyl groups free. The regioselective protection of either of these two groups has been the subject of extensive research. Two notable examples of this system include methyl 4,6-*O*-isopropylidene-α-D-

mannopyranoside and the corresponding 4,6-*O*-benzylidene both of which have a *cis*-2-axial-3-equatorial diol in which reactions at the more sterically accessible 3-OH are generally preferred.

Regioselective manipulations of the 2-OH and 3-OH of methyl 4,6-*O*-benzylidene systems have been reported using stannylene acetals (Grindley, 1994, 2008; Grindley, 1998; Wuts & Greene, 2007). Stannylene-based methods require a discrete step to introduce the stannylene acetal and require stoichiometric quantities of the reagent. Conversely, methods require catalytic quantities of Lewis acids have also been reported. Selective methylations using diazomethane in the presence of Lewis acids, such as BF_3 and tin(II) chloride, have been reported (Aritomi & Kawasaki, 1970; Chittenden, 1973; Chittenden, 1975a, 1975b, 1979b; Robins, Lee, & Norris, 1975; Robins, Naik, & Lee, 1974). While the use of diphenyldiazomethane has shown some degree of regioselectivity during mono-alkylations involving *cis* vicinal diol systems such as methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside and methyl 4,6-*O*-benzylidene-α-D-mannopyranoside, diazo [*bis*(4-methylphenyl)methane] and diazo [*bis*(4-methoxyphenyl)methane] have demonstrated a much higher degree of selectivity for the 3-OH position (Petursson & Webber, 1982; Petursson, 1979; Petursson et al., 2014) as shown in Scheme 1. Studies have demonstrated that tin(II) bromide is also an efficient catalyst for mono-alkylations of vicinal diols (Petursson & Jonsdottir, 2012; Petursson, 2009). More recent investigations have shown that the role of catalyst concentration may also be important in determining the selectivity of tin(II) halide catalysts (Petursson et al., 2014).



Scheme 1 – $SnCl_2$-catalzyed mono-etherification of vicinal diols with diaryldiazomethane

This study focuses upon the use of tin(II) chloride and tin(II) bromide as catalysts for the introduction of diaryl diazo compounds of methyl 4,6-*O*-benzylidene α-D-mannopyranoside and 4,6-*O*-isopropylidene-α-D-mannopyranoside.

2 Results and Discussion

Five diazo compounds (**Figure 1**), Diazodiphenylmethane (**1**), diazo-[*bis*(4-methylphenyl)methane] (**2**), diazo-[*bis*(4-methoxyphenyl)methane] (**3**), diazo-[*bis*(4-chlorophenyl)methane] (**4**), or diazofluorene (**5**) were prepared in good yields via the oxidation of the corresponding hydrazone as previously described (Petursson, 1979).

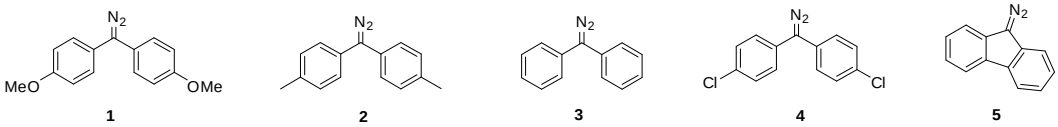
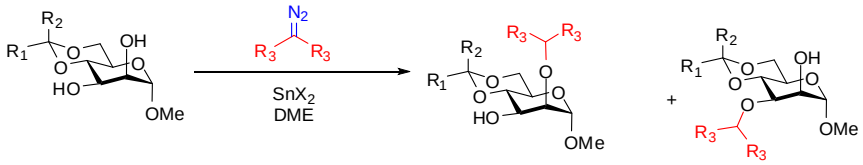


Figure 1 – Diazo compounds used for the preparation of mono-ethers of mannopyranosides

Methyl 4,6-O-isopropylidene-α-D-mannopyranoside

Treatment of methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside with diazo compounds either diazodiphenylmethane (**3**), diazo-[*bis*(4-methylphenyl)methane] (**2**), diazo-[*bis*(4-methoxyphenyl)methane] (**1**), diazo-*bis*-[(4-chlorophenyl)methane] (**4**), or diazofluorene (**5**) in the presence of tin(II) chloride or tin(II) bromide resulted in a mixture of the corresponding 2-*O* and 3-*O* ethers as shown in **Scheme 2**. Initially, this reaction series was attempted at catalyst concentrations of 6.6 mM although the reactions proceeded too quickly to be monitored kinetically by HPLC. Thus, reactions were performed at catalyst concentrations of 1.7 mM and were monitored via. Relative amounts of the resulting 2-*O* and 3-*O* ethers as observed by HPLC were in good general agreement with the quantities isolated and shown in Table 1.



Scheme 2 – Tin(II) halide-catalyzed mono-etherification of 4,6-acetals of methyl mannopyranosides with diaryldiazomethane

Reactions generally gave good yields with the exception of reactions involving (3) which resulted in consistently low yields despite demonstrating high regioselectivity for the 3-OH position with none of the corresponding 2-*O* ether being detected. In the case of alkylations with diazo compounds (1) and (3), $SnCl_2$ demonstrated a greater selectivity for the 3-OH position while the opposite is the case for (2). $SnBr_2$ gave slightly higher selectivity when (5) was used as the alkylating agent.

Table 1 - Reaction times and yields of mono-etherifications of methyl 4,6-*O*-isopropylidene α-D-mannopyranoside with $SnCl_2$ and $SnBr_2$

	$SnCl_2$			**$SnBr_2$**		
Diazo Compound	**Overall Yield** (%)	**2:3 ratio**	**Time** (hrs)	**Overall Yield** (%)	**2:3 ratio**	**Time** (hrs)
1	56.1	0:1	<3 min	38.6	0:1	<2 min
2	88.2	1:34.2	0.33	88.2	0:1	2 min
3	94.9	1:26.1	2.4	97.7	1:5.6	1.2
4	98.5	1:43.8	6	91.3	1:3.4	3
5	89.6	1.4:1	72	74.7	3.8:1	72

Interestingly, the ratio of 2-*O*- and 3-*O*-ether end products differed between $SnCl_2$ and $SnBr_2$-catalzyed reactions as highlighted in Figure 2. Generally, tin(II) chloride catalyzed alkylations gave predominately the 3 ether with the exception of diazofluorene was used which resulted in a roughly equal mixture of the 2-*O*- and 3-*O* ether. Tin(II) bromide catalyzed reactions, however, produced more of the 2-ether than the corresponding tin(II) chloride reactions. Diazofluorene gave predominately the 2-*O*-ether. A general trend is observed that the most reactive diazo compounds favor the formation of the 3-OH ether whereas the less reactive diazo compounds (diazo [*bis*-(4-chlorophenyl)methane] and diazofluorene) yield more of the 2-*O*-ether.

The preference for reaction at the 3-OH position is not surprising as this hydroxyl is generally regarded to be more reactive than the 2-OH due to the hydrogen bonding with the neighboring 2-OH. It is more difficult to explain the increased propensity for 2-*O*-ether formation with the less reactive diazo compounds.

These results stand in contrast to the results originally reported by Petursson (Petursson & Webber, 1982; Petursson, 1979). In Petursson's work, $SnCl_2$-catalyzed mono-etherifications using these five diazo compounds gave different ratios of end products and reaction times although overall yields were similarly. A notable example of this is the reaction of diazo [*bis*-(4-chlorophenyl)methane] for which Petursson reported a roughly 50-50 distribution of the resultant mono-ethers. Here, a much higher selectivity for alkylation at the 3-OH position was observed. Additionally, Petursson's reaction with diazofluorene gave 70% of the 2-ether, 13% of an unresolved mixture (composition not reported), and only 5.4% of the corresponding 3-*O*-ether. A notable difference between this work and that reported by Petursson and Webber (1982) is the difference in catalyst concentration (5 mM) whereas the work reported here uses 1.7 mM. Indeed, subsequent work has revealed that the concentration of the tin halide catalyst plays a role in the end product ratios (Petursson et al., 2014). A mechanism to explain this catalyst concentration dependence of the regioselectivity has been proposed by Petursson et al. (2014).

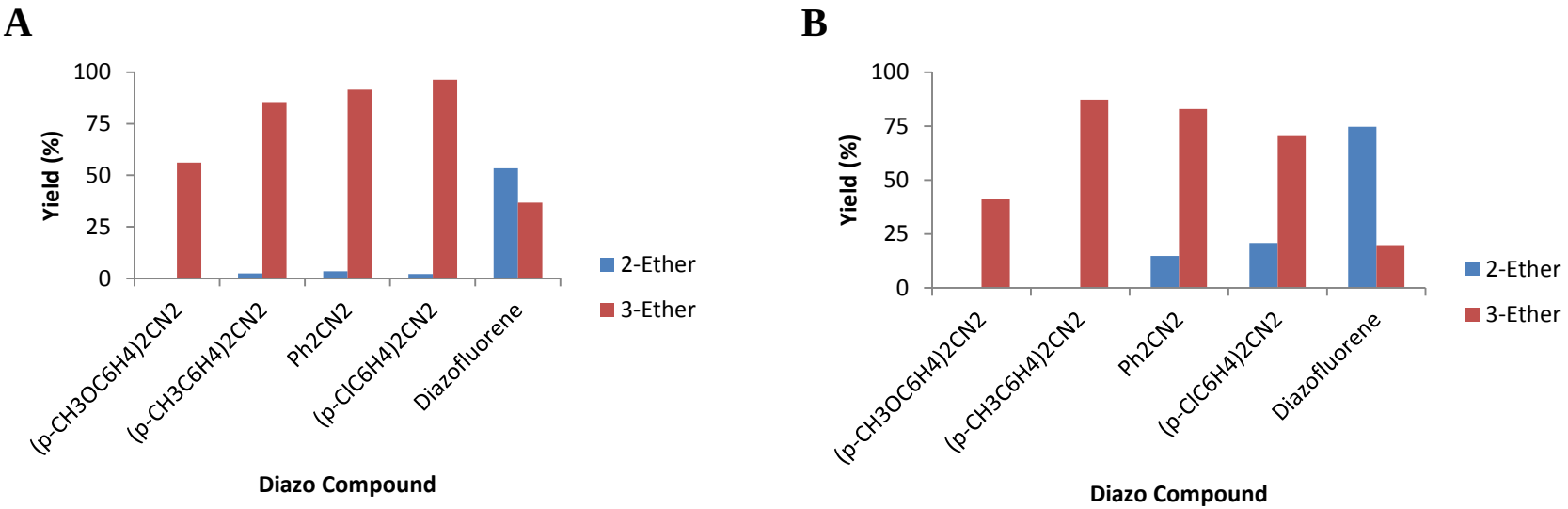


Figure 2- Regioselectivity and yields between reactions of diazo compounds and methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside using $SnCl_2$ **(A)** or $SnBr_2$ **(B)** catalysts.

Reaction involving methyl 4,6-O-benzylidene-α-D-mannopyranoside

Unlike reactions involving methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside, the reactions involving methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (**7**) and diazo compounds (**1-5**) almost exclusively the 3-*O* ether in good yields with the exception of the reactions involving (**3**) and (**5**) as summarized in Table 2.

Table 2 Reaction times and yields of mono-etherfications of methyl 4,6-*O*-benzylidene α-D-mannopyranoside with $SnCl_2$ (6.6 mM) and $SnBr_2$ (6.5 mM)

	$SnCl_2$			**$SnBr_2$**		
Diazo Compound	**Overall Yield** (%)	**2:3 ratio**	**Time** (hrs)	**Overall Yield** (%)	**2:3 ratio**	**Time** (hrs)
1	58.2	0:1	<0.25	61.0	0:1	<0.25
2	79.8	0:1	26	92.4	0:1	21
3	81.7	1:12.9[1]	72	73.7	1:7.55[1]	46
4	73.1	0:1	56*	67.1	0:1	53*
5	67.3	0:1	66*	56.3	0:1	67*

[1]Based on HPLC data, [*]Catalyst fell out of solution

The reaction times are typically on the order of days; this may be due to the steric bulk of the benzylidene group preventing access of the diazo compound to the tin(II) halide-vicinal diol system. Generally, the tin(II) bromide catalyzed reactions gave noticeably shorter reaction times in most cases which is also evident from the kinetic data obtained by following the reactions via HPLC (supplementary material, **Appendix C**). The small quantity of the 2-*O*-benzhydyl ether observed on the HPLC was not isolated in either the tin(II) chloride or tin(II) bromide reaction. The reaction of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside produced slightly more of the 2-ether as evidenced by the HPLC analysis. Interestingly, the ratio of end products shifts very quickly after the onset of the reaction.

These results are largely consistent with the results with those reported by Petursson and Webber (1982). In general, the $SnBr_2$-catalyzed reactions proceed more quickly than those using tin(II) chloride. During

the reactions involving diazo-*bis*-[(4-chlorophenyl)methane] and diazofluorene, the catalyst fell out of solution. This may imply destruction of the catalyst as has been observed with the methyl 4,6-*O*-benzylidene-α-D-glucopyranoside system (Pétursson, 2001).

The results diverge somewhat from previously published work on the tin(II) chloride-catalyzed etherfication of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside and methyl 4,6-*O*-isopropylidene-α-D-mannypranyoside (Petursson & Webber, 1982). Subsequent investigations (Petursson et al., 2014) have revealed that catalyst concentration is an important factor and differences in selectivity observed maybe due to differences in catalyst in solution.

3 Conclusion

Tin(II) chloride and tin(II) bromide catalysis of the reactions of diaryldiazomethanes with vicinal diols provide a regioselective method for the introduction of diarylmethyl ether protection of partially protected mannopyranosides. Tin(II) bromide gives slightly different selectivities from tin(II) chloride. Diazo *bis*(4-methylphenyl)methane is a highly efficient and regioselective reagent in for the protection of the 3-OH of 4,6-protected pyranosides.

4 Experimental

4.1 General methods – All reagents were obtained from Sigma-Aldrich unless otherwise noted. 1,2-dimethoxyethane (DME) was distilled from and stored over sodium. Anhydrous tin(II) chloride and tin(II) bromide were obtained from Sigma Aldrich. Methyl 4,6-*O*-isopropylidene-α-D-mannypranyoside, methyl 4,6-*O*-benzylidene α-D-mannypranyoside, and all diazo compounds were prepared as previously describe (Petursson, 1979).

Preparative chromatography was performed using silica gel (60Å, 230-400 mesh); column dimensions were 2.2x20 cm unless otherwise noted. Where chromatographic separations were incomplete, quantities of 2- and 3-ethers were estimated from the Ar_2-C<u>H</u>O- peak in the proton NMR

spectrum. Thin-layer chromatography was performed on Silica gel TLC cards with a fluorescent indicator were obtained from Fluka; TLC plates were visualized using a UV lamp (λ_{254}) and sprayed with 0.2% w/v cerium(IV) sulfate 5% w/v ammonium molybdate in 2.0 M sulfuric acid and visualized by heating.

^{1}H and ^{13}C NMR Spectrum were obtained using a Bruker AV400 Nuclear Magnetic Resonance spectrometer using $CDCl_3$ using trimethylsilane (TMS) as an external standard. All melting points were obtained using a Thiel tube and are uncorrected.

HPLC analysis was performed on a Shimadzu UFLC using two 20-AD solvent pumps and a 20-A UV-VIS Detector at 254 nm, with a DGU-$20A_3$ online degasser and a Rheodyne manual sample injector equipped with a 20 µL loop. Separation was achieved using a reverse phase column (Supleco, 150mm x 4.6 mm, 3 µm) with a guard column (Supelco, 20mm x 4.0, 3 µm) mm C18 guard cartridge. Mobile phase was rigorously degassed (sonic bath, 1 hour) prior to use and was delivered at a flow rate of 1 mL per minute composed of unbuffered 20% water and 80% methanol. 10 µL of reaction sample was diluted with 240 µL of mobile phase prior to injection; injection volume was 20 µL. Retention times of analytes were verified using characterized products from relevant separations.

4.2 Reactions of diazodiphenylmethane with methyl 4,6-O-isopropylidene-α-D-mannopyranoside

4.2.1 Tin(II) chloride catalyzed

Methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside, 234 mg, 1.00 mmol, was placed in a 25mL round bottom flask with tin(II) chloride, 6.3 mg, 0.033 mmol, before being dissolved in dry DME, 20 mL. Diphenyldiazomethane, 291 mg, 1.50 mmol, (1.5 eq) was added. After 145 minutes, the reaction solution was light pink and TLC (4:1 Hexane/Ethyl acetate) indicated that most of the starting material had been converted to products. The DME was removed using a rotary evaporator at 40°C and the material was re-suspended in 4:1 hexane/ethyl acetate and loaded onto a 2.2x20 cm column packed with silica gel using 4:1 hexane/ethyl acetate. Thirty two ~15 mL fractions were collecting by eluting with 4:1 hexane/ethyl acetate. Fractions 9-10, 5.4 mg contained the 2-ether, fractions 11-14 contained an unresolved mixture, 184 mg (2:3 ratio, 0.05:1.00) and fractions 15-28 yielded the 3-*O*-ether, 190.6 mg. Overall yield 94.9% (3.7% 2-ether, 96.3% 3-ether).

4.2.2 Tin(II) bromide catalyzed

Methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside, 234 mg, 1.00 mmol, was placed in a 25 mL round bottom flask with tin(II) bromide, 9.0 mg, 0.032 mmol, before being dissolved in dry DME, 20 mL. Diphenyldiazomethane, 291 mg, 1.50 mmol, (1.5 eq) was added. The reaction solution was light pink after 30 minutes and finished after 70 minutes. Examination by TLC (4:1 hexane/ethyl acetate) indicated that most of the starting material had been converted to products. The DME was removed using a rotary evaporator at 40°C and the material was re-suspended in 4:1 hexane/ethyl acetate and loaded onto a 2.2x20 cm column packed with silica gel using 4:1 hexane/ethyl acetate. Thirty six 5 mL fractions were collected by elution 4:1 hexane/ethyl acetate. Fractions 10-11 were pooled and evaporated yielding the 2-*O*-ether, 43.1 mg, fractions 12-15 were pooled and evaporated yielding an unresolved mixture, 194 mg, and fraction 16-29 were pooled and evaporated yielding

the 3-*O*-ether, 154.2 mg. Overall yield 97.7% (15.1% 2-ether, 84.9% 3-*O*-ether).

Methyl 4,6-*O*-isopropylidene-2-*O*-diphenylmethyl-α-D-mannopyranoside: (R_f=0.195), SP210510A ^{1}H NMR (400 MHz, *CDCl*$_3$ δ ppm 1.38 (s, 3H, C$\underline{H}_3$), 1.49 (s, 3H, C$\underline{H}_3$), 2.03 (s, broad 1H, 3-OH), 3.17 (s, 3H, OMe), 3.51 (m, 1H, H-5), 3.80 (m, 4H, H2-4, H6B), 3.93 (t, *J* = 9.41, 9.41 Hz, 1H, H6A), 4.47 (s, 1H, H-1), 5.55 (s, 1H, C$\underline{H}$Ph$_2$), 7.19-7.28 (m, 10H, CH$\underline{Ph}_2$),. ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 19.35, (CH_3), 29.34, (CH_3), 54.86, (OCH_3), 62.42, (C3), 64.25, (C5), 72.27, (C4), 77.54, (C6), 84.52, (C1), 99.85, (CPh_2), 100.04, ($C(CH_3)_2$), 127.21, 127.35, 127.85, 127.91, 128.51, 128.65, (C_{Ar}).

Methyl 4,6-*O*-isopropylidene-3-*O*-diphenylmethyl-α-D-mannopyranoside: (R_f=0.146), (SP210510C) ^{1}H NMR (400 MHz, *CDCl*$_3$ δ ppm 1.36 (s, 3H, C$\underline{H}_3$), 1.41 (s, 3H C$\underline{H}_3$), 2.67 (s, broad, 1H, 2-OH), 3.22 (s, 3H, OC$\underline{H}_3$), 3.51 (m, 1H, H-6A), 3.73-3.78 (m, 3H, H-3, H-5, H-6B), 3.88 (dd, *J* = 3.55, 1.37 Hz, 1H, H-2), 3.94 (t, 1H, *J*=9.41, H-4) 4.09 (m, 1H, 4-H), 4.63 (d, *J* = 1.30 Hz, 1H, H-1), 5.75 (s, 1H, C$\underline{H}$Ph2), 7.13-7.37 (m, 10H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 19.26, (CH_3), 29.38, (CH_3), 54.84, (OCH_3), 62.50, (C3), 63.91, (C5), 71.61, (C4), 74.91, (C6), 83.22, (C1), 99.69, (CPh_2), 100.01, ($C(CH_3)_2$), 127.18, 127.41, 127.475, 127.91, 128.16, 128.665, (C_{Ar}).

4.3 Reactions of diazo[bis(4-methylphenyl)]methane with methyl 4,6-O-isopropylidene-α-D-mannopyranoside

4.3.1 Tin(II) chloride catalyzed

Methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside, 234 mg, 1.00 mmol, was placed in a 25 mL round bottom flask with tin(II) chloride, 6.3 mg, 0.033 mmol, before being dissolved in dry DME, 20 mL. Diazo[*bis*(4-methylphenyl)]methane, 333 mg, 1.5 mmol (1.5 eq), was added. The reaction solution bubbled profusely and was light purple in less than 20 minutes and TLC (4:1 hexane/Ethyl acetate) indicated that most of the

starting material had been converted to products. The DME was removed using a rotary evaporator at 50°C and the material was re-suspended in 4:1 hexane/ethyl acetate and loaded onto a 2.2x20 cm column packed with silica gel using 4:1 hexane/ethyl acetate. About 400 mL of 4:1 hexane/ethyl acetate was run and collected at 10 mL fractions. Fractions 10-13 were pooled and evaporated to produce the 2-ether, 7 mg (the faster component); fractions 14-16 were pooled and evaporated yielding an unresolved mixture, 100 mg; fraction 17-32 were pooled and evaporated yielding the 3-ether, 271 mg. Overall yield: 378 mg; 88.2% total yield; 2-*O*-ether 11.8 mg, 2.7%; 3-*O*-ether 366.2 mg, 85.5%.

4.3.2 Tin(II) bromide catalyzed

Methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside, 234 mg, 1.00 mmol, was placed in a 25 mL round bottom flask with tin(II) bromide, 9.0 mg, 0.032 mmol, before being dissolved in dry DME, 20 mL. Diazo[*bis*(4-methylphenyl)]methane, 333 mg, 1.5 mmol (1.5 eq), was added. The reaction solution bubbled profusely and was light purple in less than 5 minutes and TLC (4:1 hexane/Ethyl acetate) indicated that most of the starting material had been converted to products. The DME was removed using a rotary evaporator at 50°C and the material was re-suspended in 4:1 hexane/ethyl acetate and loaded onto a 2.2x20 cm column packed with silica gel using 4:1 hexane/ethyl acetate. About 400 mL of 4:1 hexane/ethyl acetate was run and collected at 10 mL fractions. Fractions 15-17 were pooled and evaporated to yield the 2-ether, 3 mg; fractions 18-19 were pooled and evaporated yielding an unresolved mixture, 42 mg; fraction 20-32 were pooled and evaporated yielding the 3-ether, 333 mg. Overall yield: 378 mg, 88.2%, 2-*O*-ether 4.2 mg, 1.0%; 3-*O*-ether 373.8 mg, 87.2%.

Methyl 4,6-*O*-isopropylidene-2-*O*-*bis*(4-methylphenyl)methyl-α-D-mannopyranoside: SP161009A (10 and 11) ^{1}H NMR (400 MHz, *Solvent* δ ppm 1.37 (s, 1H, PhC$\underline{H}_3$), 1.48 (s, 3H, PhC$\underline{H}_3$), 2.03 (s, broad 1H, 3-OH), 2.24 (s, 3H, CHC$\underline{H}_3$), 2.29 (s, 3H, CHC$\underline{H}_3$), 3.18 (s, 3H, OC$\underline{H}_3$), 3.51 (m, 1H, H-6A), 3.75-3.81 (m, 4H, H-2, H-3, H5, H-6B), 3.92 (t, *J* = 9.39, 9.39 Hz, 1H, H4), 4.49

(s, 1H, H-1), 5.46 (s, 1H, C<u>H</u>($CH_3Ph)_2$), 7.05-7.17 (m, 8H, aromatic).

Methyl 4,6-*O*-isopropylidene -3-*O*-*bis*(4-methylphenyl)methyl-α-D-mannopyranoside: (SP161009C) ^{1}H NMR (400 MHz, *Solvent* δ ppm 1.36 (s, 3H, PhC<u>H</u>$_3$), 1.42 (s, 3H, PhC<u>H</u>$_3$), 2.24 (s, 3H, CHC<u>H</u>$_3$), 2.26 (s, 3H, CHC<u>H</u>$_3$), 2.62 (d, *J* = 0.88 Hz, 1H, 2-OH), 3.22 (s, 3H, OC<u>H</u>$_3$), 3.51 (td, *J* = 9.62, 7.90, 7.90 Hz, 1H, H-6A), 3.71 (dd, *J* = 9.34, 3.56 Hz, 1H, H-3), 3.75-3.86 (s, 2H, ZZZ), 3.77 (s, 1H, ZZZ), 3.86 (d, *J* = 3.54 Hz, 1H, ZZZ), 4.07 (t, *J* = 9.58, 9.58 Hz, 1H, H-4), 4.62 (d, *J* = 1.19 Hz, 1H, H-1), 5.68 (s, 1H, C<u>H</u>bis-(*p*-CH_3Ph)), 7.05-7.13 (m, 8H, aromatic), ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 19.26, (CH_3),21.14, (Ph<u>C</u>H_3), 21.21, (Ph<u>C</u>H_3), 29.39, (CH_3), 54.81, (OCH_3), 62.53, (C3), 63.94, (C2), 70.32, (C5), 71.61, (C4), 74.68, (C6), 82.87, (C1), 99.67, (CPh_2), 101.03, ($C(CH_3)_2$), 127.13, 127.33, 128.82, 129.32, 137.05, 137.51, 138.99, 139.42, (C_{Ar}).

4.4 Reactions of diazo[bis(4-methoxyphenyl)]methane with methyl 4,6-O-isopropylidene-α-D-mannopyranoside

4.4.1 Tin(II) chloride catalyzed

Methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside, 234 mg, 1.00 mmol, was placed in a 25 mL round bottom flask with tin(II) chloride, 6.3 mg, 0.033 mmol, before being dissolved in dry DME, 20 mL. Diazo[*bis*(4-methoxyphenyl)]methane, 559 mg, 2.20 mmol (2.2 eq), was added. The reaction solution bubbled profusely and was light purple in less than 3 minutes and TLC (4:1 hexane/ethyl acetate) indicated that most of the starting material had been converted to products and byproducts. The DME was removed using the rotary evaporator and the material was dry loaded onto a 2.2x20 cm column packed with silica gel using 4:1 hexane/ethyl acetate. One hundred 10 mL fractions were collected; fraction 70-96 were pooled and evaporated yielding the 3-*O*-ether, 243.6 mg, 73.2%.

4.4.2 Tin(II) bromide catalyzed

Methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside, 234 mg, 1.00 mmol, was placed in a 25 mL round bottom flask with tin(II) bromide, 9.0 mg, 0.032 mmol, before being dissolved in dry DME, 20 mL. Diazo[*bis*(4-methoxyphenyl)]methane, 559 mg, 2.2 mmol, 2.2 eq, was added. The reaction solution bubbled profusely and was light purple in less than 3 minutes and TLC (4:1 hexane/ethyl acetate) indicated that most of the starting material had been converted to products and byproducts. The DME was removed using the rotary evaporator and the material was dry loaded onto a 2.2x20 cm column packed with silica gel using 4:1 hexane/ethyl acetate. One hundred 10 mL fraction were collected; fraction 60-95 were pooled and evaporated yielding the 3-*O*-ether, 144.1 mg, 38.6.2% of the 3-*O*-ether.

Methyl 4,6-*O*-isopropylidene-3-*O*-bis(4-methoxyphenyl)methyl-α-D-mannopyranoside: (SP210610A) ^{1}H NMR (400 MHz, *CDCl*$_3$ δ ppm 1.49 (s, 3H, CHC$\underline{H}_3$), 1.56 (s, 3H, CHC$\underline{H}_3$), 2.72 (d, *J* = 1.01 Hz, 1H, 2-OH), 3.34 (s, 3H, OC$\underline{H}_3$), 3.64 (m, 1H), 3.80 (m, 1H), 3.85 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.87 (s, 1H), 3.89 (d, *J* = 2.35 Hz, 1H), 3.94 (td, *J* = 6.38, 3.24, 3.24 Hz, 1H), 4.19 (t, *J* = 9.59, 9.59 Hz, 1H), 4.73 (d, *J* = 1.21 Hz, 1H), 5.77 (s, 1H, $CHAr_2$), 6.95-7.25 (m, 8H, aromatic).

4.5 Reactions of diazo[bis(4-chlorophenyl)]methane with methyl 4,6-O-isopropylidene-α-D-mannopyranoside

4.5.1 Tin(II) chloride catalyzed

Methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside, 234 mg, 1.00 mmol, was placed in a 25 mL round bottom flask with tin(II) chloride, 6.3 mg, 0.033 mmol, before being dissolved in dry DME, 20 mL. Diazo[*bis*(4-chlorophenyl)]methane, 354 mg, 1,35 mmol (1,35 eq). The reaction mixture was light yellow after 6 hours. The solvent was removed on the rotary evaporator at 40°C. The resultant mixture was re-dissolved in 4:1 hexane/ethyl acetate and loaded onto a 2.2x20 cm column of silica gel packed with 4:1 hexane/ethyl acetate. Forty ~10 mL fractions were

collected by 4:1 hexane/ethyl acetate. Appropriate fractions were pooled and evaporated yielding the 2-ether, 1.9 mg, an unresolved mixture, 150.5 mg and the 3-ether, 309.9 mg. Total yield 98.7%; 2-ether, 10.5 mg, 2.3%; 3-ether, 451.8 mg, 97.7%.

4.5.2 Tin(II) bromide catalyzed

Methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside, 234 mg, 1.00 mmol, was placed in a 25 mL round bottom flask with tin(II) bromide, 9.0 mg, 0.032 mmol, before being dissolved in dry DME, 20 mL. Diazo[*bis*(4-chlorophenyl)]methane, 354 mg, 1.35 mmol, 1.35 eq, was added. After 4 hours, the reaction mixture was light yellow. The solvent was removed on the rotary evaporator at 40°C and the resultant mixture was re-dissolved in 4:1 hexane/ethyl acetate and loaded onto a 2.2x20 cm column of silica gel packed with 4:1 hexane/ethyl acetate. Forty ~10 mL fractions were collected by 4:1 hexane/ethyl acetate. Fractions were pooled and evaporated yielding the 2-ether, 84.6 mg, an unresolved mixture, 134.3 mg and the 3-ether, 209.7 mg. Total yield 91.5%; 2-ether 97.8 mg, 22.8%; 3-ether 330.8 mg, 77.2%.

Methyl 4,6-*O*-isopropylidene-2-*O*-*bis*(4-chlorophenyl)methyl-α-D-mannopyranoside; SP150610A ^{1}H NMR (400 MHz, *CDCl*$_3$ δ ppm 1.37 (s, 3H, CHC$\underline{H}_3$), 1.48 (s, 3H, CHC$\underline{H}_3$), 2.01 (s, broad, 1H, 3-OH), 3.21 (s, 3H, OC$\underline{H}_3$), 3.52 (dd, *J* = 9.05, 6.94 Hz, 1H, H-6A), 3.75-3.87 (m, 4H, H-2, H-3, H-5, H-6B), 3.93 (t, *J* = 9.57, 9.57 Hz, 1H, H-4, 4.46 (d, *J* = 1.29 Hz, 1H, H-1), 5.57 (s, 1H, C$\underline{H}$(4-ClPh)$_2$), 7.32-7.14 (m, 1H, aromatic).

Methyl 4,6-*O*-isopropylidene-3-*O*-*bis*(4-chlorophenyl)methyl-α-D-mannopyranoside; ^{1}H NMR (400 MHz, *CDCl*$_3$ δ ppm 1.46 (s, 3H, CHC$\underline{H}_3$), 1.52 (s, 3H, CHC$\underline{H}_3$), 2.58 (d, broad, *J* = 0.63 Hz, 1H, 2-OH), 3.35 (s, 3H, OC$\underline{H}_3$), 3.62 (m, 1H, H-6A), 3.79-3.89 (m, 3H, H-3, H-5, H-6B), 3.97 (dd, *J* = 3.50, 1.40 Hz, 1H, H-2), 4.21 (m, 1H, H-4), 4.74 (d, *J* = 1.31 Hz, 1H, H-1), 5.79 (s, 1H, C$\underline{H}$(4-ClPh)$_2$), 7.25-7.40 (m, 8H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 19.29, (CH_3), 29.38, (CH_3), 54.89, (OCH_3), 62.44, (C3), 63.96, (C2), 70.36, (C5), 71.53, (C4), 75.11, (C6), 81.92, (C1), 99.71,

(CPh_2), 100.97, ($C(CH_3)_2$), 128.41, 128.44, 128.67, 128.98, 133.52, 133.96, 139.94, 140.27, (C_{Ar}).

4.6 Reactions of diazofluorene with methyl 4,6-O-isopropylidene-α-D-mannopyranoside

4.6.1 Tin(II) chloride catalyzed

Methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside, 234 mg, 1.00 mmol, was placed in a 25 mL round bottom flask with tin(II) chloride, 6.3 mg, 0.033 mmol, before being dissolved in dry DME, 20 mL. Diazofluorene, 288 mg, 1.50 mmol, (1.50 eq) was added. The reaction was followed by TLC (4:1 Hexane/Ethyl acetate) and HPLC. After 72 hours both TLC and HPLC indicated that the majority of the starting materials had reacted. The DME was removed using the rotary evaporator and the material was redissolved in 4:1 hexane/ethyl acetate and loaded onto a 2.2x20 cm column packed with silica gel and 4:1 hexane/ethyl acetate. About 900 mL of 4:1 hexane/ethyl acetate was run and collected as fifty x10 mL fractions. Fraction 19-23 were pooled and evaporated yielding the 2-ether, 112.8 mg; fraction 24-33 contained an unresolved mixture of the 2-ether and the 3-ether, 99 mg; fractions 38-48 were pooled and evaporated which yielded the 3-ether, 45.1 mg of. Overall yield 89.0%; 2-ether 212.3 mg, 59.5%; 3-ether 144.6 mg, 40.5%.

4.6.3 Tin(II) bromide catalyzed

Methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside, 234 mg, 1.00 mmol, was placed in a 25 mL round bottom flask with tin(II) bromide, 9.0 mg, 0.032 mmol, before being dissolved in dry DME, 20 mL. Diazofluorene, 288 mg, 1.50 mmol, (1.50 eq) was added. The reaction was followed by TLC (4:1 Hexane/Ethyl acetate) and HPLC. After 72 hours both TLC and HPLC indicated that the majority of the starting materials had reacted. The DME was removed using the rotary evaporator and the material was redissolved in 4:1 hexane/ethyl acetate and loaded onto a 2.2x20 cm column packed with silica gel and 4:1 hexane/ethyl acetate. About 900 mL of 4:1 hexane/ethyl acetate was run and collected as fifty about 15 mL fractions. Fraction 17-22 were pooled and evaporated yielding the 2-

ether, 162.5 mg. Fraction 23-33 contained an unresolved mixture of the 2-ether and the 3-ether, 181.3 mg; fractions 34-44 were pooled and evaporated which yielded the 3-ether, 32.7 mg. Overall yield: 376.5 mg or 94.5%; 2-ether 297.7 mg, 79.1%; 3-ether 78.8 mg, 20.9%).

Methyl 2-*O*-(9*H*-fluoren-9-yl)-4,6-*O*-isopropylidene-α-D-mannopyranoside: (R_f=0.22). ^{1}H NMR (400 MHz, *CDCl*$_3$) δ ppm 1.37 (s, 3H, C$\underline{H}_3$), 1.44 (s, 3H, C$\underline{H}_3$), 2.17 (s, broad, 1H, 3-OH), 3.20 (s, 3H, OCH_3), 3.51 (dt, *J* = 9.33, 9.31, 6.07 Hz, 1H, H-6A), 3.74-3.89 (m, 4H, H-2, H-3, H-5, H-6B), 3.96 (dd, *J* = 3.25, 1.42 Hz, 1H, H-4), 4.67 (d, *J* = 1.35 Hz, 1H, H-1), 5.61 (s, 1H, C$\underline{H}$Ar), 7.30-7.55 (m, 8H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 19.41, (CH_3), 29.34, (CH_3), 55.00, (OCH_3), 62.41, (C3), 64.31, (C2), 68.87, (C5), 72.00, (C4), 77.72, (C6), 81.87, (C1), 100.06, (CPh_2), 100.34, ($C(CH_3)_2$), 120.09, 120.14, 125.68, 125.76, 127.79, 127.81, 129.41, 140.51, 140.70, 142.61, 143.24, (CAr).

Methyl 3-*O*-(9*H*-fluoren-9-yl)-4,6-*O*-isopropylidene-α-D-mannopyranoside: (R_f=0.12). (SP310510E) ^{1}H NMR (400 MHz, *CDCl*$_3$) δ ppm 1.38 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 2.64 (s, broad, 1H, 2-OH), 3.26 (s, 3H, OCH_3), 3.54-3.57 (m, 1H, H-6A), 3.79 (m, 1H, H-3), 3.81-3.90 (m, 2H. H-5, H-6B), 3.95 (dd, *J* = 9.37, 3.55 Hz, 1H, H-2), 4.10 (t, *J* = 9.55, 9.55 Hz, 1H, H-4), 4.63 (d, *J* = 1.25 Hz, 1H, H-1), 5.70 (s, 1H, C_HAr), 7.16-7.59 (m, 8H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 19.46, (CH_3), 29.39, (CH_3), 54.89, (OCH3), 62.44, (C3), 64.23, (C2), 71.12, (C5), 71.19, (C4), 76.18, (C6), 82.36, (C1), 99.85, (CPh_2), 101.11, ($C(CH_3)_2$), 119.99, 125.42, 124.75, 127.66, 129.15, 129.26, 140.25, 140.52, 143.42, 143.69, (CAr).

4.7 Reactions of diazodiphenylmethane with methyl 4,6-O-benzylidene-α-D-mannopyranoside

4.7.1 Tin(II) chloride catalyzed

Methyl 4,6-*O*-benzylidene-*α*-D-mannopyranoside, 141 mg, 0.5 mmol, was placed in a 10 mL round bottom flask and dissolved in 10 mL of

DME. Tin(II) chloride, 12.5 mg, 0.0659mmol, was added followed by diazodiphenylmethane, 146 mg, 0.752 mmol (1.5 eq). After 72 hours, the solution was light yellow and the TLC (4:1 Hexane/Ethyl Acetate)showed most of the starting material had reacted; the solvent was removed on a rotary evaporator at 55°C under reduced pressure. The material was chromatographed on silica gel (2.2x20 cm) using an isocratic elution of 4:1 hexane/ethyl acetate giving methyl 4,6-*O*-benzylidene-3-*O*-diphenylmethyl-α-D-mannopyranoside, 183 mg, 81.7%.

4.7.2 Tin(II) bromide catalyzed

Methyl 4,6-*O*-benzylidene-α-D-mannopyranoside, 141 mg, 0.5 mmol, was placed in a 10 mL round bottom flask and dissolved in 10 mL of DME. Tin(II) bromide, 18.0 mg, 0.0646mmol, was added followed by diazodiphenylmethane, 146 mg, 0.752 mmol (1.5 eq). Bubbles readily evolved and the deep red color of the solution faded rapidly. The reaction was followed by TLC (4:1 Hexane/EtOAc). After 46 hours, the reaction mixture was placed on the rotary evaporator at about 55°C. The materials was chromatographed on a column of silica gel (2.2x20 cm) and the product eluted with 4:1 Hexane/EtOAc giving methyl 4,6-*O*-benzylidene-3-O-diphenylmethyl-α-D-mannopyranoside, 165 mg, 73.7%.

Methyl 4,6-*O*-benzylidene-3-*O*-diphenylmethyl-α-D-mannopyranoside: *(SP251109A)* ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.60 (s, 1H, broad -OH), 3.25 (s, 3H –OC<u>H</u>$_3$), 3.69 (m, 1H, H-5), 3.78 (t, *J* = 10.21, 10.21 Hz, 1H, H-6A), 3.91 (dd, *J* = 9.51, 3.48 Hz, 1, H-3), 3.96 (m, 1H, H-2), 4.08 (t, *J* = 9.40, 9.40 Hz, H-6B), 4.19 (dd, *J* = 10.02, 4.62 Hz, 1H, H-4), 4.68 (d, $J_{H1,H2}$=1.26 Hz, 1H, H-1), 5.55 (s, 1H, =Ph$_2$C<u>H</u>), 5.73 (s, 1H, PhC<u>H</u>-), 7.51-7.11 (m, 15H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.95, (O<u>C</u>H$_3$), 63.20, (C_3), 68.97, (C_2), 69.96 (C_5), 74.59, (C_4), 78.65, (C_6), 82.95, (C_1), 101.03, (<u>C</u>HPh$_2$), 101.69, (<u>C</u>HPh), 126.15, 127.15, 127.38, 127.58, 128.01, 128.24, 128.74, 128.97, (C_{Ar}).

4.8 Reactions of diazo[bis(4-methylphenyl)]methane with methyl 4,6-O-benzylidene-α-D-mannopyranoside

4.8.1 Tin(II) chloride catalyzed

Methyl 4,6-*O*-benzylidene-α-D-mannopyranoside, 141 mg, 0.5 mmol, was placed in a dry 10 mL round bottom flask and dissolved in 10 mL of dry DME. Tin(II) chloride, 12.5 mg, 0.0659 mmol, was added followed by diazo-[*bis*-(4-methylphenyl)methane], 167 mg, 0.75 mmol, (1.5 eq). The reaction was followed by TLC (4:1 hexane/EtOAc) and by HPLC. After 26 hours, the reaction mixture was evaporated on a rotary evaporator (~55°C, -1 bar) and chromatographed on a column of silica gel (20x 2.2 mm) using 4:1 hexane/EtOAc yielding methyl 4,6-*O*-benzylidene-3-*O*-di(4-methylphenyl)methyl-α-D-mannopyranoside, 190 mg, 79.8%.

4.8.2 Tin(II) bromide catalyzed

Methyl 4,6-*O*-benzylidene-α-D-mannopyranoside, 141 mg, 0.5 mmol, was placed in a dry 10 mL round bottom flask and dissolved in 10 mL of dry DME. Tin(II) bromide, 18.0 mg, 0.0646 mmol, was added followed by diazo-[*bis*-(4-methylphenyl)methane], 167 mg, 0.75 mmol, (1.5 eq). The reaction was followed by TLC (4:1 Hexane/EtOAc). After 21 hours, the reaction mixture was evaporated on a rotary evaporator at about 55°C and was loaded on to a column of silica gel (2.2x 20 cm) packed with 4:1 hexane/EtOAc. About 500 mL of 4:1 hexane/EtOAc was used to collect forty about 12 mL fractions. Fractions 18-33 were pooled and evaporated on a rotary evaporator at ~40°C to give methyl 4,6-*O*-benzylidene-3-*O*-di(4-methylphenyl)methyl-α-D-mannopyranoside, 220 mg, 92.4%.

Methyl 4,6-*O*-benzylidene-3-*O*-*di*-(4-methylphenyl)methyl-α-D-mannopyranoside: SP251109C ^{1}H NMR (400 MHz, *CDCl$_3$* δ ppm 2.23 (s, 3H, -PhCH_3), 2.25 (s, 3H,-PhCH_3), 2.62 (broad, d, *J* = 1.00 Hz, 1H, 2-OH), 3.25 (s, 3H, OMe), 3.69 (m, 1H, H-5), 3.78 (t, *J* = 10.22, 10.22 Hz, 1H, H-6A), 3.89 (dd, *J* = 9.52, 3.51 Hz, 1H, H-3), 3.96 (m, 1H, H-2), 4.05 (dd, *J* = 12.08, 6.74 Hz, 1H, H-6B), 4.19 (dd, *J* = 10.03, 4.65 Hz, 1H, H4), 4.67 (d, *J* = 1.22 Hz, 1H, H1),

5.55 (s, 1H, C<u>H</u>Ph2), 5.66 (s, 1H, C<u>H</u>Ph), 6.97-7.47 (m, 13H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 21.17, (CH_3), 21.21, (CH_3), 54.93, (O<u>C</u>H_3), 63.17, (C_3), 68.98, (C_2), 69.90 (C_5), 74.41, (C_4), 78.66, (C_6), 82.66, (C_1), 101.02, (<u>C</u>HPh_2), 101.66, (<u>C</u>HPh), 126.15, 127.13, 127.26, 128.21, 128.92, 128.39, (C_{Ar}).

4.9 Reactions of diazo[bis(4-methoxyphenyl)]methane with methyl 4,6-O-benzylidene-α-D-mannopyranoside

4.9.1 Tin(II) chloride catalyzed

Methyl 4,6-*O*-benzylidene-α-D-mannopyranoside, 141 mg, 0.5 mmol, was placed into a dry 10 mL round bottom flaks and dissolved in 10 mL of dry DME. Tin(II) chloride, 12.5 mg, 0.0659 mmol, was added followed diazo[*bis*-(4-methoxyphenyl)]methane, 190 mg, 0.75 mmol. Bubbles evolved from the solution immediately. The reaction was followed by TLC (4:1 Hexane/EtOAc) and by HPLC. The reaction solution rapidly evolved bubbles and went from a dark purple to a light purple color in several minutes. After 15 minutes, the solvent was removed on a rotary evaporator at about 65°C and run on a 2.2cm x 25 cm column of silica gel eluting with 4:1 hexane/ethyl acetate. Sixty 15 mL fractions were collected. Fractions 16-40 were pooled giving methyl 4,6-*O*-benzylidene-3-O-di(4-methoxyphenyl)methyl-□-D-mannopyranoside, 147 mg, 58.2%.

b)Tin(II) bromide catalyzed

Methyl 4,6-*O*-benzylidene-*α*-D-mannopyranoside, 141 mg, 0.5 mmol, was placed into a dry 10 mL round bottom flaks and dissolved in 10 mL of dry DME. Tin(II) bromide, 18.0 mg, 0.0646mmol, was added followed by diazo[*bis*-(4-methoxyphenyl)]methane, 190 mg, 0.75 mmol (1.5 eq). Bubbles evolved from the solution immediately. The reaction was followed by TLC (4:1 hexane/EtOAc) and by HPLC. The reaction solution rapidly evolved bubbles and went from a dark purple to a light purple color in less than 15 minutes. The solvent was removed on a rotary evaporator at about 65°C and run on a 2.2 cm x 25 cm column of silica gel packed with 4:1 hexane/ethyl acetate. 52 ~15 mL tubes were collected

by eluting 600 mL of 4:1 hexane/ethyl acetate. Fractions 35-52 were pooled and gave methyl 4,6-*O*-benzylidene-3-*O*-di(4-methoxyphenyl)methyl-α-D-mannopyranoside, 154 mg, 61.0%.

Methyl 4,6-*O*-benzylidene-3-*O*-*bis*(4-methoxyphenyl)methyl-α-D-mannopyranoside: NMR: SP210610A ^{1}H NMR (400 MHz, *CDCl*$_3$ δ ppm 1.49 (s, 3H, OC<u>H</u>$_3$), 1.56 (s, 1H, OCH$_3$), 2.72 (d, broad, *J* = 1.01 Hz, 1H, 2-OH), 3.34 (s, 3H, OCH$_3$), 3.59-3.83 (m, 4H, H-6A, H-2, H-3, H-4), 3.85-3.89 (m, 2H, H-5, H-6B), 3.94 (td, *J* = 6.38, 3.24, 3.24 Hz, 1H, H-2), 4.19 (t, *J* = 9.59, 9.59 Hz, 1H, H-4), 4.73 (d, *J* = 1.21 Hz, 1H, H-1), 5.77 (s, 1H, C<u>H</u>Ar$_2$), 6.85-7.31 (m, 13H, aromatic).

4.10 Reactions of diazo[bis(4-chlorophenyl)]methane with methyl 4,6-O-benzylidene-α-D-mannopyranoside

4.10.1 Tin(II) chloride catalyzed

Methyl 4,6-*O*-benzylidene-α-D-mannopyranoside, 141 mg, 0.5 mmol, was placed into a dry 10 mL round bottom flaks and dissolved in 10 mL of dry DME. Tin(II) chloride, 12.5 mg, 0.0659 mmol, was added followed diazo[*bis*-(4-chlorophenyl)]methane, 196.6 mg, 0.75 mmol (1.5 eq). The reaction was monitored by TLC (4:1 hexane/ethyl acetate) and by HPLC. After about 24 hours, the catalyst had fallen out of solution so an additional 16.6 mg tin(II) chloride was added. The reaction was complete after 56 hours and the DME was removed on the rotary evaporator and loaded onto a 2.2x20 cm column of silica gel eluting with 4:1 hexane/ethyl acetate. Thirty six about 15 mL fractions were collected; fractions 1-36 were pooled and the solvent removed to give methyl 4,6-*O*-benzylidene-3-O-di(4-chlorophenyl)methyl-α-D-mannopyranoside, 189.1 mg, 73.1%.

Methyl 4,6-*O*-benzylidene-3-*O*-di(4-chlorophenyl)methyl-α-D-mannopyranoside: ^{1}H NMR (400 MHz, Solvent δ ppm 2.47 (s, broad, 1H, 2-OH), 3.27 (s, 3H, OMe), 3.69 (m, 1H, H-5), 3.78 (t, J = 10.22, 10.22 Hz, 1H, H6A), 3.84 (dd, *J* = 9.60, 3.45 Hz, 1H, H-2??), 3.94 (dd, *J* = 3.37, 1.31 Hz, 1H, H-3??), 4.05 (m, 1H, H6B), 4.19 (dd, *J* = 10.04, 4.60 Hz, 1H, H-4), 4.68 (d, *J* = 1.25 Hz, 1H, H-1), 5.52 (s, 1H, C<u>H</u>Ph$_2$), 5.65 (s, 1H, C<u>H</u>Ph), 7.10-7.19 (m, 1H), 7.22-7.26 (m, 5H, CH<u>Ph</u>), 7.32-7.40-(m, 8H, CH(<u>Ph</u>Cl)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 55.01, (O<u>C</u>H$_3$), 63.21, (C_3), 68.93, (C_2), 70.01 (C_5), 74.79, (C_4), 78.58, (C_6), 81.74, (C_1), 100.98, (<u>C</u>HPh$_2$), 101.84, (<u>C</u>HPh), 126.11, 128.31, 128.43, 128.53, 128.60, 129.03, 129.15(C_{Ar}).

4.10.2 Tin(II) bromide catalyzed

Methyl 4,6-*O*-benzylidene-α-D-mannopyranoside, 141 mg, 0.5 mmol, was placed into a dry 10 mL round bottom flaks and dissolved in 10 mL of dry DME. Tin(II) bromide, 18.0 mg, 0.0646mmol, was added followed

by diazo[*bis*(4-chlorophenyl)]methane, 196.6 mg, 0.75 mmol (1.5 eq). The reaction was monitored by TLC (4:1 Hexane/ethyl acetate) and by HPLC. After about 24 hours, the catalyst had fallen out of solution so an additional 18 mg of tin(II) bromide was added. The reaction was complete after 53 hours and the DME was removed on the rotary evaporator and loaded onto a 2.2x20 cm column of silica gel eluting with 4:1 hexane/ethyl acetate. Forty about 15 mL fractions were collected; fractions 1-36 were pooled and the solvent removed to give methyl 4,6-*O*-benzylidene-3-*O*-di(4-chlorophenyl)methyl-α-D-mannopyranoside, 173.3 mg, 67.1%.

*4.11 Reactions of 9-diazofluroene with methyl 4,6-O-*benzylidene-*α-D-mannopyranoside*

4.11.1 Tin(II) chloride catalyzed

Methyl 4,6-*O*-benzylidene-α-D-mannopyranoside, 141 mg, 0.5 mmol, was placed into a dry 10 mL round bottom flaks and dissolved in 10 mL of dry DME. Tin(II) chloride, 12.5 mg, 0.0659 mmol, was added followed diazofluorene, 144 mg, 0.75 mmol (1.5 eq). An additional 12 mg of $SnCl_2$ was added after 30 hours as the catalyst had fallen out of solution as a white precipitate. After 66 hours, the solvent was removed on a rotary evaporator at about 55°C. The material was loaded onto a 2.2x20 cm column of silica gel packed with 4:1 Hexane/Ethyl Acetate. 500 mL of 4:1 Hexane/Ethyl Acetate was run and collected as forty six 12.5 mL fractions. Fractions 28-46 were pooled and the solvent was removed on the rotary evaporator at about 45°C to give methyl 4,6-*O*-benzylidene-3-*O*-fluorenyl-α-D-mannopyranoside, 150 mg, 67.3%.

4.11.2 Tin(II) bromide catalyzed

Methyl 4,6-*O*-benzylidene-α-D-mannopyranoside, 141 mg, 0.5 mmol, was placed into a dry 10 mL round bottom flaks and dissolved in 10 mL of dry DME. Tin(II) bromide, 18.0 mg, 0.0646mmol, was added followed by diazofluorene, 144 mg, 0.75 mmol (1.5 eq). After 24 hours, the catalyst had fallen out of solution and an additional 18 mg was added. After 48 hours, an additional 18 mg of catalyst was added. After 67

hours, the solvent was removed on a rotary evaporator at about 55°C. The material was loaded onto a 2.2x20 cm column of silica gel packed with 4:1 Hexane/Ethyl Acetate. Five hundred mL of 4:1 hexane/Ethyl Acetate was run and collected as forty six about 15 mL fractions. Fractions 28-46 were pooled and the solvent was removed on the rotary evaporator at about 45°C giving methyl 4,6-*O*-benzylidene-3-*O*-fluorenyl-α-D-mannopyranoside, 126 mg, 56.5%.

Methyl 4,6-*O*-benzylidene-3-*O*-fluorenyl-α-D-mannopyranoside. ^{1}H NMR (400 MHz, *CDCl$_3$* δ ppm 2.70 (s, broad, 1H, 2-OH), 3.28 (s, 3H, OMe), 3.77 (m, 2H, H-5 and XXX), 4.07 (m, 2H, XXX), 4.21 (m, 1H), 3.88 (d, *J* = 1.66 Hz, 1H, XXX), 4.67 (d, *J* = 1.36 Hz, 1H, H-1), 5.59 (s, 1H, CHFl), 5.68 (s, 1H, CHPh), 7.10-7.62 (m, 13H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 55.00, (OCH_3), 63.39, (C_3), 68.97, (C_2), 70.92 (C_5), 75.62, (C_4), 78.37, (C_6), 82.24, (C_1), 101.05, (CFl), 102.03, (CHPh), 119.97, 120.00, 125.57, 126.29, 127.74, 128.23, 129.04, 129.25, 129.34 (C_{Ar}).

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III

Manuscript III - Regioselective mono-alkylation of methyl 4,6-*O*-α-D-glucopyranoside using tin(II) halides

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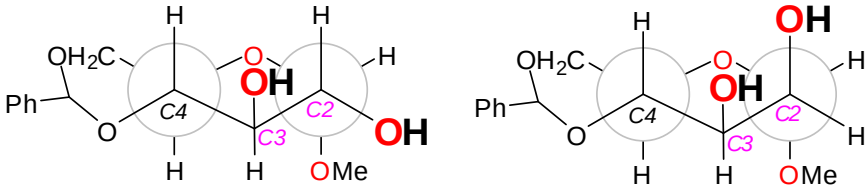
1 Introduction

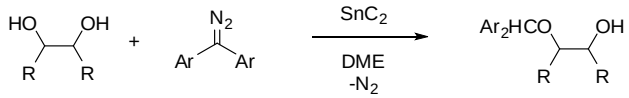
Recent work on the use of tin(II) halide catalysts for the introduction of diaryl ethers to 4,6-protected mannopyranoside systems using diazo compounds has demonstrated diaryl diazo compounds have a greater selectivity for the 3-OH position while diazofluorene has an incomplete selectivity for the 2-OH position (**Manuscript II).** Further work with 4,6-*O*-isopropylidene-a-D-mannopyranosides has demonstrated that high concentrations of the tin(II) chloride catalyst favor alkylation at the 3-OH position when diary diazo compounds are used while high catalyst concentrations favor reaction at the 2-OH position when diazofluorene is used (Petursson et al., 2014).

The vicinal diol pair of both methyl 4,6-*O*-benzylidene-α-D-glucopyranoside and methyl 4,6-*O*-benzylidene-α-D-mannopyranoside have dihedral angles of 60° although they have *trans* and *cis*-configurations, respectively (Figure 1). Initial work on tin(II) chloride-catalzyed reactions of Methyl 4,6-*O*-benzylidene- α -D-glucopyranoside with diazodiphenylmethane showed poor results which was attributed to the trans configuration of the vicinal diol pair (Petursson & Webber, 1982; Petursson, 1979).

Figure 1 – Newman projections of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside and the methyl 4,6-*O*-benzylidene-α-D-glucopyranoside



Subsequent work on *cis*- and *trans*-1,2-hexanediol demonstrated that tin(II) chloride catalyzed reactions with diazodiphenylmethane occur more slowly in the case of the trans system. and methyl 4,6-*O*-α-benzylidene-α-D-mannopyranoside demonstrated that the reaction does take place but much more slowly than with *cis*-1,2-hexandiol or the cis-diol pair of Methyl 4,6-*O*-benzylidene-mannopyranoside. Furthermore, catalyst destruction was observed in the case of the *trans*-hexanediol system Ultimately, the use of diazodiphenylmethane was previously used with a tin(II) chloride as a catalyst to protect methyl 4,6-*O*-benzylidene-α-D-glucopyranoside in 88.7% overall yield of which 19.6 was the corresponding 2-*O*-benzhydryl ether and 69.1% of the 3-*O* ether. (Pétursson, 2001).



Scheme 1 – $SnCl_2$-catalzyed mono-etherification of vicinal diols with diaryldiazomethane

This study focuses upon the use of tin(II) chloride and tin(II) bromide as catalysts for the introduction of diaryl diazo compounds of methyl 4,6-*O*-benzylidene α-D-glucopyranoside.

2 Results and Discussion

Five diazo compounds (**Figure 3**), diazo-[*bis*(4-methoxyphenyl)methane] (**1**), diazo-[*bis*(4-methylphenyl)methane] (**2**), diazodiphenylmethane (**3**), diazo-[*bis*(4-chlorophenyl)methane] (**4**), or

diazofluorene (**5**) were prepared in good yields via the oxidation of the corresponding hydrazone as previously described (Petursson, 1979).

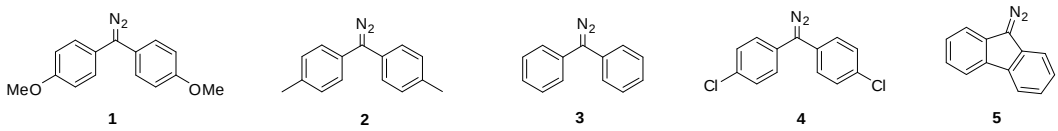


Figure 3 – Diazo compounds used in this study; diazo-[*bis*(4-methoxyphenyl)methane] (**1**), diazo-[*bis*(4-methylphenyl)methane] (**2**), diazodiphenylmethane (**3**), diazo-[*bis*(4-chlorophenyl)methane] (**4**), or diazofluorene (**5**)

Reactions of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**6**) with diazo compounds either diazodiphenylmethane (**1**), diazo-[*bis*(4-methylphenyl)methane] (**2**), diazo-[*bis*(4-methoxyphenyl)methane] (**3**), diazo-*bis*-[(4-chlorophenyl)methane] (**4**), or diazofluorene (**5**) in the presence of tin(II) chloride or tin(II) bromide resulted in a mixture of the corresponding 2-*O*- and 3-*O*- ethers. The reactions were followed kinetically via HPLC (**data not shown**). The quantities of 2-*O* and 3-*O* ether end products isolated were in very good agreement product formation observed on the HPLC. The reaction times and isolated yields for each combination of tin(II) halide and diazo compound are presented in Table 1.

Table 1 - Reaction times and yields of mono-etherifications of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside with $SnCl_2$ and $SnBr_2$

	$SnCl_2$			$SnBr_2$		
Diazo Compound	**Yield** (%)	**2:3**	**Time** (hrs)	**Yield** (%)	**2:3**	**Time** (hrs)
1 Diazo *bis*(4-methoxyphenyl)methane	44.8	0:1	4[d]	49.4	0:1	3[d]
2 Diazo *bis*(4-methylphenyl)methane	49.3	0:1	0.25[a]	55.8	0:1	0.25[b]
3 Diazodiphenylmethane	94.0	0.34	48	98.1	0.28	46*
4 Diazo *bis*(4-chlorophenyl)methane	89.2	0:1	56*	85.1	0:1	53**[c]
5 Diazofluorene	ND	ND	>168*[e]	ND	ND	>168*[e]

*catalyst fell out of solution, additional SnX_2 added, [a] additional 1 eq of diazocompound added, [b] additional 1.5 eq of diazocompound added, [c] additional 2.5 eq of diazocompound added, [d] additional 5 eq of diazocompound added, [e] greater than 10 additional equilvance required; ND – Not determined

The tin(II) halide reactions involving diazodiphenylmethane and diazo-[*bis*-(4-chlorophenyl)methane)] resulted in good overall yields. The reaction of diazodiphenylmethane gave a mixture of the 2-*O* and 3-*O* ether in less than 48 hours with no problems involving catalyst precipitation being observed. The reactions involving diazo-[*bis*-(4-chlorophenyl)methane)], however, resulted in the 3-*O*-ether exclusively although the addition of an additional 1.5 molar equivalence of the diazo compound was required to drive the reaction to completion.

The reactions using diazo *bis*(4-methylphenyl)methane and diazo *bis*(4-methoxyphenyl)methane gave the corresponding 3-*O*-ether. Both reactions involving diazo *bis*(4-methylphenyl)methane required the addition of 1 and 1.5 molar equivalence of the diazo compound to reach completion. The overall yield in both cases was low. These reactions were repeated and gave nearly identical yields (results not shown). Both the tin(II) chloride and tin(II) bromide reactions with diazo *bis*(4-methoxyphenyl)methane required the addition of 5 extra molar equivalence of the diazo compounds and both tin(II) halide reactions gave poor yields. The separation of these reactions mixtures was complicated by the large quantity of co-products from side reactions involving the diazo compound.

Previous reactions involving tin(II) halide reactions of methyl 4,6-*O*-isopropylidene- and methyl 4,6-*O*-benzylidene-α-D-mannoyranoside with diazo *bis*(4-methylphenyl)methane demonstrated yields in excess of 85%

(Manuscript II). Here, methyl 4,6-*O*-benzylidene-α-D-glucopyranoside gave consistently poor yields with both tin(II) chloride and tin(II) bromide but excellent 3-OH selectivity but did require the addition of an additional 1.5 molar equivalence of the diazo compound. TLC examination indicated that all of the starting material had reacted and no traces of the di-ether were observed.

Interestingly, the attempted reaction of tin(II) chloride and tin(II) bromide-catalyzed reactions of diazofluorene and methyl 4,6-*O*-benzylidene-α-D-glucopyranoside required many additions of tin(II) halide catalyst due to catalyst precipitation. Additionally, over 10 molar equivalence of diazofluorene needed to be added over the first seven days of the reaction. After seven days, large quantities of the starting material was still apparent on the TLC plate and both sets of reactions were abandoned. Preliminary HPLC analysis suggest that the 3-*O*-fluorenyl ether was favored and no peaks that could be attributed to the 2-*O*-ether were detected.

Previous work by (Pétursson, 2001) with and *cis*- and *trans*-1,2-heaxanediol showed that tin(II) chloride-catalyzed reactions had higher pseudo first order rate constants using lower concentrations of catalyst. Interestingly, preparative-scale work using methyl 4,6-*O*-benzylidene- α-D-glucopyranoside using a tin(II) chloride concentration of only 3 mM was complete within 5 hours. Here, a slightly higher catalyst concentration (3.3 mM) was used and had a reaction time of 48 hours (compare with HPLC data).

The role of tin(II) chloride concentration on reactions between diazo compounds and 4,6-*O*-isopropylidene α-D-mannopyranoside found that reactions with diaryldiazo compounds favored reactions at the 3-OH position at high catalyst concentrations whereas more of the 2-*O* ethers were formed at low concentrations of catalyst. The opposite trend was observed trend was observed with diazofluorene with high catalyst concentrations favoring the 2-OH (Petursson et al., 2014). Further work with methyl 4,6-benzyldiene-α-D-gluopyranoside is needed to see if a similar phenomenon regarding tin(II) halide is observed. Furthermore,

fine-tuning of the catalyst concentration may result increased catalyst stability and shorter reaction times.

3 Conclusions

Tin(II) halide catalyzed etherfications of methyl 4,6-*O*-benzylidene-α-D-gluopyranoside resulted in regioselective protection of the 3-OH position when diazo-[*bis*-(4-methylphenyl)methane], diazo-[*bis*-(4-methoxyphenyl)methane], and diazo-[*bis*-(4-chlorophenyl)methane] were used as alkyl donors with overall yields of approximately 50% except for the chloro derivative which gave 85-89% yield. Reaction series involving diazodiphenyl methane resulted in a mixture of the 2-*O* and 3-*O* ethers with an overall yields greater than 94%. Reactions with long reaction times frequently suffered from the catalyst falling out of solution necessitating the addition of additional catalyst and diazo compounds. Attempted reactions involving diazofluorene required reaction times in excess of one week and greater than 10 additional equivalence of the diazo compound.

4 Experimental

4.1 General methods – All reagents were obtained from Sigma-Aldrich unless otherwise noted. 1,2-dimethoxyethane (DME) was distilled from and stored over sodium. Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, Anhydrous tin(II) chloride and tin(II) bromide were obtained from Sigma Aldrich. Diazo compounds were prepared as previously describe (Petursson, 1979).

Preparative chromatography was performed using silica gel (60Å, 230-400 mesh); column dimensions were 2.2x20 cm unless otherwise noted. Where chromatographic separations were incomplete, quantities of 2- and 3-ethers were estimated from the Ar_2-C<u>H</u>O- peak in the proton NMR spectrum. Thin-layer chromatography was performed on Silica gel TLC cards with a fluorescent indicator were obtained from Fluka; TLC plates were visualized using a UV lamp (λ254) and sprayed with 0.2% w/v cerium(IV) sulfate 5% w/v ammonium molybdate in 2.0 M sulfuric acid and visualized by heating. ^{1}H and ^{13}C NMR Spectrum were obtained

using a Bruker AV400 Nuclear Magnetic Resonance spectrometer using $CDCl_3$ using trimethylsilane (TMS) as an external standard. All melting points were obtained using a Thiel tube and are uncorrected. HPLC analysis was performed on a Shimadzu UFLC using two 20-AD solvent pumps and a 20-A UV-VIS Detector at 254 nm, with a DGU-$20A_3$ online degasser and a Rheodyne manual sample injector equipped with a 20 µL loop. Separation was achieved using a reverse phase column (Supleco, 150mm x 4.6 mm, 3 µm) with a guard column (Supelco, 20mm x 4.0, 3 µm) mm C18 guard cartridge. Mobile phase was rigorously degassed (sonic bath, 1 hour) prior to use and was delivered at a flow rate of 1 mL per minute composed of unbuffered 20% water and 80% methanol. 10 µL of reaction sample was diluted with 240 µL of mobile phase prior to injection; injection volume was 20 µL. Retention times of analytes were verified using characterized products from relevant separations.

4.2 Reactions of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside with diazodiphenylmethane

4.2.1 Tin(II) chloride catalyzed

Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside ,282.3 mg, 1 mmol, was dissolved in 20 mL of dry DME; of $SnCl_2$, 12.5 mg, was added followed by 679.8 mg (1.5 mmol, 1.5 eq.) of diphenyldiazomethane. The reaction was followed by TLC (4:1 Hexane/EtOAc) and by HPLC. After 58 hours, the solvent was removed on a rotary evaporator (65°C, -1 bar) and run on a 2.2 cm x 25 cm column of silica gel packed with 19:1 hexane/ethyl acetate. 130 10 mL tubes were collected by eluting a 19:1 to 4:1 hexane/ethyl acetate gradient. Fractions 72-92 were pooled and reduced in volume yielding 107.2 mg of methyl 4,6-*O*-benzylidene-2-*O*-benzhydryl-α-D-glucopyranoside was recovered Fractions 104 to 124 were pooled and reduced in volume yielding 314.4 mg of the 3-ether. 94.0 % overall yield.

4.2.2 Tin(II) bromide Catalyzed

Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside ,282.3 mg, 1 mmol was dissolved in 20 mL of dry DME; 18 mg of $SnBr_2$ was added followed by 679.8 mg (1.5 mmol, 1.5 eq.) of diphenyldiazomethane. The reaction was followed by TLC (4:1 Hexane/EtOAc) and by HPLC. An additional 5 mg of $SnBr_2$ was added after 48 hours. After 56 hours, the color had diminished and TLC showed no traces of starting material the solvent was removed on a rotary evaporator (65°C, -1 bar) and run on a 2.2cm x 25 cm column of silica gel packed with 19:1 hexane/ethyl acetate. 90 15 mL tubes were collected by eluting a 19:1 to 4:1 hexane/ethyl acetate gradient. Fractions 44-57 were pooled and reduced in volume yielding 89.6 mg of methyl 2-O-benzhydryl-4,6-O-benzylidene-α-D-glucopyranoside was recovered. Fractions 62 to 87 were pooled and reduced in volume yielding 324.1 mg of the 3-ether. 98.1 % overall yield.

Methyl 2-*O*-diphenylmethyl-4,6-*O*-benzylidene-α-D-glucopyranoside: ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm 2.40 (s, broad, 1H, 3-OH), 3.25 (s, 3H, OCH_3), 3.40 (t, *J* = 9.40, 9.40 Hz, 1H), 3.50 (dd, *J* = 9.27, 3.65 Hz, 1H), 3.60 (t, *J* = 10.29, 10.29 Hz, 1H), 3.75 (dt, *J* = 9.93, 9.81, 4.79 Hz, 1H), 4.16 (m, 2H), 4.42 (d, *J* = 3.62 Hz, 1H), 5.43 (s, 1H, CHPh), 5.58 (s, 1H, $CHPh_2$), 7.27 (m, 15H, aromatic).

Methyl 3-*O*-diphenylmethyl-4,6-*O*-benzylidene-α-D-glucopyranoside: ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm 2.40 (s, broad, 1H, 3-OH), 3.25 (s, 3H, OCH_3), 3.40 (t, *J* = 9.40, 9.40 Hz, 1H), 3.50 (dd, *J* = 9.27, 3.65 Hz, 1H), 3.60 (t, *J* = 10.29, 10.29 Hz, 1H), 3.75 (dt, *J* = 9.93, 9.81, 4.79 Hz, 1H), 4.16 (m, 2H), 4.42 (d, *J* = 3.62 Hz, 1H), 5.43 (s, 1H, CHPh), 5.58 (s, 1H, $CHPh_2$), 7.27 (m, 15H, aromatic).

4.3 Reactions of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside with diazo-[*bis*-(4-methylphenyl)methane]

4.3.1 Tin(II) chloride catalyzed

Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside**,** 282.3 mg, 1 mmol, was dissolved in 20 mL of dry DME; $SnCl_2$, 12.5 mg, of was added followed by diazo-[*bis*-(4-methylphenyl)methane], 444.6 mg, 2 mmol. The reaction was followed by TLC (4:1 Hexane/EtOAc). Additional diazo-[*bis*-(4-methylphenyl)methane], 222.2 mg, 1 mmol, was added after several minutes. After 15 minutes the color had diminished and the solvent was removed on a rotary evaporator (65°C, -1 bar) and run on a 2.2cm x 25 cm column of silica gel packed with 9:1 hexane/ethyl acetate. 55x10 mL tubes were collected by eluting a 9:1 to 4:1 hexane/ethyl acetate gradient. Fractions 23-50 were pooled and reduced in volume yielding 235.0 mg of methyl 4,6-*O*-benzylidene-3-*O*-benzhydryl-α-D-glucopyranoside was recovered. 49.3 % overall yield.

4.3.2 Tin(II) bromide catalyzed

Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside**,** 282.3 mg, 1 mmol, was dissolved in 20 mL of dry DME; $SnBr_2$,12.5 mg, of was added followed by 444.6 mg (2 mmol, 2 eq.) of diazo-[*bis*-(4-methylphenyl)methane]. The reaction was monitored by TLC (4:1 Hexane/EtOAc) and by HPLC. The reaction solution rapidly evolved bubbles and went from a dark purple to a light purple color in 10 minutes. An additional 222.2 mg, 1 mmol) of dimethyldiphenyldiazomethan was added. After 15 minutes the color had diminished and the solvent was removed on a rotary evaporator (65°C, -1 bar) and run on a 2.2cm x 25 cm column of silica gel packed with 9:1 hexane/ethyl acetate. 55x10 mL tubes were collected by eluting a 9:1 to 4:1 hexane/ethyl acetate gradient. Fractions 23-50 were pooled and reduced in volume yielding 235.0 mg of methyl 3-*O*-benzhydryl-4,6-*O*-benzylidene-α-D-glucopyranoside was recovered. 49.3 % overall yield.

4.4 Reactions of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside with diazo-[*bis*-(4-chlorophenyl)methane]

4.4.2 Tin(II) chloride catalyzed

Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside**,** 141.2 mg, 0.5 mmol, was dissolved in 10 mL of dry DME; $SnCl_2$,6 mg, of was added followed by 329.9 mg, 1.75 mmol, of diazo-[*bis*-(4-chlorophenyl)methane]. The reaction was monitored by TLC (4:1 Hexane/EtOAc). An additional 6 mg of $SnCl_2$ was added after 24 hours. After 56 hours, the solvent was removed on a rotary evaporator (65°C, -1 bar) and run on a 2.2cm x 25 cm column of silica gel packed with 9:1 hexane/ethyl acetate. 66x10 mL tubes were collected by eluting a 4:1 hexane/ethyl acetate gradient. Fractions 34-60 were pooled and reduced in volume yielding 230.8 mg of methyl 3-*O*-benzhydryl-4,6-*O*-benzylidene-α-D-glucopyranoside was recovered. 89.2 % overall yield.

4.4.1 Tin(II) bromide catalyzed

Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside**,** 141.2 mg, 0.5 mmol, was dissolved in 10 mL of dry DME; $SnBr_2$,9 mg, of was added followed by 329.9 mg, 1.75 mmol, of diazo-[*bis*-(4-chlorophenyl)methane]. The reaction was monitored by TLC (4:1 Hexane/EtOAc). An additional 27 mg of $SnBr_2$ and 270 mg of diazo-[*bis*-(4-chlorophenyl)methane] was added over 36 hours. After 53 hours, the solvent was removed on a rotary evaporator (65°C, -1 bar) and run on a 2.2cm x 25 cm column of silica gel packed with 9:1 hexane/ethyl acetate. 66x10 mL tubes were collected by eluting a 4:1 hexane/ethyl acetate gradient. Fractions 23-42 were pooled and reduced in volume yielding 220.2 mg of methyl 3-*O*-benzhydryl-4,6-*O*-benzylidene-α-D-glucopyranoside was recovered. 85.1 % overall yield.

4.5 Reactions of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside with diazo-[bis-(4-methoxyphenyl)methane]

4.4.2 Tin(II) chloride catalyzed

Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside**,** 282.3 mg, 1 mmol, was dissolved in 20 mL of dry DME; $SnCl_2$,12.5 mg, of was added followed by 635.7 mg, 2.5 mmol, of diazo-[*bis*-(4-methoxyphenyl)methane]. The reaction was monitored by TLC (4:1 Hexane/EtOAc). An additional 1271.4 mg, 5mmol of diazo-[*bis*-(4-methoxyphenyl)methane]. After 15 minutes, the solvent was removed on a rotary evaporator (65°C, -1 bar) and run on a 2.2cm x 25 cm column of silica gel packed with 9:1 hexane/ethyl acetate. 160x10 mL tubes were collected by eluting a 4:1 hexane/ethyl acetate gradient. Fractions 121-150 were pooled and reduced in volume yielding 227.74 mg of methyl 3-*O*-benzhydryl-4,6-*O*-benzylidene-α-D-glucopyranoside was recovered. 44.8 % overall yield.

4.4.1 Tin(II) bromide catalyzed

Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside**,** 282.3 mg, 1 mmol, was dissolved in 20 mL of dry DME; $SnBr_2$,19 mg, of was added followed by 635.7 mg, 2.5 mmol, of diazo-[*bis*-(4-methoxyphenyl)methane]. The reaction was monitored by TLC (4:1 Hexane/EtOAc). An additional 1271.4 mg, 5 mmol of diazo-[*bis*-(4-methoxyphenyl)methane]. After 15 minutes, the solvent was removed on a rotary evaporator (65°C, -1 bar) and run on a 2.2cm x 25 cm column of silica gel packed with 9:1 hexane/ethyl acetate. 160x10 mL tubes were collected by eluting a 4:1 hexane/ethyl acetate gradient. Fractions 132-160 were pooled and reduced in volume yielding 251.3 mg of methyl 3-*O*-benzhydryl-4,6-*O*-benzylidene-α-D-glucopyranoside was recovered. 49.4% overall yield.

4.6 Attempted reactions of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside with diazofluorene

4.6.2 Tin(II) chloride catalyzed

Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, 282.3 mg, 1 mmol, was dissolved in 20 mL of dry DME; $SnCl_2$,12.5 mg, of was added followed by 388.7 mg, 2 mmol, of diazofluorene. The reaction was monitored by TLC (4:1 Hexane/EtOAc). Over the course of 168 hours, an additional 1943 mg of diazofluorene and 62.5 mg of SnCl2 was added; at this time, a large quantity of the starting material remained

4.6.1 Tin(II) bromide catalyzed

Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside**,** 282.3 mg, 1 mmol, was dissolved in 20 mL of dry DME; $SnBr_2$,19 mg, of was added followed by 388.7 mg, 2 mmol, of diazofluorene. The reaction was monitored by TLC (4:1 Hexane/EtOAc). Over the course of 168 hours, an additional 1943 mg of diazofluorene was added at which time a significant quantity of starting material remained.

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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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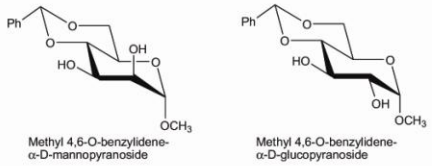

Figure 1. Methyl 4,6-O-benzylidene-α-D-mannopyranoside and the gluco equivalent contain vicinal diol systems, *ax–eq* and *eq–eq* respectively.

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 $SnCl_2.2H_2O$ 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

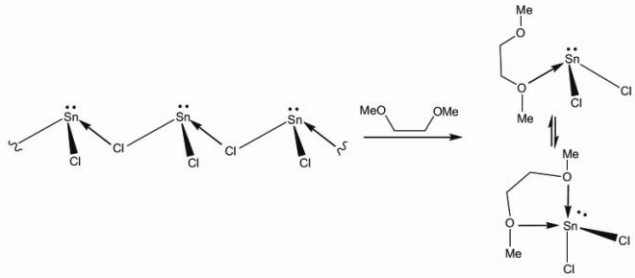

Figure 2. Depolymerisation of $SnCl_2$ chains by donor solvent.

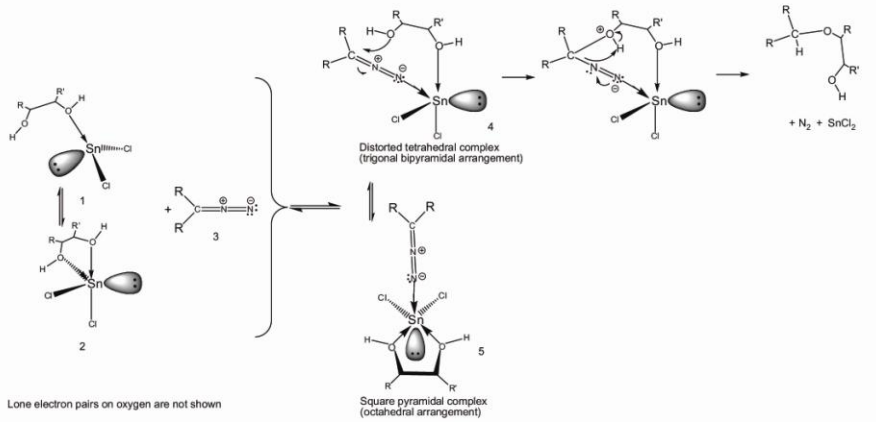

Figure 3. Suggested partial mechanism for the tin(II) chloride catalysed reaction.

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 (%)
$(p\text{-}CH_3C_6H_4)_2CN_2$	98	1.9			76	24		
Total yield (%)	87				60			
$(p\text{-}ClC_6H_4)_2CN_2$	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	

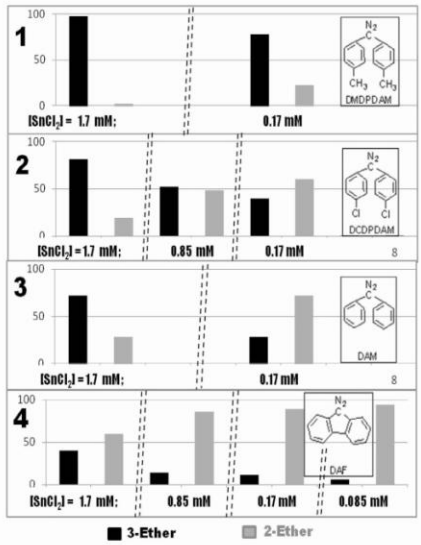

Figure 4. The relative yields of the 3- and the 2-ethers from the etherification reactions of methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside with diazo[bis(4-methylphenyl)]methane (1), diazo[bis(4-chlorophenyl)]methane (2), diazomethane (3) and diazofluorene (4) for varying concentrations of the $SnCl_2$ 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-*CHO*– 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.[22] 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; $C_{23}H_{26}Cl_2O_6$·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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Appendix A - Spectral data for diazo compounds

Table 12 - Summary of Extinction Coefficients of Selected Diazo compounds

Compound	λ_{max} (nm)	$\varepsilon_{@max}$ ($M^{-1}cm^{-1}$)	**Physical characteristics**
Diphenyldiazomethane	525,3	92,02	Red
Dimethyldiphenyldiazomethane	537,6	100,38	Purple
Dichlorodiphenyldiazomethane	520	116,55	Dark red
Dimethoxydiphenydiazomethane	548	100,44	Light purple
Diazofluorene	495,8	18,67	Red-orange

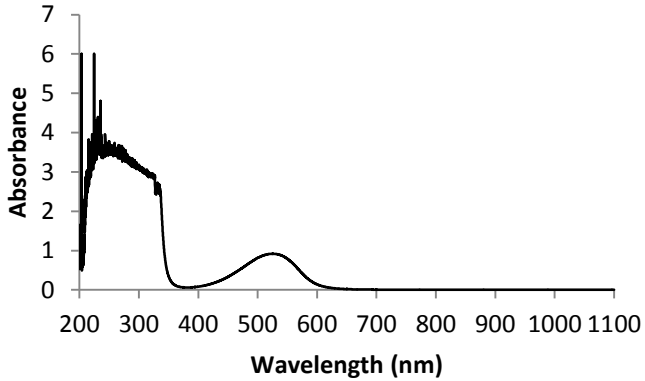


Figure 71 – UV-Visible absorption spectra for diazodiphenylmethane

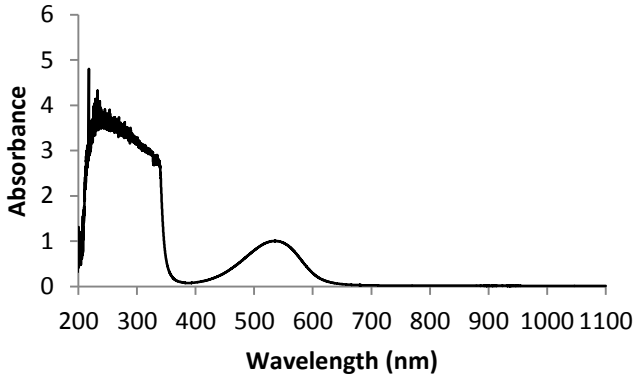


Figure 72 - UV-Visible absorption spectra for diazo-[bis-(4-methylphenyl)methane]

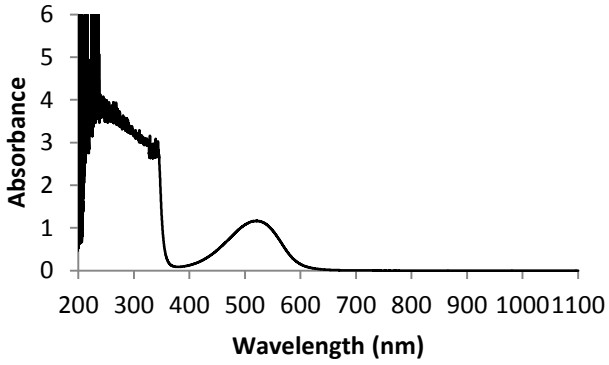


Figure 73 - UV-Visible absorption spectra for diazo-[bis-(4-chlorophenyl)methane]

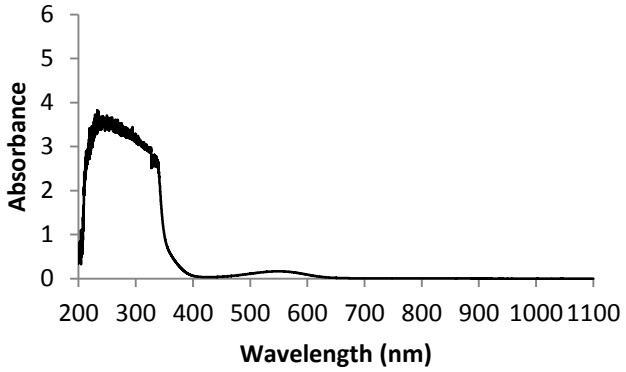


Figure 74 - UV-Visible absorption spectra for diazo-[bis-(4-methoxyphenyl)methane]

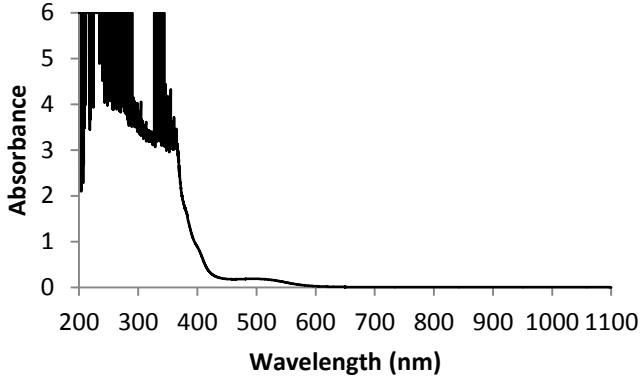


Figure 75 - UV-Visible absorption spectra for diazofluorene

Appendix B – Kinetic data for Magtrieve™ oxidations of diaryl hydrazones

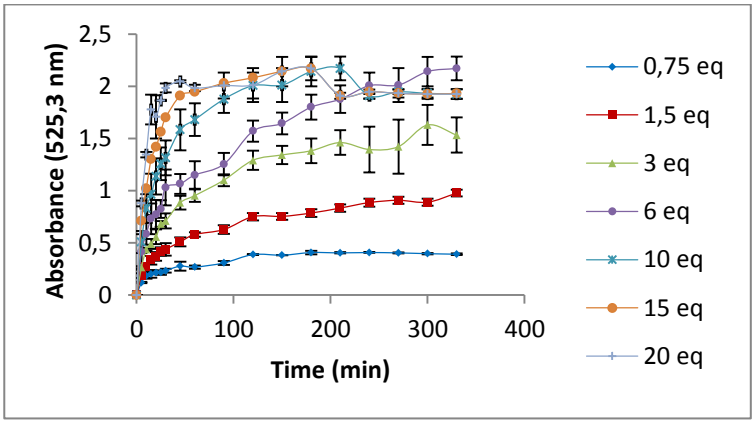


Figure 76 - Kinetic plot of synthesis of diazodiphenyl methane with varying molar equivalence of Magtrieve™. Data points represent average of triplicate values ± standard deviation

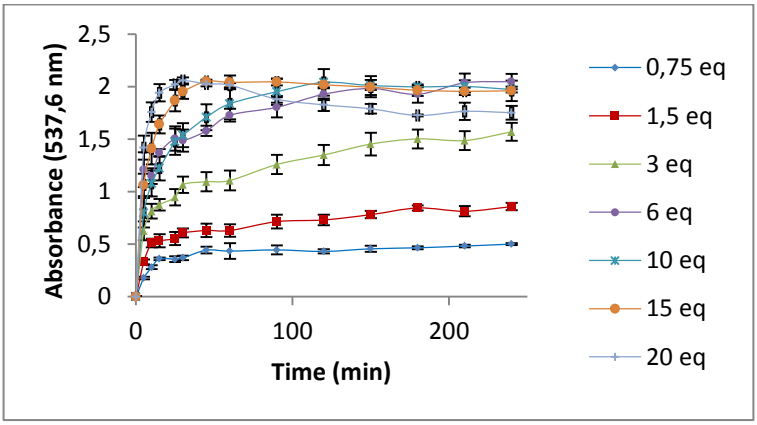


Figure 77 - Kinetic plot of synthesis of diazo *bis*(4-methylphenyl)methane with varying molar equivalence of Magtrieve™. Data points represent average of triplicate values ± standard deviation

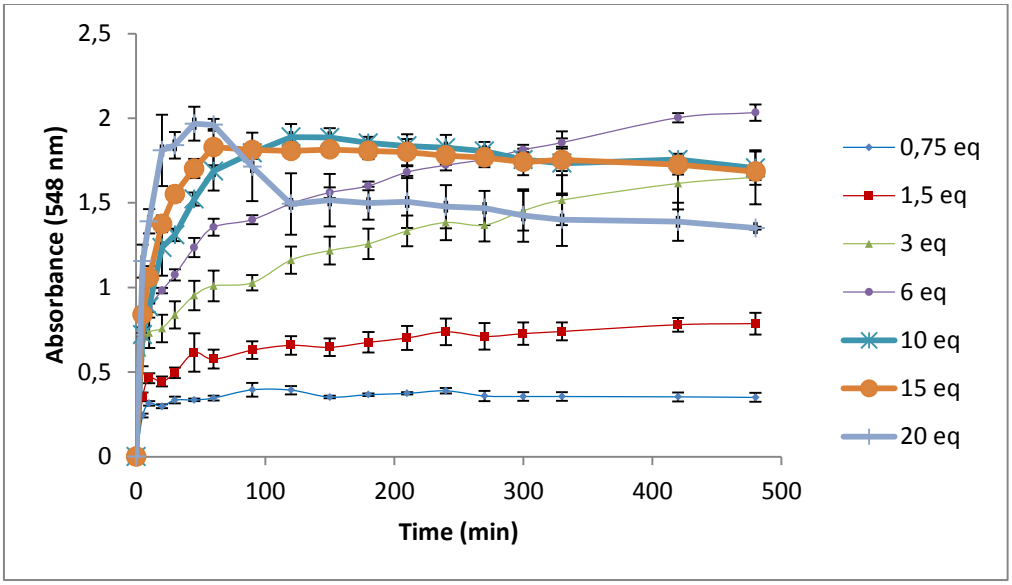


Figure 78 - Kinetic plot of synthesis of Diazo *bis*(4-methoxyphenyl)methane with varying molar equivalence of Magtrieve™. Data points represent average of triplicate values ± standard deviation

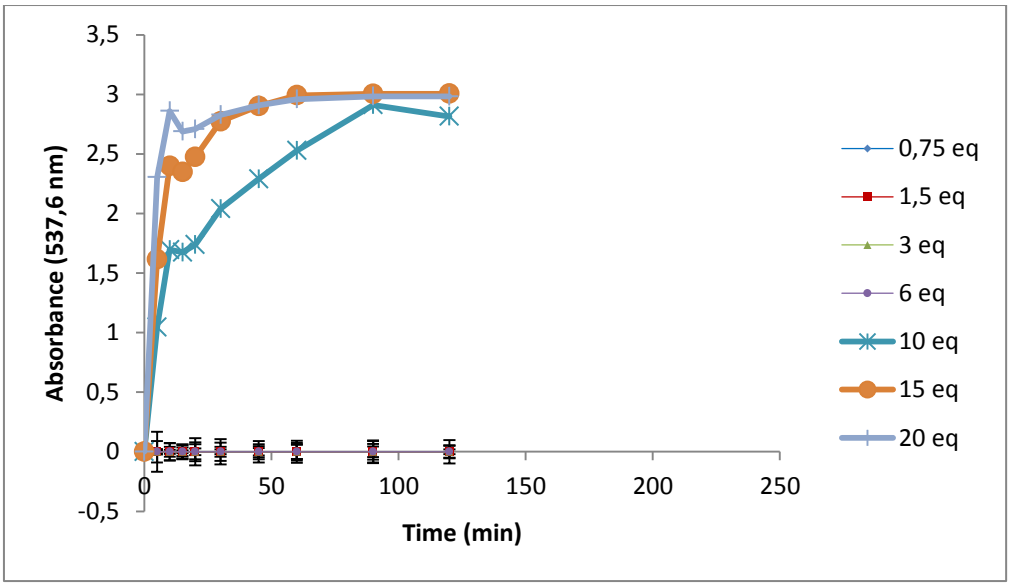


Figure 79 - Kinetic plot of synthesis of diazo *bis*(4-chlorophenyl)methane with varying molar equivalence of Magtrieve™. Data points represent average of triplicate values ± standard deviation

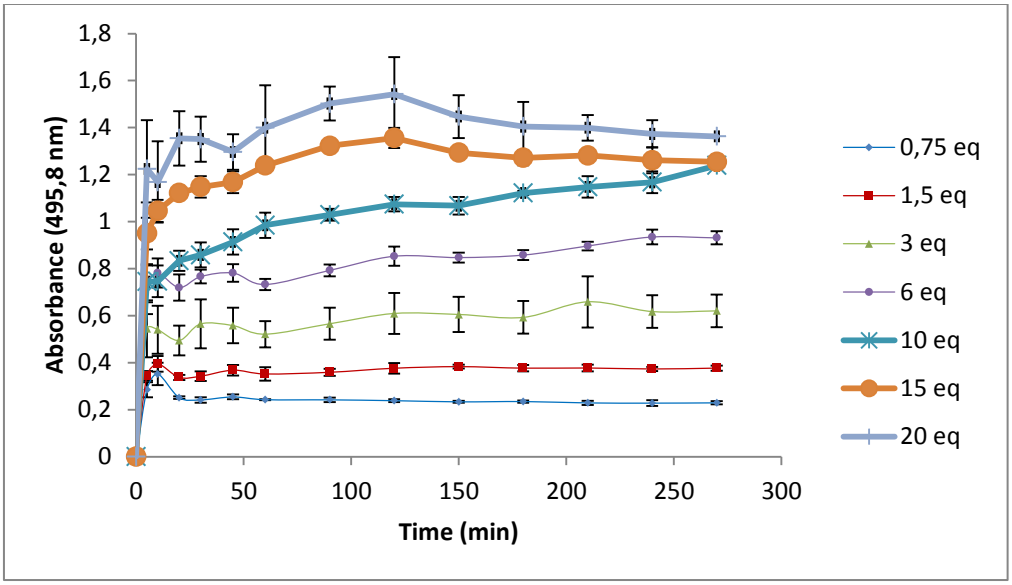


Figure 80 - Kinetic plot of synthesis of diazofluorene with varying molar equivalence of Magtrieve™. Data points represent average of triplicate values ± standard deviation

Appendix C - Kinetic data for tin(II) halide-catalyzed reactions of protection of partially protected monosaccharides with diazo compounds

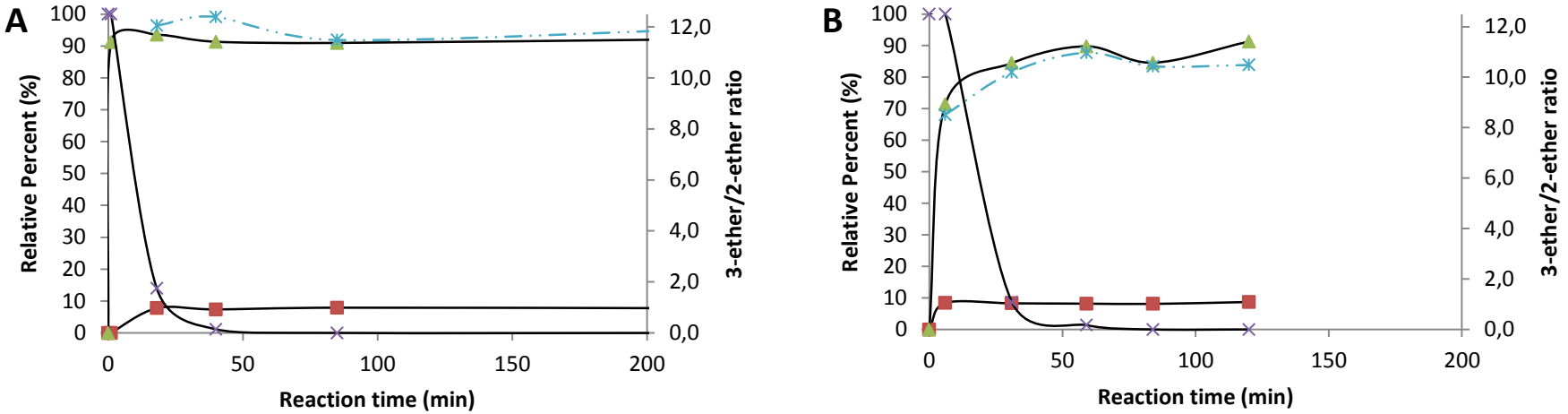


Figure 81 - Reactions of methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside with diazodiphenylmethane using tin(II) chloride (**A**) and tin(II) bromide (**B**); ■-2-ether, ▲- 3-ether, X-diazodiphenylmethane, *-3:2-ether ratio

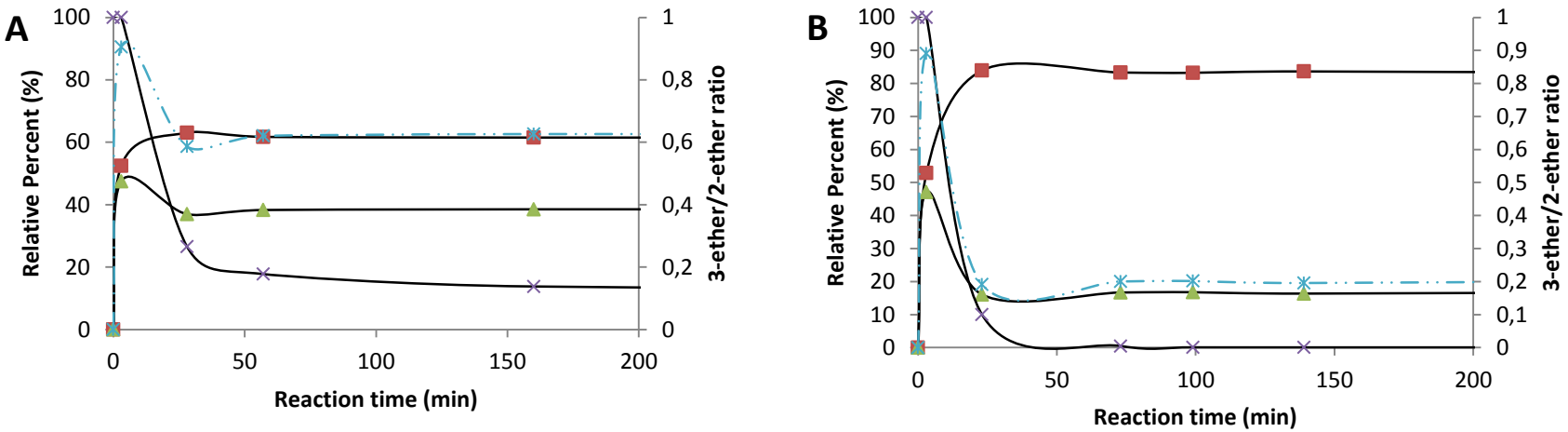


Figure 82 - Reactions of methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside with diazofluorene using tin(II) chloride (**A**) and tin(II) bromide (**B**); ■-2-ether, ▲- 3-ether, X-diazofluorene, *-3:2-ether ratio

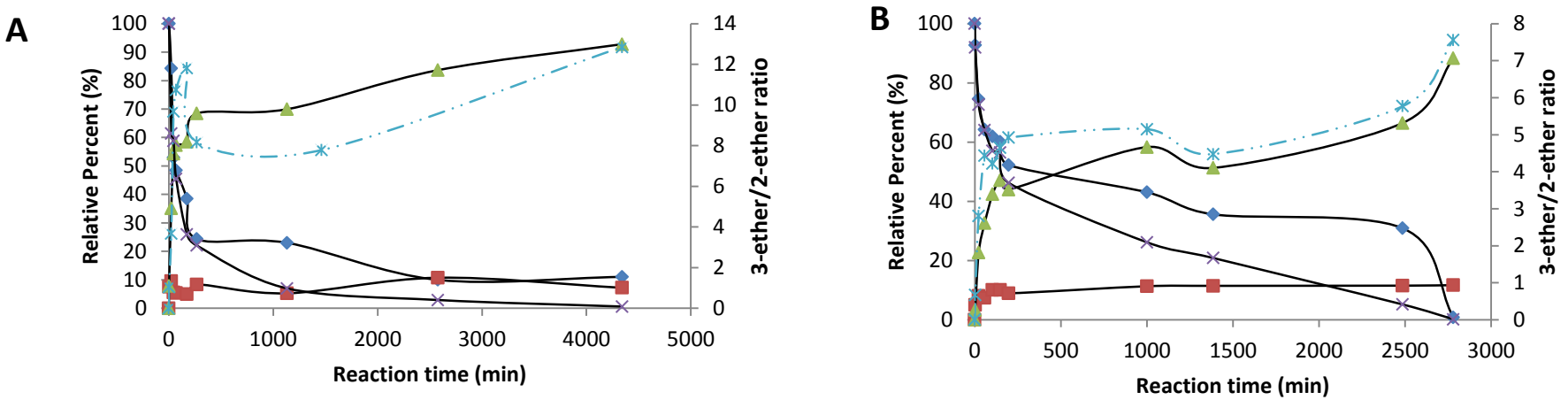


Figure 83 - Reactions of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside with diazodiphenylmethane using tin(II) chloride (**A**) and tin(II) bromide (**B**); ♦- methyl 4,6-*O*-benzylidene-α-D-mannopyranoside, ■-2-ether, ▲- 3-ether, X – diazodiphenylmethane, *- 3-ether/2-ether ratio

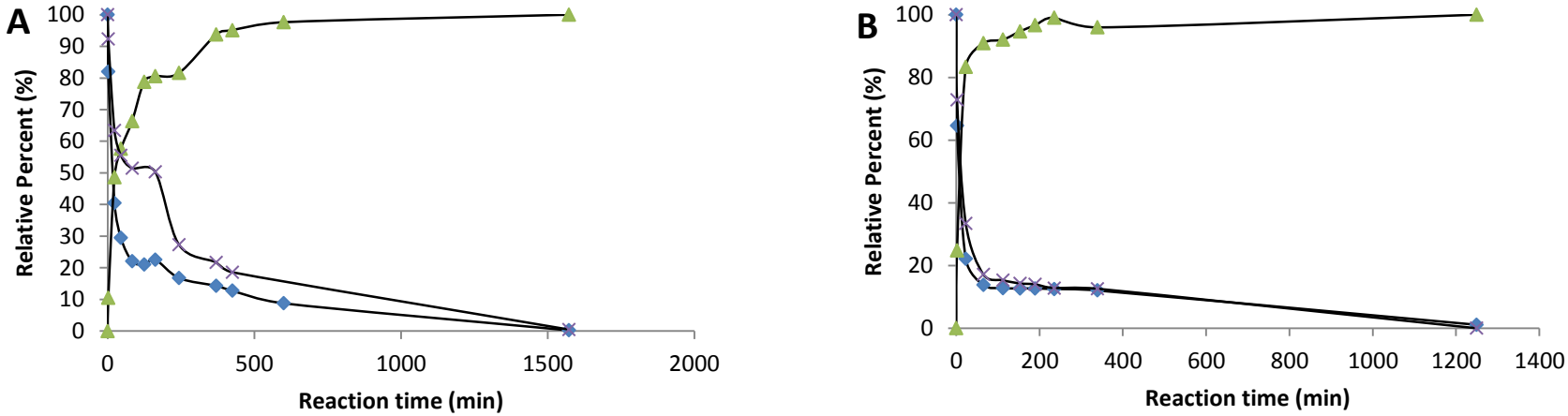


Figure 84 - Reactions of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside with diazo-[*bis*-(4-methylphenyl)methane] (2) using tin(II) chloride (**A**) and tin(II) bromide (**B**); ♦- methyl 4,6-*O*-benzylidene-α-D-mannopyranoside, ▲- 3-ether, X – diazo-[*bis*-(4-methylphenyl)methane].

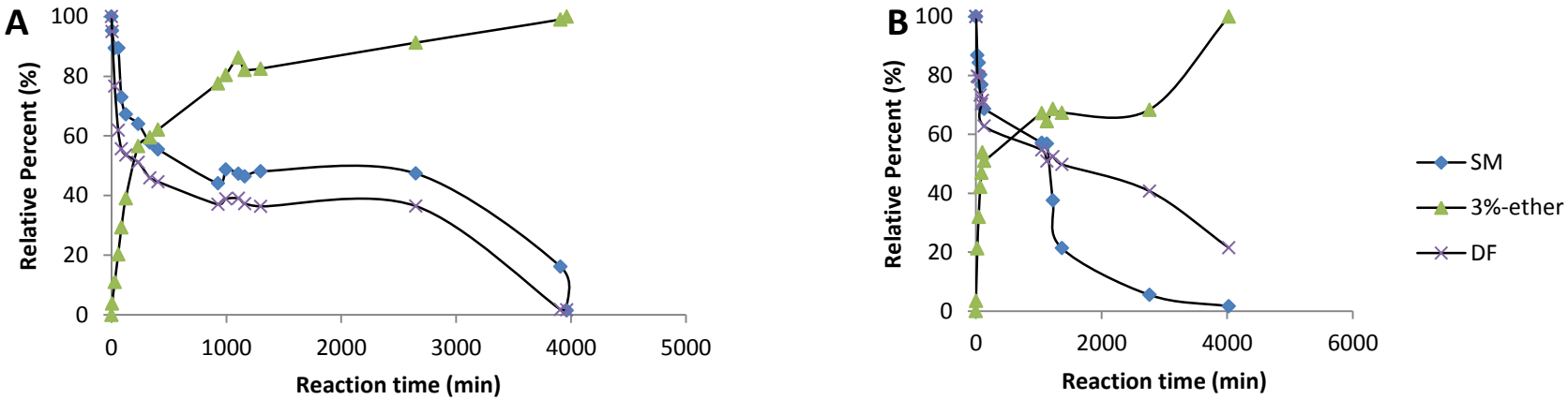
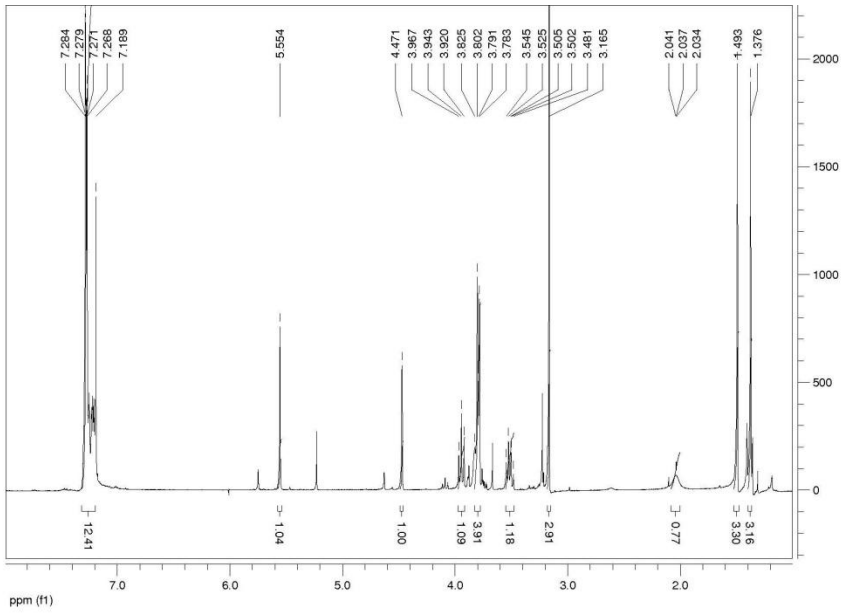
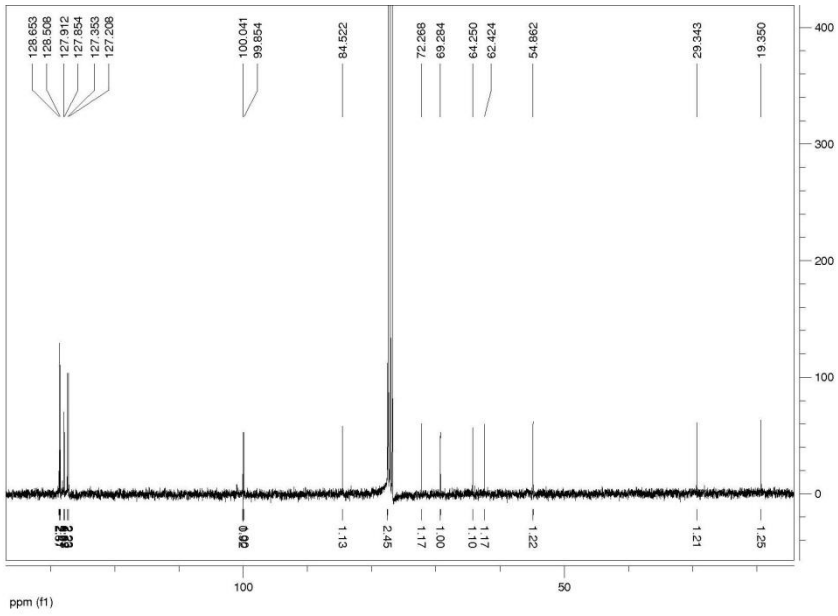


Figure 85 - Reactions of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside with diazofluorene using tin(II) chloride (**A**) and tin(II) bromide (**B**); ♦- methyl 4,6-*O*-benzylidene-α-D-mannopyranoside, ■-2-ether, ▲- 3-ether, X – diazo-[bis-(4-methylphenyl)methane].

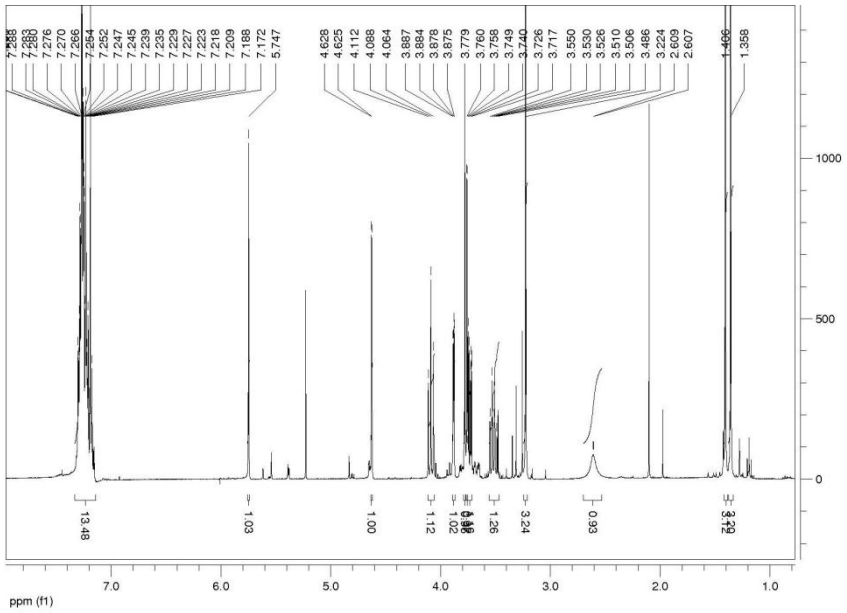
Appendix D - NMR spectra for selected compounds

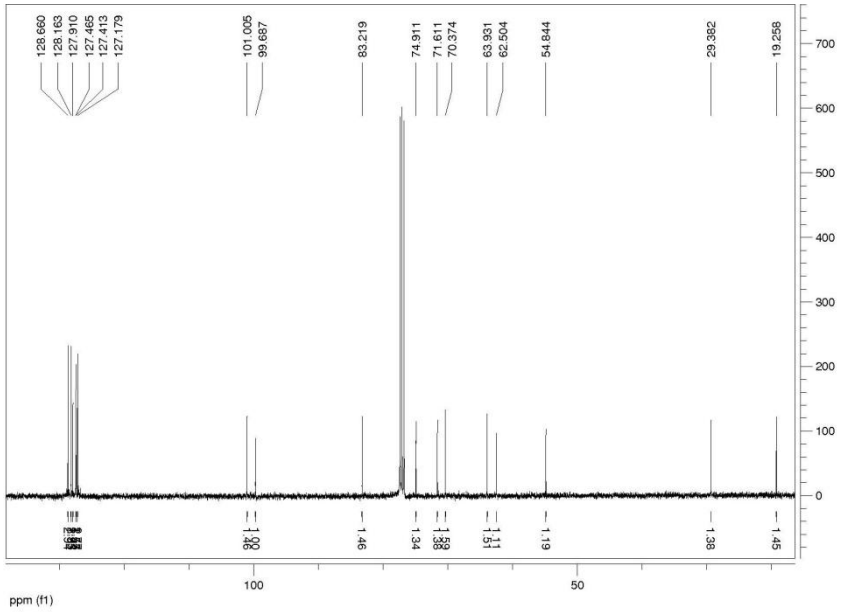
Methyl 2-*O*-[di(phenyl)methyl]-4,6-*O*-isopropylidene-α-D-mannopyranoside



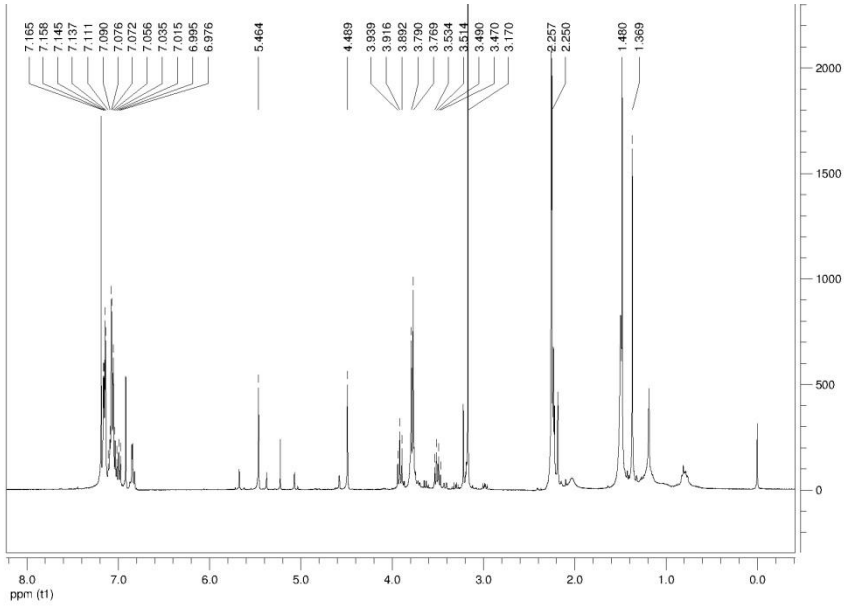


Methyl 3-*O*-[di(phenyl)methyl]-4,6-*O*-isopropylidene-α-D-mannopyranoside

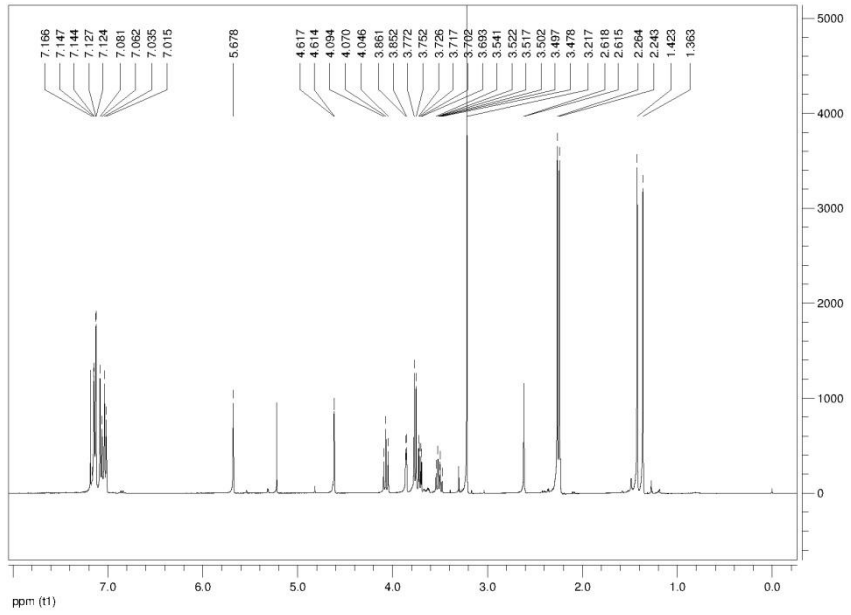


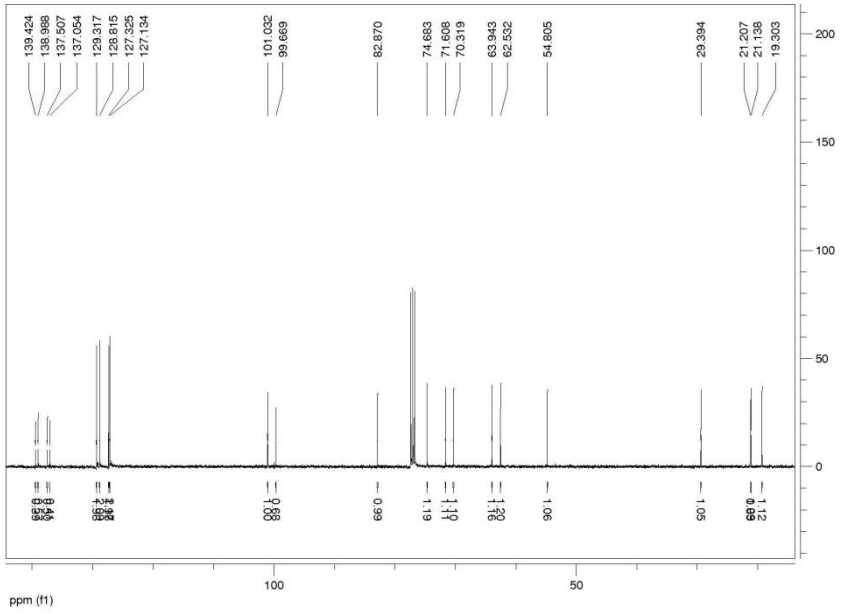


Methyl 2-*O*-[di(4-methylphenyl)methyl]-4,6-*O*-isopropylidene-α-D-mannopyranoside

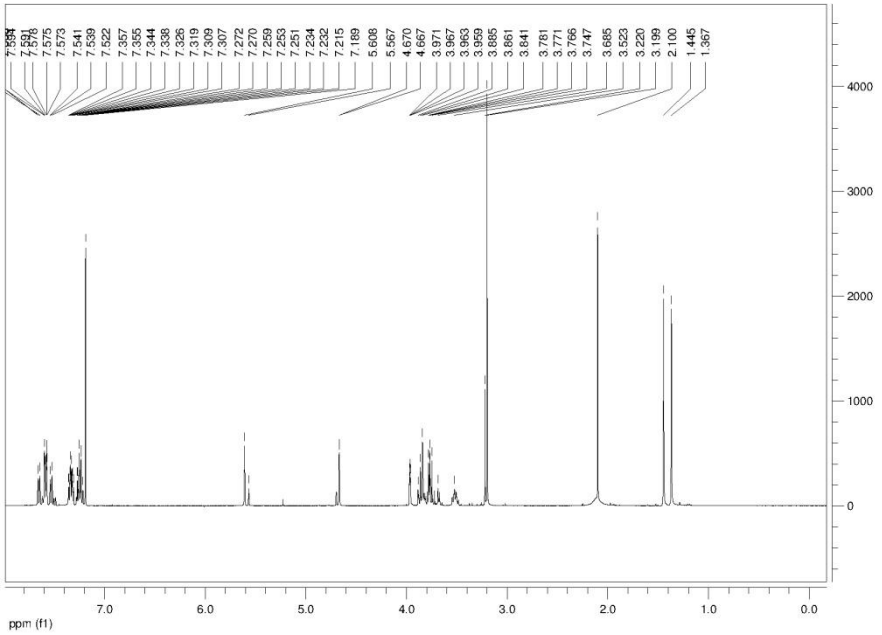


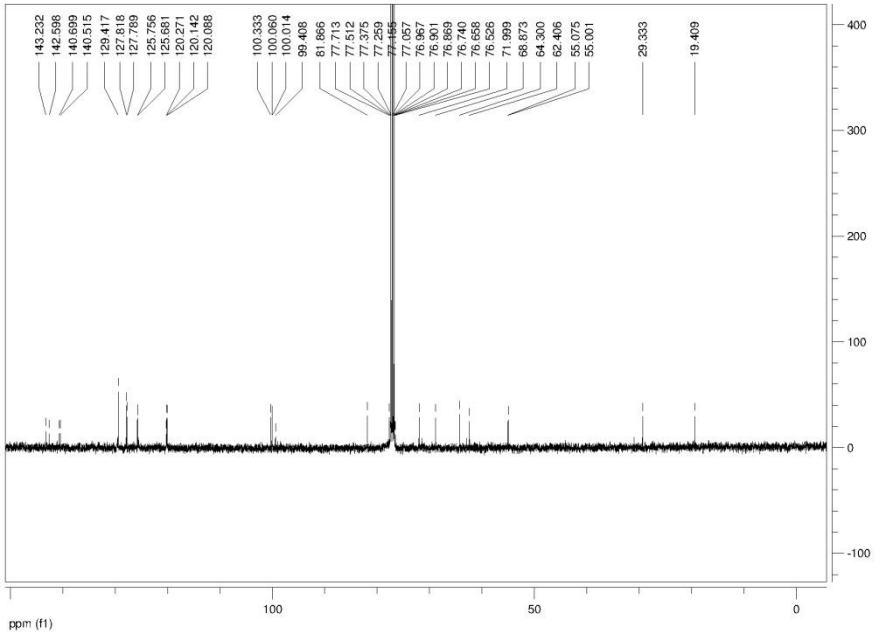
Methyl 3-*O*-[di(4-methylphenyl)methyl]-4,6-*O*-isopropylidene-α-D-mannopyranoside



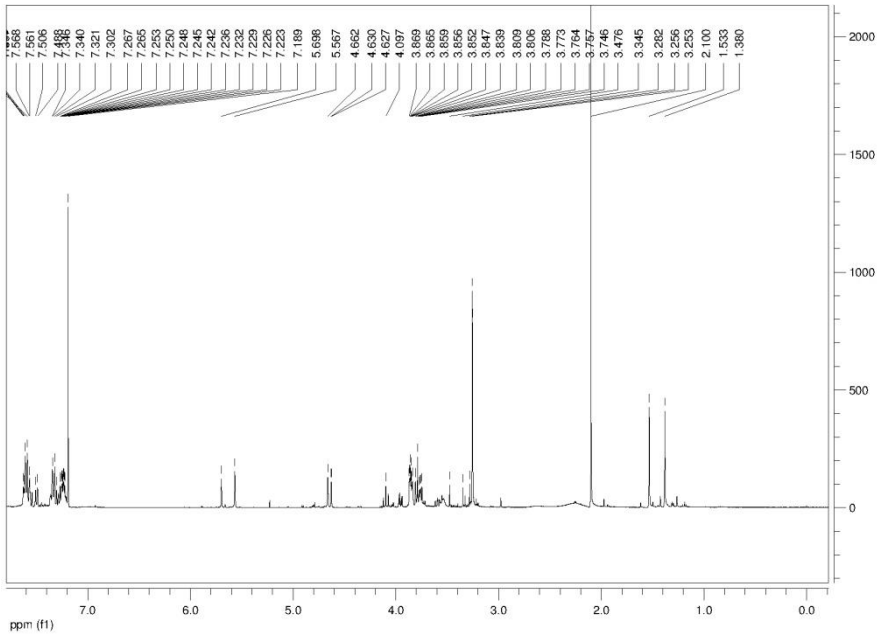


Methyl 2-*O*-(9H-fluoen-9-yl)-4,6-*O*-isopropylidene-α-D-mannopyranoside

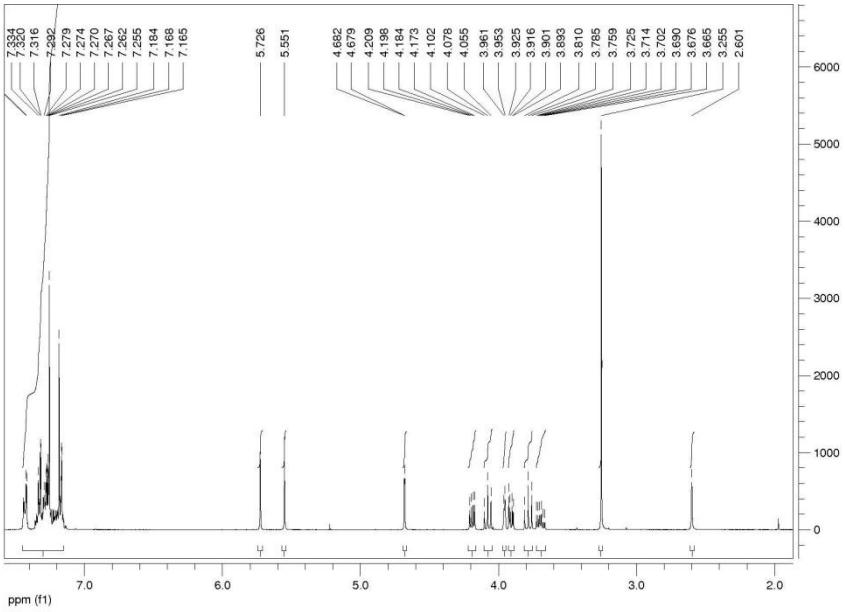


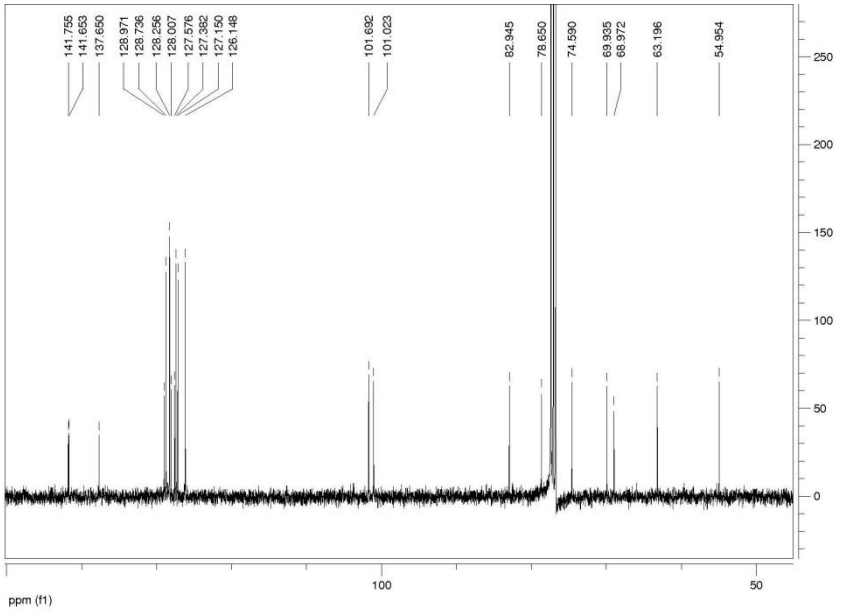


Methyl 3-*O*-(9H-fluoen-9-yl)-4,6-*O*-isopropylidene-α-D-mannopyranoside

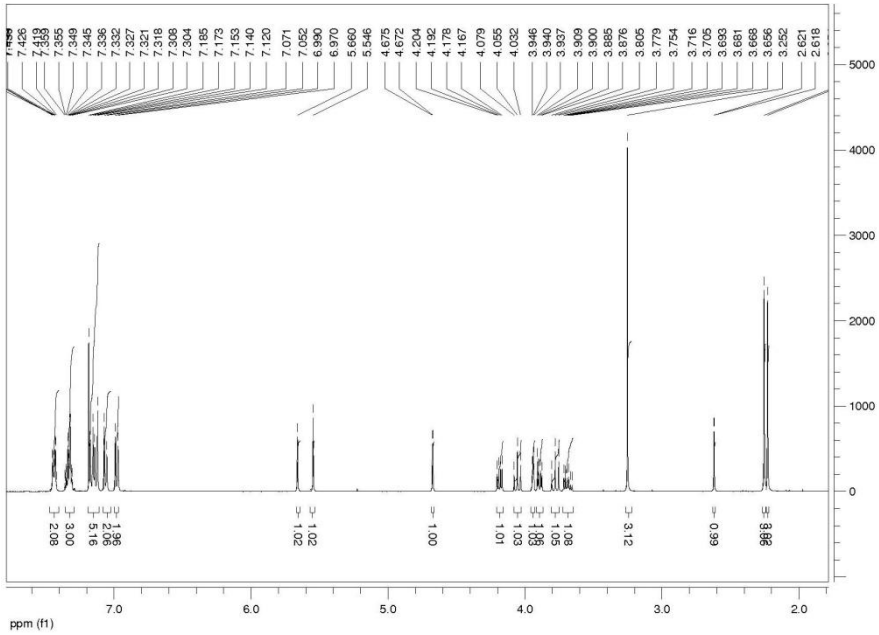


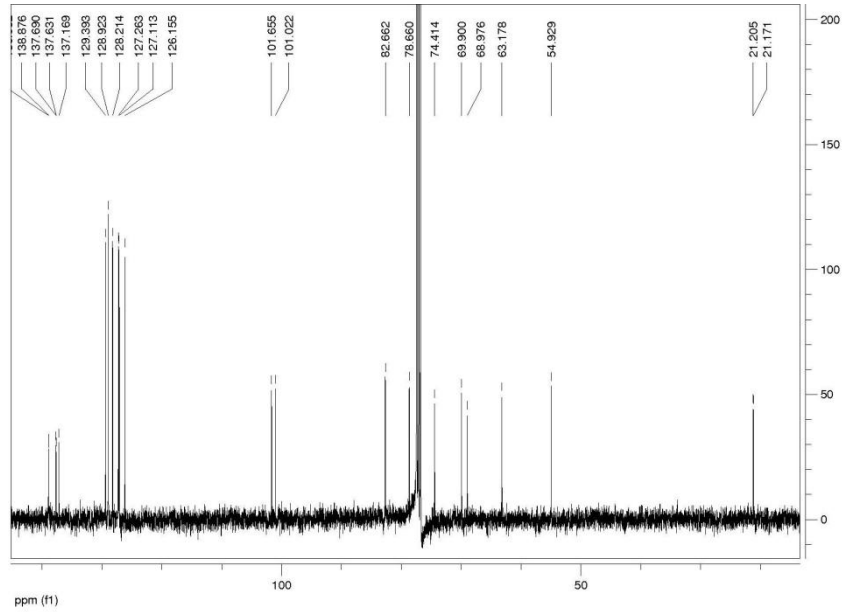
Methyl 3-*O*-[di(phenyl)methyl] 4,6-*O*- benzylidene-α-D-mannopyranoside



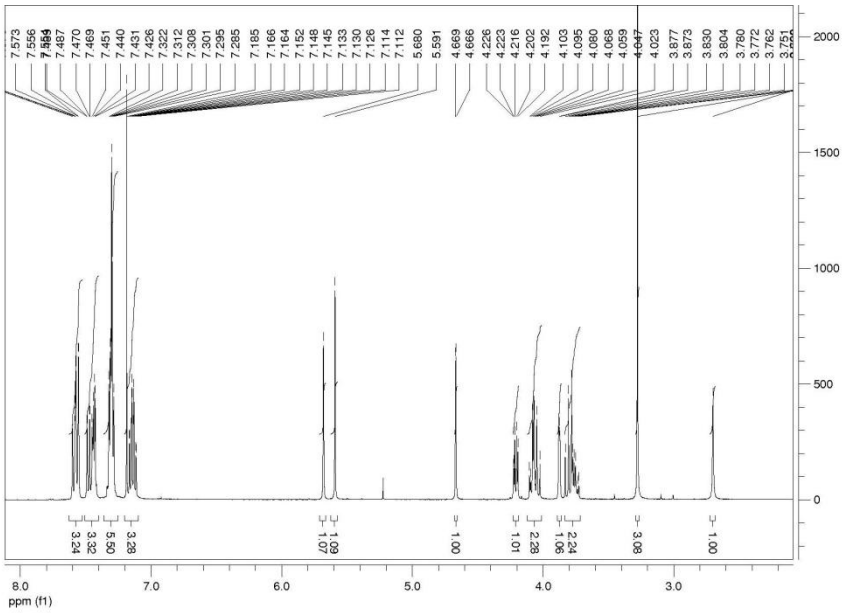


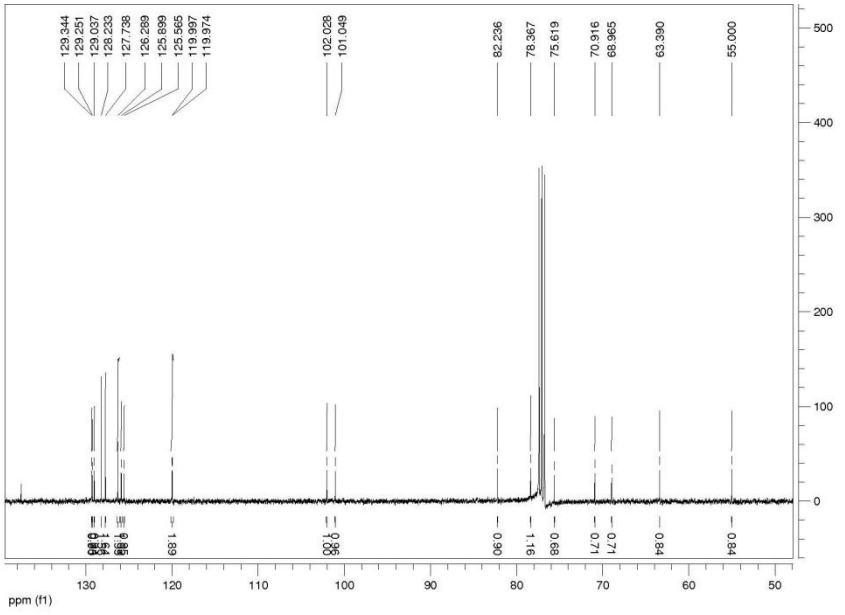
Methyl 3-*O*-[di(4-methylphenyl)methyl]-4,6-*O*- benzylidene-α-D-mannopyranoside





Methyl 3-*O*-(9H-fluoen-9-yl)-4,6-*O*-benzylidene -α-D-mannopyranoside





Methyl 4,6-*O*-benzylidene-2-*O*-diphenylmethyl-*α*-D-glucopyranoside