Oxidation and Evaluation of Calcium-Complexing Properties of Certain Oligosaccharides. Synthesis of Model Compounds for Glucose-Based Polysaccharides.

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Thesis presented for the degree of
Doctor of Philosophy

The University of Edinburgh 1998

Declaration

I declare that this thesis is my own composition, that the work of which it is a record has been carried out by myself, and that it has not been submitted in any previous application for a higher degree.

The thesis describes the results of research carried out in the Department of Chemistry of the University of Edinburgh, under the supervision of Dr. I. Gosney since the 3rd of October 1994, the date of my admission as a research student.

Stuart Gebbie

For my Mum and Dad. Thanks.

Acknowledgments

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To the various technical staff of the department I would like to offer my thanks for the provision of services during my time, in particular John Miller for his good humoured NMR service and Stuart Johnstone for his mildly amusing(?) jokes.

À ma petite Shtroumpfette, merci beaucoup pour toutes les choses que tu as faites quand tu étais ici à Edimbourg, et aussi merci pour tous les sourires que tu me fais chaque fois qu'on est ensemble.

Lastly, I would like to thank all the people who have made the years of my Ph.D. so enjoyable; Looney Tunes Abass, Allan Doyle, Lozenge Joly, Deek Kilgour, Potato McPherson and Stork Thorburn from the Lab and Anita Long (my Elf-like helper) and Kay Wilson from the Real World - I doubt you'll ever know how much of an effect you've had on my life. Cheers!

Courses Attended

The following is a statement of the courses attended during the period of research:-

1 Current Topics in Organic Chemistry, various speakers, Department of Chemistry, University of Edinburgh, 3 years attendance.

2 Organic Research Seminars, various speakers, Department of Chemistry, University of Edinburgh, 3 years attendance.

3 Royal Society of Chemistry, Perkin Division (Scottish Section), annual meeting, various speakers, 3 years attendance.

4 Development, Explanation and Applications of NMR Spectroscopy, Dr. I. Sadler and Dr. P. Barlow, Department of Chemistry, The University of Edinburgh, 1995.

5 Industrial Chemistry, Zeneca Grangemouth, various speakers, Department of Chemistry, The University of Edinburgh, 1995.

6 The Discovery of Agrochemicals, Dr. C. Godfrey and Dr. T. Perrior, Zeneca Agrochemicals, Department of Chemistry, The University of Edinburgh, 1995.

7 Ames Symposium Combinatorial Libraries, various speakers, Department of Chemistry, The University of Edinburgh, 1996.

8 Synthesis of Fine Chemicals, Prof. S. McKillop, East Anglia University, Department of Chemistry, The University of Edinburgh, 1996.

9 Current Developments in Medicinal Chemistry, Prof. R. Ramage and Dr. S. Flitsch, Department of Chemistry, The University of Edinburgh, 1997.

10 Patents - Protecting and Commercialising Inventions, various speakers, Zeneca Specialities, Department of Chemistry, The University of Edinburgh, 1997.

Abstract

The improved synthesis of two methyl glycosides, *viz.* methyl 4-*O*-methyl-α-D-glucopyranoside and methyl 4–*O*–(α–D–glucopyranosyl)–α–D–glucopyranoside (methyl α-maltoside) from readily available starting materials is described for use as model compounds for oxidative studies of the industrially important polysaccharide amylose.

Attempts to acetylate methyl α-D-glucoside regioselectively proved fruitless, whilst regioselective pivaloylation was more successful, albeit in yields of poor synthetic utility. In a variation to this approach, the glycoside is synthesized *via* selective tri-*O*-benzoylation of methyl α-D-glycoside with the regiospecificity of the reaction being a function of the relative strengths of intramolecular hydrogen bound rings, which are governed by the conditions under which the reaction is performed. In the second step, methylation of the free hydroxy group can only be achieved under pressure with silver oxide as catalyst. The target compound is obtained in the final step by conventional cleavage of the ester functions.

Initial attempts to synthesise methyl α-maltoside were convergent, being conducted with variants of the Koenigs-Knorr methodology and using reactions of previously prepared haloglucosides with variously protected 4-hydroxy methyl α-D-glucosides. No combination of catalysts could be found to activate either of the substrates, or in an alternative strategy, mediate the reaction between a halomaltoside and an alkoxy nucleophile. The target maltoside is formed eventually *via* the selective anomeric deprotection of per-*O*-acetylated maltose, followed by stereospecific methylation in a manner similar to that described previously. It is found that in this penultimate step an intramolecular silver alkoxy - esteric salt inhibits mutarotation, thus allowing the predominant formation of the α-anomer. Further deacetylation gives rise to methyl α-maltoside in 63% yield and in only three steps.

Attempts to extend this approach to the synthesis of methyl 4-*O*-(4′-*O*-(α-D-glucopyranosyl)-α-D-glucopyranosyl)-α-D-glucopyranoside (methyl α-maltotrioside) are described. Unfortunately, the stereospecific addition of methyl tri-*O*-acetyl-4-iodo-α-D-galactoside, and also methyl 4-iodo-α-D-galactoside, to anomerically deprotected per-*O*-acetylated maltose failed.

Evaluation of both methyl glycosides as potential models for oxidation studies on glucose-based polysaccharides has been carried out with (i) 2,2,6,6-tetramethylpiperidinyloxy radical (TEMPO), which is selective for oxidation of primary alcohols, and (ii) a two-step process with sodium periodate followed by sodium chlorite to bring about oxidative glycol cleavage at $C_{2,3}$. Both processes provided specific ^{13}C NMR spectroscopic data to be used

for later comparison with the products of less well-defined oxidation systems, *e.g.* ruthenium trichloride in 30% hydrogen peroxide.

Similar oxidations are used to produce oxidised oligosaccharides from α- and β-cyclodextrin for use in potentiometric studies to determine calcium-ion concentrations *via* an ion selective electrode. This data in conjunction with computer modeling software is used to probe the calcium-complexing properties of oxidised oligosăccharides in solution. Evidence is provided to show that the geometry of the calcium complex is not that previously assumed, *i.e.* it does not appear to involve the close approach of electrostatically charged and coiled molecules, but instead is more likely to involve two neighbouring units within the oxidised oligosaccharide folding back on each other to form a pocket into which the calcium ion can fit.

1.0 Introduction

2.0 Results and Discussion

3.0 Experimental

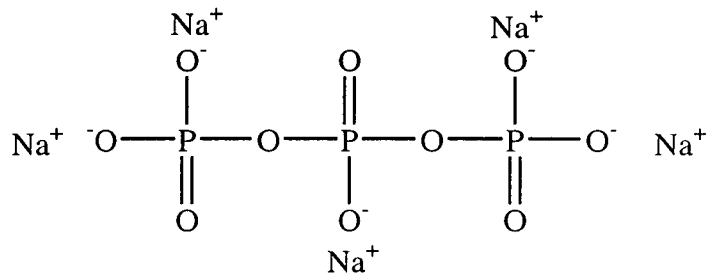
1.0 Introduction

1.1 Background

1.1.1 Phosphates in detergents

As a consequence of the presence of substantial quantities of calcium and magnesium ions in much of the world's water supplies, commonly used laundry detergents amongst other products must contain so-called "builders" whose purpose is primarily to prevent the formation of insoluble inorganic salts of surfactants and thus the precipitation of mineral salts.

These "builders" form soluble complexes with the relevant metal and hence prevent any deposition. Of these the most commonly used is pentasodium triphosphate, more commonly known as sodium tripolyphosphate (STP) **1**.



1

STP is a particularly efficient builder and has been shown to be physiologically safe and moreover is industrially attractive since it can be produced at low cost[1]. Its importance industrially is illustrated by its estimated consumption from 1982 until 1995[2], as outlined in Figure 1.

Estimated Worldwide STP Consumption 1982-1995

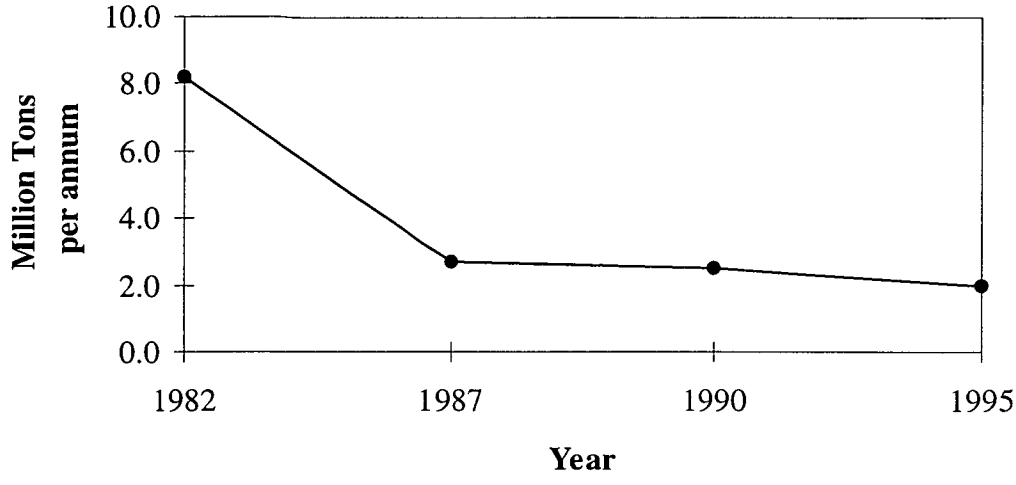


Figure 1

The rapid decline between 1982 and 1987 from where consumption has largely leveled out, was due to the imposition or voluntary agreement concerning the level of phosphates permissible in detergents, some of which are given in Table 1.

Location	Limit permissible (%)	Implementation	Regulatory status
Austria	22	1987	regulation
Canada	9	1973	regulation
Germany†	22	1984	regulation
Italy	4	1988	regulation
Japan	17	1978	voluntary agreement
Netherlands	22 0	1987 1990	voluntary agreement
Norway	12	1986	regulation
U.S.A.	0-35	state specific, governed by local regulation	

†Legislation implemented by government of West Germany

Table 1

The implementation of these limits was due to concern voiced over the environmental impact of discharged phosphate species into the aquatic environment.

1.1.2 Environmental concerns

In spite of the combination of outstanding performance and excellent economic properties associated with STP, its inclusion into domestic detergents does have a serious drawback in that once drained, waste water can be discharged into surface waters where it can (amongst other factors) lead to the eutrophication of lakes and stagnant waters, also known as "Algal Bloom". In such a case, phosphates act as

nutrient for the growth of algae, and in summer when the level of light is not a limiting growth factor, a high concentration of phosphates leads to uncontrolled microbial growth. The high volume of algae produced deprives the deeper water areas of light and oxygen which in turn initiates the cycle of anaerobic degradation of algae which consequently serves to further starve the water of its dissolved oxygen. Furthermore, this anaerobic decomposition is known to release both H_2S and Me_2S into the atmosphere[3].

Many serious instances of this have been reported, notably in the U.K.[4,5], South Africa[6] and particularly in the Great Lakes of the United States[7]. Moreover, the problem is not exclusively limited to still waters, as was observed in the sea eutrophication of the Adriatic[8,9], in the North Sea[10] and off the coast of Japan[11].

Though phosphorus alone is not solely responsible for this process (nitrogen is also involved) it is the most easily controlled factor simply by reducing the level of phosphates discharged since there are many naturally occurring nitrogen fixing blue-green algae[12,13].

It should be noted here that it is not strictly STP which is responsible for eutrophication but orthophosphate, produced by the slow hydrolysis of STP. The half-life of STP is however 1-3 years[14] although this is enhanced by certain microorganisms[15]. Thus the problem of STP discharge can be considered to be a relatively long-term one.

There are four[16] main strands to the drive to reduce the levels of phosphates discharged into the marine environment, outlined below:

- biological removal from waste water particularly by the *Acinetobacter*[17] family of bioorganisms.
- chemical removal *via* precipitation engendered by the addition of Fe(III) or Al(III) salts.
- softening of water prior to use by ion-exchange or the addition of aerated alkali solutions to reduce the concentration of both calcium and magnesium, and so lessen the need for a builder.
- development of STP substitutes.

1.1.3 Phosphate alternatives

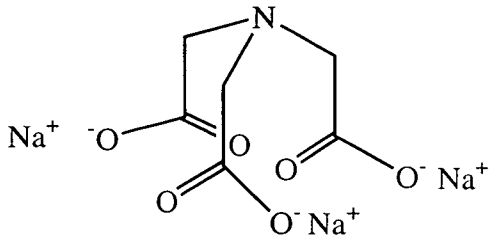
The requirements for any replacement to STP being widely industrially acceptable are that:

- it has good binding properties to principally calcium but also magnesium
- it is biodegradable and non-toxic
- it is cheap
- it is preferably water soluble

A wide diversity of compounds have been examined as potential replacements, some of which are detailed below.

1.1.3.1 Aminocarboxylic acids

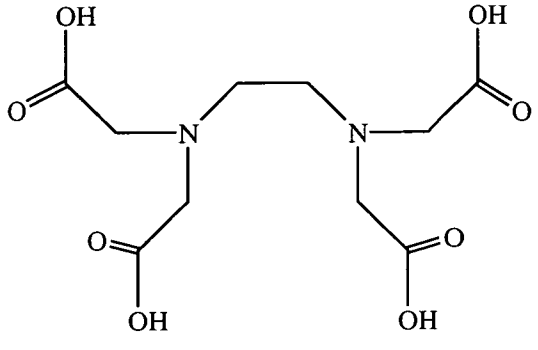
The most initially promising of all the potential STP replacements was the sodium salt of nitrilotriacetic acid, **2**.



2

It had been shown that **2** was more efficient at calcium and magnesium binding than was STP, and moreover it was also readily biodegradable[18,19]. However later studies[20-30] noted that there were serious toxicological problems, notably a chromosome breaking effect and mutagenic effects. Thus doubts about the long term safety of **2** meant that it never led to any large-scale usage outside Canada (where it is used in fairly large quantities *ca.* 36000 tons / year).

Other aminocarboxylic acids were investigated in view of the partial success enjoyed with **2**. Thus ethylenediaminetetraacetic acid (EDTA) **3** and hydroxy ethylenediaminetriacetic acid (HEDTA) **4** were examined.



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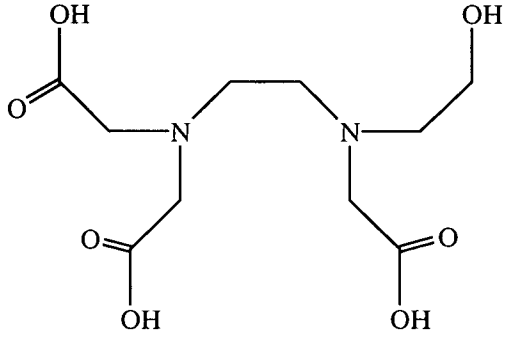

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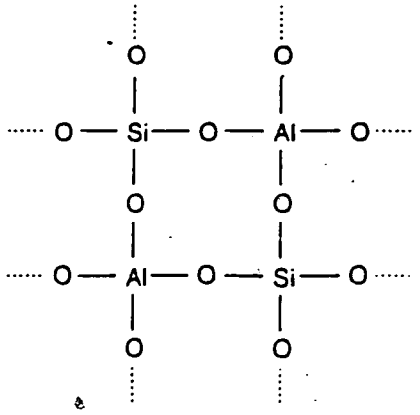
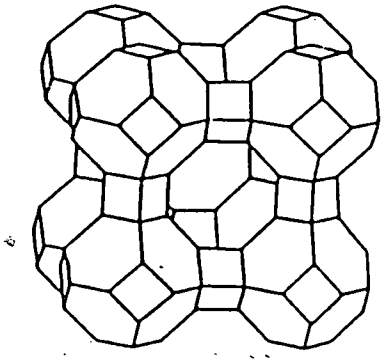
Although both **3** and **4** have excellent chelating properties for most metals as a result of the "Chelate Effect" they have found only limited application in waste-water treatment. This is largely as a consequence of their relatively high price and their poor biodegradability. Also, such compounds do not enjoy any significant selectivity in metal complexation. This in turn can pose a serious problem with regard to the mobilization of heavy metals otherwise removed in the waste water treatment processes. As complexes such metals are essentially harmless, however on the eventual degradation of the ligand the metal is released into the environment leading potentially to high metal concentrations in sedimentary deposits.

1.1.3.2 Zeolites

Of all the phosphate substitutes commonly used, the most prevalent is Zeolite NaA[31], **5** an aluminosilicate material of formula $Na_{12}[Al_{12}Si_{12}O_{48}].27H_2O$.





5

5 is employed as a finely divided powder consisting of cubic crystals with a cavity diameter of *ca.* 1.5μm which initially contain water molecules, but will

exchange to chelate calcium and to a lesser extent magnesium. Magnesium is chelated much less rapidly because of the stronger coordination to water.

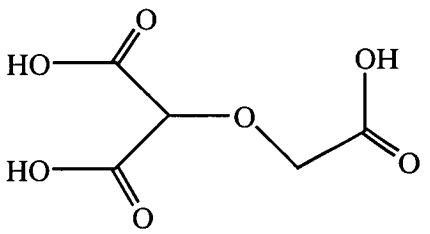
On a molecular scale **5** is much larger than any metal ions present, and so it is necessary to use a so-called "co-builder" which serves one of two purposes. Firstly it can act as a dispersant, typically being a polycarboxylate or phosphonate which inhibits the deposition of solid calcium complexes by inhibiting the rate of crystal growth. Alternatively a suitable complexing agent such as **2** will be employed to adsorb onto a calcium containing precipitate from which it will subsequently desorb as its calcium complex, which upon dissociation will exchange the metal with **5**.

Although non-toxic **5** does have a serious drawback in that it is completely insoluble, and because of the small particle sizes involved, is very difficult to remove in waste water treatment, thus considerable quantities are annually discharged. Whilst the aluminium remains bound it can be considered non-toxic however problems arise when the compound undergoes hydrolysis, with a half-life in neutral water reported as 2 months[32]. Moreover because of the efficiency with which **5** sequesters a range of metal ions, the possibility of heavy metal ions being released into the environment on hydrolysis of this discharged material is significant.

1.1.3.3 Carboxylates

Many etheric carboxylates[33-41] have been studied, with the most promising being carboxymethyl tartronate **6** and carboxymethyl oxysuccinate **7**, although

neither has ever enjoyed any industrial utility, presumably because of the relatively high cost of their production.



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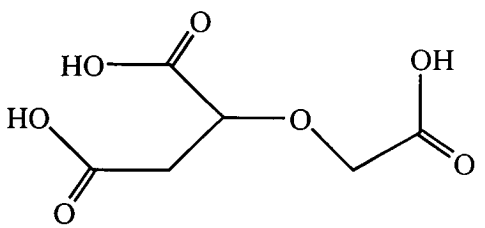
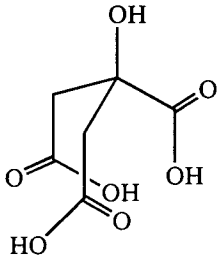


7

Further examples of this class of compounds exist, most notably citric acid **8**, glucaric acid **9**, oxydisuccinic acid **10**, propylene glycol disuccinic acid **11**, and tartrate disuccinic acid **12** and glycerol trisucceninic acid **13**. Of these only citric acid **8** enjoys a large commercial utility.



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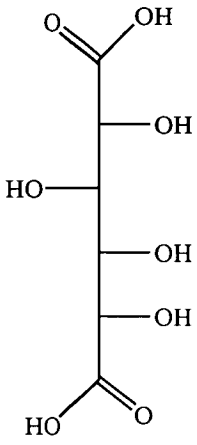

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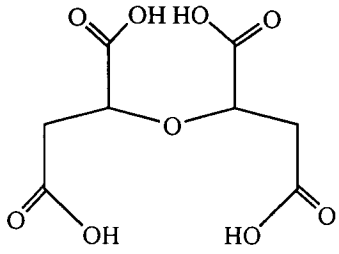

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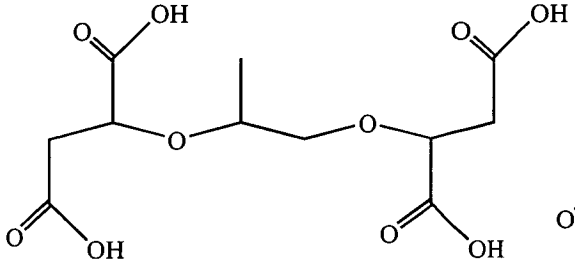

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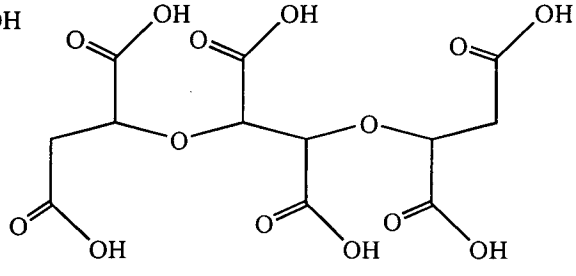

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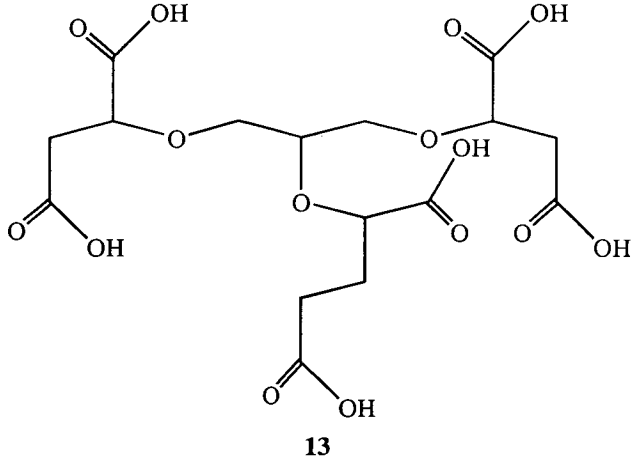


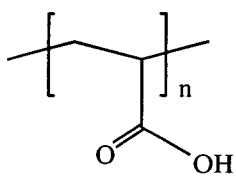
13

The drawback with all of these compounds *i.e.* **8** - **13** is that they perform rather less efficiently than either **6** or **7** and thus relatively large quantities must be used which in turn places a large biological oxygen demand on the discharged water.

1.1.3.3 Polycarboxylates

As previously mentioned, polycarboxylates often find application as anti-redeposition agents by inhibiting the rate of crystal growth, and carboxymethyl cellulose[42] has been widely used for many years for this purpose. It was then intended to combine the search for a suitable builder and dispersant into one molecule.

Some common co-builders were indeed studied, with the only polymers which have attracted any significant industrial interest being polyacrylate **14**, polyacrylate-maleate **15**, polyglyoxylate **16** and polyhydroxyacrylate **17**.



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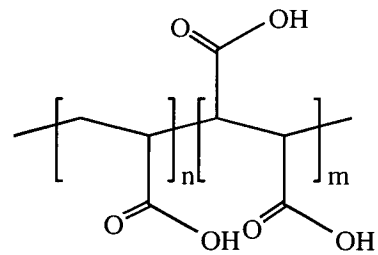

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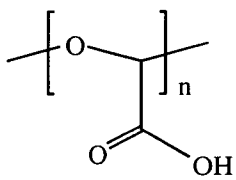

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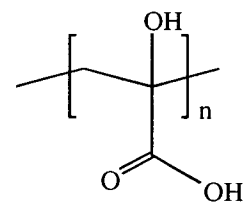


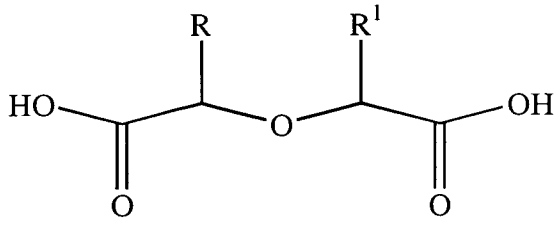
17

The principal drawback with this class of compounds though is that whilst they are physiologically harmless they are only poorly biodegradable[43]. Moreover, they are commonly precipitated during the waste water treatment cycle.

Although polycarboxylates have never found widespread commercial utility, they did shift the focus of attention towards the search for (bio)degradable polyelectrolytic detergent additives.

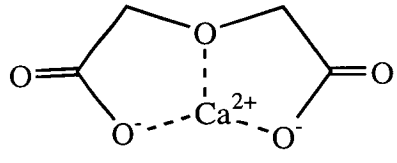
1.1.3.4 Oxidised carbohydrates

It has been previously detailed that an α-hydroxy or α-oxycarboxylic acid function within a molecule is a favourable structural unit for the complexation of calcium (II)[44,45]. Of particular importance is the moiety **18** closely related to oxydiacetic acid (ODA) **19**.



18 R / R^1 = H /Alkyl / Alkoxy
19 R = R^1 = H

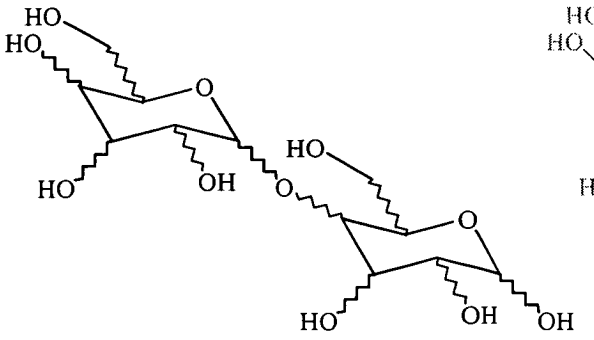
19 has been shown to form tridentate complexes with calcium (II) chelating through the etheric and hydroxylic oxygens, forming a planar W-shaped complex **20**.



20

If the stability of this complex is indeed due to the inclusion of the ODA type unit **19** then this should surely be a prerequisite in the search for any new ligands.

Examination of a generic disaccharide **21** which has undergone oxidative 2,3-glycol cleavage to the diacid **22** then provides such a unit.



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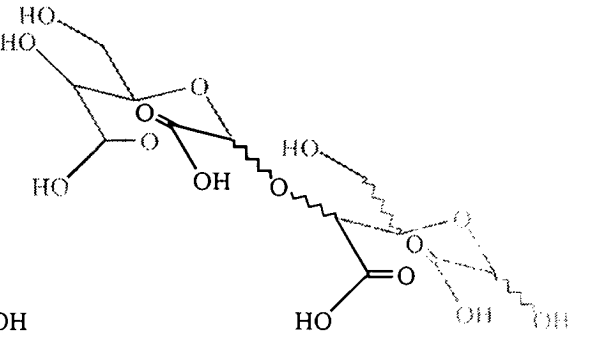

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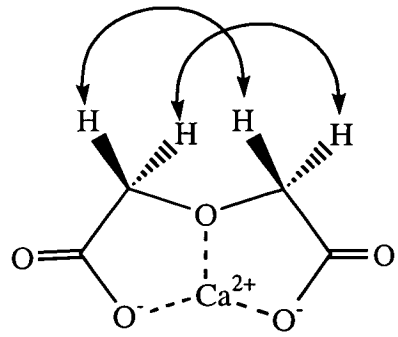
Compounds possessing this ODA type moiety such as **22** would not be expected to perform quite as efficiently as calcium ligands as does **19**, due to two major differences. Firstly, in **19** there are no sterically demanding groups which obviously allows for a more facile formation of a planar complex, although there is a small *syn*-1,3 interaction between the methylene protons. Introduction of sterically demanding functionalities at these positions will of course increase this interaction and so lead to twisting, which in turn will lower the stability of the complex, as shown in Figure 2.

small *syn*-1,3 interactions



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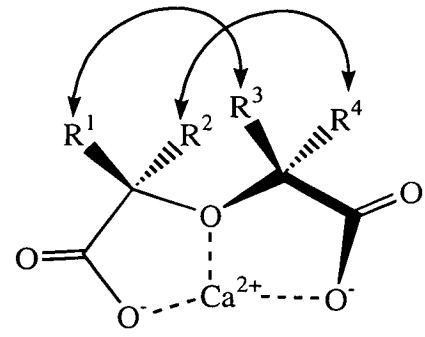
larger *syn*-1,3 interactions



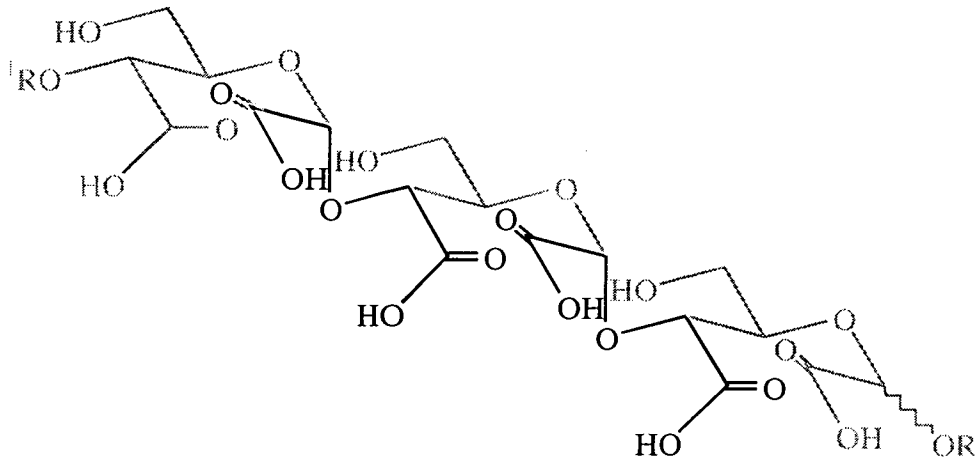
23

Figure 2

Furthermore, in **20** the chelation involves the etheric and hydroxylic oxygens, however where an oxidised carbohydrate is chelating, there is no etheric oxygen, only one involved in an acetal moiety. Thus, the overall electronic donating effect will be reduced with respect to **20**.

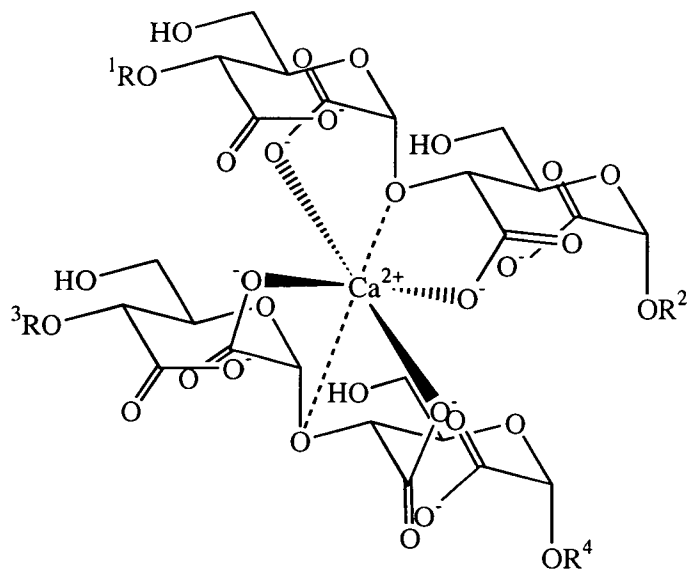
This said, there is the distinct advantage of using a large molecule such as a polysaccharide derivative in that the dispersant properties of these molecules are well known. Moreover, Nieuwenhuizen[46-48] has shown that there are some favourable effects of increasing size and carboxylic acid content on the overall sequestering ability of the molecule. Furthermore, he has also indicated using Dy (III) (since lanthanide complexes are often isostructural with their calcium analogues) induced shifts in ^{17}O NMR experiments that at least two units of **22** are involved in the binding of each Ca(II). This would of course help to stabilize the complex with respect to the necessary twist and reduced electronic interaction from the more stable complex **20**.

Extrapolation of this argument and consideration with molecular models by Nieuwenhuizen showed apparently that the involvement of two neighbouring units such as in **24** is impossible through steric demands.



24

Thus, he surmised that there exists some co-operation between non-neighbouring carboxylate groups, which he rationalizes as forming complex **25** for the oxidised glucose polymer series[49].



25

Thus for any oxidised polysaccharide to be of commercial utility it must meet three criteria, namely:

- the polysaccharide from which it is derived should be readily available and preferably inexpensive
- it should be oxidisable under fairly mild conditions using commercial materials
- it should be (bio)degradable

Two widely available and currently heavily used industrial materials immediately come to mind.

1.2 Starch

1.2.1 Background

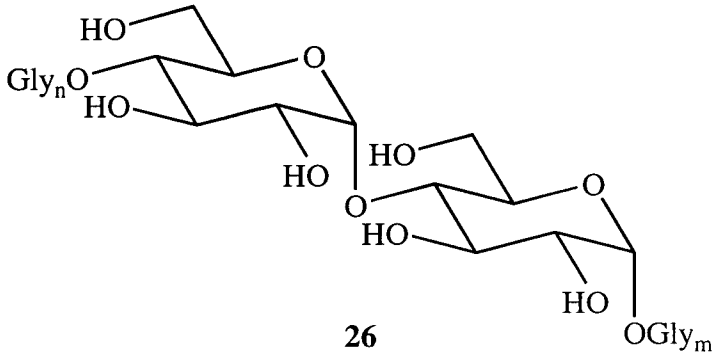
The simplest and most readily available material to fulfill these criteria is starch, naturally produced by plants as a store of D-glucose which is liberated as required under enzymatic degradation. It is currently widely used making it a cheap material and moreover there exists an infinite supply[50].

It is composed of two α-D-glucose based polysaccharides, namely water-soluble amylose typically comprising *ca.* 20% by weight with the remainder being water-insoluble amylopectin, though the relative quantities are largely determined by the plant from which the starch has been extracted. Viewed as a single entity it is by

far too complex to easily understand, and so should be considered in terms of its constituents.

1.2.2 Amylose[51]

Comprising of a linear chain of 1→4 α-D-glucopyranosides, amylose **26** typically consists of *ca.* 1000 - 4000 glucose units.



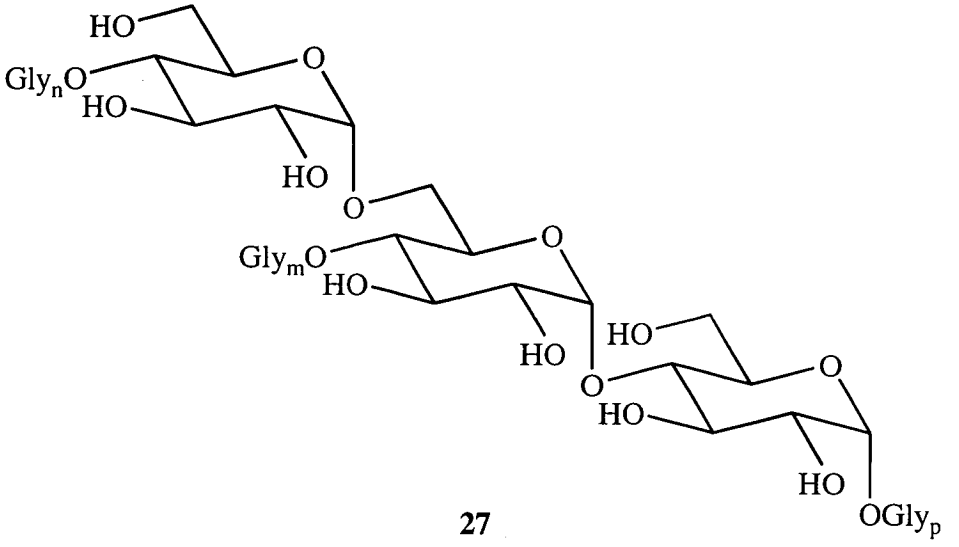
26

It is fractionated from native starch by precipitation as (usually) its thymol complex, followed by purification by repeated precipitation as its *n*-butanol complex. As with any polymer it does not have a well defined, narrow mass band, but a Gaussian distribution which makes its study difficult.

The structure of **26** is however remarkably consistent with little or no branching, which in turn makes it particularly attractive as a potential precursor to a polycarboxyl polysaccharide for use as a detergent builder. Moreover it is known to form a spiral helix in solution containing cavities of sufficient size to entrap a variety of molecules and ions (in fact it is this phenomenon which is responsible for the widely known "Iodine Starch test").

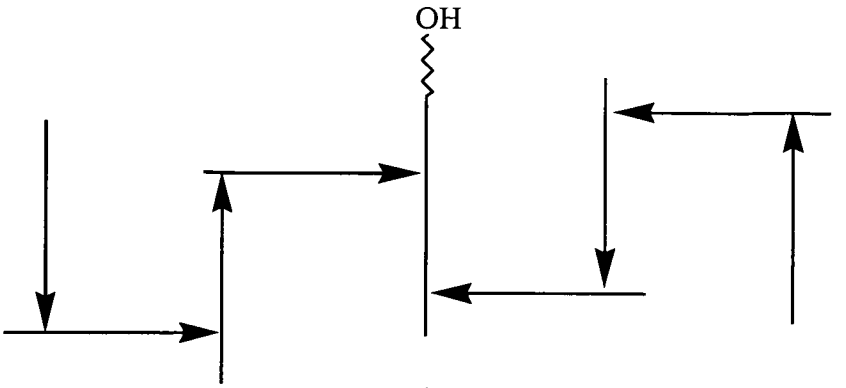
1.2.3 Amylopectin[51]

Considerably larger than **26**, amylopectin **27** shares for the most part the structural features of amylose.



27

The major difference between **26** and **27** aside from sheer size is that here with **27**, around 4% of all glucose units will have a 1→6 α-D-linkage, known as a "branching point". Comprised of up to 1 000 000 glucose units, **27** contains many small chains of *ca.* 25 unit length, arranged in a highly diffuse order schematically illustrated as **28** (broadly similar to the carbohydrate store in animals, *i.e.* glycogen which has smaller chain lengths of *ca.* 12-18 units).



28

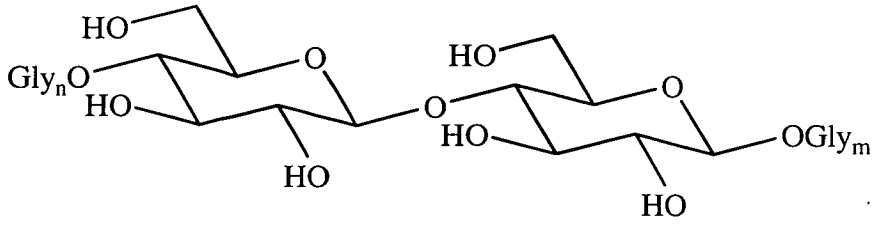
Chain of *ca.* 25 units

Branch point

The drawback to the potential use of **28** is a consequence of its size, and that is its solubility. Furthermore the sheer size of **28** means that where any reagents are applied there will necessarily be a concentration gradient across the molecule. Thus, if for argument's sake the overall shape of **28** is considered to be spherical, then it becomes exceptionally difficult to introduce any reagent at equal concentration to both the interior and exterior of the sphere. This consequently can then lead to rapid over-reaction of exposed portions of the molecule whilst the great majority remains unchanged.

1.3 Cellulose[51]

Another plant derivative, cellulose **29** is the chief component of wood and plant fibres consisting of a polymeric linear chain of 1→4 β-D-glucopyranosides.



29

Again of considerable size, it contains typically *ca.* 1500-6000 units per molecule, however unlike structurally similar amylose **26**, cellulose is particularly insoluble as the long chains lie alongside one another, undoubtedly held together by hydrogen bonding forming many bundles which twist together to form rope-like structures. This has been long exploited by man particularly for clothing - cotton is almost pure cellulose.

1.4 Polymeric precursor revisited

From a combination of solubility and also consistency of structure, amylose would seem to be the material of choice, however it is more likely that to be applied as an industrial material the desired polycarboxyl material should best be prepared from native starch to minimise costs. Purely for the initial consideration of oxidative conversions it is much better to consider principally the reactions of amylose since the lack of branch points will lead to fewer complications, as will the relative ease of solubility.

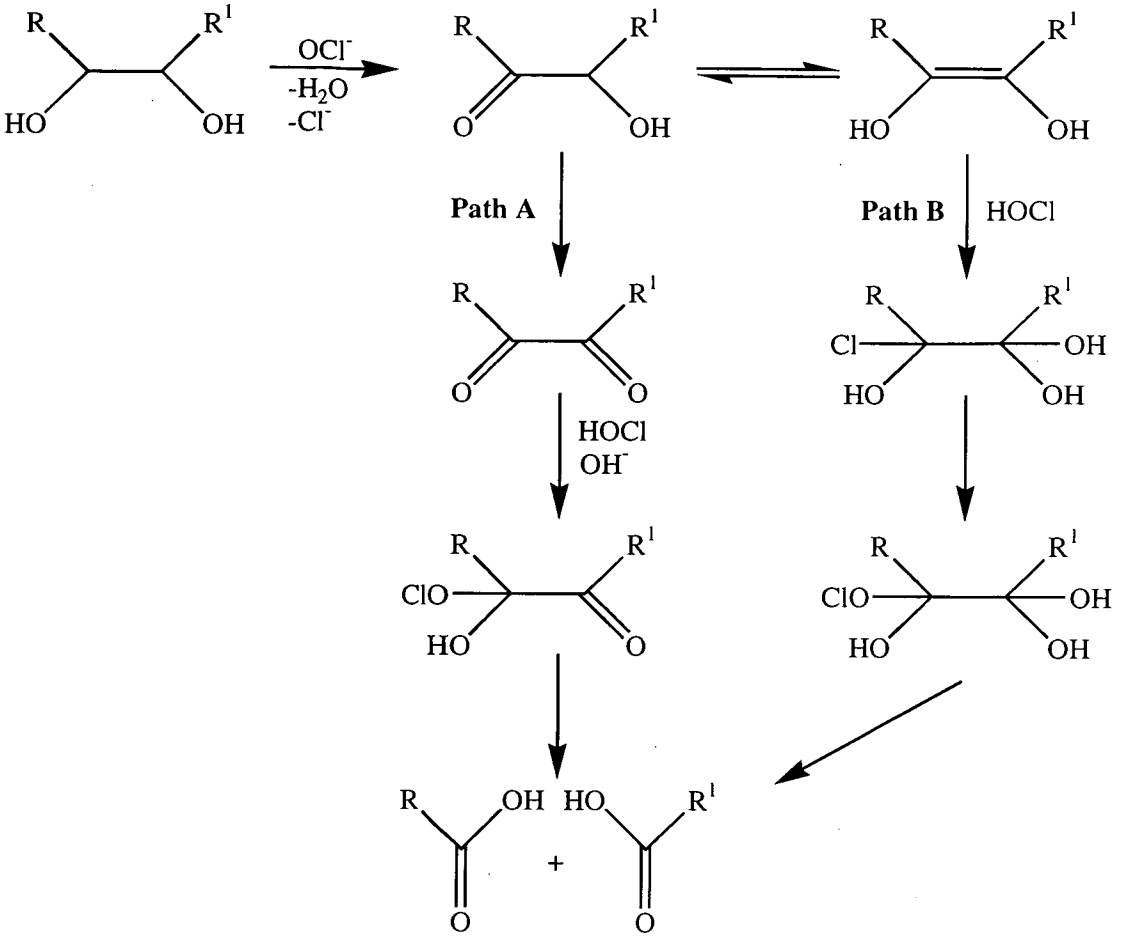
It has already been shown that crucial to the success of the polycarboxyl material as calcium ligand is the presence of many neighbouring ODA-type structures. Thus the efficiency with which the oxidative glycol cleavage is performed is critical. Presently there exist a wide variety of such methods, some of which are currently industrially employed and are outlined below.

1.5 Oxidative glycol cleavage

1.5.1 Hypochlorite oxidation

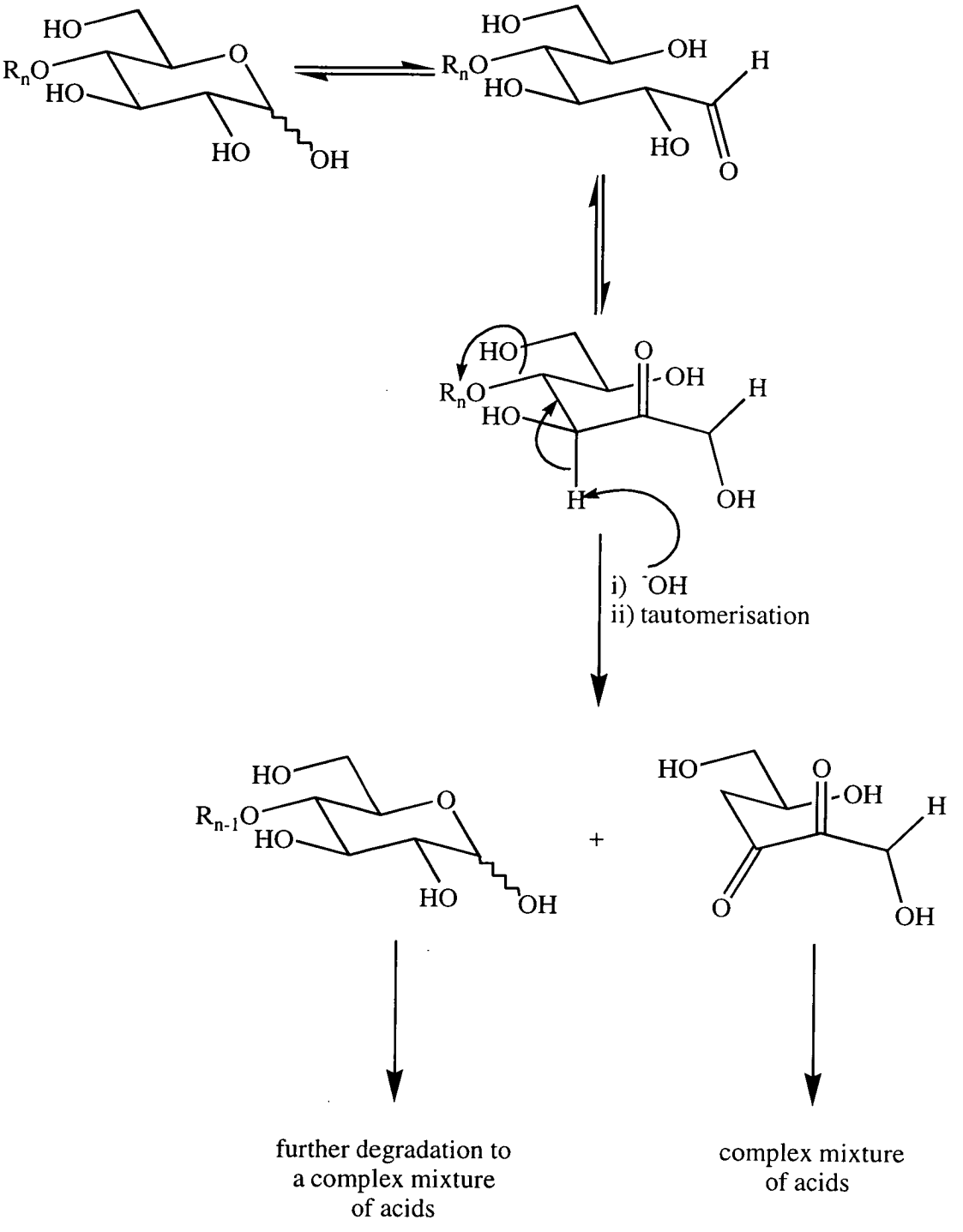
At a molar ratio of 3:1 hypochlorite : anhydroglucose units (AHG), C(2) - C(3) glycol cleavage occurs to give 2,3 dicarboxyl compounds of up to 45% of the initial glucose units in the polymer[52,53]. C(6) oxidation is not observed, as shown by lack of glucuronic acid on hydrolysis of the polymer product.

The glycol cleavage mechanism has been tentatively proposed by Van Bekkum as that shown in Scheme 1[52,54]. This may operate in tandem with a homolytic pathway involving hydroxyl or chloroxy radicals which to date has not been investigated fully. Studies on alginic acid oxidation indicate that the enediol mechanism prevails (Path B).

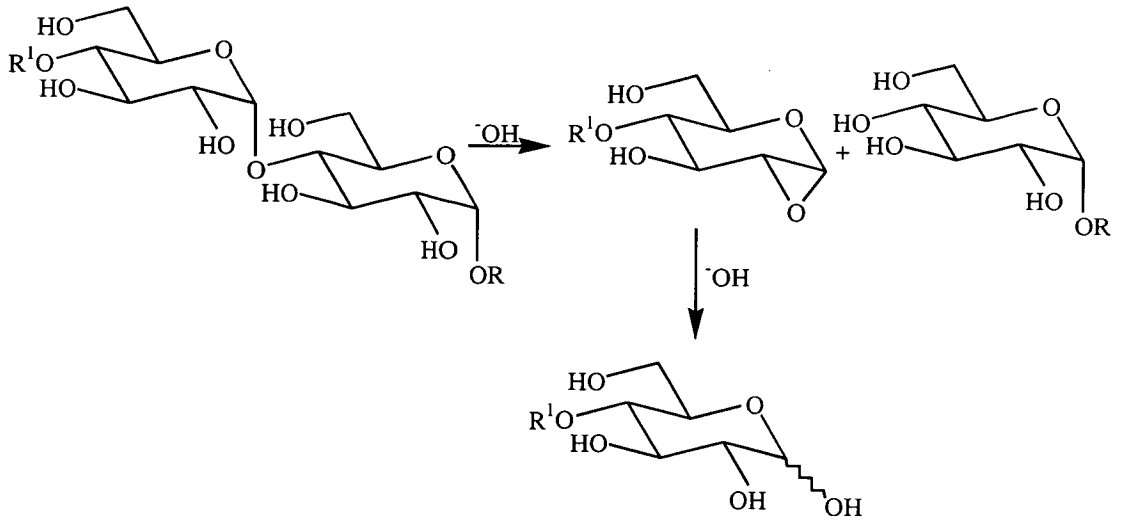


Scheme 1

As expected, oxidation in an alkaline medium leads to fairly severe depolymerisation[5] through oxidation of the end units (Scheme 2)[56], and cleavage of the glycosidic linkages (Scheme 3)[56].


HO
R_nO
HO
O
HO
OH
HO
R_nO
HO
OH
H
HO
O
HO
R_nO
HO
O
OH
H
H
OH
i) ^-OH
ii) tautomerisation
HO
$R_{n-1}O$
HO
O
HO
OH
+
HO
O
OH
H
O
OH
further degradation to a complex mixture of acids
complex mixture of acids

Scheme 2



Scheme 3

Addition of Co^{II} salts which normally accelerate hypochlorite oxidations do not affect the reaction rate of polysaccharide oxidation, although they do lower the average molecular weight of the products, *i.e.* it increases glycosidic cleavage and / or reducing end group oxidation[52]. This is perhaps an indication that no homolytic reaction is required in the polysaccharide oxidation, since cobalt (II) salts are typically used in this type of situation to generate chloroxy radicals from the hypochlorite ion according to equation **1**.

$$Co^{2+} + {}^{-}OCl \rightarrow Co^{+} + {}^{\cdot}OCl \qquad \mathbf{1}$$

In acidic solution, hypochlorous acid is formed, which can oxidise the C(6) hydroxy group in polysaccharides, hence the reaction is most selective (and least degradative) at pH 7[55].

Yields can be increased by addition of a bromide catalyst such as sodium bromide[57]. This increase can be attributed to conversion of bromide to hypobromite by hypochlorite as illustrated in Figure 3 since HOBr has a slightly higher pK_a than does HOCl, and moreover reacts faster and at higher pH (>9) than hypochlorite.

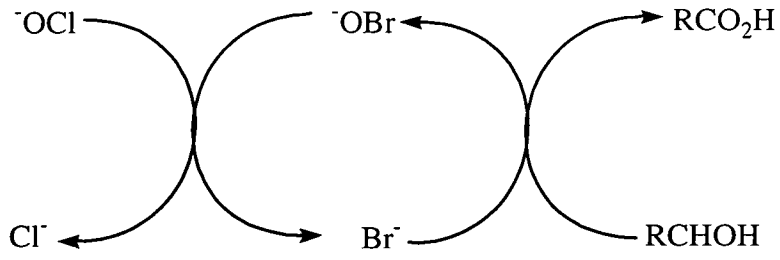
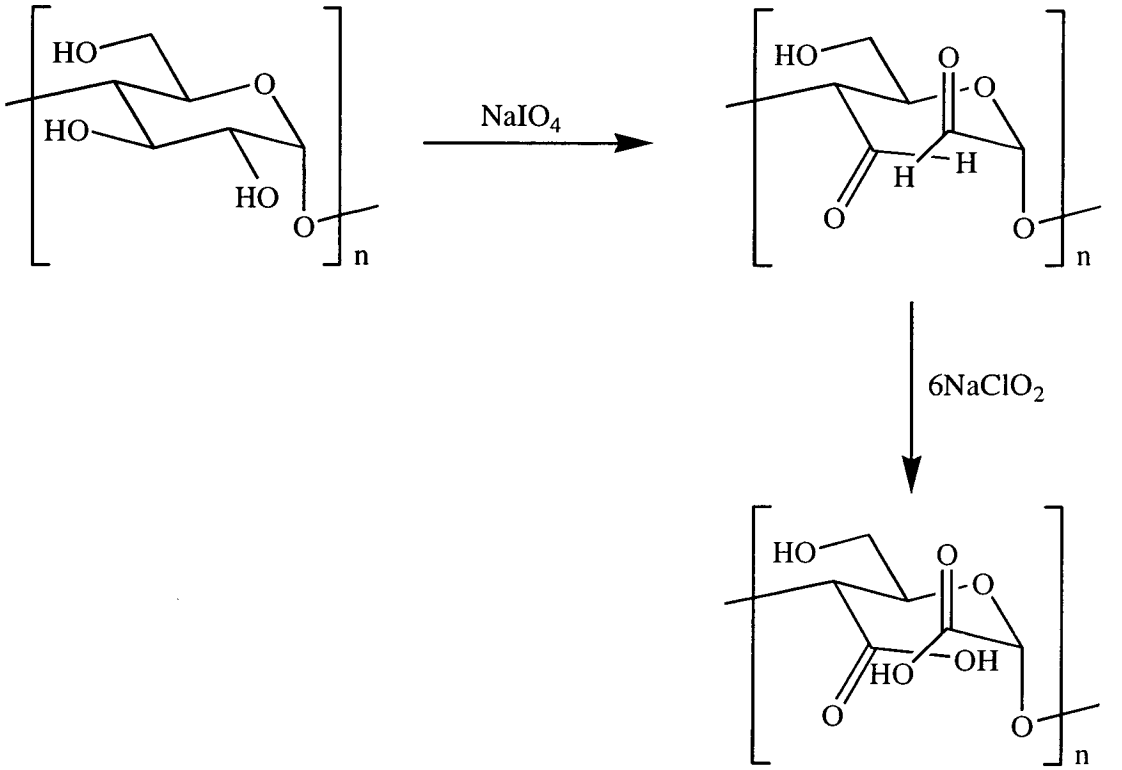


Figure 3

Furthermore a relatively low concentration of hypochlorite can be maintained throughout the reaction. These factors together inhibit the decomposition of hypochlorite to hypochlorous acid which dissociates at pH levels above 7, leading to side reactions and decomposition. Where the oxidation is performed at pH <7 extensive glycosidic hydrolysis is observed leading to large-scale depolymerisation.

1.5.2 Chlorite oxidation

C(2) and C(3) oxidation to dicarboxyl groups can be performed more efficiently by using a two step sequence involving initial selective and highly efficient periodate oxidation, followed by chlorite oxidation, (Scheme 4)[54,58-60].



Scheme 4

The overall process is inefficient, through inefficient use of the oxidant, since for each equivalent of chlorite involved in the oxidation, another two are consumed through the formation of chlorine dioxide in a side reaction, (Equations 2 and 3).

$$R\text{-}CHO + ClO_2^- \rightarrow RCOO^- + HOCl \qquad \mathbf{2}$$

$$HOCl + 2ClO_2^- \rightarrow 2ClO_2 + Cl^- + OH^- \qquad \mathbf{3}$$

Interestingly, hydrogen peroxide can be used as an inexpensive and efficient scavenger of hypochlorous acid, (Equation 5), and in consequence reduce the consumption of chlorite by four moles[61].

$$HOCl + H_2O_2 \rightarrow HCl + H_2O + O_2 \qquad \mathbf{4}$$

Using 2 moles chlorite : 2 moles peroxide produces a reaction which is less chain degrading and slightly more efficient than that using six equivalents of chlorite. Yields of up to 85% conversion of dialdehyde units can be achieved, but there is some resistance to oxidation due to the formation of intramolecular hemiacetals, as shown in Figure 3.

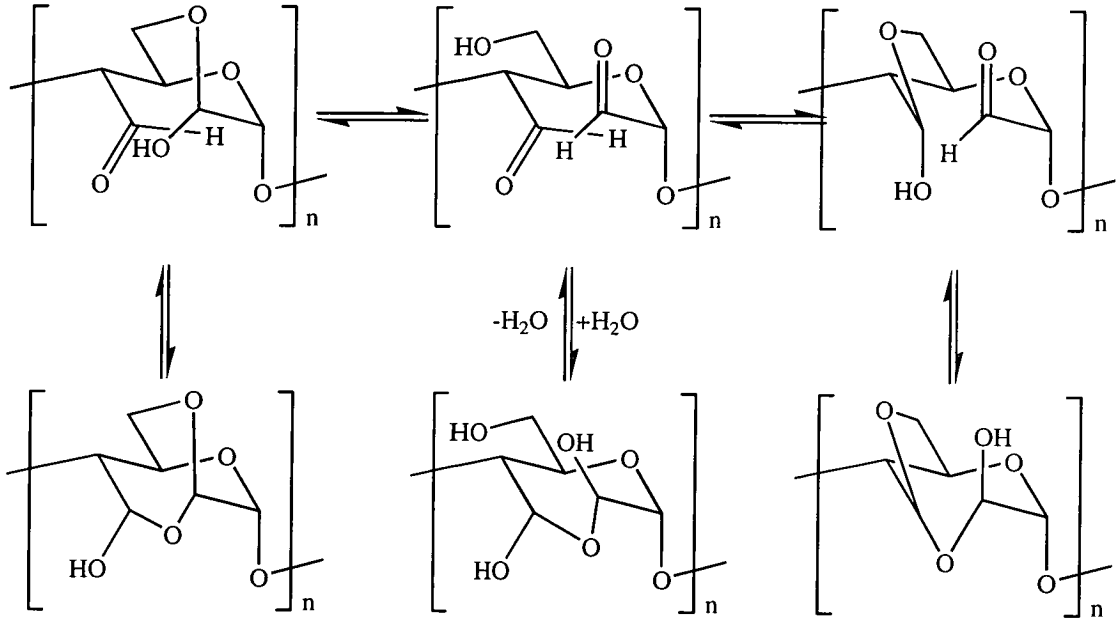


Figure 3

The scavenging reaction (Equation 4), is catalysed by alkali, the presence of which causes extensive depolymerisation.

1.5.3 Aqueous bromine oxidation

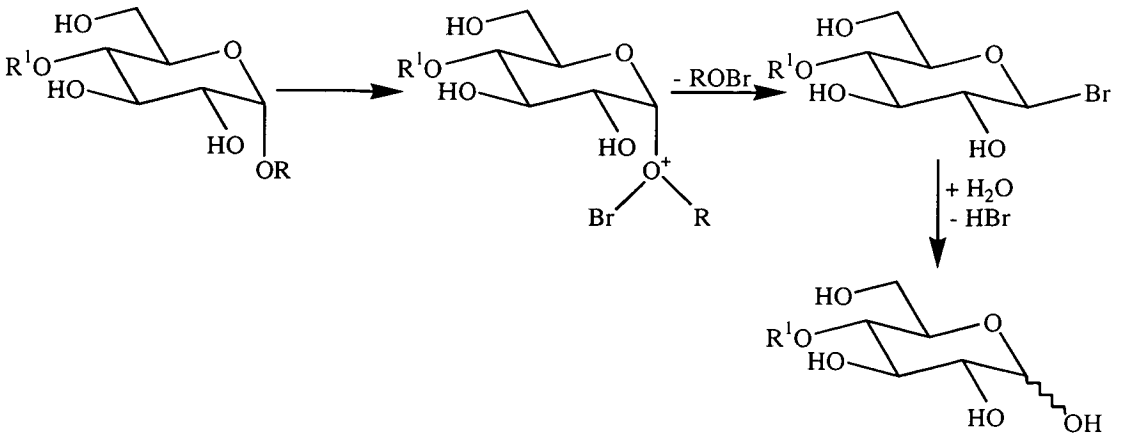
Oxidation with bromine in aqueous solution at pH 7 is a selective method of introducing carbonyl groups into various types of glycosidic units[62]. The overall process involves C(2)-C(3) cleavage to form carboxyl units, with inevitable depolymerisation. Indeed, the average molecular weight of the products decreases with increasing oxidant concentration[63,64]. More severe conditions (lower pH, higher oxidant concentration) are reported to introduce aldehyde and carboxyl units at C(6).

Oxidation of amylose (and amylopectin) give functional group ratios that depend upon pH[65], *e.g.*

	pH	Aldehyde	Carboxyl
Amylose	6 - 7	3	1
"	8	1	1

Oxidation of amylopectin is less variable with pH, although fewer carboxyl groups arise with increasing pH. Both polymers show similar reactivity at oxidisable sites, [C(2) and C(3)].

As noted above, there is extensive depolymerisation during oxidation. This is possibly due to β-alkoxy elimination reactions engendered by keto groups at C(2) or C(3) (or by aldehyde or carboxyl groups at C(6)). It is also possible that bromonolysis occurs at the α bond to the glycosidic oxygen coupled with solvolysis as outlined in Scheme 5.



Scheme 5

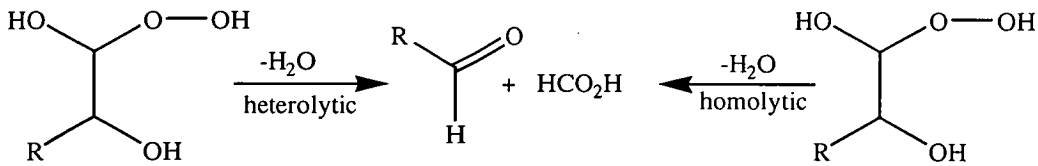
Model studies with methyl α- and β-D-glycosides show the oxidation occurs initially *via* the formation of a keto glycoside (optimised at pH 7) in the 2 (favoured), 4 or 6 positions (β anomer less selective with 2, 4 and 6 carbonyls formed in equal amounts)[66,67]. The selective formation of these keto groups indicates that there are steric factors affecting the position of oxidation, with reaction at C(3) being prevented by the methoxy group. Assuming a $^4C_1$ conformation, there is a 1,3 diaxial interaction between the hydrogen to be eliminated and the methoxy group, and consequently the approach of the oxidant is hindered.

Further oxidation then takes place by a mechanism presumably involving enolization, followed by hypobromite attack and then elimination of HBr, such a mechanism being analogous to the enediol mechanism outlined in Scheme 1 (Path B).

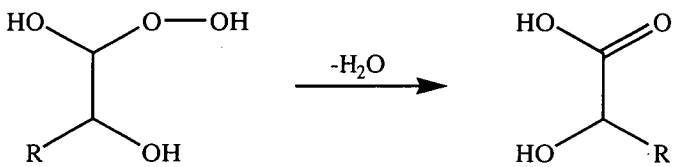
1.5.4 Hydrogen peroxide oxidation

Possibly the most environmentally appealing oxidant, the action of alkaline hydrogen peroxide on polysaccharides appears to be mainly degradative[68,69] coupled with extensive oxidation of the reducing end units[70]. This degradation can occur by five different pathways as outlined in Scheme 6[71].

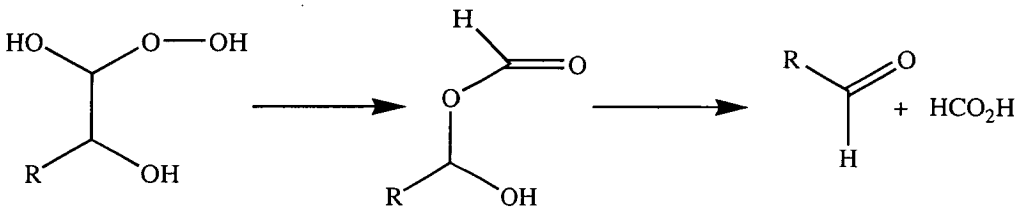
a) α - hydroxy hydroperoxide cleavage



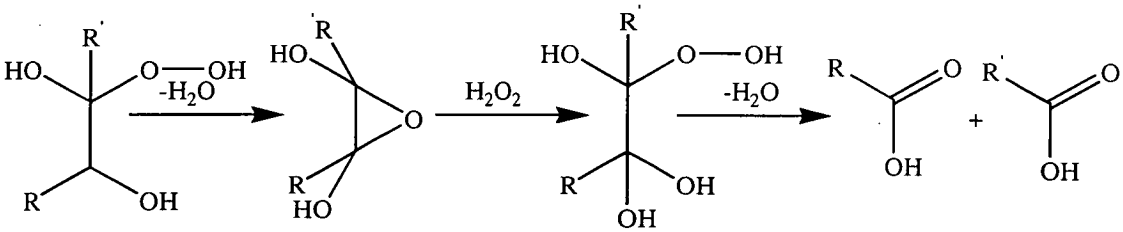
b) ester mechanism



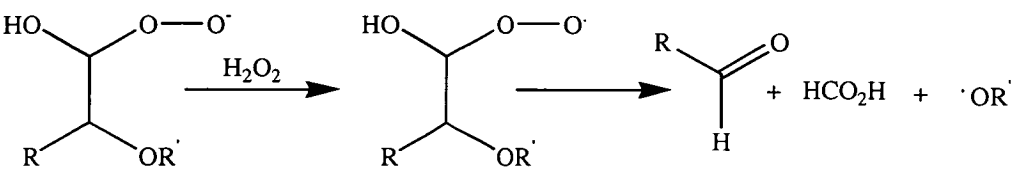
c) Baeyer-Villiger mechanism



d) dihydroxy - epoxide mechanism, "The Hock cleavage"

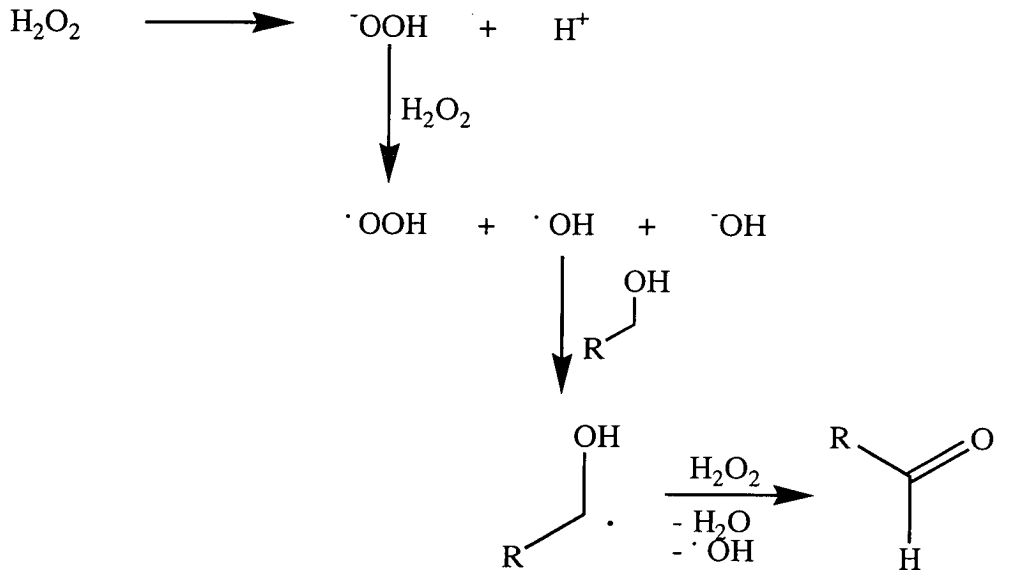


e) peroxy radical mechanism



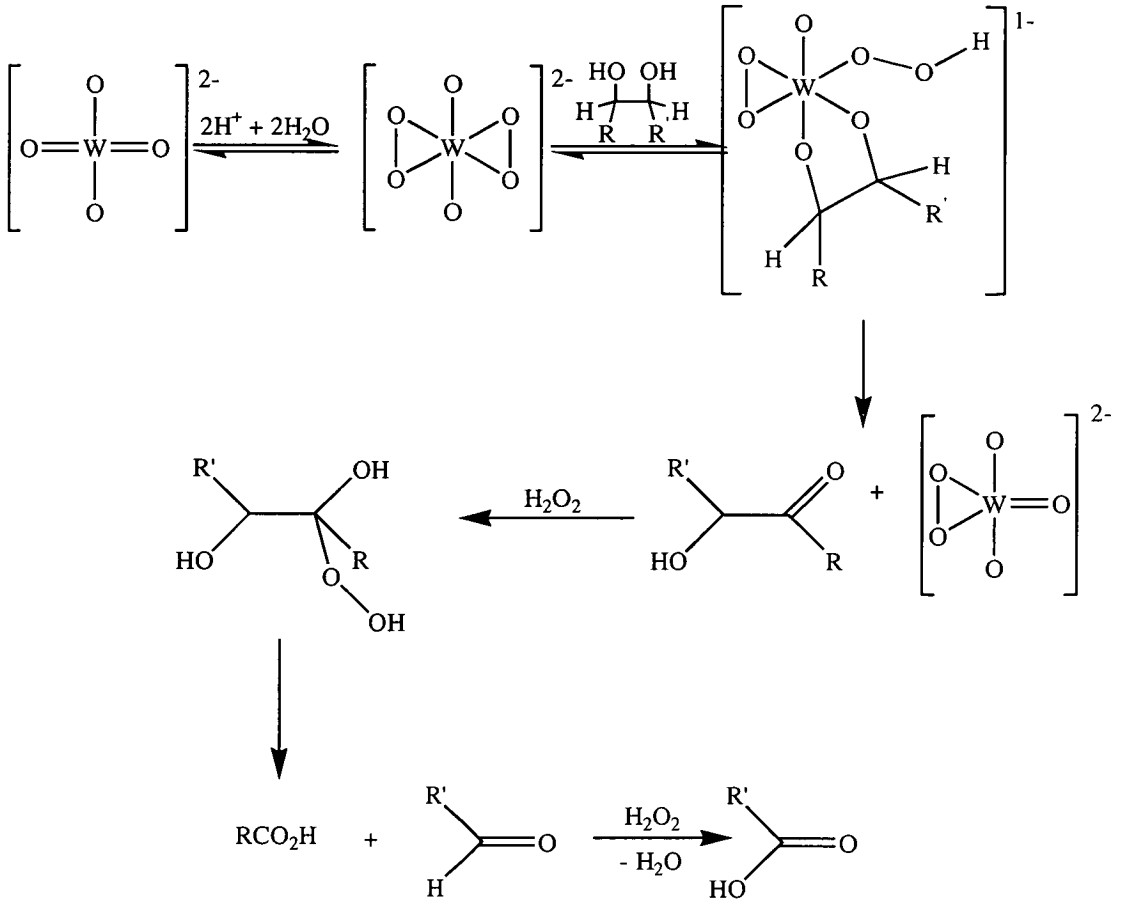
Scheme 6

All the degradations in Scheme 6 are initiated by the attack of a hydroperoxy anion at a carbonyl group, the formation of which under the given conditions requires hydroxy radicals. These can be generated from hydrogen peroxide by either alkaline conditions as depicted in Scheme 7 although this is a relatively slow process, or various metal ions (*e.g.* Fenton's reagent, copper, manganese), present deliberately or as impurities.



Scheme 7

The process of degradation can be partially overcome by using tungstate hydrogen peroxide with an excess of peroxide to inhibit *tris*-diol salt formation[72]. The reaction then proceeds *via* a heterolytic pathway as shown in Scheme 8.

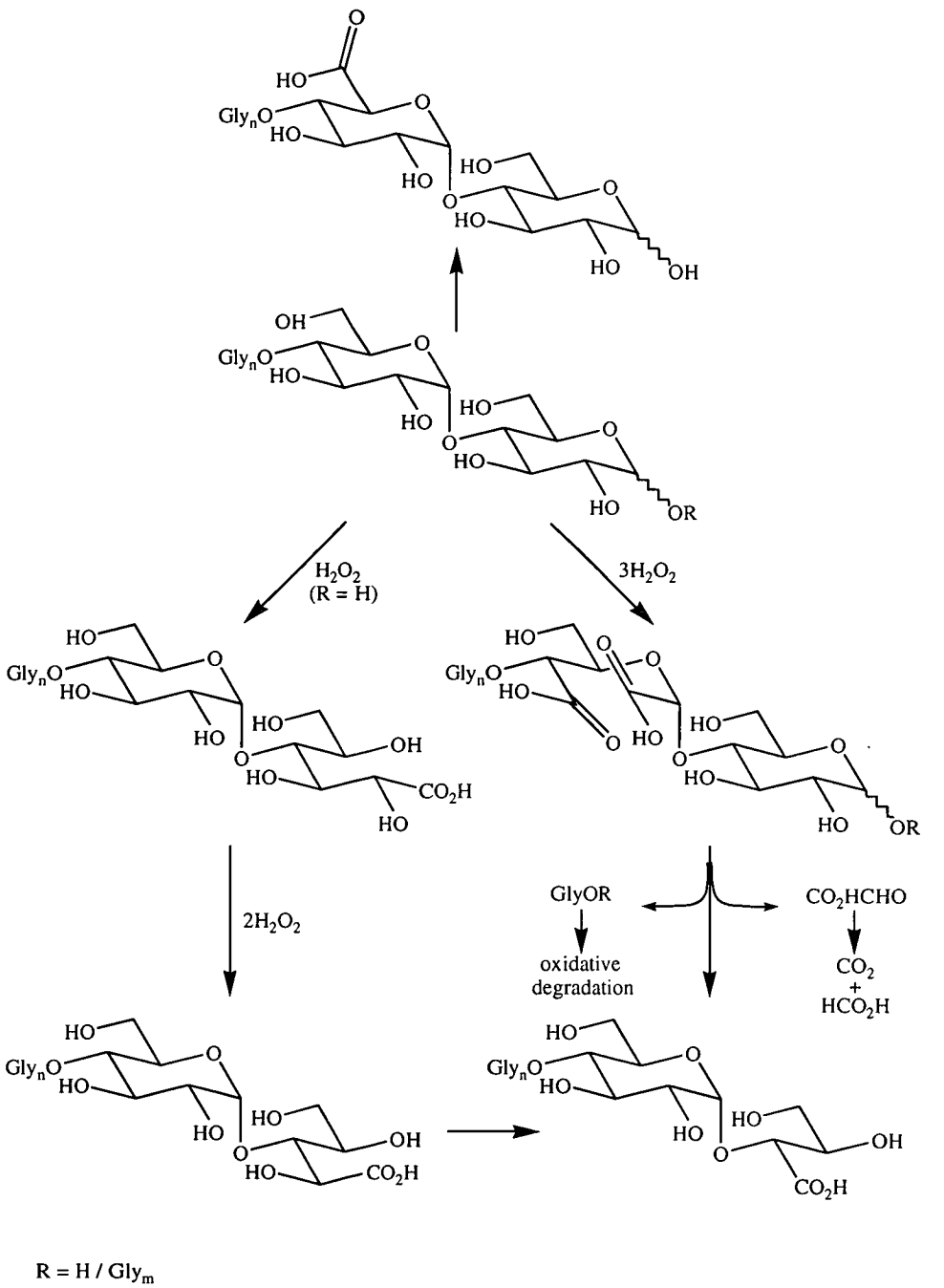


Scheme 8

In this system, low pH is desirable for the oxidation efficiency. Since the active species is tungstic acid protonation increases the rate of oxidation, and hence the oxidation occurs with greatest ease at low pH. However, at pH < 2, the rate of hydrolysis of the glycosidic bond in carbohydrates greatly increases.

Moreover, the reaction products preferentially complex to the tungsten centre which leads to catalyst poisoning and so low yields. There are also two competing reactions, involving C(2)-C(3) glycol cleavage, and stepwise decarboxylation at the reducing end. The outcome is further complicated by partial C(6) oxidation as shown in Scheme 9. It should be noted here that primary alcohol oxidation under the given

conditions is a relatively slow process, and it may indicate another piece of chemistry occurring, *e.g.* indiscriminate radical attack, some factor slowing the rate of secondary oxidation, or possibly some other macromolecular effect.



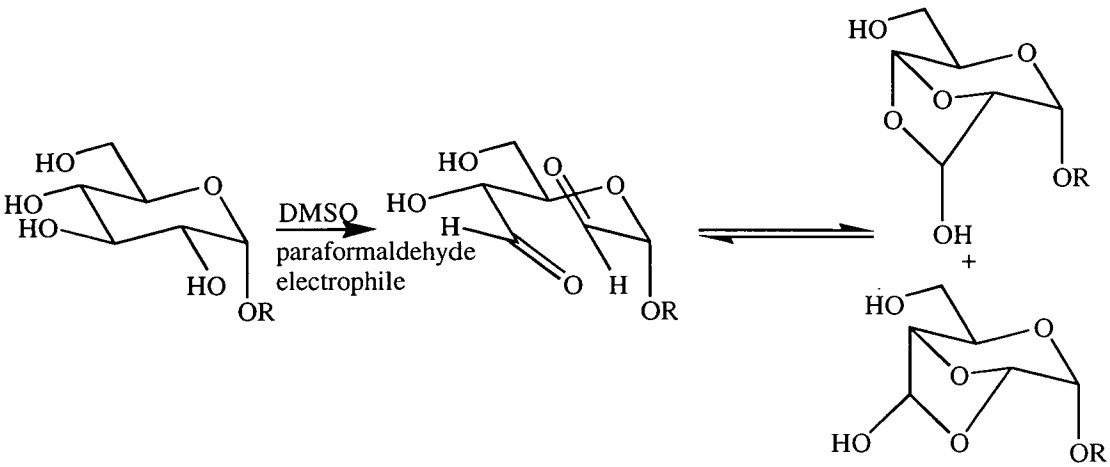
Scheme 9

1.5.5 Dimethylsulfoxide based oxidations

DMSO-paraformaldehyde has been shown to be a selective oxidant of homopolysaccharides, through the reversible formation of a hemiacetals between both the 6- and 2-hydroxy groups and formaldehyde, resulting in polyoxymethylol chains of statistical length (depending on reaction conditions). An electrophile used in conjunction with DMSO, such as an acid anhydride, will oxidise the only available hydroxy group (*i.e.* C(3)) smoothly[73,74].

If the C(6) hydroxy group is blocked then there is predominantly oxidation at C(2), since this is sterically favoured. It should be noted however that even with a free C(6) hydroxy group there is some C(2) oxidation (accounting for *ca.* 10% of all oxidised sites of amylose under these conditions), reflecting the reversibility of the hemiacetal formation.

Oxidation of methyl glycopyranosides (as polysaccharide models) in DMSO by periodic acid showed no selectivity in oxidation, with C(2)-C(3) or C(3)-C(4) cleaved to dialdehyde. However, with a 1→4 homopolysaccharide this reaction will presumably only result in C(2)-C(3) cleavage. Moreover, the reaction stops at a dialdehyde compound, the reason being postulated as the formation of two internal acetals, outlined in Scheme 10 (R=Me).



Scheme 10

1.5.6 Depolymerisation

As already mentioned, the principal drawback to all of the above oxidation methodologies is the extensive depolymerisation which occurs. Amongst other difficulties this presents depolymerisation will consequently lessen the potential of the product to act as a surfactant since these properties are directly related to the size of the molecule.

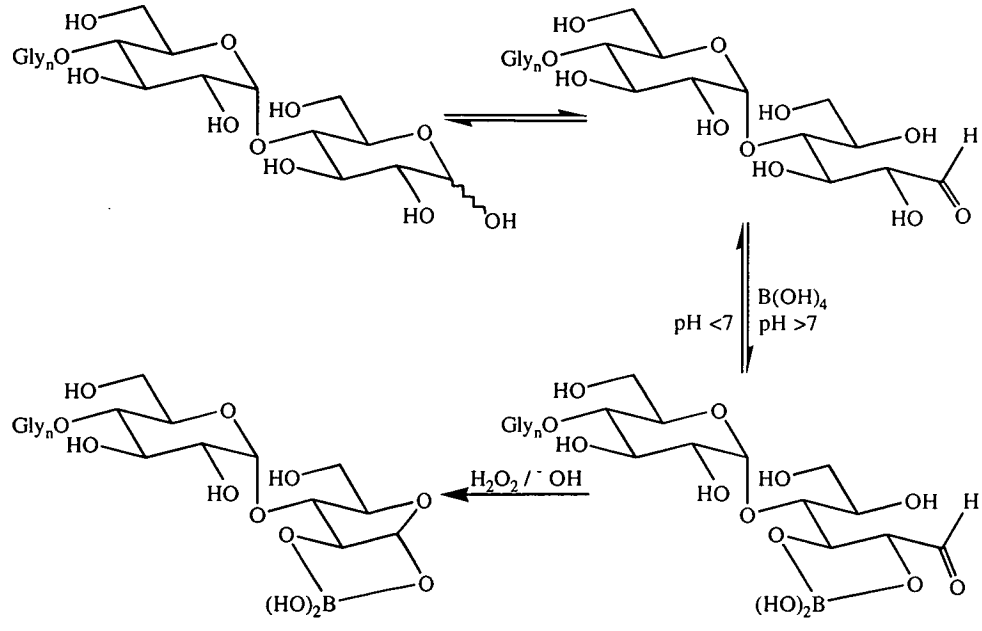
In an attempt to alleviate this and other problems, many novel and alternative approaches have been tried in an attempt to either use milder conditions, or to include some dynamic protecting group as a reagent.

Possibly the most obvious approach to take is to use an enzymatic oxidation where by careful choice of enzyme the extent of depolymerisation could be substantially reduced if not eradicated. However the most common enzymatic oxidations with this type of polymer are performed on the primary alcohol by enzymes such as *Galactose oxidase*. Moreover enzymatic oxidation on the scale

required by industry is not seen as a particularly viable method[75], with the preference being to use a cheaper and more readily available alternative with the absolute preference being the use of either oxygen or hydrogen peroxide in the presence of some catalyst.

Obviously the use of soluble catalysts with this type of compound is to be avoided, since their recycling is difficult at best (a major disadvantage to using the moderately expensive sodium periodate mentioned previously). Thus, research is focusing upon the use of heterogeneous oxidation catalysts[76] which it is hoped will eventually be of use in continuous mode operation. Currently the literature does not hold many examples of this type for oxidative glycol cleavage though there are examples, principally using magnesium or platinum based catalysts for the less industrially attractive primary alcohol oxidation.

One of the most ingenious solutions to these degradations was proposed by the group of van Bekkum[77] who use a dynamic borate ester protecting group to protect the reducing end of the polysaccharide. Thus they exploit the availability of a *trans-vic* diol relationship in glucose to form preferentially a borate ester under alkaline conditions as shown in Scheme 11. They do not however make any mention of degradative effects which under alkaline conditions would be expected.



Scheme 11

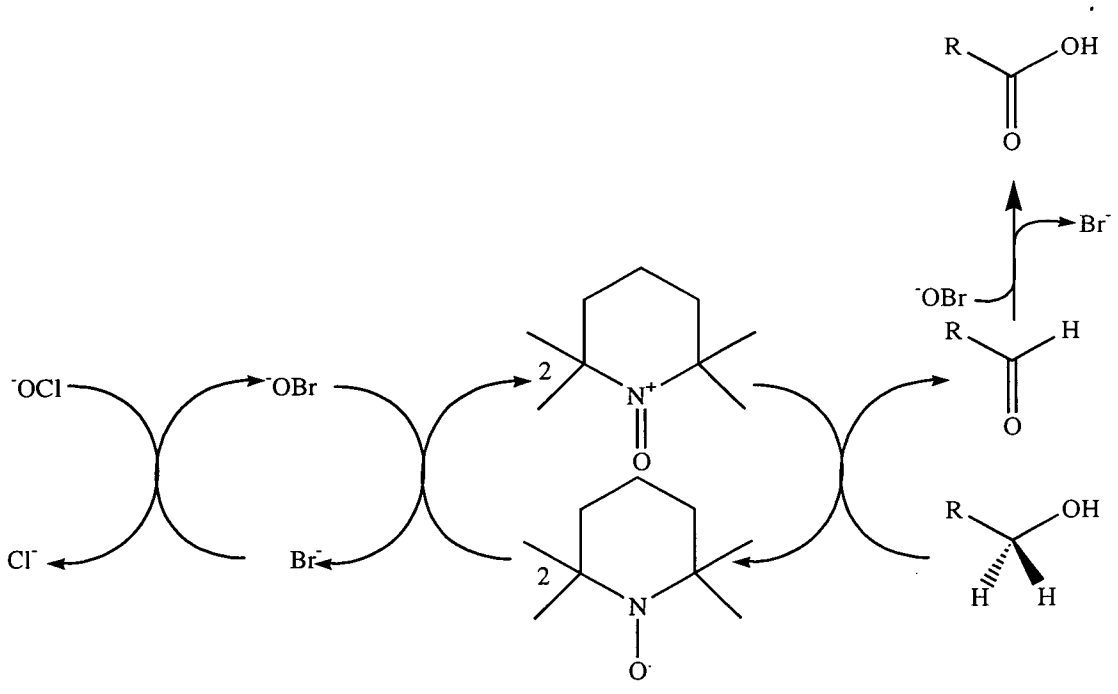
1.6 C(6) Oxidation

Although less attractive industrially, regioselective oxidation of the primary alcohol in a variety of carbohydrates has received considerable attention.

Kenyon and Yackel[78,79] noticed that the oxidative action of nitrogen dioxide on cellulose produces mainly polyuronic acid species, *i.e.* C(6) is oxidised with little apparent degradation. The reaction appears highly efficient, with >90% conversion of primary alcohols to carboxyl groups. Kerr[80] later repeated the work using amylose and amylopectin, and found that this oxidation is not as selective as was first thought. Indeed, he realised that Kenyon's results had been influenced by the oxidation of terminal aldehyde groups, formed by hydrolytic cleavage of the polymer.

Nevell[81] showed that liquid N_2O_4 could be used to oxidise C(6) of cellulose, however, the heterogeneous conditions employed mean that the more accessible chains are excessively exposed to the reagent before the others can react, and so depolymerisation is severe (and moreover, the products contain nitrogen). He later expanded this work, and showed sodium nitrite could be used as a more efficient oxidant[82,83]. Such oxidation of cellulose was not absolutely C(6) specific, but resulted in C(2) and C(3) keto groups which could be stereoselectively reduced with aqueous sodium borohydride. Repetition of this work with amylose showed that severe depolymerisation arose, presumably from non-specific oxidation, however, it was noted that this may be controlled by carrying out the oxidation in steps, with borohydride reduction after each. (This would however, have its own associated problems, since under the alkaline conditions of the borohydride treatment, β-elimination engendered by the keto groups would compete with reduction).

Van Bekkum[84] recently showed that 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) could be used to oxidise primary hydroxyl groups in polysaccharides. The procedure is a two-step, one-pot one mediated by TEMPO, with hypobromite used as the regenerating oxidant shown in Scheme 12.



Scheme 12

Competing secondary hydroxyl oxidation is relatively slow, and is inhibited where pH>9 (the reaction is generally carried out at pH≈11). Yields >98% are reported for starch, with 98% C(6) selectivity, however, no mention is made of any degradative effects, which would again be expected under alkaline conditions.

2.0 Discussion

2.1 Model Compounds

2.1.1 Preamble

When examining or designing any process which involves a complex natural molecule, it is often prudent to examine a smaller, representative model system. This approach has many advantages, but of course also inherent drawbacks. The principal advantages are outlined below:

- Consistency of starting materials, both in terms of chemical consistency and size. By their very nature, natural polymers will not be of a rigidly defined size, more of a Gaussian distribution of molecular masses. This in turn means that an average molecular weight can be inferred, though it is obviously then self-evident that all reaction stoichiometries will similarly be approximate.
- Analytical investigation. Many modern analytical techniques (with specific reference to nuclear magnetic resonance spectroscopy) widely used in organic chemistry rely on particular atoms occupying well defined environments. Where large polymers are subject to spectroscopic analysis, often the resulting data is characterised by broad, overlapping absorbtions when more useful data would be obtained in the form of narrow identifiable absorbtions. This effect is a result of the spectrometer averaging the signals produced by chemically equivalent nuclei, that are made magnetically inequivalent by macromolecular effects such as twisting and coiling. To further confuse matters, very little information can be gleaned on the mass of the great majority of polymer reaction products

since there is a distribution in the masses of starting materials as mentioned already. Furthermore, most common spectroscopic mass determinations are inapplicable since there is the obvious difficulties incumbent upon producing a volatile charged molecule, and even when this is achieved it then requires considerable computation to interpret the data produced from the many possible multiply charged species. The use of a small model means that spectroscopic data is much more readily obtained and interpreted.

- Purification. Where large molecules, and especially very polar ones are involved, there is often no way to purify the products of reactions performed on them. A simple example would be to consider the difficulties involved in separating two products differing by fifty of their repeating units in molecules composed of over three hundred units. Obviously their gross molecular properties are essentially identical, and consequently to all intense purposes inseparable. Thus, it is greatly beneficial to use a small, well defined model, whose reaction products are more likely to exhibit sufficient differences in molecular properties to allow purification.

Of course no system is perfect, and there are disadvantages to be found in attempting to model any system. The principle disadvantage to using this modeling approach is something noted above also as an advantage. Whilst macromolecular effects pose considerable problems in analyses, such effects can often influence a reaction to a much greater effect than can ever be accounted for by a small

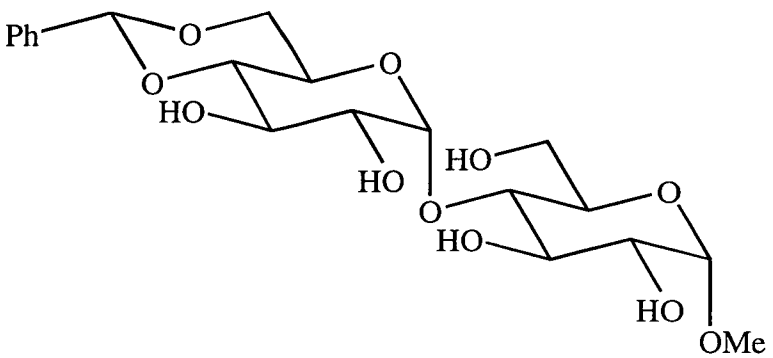
compound. Thus for example in a given solvent such as water, a large polymer may form coils with hydroscopic outer coils and hydrophobic inner pockets (any number of examples of this type of behaviour can be found by looking at proteins, which themselves are a peculiar branch of natural polymer chemistry). In turn, this means that any reagent introduced into such a solution will be at far greater relative concentrations on the outer part of the molecule than in the inner core, and it is not inconceivable that a reaction might need a much larger reagent concentration to be initiated than would be predicted by a small model, the molecular changes thus produced then altering the macromolecular properties permitting the polymer to behave more akin to the smaller model.

However this said, the benefits to be realised in using a small model compound significantly outweigh the disadvantages, providing no attempt is made to account for any macromolecular effects in the modeling process. More realistically, the whole process of modeling should be considered as a first step to understanding the gross reaction properties of a large molecule.

2.1.2 Dimeric model

Before embarking on any form of model studies, it is important to decide on the properties of the macromolecule which are required in this smaller model compound. Since here the interest lay in studying oxidations of starch which as previously described (see 1.2) is composed of two glucose based polymers, namely amylopectin and amylose, the model compound should likewise be glucose based,

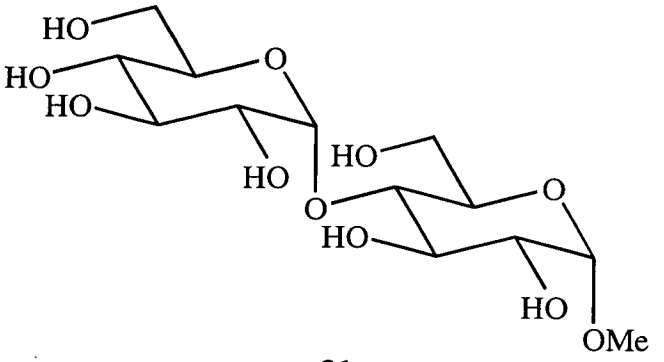
not least since this maintains the correct stereochemistry. Also, by far the most labile bond in the polymers is the glycosidic linkage, and so the chosen model should also contain at least one. Finally, since the glycosidic bonds in amylopectin comprise approximately 4% 1→6 linkages (which make the "branching points" mentioned previously) alongside the 1→4 linkages, the model should have a protected primary alcohol. The simplest molecule which fulfills these criteria is methyl 4-*O*-(4′,6′-*O*-benzylidene-α-D-glucopyranosyl)-α-D-glucopyranoside, **30**.



30

It should be noted here that the reducing position of this model has been blocked by a methyl group. The reasoning behind this is simply that in the great majority of glucose units in either amylose or amylopectin the anomeric position is blocked by the next glucose unit in the polymer. The methyl glycoside was chosen since it was the smallest possible carbon based group and so could be expected to show the least adverse effect.

Formation of the benzylidene acetal was not expected to pose any great difficulties, and so work initially focused on the synthesis of methyl 4-*O*-(α-D-glucopyranosyl)-α-D-glucopyranoside, **31**, also known as methyl α-maltoside[85-88].

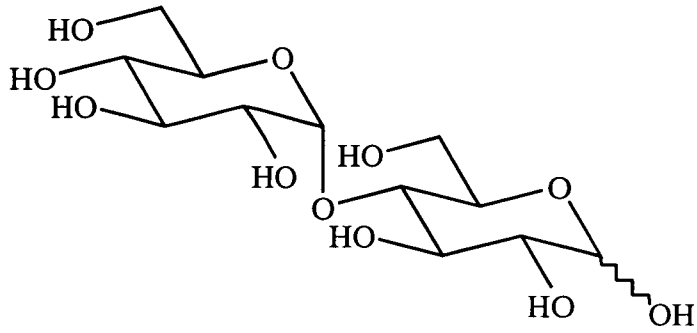


31

2.1.2.1 Attempted acid catalyzed glycosidic methylation

Maltose **32**, the octahydroxy precursor to **31** is readily available, and it was initially hoped to form the methyl acetal using some form of acid catalysis. Whilst of course the glycosidic bond is labile under acidic conditions, previous work in other groups had shown that it was possible to form glycosidic methyl acetals of oligomeric carbohydrates, albeit typically in only very low yield[85-88].

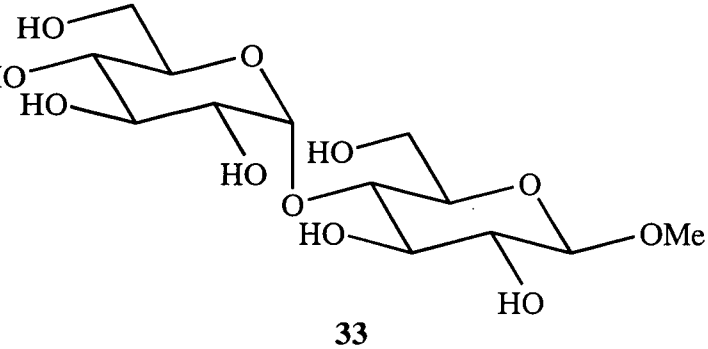
It was felt that a possible contributor to these low yields would be the presence of water, and so the glycosyl formation was attempted under anhydrous conditions, shown in Scheme 13.



32

a) $HCl_{(g)}$, MeOH
b) $HCl_{(g)}$, MeOH,
4Å mol. sieves

31 +

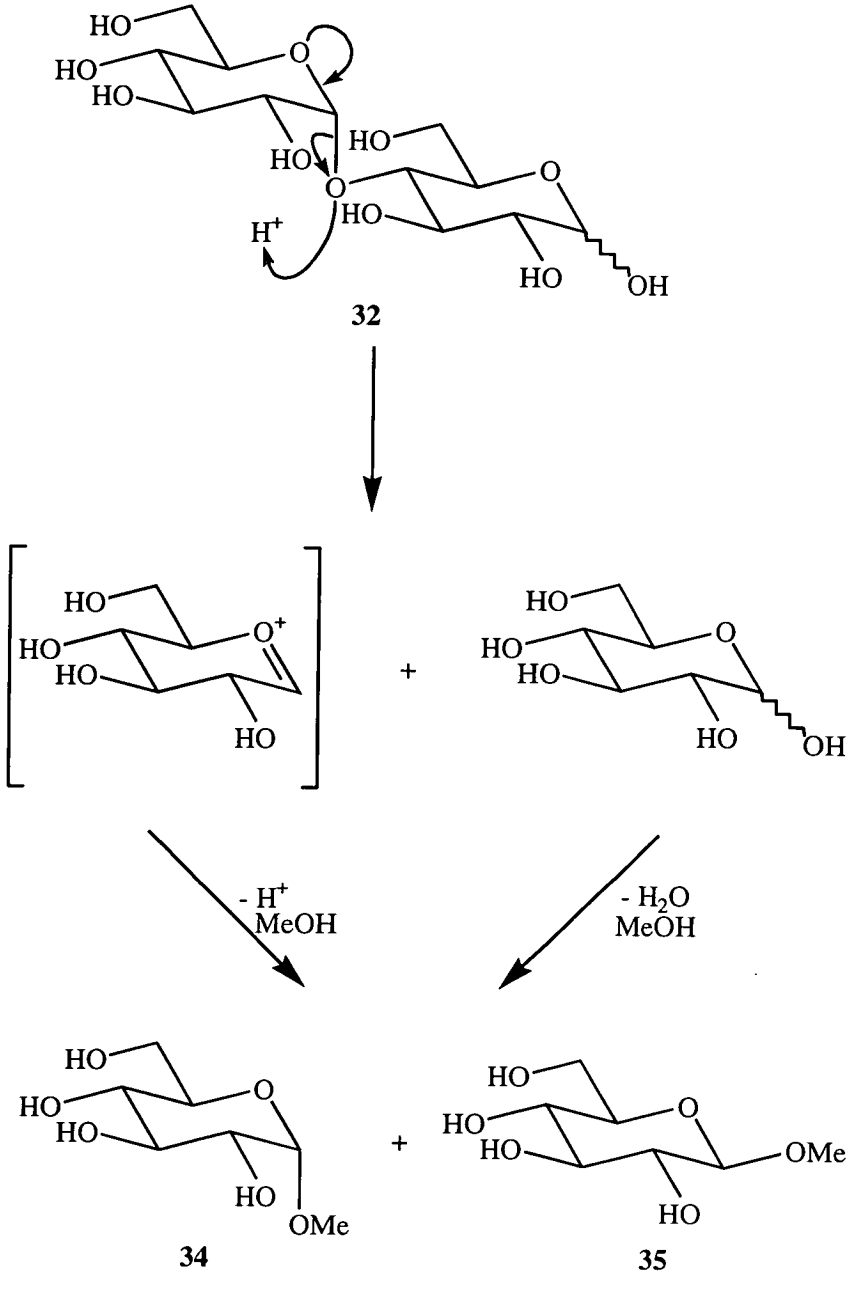


33

Scheme 13

Since the reaction was allowed to proceed under thermodynamic control, any glycosylation would result in the production of an anomeric mixture of *ca.* 3:1 **31**:**33** (*i.e.* α:β). However, it is well documented in carbohydrate chemistry that anomerically isomeric materials typically exhibit physical properties differing enough to allow for ready separation by recrystallisation. Thus, no major difficulties were anticipated in the purification and separation of the reaction product.

However, perhaps not unexpectedly under the initial reaction conditions (a), only a mixture of methyl glycosides (**34** and **35**) of the breakdown products were observed as a result of acidic hydrolysis followed by methylation, shown in Scheme 14.



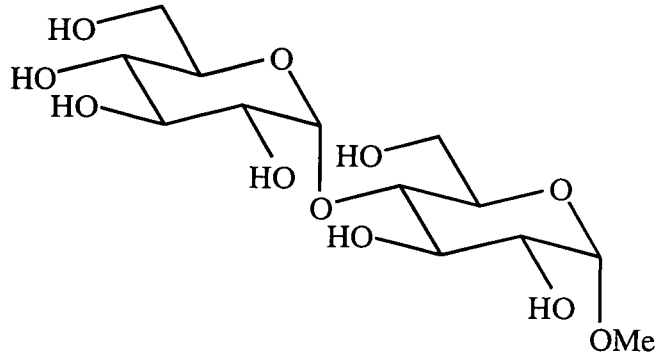
Scheme 14

In an attempt to maintain the anhydrous conditions throughout the reaction, rigorously dried 4Å molecular sieves were included in the reaction mixture. These however were found to scavenge for hydrochloric acid more efficiently than for water, and so no reaction was observed.

In light of this it was decided to tackle this synthesis using a convergent synthetic approach.

2.1.2.2 Retrosynthetic analysis

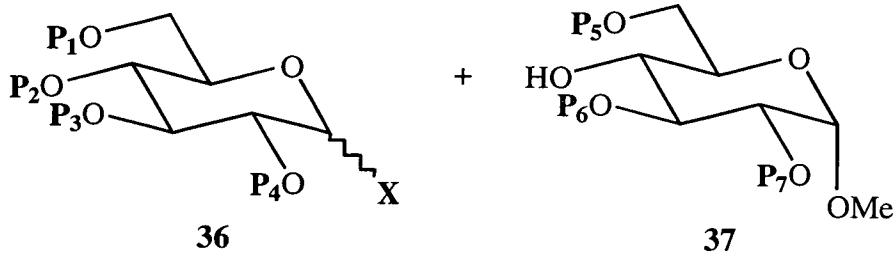
When applying common retrosynthetic analysis to **31** the obvious disconnection is that of the bond to the methyl glycoside. However as previously noted, this proved to be problematic. Thus the next most logical disconnection was that of the other glycosidic bond, yielding two glucose based precursors **36** and **37** as shown in Scheme 15.



31

Deprotection

Stereospecific glycosidation



36 **37**

P_x = Protecting group
X = Leaving Group

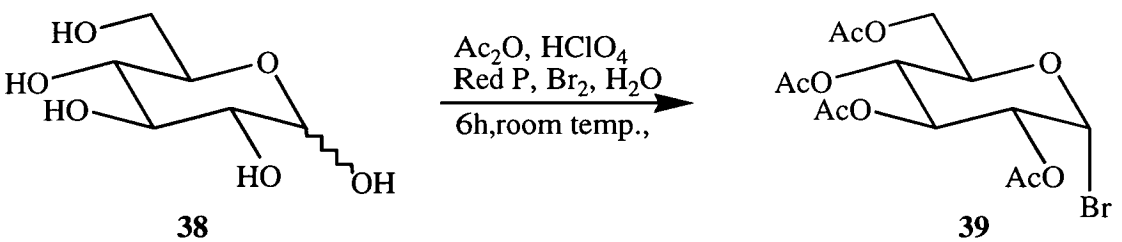
Scheme 15

Closer examination of the criteria that both **36** and **37** must meet, points towards a protecting group strategy such that the relevant groups can be manipulated independently in high yield.

The key step in this approach would of course be the stereospecificity or otherwise of the glycosidation step. There exist a variety of means to control stereospecificity in this type of reaction with the most convenient featuring as a suitably protected precursor a glycosyl halide.

2.1.2.3 Choice and synthesis of 36

Of the two glucose based molecules **36** and **37**, **36** appears to be the simplest to synthesize. Having decided that a glycosyl halide would be the most readily synthesized type of compound possessing a sufficiently labile leaving group, a search of the literature yielded a simple compound possessing all the salient features, namely **39** *i.e.* **36**: $P_1 = P_2 = P_3 = P_4 = Ac$; X = Br, which could be readily synthesized from D-glucose **38**, as outlined in Scheme 16.



38 **39**

Scheme 16

The obvious drawback to the use of a glucosyl halide though is that the halide will invariably occur as the α-anomer as it is more thermodynamically stable than its β-isomer. This is simply due to this particular orientation allowing the minimum

orbital overlap between the lone pairs of the oxygen and the halide[90], illustrated in Figure 4.

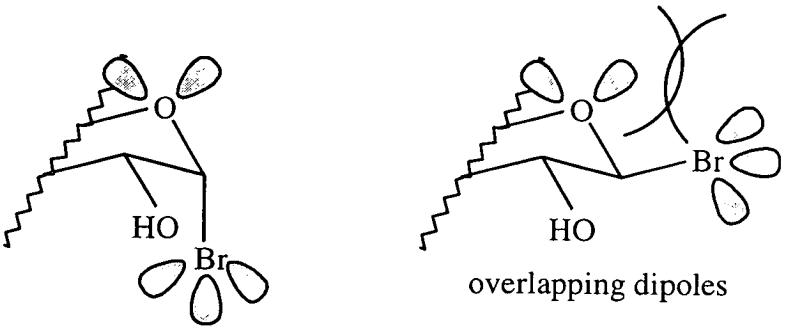


Figure 4

The stability of the α-halide of course then poses a problem in that since it is an active leaving group the most probable course of any nucleophilic attack will result in the formation of a β-product by simple displacement as shown in Figure 5.

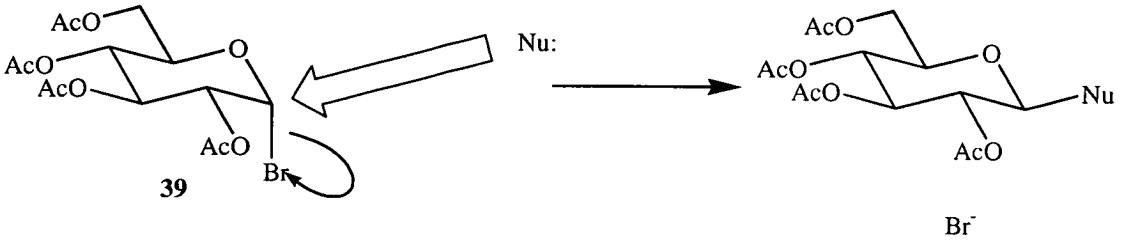


Figure 5

It is possible however to exploit the natural instability of the β-anomer to direct the stereochemistry in the opposite manner. Thus, when tetrabutylammoniumbromide is added to a solution of **39**, the resulting mixture comprises an equilibrium mixture of α- and β-halides. Although the α-halide is

considerably more thermodynamically stable than its β-analogue (Paulsen[90] has calculated a ratio of 13:1 α:β), the β-anomer is much more reactive due to its instability. This difference is further accentuated by performing the reaction in a solvent of low polarity (here dichloromethane) which has the net effect of making the β-anomer even less stable which in turn makes it a more reactive substrate. Thus, by careful control of the reaction conditions, it is possible to directly influence the stereospecific progress of this type of reaction.

2.1.2.4 Choice and synthesis of 37

Having synthesized the active glyscosyl donor **36**, all that remained was to design and then synthesize the nucleophile **37**. The chirality of this molecule obviously suggests that it be derived from commercially available methyl α-D-glucoside **43**, shown retrosynthetically in Figure 6.

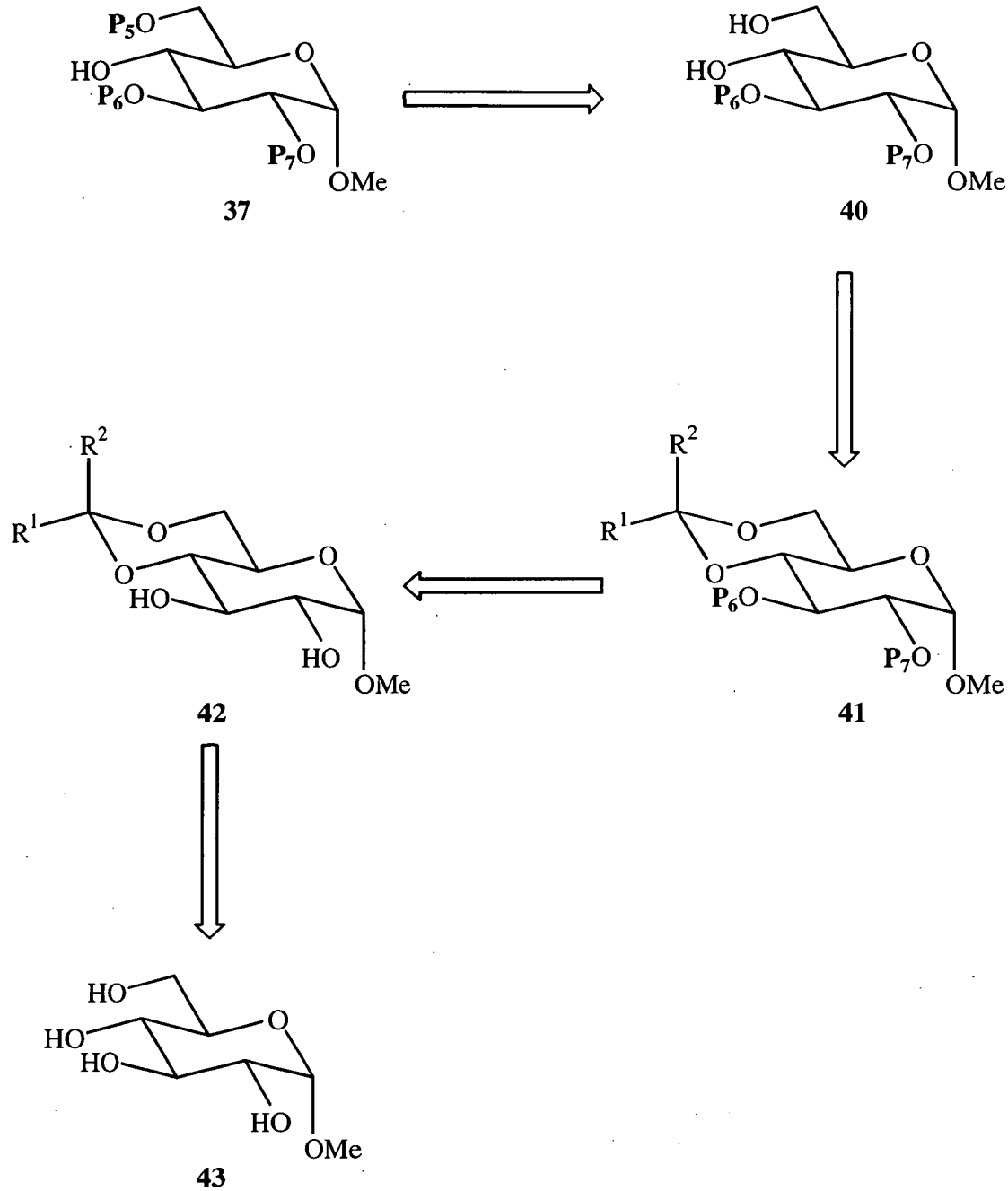


Figure 6

Working backwards through the retrosynthesis, the initial synthetic step is most easily performed by exploiting the 1,3 relationship between the hydroxy groups on positions 4 and 6 of the ring to form a cyclic acetal.

Formation of acetal **42** then allows the protection of the two remaining free hydroxyls with some group which must be stable under the conditions necessary for the deprotection of the cyclic acetal, and the subsequent protection of the primary alcohol.

The penultimate synthetic step then must be deprotection of the acetal to yield the diol **40**, the exact conditions being determined with the initial choice of acetal.

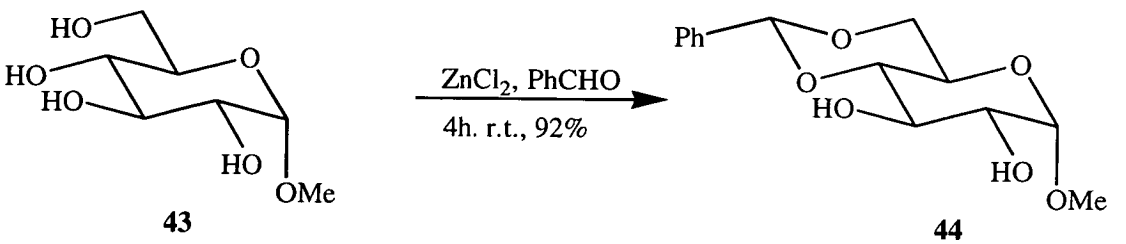
Finally, the primary hydroxyl group of diol **40** can be selectively protected using some bulky group and exploiting the different relative rates of reaction between it and the secondary alcohol to yield **39**.

2.1.2.5 Formation of acetal 42[91-97]

There exists a large range of cyclic acetals used as diol protecting groups in carbohydrate chemistry. Of these, the two most commonly used are isopropylidene acetals, typically derived from acetone and benzylidene acetals. In this case however, an isopropylidene acetal is unsuitable as any attempted synthesis would also result in the formation of methyl 2,3:4,6 diisopropylidene-α-D-glucopyranoside. Hence, the obvious choice is to use a benzylidene acetal.

Many synthetic approaches can be taken to this type of compound and there exist a variety of substituted analogues from which to choose. For convenience, both in terms of protection and deprotection, and cost, it was decided to form the 4,6-*O*-

benzylidene acetal **44** using a Lewis acid mediated reaction with benzaldehyde, outlined in Scheme 17.



43 **44**

Scheme 17

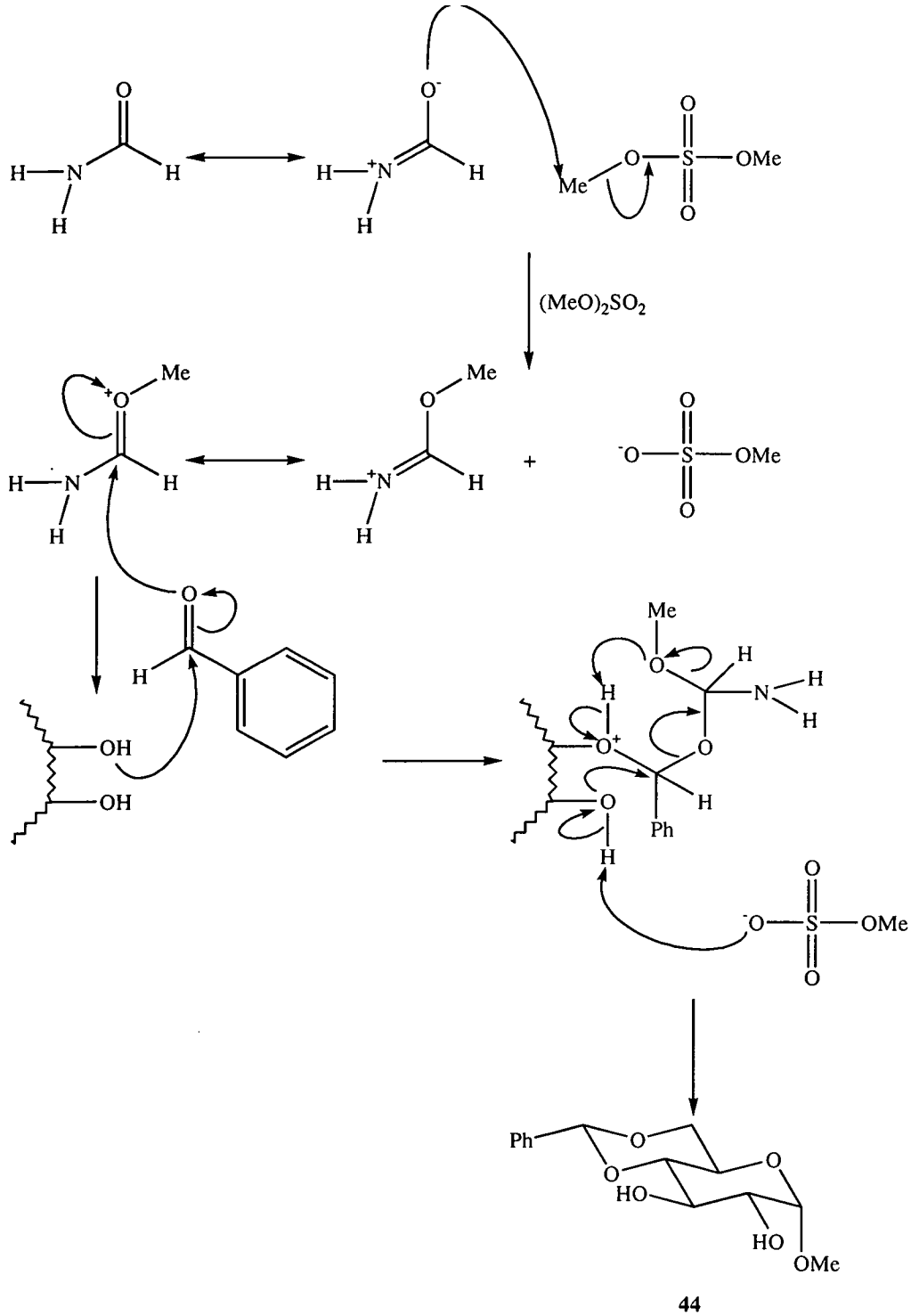
Whilst this reaction is effective on a small scale it does suffer in that as the scale increases so the yield decreases (*ca.* 60% for 8g of starting material). The reasoning behind this is simply that the whole reaction must be done under strictly anhydrous conditions, however as the acetal forms, so water is liberated. This interacts with zinc chloride (previously fused then finely ground under an atmosphere of argon), and the reaction mixture becomes very dense which in turn makes agitation difficult. Thus, the yield appears to be determined by the extent to which the mixture is maintained stirring. At the point where the reaction is no longer able to stir efficiently no further reaction is observed.

There are two literature approaches to circumvent this problem both of which were examined. Firstly, since the difficulties are a result of the liberation of water, it seemed natural to examine the use of a benzaldehyde analogue as a precursor. Specifically, α,α-dimethoxytoluene was used since it liberates not water but methanol on acetalation. Whilst partly successful, the dimethyl acetal is not as

reactive as the aldehyde and so the observed yields showed no improvements over the previous approach, (*c.f.* 43% vs. 60%).

Since the problem had been approached in terms of the acetal precursor, it then seemed logical to re-examine the step with a different catalyst. To this end, the pyridinium salt of *para*-toluenesulfonic acid[98] (PTSA) was employed with *N,N*-dimethylformamide as solvent. The salt was chosen since it is commonly employed as a very mild acid catalyst and protic acids were to be avoided to minimise hydrolysis of the glycosidic methyl acetal. Although partially successful only poor yields were obtained (*ca.* 25%).

Since a Lewis acid, and a masked protic acid had been previously employed it was decided to examine the possibility of base catalysis. An overriding concern though is the relative insolubility of the glucoside, meaning only a narrow choice of solvents were available. Thus, a combined dimethylsulfate-dimethylformamide[99] system was examined. The advantage of this type of system was that the presence of water should have no effect on the progress of the reaction and furthermore, there could be no problems with solvent-base incompatability since it is the solvent that is being exploited. With this methodology a methylsulfinyl anion is generated to which is then added the diol substrate followed by the aldehyde, detailed in Scheme 18.



44

Scheme 18

Yields from this reaction varied from no reaction to 32%, with no obvious reason for this unreliability. Also it should be noted that the formation of the sulfinyl

anion is somewhat akin to the formation of a Grignard reagent, temperamental and apparently depends on some unobserved variable.

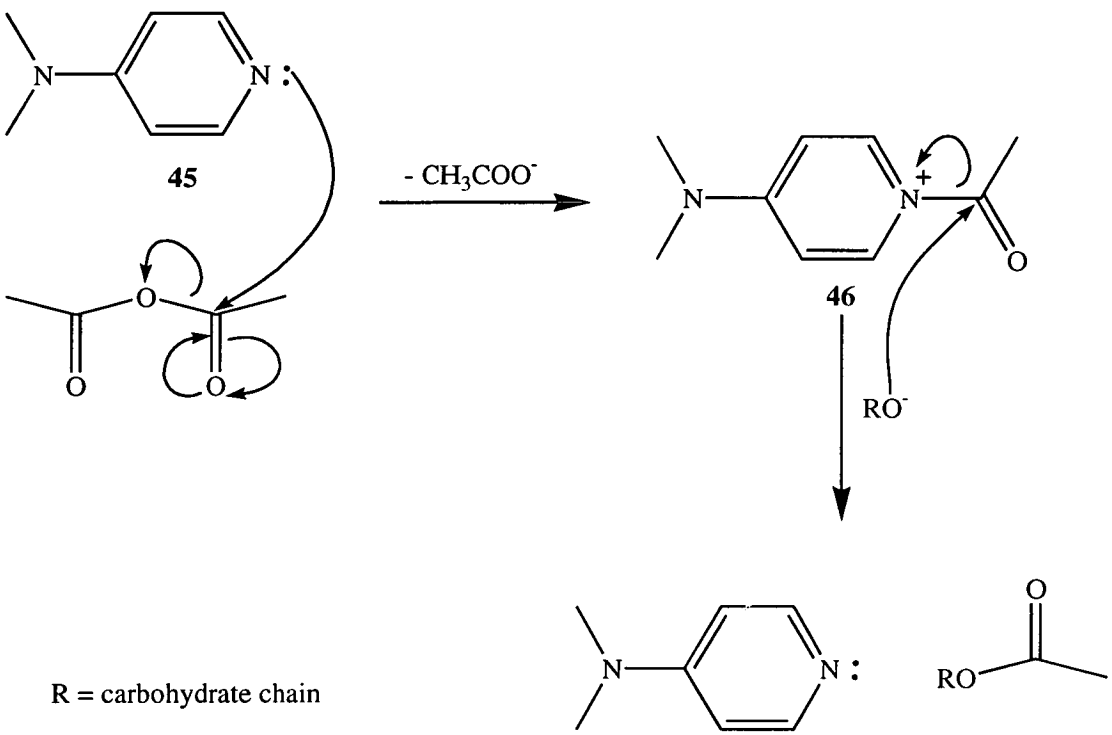
None of these approaches had made a significant improvement to the yields obtained under Lewis acid catalysis, however the yield was raised by eliminating the need to stir the reaction at all[100]. Thus in place of a conventional round bottom flask with a magnetic stirrer bar, a Quickfit conical flask was charged with the catalyst and aldehyde. This was then placed in an ultrasonic bath and sonicated until the catalyst had dissolved whereupon the glucoside was added, sonication resumed and the reaction progress monitored by thin layer chromatography. The conical flask apparently seems less able to deflect the ultra-sonic waves than a round bottom flask, and so agitation is more efficient, with a concurrent yield increase. By this methodology a yield of *ca.* 74% was obtained for 4.8g starting material (*c.f. ca.* 60% for zinc chloride mediated acetalation).

2.1.2.6 Protection of diol 42

Having formed the acetal a suitable orthogonal protecting group was required that was easily formed, the simplest and most convenient being an acetyl ester. Such acetates find widespread use in carbohydrate chemistry, and there are many examples of synthetic procedures for their preparation[101-103].

The most common route to such esters is by addition of acetic anhydride to a solution of the alcohol in pyridine followed by a period of reflux. Whilst generally

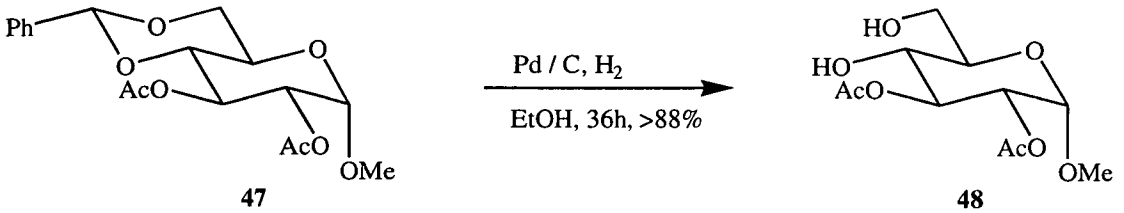
satisfactory, it was found that yields for this reaction could be improved by the use of the hypernucleophilic catalyst *N,N*-dimethylaminopyridine[104] **45**. Moreover, use of this reaction system makes the work-up and general handling far more convenient since the reaction is more efficient in solvents of low polarity. Thus using dichloromethane as solvent, the reaction would go to completion (yields >95%) within 1 hour at room temperature. Conversely, using pyridine as solvent necessitates at least 4 hours reflux to attain yields above *ca.* 80%. The rationale for this being that the resonance stabilised acyl pyridinium salt **46** which is the active species becomes less stable as the polarity of the solvent decreases, shown in Scheme 19.



Scheme 19

2.1.2.7 Deprotection of benzylidene acetal 47[105]

Having designed the protecting group strategy in an orthogonal fashion, it was a fairly trivial exercise to selectively deprotect the aromatic acetal, and indeed this was achieved in high yield by catalytic low pressure hydrogenation with palladium on charcoal, shown in Scheme 20.

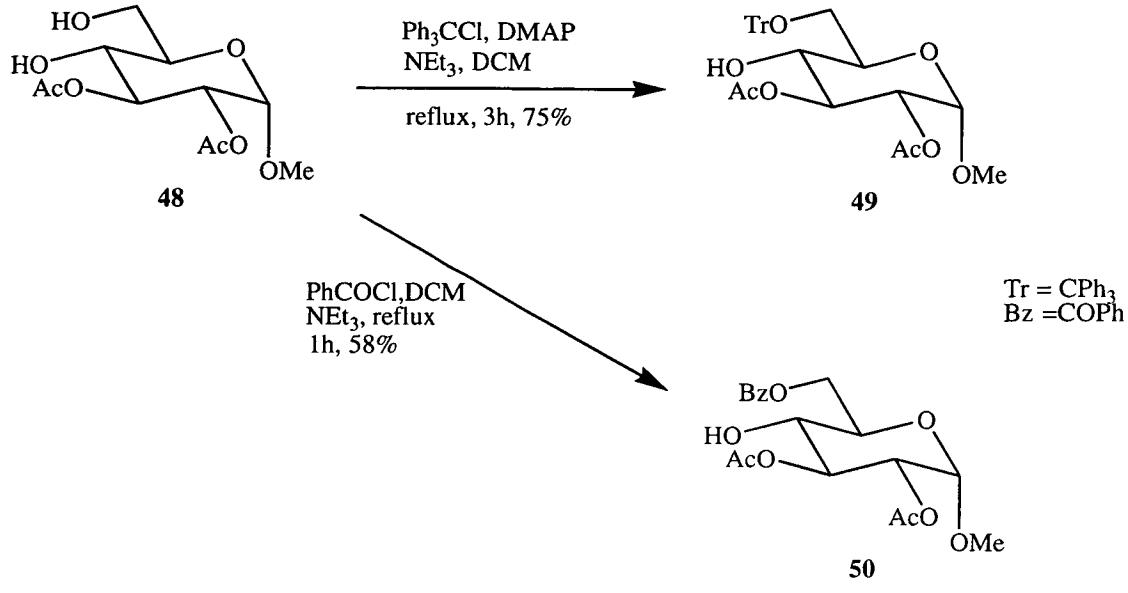


47 48

Scheme 20

2.1.2.8 Selective primary alcohol protection

All that remained to complete the retrosynthetic analysis shown in Figure 6 was to form compound **37** containing a free hydroxyl group at the 4-position.. The obvious choice to form this compound was to selectively[106-108] protect the primary alcohol as the triphenylmethyl ether. Using such a sterically demanding group allows control of the regiochemistry since the 4-hydroxy position is too close to the ring to form any appreciable quantity of the regio-isomeric ether. This was indeed the route initially followed, illustrated in Scheme 21.



Scheme 21

Although selective, the formation of trityl ether **49** proved problematic in that purification was difficult, and could only be achieved satisfactorily by chromatographic methods. Standard wet and dry flash chromatography on silica proved difficult since the ether is cleaved readily under these conditions. This was partially aleviated by using triethylamine as a co-eluant (*ca.* 3%), or by using neutral grade alumina as the stationary phase. However, it was found that by careful manipulation of the reaction conditions it was possible to form selectively the primary benzoyl ester **50**, albeit with slightly lower selectivity, which was much more easily purified.

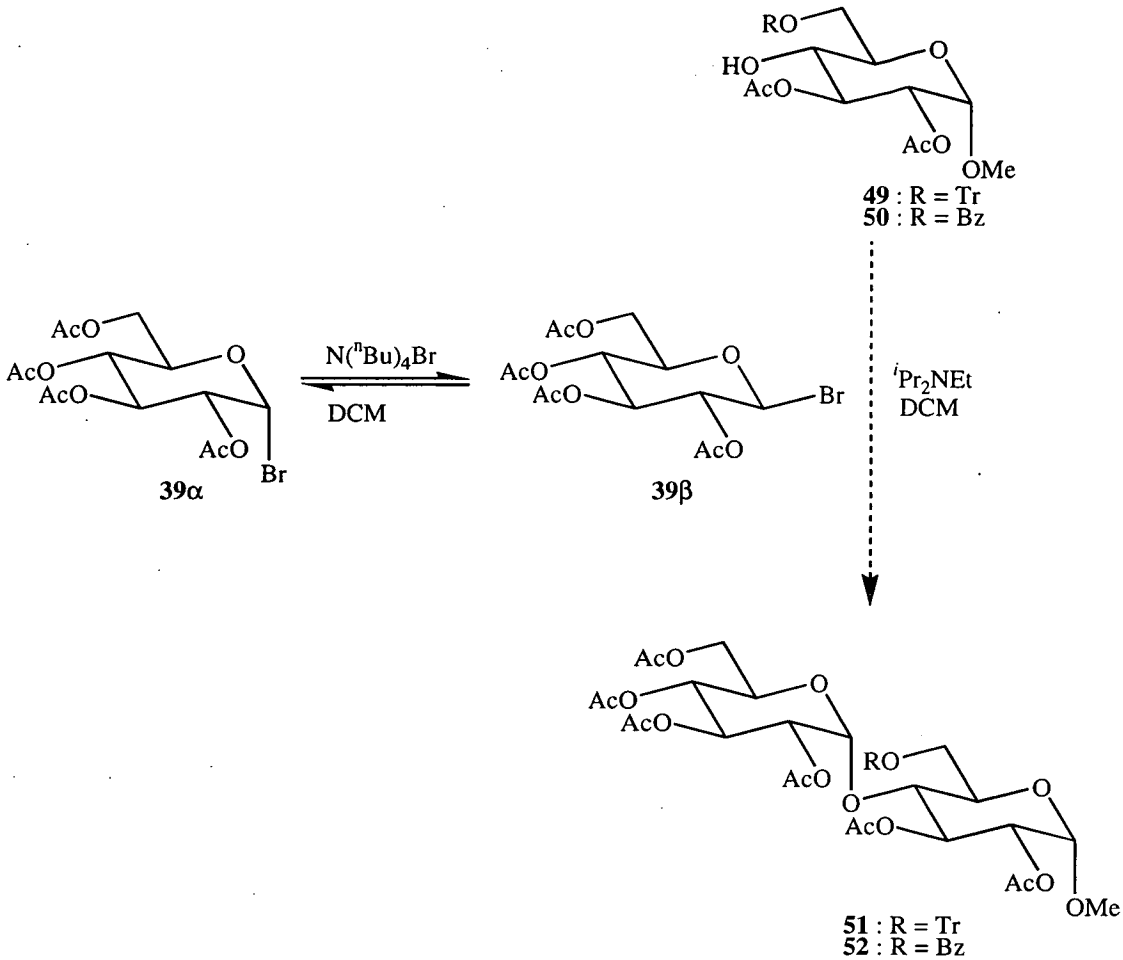
Even though the selectivity decreases relative to trityl ether formation the benzoyl ester is a much more robust protecting group, and in fact offers a slight advantage over the trityl ether in that the deprotection conditions required for the

acetate esters also deprotects the benzoate ester, thereby saving one further step, *i.e.* the acidic deprotection of the trityl ether.

2.1.2.9 Attempted convergent synthesis[109-112]

Having assembled the relevant components from the retrosynthetic analysis outlined in Scheme 3, namely **39** and **49** (or alternatively **50**), to be used to control the regiochemistry, all that required was to manipulate the reaction conditions in such a fashion as to control the stereochemical addition.

As previously noted, the use of α-glycosyl halides in this type of chemistry poses a problem in that the favoured product results from simple displacement, producing the undesired anomer. Thus, some other reagent must be present to otherwise govern the progress of the reaction. Here tetrabutylammoniumbromide (TBAB) was used to form a catalytic mixture of α- and β-halides, with a view to exploiting the inherent instability of the β-halide to kinetically control the stereochemical progress of the reaction, mediated by Hünig's base, and outlined in Scheme 22.

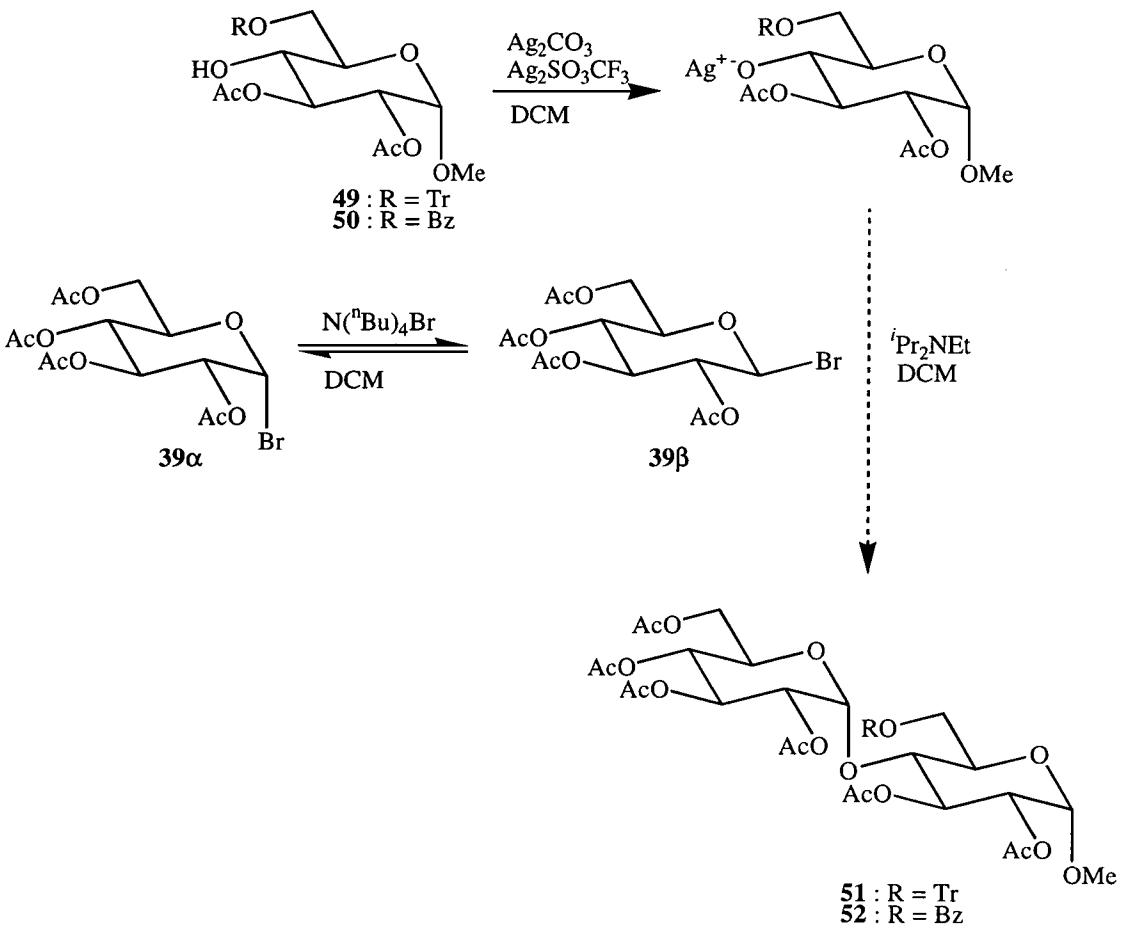


Scheme 22

Despite repeated attempts under a variety of conditions, using both nucleophiles *i.e.* **49** and **50** no coupling was observed, even after 40 hours reflux.

This was possibly not surprising, with the suggestion mooted that the hydroxy group is simply not an active enough nucleophile to affect reaction. In fact it is noted in the literature[90,110,117] that the 4-hxdroxy position in the α-glucopyranoside series is only weakly reactive as a nucleophile, much less so than the equivalent groupings on ring carbons 2,3 and 6.

Furthermore, Paulsen[90] has noted that the efficiency of these types of reaction are often governed by a complex combination of substrate reactivity, catalyst activity and solvent effects, and moreover that it is often necessary to employ a combination of catalysts, notably mercuric or silver salts in conjunction with a halide ion source. Thus, a two-pot coupling procedure was attempted, as shown in Scheme 23.



Scheme 23

Again no reaction was observed here. It should be noted that whilst the alcohol (**49** or **50**) was recovered unaltered after the reaction the halide was no longer

present, instead the equivalent tetraacetyl aldose was recovered. This alongside the low reactivity of the hydroxy may provide a partial insight into the reason for the reaction's failure.

Presumably the action of TBAB on the halide proceeds normally, but instead of forming the unstable β-halide through which the reaction proceeds, the stable intramolecular acetoxy salt **53** forms, detailed in Figure 7.

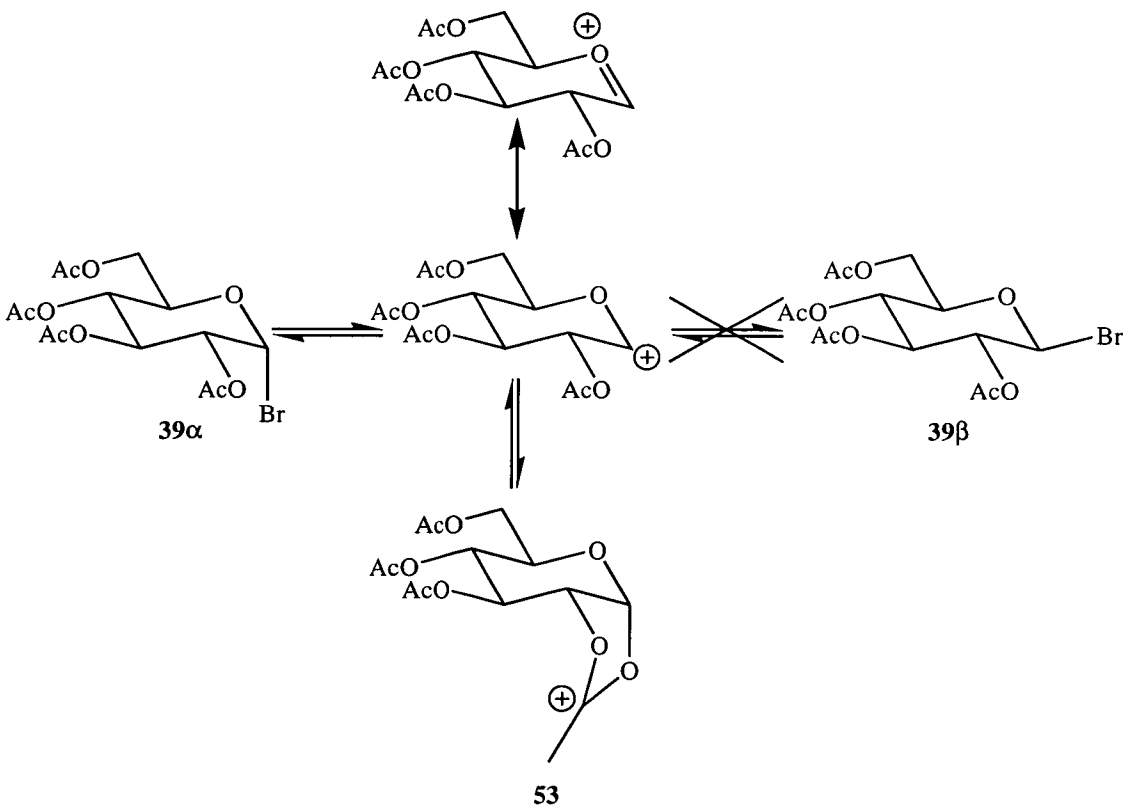


Figure 7

The formation of this type of acetoxy salt is well documented in the literature[117] and is often exploited in the formation of β-glycosides. Thus with hindsight the use of a glycosyl bromide bearing an acetate group in the C-2 position

is in fact likely to preclude the synthesis of the desired disaccharide **51** or **52** in that should a suitably reactive nucleophile have been present the predominant reaction product would have been of the undesired β-configuration. In this system it is possible that given time and perseverance a combination of catalysts and conditions could have been found to minimise or influence this type of interaction and promote the desired glycosidation.

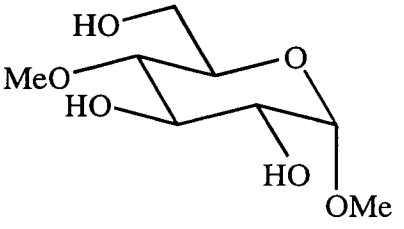
Although never examined, there exists in the literature[90,110] alternative approaches for the synthesis of this class of compounds, *i.e.* the family of α-D-glucopyranosyl-(1→4)-D-glucopyranosides, to the use of glucopyranosyl halides. These include amongst others the activation of the anomeric position *via* the use of anomeric *O*-alkenyl groups. Also commonly used is the β-*N*-methylacetimidoyloxy moiety, formed by reaction of the corresponding glucopyranosyl halide with *N*-methylacetamide in the presence of silver(I) oxide and diisopropylamine. Related to this approach is the use of trichloroacetimidates as leaving group which is more convenient than the use of the *N*-methylacetimidoyloxy moiety since these imidates can be prepared directly from the aldose under basic conditions. Also reported, though a less popular approach, is the use of 1-thio-β-glucopyranosides with either pyridyl, pyrimidyl or benzothiazolyl, *i.e.* non-participating neighbouring groups borne by the 2-position.

However it was decided that time would be better employed focusing on a simpler model, more readily prepared.

2.1.3 Monomeric model[92-97]

2.1.3.1 Preamble

Whilst bearing in mind the criteria which must be fulfilled with any model compound, which had led to the initial choice of **30**, a simplified though less representative model was chosen, namely methyl 4-*O*-methyl-α-D-glucopyranoside **54**.



54

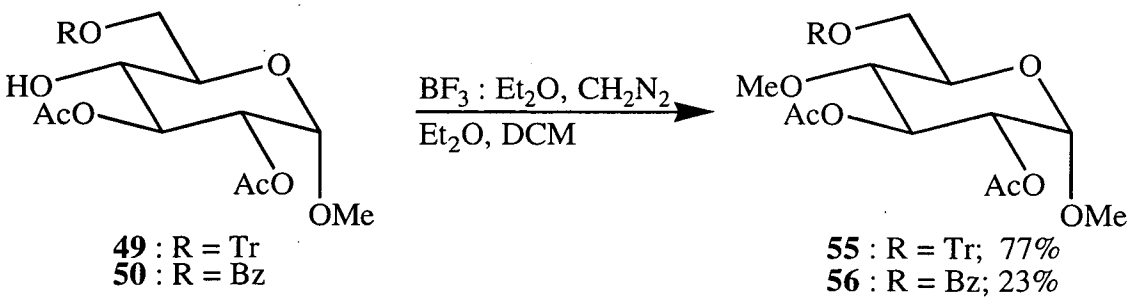
The great benefit to this compound over **31** was that there existed two precursors to it from the previous work on the convergent maltoside synthesis, being **49** and **50** each requiring only methylation and subsequent deprotection.

However the penalty for this ease of preparation was that since there was no second pyranose ring present at C(4), many chain degradative processes, so prevalent in polysaccharide oxidations would be unaccounted for since the 4-methoxy group is a much poorer leaving group than a pyranose ring.

2.1.3.2 Formation of 4-*O*-methyl ethers of 49 and 50

Several strategies for the methylation of alcohols **49** and **50** were examined. Simplest of these was a boron trifluoride mediated diazomethane insertion[113], and

whilst this was amenable to small scale methylations of **49** it performed poorly with **50** and on scales larger than *ca.* 100mg of **49**, shown in Scheme 24.



49 : R = Tr
50 : R = Bz

55 : R = Tr; 77%
56 : R = Bz; 23%

Scheme 24

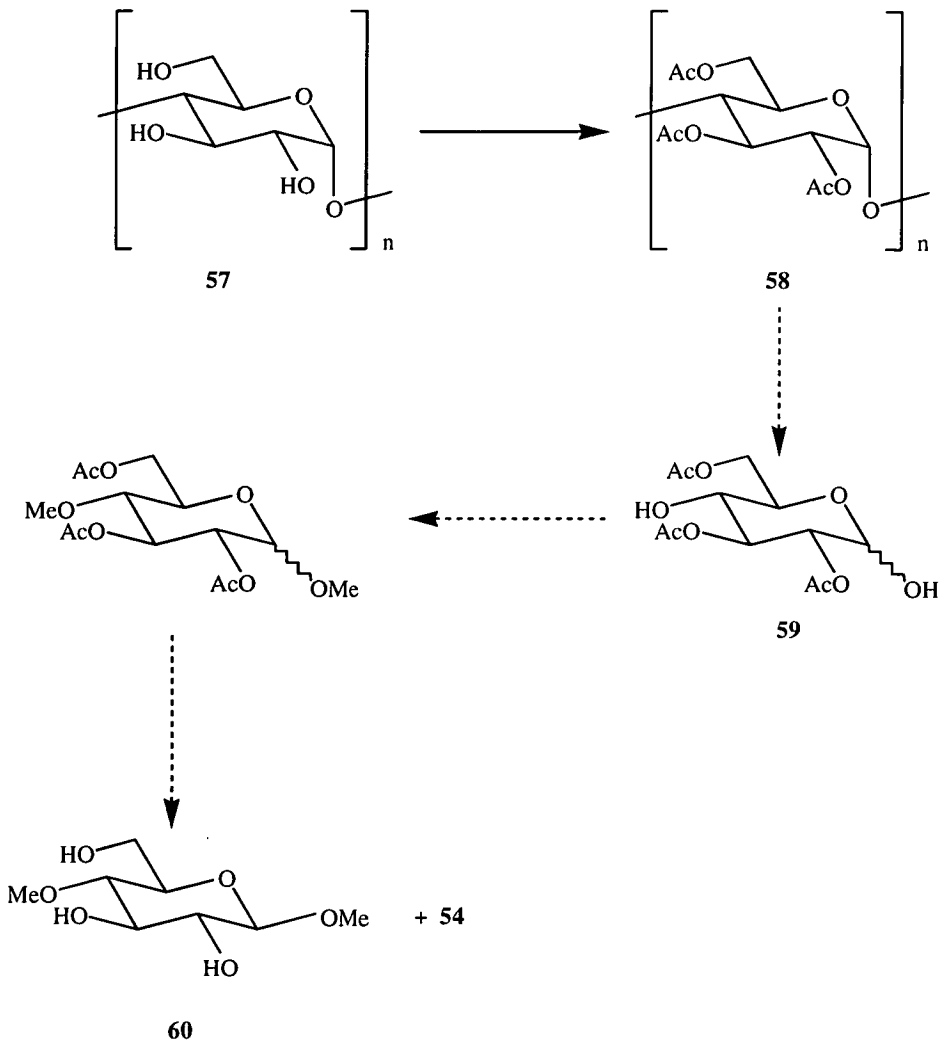
The relevant deprotection steps[105,114] were then routinely performed on glucoside **55** to yield **54** in 44% overall yield (though this sharply decreases as the scale of the benzylidenation and primary alcohol protection steps are increased).

Although a successful route had been demonstrated to yield ether **54**, it was felt to be unsatisfactory since it was cumbersome (involving a total of 7 steps) and time consuming. It was thus decided to investigate other possible routes, with a view to organising a synthetic pathway which was both convenient and amenable to scale-up.

2.1.3.3 Attempted amylose based synthesis of 54

Previous synthetic approaches had centred around using a small compound to mimic a larger compound, possessing the relevant stereochemistry. It then seemed possible to exploit this relationship in reverse to form **54** from amylose. Thus it

seemed logical to start from amylose **57**, protect the free hydroxyls to **58** and cleave the polymer to the free hydroxy aldose **59** which would then be subjected to di-*O*-methylation prior to deprotection of the 2-,4- and 6-positions to yield the desired compound **54** with its β-anomer **60**, outlined in Scheme 25.



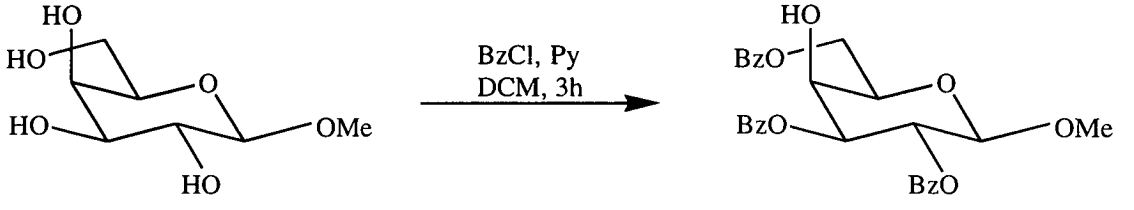
Scheme 25

Although notable for its simplicity, this approach suffers inasmuch as the product from the initial acetylation step, whilst appearing promising by crude ^{1}H and

^{13}C NMR, poses an incredible problem to deal with. The resultant brown tar is difficult to handle at best, and any attempt to perform the acidic hydrolysis on this crude material is fruitless and for this reason this approach was abandoned[115].

2.1.3.4 Regioselective tri-*O*-benzoylation

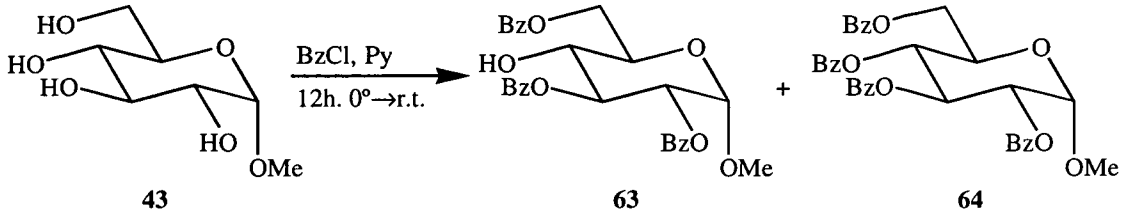
Following work done within the Flitsch group in Edinburgh[116], the formation of methyl 2,3,6-tri-*O*-benzoyl-β-D-galactopyranoside **61** (in 59% yield) had been observed during a polybenzoyl protection of methyl β-D-galactopyranoside **62**, shown in Scheme 26.



62 **61**

Scheme 26

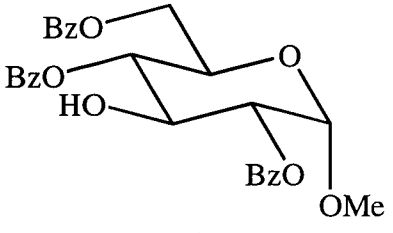
It was thus decided to try and apply this work to the large scale synthesis of **54**. Worthy of note here is the obvious difference in anomeric configuration of **61** to the desired α-methyl acetal, however it was felt that this moiety was so far removed from the majority of reacting centres that it would pose no considerable difficulties. Hence, to a rigorously dried sample of **43** slurried in dichloromethane was added pyridine, followed by benzoyl chloride, outlined in Scheme 27.



43 63 64

Scheme 27

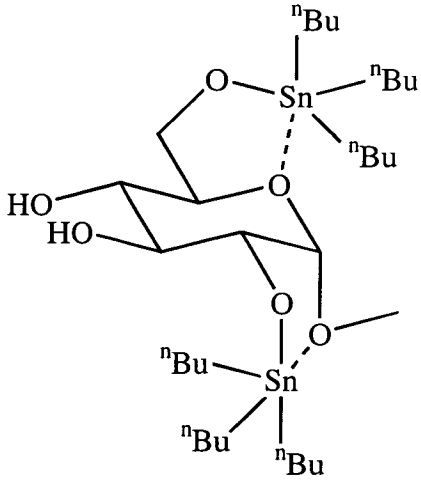
The desired triester **63** was isolated in 48% yield along with the tetraester **64** (13%). The reasoning for the regioselective formation of **63** was not initially clear, since the literature predicts that based on solely stereochemical demands and differing relative rates of reaction[117], the 3-hydroxy isomer of **63** should be formed in preference, *i.e.* **65**.



65

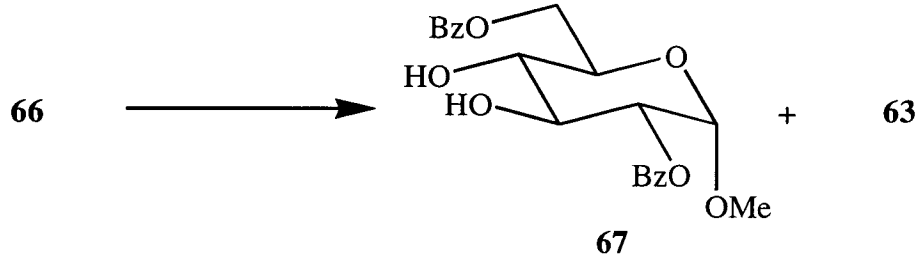
Helm and Kaichang[118] had shown that **63** could be synthesised in 90% yield again from **43** in the presence of a vast excess of bis(tributyltin) oxide in refluxing toluene. This is an improvement on the work of the group of Ogawa[119], who detailed the use of trialkyltin alkoxides as regioselective control agents.

Ogawa ascribes the regioselective control in the bis(tributyltin) oxide mediated polybenzoylation to the initial formation of two intramolecular stannylated five-membered rings, **66**.



66

The alkoxide bonds are now of course activated towards nucleophilic attack, and so addition of two equivalents of benzoyl chloride yields the 2,6-dibenzoate ester **67** and the 2,3,6-tribenzoate ester **63** in 81% and 18% yields respectively, as shown in Scheme 28.



Scheme 28

Whilst the formation of **67** lends credence to the intramolecular stannyl complex theory there is no explanation offered as to the regioselectivity of the next benzoylation. Moreover, by their own work they have shown that these

intramolecular stannyl complexes can only be readily formed where a *cis*-vicinal diol relationship exists, and there is no such relationship present in diol **67**.

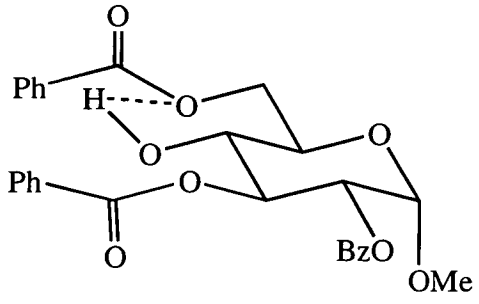
Thus, the regioselectivity control can only be partially under the influence of the stannylated alkoxy species. To try to offer some explanation for the differentiation between the two regioisomers **63** and **65**, computer modelling software was employed in an attempt to demonstrate that were the two regio-isomers respectively thermodynamic and kinetic reaction products of the third benzoylation reaction, then under reversible conditions one should prevail over the other. Using calculations generated with a MM2 forcefield it can be seen that **63** has a lower free energy and so would be expected to form in preference to **65** where thermodynamic reaction conditions control.

Compound	$\mathbf{E_{total}}$	$E_{stretch}$	E_{bend}	$E_{stretch\text{-}bend}$	$E_{torsion}$	$E_{non\text{-}VdW}$	E_{VdW}	$E_{dipole\text{-}dipole}$
63	**48.3**	3.1	19.5	1.2	-9.6	-9.7	28.7	15.1
65	**50.8**	3.1	18.6	1.2	-2.4	-10.3	29.4	11.2

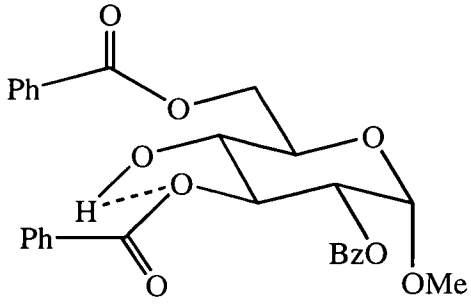
Energies reported as kcal mol^{-1}

Returning to the molecule, a possible explanation for the regioselectivity can be found on correlation with ^1H NMR data, where a doublet of triplets at *ca.* 3.92 ppm and a broad doublet at *ca.* 3.70 ppm can be seen, corresponding to the axial proton on carbon 4 and the hydroxylic proton respectively. This indicates that there is some restricted rotation around the O-H bond, which in turn indicates the presence of some hydrogen bonding. Four possibilities exist for intramolecular hydrogen

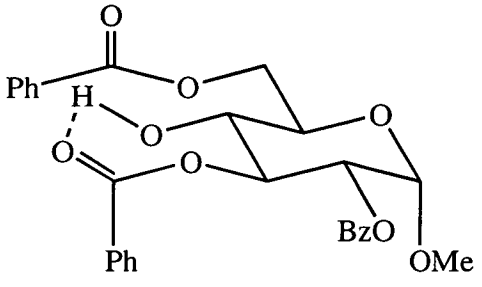
bonding, namely **68** - **71** (with the steric demands imposed by the protecting groups and the pyranose ring itself, intermolecular H - bonding is unlikely).



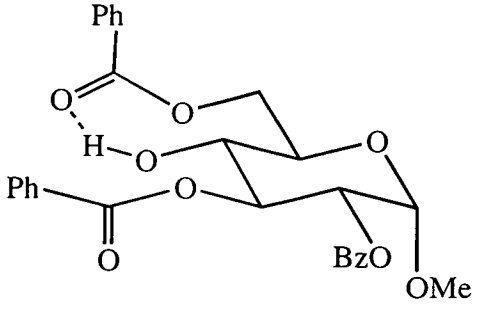
68



69



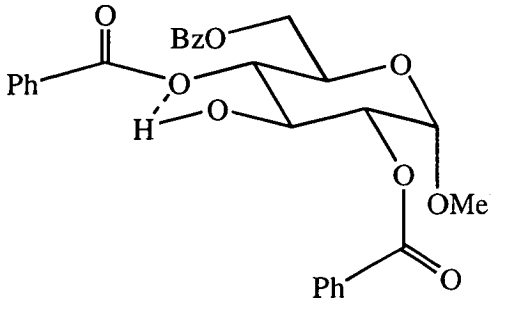
70



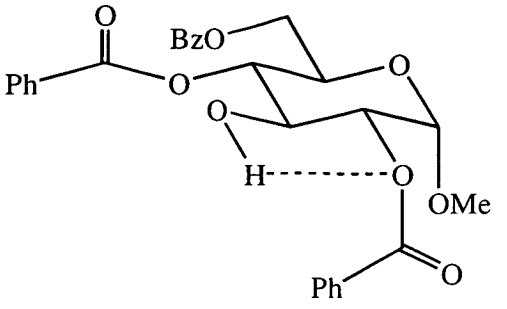
71

Whilst it may be expected that the keto groups would play a dominant role in H-bonding, these possible arrangements, namely **70** and **71** require respectively the formation of seven- and eight-membered rings. Neither of these will be as stable as the six- and five-membered rings produced *via* the involvement of the bridging oxygens as chelant.

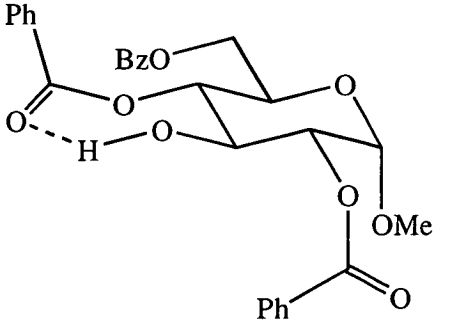
Applying a similar argument to isomer **65** there exists again four possible conformations **72** - **75**.



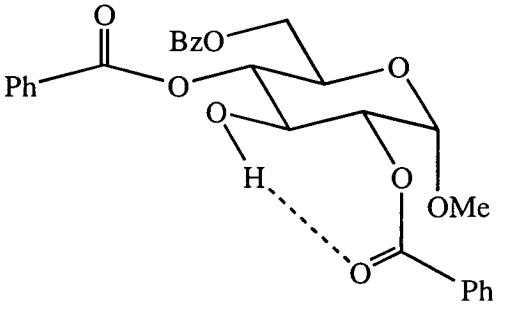
72



73



74



75

Inspection of these four conformations shows that hydrogen bonding involving the benzoyl ester on ring carbon 2, *i.e.* **73** and **75** is unlikely due to the distance involved. Moreover where the interaction is between the 4-benzoate ester and the hydroxyl group, only a five- and seven-membered ring are possible (**72** and **74** respectively).

This would indicate then that the regioselectivity of this benzoylation is not solely controlled by the presence of an alkoxy stannyl complex, as described by Ogawa, but a combination of features. To test this theory, the reaction was performed under conditions designed to allow for thermodynamic control of reaction products. Thus, with all other conditions held as previously, the addition of benzoyl chloride was performed much more slowly (over 1h. *c.f.* 10min. previously), with the

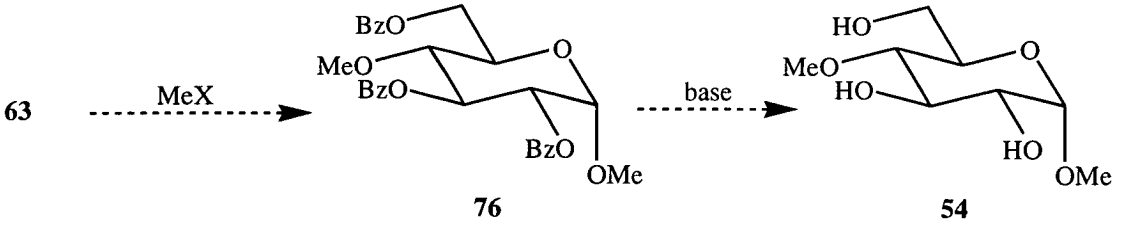
intention that this would allow time for the reaction to come to thermodynamic equilibrium, assuming tetraester **64** to be the kinetic product rapidly formed *via* a reversible reaction and **63** the thermodynamic product. Somewhat gratifyingly, this yielded the desired compound **63** in 76% yield (*c.f.* 48% for a more rapid addition). The reaction was again repeated, using toluene as solvent as does Helm, in place of the more commonly used dichloromethane, however here **63** was isolated in only 58% yield. This would seem to indicate that the regioselectivity enjoyed by this reaction is indeed a function of a variety of different variables. The absence of regio-isomer **65** would seem to indicate that either there is a sufficiently large energy barrier to prevent its formation or that this barrier is small enough to facilitate the rapid regio-isomerism *viz.* **65** to **63**.

Solvent effects look to play a major role, and this is completely to be expected if the presence of intramolecular hydrogen bound complexes are influencing the reaction course, since as the polarity of the solvent changes so too will the relative strengths of these complexes.

Although never pursued to optimisation, it is believed that the yield could be increased still further simply by a much longer addition period or alternatively performing the reaction at elevated temperatures, since the unaccounted benzoyl chloride is consumed in the formation of tetraester **64** which as noted above is assumed to be the kinetic product.

2.1.3.5 Methylation of triester 63

To synthesize the desired methyl 4-*O*-methyl-α-D-glucopyranoside **54** all that was required from this point was to perform a methylation of **63** and subsequent deprotection, as outlined in Scheme 29.



Scheme 29

The methodology of choice for the methylation of **63** was to use a diazomethane insertion reaction mediated by boron trifluoride etherate, since this would provide the simplest work-up. This proved to be a poor approach, resulting at best in yields of *ca.* 20%, and here only where vast excesses of both reagents were employed.

As an alternative it was decided to use a suitable combination of electrophile and base, with the simplest electrophile being iodomethane. Thus, a variety of bases were tried including pyridine, triethylamine, lithium diisopropylamine, sodium dimethylsulfinyl and sodium hydride in a range of different solvents of varying polarity and in the presence or absence of nucleophile activators such as *N,N*-dimethylaminopyridine. Of these, only a slurried suspension of dry sodium hydride in ether proved to be of any synthetic utility albeit in moderate yield (*ca.* 38-58%).

On reflection though this is perhaps not unpredictable since the assumption has already been made that the regioselective formation of **63** is at least in part governed by the formation of intramolecular hydrogen bound rings, which will serve to hold the benzoyl groups close to the hydroxyl group. Thus, it was not unsurprising that it was only the smallest of all the bases which were tried which showed any degree of success. Moreover, since the reaction was performed in a solvent of relatively low polarity the size of the associated solvent cages can also be assumed to be fairly small.

Even so, for the purposes of scale-up this was not a particularly effective methylation strategy, and so attention turned to the traditional "Purdie" approach to saccharide methylation, *i.e.* the reaction of some saccharide derivative in neat iodomethane in the presence of silver oxide.

2.1.3.6 Silver oxide mediated methylation of 63

Attempts to methylate **63** under the much used "Purdie" conditions[120] mentioned above proved only to be of moderate synthetic utility with yields ranging from 34% - 62%. However, when a slight modification of the conditions was applied[121], a wholly more satisfying yield was obtained. Thus, **63** was dissolved in acetonitrile in a thick-walled sealable glass tube, and to this was added silver(I) oxide. After 5 min. stirring, cold iodomethane was added, the tube sealed and heated to reflux where it was maintained for 2½h. to furnish **76** in 80% yield. Initial

attempts under typical refluxing conditions had shown that condensation of iodomethane was inefficient so far above its boiling point, and so a sealed unit was required.

This reaction performed adequately on a small scale, but as the scale increased so the yield decreased. The decreasing yield was apparently a result of a reduction in the efficiency of stirring of the mixture. After rapid initial consumption of the silver catalyst, a hard shell formed around the unused material effectively protecting it from the reagents, and once this point had been reached no further reaction was observed. On a small-scale thermal motion appears to be sufficient to maintain a suitable dispersion of the catalyst, however on a larger scale it appears that the mixture does not heat rapidly enough to ensure a thorough dispersion.

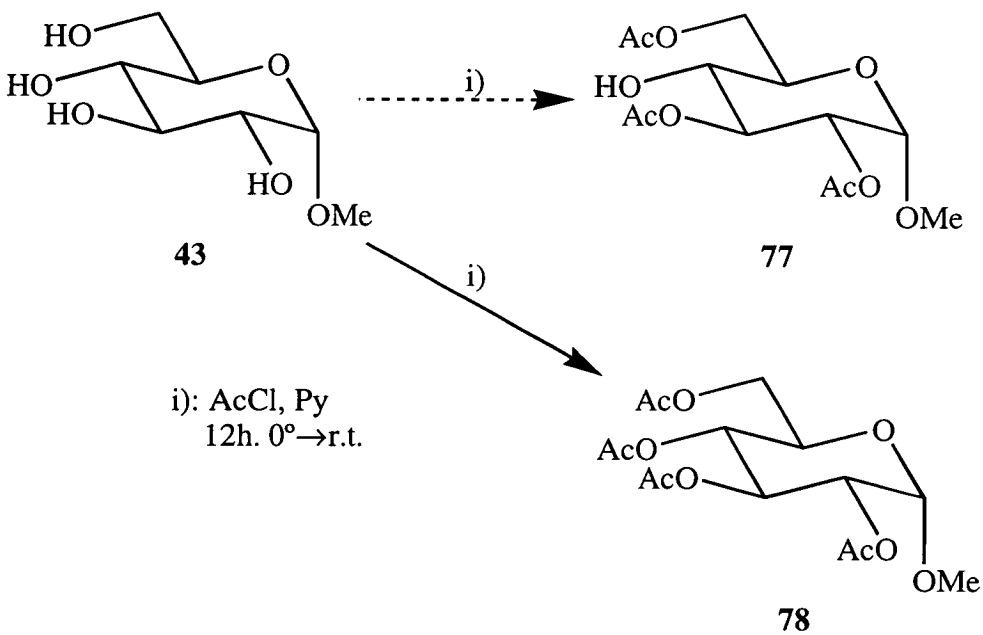
Since the reaction is performed within a sealed tube, the addition of some form of mechanical stirring is difficult. Attempts to circumvent this *via* the use of an ultra-sonic bath proved fruitless, presumably since there was no way to heat the system to the desired temperature.

If on the other hand, the mixture was preheated prior to the addition of iodomethane, it was noted that only poor yields were obtained, with the iodomethane undergoing extensive degradation, immediately producing a cloudy, slightly blue solution. Furthermore, repeated addition of vast excesses of iodomethane did not serve to improve matters to any great extent.

Thus, to allow for mechanical stirring and heating, the reaction was performed on a large-scale (82.15 g) in a stirring autoclave at 8 bar, 112°C for 94 min., whereupon **76** was isolated in 60% yield.

2.1.3.7 Attempted regioselective acetylation[122,123]

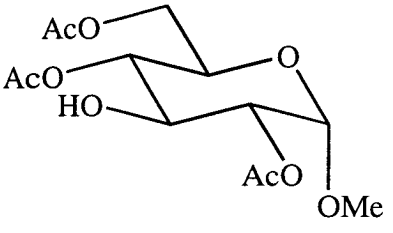
As a result partly of the success in controlling the regiochemistry of benzoylation and in the subsequent difficulties encountered during the methylation of **63**, it was decided to apply the same methodology to attempt the partial acetylation to furnish methyl 2,3,6-tri-*O*-acetyl-α-D-glucopyranoside **77**, as outlined in Scheme 30.



Scheme 30

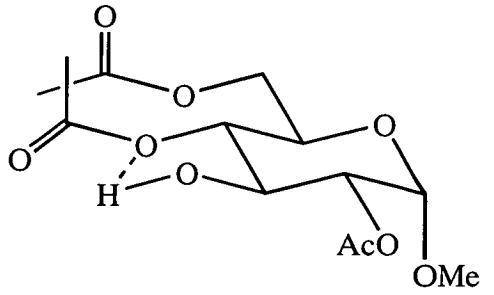
No regioselectivity was observed, with the only product being the tetraester **78** obtained in 48% yield. A review of the literature showed that the desired reaction

had been performed previously by Hanessian[124] who was examining novel methods for the preparation of partially acetylated carbohydrates using aprotic solvents in the presence of zinc chloride. It should be noted though that **77** was a minor component of the reaction mixture, comprising at most 17% yield, with the major product being the regioisomer **79** in yields of up to 38%.

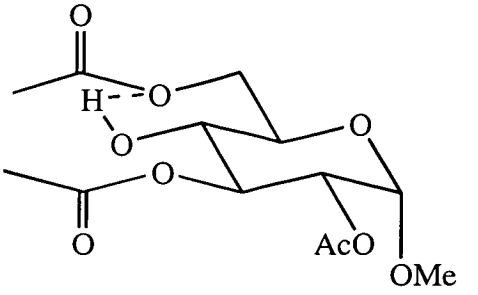


79

The observed formation of **79** in preference to **77** perhaps indicates that there is some differing stereo or electronic effect operating here than in the regioselective benzoylation. It is interesting though that some regioselectivity is observed, albeit not as prominently as in a benzoylation reaction. This might indicate that where the carbonyl bearing moiety of the ester is not particularly sterically demanding then a five-membered intramolecular hydrogen bound ring is of sufficient thermodynamic stability to impart some degree of selectivity. Moreover, there cannot be any great difference in thermodynamic stability between this five membered ring and the six membered ring which would be formed with the 2,3,6-triester **77** as the difference in regioselectivity is not particularly marked. That is, the intramolecular complex from which **79** is formed *i.e.* **80** must not be greatly more stable than complex **81** which yields **77**.

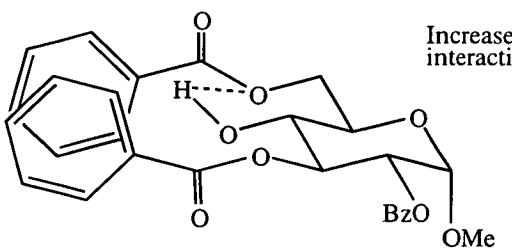


80

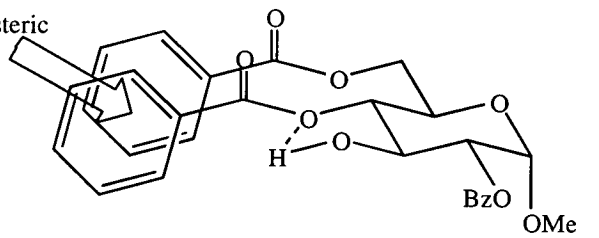


81

This does not explain however the results of the analogous benzoylation reaction which produces the 4-hydroxy triester **63**. Presumably this is as a result of the increased thermodynamic energy produced by much larger steric interactions between ester groups on C4 and C6 relative to the interaction between groups on C3 and C6. Thus it seems that, at least in part, the regioselectivity of the benzoylation reflects the reduced steric interactions found in **68** relative to **72**.



68

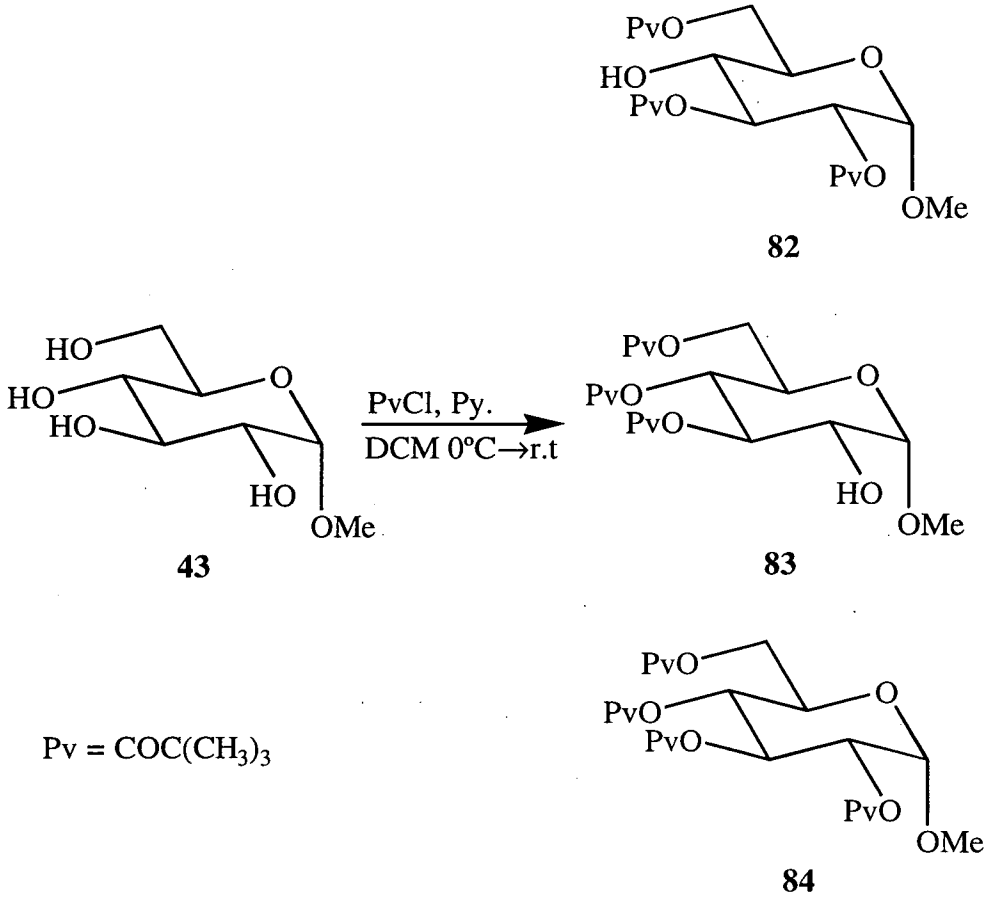


72

2.1.3.8 Attempted regioselective pivaloylation[126]

With this in mind, it was decided to try some other ester protecting group. The previously mentioned results obviously pointed towards some bulky group, and so a pivaloate ester was chosen as target. Under analogous conditions to the formation of **63** and **78**, pivaloyl chloride was dripped in to a solution of **43** slurried

in dry dichloromethane and pyridine at 0°C. Some selectivity towards the desired alcohol was observed as is shown in Scheme 31.



Scheme 31

Although **82**, *i.e.* the desired compound, was the major component of the reaction mixture, it represented only 13% yield. Also recovered were the 2-hydroxy regioisomer **83** and the tetraester **84**, respectively in 7% and 2% yield.

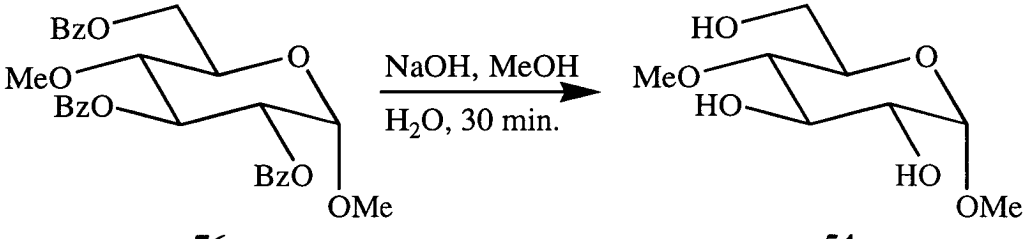
Even though this was not a particularly useful synthetic result, it did however add weight to the hypothesis that the regiospecificity is (at least partly) controlled by

the steric demands of the relevant ester, and not necessarily by the presence of any metal additives. That is to say that the presence of **83** indicates that there must be a large steric interaction between the pivaloate group borne by C2 and the axial anomeric methoxy group such that there is some differentiation between **83** and the other reaction products. Thus it appears that the position most sensitive to the size of the incoming carbonyl bearing group is C4, followed by C2.

As a consequence of this it was decided to abandon the search for other 4-hydroxy triesters which would then prove easier to methylate than did **68**.

2.1.3.9 Deprotection of 63[105]

Deprotection of **63** was accomplished quantitatively by simply stirring in a solution of wet methanol in the presence of sodium hydroxide (1.1 eq.), followed by neutralisation with an acidic ion-exchange resin, as detailed in Scheme 32.



76 **54**

Scheme 32

Thus **54** had been synthesised in three relatively simple steps in 61% overall yield, though it should be noted that neither of the first two steps were fully

optimised, and that both are amenable to scale-up (given suitable equipment for the methylation).

This overall synthesis of **54** broadly parallels some other reported syntheses[53,92-97a-d] although it offers some advantages over all these. Firstly it is considerably shorter than the majority in that here only three steps are required compared with up to seven elsewhere. Also, the synthesis is easily amenable to scale-up given suitable equipment for the 4-O-methylation and moreover no additional metal reagents are needed to direct the regiospecific hydroxy protection step.

2.1.4 Dimeric model revisited

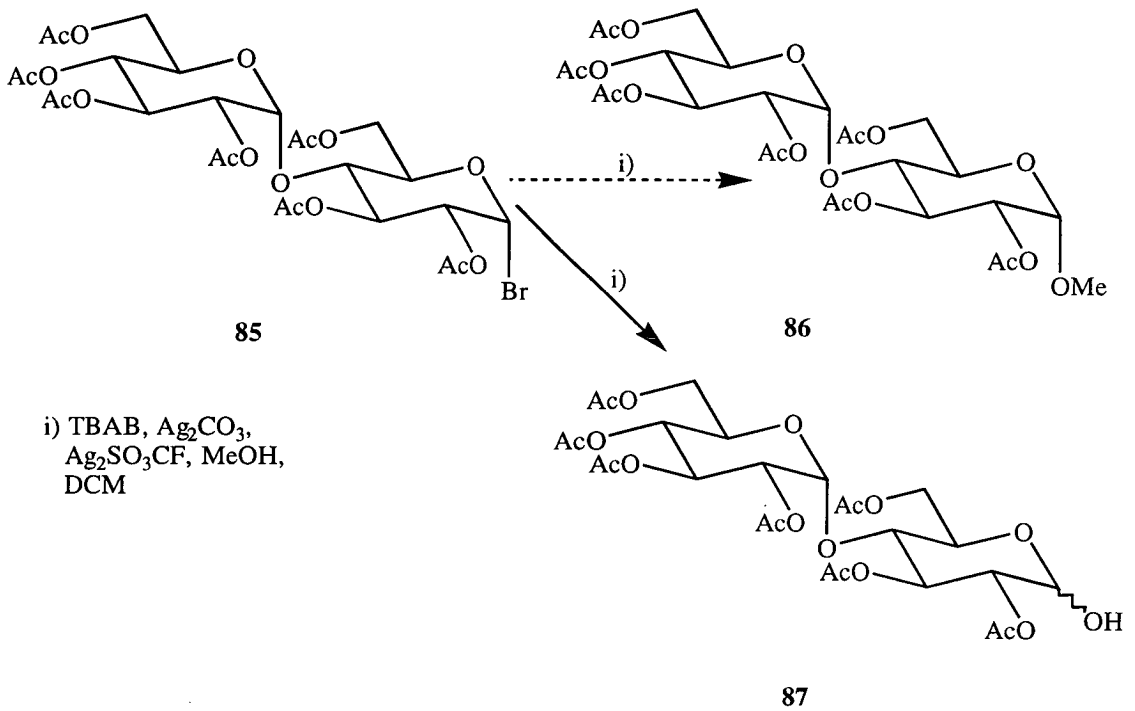
2.1.4.1 Preamble

Work had initially been abandoned on the synthesis of **31** because it had appeared that there was no simple route to its production on a relatively large scale. Re-examination of the synthesis indicated two possible routes which appeared to be of sufficient potential to warrant further examination.

2.1.4.2 Nucleophilic displacement of α-maltosyl bromo heptaacetate

A source of α-maltosyl bromo heptaacetate **85** was located, and this suggested the possibility of direct nucleophilic displacement of the halide by an alcohol to form the desired ether. This is essentially the same approach as outlined in Section 2.1.2.3 with the convergence point in the synthesis being at the reducing end

of the target molecule, rather than the glycosidic bridge, and is outlined in Scheme 33.



Scheme 33

Again, as in section 2.1.2.3, the problem of controlling the stereochemical course of the nucleophilic substitution was of paramount importance. The use of kinetic control similarly under the influence of anomeric racemization using tetrabutylammoniumbromide was explored, however no reaction was observed, even after prolonged reaction periods. On quenching however, the free aldose **87** was isolated in quantitative yield.

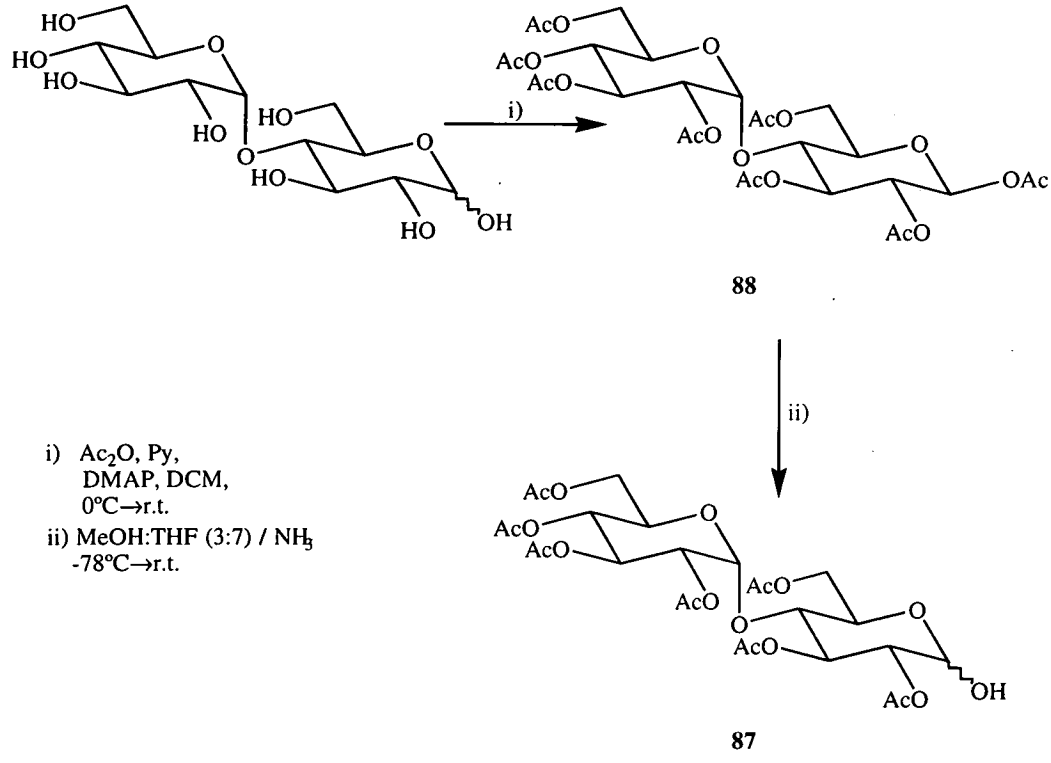
This would perhaps suggest that one (or possibly both) of the reagents is simply not reactive enough under the given conditions, whether that be in terms of

reactivity towards formation of the initial silver salt, or reactivity of this salt with the halide.

2.1.4.3 Facile anomeric deprotection of octaacetyl maltose

Following work done by the group of García-López[126] who reported the use of a mixed solvent system (methanol : tetrahydrofuran; 3:7) saturated in ammonia to exclusively deprotect the anomeric acetate group of a range of peracyl sugars, it was decided to attempt to apply this approach to the synthesis of **86**.

Thus, a quantity of β-maltose octaacetate[127] **88** was prepared by conventional means (the β-anomer forming exclusively as a result of the powerful β-directing effect of an equatorial acetate group on carbon 2 which is added prior to reaction at the anomeric centre), which was then selectively deacetylated at the anomeric position to yield the free aldose **87**, outlined in Scheme 34.



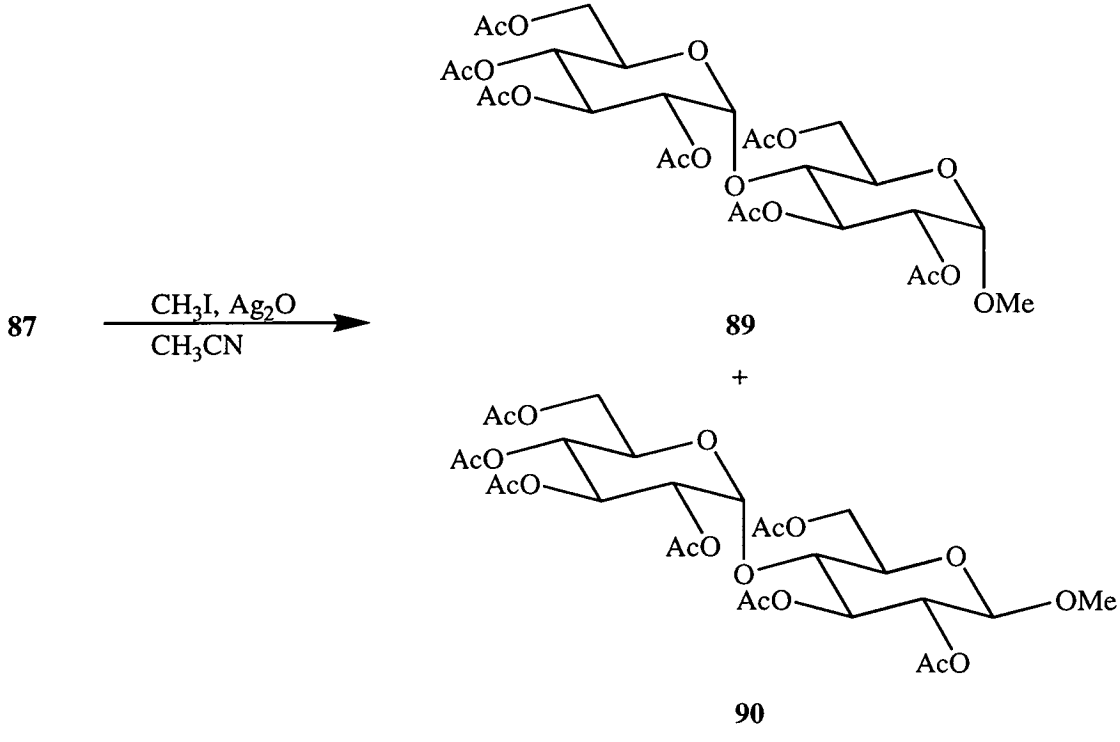
Scheme 34

As expected, peracetylation to **88** is highly efficient, with yields typically greater than 92%. Anomeric deprotection can be problematic in that reaction is relatively rapid even at low temperature, and once the anomeric ester has been removed the remaining esters are attacked. However, careful and frequent monitoring of reaction progress as the mixture warms can relatively easily produce quantitative conversions[128].

2.1.4.4 Anomeric methylation

With the aldose now liberated, all that was required was the methylation of **87** to yield a fully protected precursor to the desired disaccharide **31**. Bearing in mind the success enjoyed with the use of silver oxide in the methylation of **63** and the

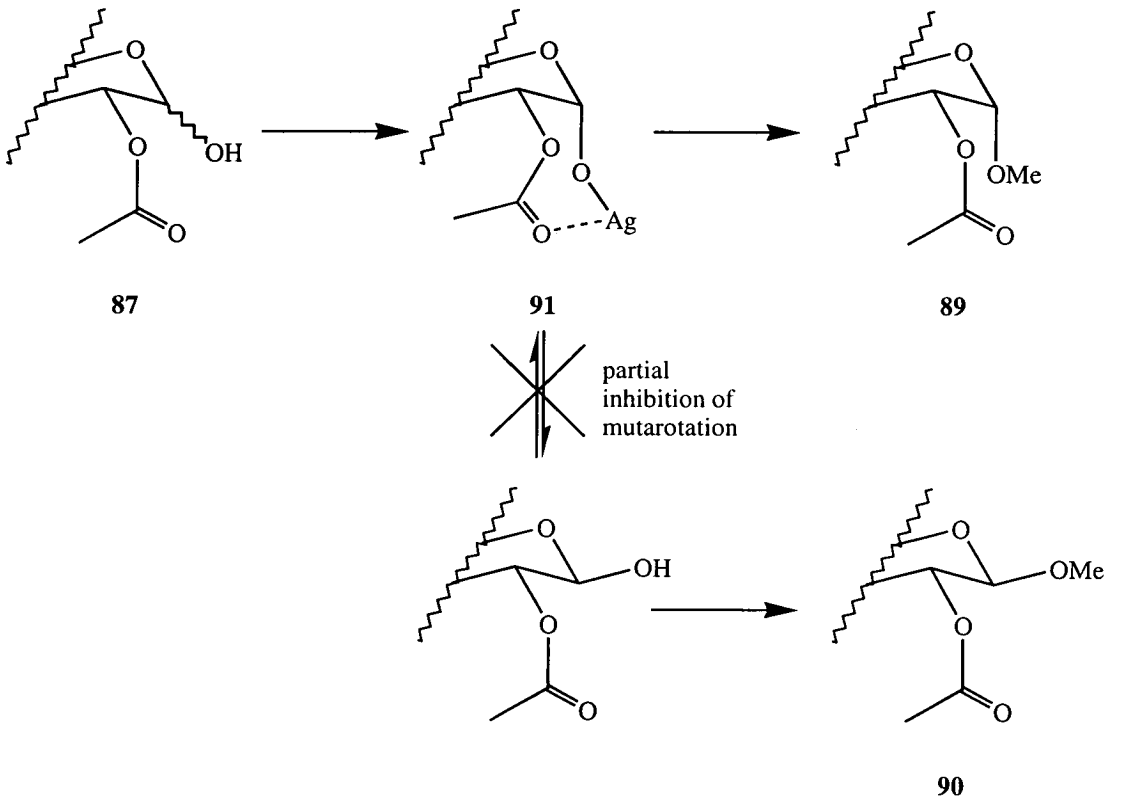
widespread use of silver(I) oxide in carbohydrate chemistry, it was decided to employ a similar methodology to this problem. Thus again the starting material was dissolved in acetonitrile to which was added silver (I) oxide and iodomethane[121], before sealing the reaction vessel and heating to *ca.* 80°C, as outlined in Scheme 35.



Scheme 35

^{1}H NMR spectroscopy revealed that under these reaction conditions, an overall conversion of 79% was obtained, albeit as a mixture of anomers (~8:1 α:β *i.e.* **89** : **90**). This mixture could be purified by selective crystallisation and removal of the β-anomer whose absolute configuration was confirmed by X-ray crystallography and is shown in Appendix.

It should be noted though that the anomeric ratio of the product is a function of the anomeric purity of the starting material. Thus, if solely **87α** is obtained *via* slow crystallisation from ethanol : water (9:1), then the obtained ratio is *ca.* 8:1 α:β. On the other hand, if **87** is used as its thermodynamic equilibrium mixture, *i.e. ca.* 3:1 α:β, then the product ratio falls to *ca.* 5:1. These results would point towards the formation of some weakly bound silver salt **91** which rapidly forms, so minimising the effects of mutarotation, as outlined in Figure 7.



87 **91** **89**

90

Figure 7

Preferentially silver complexes occupy either linear or tetrahedral geometries. In this case, a linear complex will at best be highly strained, so if this is the reason for the partial anomeric methylation control, it would be expected that either the solvent,

iodomethane or possibly a combination of both contribute to the formation of this complex.

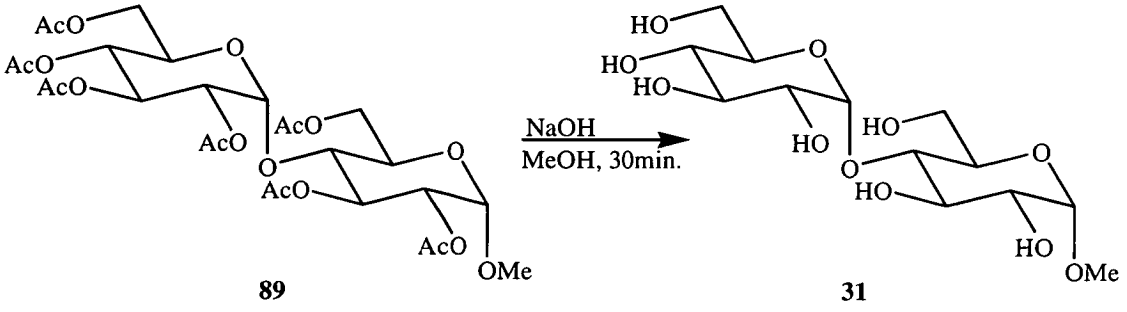
Alternatively, it may be that under the given conditions mutarotation occurs considerably more slowly than does methylation. Thus, when using anomerically pure starting material, the α aldose has insufficient time to achieve its equilibrium mixture *i.e.* ~3:1 α:β before reaction is complete and obviously the possibility of mutarotation no longer exists. Consideration of the case where an anomeric mixture (*ca.* 3:1 α:β) was used as starting material (producing a product ratio of *ca.* 5:1 α:β) would indicate that the rate of mutarotation from β → α is more rapid than from α → β, such that the material undergoing reaction is not in fact *ca.* 3:1 as assumed, but more likely containing a higher proportion of the α-anomer.

Moreover, if the reaction product ratio is simply a function of the position of the thermodynamic equilibrium mixture, then performing the reaction at ambient temperature over a prolonged reaction period should yield solely the desired anomer **89**.

Somewhat gratifyingly this proved to be the case. Where the reaction was performed at ambient temperature and under atmospheric pressure over 48 hours stirring, **89** is obtained in 83% yield.

2.1.4.5 Deprotection of methyl heptaacetyl-α-maltoside 89[105]

Complete deacetylation was conveniently accomplished in quantitative yield on stirring in a solution of methanol to which was added sodium hydroxide (freshly powdered in air) as shown in Scheme 36, yielding **31** in 63% overall yield.



89 **31**

Scheme 36

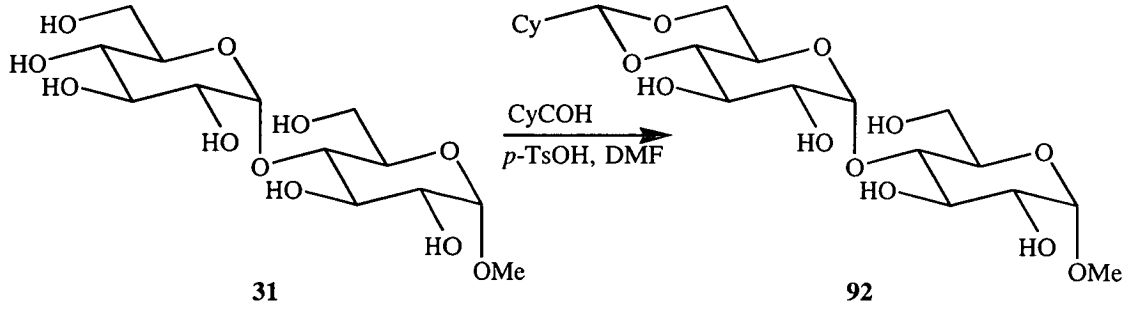
2.1.4.6 Benzylidenation of methyl α-maltoside 31

As noted previously (see 2.1.2.1), to model accurately the major features of starch, a smaller model should incorporate all the salient features. Here of course **31** has all these with the exception of a 1→6 linkage, *i.e.* a branching point. Thus, it was decided to protect this position on one pyranose ring as a 4,6-*O*-benzylidene acetal, **30**. A similar synthetic approach was employed as in the synthesis of **44**, that is, a variety of reagents with benzaldehyde including zinc chloride and pyridinium *para*-toluenesulfonic acid. Also tried were the reactions with α,α-dimethoxytoluene mediated by pyridine or zinc chloride.

Varying degrees of success were met, ranging from at best *ca.* 60% with zinc chloride and benzaldehyde agitated in an ultrasonic bath to no reaction with zinc chloride and α,α-dimethoxytoluene (which is presumably an insufficiently strong Lewis base to form an acid-base pair as with zinc chloride / benzaldehyde). Even so, purification was problematic and required the total acetylation of the crude material followed by (now much simplified) purification and subsequent deacetylation (with a concurrent yield decrease to *ca.* 50%).

2.1.4.7 Formation of the cyclohexylmethylidene acetal of methyl α-maltoside

In light of the difficulties in the purification of **30**, the analogous cyclohexylmethylidene acetal was formed to establish whether its purification was any less problematic. The synthesis was accomplished readily by stirring maltoside **31** in a solution of dry *N,N*-dimethylformamide in the presence of cyclohexane-carboxaldehyde and pyridinium *para*-toluenesulfonic acid under an atmosphere of argon over 30 hours, as detailed in Scheme 37.



31 **92**

Cy = cyclohexyl

Scheme 37

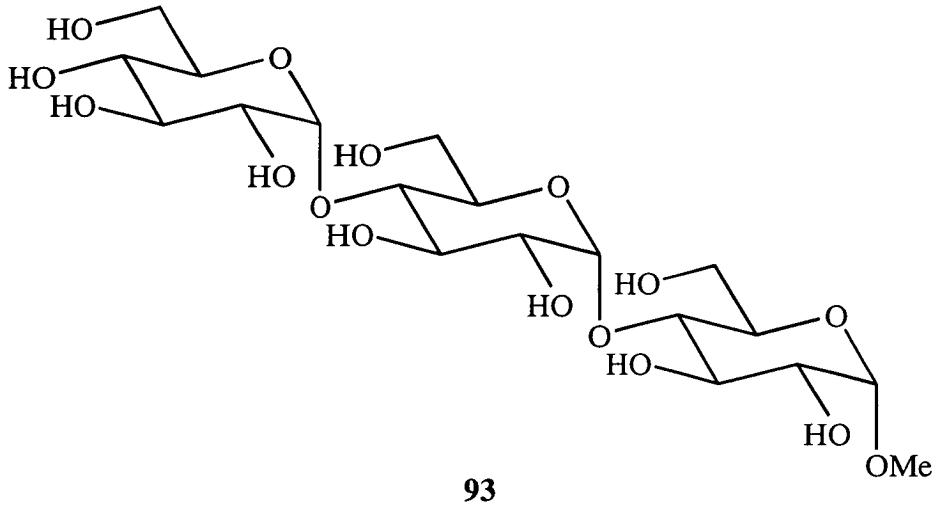
Although clean by thin-layer chromatography and by analysis of the ^{1}H and ^{13}C NMR spectra, the reaction produces a mass balance of 117%, for which no explanation was ever found.

Moreover, although this approach looked promising, it did mean that a particularly hydrophobic group was introduced into the molecule whose main reaction media would be water. Thus although **92** was never employed as a model it is relatively easily synthesised and may prove of some utility in future studies.

2.1.5 Attempted methyl α-maltotrioside formation

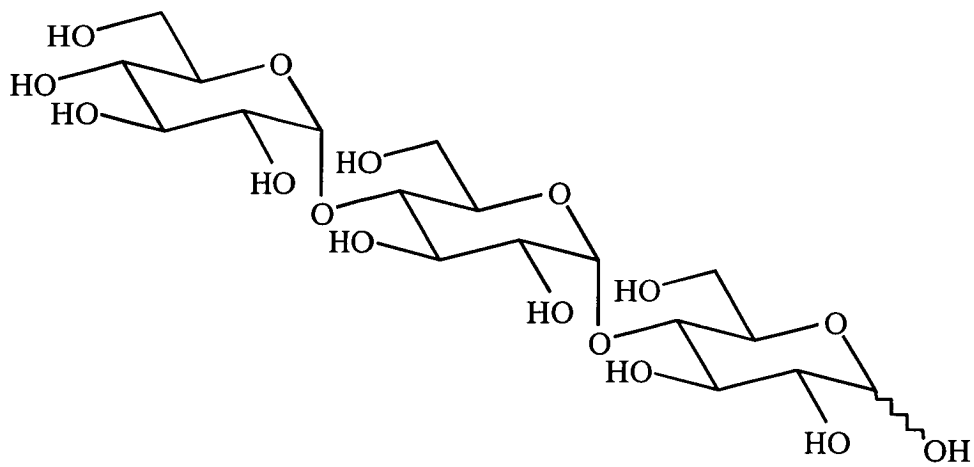
2.1.5.1 Preamble and background

In view of the success enjoyed in the preparation of **89** it was decided to establish whether this approach had general synthetic applicability to the field of α-glycoside synthesis. To this end methyl α-maltotrioside **93** was chosen as a target molecule.



93

Previously synthesised by Peat[129] in a yield of 0.25% from the action of potato-D-enzyme on amylopectin in the presence of methyl α-D-glucopyranoside, it was later produced slightly more efficiently by Cheetham[130] in 3.8% yield by the action of methanolic hydrochloric acid on maltotriose **94** which is an expensive (*ca.* £19 per gram[131]) side product from the enzymatic degradation of starch.



94

It was felt that should the analogous approach to the synthesis of **89** be applicable then all that would be required to synthesis **93** would be the replacement of iodomethane with an equivalent pyranosyl iodide, shown retrosynthetically in Figure 8.

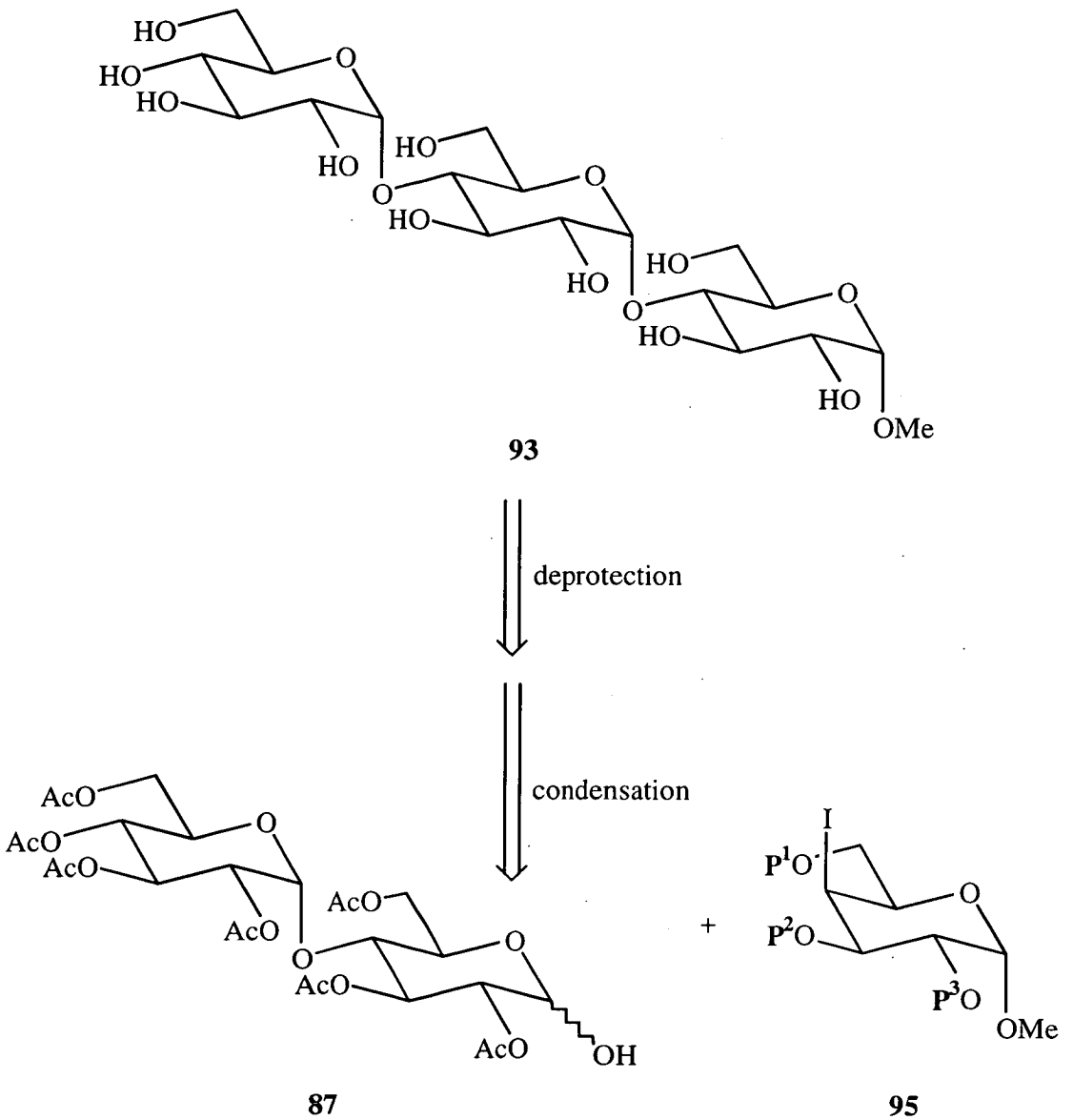
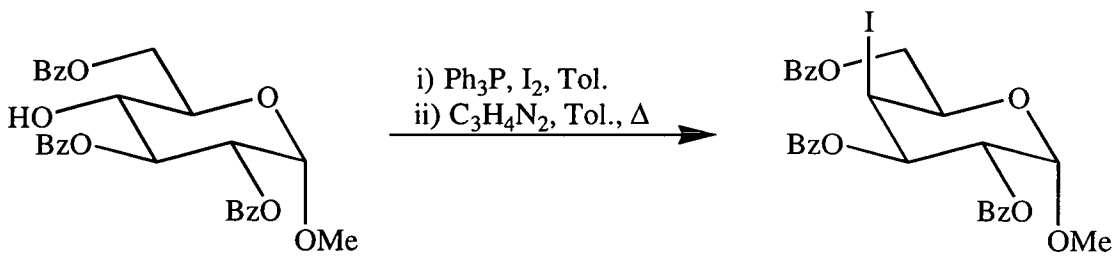


Figure 8

Of course **87** had already been synthesised in high yield, so the immediate problem became one of the synthesis of **95**. To ensure the stereochemical integrity of the end reaction product, the iodo compound had to be a methyl α-D-galactoside derivative since the reaction would necessarily involve nucleophilic attack with concomitant inversion of configuration at carbon 4. Moreover, a stock of methyl 2,3,6-tribenzoyl-α-D-glucopyranoside **68** existed which it was assumed could be easily converted into **95**, *i.e.* $\mathbf{P^1 = P^2 = P^3}$ = Bz.

2.1.5.2 Synthesis of methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-4-iodo-α-D-galactopyranoside 95

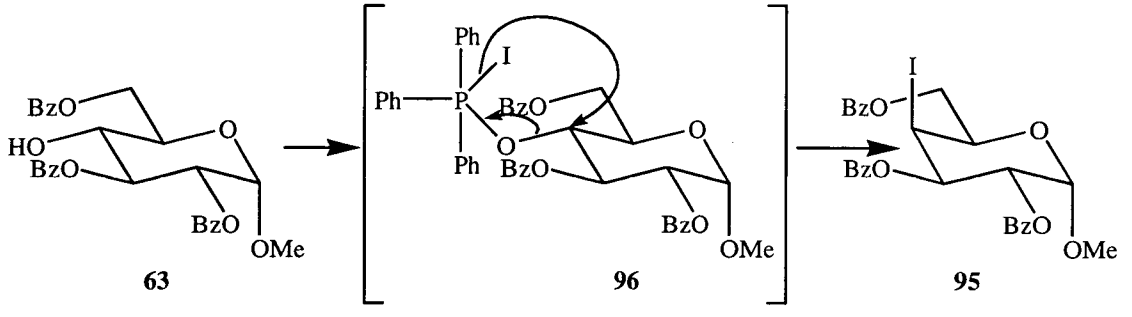
Methyl 2,3,6-tri-*O*-benzoyl-α-D-glucopyranoside **68** was easily and conveniently transformed into the iodo galactoside **95** in 86% yield following the work of Kuzuhara[132], by reaction of alcohol **63** with preformed bis-iodo triphenylphosphine in the presence of imidazole in refluxing anhydrous toluene, outlined in Scheme 38.



63 **95**

Scheme 38

Although this was a satisfying result it was slightly puzzling with respect to the expected difficulties arising from the introduction of such a large reagent into an area as sterically demanding as this hydroxy group occupies. Thus, the reaction proceeds *via* phosphineoxy iodide **96**, which then rearranges delivering the iodide into the axial position as detailed in Scheme 39.



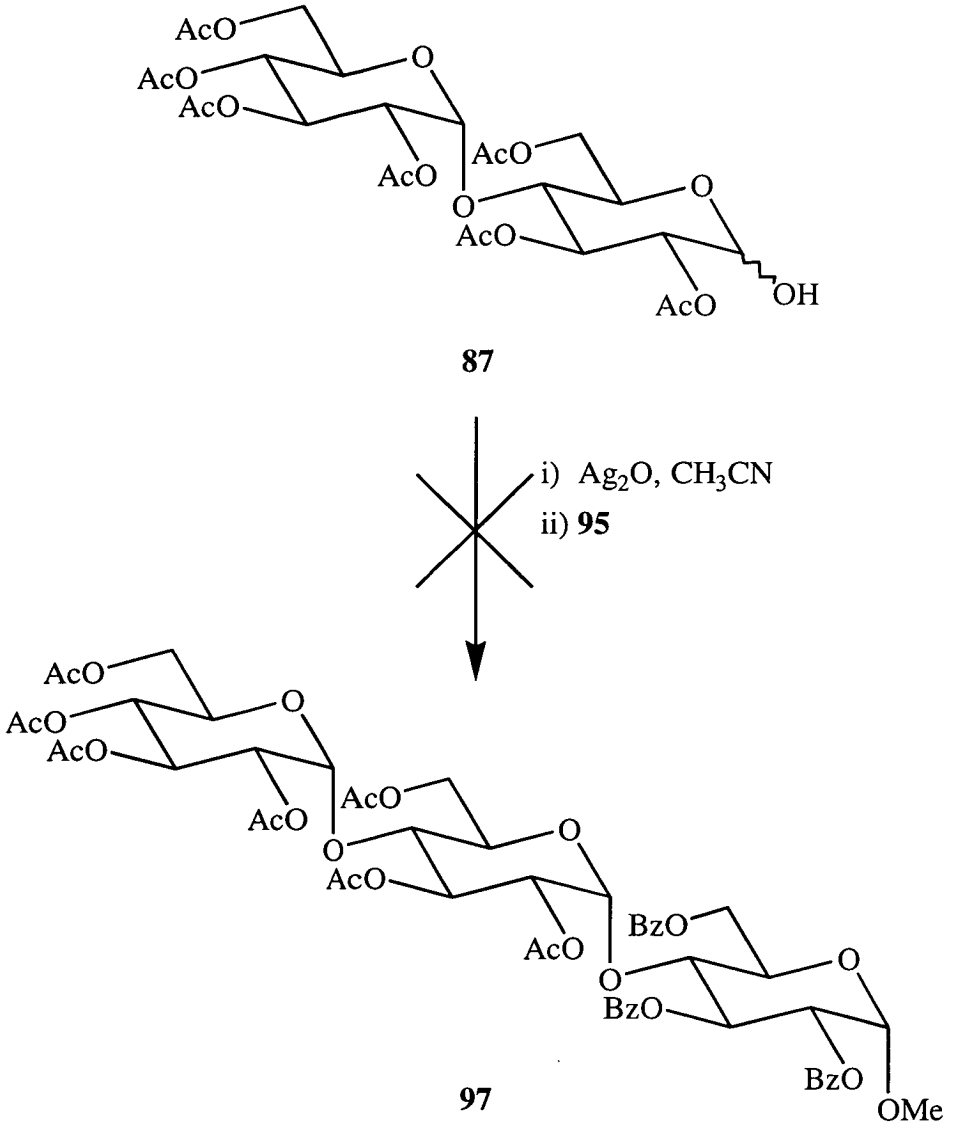
Scheme 39

A partial explanation for this unexpectedly successful reaction may lie with the choice of solvent. It may be that the intramolecular hydrogen bound complex **68** is not as strongly bound here as it is in dichloromethane, a scenario for which some evidence already exists inasmuch as **63** is formed in 76% yield in dichloromethane compared to 58% in toluene, thus suggesting a more stable intramolecular complex in the more polar solvent. Alternatively the success of this reaction may simply be a function of the elevated temperatures at which it is performed.

2.1.5.3 Attempted condensation of aldose 87 with iodo galactoside 95

Using analogous conditions to those employed in the formation of methyl α-maltoside **89** outlined in Scheme 40, aldose **87** was stirred with silver (I) oxide in

acetonitrile, where iodide **95** was slowly added in an attempt to form the methyl tribenzoylheptacetyl maltotrioside **97**. Initially this was performed at ambient temperature, but after 48 hours no reaction was observable by thin-layer chromatography and so the intended anomeric purity of the product was sacrificed and the reaction taken to reflux where it was maintained for a further 48 hours. Even here however no reaction was observed.

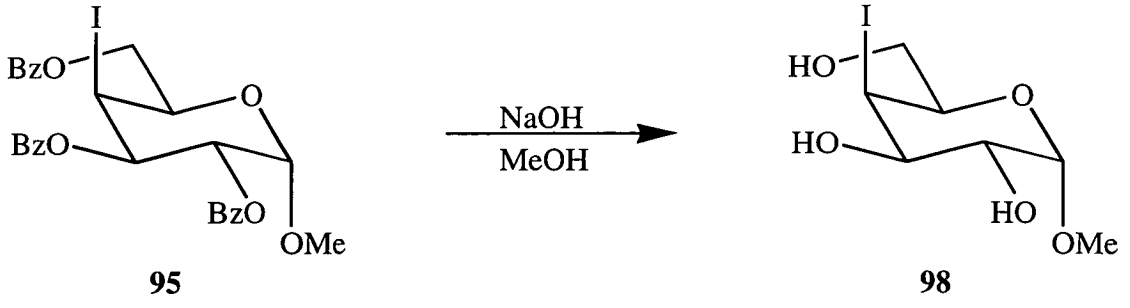


Scheme 40

This was not a particularly unexpected result with a view to performing any transformation in such a sterically demanding arena. Thus, since an iodide is typically a better leaving group than a hydroxyl, it was decided to attempt to exploit this relationship and perform the reaction under much less sterically demanding conditions. That is, if the reaction failed as a result of simple steric crowding around the equatorial position of carbon 4 in **95** then it would be prudent to liberate some space around this centre and repeat the reaction.

2.1.5.4 Deprotection of 95 to yield methyl 4-iodo-4-deoxy-α-D-galactopyranoside 98[105]

The obvious method to create some free space around C(4) was a simple deprotection of all the benzoate esters. This was accomplished as shown in Scheme 41 in 54% yield.



95 **98**

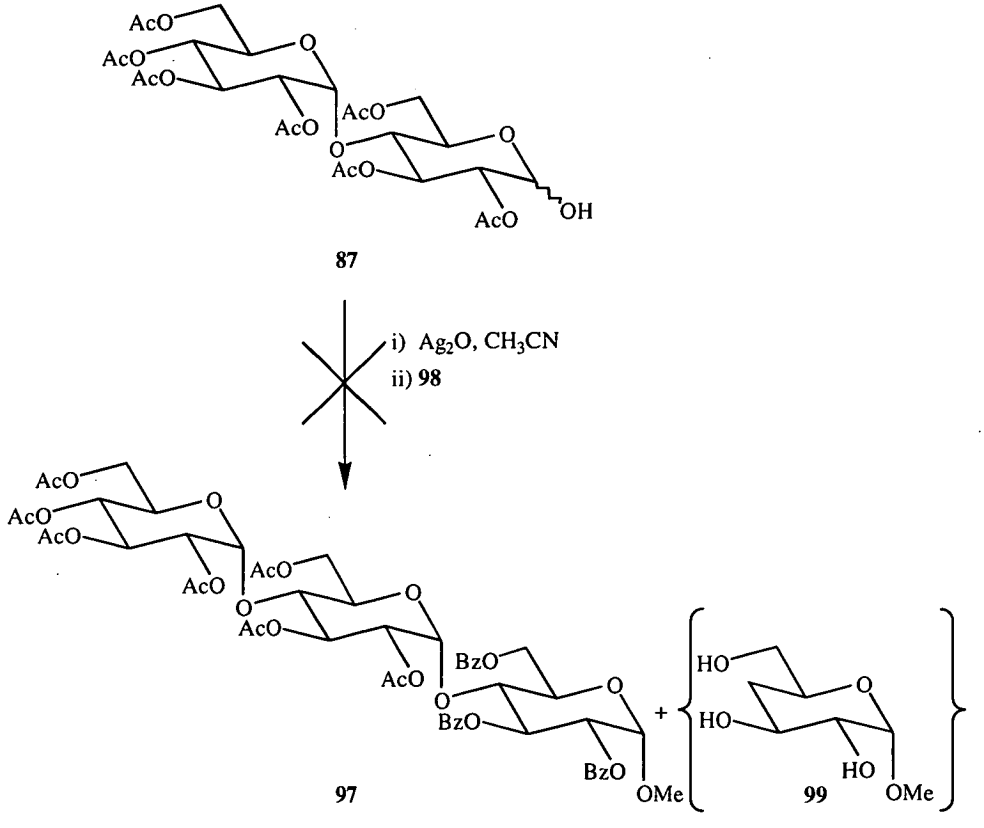
Scheme 41

The moderate yield relative to the debenzoylation of the 4-methoxy analogue **76** (quantitative) is perhaps simply a reflection of the ease of degradation of **98**. Indeed, great care was necessary to prevent the decomposition of **98**, either as a neat

oil, or on the application of heat. As a solution in chilled methanol it was however stable over a period of days.

2.1.5.5 Attempted glycosidation using methyl 4-iodo-4-deoxy-α-D-galactopyranoside

Again, following a similar protocol as outlined in Section 2.1.5.3, the iodo galactoside **98** was added to a stirring slurry of aldose **87** in acetonitrile in the presence of silver (I) oxide as shown in Scheme 42. Following 48 hours stirring, thin-layer chromatography revealed the presence of aldose **87** and a product of intermediate polarity between **87** and **98** (of which there was no evidence).



Scheme 42

The product of intermediate polarity was never able to be fully characterised, though it is possibly methyl 4-deoxyglucopyranoside **99**, resulting from some decomposition process of **98**.

2.1.5.6 Attempted anhydrous glycosidation

In an attempt to circumvent the decomposition of iodide **98**, the reaction was repeated using the same procedure under rigorously anhydrous conditions, however here again the desired product was not obtained at the expense of the material originally obtained under non-anhydrous conditions.

2.1.5.7 Modification of the silver salt

Since the reaction had failed under all of the three previously described conditions it was decided to attempt one final variation in conditions, on the premise that it may be some difficulty arising from the formation of the initial silver salt. To this end the reaction was repeated as per section 2.1.5.6 whilst substituting silver carbonate for silver oxide, however again no reaction was observed, apparently suggesting the formation of the silver salt is not implicated in the failure of the reaction.

Reviewing this synthesis it seems likely that the failure of this approach is most probably a result of the deactivation of the 4-position as a result of its inclusion in a hemiacetal. This in turn being the reasoning behind the more common synthetic approach outlined retrosynthetically in Figure 9 where the halide is borne by the

incoming anomeric carbon atom, and is displaced by the free 4-hydroxy group on the glucoside. If the synthesis is reversed as shown in Figure 9 then these difficulties may well be aleviated, however formation of iodide **100** would at best be problematic since there is no simple synthetic protocol available without resorting to acid catalysis to which the glycosidic bond is particularly susceptible.

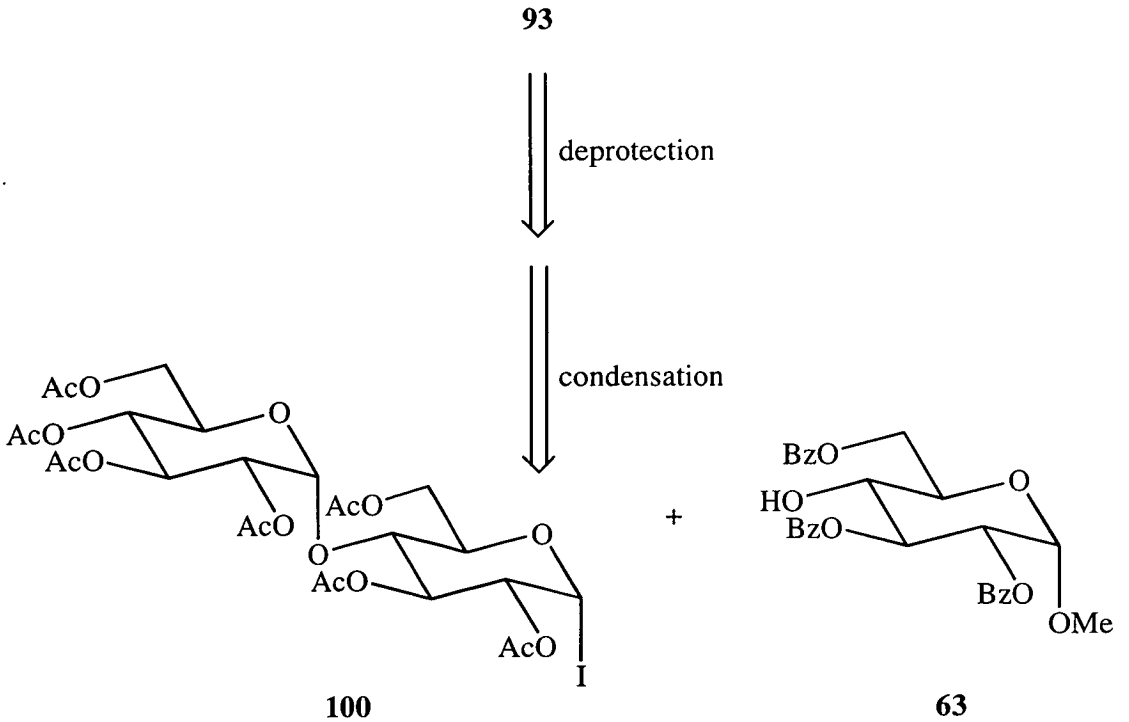


Figure 9

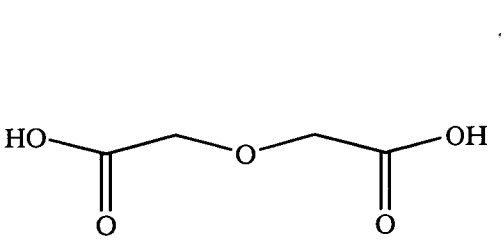
Moreover, using **100** or an alternative halo derivative would of course be likely to produce the undesired anomer without employing some form of control to the glycosidation. Also, it had been previously demonstrated how difficulties can easily arise when attempting to perform some transformation at the 4-hydroxy position in **63**.

Possibly a more rewarding approach would have been to use some other methodology detailed earlier, *e.g.* the β-trichloroacetimidate analogue of **100** with some non-participating group at C-2. However as this was not strictly relevant to the ongoing work it was abandoned.

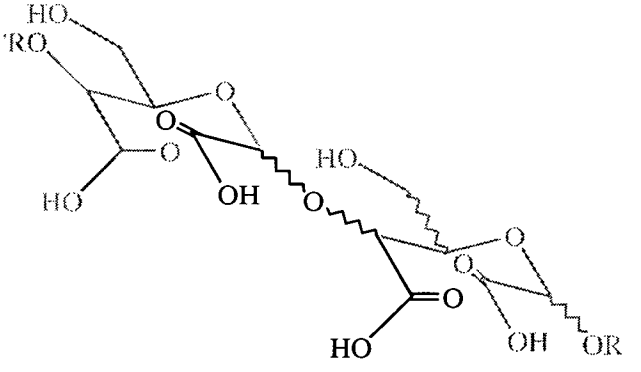
2.2 Complex geometry[133,134]

2.2.1 Preamble

It has already been noted[52] (see 1.1.3.4) that within a C2-C3 dicarboxy polysaccharide there lies a unit of similar structure to oxydiacetic acid **19**, *viz.* **101.**

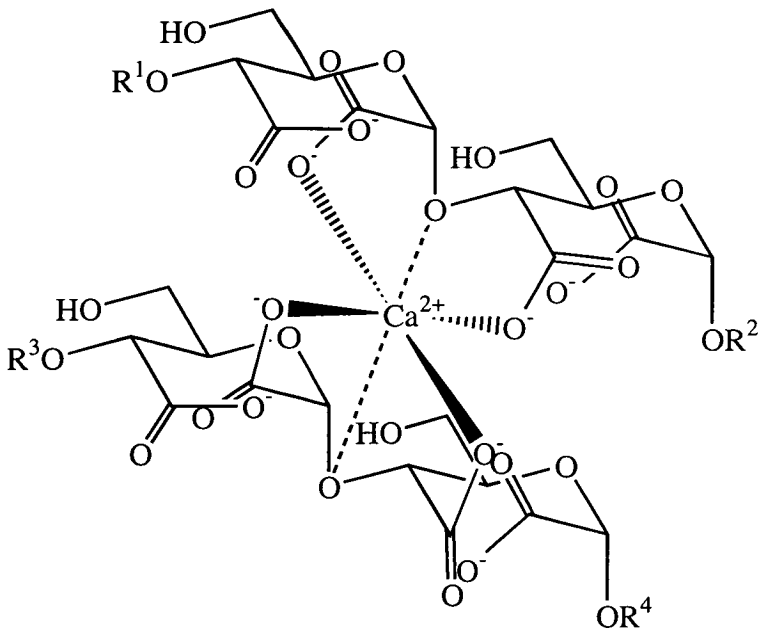


19



101

Nieuwenhuizen has postulated that where oxidised polysaccharides are found to be of use as calcium ligands it is through a complex involving two units of type **101**, and moreover that the molecular constraints cannot allow the co-operation of two neighbouring groups. Thus the complex predicted by this approach must involve two such units separated either by unoxidised portions of the chain, or by similarly oxidised groups, *viz.* **25**.



25

He then goes further and asserts that linear 1→4 α-D-based oxidised polysaccharides such as amylose will coil towards a helix with a concomitant reorientation towards the entropically favoured W-shaped ODA type groupings positioned alternatively above and below the coil, shown diagrammatically in Figure 10.

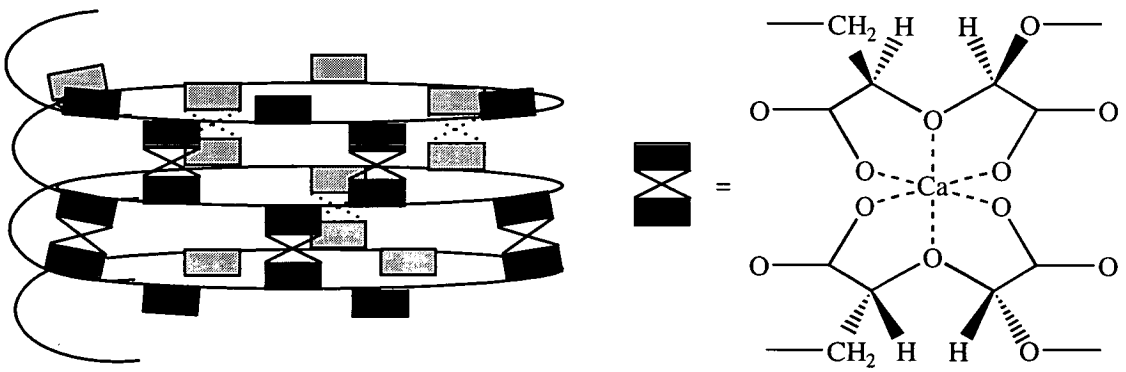


Figure 10

Later Floors contradicts this work and asserts that the enhanced sequestration abilities of these type of polysaccharides results purely from aggregation, even before complete saturation of the molecule.

Whilst it has long been known that amylose will form stable hydrogen bound helices, it is believed that after oxidation there are other influences which severely disrupt the ability to coil. Thus, the presence of two very much larger groups and their associated solvent cages, and the destruction of the pyranose ring mean that the molecule has less entropic stability.

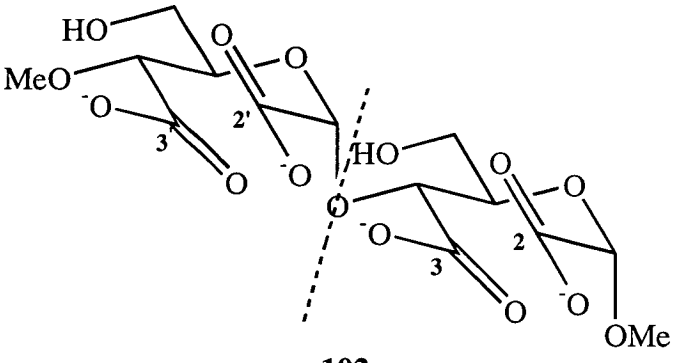
In turn this would suggest that it is unlikely that two very large, very electrostatic molecules would approach each other sufficiently closely to allow for the complexation of calcium as Nieuwenhuizen suggest, *i.e. via* **25**.

2.2.2 Disaccharide modelling

Since the hypothesis of Nieuwenhuizen seems unlikely, it was decided to investigate the possibility of forming some ligand within an oxidised disaccharide template (since this is the only model of sufficient size to form anything other than elongated bonds to calcium) using computer modelling software.

Thus the simplest possible model disaccharide derivative **102** was used as a template in studies using a combination of Tripos Associates' Alchemy v.III and Cambridge Soft's Chem3D Pro v.3.5. The four chelation possibilities of the

carboxylate groups assuming a constant involvement of the etheric oxygen (although allowing this to be of variable strength) were examined and the data is given in Table 3.



102

Model	Principal carboxylate groups involved	E_{total}	E_{bond}	E_{angle}	$E_{torsion}$	$E_{van\ der\ Waal}$
103	**3 - 2'**	**29.8**	2.1	18.5	17.9	-9.0
104	**2 - 2'**	**103.8**	17.2	47.8	20.2	18.4
105	**3 - 3'**	**23.0**	1.6	22.6	7.5	-8.2
106	**2 - 3'**	**9.1**	1.2	11.7	7.9	-11.7

Energies reported as kcal mol^{-1}

Table 3

Examination of this data yields a slightly unexpected result in that using both modelling packages, the assumed complex formation is not of type **101**, *i.e.* **103** has a greater energy then does its isomer **106**. This on a brief appraisal of the structure seems unlikely, however if the structure is simply manipulated slightly as shown in Figure 11 then this complex becomes much more apparent.

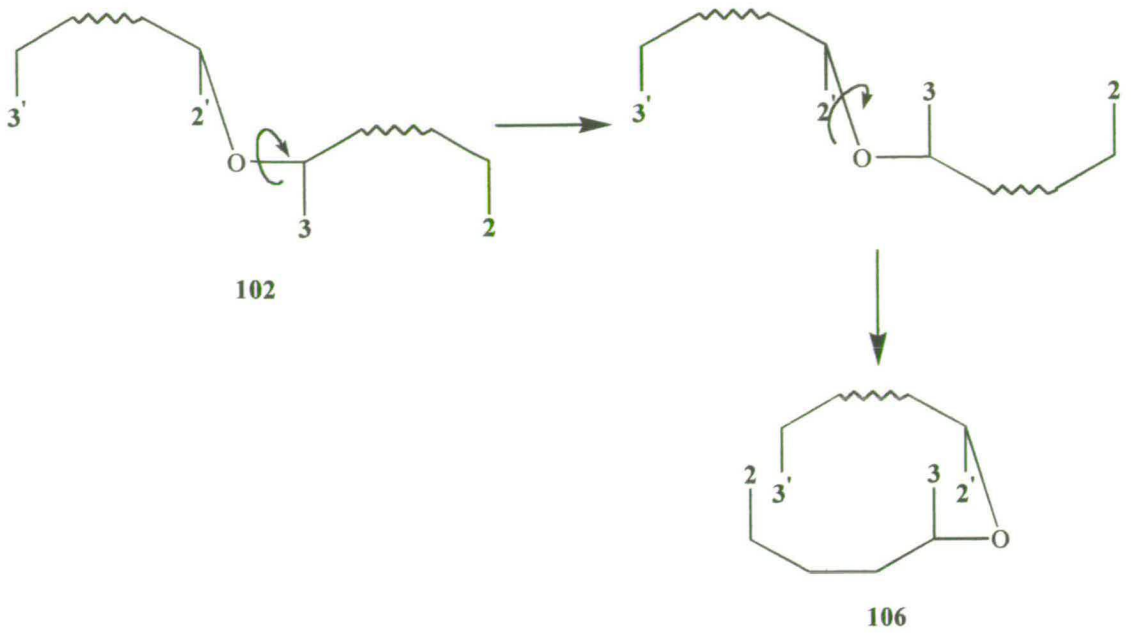
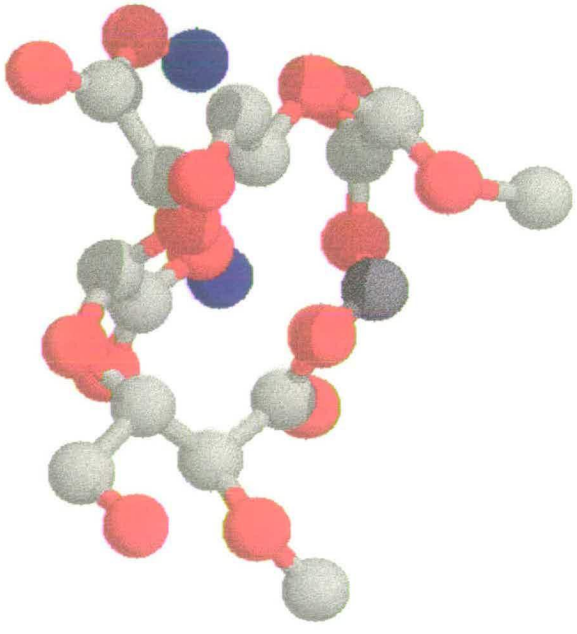


Figure 11

The calcium ion then sits inside this newly created pocket, *i.e.* **107** with blue atoms representing calcium, red oxygen and grey carbon. Hydrogen atoms have been omitted for clarity.



107

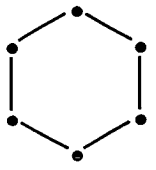
It is not absolutely clear as to the exact manner with which the rest of the complex is bound, whether that be *via* longer range interactions with the other oxygen donors in the molecule, or interactions with solvent molecules. Certainly, when water molecules are included into the molecular minimisation then a reduction in overall energy is observed, though whether this is simply a consequence of a solvation effect or as a result of a more stable complex is not clear. Nevertheless, a similar reduction was observed when the same criteria were applied to model **103** *i.e.* that which would be expected as energetically most favourable on the basis of the work of Nieuwenhuizen.

As the modelling had pointed towards a somewhat different scenario than had been expected, it was then decided to apply this to a slightly larger molecule to establish whether any more information could be gleaned.

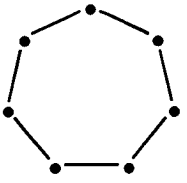
2.2.3 Polysaccharide modelling

A similar approach was taken here as earlier, using a combination of molecular modelling packages. No attempt was made to alter the mode of binding, with all interactions considered to concern the equivalent carboxyls to **2** and **3'**. The reasoning behind this being that it was felt there was sufficient flexibility within the molecule to accommodate this geometry without destabilising the complex. Preparatory examinations with a few complexes of varying interactions served to confirm this.

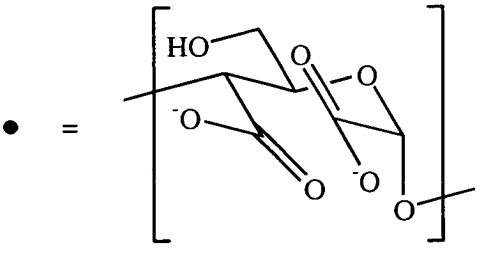
The sites of interaction were of primary interest here, and so these were varied between neighbouring moieties and those separated by one or more units. As a convenient starting point of well defined configuration and composition the C2 / C3 peroxidised derivatives of α- and β-cyclodextrin, **108** and **109** were examined.



108



109



Model	Unit positions	E_{total}	E_{bond}	E_{angle}	$E_{torsion}$	$E_{van\ der\ Waal}$
α - cyclodextrin derivatives						
110	**1,2 - 3,4**	**38.4**	3.5	39.8	39.9	-44.9
111	**1,2 - 4,5**	**40.8**	3.5	38.5	39.6	-41.0
112	**1,2 - 3,4 - 5,6**	**36.8**	3.5	42.2	36.7	-45.7
β - cyclodextrin derivatives						
113	**1,2 - 3,4**	**59.4**	3.7	44.3	35.8	-54.2
114	**1,2 - 4,5**	**47.7**	4.2	46.2	42.8	-45.5
115	**1,2 - 5,6**	**58.3**	4.2	56.6	50.4	-53.0

Energies given as kcal mol^{-1}

Table 4

Computational analysis showed that the most energetically favourable arrangement was obtained where two or three calcium ions were bound to a oxidised

polysaccharide derived from α-cyclodextrin, *i.e.* **110**, **111** or **112**. No attempt to differentiate between the three models was made since it was felt that under the constraints imposed by the modelling software the energetic differences were insufficient to allow a definitive conclusion to be drawn.

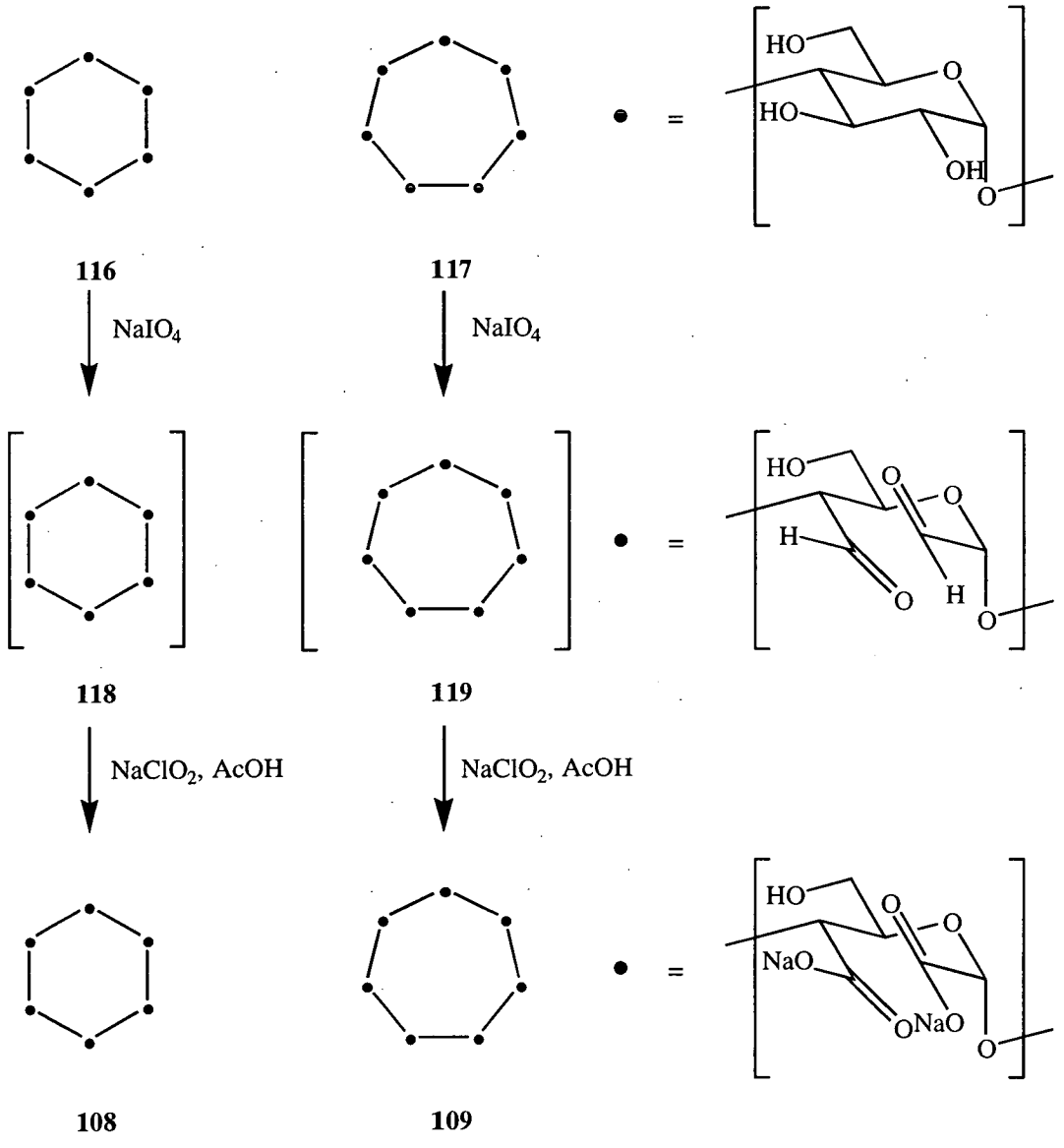
Here again some exploratory studies were made with the introduction of solvent molecules, and again they showed broadly similar trends in their effect on the overall energies, that is that each of the total energies decreased with the subsequent addition of each solvent molecule.

This was slightly unexpected since Nieuwenhuizen had previously asserted that the sequestering abilities of oxidised amylose were as a result of coiling of the polymer, with each coil containing 7 oxidised glucose units, which in turn form good ligands. Thus, it was expected that the most stable complexes should arise from ligands again containing 7 oxidised glucose units, *i.e.* those derived from β-cyclodextrin. It was thus decided to synthesize both α- and β-peroxidised polysaccharides and probe their calcium binding by physical means and subsequently correlate this to the computationally derived data.

2.2.3.1 Peroxidation of cyclodextrins 108 and 109

Cyclodextrins **116** and **117** were peroxidised under standard and highly efficient sodium periodate oxidative conditions to the polydialdehydes **118** and **119**,

which were then used immediately for subsequent oxidation with sodium chlorite to the polydiacids **108** and **109** as shown in Scheme 43.



Scheme 43

The sodium salts of polydiacids **108** and **109** were then subjected to analysis of their calcium sequestration properties *via* the standard calcium sequestration analysis of Solvay-Interox[135].

2.2.3.2 Calcium sequestration of polydicarboxy cyclodextrins 108 and 109

A standard aqueous solution of the polyacid containing potassium chloride and sodium hydroxide was titrated against a standard solution of calcium acetate, with the electrical potential across the solution measured by a Unicam calcium ion-selective electrode and a Corning double junction reference using a Metler millivolt meter. The resultant potentials were then plotted against calibration data prepared immediately beforehand.

For a comparative study, sodium tripolyphosphate (STP) was also similarly analysed. The data obtained are shown in Figure 12 in the form of the percentage of added calcium that is chelated relative to the weight of calcium this corresponds to per hundred grams of sample.

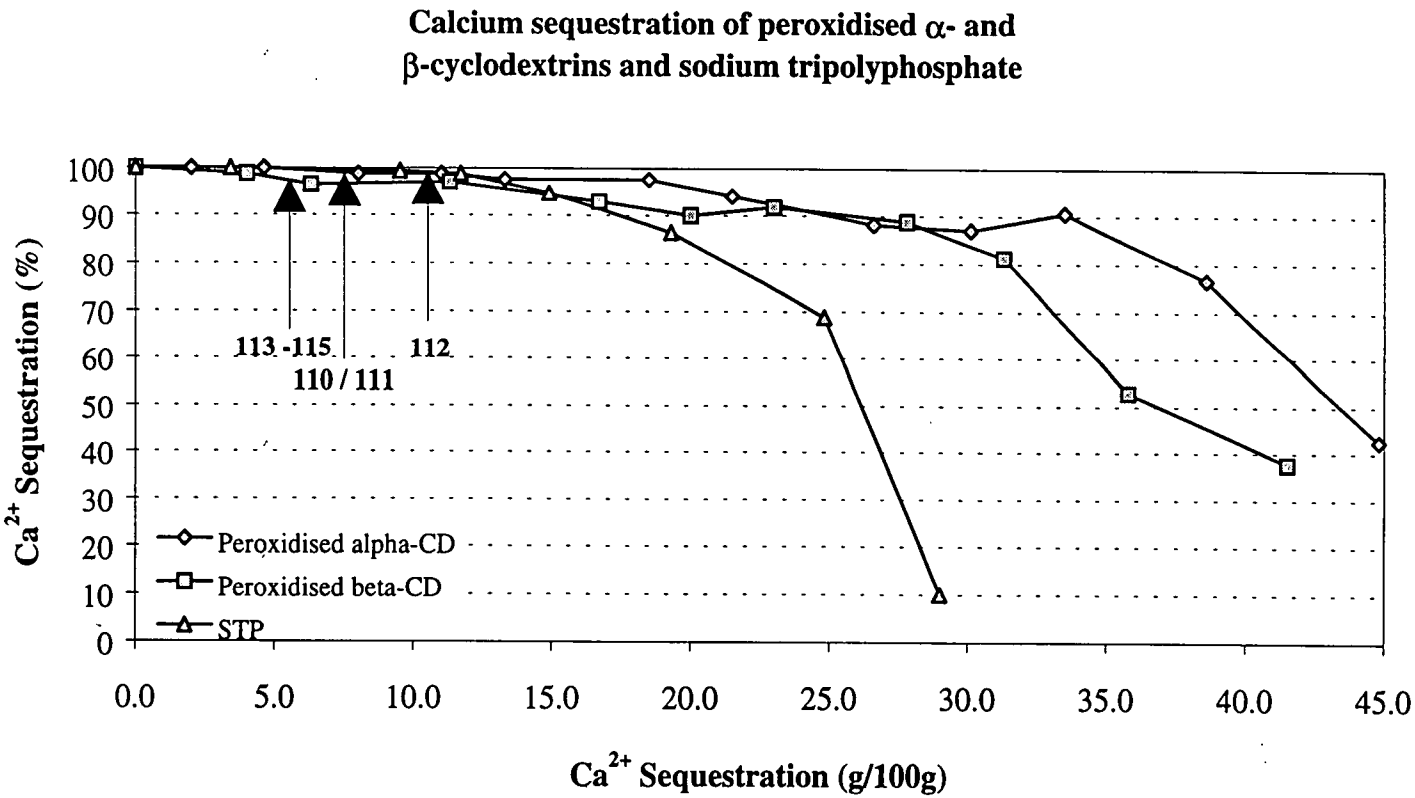

Calcium sequestration of peroxidised α- and β-cyclodextrins and sodium tripolyphosphate
Ca2+ Sequestration (%)
100
90
80
70
60
50
40
30
20
10
0
113 -115
110 / 111
112
Peroxidised alpha-CD
Peroxidised beta-CD
STP
0.0
5.0
10.0
15.0
20.0
25.0
30.0
35.0
40.0
45.0
Ca2+ Sequestration (g/100g)

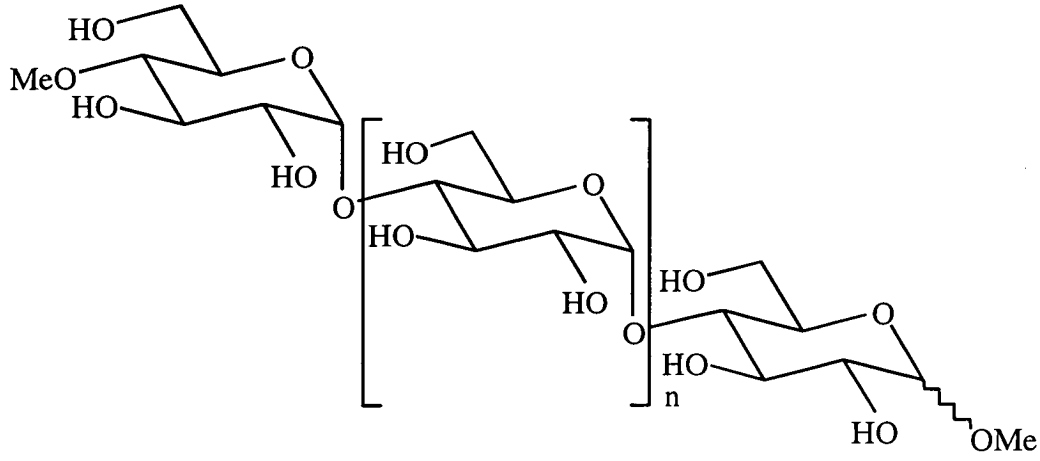
Figure 12

Examination of Figure 12 shows that as predicted by computer modelling the ligands derived from α-cyclodextrin, *i.e.* **110** - **112** proved to be the most effective. This would then imply that Nieuwenhuizen's original assertion that the efficiency with which oxidised amylose binds calcium is attributable to a seven membered coil is more likely to involve a six membered coil.

Interestingly, at the calcium sequestration levels which involve two calcium ions *i.e.* **110** and **111**, and that involving three *i.e.* **112** there is no subsequent rapid decrease in the percentage of calcium chelated. This was not however unexpected since there is a strong possibility that the binding efficiency is influenced by other macromolecular properties such as aggregation between coils. The computing power necessary to try to predict such interactions is considerable and impractical.

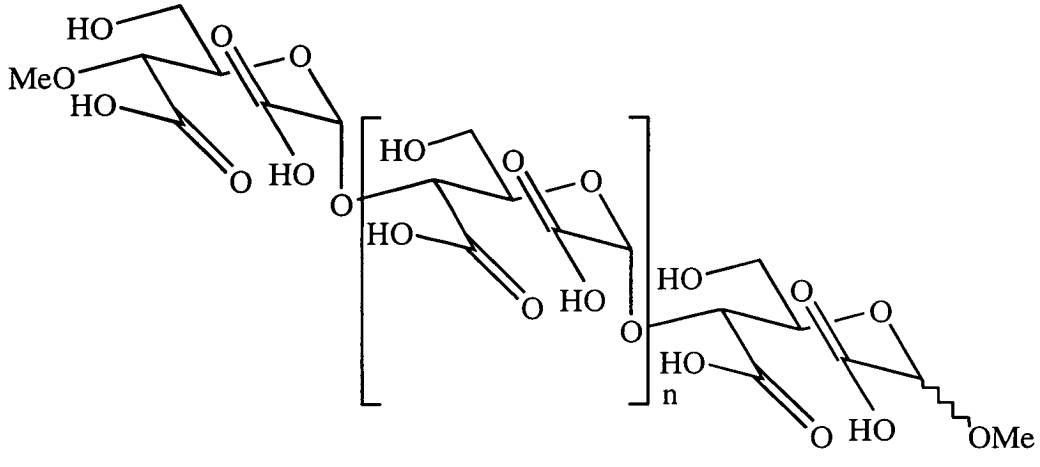
Moreover, both cyclodextrin derived ligands performed better than had been anticipated relative to the industrially used STP. This in turn has led to some interest in their industrial application.

Implicit in this work was the assumption that within the original cyclodextrin skeleton there would be sufficient suppleness to allow the molecule to behave as does oxidised amylose. To examine this and hopefully to provide further indications about the nature of the binding site it was decided to attempt the synthesis of two further models, being six and seven glucose units in length, *i.e.* **120** and **121**.



120 : n = 4
121 : n = 5

From **120** and **121** it was then anticipated that the polyacids **122** and **123** could be prepared which could then be examined as ligands by computation and electrochemical methods.

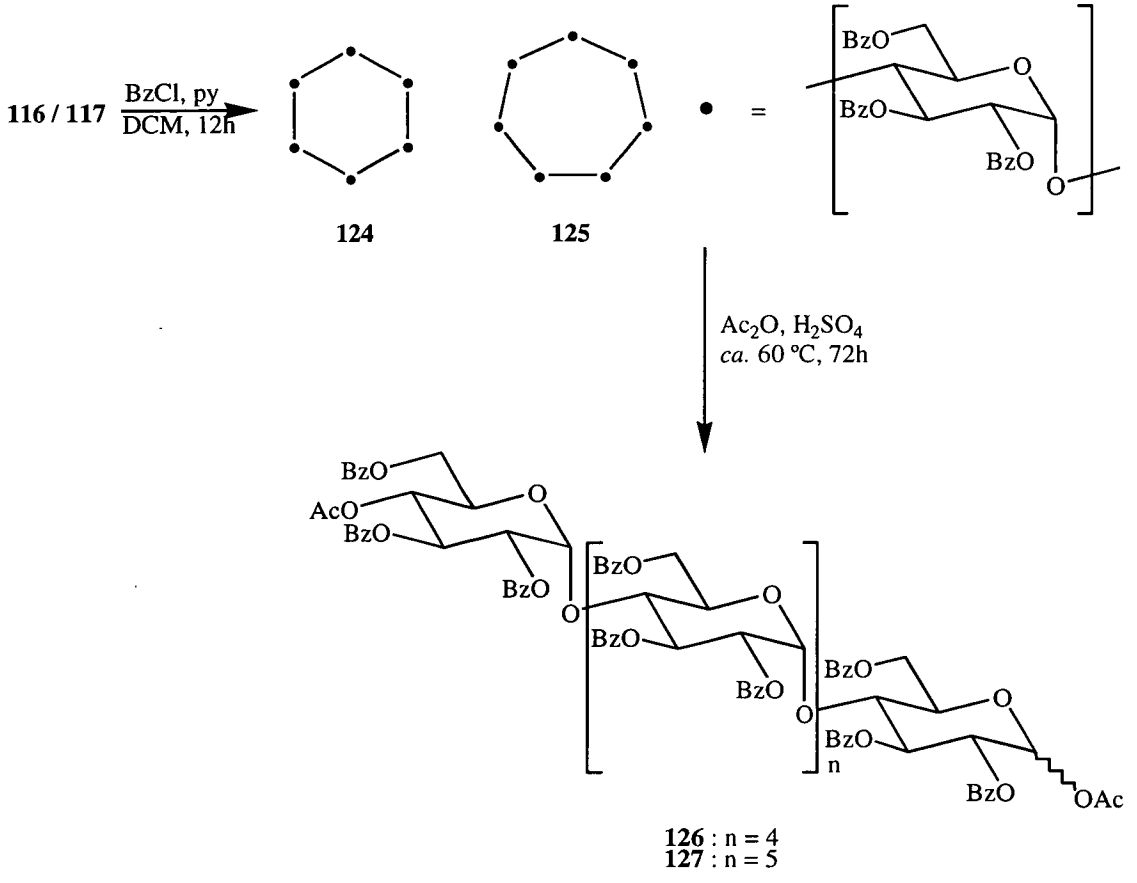


122 : n = 4
123 : n = 5

The route to both **120** and **121** both involved the use of the respective cyclodextrin as starting material, following work done by Sakairi[136].

2.2.4 Attempted preparation of hexa- and heptaaldosides 120 and 121

Sakairi had shown that perbenzoylated cyclodextrins could undergo a single glycosidic bond fission in acetic anhydride in the presence of concentrated sulfuric acid to yield a 1,4-di-*O*-acetyl perbenzoyl cyclodextrin, albeit in only moderate yield. Thus, cyclodextrins **116** and **117** were perbenzoylated and subsequently subjected to the ascribed glycosidic fission conditions as detailed in Scheme 44 to afford the diacetates **126** and **127** in 49% and 63% yields respectively.

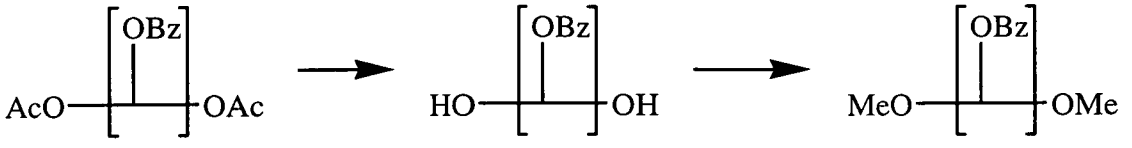


126 : n = 4
127 : n = 5

Scheme 44

Once **126** and **127** had been isolated it was then intended to employ some of the experience gained from working with the smaller models to exploit the differing reactivities of the benzoyl and acetyl esters to independently remove the acetates

leaving two free hydroxyl groups which could then be methylated, diagrammatically illustrated in Scheme 45.



Scheme 45

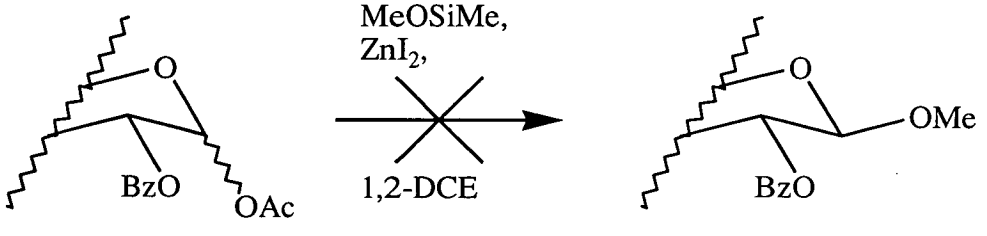
To yield the desired polymeric aldosides **120** and **121** would then only require deprotection of the benzoyl esters.

The stereochemistry of the glycosidic methyl group was not considered to be of major importance since it was much smaller than all of the other glycosidic ethers present in the molecule all of which possessed the desired α-anomeric configuration. Thus the principal interest was focussed upon selectively removing the acetates.

It was found that using the aforementioned ammonia saturated mixed solvent system was ineffective in this case (*c.f.* anomeric acetate deprotection of a peracetyl glycoside (Section 2.1.4.3)). Initial suggestions for this failure pointed towards a polarity difference however variations in the composition of solvent employed either resulted in no reaction occurring, presumably since there was insufficient ammonia present, or in complete deprotection, *i.e.* no selectivity.

With careful control of reaction conditions, ^{n}butylamine in tetrahydrofuran could be successfully employed to cleave the 4-*O*-acetate group, albeit in poor yield (34%). Although never attempted it was assumed that this free hydroxyl group could be methylated under the moderate pressure conditions employed in the preparation of **76** (see 2.1.3.5).

Sakairi had used diacetyl perbenzoyl cyclodextrins to form β-thiobenzyl glycosidic ethers *via* the direct anomeric substitution of the polyester in high yield (typically > *ca.* 98%) and so it was decided that this approach should be adopted with modified reagents in an attempt to produce the equivalent methyl glycoside (whilst accepting that the majority of products would be of the undesired anomeric configuration. Thus **127** was treated under the equivalent conditions outlined in Scheme 46.



125

Scheme 46

Even after prolonged reaction times however the reaction proved fruitless, presumably simply as a consequence of the methoxy silane being less reactive than the equivalent thiobenzyl silane.

Although the synthesis of **120** and **121** was desirable for their subsequent oxidation to respectively **122** and **123**, it was felt that the route although apparently straightforward contained too many possible pitfalls, and so was abandoned at this stage.

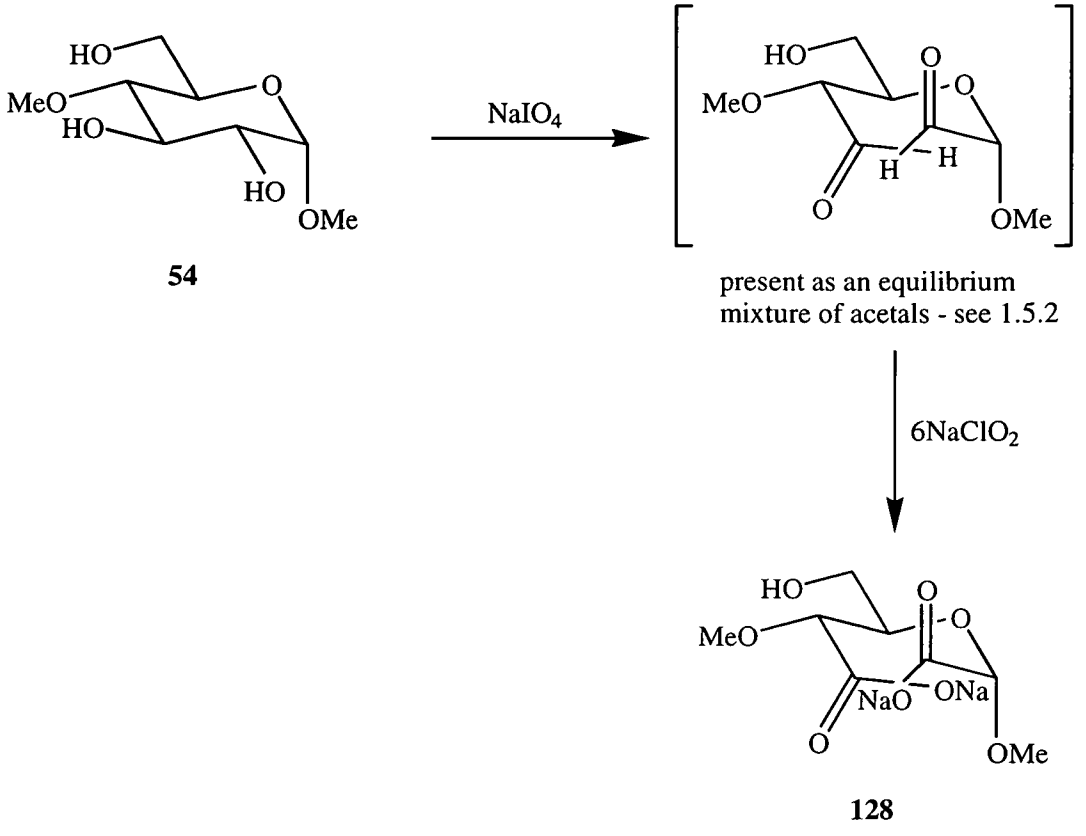
2.3 Oxidation studies[137]

2.3.1 Preamble

Following the synthesis on a convenient scale of model compounds **31** and **54** the next logical step was to perform some well defined oxidations on these compounds in order to have a set of NMR data which could then be used for comparison with the reaction products of subsequent oxidations.

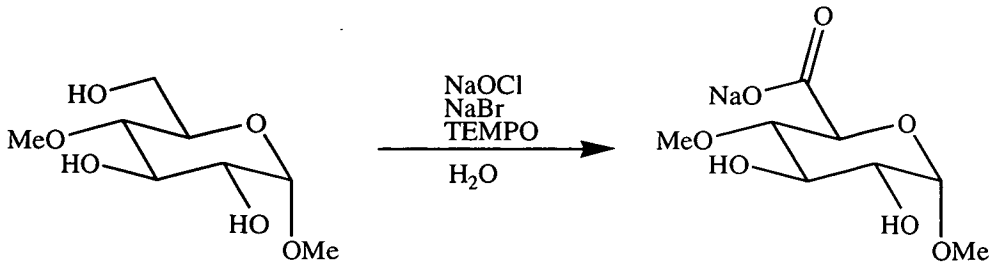
2.3.2 Preparation of monomeric standards

The principal products of any non-degradative oxidation on monomer **54** will be the product of C2 / C3 oxidative glycosidic cleavage **128** and the alduronic acid **129** produced *via* regioselective oxidation of the primary alcohol. Thus, **54** was subjected to a two stage oxidative glycol cleavage mediated by firstly sodium periodate and then sodium chlorite in 72% overall yield as detailed in Scheme 47.



Scheme 47

54 was also subjected to regioselective oxidation to the aldonic acid derivative **129** using the highly selective, kinetically controlled tetramethylpiperidnyloxy radical catalysed alcohol oxidation in 94% yield as outlined in Scheme 48.



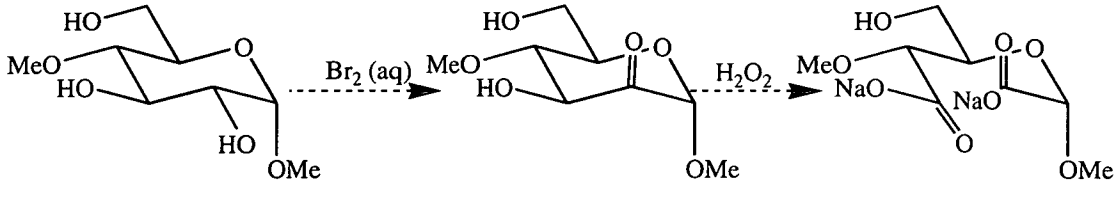
54 **129**

TEMPO = 2,2,6,6-tetramethylpiperidinyloxy radical

Scheme 48

2.3.3 Attempted combined bromine / peroxide oxidation

In an attempt to exploit the mild nature of hydrogen peroxide as an oxidant it was decided to try to create conditions such that the pH could be controlled and maintained away from the typically employed alkaline conditions, where as previously noted, the action is principally degradative (see 1.5.4). Thus, aqueous bromine was employed in an attempt to generate the C(2) keto group *i.e.* **130**, which would be a much more reactive centre for attack by peroxide, as outlined in Scheme 49.



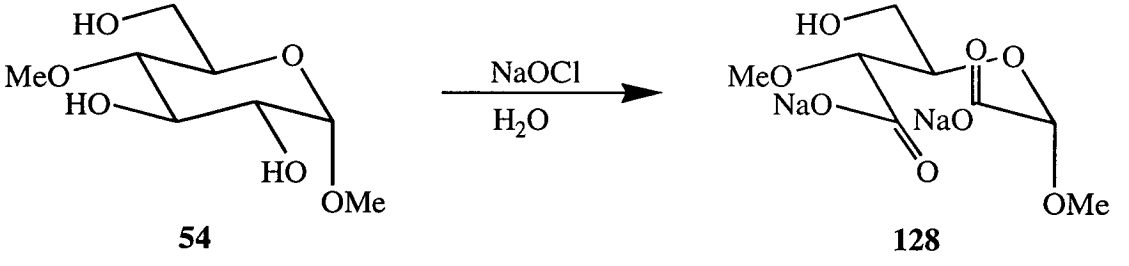
54 **130** **128**

Scheme 49

Addition of bromine to a stirring solution of **54** yielded a two spot TLC mixture, which on addition of hydrogen peroxide rapidly decomposed to an inseparable mutlispot mixture, even over a range of pH's. A possible reason for the reaction failure is the low concentration of bromine employed relative to the conditions employed in oxidation by aqueous bromine (2 eq. v.'s ≥ 25 eq. - see 1.5.3). This difference was simply a consequence of desiring an explicit two-step oxidation rather than straightforward aqueous bromine oxidation with all its associated drawbacks.

2.3.4 Sodium hypochlorite oxidation

One of the most common polysaccharide oxidations is performed using sodium hypochlorite, and so this approach was taken using **54** to ensure that the model did indeed behave as was intended as shown in Scheme 50.



54 **128**

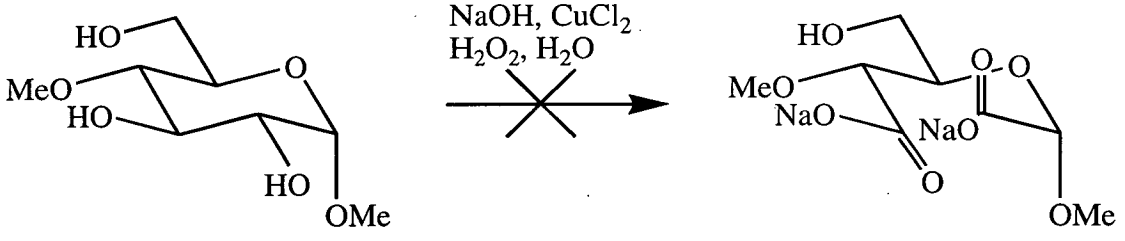
Scheme 50

Gratifyingly the desired di-acid was obtained in 44% yield based on oxidant consumption. The relatively low yield was not unexpected since when the oxidation is performed on a typical polysaccharide it is common to employ a large excess.

Here, however, to minimise the possibility of interfering side reactions two equivalents of hypochlorite were used (which is that required by the proposed literature oxidation mechanism - see 1.5.1).

2.3.5 Attempted copper chloride / hydrogen peroxide oxidation

In conjunction with some work performed by Solvay Interox[138], it was decided to try to perform selectively the C2/C3 oxidative glycol cleavage on **54** using an aqueous solution of hydrogen peroxide which it was intended to activate using a mixed copper chloride / sodium hydroxide solution, and is outlined in Scheme 51.



54 **128**

Scheme 51

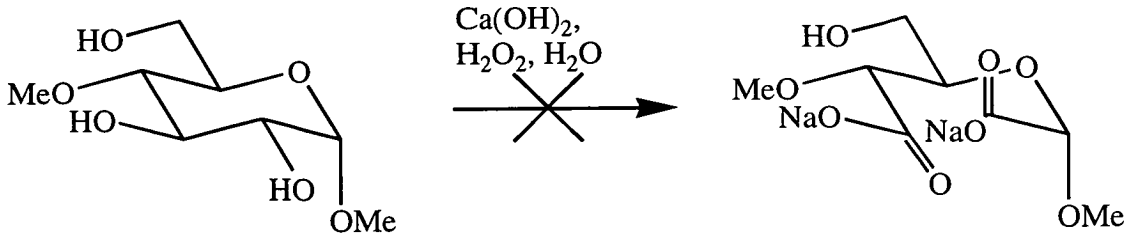
This system had shown some promise when applied to Maldex-15 by Solvay (Maldex-15 being the product of enzymatic degradation of starch with a Gaussian mass distribution centered around a chain comprising of 15 glucose units). The failure of the system when applied to **54** over a range of pH's, temperatures and reaction times may indicate that either one or other (or both) of two influences are being observed when using Maldex-15.

Firstly, hydrogen peroxide systems are relatively sensitive to the presence of metal impurities which, as outlined in 1.5.4, can generate hydroperoxy radicals which then participate in oxidative conversions. Had the Maldex-15 samples contained any metal impurities (as noted in 2.1.1, purification of large molecules such as these can be problematic) then it might be expected that these could have become involved and shifted the oxidative process towards a radically controlled one, which would be unlikely to operate on **54** under the given conditions. Indeed being able to rule out the involvement of metal impurities is a particular advantage of using **54** over Maldex-15.

Secondly and more likely is that the oxidative action and data observed by Solvay resulted from the oxidation of an aldose, liberated by glycosidic cleavage at some point in the chain or at the reducing end of the oligosaccharide. Consumption of oxidant is then related to three principal oxidative processes, as detailed in Scheme 9.

2.3.6 Attempted calcium hydroxide / hydrogen peroxide oxidation[139]

In an analogous piece of work, again carried out in conjunction with Solvay Interox, calcium hydroxide was used in an attempt to generate *in situ* calcium hydroperoxide, the anion of which was intended to act as a relatively powerful oxidant as shown in Scheme 52.



54 **128**

Scheme 52

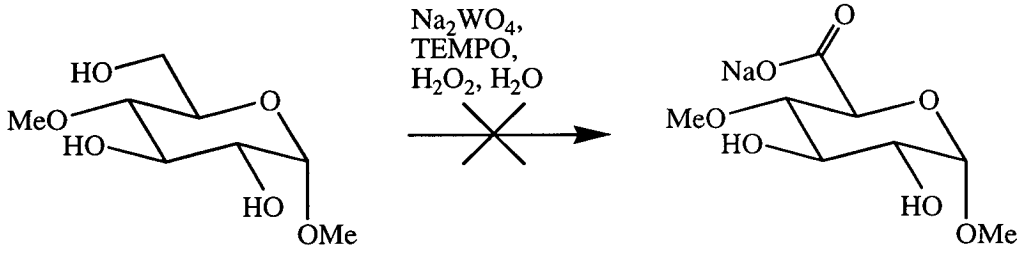
Again this had shown some promise when applied to Maldex-15, and again here no reaction was observed over a range of pH's, temperatures and reaction times. In looking for an explanation for the failure of this reaction, the same arguments as applied in 2.3.5 apply, namely that the observed oxidant consumption results from oxidations on aldoses and subsequent degradation products.

2.3.7 Attempted calcium hydroperoxide oxidation[140]

Since the *in situ* generation of the hydroperoxide detailed above had failed, it was decided to form and isolate a sample of calcium hydroperoxide and then use this to rule out the possibility that the failure of this approach was due to the failure to form the hydroperoxy anion. This was duly done, and not unexpectedly again no reaction was observed. Thus it can be assumed that when using **54**, the active species is indeed formed but is not sufficiently active to perform any reaction. However when applied to an oligosaccharide either when the reducing end is attacked, or once the molecule has undergone (at least) one glycosidic cleavage there exist a number of more reactive centers which the active species is able to act upon.

2.3.8 Attempted selective primary alcohol oxidation[141]

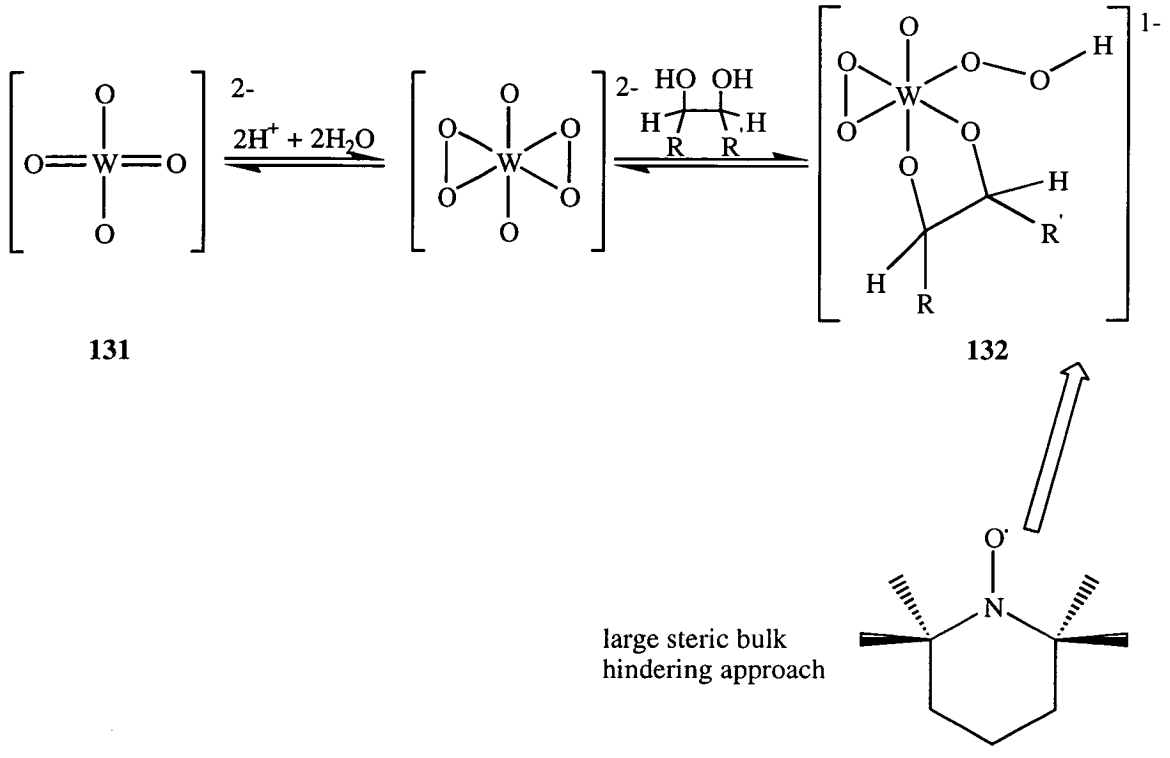
Murahashi[141] has shown previously that secondary amines can be selectively oxidised to nitrones by a combined hydrogen peroxide / sodium tungstate system. Since the TEMPO redox cycle lies within this overall transformation, it was expected that these conditions should be sufficient to drive the TEMPO cycle, and thus a selective oxidation was attempted as shown in Scheme 53.



54 **129**

Scheme 53

However, over a range of pH's from pH 7 to pH 12 no reaction was observed. The absence of any aldehyde formation would indicate that the N-oxy radical is not being oxidised to the active nitrosonium salt, which in turn may indicate that the initial oxidant **131** used to oxidise the radical to the salt is not operating. This is perhaps not unexpected since such tungstate species can form complexes **132** with *vic*-diols which then may block the approach of the sterically demanding radical, as outlined in Scheme 54.



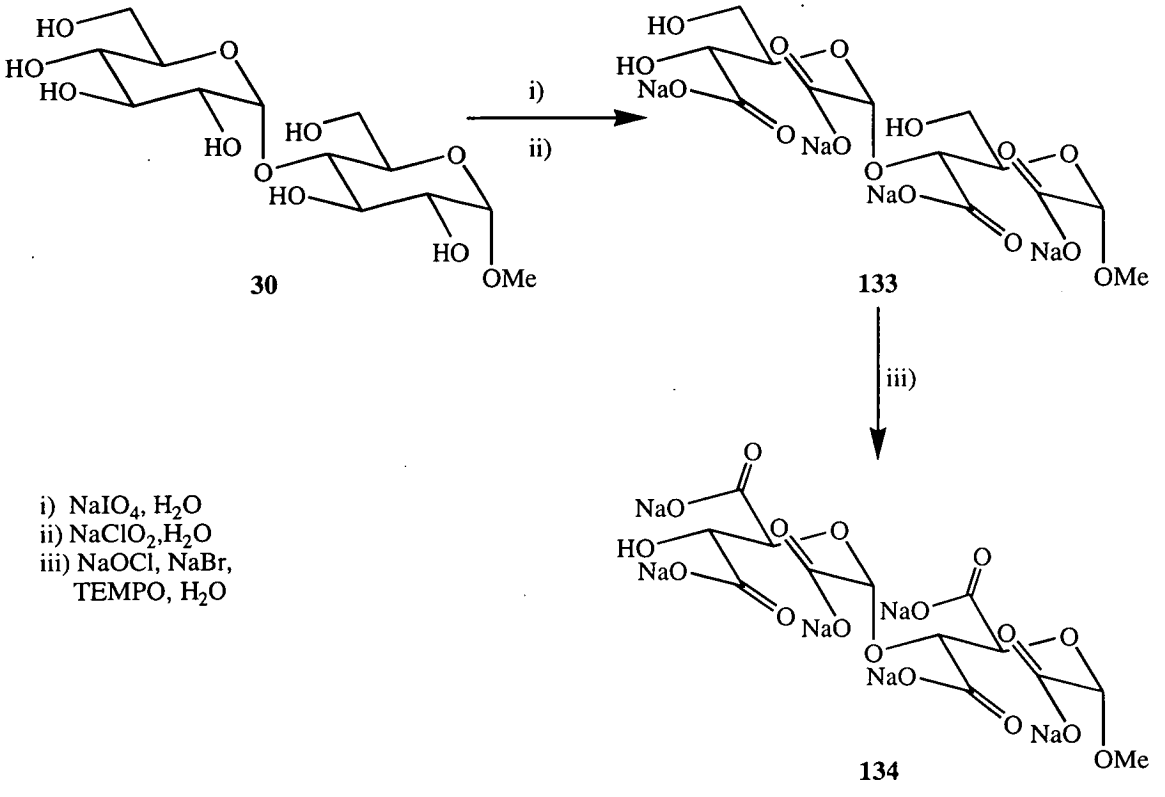
Scheme 54

When typically performed, this reaction is under the control of hypobromite, generated *in situ* from sodium hypochlorite and sodium bromide as shown in Scheme 12. This is of course much smaller than the tungstate species, and consequently the steric bulk of the radical which gives this reaction its regiospecificity can be expected to be less problematic.

2.3.9 Preparation of dimeric standards

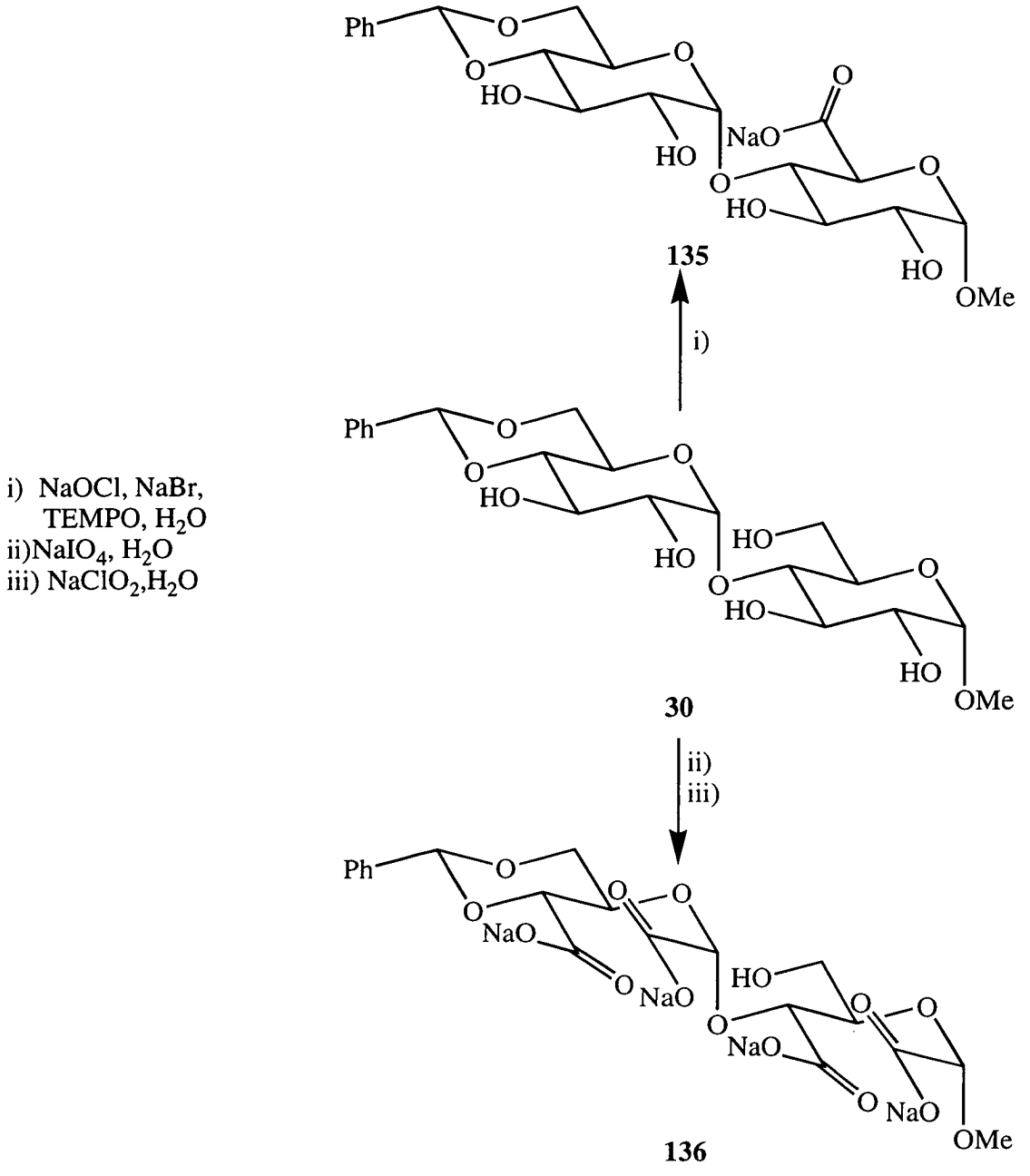
As mentioned previously, it was highly desirable to construct a series of standard compounds which could then be used in comparison with NMR data produced in later reactions.

Thus, a range of compounds were synthesized using literature methods from **31** and **30** as shown respectively in Schemes 55 and 56.



30 **133** **134**

Scheme 55



Scheme 56

2.3.10 Attempted aqueous bromine / hydrogen peroxide oxidation

Under conditions analogous to those employed whilst this approach was tried on monomer **54**, it was attempted to oxidise both **30** and **31**. Here again no reaction was observed, regardless of pH, temperature and reaction time. A similar explanation

for the reaction's failure in 2.3.3 applies here, namely that a large excess of bromine is necessary, but this is in turn likely to make the reaction a simple aqueous bromine oxidation in place of the desired two-step oxidation.

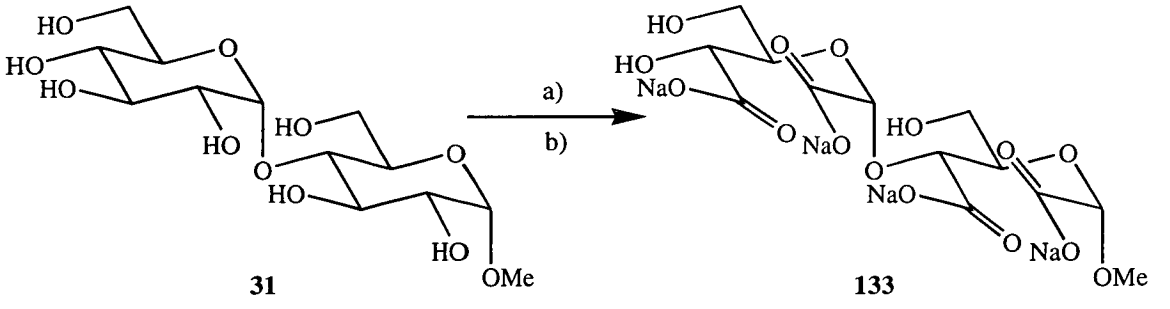
2.3.11 Ruthenium and molybdenum catalysed oxidation

It is known that a combined molybdenum and ruthenium catalytic oxidation can be used with hydrogen peroxide to effect the oxidative cleavage of alkenes. Here each metal serves a different purpose; molybdenum is employed to hydroxylate the alkene, with ruthenium employed to oxidatively cleave the resultant vicinal diol. With this in mind, it was decided to employ a variant of these conditions with disaccharide **31**.

Slightly different conditions were employed to those typically used[142]. Firstly, *t*-butanol is normally used as a solvent, with a phase transfer catalyst, however **31** is insoluble in *t*-butanol, so deionised water was employed (with the obvious emission of the phase transfer catalyst). Also, it is common to use acetic acid as a co-solvent, however it was felt that the presence of any aqueous acid was likely to be more detrimental than advantageous through glycosidic cleavage and then chain degradation, and so at no time was any mineral acid used.

Initially ruthenium trichloride was used as catalyst, being heated to reflux with **31** and deionised water where an excess of hydrogen peroxide was added slowly, and the mixture refluxed for a further 3 hours as shown in Scheme 57. Under

identical conditions a mixed molybdenum trioxide / ruthenium trichloride catalytic system was examined.



a) $RuCl_3$, MoO_3, H_2O_2
b) $RuCl_3$, H_2O_2

Scheme 57

Not unexpectedly, the same product has been isolated from both reactions (identified by NMR spectroscopy), indicating that the molybdenum trioxide plays no part in the catalytic process.

2.3.12 Attempted selective primary alcohol oxidation on dimers 30 and 31

Since a possible explanation for the failure of the tungstate catalysed TEMPO primary alcohol oxidation of monomer **54** lay with the formation of tungstate complexes, it was decided to attempt an analogous reaction with two dimeric compounds, namely **30** and **31**. The rationale behind this being that as saccharides become longer, the tendency for them to coil and fold and so allow greater hydrogen bonding becomes greater. Here it was hoped to exploit this and make it more difficult for any complex to form. However, no reaction was observed with either precursor.

This may have been a route better examined using a much larger oligosaccharide to maximize the steric interactions between it and the metal centre, although as previously noted, here other factors then become important.

2.4 Summary

It has been demonstrated herein that there exists two simple, convenient and scaleable syntheses to model compounds for the glucose based oligosaccharides, namely **31** and **54**. The synthesis of **54** offers considerable advantage over the literature method in that it involves only three steps (*c.f.* seven) and no major problems are encountered on increasing scale. Moreover, regioselective control can be achieved by performing the reaction under thermodynamic control without resorting to the need for metal activating and directing agents.

Although insufficient time did not permit a thorough investigation of potential oxidants of systems of this type, it has also been shown that both compounds have a potential for investigation of novel oxidant systems at a later date.

The geometry of the calcium complex in solution has also been probed, and it would appear that the complex is unlikely to be that proposed by Nieuwenhuizen involving coils containing seven glucose type units per turn.

3.0 Experimental

Symbols and Abbreviations

Ar	aromatic
$[\alpha]_D$	specific rotation
b	broad
cm	complex multiplet
d	doublet
δ	chemical shift
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
eq.	equivalents
FAB	fast atom bombardment
J	spin-spin coupling constant
M	mol dm^{-3}
M^+	molecular ion
mmol	millimoles
Me	methyl
mp	melting point
m	multiplet
NMR	nuclear magnetic resonance spectroscopy
Ph	phenyl
ppm	parts per million
s	singlet
TBAB	tetrabutylammoniumbromide
THF	tetrahydrofuran
TLC	thin layer chromatography
t	triplet
q	quartet
quat	quaternary

Instrumentation and General Techniques

i) NMR Spectroscopy

Routine ^{1}H NMR spectra were obtained using a Jeol PMX-60 or Oxford NMR 200 spectrometer. Higher field spectra were obtained on a Bruker AC-250 spectrometer operating at 250.13 MHz for ^{1}H and at 62.9 MHz for ^{13}C, operated by Mr J.R.A. Millar or Mr W. Kerr. Further high field spectra were obtained on a Bruker WH-360 spectrometer operating at 360.13 MHz for ^{1}H and at 90.56 MHz for ^{13}C, operated by Dr D. Reed.

Chemical shifts (δ) are reported in parts per million using tetramethylsilane (δ 0.0) as a reference.

ii) Infrared Spectroscopy

Infrared spectra were recorded on a Bio-Rad FTS-7 spectrometer. Liquid samples were recorded as thin films and solid samples as nujol or carbon tetrachloride mulls, both on sodium chloride plates.

iii) Mass Spectrometry

FAB and accurate mass measurements were obtained on a Kratos MS-50 TC spectrometer, operated by Mr A. Taylor.

iv) Elemental Analysis

Elemental analysis for carbon, hydrogen and nitrogen were carried out on a Perkin-Elmer 2400 CHN elemental analyser, operated by Mrs L. Eades.

v) X-Ray Crystallography

X-Ray crystal structures were determined on a Stoe STADI-4, four circle diffractometer, operated by Dr S. Parsons.

vi) Melting Points

Melting points were measured on a digital Gallenkamp capillary tube apparatus and are uncorrected.

vii) Optical Rotations

Optical rotations were measured on an Optical Activity AA 1000 polarimeter; readings were taken at 589 nm (the sodium D-line) using a 1 dm cell.

viii) Flash Column Chromatography

Flash column chromatography was routinely carried out using Merck silica gel 60 (mesh size 0.040 - 0.063 mm) as solid support, and a pressure of 10 p.s.i. of compressed air or water pump vacuum to aid the elution of solvent.

ix) Thin Layer Chromatography

For analytical purposes, aluminium backed plates, coated with a 0.2 mm layer of silica gel 60, and containing fluorescent indicator were used. Component spots were visualised by ultra-violet light, iodine vapour or by dipping into a 5% sulfuric acid/ethanol solution followed by gentle flaming.

x) Drying and Purification of Solvents

Dichloromethane, toluene and TCE were all dried by distilling from finely divided calcium hydride (Fisons) under an argon or nitrogen atmosphere. THF and ether were dried by distilling from sodium and benzophenone, under an argon or nitrogen atmosphere, the solvent was collected when the deep purple colour, due to sodium benzophenone ketyl, had formed. Pyridine and methanol were dried by distillation over sodium metal.

xi) Drying of Glassware and Inert Gases

Before conducting moisture sensitive reactions, reaction flasks were dried thoroughly by heating with a strong Bunsen flame whilst flushing with a strong flow of argon. Argon gas used for reactions was dried by passing the gas through a series of Dreschel vessels containing concentrated sulfuric acid, calcium chloride and self indicating silica gel.

xii) Moisture Sensitive Reactions

All moisture sensitive reactions were carried out in dry, freshly distilled solvents, under an argon atmosphere using oven or flame-dried glassware.

3.1 Attempted preparation of methyl 4–*O*–(α–D–glucopyranosyl)–α–D–glucopyranoside (methyl α-maltoside) 31

3.1.1 Attempted acid catalysed glycosidic methylation

Rigorously dried maltose **32** (0.54g, 1.5mmol) in methanol (5 ml) was added to an anhydrous solution of methanol through which had previously been bubbled hydrogen chloride gas dried over a series of drying traps (20 ml, 0.01mol). After 10 mins. stirring at room temperature the solution was rapidly evaporated *in vacuo*. The resulting solid foam was found to contain no starting material, only hydrolysis products **34** (0.39g, 64%) and **35** (0.20g, 33%), identified by comparison of ^{1}H and ^{13}C NMR spectra with authentic samples.

3.1.2 Attempted acid catalysed glycosidic methylation with 4Å mol. sieves

Rigorously dried maltose **32** (0.62g, 1.7mmol) in methanol (5 ml) was added to an anhydrous solution of methanolic hydrogen chloride (20 ml, 0.01mol) in the presence of freshly roasted 4Å molecular sieves (2.42g). After 10 mins. stirring at room temperature the solution was rapidly evaporated *in vacuo*. The resulting solid foam was found to contain no starting material, again only **34** (0.48g, 68%) and **35** (0.22g, 31%), identified by comparison of ^{1}H and ^{13}C NMR with authentic samples.

3.1.3 Synthesis of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide 39

Glucose **38** (10.24g, 57mmol) was added over 30 mins. to a solution of chloric acid (0.5ml, 3mmol) and acetic anhydride (38ml, 400mmol) maintained between *ca.* 30-40 °C. Red phosphorus (3.12g, 100mmol) was then added turning the solution red whereupon it was cooled to -10 °C. Bromine (21.41g, 134mmol) was then slowly added followed by water (3.5ml), the dark mixture then left stoppered and stirring allowing to warm to room temp. over 2 hours whereupon it was quenched on the addition of water (80 ml). The mixture was extracted with chloroform (3x30ml), and the combined organic layers back extracted with water (2x30ml), before washing with saturated sodium carbonate (50ml) and drying over magnesium sulfate. This solution was then filtered and decolourised with charcoal before filtration and evaporation *in vacuo* to **39**[89] (18.23g, 78%). **^{1}H NMR** (250.1 MHz, $CDCl_3$, δ_H ppm); 6.62 (d, 1H, $J_{1,2}$ = 4.0, H-1); 5.55 (t, 1H, $J_{2,3} = J_{3,4}$ = 10.0, H-3); 5.17 (t, 1H, $J_{3,4} = J_{4,5}$ = 10.0, H-4); 4.84 (dd, 1H, $J_{1,2}$ = 4.0, $J_{2,3}$ = 10.0, H-2); 4.36-4.27 (cm, 2H, H-6a, H-6b); 4.17-4.09 (cm, 1H, H-5); 2.12-2.05 (3xs, 12H, H-Ac). **^{13}C NMR** (62.9 MHz, $CDCl_3$, δ_C ppm); 170.5-169.2, 4xCO; 86.8, CH; 72.1, CH; 70.5, CH; 70.1, CH; 67.2, CH; 61.0, CH_2; 20.7-20.5, 4xCH_3. $[\alpha]_D$ +191, (c=1.0, $CHCl_3$) Lit.,[89] +194; M.Pt. (ether) 87-89 °C, Lit.,[89] 87-89 °C.

3.1.4 Formation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside 44

Typical small-scale experiment:

Methyl α-D-glucopyranoside (0.24g, 1.2mmol) was suspended in freshly distilled benzaldehyde (2.51g, 23.7mmol) under argon. Dry, freshly fused zinc chloride (0.25g, 1.8mmol) was added and the mixture vigorously stirred for 4 hours. Water (30ml) and ether (30ml) were then added, and the resultant solid collected by filtration, washed with water (30ml) then ether (30ml), and purified by dry flash chromatography on silica (9:1 DCM : ethanol) to furnish **44** (0.32g, 92%). **^{1}H NMR** (250.1 MHz, $CDCl_3$, δ_H ppm); 7.50-7.34 (cm, 5H, Ph); 5.50 (s, 1H, H-acetal); 4.72 (d, 1H, $J_{1,2}$ = 4.0, H-1); 4.26 (dd, 1H, $J_{1,2}$ = 4.0, $J_{2,3}$ = 8.5, H-2); 3.92-3.31 (cm, 7H, H-3, H-4, H-5, H-6a, H-6b); 3.41 (s, 3H, OMe). **^{13}C NMR** (62.9 MHz, $CDCl_3$, δ_C ppm); 136.9, C_q; 129.1, CH_{ar}; 128.2, CH_{ar}; 126.2, CH_{ar}; 101.8, CH; 99.7, CH; 80.8, CH; 72.6, CH; 71.3, CH; 68.8, CH_2; 62.2, CH; 55.4, CH_3. $[\alpha]_D$ +89, (c=0.22, water) Lit., [99] +86; M.Pt. (methanol) 165-168 °C, Lit., [99] 163-164 °C.

3.1.5 Benzylidenation of methyl α-D-glucoside *via* α,α-dimethoxytoluene

Typical large-scale experiment:

Methyl α-D-glucopyranoside (8.21g, 42.3mmol) was suspended in freshly distilled α,α-dimethoxytoluene (236.89g, 1.69mol) under argon. Dry, freshly fused zinc chloride (8.66g, 63.5mmol) was added and the mixture vigorously stirred for 4 hours. Water (50ml) and ether (50ml) were then added, and the resultant solid collected by filtration, washed with water (100ml) then ether (100ml), and purified by dry flash

chromatography on silica (9:1 DCM : ethanol) to furnish **44** (5.01g, 42%, *vide supra*).

3.1.6 Benzylidenation of methyl α-D-glucoside *via para*-toluenesulfonic acid

Typical large-scale experiment:

Methyl α-D-glucopyranoside (6.88g, 35.5mmol) was suspended in anhydrous *N,N*-dimethylformamide (100 ml) under argon to which was added pyridinium *para*-toluenesulfonic acid (0.90g, 3.6mmol). After 10 mins. stirring, freshly distilled benzaldehyde (5.64g, 0.53mmol) was added and the mixture vigorously stirred for 24 hours. Water (50ml) and ether (250ml) were then added, and the resultant solid collected by filtration, washed with water (50ml) then ether (50ml), and purified by dry flash chromatography on silica (9:1 DCM : ethanol) to furnish **44** (2.40g, 24%, *vide supra*).

3.1.7 Formation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside 44 mediated by dimethylsulfate-dimethylformamide

Typical large-scale experiment:

Dimethylsulfate (5.01g, 40mmol) was added to a rigorously dried solution of dimethylsulfoxide (65ml) and the solution warmed to 65 °C where it was maintained for 2 hours before cooling to room temperature where freshly distilled benzaldehyde (4.26g, 40mmol) and **43** (12.29g, 36mmol) were added followed by heating to *ca.* 44 °C. After 20 hours stirring, Amberlite A-21 ion-exchange resin (25.33g) was added

and the suspension stirred 15 mins. before filtration and evaporation *in vacuo* to a mobile oil which was purified by dry flash chromatography on silica (9:1 DCM : ethanol) to furnish **44** (5.72g, 32%, *vide supra*).

3.1.8 Formation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside 44 under ultrasonic agitation

Large-scale experiment:

Methyl α-D-glucopyranoside (4.78g, 2.5mmol) was suspended in freshly distilled benzaldehyde (102.50g, 98.6mmol) under argon. Dry, freshly fused zinc chloride (1.91g, 14.0mmol) was then added and the mixture immersed in an ultrasonic bath for 24 hours. Water (50ml) and ether (200ml) were then added, and the resultant solid collected by filtration, washed with water (50ml) then ether (100ml), and purified by dry flash chromatography on silica (9:1 DCM : ethanol) to furnish **44** (5.14g, 74%, *vide supra*).

3.1.9 Preparation of methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside 44

Diol **42** (0.48g, 1.7mmol) was suspended in a mixture of dichloromethane (20ml) and dry pyridine (0.40g, 5.1mmol) and N,N-dimethylaminopyridine (0.02g, 0.2mmol) added. Freshly distilled acetic anhydride (0.52g, 5.1mmol) was added and the mixture stirred under argon for 1 hour before quenching with HCl (~2M, 35ml). The aqueous layer was then extracted with dichloromethane (3x25ml), the combined organic layers washed (sat. $NaHCO_3$ then H_2O, 25ml of each), dried ($MgSO_4$) and

evaporated *in vacuo*. The resulting solid **44** is recrystallised from hexane : ether 9:1. (0.63g, >97%). **^{1}H NMR** (250.1 MHz, $CDCl_3$, δ_H ppm); 7.37 (m, 5H, Ph); 5.57 (t, 1H, $J_{2,3} = J_{3,4} = 9.5$, H-3); 5.48 (s, 1H, CHPh); 4.92 (d, 1H, $J_{1,2} = 4.0$, H-1); 4.90 (dd, 1H, $J_{2,3} = 9.0$, $J_{1,2} = 4.0$, H-2); 4.28 (q, 1H, $J_{3,4} = J_{4,5} = 10.0$, H-4); 3.92 (sx, 1H, $J_{4,5} = 10.0$, $J_{5,6} = 5.0$, $J_{5,6'} = 15.0$, H-5); 3.69 (cm, 1H, H-6); 3.39 (s, 3H, OMe); 2.08-2.04 (2xs, 6H, Ac). **^{13}C NMR** (62.9 MHz, $CDCl_3$, δ_C ppm); 170.14, CO; 169.54, CO; 136.72, C_q; 128.83, $C_{ar}H$; 127.98, $2xC_{ar}H$; 125.93, $2xC_{ar}H$; 101.31, CH; 97.36 CH; 78.96, CH_{acetal}, 71.35, CH; 38.73, CH; 68.59, CH_2; 62.09, CH; 55.11, CH_3; 20.58, CH_3(Ac); 20.52, CH_3(Ac). $[\alpha]_D$ +93, (c=1.1, $CHCl_3$) Lit.,[147] +92; M.Pt. 108-109 °C, Lit.,[147] 108-110 °C.

3.1.10 Preparation of methyl 2,3-di-*O*-acetyl-α-D-glucopyranoside 48

Benzylidene acetal **47** (1.54g, 4.2mmol) was suspended in ethanol (10ml) and stirred under a hydrogen atmosphere in the presence of palladium on charcoal (5% w/w, 1.79g ,0.8mmol) for 36 hours. The catalyst was then removed on filtration through celite, and the filtrate concentrated *in vacuo* to a viscous oil, purified by dry flash chromatography on silica (7:1 ether : ethanol) to yield **48** (0.97g, 88%). **^{1}H NMR** (250.1 MHz, $CDCl_3$ / D_2O δ_H ppm); 5.27 (t, 1H, $J_{2,3} = J_{3,4} = 10.0$, H-3); 4.85 (d, 1H, $J_{1,2} = 5.0$, H-1); 4.75 (dd, 1H, $J_{1,2} = 4.0$, $J_{2,3} = 10.0$, H-2); 3.80 - 3.74, bm, 1H, H-5); 3.69-3.59 (cm, 2H, H-6a, H-6b); 3.10-2.90 (b, 1H, H-4); 3.35 (s, 3H, OMe); 2.04-2.02 (2xs, 6H, Me (acetate)). **^{13}C NMR** (62.9 MHz, $CDCl_3$, δ_C ppm); 171.3, 2xCO;

96.6, CH; 72.7, CH; 71.1, CH; 70.8, CH; 68.9, CH; 61.4, CH_2; 55.0, OCH_3; 20.7, $CH_{3(acetate)}$; 20.6, $CH_{3(acetate)}$. $[\alpha]_D$ +130, (c=1.1, water) Lit.,[97] +138.

3.1.11 Regioselective preparation of methyl 2,3-di-*O*-acetyl-6-*O*-triphenylmethyl-α-D-glucopyranoside 49

To a dry flask was added diol **48** (0.24g, 0.9mmol) dissolved in DCM (20ml), followed by *N,N*-dimethylaminopyridine (0.01g, 0.1mmol) and freshly recrystallised and dried triphenylmethyl chloride (0.31g, 1.1mmol). Triethylamine (0.11g, 1.3mmol) was added and the mixture refluxed 19h. The mixture was then partitioned between iced water (30ml) and dichloromethane (50ml, 2x25ml); the combined organic layers then washed ($NH_4Cl_{(sat.)}$ then H_2O, 25ml of each), dried (Na_2SO_4), evaporated *in vacuo*, and purified by chromatography on neutral alumina (1:1 ether : hexane) to yield **49** (0.34g, 75%).**^{1}H NMR** (250.1 MHz, $CDCl_3$, δ_H ppm); 7.48 - 7.20 (m, 15H, 3xPh); 5.30 (t, 1H, $J_{2,3} = J_{3,4} = 8.5$, H-3), 4.89 (dd, 1H, $J_{1,2} = 4.0$, $J_{2,3} = 10.0$, H-2); 4.83 (d, 1H, $J_{1,2} = 4.0$, H-1); 3.74-3.67 (cm, 2H, CH_2); 3.42-3.35 (cm, 2H, H-4, H-5); 3.40 (s, 3H, Me); 2.67 (br, 1H, OH); 2.07 (s, 6H, Me). **^{13}C NMR** (62.9 MHz, $CDCl_3$, δ_C ppm); 171.2, CO; 170.3, OCO; 143.5, 3.C_q; 128.5, 6xC_{ar}; 127.8, 6xC_{ar}; 127.0, 3xC_{ar}; 96.5, CH; 87.0, C_q; 72.8, 2xCH; 70.7, CH; 70.0, CH; 63.6, CH_2; 59.9, OCH_3; 20.7, $OCO\underline{C}H_3$; 20.6, $OCO\underline{C}H_3$. $[\alpha]_D$ +81, (c=1.1, $CHCl_3$) Lit.,[97] +79; M.Pt. (methanol) 161-164 °C, Lit.,[97] 162-163 °C.

3.1.12 Regioselective preparation of methyl 2,3-di-*O*-acetyl-6-*O*-benzoyl-α-D-glucopyranoside 50

Diol **48** (0.59g, 2.1mmol) was dissolved in anhydrous dichloromethane (20ml) with triethylamine (0.23g, 2.3mmol), freshly distilled benzoyl chloride (0.37g, 2.2mmol) and DMAP (0.07g, 0.5mmol) cooled to -40 °C. The mixture was allowed to warm to room temperatue over 3 hours whereupon TLC (ether : hexane; 4:1) showed no reation, and so the reaction was heated to reflux for 6 hours where TLC indicated complete consumption of starting material. After cooling, aqueous hydrochloric acid (1M, 50ml) was added and the layers separated with the aqueous layer extracted with dichloromethane (2x50 ml). The combined orgainc layers were washed with saturated sodium bicarbonate (50 ml) and water (50ml) before drying (magnesium sulfate) and evaporation *in vacuo*. After wet-flash column chromatography two products were obtained being **50** (0.47g, 58%) and **130** (0.17g, 16%). **50** (250.1 MHz, $CDCl_3$ / D_2O δ_H ppm); 8.03-7.25 (cm, 5H, H-ar); 5.34 (t, 1H, $J_{2,3} = J_{3,4} = 10.0$, H-3); 4.89 (d, 1H, $J_{1,2} = 4.0$, H-1); 4.82 (dd, 1H, $J_{1,2} = 4.0$ $J_{2,3} = 10.0$, H-2); 4.65 (dd, 1H, $J_{5,6a} = 12.0$, $J_{6a,6b} = 5.0$, H-6a); 4.53 (dd, 1H, $J_{5,6b} = 2.0$, $J_{6a,6b} = 12.0$, H-6b); 3.98-3.91 (cm, 1H, H-5); 3.66 (t, 1H, $J_{3,4} = J_{4,5} = 9.5$, H-4); 3.37 (s, 3H, OMe), 2.04 (s, 6H, 2xCH_3); **^{13}C NMR** (62.9 MHz, $CDCl_3$, δ_C ppm); 171.2, CO; 170.2, CO; 166.7, CO; 133.1, CH_{ar}; 129.8, CH_{ar}; 129.5, CH_{ar}; 128.2, CH_{ar}; 96.6, CH; 72.6, CH; 70.6, CH; 69.6, CH; 69.1, CH; 63.2, CH_2; 55.0, CH_3; 20.6, 2xCH_3. $[\alpha]_D$ +108, (c=1.04, $CHCl_3$) Lit.,[148] +103. **130** (250.1 MHz, $CDCl_3$ δ_H ppm); 8.01-7.25 (cm, 10H, H-ar); 5.72 (t, 1H, $J_{2,3} = J_{3,4} = 9.5$, H-3); 5.42 (t, 1H, $J_{3,4} = J_{4,5} = 10.0$, H-4); 5.01-4.98 (br, 1H, H-1); 4.96 (dd, 1H, $J_{1,2} = 4.0$ $J_{2,3} = 10.0$, H-2); 4.52 (dd, 1H, $J_{5,6a}$ =

3.0, $J_{6a,6b}$ = 12.0, H-6a); 4.38 (dd, 1H, $J_{5,6b}$ = 5.0, $J_{6a,6b}$ = 12.0, H-6b); 4.25 (ddd, 1H, $J_{4,5}$ = 10.0, $J_{5,6a}$ = 3.0, $J_{5,6b}$ = 5.0, H-5); 3.47 (s, 3H, OMe); 2.07 (s, 3H, CH_3); 1.89 (s, 3H, CH_3). **^{13}C NMR** (62.9 MHz, $CDCl_3$, δ_C ppm); 170.0, CO; 169.7, CO; 165.9, CO; 165.1, CO; 133.4, CH_{ar}; 132.9, CH_{ar}; 129.7, CH_{ar}; 129.5, CH_{ar}; 129.4, CH_{ar}; 128.4, CH_{ar}; 128.3, CH_{ar}; 128.2, CH_{ar}; 96.6, CH; 70.7, CH; 69.6, CH; 69.5, CH; 67.2, CH; 62.3, CH_2; 55.3, CH. $[\alpha]_D$ +122, (c=1.0, $CHCl_3$).

3.1.13 Attempted nucleophilic displacement of tetra-*O*-acetyl-α-glucosyl bromide by methyl 2,3-di-*O*-acetyl-6-*O*-triphenylmethyl-α-D-glucopyranoside

Typical experiment:

Bromide **39** (0.23g, 0.6mmol) was dissolved in anhydrous dichloromethane (16ml) to which was added tetrabutylammoniumbromide (0.21g, 0.6mmol) and allowed to stir at room temperature for 4 hours. Diisopropylethylamine (0.08ml, 0.5mmol) was then added followed 15 mins. later by alcohol **49** (0.25g, 0.5mmol). After 40 hours stirring, no reaction was observable by TLC (ether : hexane; 4:1) and so the reaction was heated to reflux where it was maintained for 16 hours. Again TLC showed no reaction. Starting alcohol **49** was recovered unaltered on partitioning the reaction mixture between hydrochloric acid (2M, 30ml) and dichloromethane (30ml), then extracting the aqeuous layer with ether (2x30ml) and washing the combined organic layers with water (30 ml) before drying (sodium sulfate), evaporating and wet-flash chromatography.

3.1.14 Attempted nucleophilic displacement of tetra-*O*-acetyl-α-glucosyl bromide by methyl 2,3-di-*O*-acetyl-6-*O*-benzoyl-α-D-glucopyranoside

Typical experiment:

Bromide **39** (0.22g, 0.6mmol) was dissolved in anhydrous dichloromethane (16ml) to which was added tetrabutylammoniumbromide (0.24g, 0.6mmol) and allowed to stir at room temperature for 4 hours. Diisopropylethylamine (0.10ml, 0.5mmol) was then added followed 15 mins. later by alcohol **50** (0.18g, 0.5mmol). After 40 hours stirring, no reaction was observable by TLC (ether : hexane; 4:1) thus the reaction was heated to reflux where it was maintained for 16 hours. Again TLC showed no reaction. Starting alcohol **50** was recovered on partitioning the reaction mixture between hydrochloric acid (2M, 30ml) and dichloromethane (30ml), then extracting the aqeuous layer with further dichloromethane (2x30ml) and washing the combined organic layers with water (30 ml) before drying (sodium sulfate), evaporating and wet-flash chromatography.

3.1.15 Attempted silver carbonate / silver triflate catalysed nucleophilic displacement using alcohol 49

Typical experiment:

Bromide **39** (0.40g, 1.3mmol) was dissolved in anhydrous dichloromethane (15ml) to which was added tetrabutylammoniumbromide (0.46g, 1.4mmol) and allowed to stir at room temperature for 4 hours. Separately, diisopropylethylamine (0.09g, 0.9mmol) was added to alcohol **49** (0.32g, 0.8mmol) in dichloromethane (10 ml) at 0 °C followed 15 mins. later by silver triflate (0.06g, 0.2mmol) and silver carbonate

(0.46g, 1.6mmol). After 10 mins. further stirring, the bromide solution was dropwise added and the mixture wrapped in silver foil and left stirring for 40 hours after which time no reaction was observed by TLC (ether : hexane; 4:1) and so the reaction was heated to reflux where it was maintained for 16 hours. Again TLC showed no reaction. Starting alcohol **49** was recovered on partitioning the reaction mixture between hydrochloric acid (2M, 30ml) and dichloromethane (30ml), then extracting the aqeuous layer (2x30ml) and washing the combined organic layers with water (30 ml) before drying (sodium sulfate), evaporating and wet-flash chromatography.

3.1.16 Attempted silver carbonate / silver triflate catalysed nucleophilic displacement using alcohol 50

Typical experiment:

Bromide **39** (0.42g, 1.3mmol) was dissolved in anhydrous dichloromethane (15ml) to which was added tetrabutylammoniumbromide (0.44g, 1.4mmol) and allowed to stir at room temperature for 4 hours. Separately, diisopropylethylamine (0.14g, 1.4mmol) was added to alcohol **50** (0.66g, 1.3mmol) in dichloromethane (10ml) at 0 °C followed 15 mins. later by silver triflate (0.08g, 0.3mmol) and silver carbonate (0.50g, 1.8mmol). After 10 mins. further stirring, the bromide solution was dropwise added and the mixture wrapped in silver foil and left stirring for 42 hours, after which time no reaction was observed by TLC (ether : hexane; 4:1) and so the reaction was heated to reflux where it was maintained for 18 hours. Again TLC showed no reaction. Starting alcohol **50** was recovered on partitioning the reaction mixture between hydrochloric acid (2M, 30ml) and dichloromethane (30ml), then extracting

the aqeuous layer (2x30ml) and washing the combined organic layers with water (30 ml) before drying (sodium sulfate), evaporating and wet-flash chromatography.

3.2 Preparation of methyl 4-*O*-methyl-α-D-glucopyranoside 54

3.2.1 Diazomethane mediated etherification of alcohol 49

Potassium hydroxide (2.81g, 50.1mmol) was dissolved in water (2ml) and mixed with ether (8ml) and 2-(-2-ethoxyethoxy) ethanol (7ml) in a Diazald® diazomethane generator at 50°C. *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (5.08g, 23.7mmol) in ether (35 ml) was slowly added, and the resultant etheric diazomethane (approx. 2.6g CH_2N_2) solution distilled into a cooled clearseal flask, where it was dried over potassium hydroxide pellets for 4 hours. Methyl 2,3-di-*O*-acetyl-6-*O*-triphenylmethyl glucopyranoside **49** (0.12g, 0.2mmol) was dissolved in dry dichloromethane (10 ml) in a firepolished flask, flushed with argon, to which was added borontriflouride etherate (1.0ml, 8.1mmol). The dry diazomethane was then slowly decanted into the mixture until a faint yellow colour persisted, whereupon the reaction was left to stir 4 hours. TLC (ethyl acetate : cyclohexane ; 1:4 ; Al_2O_3) showed a faster running spot, which was isolated as a colourless oil after filtration through celite, then washing with $NaHCO_3$ (10%, 50 ml), water (50 ml), drying ($MgSO_4$) and evaporation, by dry flash chromatography on neutral alumina to furnish methyl 2,3-di-*O*-acetyl-6-*O*-triphenylmethyl-4-*O*-methyl-α-D-glucopyranoside **55** (0.09g, 77%). **^{1}H NMR** (250.1 MHz, $CDCl_3$, δ_H ppm); 7.51 - 7.22 (m, 15H, 3xPh); 5.21 (t, 1H, $J_{2,3} = J_{3,4} = 9.0$, H-3), 4.85 (dd, 1H, $J_{1,2} = 4.0$, $J_{2,3}$ =

10.0, H-2); 4.83 (d, 1H, $J_{1,2}$ = 4.0, H-1); 3.66-3.48 (cm, 2H, CH_2); 3.45-3.30 (cm, 2H, H-4, H-5); 3.40 (s, 3H, OMe); 3.33 (s, 3H, OMe); 2.10 (s, 6H, OMe). **^{13}C NMR** (62.9 MHz, $CDCl_3$, δ_C ppm); 170.8, CO; 170.1, OCO; 141.5, 3.$C_{q(ar)}$; 128.3, 6xC_{ar}; 127.3, 6xC_{ar}; 127.0, 3xC_{ar}; 96.6, CH; 86.9, C_q; 72.8, 2xCH; 70.5, CH; 70.0, CH; 63.2, CH_2; 60.1, OCH_3; 57.2, CH_3; 20.3, OCO$\underline{C}H_3$; 20.1, OCO$\underline{C}H_3$. $[\alpha]_D$ +88, (c=1.0, $CHCl_3$), Lit.[97c] +92. M.Pt. (methanol) 151-153 °C, Lit.,[97c] 153-156 °C.

3.2.2 Diazomethane mediated etherification of alcohol 50

Potassium hydroxide (2.72g, 49.4mmol) was dissolved in water (2ml) and mixed with ether (8ml) and 2-(-2-ethoxyethoxy) ethanol (7ml) in a Diazald® diazomethane generator at 50°C. *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (5.04g, 23.5mmol) in ether (35ml) was slowly added, and the resultant etheric diazomethane (approx. 2.6g CH_2N_2) solution distilled into a cooled clearseal flask, where it was dried over potassium hydroxide pellets for 4 hours. Methyl 2,3 di-*O*-acetyl-6-*O*-benzoyl-α-D-glucopyranoside **50** (0.11g, 0.2mmol) was dissolved in dry dichloromethane (10ml) in a firepolished flask, flushed with argon, to which was added borontrifluoride etherate (1.1ml, 8.4mmol). The dry diazomethane was then slowly decanted into the mixture until a faint yellow persisted, whereupon the reaction was left to stir 4 hours. TLC (ethyl acetate : cyclohexane ; 1:4 ; Al_2O_3) showed a faster running spot, which was isolated as a colourless oil after filtration through celite, then washing with $NaHCO_3$ (10%, 50 ml), water (50 ml), drying ($MgSO_4$) and evaporation, by dry flash chromatography on neutral alumina to yield methyl 2,3-di-*O*-acetyl-6-*O*-benzoyl-4-*O*-methyl-α-D-glucopyranoside **56** (0.03g, 23%).**^{1}H NMR** (250.1 MHz, $CDCl_3$, δ_H

ppm); 7.92 (cm, 5H, H-ar); 5.30 (t, 1H, $J_{2,3} = J_{3,4} = 10.0$, H-3); 4.89 (d, 1H, $J_{1,2} = 4.0$, H-1); 4.82 (dd, 1H, $J_{1,2} = 4.0$ $J_{2,3} = 10.0$, H-2); 4.60 (dd, 1H, $J_{5,6a} = 12.0$, $J_{6a,6b} = 5.0$, H-6a); 4.50 (dd, 1H, $J_{5,6b} = 2.0$, $J_{6a,6b} = 12.0$, H-6b); 4.11-3.94 (cm, 1H, H-5); 3.70 (t, 1H, $J_{3,4} = J_{4,5} = 9.5$, H-4); 3.44 (s, 3H, OMe); 3.36 (s, 3H, OMe); 2.04 (s, 6H, 2xCH_3); **^{13}C NMR** (62.9 MHz, $CDCl_3$, δ_C ppm); 171.8, CO; 169.8, CO; 166.6, CO; 135.2 CH_{ar}; 129.6, CH_{ar}; 129.3, CH_{ar}; 128.1, CH_{ar}; 96.8, CH; 72.5, CH; 70.6, CH; 69.6, CH; 69.2, CH; 63.4, CH_2; 55.0, CH_3; 54.7, CH_3; 20.6, 2xCH_3. Elemental Analysis; C: 57.45%, H: 6.12%, N: 0%, Requires; C: 57.57%, H: 6.10%, N: 0%.

3.2.3 Total deprotection of methyl 2,3-di-*O*-acetyl-6-*O*-triphenylmethyl-4-*O*-methyl-α-D-glucopyranoside 55

Methyl 2,3-di-*O*-acetyl-4-*O*-methyl-6-*O*-trityl-α-D-glucoside **55** (0.54g, 1.0mmol) was dissolved in methanol (10ml) which was made acidic by addition of HCl (2M, 5ml). After stirring for 15 mins. at room temperature, the mixture was taken to pH 11 by addition of freshly ground sodium hydroxide where it was maintained for a further 30 mins. before neutralising with Amberlite IR-120 (H^+) ion-exchange resin. The resultant solution was then evaporated *in vacuo* and the solid produced washed with methanol (10 ml) which was again evaporated before being subjected to dry-flash chromatography to yield methyl 4-*O*-methyl-α-D-glucopyranoside **54** (0.19g, 88%) as a solid foam. **^{1}H NMR** (250.1 MHz, CD_3OD, δ_H ppm); 4.74 (d, 1H, $J_{1,2} = 4.0$, H-1); 3.84-3.34 (cm, 5H, H-2, H-3, H-5, CH_2); 3.50 (s, 3H, CH_3); 3.35 (s, 3H, CH_3); 3.15 (t, 1H, $J_{3,4} = J_{4,5} = 9.5$, H-4). **^{13}C NMR** (62.9 MHz, $CDCl_3$, δ_C ppm); 99.1, CH;

79.2, CH; 72.8, CH; 71.2, CH; 70.5, CH; 60.2, CH_2; 59.9, CH_3; 55.0, CH_3; $[\alpha]_D$ +164, (c=1.1, water) Lit.,[118] +167; M.Pt. 98-100 °C, Lit.,[118] 95-96 °C.

3.2.4 Deprotection of methyl 2,3-di-*O*-acetyl-6-*O*-benzoyl-4-*O*-methyl-α-D-glucopyranoside 56

Methyl 2,3-di-*O*-acetyl-4-*O*-methyl-6-benzoyl-α-D-glucoside **56** (0.47g, 1.2mmol) was dissolved in methanol (20ml) which was then taken to pH 11 by addition of freshly ground sodium hydroxide where it was maintained for 30 mins. before neutralising with Amberlite IR-120 (H^+) ion-exchange resin. The resultant solution was then filtered and evaporated *in vacuo* and the solid produced washed with methanol (10 ml) which was again evaporated before being subjected to dry-flash chromatography to yield **54** (0.26g, 100%, *vide supra*).

3.2.5 Acetylation of amylose

Amylose (4.57g, 28.2mmol as anhydro glucose units) was suspended in anhydrous pyridine (3.96g, 50.0mmol) and dichloromethane (50ml) and stirred at room temperature whilst DMAP (0.34g, 2.8mmol) was added, followed after 15 mins. by freshly distilled acetic anhydride (5.11g, 50.0mmol). After 14 hours refluxing, the mixture was cooled and partitioned between hydrochloric acid (2M, 100ml) and dichloromethane (100ml), with the aqeuous layer extracted a further twice (2x50ml), before washing the combined organic layers with aqueous saturated sodium

bicarbonate (100ml), water (50ml), drying (magnesium sulfate) and evaporation under reduced pressure to an unpurifiable viscous heavy brown / black tar (9.76g).

3.2.6 Regioselective formation of methyl 2,3,6-tri-*O*-benzoy-α-D-glucopyranoside 63

Methyl α-D-glucopyranoside **43** (1.08g, 5.6mmol) was dissolved in dry, freshly distilled pyridine (1.86g, 23.5mmol) and dry dichloromethane (12 ml) in an argon flushed flask, which was cooled to 0°C and stirred 30 mins. Freshly distilled benzoyl chloride (2.18g, 15.5mmol) was then slowly added, and the mixture allowed to warm to room temperature over 12 hours. The reaction was quenched on addition of HCl (1M, 10 ml) and extracted with ether (2x50 ml), washed with water (2x50 ml), dried ($MgSO_4$) and evaporated. The resulting solid foam was purified by flash chromatography on silica to yield **63** (1.35g, 48%). **^{1}H NMR** (250.1 MHz, $CDCl_3$, δ_H ppm); 5.85 (dd, 1H, $J_{2,3}$ = 10.0, $J_{3,4}$ = 9.5, H-3); 5.26 (dd, 1H, $J_{1,2}$ = 4.0, $J_{2,3}$ = 10.0, H-2); 5.16 (d, 1H, $J_{1,2}$ = 4.0, H-1); 4.77 (dd, 1H, $J_{5,6a}$ = 5.0, $J_{6a,6b}$ = 12.0, H-6a); 4.65 (dd, 1H, $J_{5,6b}$ = 2.0, $J_{6a,6b}$ = 12.0, H-6b); 4.14 (dq, 1H, $J_{4,5}$ = 10.0, $J_{5,6a}$ = 5.0, $J_{5,6b}$ = 2.0, H-5); 3.92 (dt, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.5, $J_{4,OH}$ = 5.0, H-4); 3.70 (bd, 1H, $J_{4,OH}$ = 5.0, OH). **^{13}C NMR** (62.9 MHz, $CDCl_3$, δ_C ppm); 166.9, CO;166.7, CO; 165.8, CO; 133.3, C_{ar}; 133.1, C_{ar}; 133.1, C_{ar}; 129.7, C_{ar}; 129.6, C_{ar}; 129.6, C_{ar}; 129.4, C_{ar}; 129.0, C_q; 128.8, C_q; 128.3, C_{ar}; 128.2, C_{ar}; 128.2, C_{ar}; 96.8, CH; 73.5, CH; 71.3, CH; 69.8, CH; 69.4, CH; 63.3, CH_2; 55.2, CH_3; $[\alpha]_D$ +145, (c=1.0, chloroform) Lit.,[118] +148; M.Pt. (ether) 128-130 °C, Lit.,[118] 129-130 °C.

3.2.7 Regioselective 2,3,6-tri-*O*-benzoylation of 43 in dichloromethane under slow addition conditions

Similar general protocol as for 3.2.6 with the addition of benzoyl chloride in anhydrous dichloromethane controlled by pump addition over *ca.* 1 hour to yield **63** (0.22g, 76%, *vide supra*).

3.2.8 Regioselective 2,3,6-tri-*O*-benzoylation of 43 in toluene under slow addition conditions

Similar general protocol as for 3.2.6 with the addition of benzoyl chloride in anhydrous toluene contolled by pump addition over *ca.* 1 hour to yield **63** (0.18g, 58%, *vide supra*).

3.2.9 Methylation of triester 63 to methyl 2,3,6-tri-*O*-benzoyl-α-D-glucopyranoside 76 using diazomethane

Typical experiment:

Ether (10ml), diglyme (8ml) and potassium hydroxide (2.65g, 48.1mmol) were cooled with stirring in a Diazald® kit, to which freshly pulverised *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (9.00g, 42.0mmol) was added. The diazomethane formed was distilled into a flask, previously charged with alcohol **63** (3.04g, 6.0mmol) and borontrifluoride etherate (1.1ml, 8.4mmol). After stirring overnight, polymethylene was removed by filtration and the filtrate concentrated *in vacuo* then

purified by wet-flash chromatography on silica to yield **76** as a syrup (0.66g, 21%). **^{1}H NMR** (250.1 MHz, $CDCl_3$, δ_H ppm); 8.14-7.25 (cm, 15H, CH_{ar}); 6.02 (t, 1H, $J_{2,3}$= $J_{3,4}$ = 9.5, H-3); 5.19 (dd, 1H, $J_{1,2}$=3.5, $J_{2,3}$=10.0, H-2); 5.15 (d, 1H, $J_{1,2}$=4.0, H-1); 4.67-4.64 (cm, 2H, CH_2); 4.14 (ddd, 1H, $J_{4,5}$=10.0, $J_{5,6}$=4.0, $J_{5,6'}$=3.0, H-5); 3.66 (t, 1H, $J_{3,4}$= $J_{4,5}$= 9.5, H-4); 3.46 (s, 3H, CH_3); 3.43 (s, 3H, CH_3). **^{13}C NMR** (62.9 MHz, $CDCl_3$, δ_C ppm); 166.1, CO; 165.8, CO; 165.4, CO; 133.2, CH_{ar}; 133.1, CH_{ar}; 133.0, CH_{ar}; 132.9, C_{ar}; 129.7, 2xCH_{ar}; 129.6, 2xCH_{ar}; 129.5, 2xCH_{ar}; 129.4, C_q; 128.8, C_q; 128.3, 2xCH_{ar}; 128.2, 4xCH_{ar}; 96.7, CH; 78.2, CH; 72.3, CH; 71.9, CH; 68.4, CH; 63.1, CH_2; 60.3, CH_3; 55.2, CH_3. $[\alpha]_D$ +128, (c=1.0, chloroform) Lit.,[118] +132.

3.2.10 Attempted pyridine mediated etherification of 63

Typical experiment:

A dry argon flushed flask was charged with alcohol **63** (0.12g, 0.2 mmol) dissolved in dry dichloromethane (4 ml). Freshly distilled pyridine (0.23 ml, 2.8 mmol) was injected and the mixture stirred for 30 mins. whereupon dry iodomethane (0.20 ml, 3.2 mmol) was added. No reaction was observed under any conditions by TLC (cyclohexane : ethyl acetate 2:1; silica).

3.2.11 Attempted triethylamine mediated etherification of 63

Typical experiment:

A dry argon flushed flask was charged with alcohol **63** (0.13g, 0.2 mmol) dissolved in dry dichloromethane (4 ml). Freshly distilled triethylamine (0.21 ml, 2.7 mmol)

was injected and the mixture stirred for 30 mins. whereupon dry iodomethane (0.22 ml, 3.2 mmol) was added. No reaction was observed under any conditions by TLC (cyclohexane : ethyl acetate 2:1 silica).

3.2.12 Attempted lithium diisopropylamine mediated etherification of 63

Typical experiment:

^{n}Butyl lithium (1.6M in hexane, 0.33ml, 0.53mmol) was added slowly to an argon flushed flask previously charged with diisopropylamine (0.07ml, 0.53mmol), in anhydrous tetrahydrofuran (5ml) at 0°C. After 30 mins. stirring, the mixture was cooled to -78°C where alcohol **63** (0.23g, 0.44mmol) in dry THF (5ml) was added over 30 mins. Freshly distilled iodomethane (0.10ml, 1.6mmol) was then added and the mixture stirred and allowed to warm to room temp. TLC (cyclohexane : ethyl acetate 2:1 silica) showed no reaction under any conditions.

3.2.13 Attempted sodiumdimsyl mediated etherification of 63

Typical experiment:

Sodium hydride (0.60g, 24.1mmol), dried from its mineral oil suspension by successive pentane washes, was suspended under argon in dry dimethylsulfoxide at 60°C for 90 mins.The now green suspension was cannulated into a dry flask charged with alcohol **63** (0.11g, 0.2mmol) and the mixture cooled to 0°C before the addition of fresh iodomethane (0.21ml, 3.4mmol). No reaction was observed after any time stirring at room temp.

3.2.14 Silver oxide catalysed methylation of 63

A Karius tube was charged with alcohol **63** (0.78g, 1.5mmol) dissolved in acetonitrile (10 ml) at 0 °C. Silver oxide (0.39g, 1.7mmol) was added and the suspension left for 5 mins. after which iodomethane (8ml, 129mmol, previously filtered through activated alumina) was added. The tube was sealed and the mixture heated at 100 °C for 2½ hours, where it was cooled to 0 °C and filtered through celite. Evaporation *in vacuo* produces a faintly yellow oil, which after flash chromatography on silica (hexane → hexane : ether 2 : 1) yields methyl 2,3,6-tri-*O*-benzoyl-α-D-glucopyranoside **76** as colourless crystals (0.64g, 80 %, *vide supra*).

3.2.15 Autoclave methylation of 63

An autoclave basin was charged with methyl 2,3,6-tri-*O*-benzoyl-α-D-glucopyranoside **63** (82.75g, 163.4mmol) in acetonitrile (150ml) and cold iodomethane (278.25g, 1.96mol). Silver oxide (34.27g, 245.1mmol) was then rapidly added and the unit sealed and heated to 112 °C (8 bar) for 94 mins. After this time it was allowed to cool to 18 °C over 1 hour, whereupon it was filtered through a plug of magnesium sulphate, evaporated *in vacuo*, and purified by column chromatography on silica to yield **76** (51.02g, 60 %, *vide supra*).

3.2.16 Attempted regioselective acetylation of methyl α-D-glucopyranoside

Freshly dried methyl α-D-glucoside **43** (3.35g, 17.3mmol) was suspended in dry dichloromethane (10 ml) in an argon flushed flask. Freshly distilled pyridine (4.11g,

52.0mmol) was then added, and the mixture cooled to -40 °C. After 10 mins. stirring, dry acetyl chloride (3.26g, 52.1mmol) was injected forming the mixture into a paste. After 1 hour warming to room temp. the reaction was quenched with hydrochloric acid (1M, 100ml), and extracted into dichloromethane (50ml). The aqueous layer was extracted with two further portions of dichloromethane (20ml), and the combined organic layers washed with sat. sodium bicarbonate (100ml), then water (100ml) and dried over magnesium sulphate, before evaporation *in vacuo* to a colourless oil which on standing forms spectroscopily clean needles of methyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside **78**[149] (3.23g, 48%). **^{1}H NMR** (250.1 MHz, $CDCl_3$, δ_H ppm); 5.43 (dd, 1H, $J_{2,3}$ = 10.0, $J_{3,4}$ = 9.5, H-3); 5.02 (dd, 1H, $J_{3,4}$ = 9.5, $J_{4,5}$ = 10.0, H-4); 4.91 (d, 1H, $J_{1,2}$ = 4.0, H-1); 4.85 (dd, 1H, $J_{1,2}$ = 4.0, $J_{2,3}$ = 10.0, H-2); 4.22 (dd, 1H, $J_{5,6a}$ = 4.5, $J_{6a,6b}$ = 12.0, H-6a); 4.06 (dd, 1H, $J_{5,6b}$ = 2.5, $J_{6a,6b}$ = 12.0, H-6b); 3.94 (ddd, 1H, $J_{4,5}$ = 10.0, $J_{5,6a}$ = 4.5, $J_{5,6b}$ = 2.5, H-5); 3.37 (s, 3H, OMe); 2.05 (s, 3H, OAc); 2.03 (s, 3H, OAc); 1.98 (s, 3H, OAc); 1.96 (s, 3H, OAc). **^{13}C NMR** (62.9 MHz, $CDCl_3$, δ_C ppm); 170.5, CO; 169.9, CO; 169.9, CO; 169.4, CO; 96.6, CH; 70.6, CH; 69.9, CH; 68.3, CH; 66.9, CH; 61.7, CH_2; 55.3, CH_3; 20.5, 3xCH_3; 20.4, CH_3. $[\alpha]_D$ +138, (c=1.1, $CHCl_3$) Lit.,[149] +133; M.Pt. (pet. ether) 100-1103 °C, Lit.,[149] 100-102 °C.

3.2.17 Regioselective formation of methyl 2,3,6-tri-*O*-pivaloyl-α-D-glucopyranoside

Freshly dried methyl α-D-glucopyranoside 43 (1.44g, 7.4mmol) was suspended in dry dichloromethane (10 ml) in an argon flushed flask. Freshly distilled pyridine

(1.74g, 22.0mmol) was then added, and the mixture cooled to 0 °C. After 10 mins. stirring, dry pivaloyl chloride (2.8ml, 23.1mmol) was injected and the mixture allowed to warm to room temp. with stirring over 18 hours. The reaction was quenched with hydrochloric acid (1M, 100ml), and extracted into dichloromethane (50ml). The aqueous layer was extracted with two further portions of dichloromethane (20ml), and the combined organic layers washed with sat. sodium bicarbonate (100ml), then water (100ml) and dried over magnesium sulphate, before evaporation *in vacuo* to a syrup which was subjected to column chromatography to yield three components: methyl 2,3,6-tri-*O*-pivaloyl-α-D-glucopyranoside **82** (0.43g, 13 %) **^{1}H NMR** (250.1 MHz, $CDCl_3$, δ_H ppm); 5.30 (dd, 1H, $J_{2,3}$ = 10.0, $J_{3,4}$ = 9.0, H-3); 4.89 (d, 1H, $J_{1,2}$ = 3.5, H-1); 4.75 (dd, 1H, $J_{1,2}$ = 3.5, $J_{2,3}$ = 10.0, H-2); 4.17 (dd, 1H, $J_{5,6a}$ = 2.5, $J_{6a,6b}$ = 12.0, H-6a); 4.10 (dd, 1H, $J_{5,6b}$ = 5.0, $J_{6a,6b}$ = 12.5, H-6b); 3.94 (ddd, 1H, $J_{4,5}$ = 10.0, $J_{5,6a}$ = 2.0, $J_{5,6b}$ = 5.0, H-5); 3.45 (dd, 1H $J_{3,4}$ = 9.5, $J_{4,5}$ =; 10.0, H-4); 3.35 (s, 3H, OMe); 1.20 (s, 9H, 3xCH_3); 1.19 (s, 9H, 3xCH_3); 1.16 (s, 9H, 3xCH_3). **^{13}C NMR** (62.9 MHz, $CDCl_3$, δ_C ppm); 179.2, CO; 178.7, CO; 177.7, CO; 96.5, CH; 72.6, CH; 70.5, CH; 70.4, CH; 69.8, CH; 62.9, CH_2; 55.2, CH_3; 38.8, C_q; 38.7, C_q; 38.6, C_q; 27.1, 3xCH_3; 27.0, 3xCH_3; 26.8, 3xCH_3; $[\alpha]_D$ +95, (c=1.0, chloroform) Lit.,[125] +87; M.Pt. 75-76 °C, Lit.,[125] 75-77 °C. Methyl 3,4,6-tri-*O*-pivaloyl-α-D-glucopyranoside **83** as a syrup (0.23g, 7%) **^{1}H NMR** (250.1 MHz, $CDCl_3$, δ_H ppm); 4.88 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 10.0, H-3); 4.67 (dd, 1H, $J_{1,2}$ = 4.0, $J_{2,3}$ = 10.0, H-2); 4.34 (d, 1H, $J_{1,2}$ = 4.0, H-1); 4.17 (dd, 1H, $J_{5,6a}$ = 2.5, $J_{6a,6b}$ = 12.0, H-6a); 4.10 (dd, 1H, $J_{5,6a}$ = 5.0, $J_{6a,6b}$ = 12.5, H-6b); 4.04 (dd, 1H, $J_{3,4}$ = 9.5, $J_{4,5}$ = 10.0, H-4); 3.94 (ddd, 1H, $J_{4,5}$ = 10.0, $J_{5,6a}$ = 2.0, $J_{5,6b}$ = 5.0, H-5); 3.35 (s, 3H, OMe); 1.20 (s,

9H, 3xCH_3); 1.19 (s, 9H, 3xCH_3); 1.15 (s, 9H, 3xCH_3). **^{13}C NMR** (62.9 MHz, $CDCl_3$, δ_C ppm); 178.2, CO; 178.1, CO; 178.0, CO; 96.9, CH; 73.4, CH; 70.5, CH; 70.3, CH; 67.4, CH; 62.1, CH_2; 55.4, CH_3; 38.8, C_q; 38.7, C_q; 38.6, C_q; 27.0, 3xCH_3; 26.9, 3xCH_3; 26.8, 3xCH_3; $[\alpha]_D$ +115, (c=1.0, chloroform) Lit.,[125] +103. Methyl 2,3,4,6-tetra-*O*-pivaloyl-α-D-glucopyranoside **84** (0.08g, 2%) **^{1}H NMR** (250.1 MHz, $CDCl_3$, δ_H ppm); 5.54 (t, 1H, $J_{2,3} = J_{3,4} = 10.0$, H-3); 5.07 (t, 1H, $J_{3,4} = J_{4,5} = 10.0$, H-4); 4.94 (d, 1H, $J_{1,2} = 4.0$ H-1); 4.78 (dd, 1H, $J_{1,2} = 4.0$, $J_{2,3} = 10.0$, H-2); 4.18 - 3.96 (cm, 3H, H-5, CH_2); 3.37 (s, 3H, OMe); 1.21 (s, 9H, 3xCH_3); 1.14 (s, 9H, 3xCH_3); 1.13 (s, 9H, 3xCH_3); 1.10 (s, 9H, 3xCH_3). **^{13}C NMR** (62.9 MHz, $CDCl_3$, δ_C ppm); 177.9, CO; 177.6, CO; 176.8, CO; 176.4, CO; 96.4, CH; 71.1, CH; 69.4, CH; 67.7, CH; 67.4, CH; 61.8, CH_2; 55.4, OCH_3; 38.7, C_q; 38.6, 2xC_q; 38.6, C_q; 27.1, 3xCH_3; 27.0, 3xCH_3; 26.9, 3xCH_3; 26.8, 3xCH_3. $[\alpha]_D$ +116, (c=1.0, chloroform) Lit.,[126] +102; M.Pt. 82-84 °C, Lit.,[126] 83-85 °C.

3.2.18 Deprotection of 76 to methyl 4-*O*-methyl-α-D-glucopyranoside

Ether **76** (0.18g, 0.4mmol) was dissolved in methanol (4ml) and stirred rapidly while powdered sodium hydroxide (0.02g, 0.5mmol) was added. After ½ hour stirring the reaction was quenched by the addition of Amberlite (120) H^+ ion exchange resin, stirring (5 mins) and filtration. The resulting faintly yellow oil was then purified to colourless crystals by slow crystallisation from an ethanol : toluene mixture to yield pure **54** (0.07g, > 99%, *vide supra*).

3.3 Revised synthesis of methyl α-maltoside

3.3.1 Attempted nucleophilic displacement of hepta-*O*-acetyl-α-maltosyl bromide 85

Hepta-*O*-acetyl-α-maltosyl bromide **12** (0.22g, 0.3mmol) was dissolved in dry dichloromethane (10ml) and injected into a dry argon flushed flask charged with freshly roasted 4Å molecular sieves (1.79g). TBAB (0.19g, 0.6 mmol) in dichloromethane (2ml) was added and the mixture stirred for 5 mins. before the addition of dry methanol (0.03ml, 0.7mmol) and a further 5 mins. stirring. Light was excluded from the mixture and silver carbonate (0.11g, 4.9mmol) and silver triflate (0.04g, 0.1mmol) were added. After stirring for 4 days, the mixture is filtered through celite and evaporated to hepta-*O*-acetylmaltose **87** (0.20g, 100%). α - form **^{1}H NMR** (250.1 MHz, $CDCl_3$, δ_H ppm); 5.52 (dd, 1H, $J_{2,3}$ = 9.0, $J_{3,4}$ = 10.0, H-3); 5.37 (d, 1H, $J_{1',2'}$ = 4.0, H-1'); 5.30 (d, 1H, $J_{1,2}$ = 4.0, H-1); 5.22 (t, 1H, $J_{2',3'}$ = 9.0, $J_{3',4'}$ = 9.0, H-3'); 5.00 (dd, 1H, $J_{4',5'}$ = 10.0, H-4'); 4.70 (dd, 2H, $J_{2,3}$ = 10.0, H-2, H-2'); 4.43 (dd, 1H, $J_{5,6a}$ = 3.0, $J_{6a,6b}$ = 13.0, H-6a); 4.26-4.14 (cm, 3H, H-5, H-6a', H-6b); 3.99 (dd, 1H, $J_{5',6a'}$ = 3.5, $J_{6a',6b'}$ = 12.0, H-6'a); 3.99-3.89 (cm, 2H, H-4, H-5'); 2.08-1.94 (21H, 7xCH_3); **^{13}C NMR** (62.9 MHz, $CDCl_3$, δ_C ppm); 170.5-169.3, 7x$COCH_3$; 95.3, CH; 89.7, CH; 72.5 CH; 72.1, CH; 71.4, CH; 69.8, CH; 69.2, CH; 68.2, CH; 67.8, CH; 67.4, CH; 62.6, CH_2; 61.2, CH_2; 20.7-20.3 7x$COCH_3$. $[\alpha]_D$ +101, (c=1.1, chloroform) Lit.,[143] +98; M.Pt. (ethanol : water, 9:1) 175-177 °C, Lit.,[143] 176-179 °C. β - form **^{1}H NMR** (250.1 MHz, $CDCl_3$, δ_H ppm); 5.37 (d, 1H, $J_{1',2'}$ = 4.0, H-1'); 5.30 (t, 1H, $J_{2,3}$ = 9.0, $J_{3,4}$ = 9.0, H-3); 5.22 (t, 1H, $J_{2',3'}$ = $J_{3',4'}$ = 9.0, H-3'); 5.00 (dd, 1H, $J_{4',5'}$ = 10.0, H-4'); 4.81 (dd, 1H, H-2'); 4.72-4.65 (cm, 2H, H-1, H-2); 4.43 (dd, 1H,

$J_{5,6a}$ = 3.0, $J_{6a,6b}$ = 13.0, H-6a); 4.26-4.14 (cm, 2H, H-6b, H-6'a); 3.99 (dd, 1H, $J_{5',6a'}$ = 3.5, $J_{6a',6b'}$ = 12.5, H-6'a); 3.99-3.89 (cm, 2H, H-5', H-4); 3.75-3.66 (cm, 1H, H-5); 2.08-1.95 (21H, 7x$COCH_3$). **^{13}C NMR** (62.9 MHz, $CDCl_3$, δ_C ppm); 170.5-169.3, 7x$COCH_3$; 95.3, CH; 94.6, CH; 74.8, CH; 73.5, CH; 72.5, CH; 69.8, CH; 69.2, CH; 68.2, CH; 67.8, CH; 67.4, CH; 62.6, CH_2; 61.2, CH_2; 20.7-20.3, 7x$COCH_3$. $[\alpha]_D$ +95, (c=1.0, chloroform) Lit.,[143] +86; M.Pt. 177-178 °C, Lit.,[143] 179-180 °C.

3.3.2 Per-*O*-acetylation of maltose

To a rapidly stirring suspension of a rigorously dried sample of **32** (19.10g, 56mmol) in dichloromethane (150ml) and pyridine (47.8ml, 591mmol) was added *N,N*–dimethylaminopyridine (0.14g, 1.1mmol) under argon at 0°C. After 30min., freshly distilled acetic anhydride (55.8ml, 591mmol) was added slowly to the reaction mixture and when TLC (ethyl acetate : cyclohexane 4:1) had indicated the formation of one major fraction and no remaining starting material, it was quenched by addition of hydrochloric acid (2M, 200ml). After separation and extraction with dichloromethane (3x25ml), the combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (200ml), then saturated aqueous sodium chloride (200ml) and dried over magnesium sulfate before evaporation *in vacuo* to give an amorphous colourless solid (34.84g, 92%) of sufficient purity to use without further purification in subsequent steps. **^{1}H NMR** (250.1 MHz, $CDCl_3$, δ_H ppm); 5.68 (d, 1H, $J_{1,2}$ = 8.0, H-1); 5.30 (d, 1H, $J_{1',2'}$ = 4.0, H-1'); 5.28-5.20 (cm, 2H, H-3, H-3'); 5.01 (t, 1H, $J_{3',4'} = J_{4',5'}$ = 10.0, H-4'); 4.91 (dd, 1H, $J_{2,3}$ = 9.0, H-2); 4.80 (dd, 1H, $J_{2',3'}$ = 10.0, H-2'); 4.37 (dd, 1H, $J_{5,6a}$ = 2.0, $J_{5,6b}$ = 5.0, H-6a); 4.24-4.13 (cm,

2H, H-6b, H-6a'); 4.03-3.95 (cm, 2H, H-4, H-6b'); 3.90-3.85 (cm, 1H, H-5'); 3.81-3.75 (cm, 1H, H-5); 2.07-1.93 (cm, 8x$COCH_3$); **^{13}C NMR** (62.9 MHz, $CDCl_3$, δ_C ppm); 170.3-168.5, 8x*C*OCH_3; 95.5, CH; 91.0, CH; 75.0, CH; 72.8, CH; 72.3, CH; 70.7, CH; 69.8, CH; 69.1, CH; 68.4, CH; 67.8, CH; 62.3, CH_2; 61.2, CH_2; 20.8-20.2, 8xCO*C*H_3; $[\alpha]_D$ +65, (c=1.0, ethanol) Lit.,[145] +64; M.Pt. 157-159 °C, Lit.,[145] 159-160 °C.

3.3.3 Selective anomeric deprotection of octa-*O*-acetyl maltose 88

Typical experiment[144]:

β-Maltose octa-*O*-acetate **88** (20.00g, 29.5 mmol) was added at –78°C to a mixed solvent (methanol : tetrahydrofuran 3 : 7, 450 ml) through which ammonia had been bubbled vigorously over a 25 min. period. After stirring for 10 min., the reaction was allowed to warm to room temperature. When TLC (ethyl acetate : cyclohexane 4:1) had indicated the complete consumption of the starting material and the formation of a single, more polar fraction, the solvent and excess ammonia were removed by rapid evaporation *in vacuo* to yield a pale yellow syrup which solidified on standing to a glass. Although not essential, this glass may be recrystallised slowly from ethanol : water (9:1) to provide hepta-*O*-acetyl-α-maltose **87α** solely, or as an anomeric mixture of **87α** and **87β** from *iso*-propanol to yield (*vide supra*) an amorphous solid (15.61g, 82%).

3.3.4 Anomeric methylation of hepta-*O*-acetylmaltose 87

To a Soveril-joint ampoule containing aldose **87** (1.01g, 1.6mmol) suspended in acetonitrile (7ml) was added silver oxide (0.44g, 1.9mmol) and the mixture was stirred for 5 min. with the vessel protected from light. After this time, iodomethane (0.15ml, 1.9mmol, freshly filtered through a plug of neutral aluminium oxide) was added, the vessel sealed and immersed in an oil bath at *ca.* 90 °C for 90 min. Upon cooling to room temperature, the reaction mixture was diluted with dichloromethane (20ml), filtered through a plug of celite and evaporated *in vacuo* to give a faintly yellow solid foam which was recrystallised from ethanol as a colourless amorphous solid (0.86g, 81%, α:β 8:1 by ^{1}H NMR spectroscopy). Methyl hepta-*O*-acetyl-α-maltoside **89** **^{1}H NMR** (250.1 MHz, $CDCl_3$, δ_H ppm); 5.35 (d, 1H, $J_{1,2}$ = 4.0, H-1); 5.30-5.11 (cm, 2H, H-3, H-3'); 4.99 (t, 1H, $J_{3',4'}$ = $J_{4',5'}$ 10.0, H-4'); 4.82 (d, 1H, $J_{1',2'}$ = 4.0, H-1'); 4.75 (dd, 1H, $J_{2,3}$ = 9.0, H-2); 4.41 (cm, 1H, H-2'); 4.30-4.16 (cm, 3H, H-5, H-6a, H6b'); 4.01-3.75 (cm, 3H, H-4, H-6a', H-6b); 3.66-3.57 (cm, 1H, H-5'); 3.43 (s, 3H, OCH_3); 2.09-1.94 (cm, 21H, 7x$COCH_3$). **^{13}C NMR** (62.9 MHz, $CDCl_3$, δ_C ppm); 170.3-169.2, 7x*C*OCH_3; 100.9, CH; 95.3, CH; 75.2, CH; 72.5, CH; 71.9, 2xCH; 69.8, CH; 69.1, CH; 68.3, CH; 67.8, CH; 62.6, CH_2; 61.3, CH_2; 56.8, OCH_3; 20.7-20.4, 7xCO*C*H_3. $[\alpha]_D$ +125, (c=1.0, chloroform) Lit.,[145] +132; M.Pt. (*iso*-propanol) 65-67, Lit.,[145] 66-69.

3.3.5 Stereoselectively controlled anomeric methylation of hepta-*O*-acetyl-α-maltose 87

To an anomeric mixture of aldose **87** (1.01g, 1.6mmol) suspended in acetonitrile (7 ml) in the dark, was added silver oxide (0.77g, 3.3mmol) with stirring. After 15 min.,

iodomethane (0.21ml, 3.3mmol, freshly filtered through a plug of neutral aluminium oxide) was added and the mixture left to stir over a 72h period after which the reaction mixture was diluted with dichloromethane (20ml), filtered through a plug of celite, and evaporated *in vacuo* to a solid foam which was recrystallised from isopropanol to yield methyl hepta-*O*-acetyl-α-maltoside **89** (*vide supra*) as colourless needles (0.86g, 83%) which were used for X-Ray diffraction studies (see Appendix).

3.3.6 Deprotection of maltoside 89 to yield methyl α-D-maltoside

To a rapidly stirred solution of **89** (4.53g, 7.0mmol) in methanol (25ml) was added freshly ground sodium hydroxide (0.98g, 24.4mmol). After 10 min., TLC (ethyl acetate) showed complete consumption of starting material and the presence of only one very polar fraction. The reaction mixture was neutralised by the addition of Dowex MR-3 ion exchange resin, and evaporated *in vacuo* to a hydroscopic solid foam of methyl α-D-maltoside **31** (2.48g, 100%). **^{1}H NMR** (250.1 MHz, D_2O, δ_H ppm); 5.20 (d, 1H, $J_{1,2}$ = 4.0, H-1); 4.29 (d, 1H, $J_{1',2'}$ = 8.0, H-1'); 4.10-3.22 (cm, 12H, ring protons); 3.46 (s, 3H, OCH_3); **^{13}C NMR** (62.9 MHz, D_2O, δ_C ppm); 101.4, CH; 100.1, CH; 78.5, CH; 74.8, CH; 74.0, CH; 73.6, CH; 72.7, CH; 72.0, CH; 71.3, CH; 70.0, CH; 61.8 CH_2; 61.6, CH_2; 55.6 OCH_3 $[\alpha]_D$ +176, (c=1.0, water) Lit.,[148] +174.

3.3.7 Benzylidenation of methyl α-maltoside 31

Benzaldehyde (1.08, 7.7mmol) and previously fused zinc chloride (0.48g, 0.4mmol) were mixed in an ultra-sonic bath under an atmosphere of argon. Once all the catalyst

had dissolved, methyl maltoside **31** (0.10g, 0.3mmol) was added and the reaction mixture sonicated at room temperature for 36 hours at which point it was diluted with methanol (1ml) and the acetal precipitated by the addition of ether. The solid was collected and dried under high vacuum to furnish the crude acetal which was purified by protection as the per-*O*-acetate (under conditions outlined in 3.3.2) and subsequent deprotection (under conditions outlined in 3.3.6) to furnish *methyl 4′,6′-O-benzylidene-α-maltoside* **30** as a heavy oil (0.07g, 59%). **^{1}H NMR** (250.1 MHz, D_2O, δ_H ppm); 8.05-7.32 (cm, 5H, H_{ar}); 5.57 (s, 1H, H_{acetal}); 5.15 (d, 1H, $J_{1,2}$ = 4.0, H-1); 4.18 (d, 1H, $J_{1',2'}$ = 8.0, H-1'); 3.86-3.00 (cm, 12H, H-ring); 3.52 (s, 3H, OMe); **^{13}C NMR** (62.9 MHz, D_2O, δ_C ppm); 136.8, C_q; 128.8, CH_{ar}; 128.0, CH_{ar}; 126.4, CH_{ar}; 101.4, CH; 100.1, CH; 80.8, CH; 78.5, CH; 74.8, CH; 74.0, CH; 73.6, CH; 72.7, CH; 72.0, CH; 71.3, CH; 70.0, CH; 61.8 CH_2; 61.6, CH_2; 55.6 OCH_3. MS m/z (FAB); 444, M^+;122, $PhCO_2$; 31, OMe; Accurate mass (FAB) M^+; 444.43482, Requires 444.43572 $[\alpha]_D$ +118° (c=1, water).

3.3.8 Cyclohexylidenation of methyl α-maltoside 31

To a solution of maltoside **30** (0.10g, 0.3mmol) in anhydrous *N,N*-dimethylformamide (2ml) was added cyclohexanecarboxaldehyde (0.75ml, 6.2mmol) followed by pyridinium *para*-toluenesulfonic acid (0.01g, 0.04mmol). The mixture was allowed to stir under argon overnight after which time TLC (ether : ethanol; 4:1) showed no remaining starting material. The reaction was quenched with an ion-exchange resin (Dowex MR-3), stirred 5 mins. then filtered and evaporated to furnish *methyl 4′,6′-O-cyclohexylmethylidene-α-maltoside* **92** as a heavy syrup (0.15g, 117%

mass balance). **^{1}H NMR** (250.1 MHz, D_2O, δ_H ppm); 5.23 (d, 1H, $J_{1,2}$ = 4.0, H-1); 4.39 (d, 1H, J = 5.0, H-acetal); 4.29 (d, 1H, $J_{1',2'}$ = 8.0, H-1'); 4.27-3.04 (cm, 12H, H-ring); 3.62 (s, 3H, OMe); 2.01-1.00 (cm, 10H, H-Cy); **^{13}C NMR** (62.9 MHz, D_2O, δ_C ppm); 125.1, CH; 103.4, CH; 101.6, CH; 80.2, CH; 79.9, CH; 75.8, CH; 74.6, CH; 72.8, 2xCH; 72.7, CH; 70.3, CH; 67.5, CH_2; 63.3, CH; 60.4, CH_2; 55.5, CH_3; 26.7-24.6, 5xCH_2. MS m/z (FAB); 451, MH^+; 31, OMe; Accurate mass (FAB) MH^+; 451.5211 Requires 451.4913 $[\alpha]_D$ +143° (c=1, water).

3.4 Attempted formation of methyl α-maltotrioside 93

3.4.1 Iodination of alcohol 63

To a solution of tribenzoate ester **63** (2.03g, 4.0mmol) in dry toluene (50ml) under an atmosphere of argon was added iodine (1.92g, 7.6mmol). This bright red solution was stirred at room temperature for 5 mins. whereupon imidazole (1.14g, 16.8mmol) was added followed 5 mins. later by triphenylphosphine (4.41g, 16.8mmol) and the mixture heated to reflux where it was maintained for 90 mins. at which point TLC (ethyl acetate : cyclohexane; 1:2) showed no remaining starting material. After cooling to room temperature the reaction was diluted with toluene (50ml) and washed successively with saturated aqeuous sodium bicarbonate (100ml), sodium thiosulfate (100ml), brine (100ml) and water (50ml) before drying (magnesium sulfate), filtration and evaporation under reduced pressure to yield a colourless viscous oil which was purified by wet-flash chromatography to yield methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-4-iodo-α-D-galactopyranoside **95** (2.12g, 86%) as a colourless

syrup. **^{1}H NMR** (250.1 MHz, $CDCl_3$, δ_H ppm); 8.19-7.25 (cm, 15H, H-ar); 5.63 (dd, 1H, $J_{1,2}$ = 4.0, $J_{2,3}$ = 10.5, H-2); 5.20 (d, 1H, $J_{1,2}$ = 4.0, H-1); 5.14 (dd, 1H, $J_{2,3}$ = 10.5, $J_{3,4}$ = 4.0, H-3); 4.93 (dd, 1H, $J_{3,4}$ = 4.0, $J_{4,5}$ = 2.0, H-4); 4.60 (dd, 1H, $J_{5,6a}$ = 7.0, $J_{6,6a}$ = 11.5, H-6a; 4.38 (dd, 1H, $J_{5,6b}$ = 5.0, $J_{6,6a}$ = 11.5, H-6b); 3.83 (ddd, 1H, $J_{5,6a}$ = 7.0, $J_{5,6b}$ = 5.0, $J_{6a,6b}$ = 11.5, H-5); 3.44 (s, 3H, OMe). **^{13}C NMR** (62.9 MHz, $CDCl_3$, δ_C ppm); 165.9-165.2, 3xCO; 133.6-133.2, 3xC_{quat}; 130.1-128.3, 15xCH_{ar}; 97.4, CH; 71.2, CH; 68.4, CH; 68.3, CH_2; 66.0, CH; 55.3, CH_3; 35.3, CH; $[\alpha]_D$ +69, (c=1.0, chloroform) Lit.,[132] +72.

3.4.2 Attempted condensation of alcohol 87 with iodide 95

Typical experiment:

To a suspension of heptaacetyl maltose **87** (0.11g, 0.2mmol) in acetonitrile (1.5ml) was added silver oxide (0.08g, 0.3mmol) and the resultant suspension stirred for 5 mins. isolated from light whereuopn **95** (0.12g, 0.2mmol) in acetonitrile (1.5ml) was added. After prolonged stirring at room temperature and laterly prolonged refluxing no reaction was observable by TLC (ether).

3.4.3 Debenzoylation of methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-4-iodo-α-D-galactopyranoside 95

95 (0.07g, 0.1mmol) was stirred in methanol (5ml) for 5 mins. where freshly ground sodium hydroxide (0.01g, 0.2mmol) was added. After 15 mins. at room temperature TLC (ethyl acetate : cyclohexane; 1:2) showed no remaining starting material and so

the reaction was quenched on the addition of an ion-exchange resin (Dowex MR-3), filtered and evaporated to yield spectroscopically clean methyl 4-deoxy-4-iodo-α-D-galactopyranoside **98** as a slightly yellow gum (0.02g, 54%) **^{1}H NMR** (250.1 MHz, CD_3OD, δ_H ppm); 4.10-3.00 (cm, 6H, H-ring); 3.81 (s, 3H, OMe); NB H-1 obscured by CD_3OH; **^{13}C NMR** (62.9 MHz, CD_3OD, δ_C ppm); 99.6, CH; 71.1, CH; 68.7, CH; 67.6, CH; 65.9, CH_2; 53.8, OMe; 46.1, CH. $[\alpha]_D$ +122, (c=1.0, chloroform) Lit.,[132] +129.

3.4.4 Attempted condensation of alcohol 87 with iodide 98

Typical experiment:

To a suspension of hepta-*O*-acetyl maltose **87** (0.42g, 0.1mmol) in acetonitrile (1ml) was added silver oxide (0.31g, 1.3mmol) and the resultant suspension stirred for 5 mins. isolated from light whereupon **95** (0.20g, 0.1mmol) in acetonitrile (1ml) was added. After prolonged stirring at room temperature and laterly prolonged refluxing no reaction was observable by TLC (ether).

3.4.5 Attempted anhydrous condensation of 87 with iodide 98

Typical experiment:

To a solution of hepta-*O*-acetyl maltose **87** (0.10g, 0.2mmol) in acetonitrile (1ml) was added silver oxide (0.07g, 0.3mmol) under an atmosphere of argon and protected from light, followed by a solution of rigorously dried iodide **98** (0.05g, 0.2mmol).

After prolonged stirring and subsequent refluxing no reaction was observed, and unreacted **87** recovered.

3.4.6 Silver carbonate mediated attempted anhydrous condensation of 87 with iodide 98

Typical experiment:

To a solution of hepta-*O*-acetyl maltose **87** (0.12g, 0.2mmol) in acetonitrile (1ml) was added silver carbonate (0.07g, 0.3mmol) under an atmosphere of argon, protected from light, followed by a solution of rigorously dried **98** (0.06g, 0.2mmol) in acetonitrile (1ml). After prolonged stirring and subsequent refluxing no reaction was observed and unreacted **87** again recovered.

3.5 Oxidation of cyclodextrins 116 & 117

3.5.1 Sodium periodate oxidation

Typical experiment:

α-cyclodextrin (0.48g, 0.5mmol) was suspended in distilled water (10 ml) and the mixture protected from light. Sodium periodate (0.87g, 4.1mmol) was then added and the reaction stirred at room temp. for 2 days. After this time, the resultant clear solution is ion-exchanged (2x1 eq. Dowex MR-3 ion exchange resin), filtered and freeze dried.

3.5.2 Sodium chlorite oxidation

Typical experiment:

Polydialdehyde (0.25g, 0.2mmol) was dissolved in distilled water (10 ml) and cooled to 10°C. Sodium chlorite (0.60g, 6.6mmol) and acetic acid (0.49g, 8.1mmol) in water (12 ml) were then sequentially added over 1 hour. Following 24 hours stirring, the mixture was purged with argon until the solution was colourless, whereupon it was made alkaline by addition of NaOH and then diluted with two volumes of ethanol : water 2:1. The resulting precipitate was collected at the pump, dissolved in distilled water and freeze dried.

3.5.3 Calcium sequestration of 108 & 109

Typical experiment:

Standard calcium acetate (*ca.* 0.1M) was titrated into a standard (100ml) aqeuous solution of the sample (*ca.* 0.10g) containing potassium chloride (2ml, *ca.* 4M) and sodium hydroxide (10 ml, *ca.* 0.1M). The potential was measured between a Unicam calcium ion selective electrode and a Corning double junction calomel reference using a Metler Delta 320 millivolt meter. Calibration data is prepared immediately beforehand using standard calcium acetate solutions.

	Ca^{2+} sequestration (g/100g)		
Sequestration g/100g	**108 (%)**	**109 (%)**	**STP (%)**
0.0	100		
0.0		100	
0.0			100
2.0	100		
3.4			100
4.0		98.8	
4.6	100		
6.3		96.5	
8.0	98.8		
9.5			99.4
11.0	98.8		
11.3		97.1	
11.7			98.8
13.3	97.6		
14.9			94.7
16.7		92.9	
18.5	97.6		
19.3			86.5
20.0		90	
21.5	94.1		
23.0		91.8	
24.8			68.8
26.6	88.2		
27.8		88.8	
29.0			10
30.1	87.1		
31.3		81.2	
33.5	90.6		
35.8		52.9	
38.6	76.5		
41.5		37.6	
44.8	42.4		
48.1		32.4	
50.1	40		
58.2		13.5	

3.6 Attempted preparation of hexa- and hepta-aldosides 120 & 121

3.6.1 Per-*O*-benzoylation of cyclodextrins 116 & 117

Typical experiment:

β-cyclodextrin (0.88g, 0.9mmol) was added with stirring to a solution of dry pyridine (10.14g, 147mmol) and freshly distilled benzoyl chloride (10.32g 73.4mmol), protected from atmospheric moisture, and stirred for 72 hours at *ca.* 50 °C. The resulting brown solution was partitioned between dichloromethane (200ml) and water (200ml), with the aqeuous layer extracted with further portions of dichloromethane (2x50ml) before the combined organic layers were dried over magnesium sulfate, decolorised wit deactivated charcoal, filtered through a celite pad and concentrated *in vacuo* to ¼ volume at which point the spectroscopically clean per-*O*-benzoylated cyclodextrin was isolated by precipitation on addition of cyclohexane. Hexakis-*O*-benzoyl-α-cyclodextrin **124** (2.89g, 95%) **^{1}H NMR** (250.1 MHz, $CDCl_3$, δ_H ppm); 8.20-6.88 (cm, 15H, H-Ar); 5.60 (t, 1H, $J_{1,2}$ = 3.5, H-1); 5.10-4.80 (cm, 5H, H-2, H-3, H-5, CH_2); 4.31 (t, $J_{3,4}$ = $J_{4,5}$ = 10.0, H-4). **^{13}C NMR** (62.9 MHz, $CDCl_3$, δ_C ppm); 166.8, CO; 165.9, CO; 164.4, CO; 133.5-127.4, 9xCH_{ar} & 3xC_{quat}; 98.8, CH; 78.9, CH; 72.0, CH; 71.5, CH; 70.0, CH; 63.4, CH_2. $[\alpha]_D$ +49, (c=1.0, chloroform) Lit.,[136] +66. Heptakis-*O*-benzoyl-β-cyclodextrin **125** (98%). **^{1}H NMR** (250.1 MHz, $CDCl_3$, δ_H ppm); 8.24-6.86 (cm, 15H, H-Ar); 5.58 (t, 1H, $J_{1,2}$ = 3.5, H-1); 5.08-4.80 (cm, 5H, H-2, H-3, H-5, CH_2); 4.30 (t, $J_{3,4}$ = $J_{4,5}$ = 10.0, H-4). **^{13}C NMR** (62.9 MHz, $CDCl_3$, δ_C ppm); 166.6, CO; 166.3, CO; 166.2, CO; 133.8-127.9, 9xCH_{ar} & 3xC_{quat}; 97.8, CH; 77.7, CH; 72.1, CH; 71.9, CH; 70.1, CH; 63.5, CH_2; $[\alpha]_D$ +25, (c=1.0, chloroform) Lit.,[136] +18.

3.6.2 Glycosidic fission of per-*O*-benzoylated cyclodextrins 124 & 125

Typical experiment:

A sample of the dried per-*O*-benzoyl cyclodextrin (1.08g, 0.3mmol) was dissolved in a mixed solvent; acetic anhydride : concentrated sulfuric acid (49:1, 10ml) and heated to *ca.* 55 °C where it was maintained over 48 hours. At this point the reaction mixture was cooled to room temperature whereupon solid sodium bicarbonate was added until no further gas was evolved. After filtration, toluene (3x25ml) was added and the solvent azeotropically distilled *in vacuo* prior to purification by wet-flash column chromatography to yield *O*-(4-*O*-acetyl-2,3,6-tri-*O*-benzoyl-α-D-glucopyranosyl)-(1→4)-(tetrakis[*O*-2,3,6-tri-*O*-benzoyl-α-D-glucopyranosyl)-(1→4)]-1-*O*-acetyl-2,3,6-tri-*O*-benzoyl-α-D-glucopyranose **126** (0.58g, 52%) **^{1}H NMR** (250.1 MHz, $CDCl_3$, δ_H ppm); 8.11-6.66 (cm, 90H, H-Ar); 6.55 (d, 1H, $J_{1,2}$ = 3.5, H-1^1); 6.00-4.22 (cm, 41H, 5xH-1, 6xH-2, 6xH-3, 6xH-4, 6xH-5, 6xCH_2); 2.28 (s, 3H, OAc) ; 2.00 (s, 3H, OAc). **^{13}C NMR** (62.9 MHz, $CDCl_3$, δ_C ppm); 170.0-163.9, 20xCO; 133.6-127.5, 54xCH_{ar} & 18xC_{quat}; 98.8, CH; 96.9, CH; 96.8, CH; 96.7, CH; 96.6, CH; 90.0, CH; 77.1, CH; 74.0, CH; 73.6, CH; 73.4, CH; 72.1, 2xCH; 72.0, CH; 71.7, 2xCH; 71.1, 3xCH; 70.8, 3xCH; 70.5, 2xCH; 70.0, 3xCH; 69.0, CH; 68.3, CH; 62.9, CH_2; 62.8, 4xCH_2; 62.5, CH_2; 62.0, CH_2; 21.0, CH_3; 20.4, CH_3; $[\alpha]_D$ +69, (c=1.0, chloroform) Lit.,[136] +76. *O*-(4-*O*-acetyl-2,3,6-tri-*O*-benzoyl-α-D-glucopyranosyl)-(1→4)-(pentakis[*O*-2,3,6-tri-*O*-benzoyl-α-D-glucopyranosyl)-(1→4)]-1-*O*-acetyl-23,6-tri-*O*-benzoyl-α-D-glucopyranose **127** (0.44g, 64%). **^{1}H NMR** (250.1 MHz, $CDCl_3$, δ_H ppm); 8.07-6.72 (cm, 105H, H-Ar); 6.51 (d, 1H, $J_{1,2}$ = 3.5, H-1^1); 5.95-4.20 (cm, 48H, 6xH-1, 7xH-2, 7xH-3, 7xH-4, 7xH-5, 7xCH_2); 2.20

(s, 3H, OAc) ; 1.95 (s, 3H, OAc). **^{13}C NMR** (62.9 MHz, $CDCl_3$, δ_C ppm); 169.1-164.0, 23xCO; 133.5-127.7, 63xCH_{ar} & 21xC_{quat}; 98.0, CH; 96.8, 3xCH; 96.7, CH; 96.6, 3xCH; 96.5, CH; 89.8, CH; 77.2, CH; 74.0, CH; 73.6, CH; 73.4, CH; 72.1, 3xCH; 72.0, CH; 71.7, 2xCH; 71.2, 3xCH; 70.8, 4xCH; 70.5, 2xCH; 70.0, 4xCH; 69.0, CH; 68.4, CH; 62.9, CH_2; 62.8, 4xCH_2; 62.4, CH_2; 62.0, CH_2; 20.9, CH_3; 20.4, CH_3; $[\alpha]_D$ +72, (c=1.1, chloroform) Lit.,[136] +67.

3.6.3 Attempted anomeric deprotection of 126 & 127

Typical experiment:

The per-ester (1.08g, 0.3mmol), was added at –78°C to a mixed solvent (methanol : tetrahydrofuran 3 : 7, 150ml) through which ammonia had been bubbled vigorously over a 25 min. period. After stirring for 10 min., the reaction was allowed to warm to room temperature. TLC (ethyl acetate) indicated the complete consumption of the starting material and the formation of a single, more polar fraction being the product of complete deprotection, or no reaction even over prolonged reaction times.

3.6.4 Regioselective 4-*O*-acetyl deprotection of 126

Typical experiment:

A solution of totally protected oligosaccharide **126** (0.20g, 0.3mmol) was stirred at room temperature in anhydrous tetrahydrofuran (10ml) under an atmosphere of argon and to this was added ^{n}butylamine (0.03g, 0.4mmol) and the solution heated to *ca.* 66 °C where it was maintained for 14 hours before dilution with DCM (25ml) and evaporation *in vacuo*. The resultant syrup was diluted in DCM (25ml) and

successively washed with hydrochloric acid (2M, 25ml), saturated aqueous sodium bicarbonate (25ml), brine (25ml) and water (25ml) before drying over magnesium sulfate and evaporation to a syrup which was purified by wet-flash column chromatography to yield *O*-(2,3,6-tri-*O*-benzoyl-α-D-glucopyranosyl)-(1→4)-(tetrakis[*O*-2,3,6-tri-*O*-benzoyl-α-D-glucopyranosyl)-(1→4)]-1-*O*-acetyl-2,3,6-tri-*O*-benzoyl-α-D-glucopyranose (0.08g, 34%) as an amorphous solid. **^{1}H NMR** (250.1 MHz, $CDCl_3$, δ_H ppm); 8.09-6.67 (cm, 90H, H-Ar); 6.53 (d, 1H, $J_{1,2}$ = 3.5, H-1^1); 5.98-4.22 (cm, 41H, 5xH-1, 6xH-2, 6xH-3, 6xH-4, 6xH-5, 6xCH_2); 3.48 (d, 1H, $J_{4,OH}$ = 5.0, OH [NB disappears on shaking with D_2O]); 2.28 (s, 3H, OAc). **^{13}C NMR** (62.9 MHz, $CDCl_3$, δ_C ppm); 170.4-163.7, 19xCO; 133.8-127.5, 54xCH_{ar} & 18xC_{quat}; 98.9, CH; 96.9, CH; 96.8, CH; 96.7, CH; 96.6, CH; 90.0, CH; 77.1, CH; 74.0, CH; 73.8, CH; 73.4, CH; 72.1, 2xCH; 72.0, CH; 71.8, 2xCH; 71.1, 3xCH; 70.8, 3xCH; 70.5, 2xCH; 70.2, 3xCH; 69.0, CH; 68.2, CH; 62.8, CH_2; 62.7, 4xCH_2; 62.5, CH_2; 62.0, CH_2; 21.0, CH_3; $[\alpha]_D$ +62, (c=1.1, chloroform) Lit.,[136] +64.

3.6.5 Attempted anomeric substitution of 126 & 127

Typical experiment:

The diacetate (0.51g, 0.1mmol) was dissolved in 1,2-DCE (10ml) under an atmosphere of argon, and to this was added zinc iodide (0.72g, 1.5mmol). After 15 mins. stirring, methoxytrimethyl silane (0.16g, 1.0mmol) was added and the suspension stirred at room temperature over a range of times. No reaction was observed by TLC (DCM, silica).

3.7 Oxidative studies[137]

3.7.1 $C_{2,3}$ oxidative glycol cleavage of 54

Triol **54** (0.24g, 1.2mmol) was dissolved in deionised water (5ml) at room temperature and isolated from light. Sodium periodate was then added (0.28g, 1.3mmol), the vessel sealed and stirred at ambient temperature for 2 days where it was twice ion-exchanged with 3 equivalents of Dowex® MR-3 mixed bed ion exchange resin. To this clear soultion was added sodium chlorite (77% aq. soln, 0.42g, 3.5mmol) and glacial acetic acid (0.27g, 4.5mmol) before stirring the mixture for a further 14 hours after which time the slightly blue solution had a stream of argon bubbled through it until colourless. After making the mixture alkaline on the addition of sodium hydroxide (*ca.* 0.3M) the resulting precipitate is dissolved in water(10ml), ion-exchanged with 3 equivalents of Dowex® MR-3 mixed bed ion exchange resin collected at the water pump and dried under high vacuum to furnish *2((S)-methoxy-3-O-((S)-carboxymethoxy)-butan-4-ol-oic acid* **131** (0.18g, 72%). **^{13}C NMR** (62.9 MHz, D_2O, δ_C ppm); 170.7, CO_2H; 168.8, CO_2H; 101.3, CH; 82.4, CH; 73.0, CH; 71.2, CH_2; 61.1, CH_3; 55.8, CH_3. $[\alpha]_D$ +107, (c=1.1, water). Accurate mass (FAB), 239.2047; Requires 239.2056.

3.7.2 Regioselective primary alcohol oxidation of 54

A solution of standardised sodium hypochlorite (1.8mmol) was diluted with deionised water (5ml) and cooled to 0 °C whereupon it was added to a rapidly stirring solution of **54** (0.12g,0.6mmol), TEMPO (0.1M, 40µl) and sodium bromide (0.01g,

0.1mmol). After 45 mins. stirring, TLC (DCM : 5% acetic acid, silica) indicated complete consumption of starting materials and so the reaction was quenched by addition of ethanol (5ml). A further (35ml) portion was then added slowly, precipitating a colourless solid which was collected and purified by to silica gel chromatography (chloroform : methanol : acetic acid; 20:5:1) then dried under high vacuum to yield methyl 4-*O*-methyl-α-D-glucopyranosiduronic acid **132** (0.12g, 94%). **^{13}C NMR** (62.9 MHz, D_2O, δ_C ppm); 170.3, CO_2H; 98.9, CH; 79.4, CH; 73.0, CH; 72.8, CH; 70.9, CH_2; 60.0, CH_3; 55.2, CH_3; $[\alpha]_D$ +125, (c=1.2, water) Lit.,[118] +129.

3.7.3 Attempted bromine-hydrogen peroxide oxidation of 54

A solution of **54** (0.11g, 0.3mmol) in deionised water (2ml) was added to a solution of bromine (0.09g, 0.6mmol) in deionised water (2ml) at room temperature. After four hours stirring thin layer chromatography (silica, methanol : chlorofom 1:1) showed a large streak in place of the distinct starting material fraction, and so hydrogen peroxide (0.06g, 1.8mmol) was added. After the effervescing had subsided TLC revealed a complex multispot mixture which could not be seperated by chromatography on silica.

3.7.4 Sodium hypochlorite oxidation of 54

54 (0.14g, 0.7mmol) was dissolved in deionised water (5ml), and stirred rapidly while sodium hypochlorite (1.4mmol) - standardised immediately beforehand - was added. Over ca. ½ hour the pH rises initially to 9 then falls over time to 7 . Once the

oxidant had been completely consumed ethanol (1 ml) is added and the oxidised product precipitated by the addition of acteone (25 ml) and THF (10 ml). The precipitate was collected at the pump and dried under high vacuum to furnish **131** (44%, *vide supra*).

3.7.5 Attempted copper chloride-hydrogen peroxide oxidation of 54

Typical experiment:

54 (0.27g, 1.3mmol) was dissolved in deionised water (10ml) to which was added calcium chloride (0.02g, 0.1mmol) and sodium hydroxide (0.02g, 0.5mmol). The faintly yellow solution was then heated to 54 °C under a blanket of argon, where hydrogen peroxide, immediately standardised beforehand (1.2g, 0.3mmol) was added over 5 mins. (the solution immediately becoming cloudy on peroxide addition). TLC showed no reaction even after prolonged reaction times.

3.7.6 Attempted calcium hydroxide-hydrogen peroxide oxidation of 54

Typical experiment:

A solution of **54** (0.35g, 1.7mmol) in deionised water (10ml) was heated to 46 °C where calcium hydroxide (0.14g, 1.9mmol) was added to form a suspension. After 10 mins. stirring, hydrogen peroxide, immediately standardised beforehand (1.5g, 3.7mmol) was added and the mixture stirred, however TLC (DCM : 5% acetic acid, silica) indicated no reaction occurred.

3.7.7 Preparation of calcium hydroperoxide

To a rapidly stirring slurry of calcium oxide (8.14g, 145.1mmol) in deionised water (90ml) was added dropwise hydrogen peroxide (19.07g, 196.3mmol) over 90 minutes at room temperature. The resultant creamy suspension was then collected at the water pump and dried under high vacuum over 3 days. The available oxygen content was determined by titration against standard potassium permanganate, indicating a conversion to calcium hydroperoxide of 40%.

3.7.8 Attempted calcium hydroperoxide oxidation of 54

Typical experiment:

To a flask charged with **54** (0.20g, 1.0mmol) in deionised water (2.5ml) was added calcium hydroperoxide (0.16, 1.5mmol) to forming a creamy white slurry which was left stirring at room temperature overnight. Sulfuric acid (1M) was added to pH 1, and the now clear solution evaporated under high vacuum at ambient temperature. Analysis of the crude reaction product by ^{13}C NMR showed only the presence of starting material.

3.7.9 Attempted selective formation of methyl 4-O-methyl-α-D-glucopyranosiduronic acid

A flask was charged with the sugar (0.58g, 2.8mmol) in distilled water (3ml) and stirred under a blanket of argon for 10 min. at room temperature, where TEMPO (0.01g, 0.1mmol) was added, followed 10 min. later by sodium tungstate dihydrate

(0.03g, 0.1mmol). The temperature was lowered to 0 °C and the pH raised from 7 to 12 by the addition of NaOH (~1M). After 30 min. stirring, hydrogen peroxide (0.18g, 5.3mmol) was added over the course of 30 min. The pH was maintained *ca.* 11 by addition as necessary of base. Even after prolonged reaction times, no reaction was observed.

3.7.10 Preparation of tetra-acid 136

Maltoside **31** (0.40g, 1.1mmol) was dissolved in deionised water (5ml) at room temperature and isolated from light. Sodium periodate was then added (0.57g, 2.6mmol), the vessel sealed and stirred at ambient temperature for 2 days where it was twice ion-exchanged with 3 equivalents of Dowex® MR-3 mixed bed ion exchange resin. To this clear soultion was added sodium chlorite (77% aq. soln, 0.63g, 5.3mmol) and glacial acetic acid (0.41g, 6.8mmol) before stirring the mixture for a further 14 hours after which time the slightly blue solution had a stream of argon bubbled through it until colourless. After making the mixture alkaline on the addition of sodium hydroxide (*ca.* 0.3M) the resulting precipitate was collected then redissolved in water (10ml), ion exchanged with Dowex MR-3, evaporated and dried under high vacuum to furnish *butan-2-(S)-O-[(S)-carboxymethyl-O-(3'-(S)-hydroxymethyl-2'-(S)-hydroxybutanoic acid)]-3-O-(S)-(carboxymethoxymethanol)-4-ol-oic acid* **136** (0.32g, 70%). **^{13}C NMR** (62.9 MHz, D_2O, δ_C ppm); 171.4-167.7, 4xCO_2H; 103.3, CH; 100.9, CH; 78.7, CH; 75.2, CH; 74.0, CH; 73.8, CH; 62.2 CH_2; 62.0, CH_2; 56.5 OCH_3. $[\alpha]_D$ +154, (c=1.1, water). MS m/z (FAB); 92, $CO_2HCH(OH)_2$;84, $CO_2HCH(OMe)OH$; 31, OMe;

3.7.11 Preparation of hexa-acid 137

A solution of standardised sodium hypochlorite (1.8mmol) was diluted with deionised water (5ml) and cooled to 0 °C whereupon it was added to a rapidly stirring solution of **136** (0.27g,0.7mmol), TEMPO (0.1M, 40µl) and sodium bromide (0.01g, 0.1mmol). After 45 mins. stirring, TLC (ethanol : 5% acetic acid, silica) indicated complete consumption of starting materials and so the reaction was quenched on addition of ethanol (5ml). A further (25ml) portion was then added slowly, precipitating a colourless solid which was collected then redissolved in water (10ml), ion exchanged with Dowex MR-3, evaporated and dried under high vacuum yield *butan-2-(S)-*O*-[(S)-carboxymethyl-*O*-(3'-(S)-carboxy-2'-(S)-hydroxybutanoic acid)]-3-*O*-(S)-(carboxymethoxymethanol)-1,4-dioic acid* **137** (0.12g, 40%). **^{13}C NMR** (62.9 MHz, D_2O, δ_C ppm); 172.7-167.5, 6xCO_2H; 103.5, CH; 101.2, CH; 79.4, CH; 75.8, CH; 75.6, CH; 74.2, CH; 56.8 OCH_3. 92, CO2HCH$(OH)_2$;84, CO2HCH(OMe)OH; 31, OMe; $[\alpha]_D$ +88, (c=1.0, water). Accurate mass (FAB) MH^+, 444.2596; Requires 444.2608.

3.7.12 Preparation of acid 138

A solution of standardised sodium hypochlorite (1.8mmol) was diluted with deionised water (5ml) and cooled to 0 °C whereupon it was added to a rapidly stirring solution of **30** (0.31g,0.7mmol), TEMPO (0.1M, 40µl) and sodium bromide (0.01g, 0.1mmol). After 45 mins. stirring, TLC (DCM : 5% acetic acid, silica) indicated complete consumption of starting materials and so the reaction was quenched on

addition of ethanol (5ml). A further (25ml) portion was then added slowly, precipitating a colourless solid which was collected and dried under high vacuum to yield *methyl 4-O-(4',6'-O-(R)-benzylidene-α-D-glucopyrano-)-α-D-glucopyranosiduronic acid* **135** (0.28g, 88%). **^{13}C NMR** (62.9 MHz, D_2O, δ_C ppm); 171.0, CO_2H; 137.0, C_q; 130.0-126.4, 3xCH_{ar}; 101.8, CH; 100.3, CH; 81.0, CH; 78.8, CH; 75.0, CH; 74.2, CH; 73.6, CH; 72.9, CH; 72.2, CH; 71.5, CH; 70.0, CH; 62.0 CH_2; 55.8, OCH_3. MS m/z (FAB); 459, MH^+;122, $PhCO_2$; 31, OMe; Accurate mass (FAB) 459.4303, Requires 459.4288. $[\alpha]_D$ +105° (c=1, water).

3.7.13 Preparation of tetra-acid 139

Maltoside **30** (0.49g, 1.1mmol) was dissolved in deionised water (5ml) at room temperature and isolated from light. Sodium periodate was then added (0.54g, 2.2mmol), the vessel sealed and stirred at ambient temperature for 2 days where it was twice ion-exchanged with 3 equivalents of Dowex® MR-3 mixed bed ion exchange resin. To this clear soultion was added sodium chlorite (77% aq. soln, 0.46g, 3.9mmol) and glacial acetic acid (0.30g, 5.0mmol) before stirring the mixture for a further 14 hours after which time the slightly blue solution had argon bubbled through it until colourless. After making the mixture alkaline on the addition of sodium hydroxide (*ca.* 0.3M) the resulting precipitate was collected at the water pump and dried under high vacuum to furnish furnish *butan-2-(S)-carboxymethoxy-O-[2',3'-di-O-(R)-benzylidene)- butanoic acid)]-3-O-(S)-(carboxymethoxymethanol)-4-ol-oic acid* **136** (0.35g, 64%). **^{13}C NMR** (62.9 MHz, D_2O, δ_C ppm); 171.7-166.8, 4xCO_2H; 137.0, C_q; 130.0-125.8, 3xCH_{ar}; 102.0, CH; 99.8, CH; 74.0, CH; 72.5, CH;

72.0, CH; 70.0, CH; 62.3 CH_2; 61.8, CH_2; 55.9 OCH_3. MS m/z (FAB); 122, $PhCO_2$; 31, OMe;

3.7.14 Ruthenium - molybdenum catalysed oxidation

Typical experiment:

Maltoside **31** (0.11g, 0.3mmol) was dissolved in deionised water (1ml) and stirred at room temperature whilst firstly molybdenum trioxide (0.04g, 0.3mmol) and then five minutes later ruthenium chloride hydrate (0.02g, 0.1mmol) were added. This black mixture was then heated to reflux where hydrogen peroxide (0.20g, 6.2mmol) was slowly added. The mixture was maintained at reflux for 3 hours where thin layer chromatography (silica, methanol : chlorofom 1:1) revealed complete consumption of starting material. After cooling, methanol (3 ml) was added and the mixture evaporated under high vacuum to a black glass comprising **136** (74%, *vide supra*).

3.7.15 Ruthenium catalysed oxidation

Typical experiment:

Maltoside **31** (0.10g, 0.3mmol) was dissolved in deionised water (1ml) and stirred at room temperature whilst ruthenium chloride hydrate (0.02g, 0.1mmol) was added. This black mixture was then heated to reflux where hydrogen peroxide (0.21g, 6.2mmol) was slowly added. The mixture was maintained at reflux for 3 hours where thin layer chromatography (silica, methanol : chlorofom 1:1) revealed consumption

of starting material. After cooling, methanol (3 ml) was added and the mixture evaporated under high vacuum to a black glass comprising **136** (68%, *vide supra*).

3.7.16 Attempted regioselective oxidation of primary alcohol of 30 & 31

Typical experiment:

A flask was charged with maltoside **31** (0.60g, 1.7mmol) in distilled water (3ml) and stirred under a blanket of argon for 10 min. at room temperature, where TEMPO (0.02g, 0.2mmol) was added, followed 10 min. later by sodium tungstate dihydrate (0.50g, 1.7mmol). The temperature was lowered to 0 °C and the pH raised from 7 to 12 by the addition of NaOH (~1M). After 30 min. stirring, hydrogen peroxide (0.89g, 26.5mmol) was added over the course of 30 min. The pH was maintained *ca.* 11 by addition as necessary of base. Even after prolonged reaction times, no reaction was observed.

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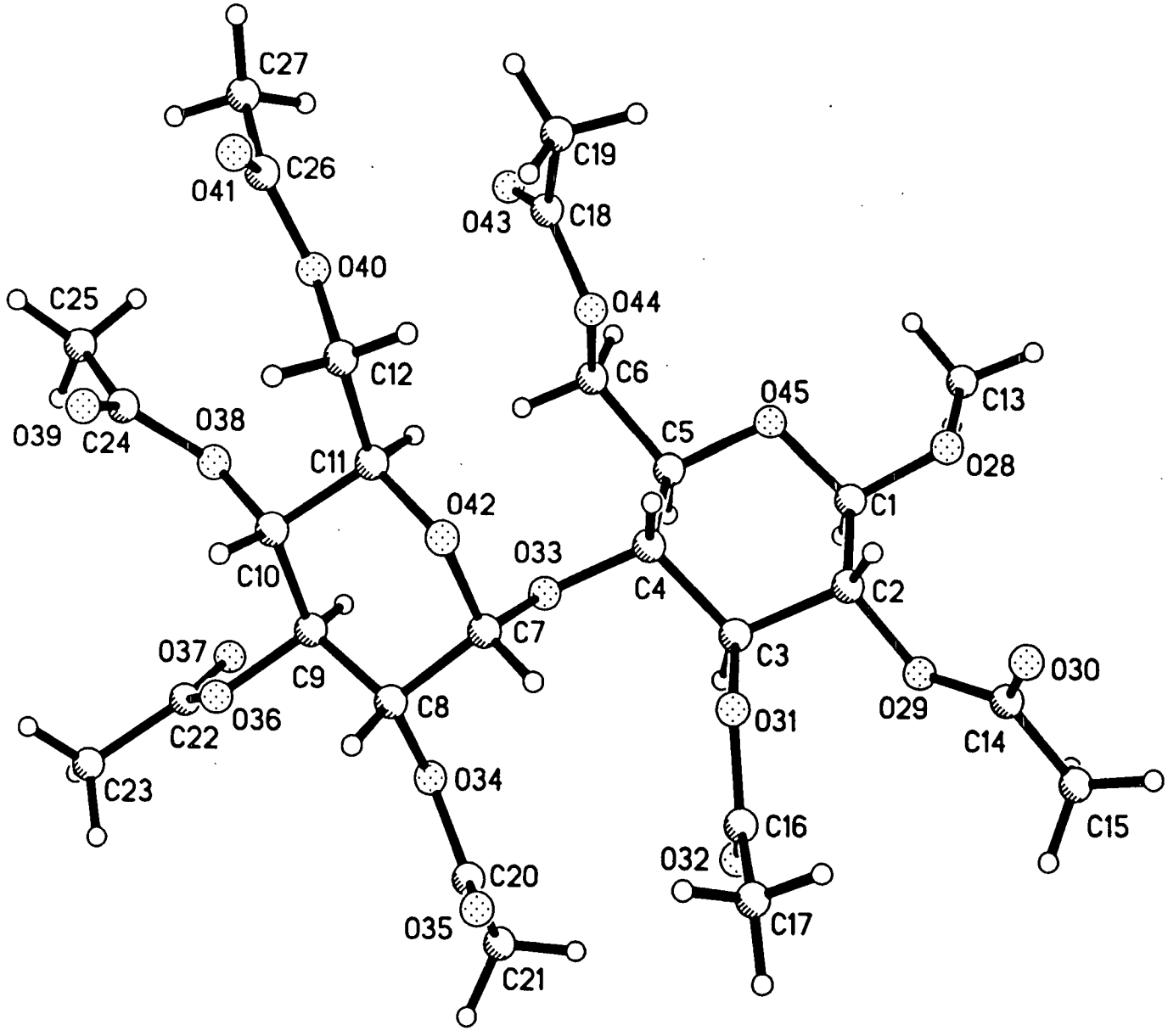
5.0 Appendix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C17

Table 1. Crystal data and structure refinement for xsg300.

A. CRYSTAL DATA	
Empirical formula	C27 H38 O18
Formula weight	650.57
Wavelength	0.68490 A (Synchrotron)
Temperature	160(2) K
Crystal system	Monoclinic
Space group	P2(1)
Unit cell dimensions	a = 5.5528(12) A alpha = 90 deg. b = 14.187(3) A beta = 90.560(6) deg. c = 20.082(5) A gamma = 90 deg.
Volume	1581.9(6) A^3
Z	2
Density (calculated)	1.366 Mg/m^3
Absorption coefficient	0.116 mm^-1
F(000)	688
B. DATA COLLECTION	
Crystal description	colourless plate
Crystal size	0.20 x 0.08 x 0.01 mm
Theta range for data collection	0.98 to 26.77 deg.
Index ranges	-6<=h<=7, -17<=k<=18, -25<=l<=21
Reflections collected	9238
Independent reflections	5824 [R(int) = 0.0353]
Scan type	Omega scans
Absorption correction	Sadabs (Tmin= 0.75, Tmax=1.00)
C. SOLUTION AND REFINEMENT.	
Solution	direct (SHELXS-86 (Sheldrick, 1990))
Refinement type	Full-matrix least-squares on F^2
Program used for refinement	SHELXTL version 5
Hydrogen atom placement	geom
Hydrogen atom treatment	Riding
Data / restraints / parameters	5823/1/415

Goodness-of-fit on F^2	1.066
Conventional R [F>4sigma(F)]	R1 = 0.0515 [4692 data]
R indices (all data)	R1 = 0.0719, wR2 = 0.1106
Absolute structure parameter	0.5(9)
Extinction coefficient	0.0173(17)
Final maximum delta/sigma	-0.017

Weighting scheme
calc w=1/[\s^2^(Fo^2^)+(0.0433P)^2^+0.0000P] where P=(Fo^2^+2Fc^2^)/3

Largest diff. peak and hole	0.237 and -0.211 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 1. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	12885(5)	2403(2)	9220(2)	25(1)
C(2)	10755(5)	1912(2)	8912(2)	23(1)
C(3)	10600(5)	2083(2)	8167(1)	19(1)
C(4)	10778(5)	3119(2)	7998(1)	18(1)
C(5)	13058(5)	3486(2)	8340(1)	20(1)
C(6)	13604(5)	4509(2)	8223(2)	22(1)
C(7)	9022(5)	3335(2)	6908(1)	19(1)
C(8)	9750(5)	3231(2)	6186(1)	18(1)
C(9)	11185(5)	4061(2)	5951(1)	16(1)
C(10)	9955(5)	4976(2)	6118(1)	17(1)
C(11)	9331(5)	5007(2)	6850(1)	17(1)
C(12)	7895(5)	5863(2)	7048(1)	21(1)
C(13)	14779(7)	2659(3)	10251(2)	45(1)
C(14)	9414(7)	455(3)	9364(2)	46(1)
C(15)	10157(11)	-533(3)	9474(3)	91(2)
C(16)	8392(5)	861(2)	7619(2)	25(1)
C(17)	5933(6)	505(3)	7489(2)	41(1)
C(18)	11980(6)	5971(2)	8528(1)	25(1)
C(19)	9852(6)	6455(2)	8808(2)	36(1)
C(20)	10225(5)	1586(2)	6006(1)	23(1)
C(21)	12034(5)	838(2)	5893(2)	28(1)
C(22)	13484(5)	4072(2)	4951(1)	17(1)
C(23)	13237(5)	4062(2)	4219(1)	27(1)
C(24)	10891(5)	6518(2)	5713(1)	20(1)
C(25)	12913(6)	7166(2)	5604(2)	30(1)
C(26)	8805(6)	7478(2)	7214(2)	28(1)
C(27)	10821(7)	8151(2)	7325(2)	45(1)
O(28)	12672(4)	2351(2)	9905(1)	33(1)
O(29)	11063(4)	921(1)	9019(1)	32(1)
O(30)	7580(5)	797(2)	9547(2)	80(1)
O(31)	8329(3)	1711(1)	7935(1)	21(1)
O(32)	10221(4)	487(2)	7469(1)	40(1)
O(33)	11127(3)	3242(1)	7299(1)	18(1)
O(34)	11275(3)	2428(1)	6094(1)	19(1)
O(35)	8095(4)	1485(1)	6033(1)	41(1)
O(36)	11318(3)	4009(1)	5236(1)	19(1)
O(37)	15331(3)	4130(2)	5258(1)	29(1)
O(38)	11693(3)	5697(1)	5975(1)	19(1)
O(39)	8821(4)	6672(1)	5598(1)	29(1)
O(40)	9637(3)	6597(1)	7150(1)	24(1)
O(41)	6727(4)	7674(2)	7178(1)	43(1)
O(42)	7869(3)	4209(1)	7010(1)	19(1)
O(43)	13872(4)	6327(1)	8399(1)	35(1)
O(44)	11557(3)	5043(1)	8438(1)	24(1)
O(45)	12844(3)	3362(1)	9037(1)	24(1)

Table 3. Bond lengths [A] and angles [deg] for 1.

C(1)-O(28)	1.385(4)
C(1)-O(45)	1.409(3)
C(1)-C(2)	1.500(4)
C(2)-O(29)	1.432(3)
C(2)-C(3)	1.517(4)
C(3)-O(31)	1.440(3)
C(3)-C(4)	1.512(4)
C(4)-O(33)	1.430(3)
C(4)-C(5)	1.526(4)
C(5)-O(45)	1.417(3)
C(5)-C(6)	1.501(4)
C(6)-O(44)	1.436(3)
C(7)-O(33)	1.408(3)
C(7)-O(42)	1.411(3)
C(7)-C(8)	1.517(4)
C(8)-O(34)	1.432(3)
C(8)-C(9)	1.500(4)
C(9)-O(36)	1.441(3)
C(9)-C(10)	1.506(4)
C(10)-O(38)	1.438(3)
C(10)-C(11)	1.514(4)
C(11)-O(42)	1.432(3)
C(11)-C(12)	1.508(4)
C(12)-O(40)	1.434(3)
C(13)-O(28)	1.424(4)
C(14)-O(30)	1.189(5)
C(14)-O(29)	1.330(4)
C(14)-C(15)	1.477(5)
C(16)-O(32)	1.187(4)
C(16)-O(31)	1.364(3)
C(16)-C(17)	1.477(4)
C(18)-O(43)	1.196(4)
C(18)-O(44)	1.349(3)
C(18)-C(19)	1.482(4)
C(20)-O(35)	1.193(3)
C(20)-O(34)	1.339(3)
C(20)-C(21)	1.481(4)
C(22)-O(37)	1.194(3)
C(22)-O(36)	1.339(3)
C(22)-C(23)	1.476(4)
C(24)-O(39)	1.191(3)
C(24)-O(38)	1.351(3)
C(24)-C(25)	1.469(4)
C(26)-O(41)	1.188(4)
C(26)-O(40)	1.340(3)
C(26)-C(27)	1.486(5)

O(28)-C(1)-O(45)	108.0(2)
O(28)-C(1)-C(2)	108.0(2)
O(45)-C(1)-C(2)	109.3(2)
O(29)-C(2)-C(1)	107.6(2)
O(29)-C(2)-C(3)	108.0(2)
C(1)-C(2)-C(3)	111.6(2)
O(31)-C(3)-C(4)	110.0(2)
O(31)-C(3)-C(2)	107.6(2)
C(4)-C(3)-C(2)	111.9(2)
O(33)-C(4)-C(3)	110.5(2)
O(33)-C(4)-C(5)	106.2(2)
C(3)-C(4)-C(5)	106.7(2)
O(45)-C(5)-C(6)	107.1(2)

O(45)-C(5)-C(4)	108.9(2)
C(6)-C(5)-C(4)	115.4(2)
O(44)-C(6)-C(5)	107.5(2)
O(33)-C(7)-O(42)	112.1(2)
O(33)-C(7)-C(8)	107.3(2)
O(42)-C(7)-C(8)	110.5(2)
O(34)-C(8)-C(9)	105.5(2)
O(34)-C(8)-C(7)	111.3(2)
C(9)-C(8)-C(7)	111.8(2)
O(36)-C(9)-C(8)	107.8(2)
O(36)-C(9)-C(10)	107.1(2)
C(8)-C(9)-C(10)	111.3(2)
O(38)-C(10)-C(9)	105.2(2)
O(38)-C(10)-C(11)	109.5(2)
C(9)-C(10)-C(11)	110.5(2)
O(42)-C(11)-C(12)	106.0(2)
O(42)-C(11)-C(10)	109.2(2)
C(12)-C(11)-C(10)	114.0(2)
O(40)-C(12)-C(11)	105.3(2)
O(30)-C(14)-O(29)	123.7(3)
O(30)-C(14)-C(15)	125.4(4)
O(29)-C(14)-C(15)	110.9(4)
O(32)-C(16)-O(31)	122.6(3)
O(32)-C(16)-C(17)	126.5(3)
O(31)-C(16)-C(17)	110.9(3)
O(43)-C(18)-O(44)	122.3(3)
O(43)-C(18)-C(19)	126.3(3)
O(44)-C(18)-C(19)	111.4(3)
O(35)-C(20)-O(34)	122.1(3)
O(35)-C(20)-C(21)	126.5(3)
O(34)-C(20)-C(21)	111.4(2)
O(37)-C(22)-O(36)	123.7(3)
O(37)-C(22)-C(23)	125.8(3)
O(36)-C(22)-C(23)	110.5(2)
O(39)-C(24)-O(38)	123.2(2)
O(39)-C(24)-C(25)	126.4(3)
O(38)-C(24)-C(25)	110.3(2)
O(41)-C(26)-O(40)	123.2(3)
O(41)-C(26)-C(27)	126.0(3)
O(40)-C(26)-C(27)	110.8(3)
C(1)-O(28)-C(13)	113.0(3)
C(14)-O(29)-C(2)	118.9(3)
C(16)-O(31)-C(3)	116.6(2)
C(7)-O(33)-C(4)	116.1(2)
C(20)-O(34)-C(8)	118.0(2)
C(22)-O(36)-C(9)	118.5(2)
C(24)-O(38)-C(10)	118.2(2)
C(26)-O(40)-C(12)	117.3(2)
C(7)-O(42)-C(11)	113.8(2)
C(18)-O(44)-C(6)	114.7(2)
C(1)-O(45)-C(5)	112.1(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for 1. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
C(1)	28(2)	25(2)	23(2)	8(1)	2(1)	2(1)
C(2)	21(2)	21(2)	27(2)	7(1)	3(1)	2(1)
C(3)	14(1)	19(1)	25(2)	4(1)	-1(1)	0(1)
C(4)	20(1)	18(1)	17(1)	2(1)	3(1)	0(1)
C(5)	19(1)	20(1)	22(2)	2(1)	-1(1)	-1(1)
C(6)	16(1)	21(2)	29(2)	-1(1)	0(1)	-1(1)
C(7)	19(1)	14(1)	23(2)	-1(1)	-1(1)	-2(1)
C(8)	15(1)	16(1)	23(2)	-2(1)	-3(1)	4(1)
C(9)	18(1)	20(1)	11(1)	-2(1)	0(1)	-1(1)
C(10)	15(1)	14(1)	21(2)	2(1)	0(1)	-5(1)
C(11)	15(1)	15(1)	21(2)	1(1)	0(1)	-2(1)
C(12)	22(2)	17(1)	23(2)	-2(1)	-1(1)	0(1)
C(13)	44(2)	62(3)	30(2)	9(2)	-18(2)	-5(2)
C(14)	44(2)	38(2)	55(3)	20(2)	4(2)	-5(2)
C(15)	104(4)	39(3)	131(5)	42(3)	24(4)	7(3)
C(16)	24(2)	20(2)	30(2)	1(1)	-1(1)	-3(1)
C(17)	27(2)	40(2)	56(2)	-13(2)	0(2)	-8(2)
C(18)	30(2)	25(2)	19(2)	-3(1)	-4(1)	0(1)
C(19)	41(2)	33(2)	35(2)	-10(2)	-1(2)	5(2)
C(20)	27(2)	14(1)	27(2)	-1(1)	-4(1)	-4(1)
C(21)	30(2)	19(2)	34(2)	-5(1)	-1(1)	2(1)
C(22)	21(1)	10(1)	21(2)	-1(1)	3(1)	3(1)
C(23)	27(2)	28(2)	24(2)	0(1)	6(1)	4(1)
C(24)	21(2)	17(1)	21(2)	1(1)	0(1)	0(1)
C(25)	29(2)	21(2)	40(2)	10(1)	0(1)	-6(1)
C(26)	39(2)	17(2)	26(2)	0(1)	0(1)	2(1)
C(27)	49(2)	19(2)	66(3)	-6(2)	-4(2)	-3(2)
O(28)	36(1)	44(1)	20(1)	9(1)	-6(1)	-6(1)
O(29)	37(1)	22(1)	39(1)	12(1)	2(1)	2(1)
O(30)	55(2)	54(2)	130(3)	39(2)	39(2)	-1(2)
O(31)	15(1)	18(1)	28(1)	0(1)	0(1)	-1(1)
O(32)	26(1)	26(1)	67(2)	-16(1)	5(1)	-1(1)
O(33)	18(1)	21(1)	14(1)	3(1)	0(1)	0(1)
O(34)	18(1)	14(1)	26(1)	-2(1)	-2(1)	1(1)
O(35)	22(1)	18(1)	82(2)	-3(1)	0(1)	-4(1)
O(36)	18(1)	22(1)	16(1)	-2(1)	1(1)	-2(1)
O(37)	17(1)	41(1)	30(1)	-4(1)	-1(1)	0(1)
O(38)	18(1)	14(1)	25(1)	2(1)	-1(1)	-3(1)
O(39)	25(1)	23(1)	39(1)	10(1)	-5(1)	1(1)
O(40)	27(1)	14(1)	31(1)	-3(1)	-3(1)	0(1)
O(41)	36(1)	24(1)	68(2)	1(1)	8(1)	9(1)
O(42)	19(1)	14(1)	24(1)	1(1)	3(1)	1(1)
O(43)	35(1)	24(1)	47(2)	-5(1)	-1(1)	-8(1)
O(44)	21(1)	20(1)	31(1)	-3(1)	0(1)	-1(1)
O(45)	30(1)	23(1)	19(1)	3(1)	-3(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 1.

	x	y	z	U(eq)
H(1)	14418(5)	2101(2)	9074(2)	30
H(2)	9240(5)	2131(2)	9129(2)	28
H(3)	11938(5)	1736(2)	7945(1)	23
H(4)	9324(5)	3470(2)	8152(1)	22
H(5)	14456(5)	3104(2)	8183(1)	24
H(6A)	15059(5)	4698(2)	8479(2)	26
H(6B)	13902(5)	4623(2)	7745(2)	26
H(7)	7883(5)	2815(2)	7023(1)	23
H(8)	8273(5)	3163(2)	5901(1)	22
H(9)	12839(5)	4046(2)	6152(1)	19
H(10)	8475(5)	5061(2)	5837(1)	20
H(11)	10849(5)	4984(2)	7122(1)	20
H(12A)	6736(5)	6039(2)	6692(1)	25
H(12B)	6994(5)	5741(2)	7463(1)	25
H(13A)	15009(25)	3336(4)	10177(10)	68
H(13B)	16181(9)	2314(13)	10086(9)	68
H(13C)	14600(19)	2539(16)	10729(2)	68
H(15A)	9689(62)	-913(6)	9086(8)	137
H(15B)	9366(53)	-779(9)	9872(11)	137
H(15C)	11908(13)	-561(5)	9536(19)	137
H(17A)	6021(6)	-123(7)	7289(10)	61
H(17B)	5089(15)	934(9)	7184(9)	61
H(17C)	5055(14)	468(15)	7910(2)	61
H(19A)	10099(17)	7139(2)	8792(10)	55
H(19B)	9635(23)	6258(12)	9271(4)	55
H(19C)	8415(9)	6289(12)	8546(7)	55
H(21A)	11616(20)	491(9)	5485(5)	41
H(21B)	12053(24)	403(8)	6272(4)	41
H(21C)	13629(8)	1124(2)	5845(10)	41
H(23A)	14834(6)	4003(14)	4019(1)	40
H(23B)	12482(34)	4651(7)	4069(2)	40
H(23C)	12233(31)	3527(9)	4082(2)	40
H(25A)	12294(6)	7775(5)	5448(9)	45
H(25B)	13988(19)	6900(7)	5268(7)	45
H(25C)	13805(22)	7255(11)	6023(3)	45
H(27A)	10201(10)	8729(7)	7529(11)	67
H(27B)	11563(28)	8304(13)	6898(3)	67
H(27C)	12026(22)	7865(7)	7622(10)	67

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A convenient large-scale synthesis of methyl α-maltoside: a simple model for amylose

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A convenient large-scale synthesis of methyl α-maltoside: a simple model for amylose

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Abstract

Methyl 4-*O*-(α-D-glucopyranosyl)-α-D-glucopyranoside (methyl α-maltoside), a model compound for amylose, has been synthesized in four steps and 63% overall yield from relatively inexpensive D-(+)-maltose.

Keywords: Methyl α-maltoside; Amylose model; Stereoselective synthesis

1. Introduction

Methyl 4-*O*-methyl-α-D-glucopyranoside has long been used as a model compound for the key polysaccharide amylose [1] in a variety of studies [2] and whilst it possesses the necessary structural features in the correct stereochemical arrangement, a considerable drawback is that the ether linkage is much more resistant to hydrolysis than the unit linkages in the natural product. A more complex, and consequently a more representative model, should contain at least one glucose-glucose linkage and also be protected at the terminal anomeric position since in the natural compound the majority of glucose units are protected at this position by other glucose units. The simplest compound to meet these criteria is methyl 4-*O*-(α-D-glucopyranosyl)-α-D-glucopyranoside (methyl α-maltoside) **5α** for which four syntheses have appeared hitherto in the literature. Of these, two routes use methyl α-D-glucopyranoside as the starting material for enzymatic transformations performed respectively by *Dextrin glycotransferase* in conjunction with amylopectin [3], and an unidentified pentylase enzyme isolated from *Bacillus macerans* with cyclohexaamylose [4]. An eight-step convergent synthetic route has also been used to construct **5α**, albeit in 31% overall yield (with no yield being given for two individual steps) [5]. Finally, Dick et al. [6] have also reported the synthesis of **5α** by a slightly shorter route based on D-(+)-maltose, but it is marred by repeated acetylation/de-acetylation steps and the necessity for both selective removal of admixed β-anomer by oxidation with chromic acid and large-scale chromatography. Herein we describe a much more efficient and practical route for the large-scale synthesis of **5α** from D-(+)-maltose **1**. This is accomplished in a straightforward manner as shown in Scheme 1 without recourse to the use of either an enzymatic step or the need for column chromatography.

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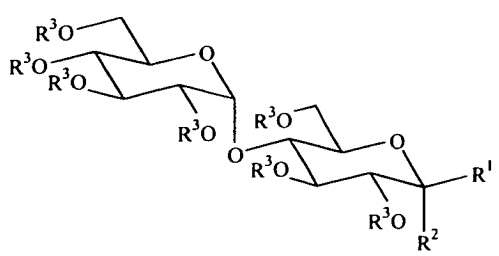

	R^1	R^2	R^3	
1α	H	OH	H	
1β	OH	H	H	i)
2β	OAc	H	Ac	ii)
3α	H	OH	Ac	
3β	OH	H	Ac	iii)
4α	H	OMe	Ac	
4β	OMe	H	Ac	iv)
5α	H	OMe	H	

Scheme 1. Reagents and conditions: (i) 10.6 eq. pyridine/10.6 eq. acetic anhydride/0.02 eq. *N,N*-dimethylaminopyridine/CH_2Cl_2/31 h/0 °C→room temperature; (ii) $NH_{3(sat)}$/MeOH:THF (3:7)/100 min/room temperature; (iii) 1.2 eq. Ag_2O/1.2 eq. MeI/MeCN/60 min/ca. 80 °C: or alternatively, 2.0 eq. Ag_2O/2.0 eq. MeI/MeCN/72 h/room temperature; (iv) 3.5 eq. NaOH/MeOH/10 min/room temperature.

2. Results and Discussion

The first step involving peracetylation of a rigorously dried sample of maltose **1** was achieved by reaction with an excess of freshly distilled acetic anhydride in the presence of *N,N*-dimethylaminopyridine [7]. Next, the resulting β-maltose octaacetate **2β** was subjected to selective anomeric deacetylation under conditions which are equally effective on milligram and hundred gram scale [8]. Thus, **2β** was stirred at low temperature in a mixed solvent (3 parts MeOH:7 parts THF) saturated with ammonia [9]. After ca. 100 min, the resulting anomeric mixture of aldoses **3** was crystallised selectively, or alternatively used without further purification in the subsequent methylation step accomplished [10] via a modification of the traditional Purdie approach. In the absence of light, methyl iodide was added to a rapidly stirred suspension of **3** (either as an anomeric mixture or anomerically pure form) and silver (I) oxide in acetonitrile. Upon heating in a Soveril-joint ampoule for 60 min, an anomeric mixture of **4** (ca. 8:1 α:β (by ^{1}H NMR spectroscopy) was obtained in 81% yield. If on the other hand, the reaction mixture was allowed to stir at ambient temperature in a sealed tube for three days and isolated from light, the α-anomer of **4** was obtained exclusively in 83% yield, presumably as a consequence of the thermodynamic equilibrium in favour of **3α**. In the last step, complete anomeric deprotection of **4α** was achieved quantitatively by stirring in methanol with wet sodium hydroxide to furnish **5α** in 63% overall yield and complete stereochemical integrity. An added benefit of this shorter route was the efficiency of all of the individual steps irrespective of whether the reactions were carried out on a small (ca. 100 mg) or large (ca. 100 g) scale.

3. Experimental

Thin-layer chromatography (TLC) was carried out on silica gel 60 F_{254} plates and visualised by dipping the plate into a solution of concentrated sulfuric acid in ethanol (5:95). ^{1}H- and ^{13}C-NMR spectra were obtained on a Bruker AC-250 spectrometer operating at 250 and 62.9 MHz, respectively. All other physical data including optical rotations which were measured on an Optical Activity AA 1000 polarimeter at 589 nm (the sodium D-line) using a 1 dm cell, unless quoted, were in accord with previously reported data.

Maltose octaacetate (**2β**).—To a rapidly stirring suspension of a rigorously dried sample of **1** (19.10 g, 56 mmol) in dichloromethane (150 mL) and pyridine (47.8 mL, 591 mmol) was added *N,N*-dimethylaminopyridine (0.14, 1.1 mmol) under argon at 0 °C. After 30 min, freshly distilled acetic anhydride (55.8 mL, 591 mmol) was added slowly to the reaction mixture and when TLC (ethyl acetate:cyclohexane 4:1) had indicated the formation of one major fraction and no remaining starting material, it was quenched by addition of hydrochloric acid (2 M, 200 mL). After separation and extraction with dichloromethane (3×25 mL), the combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (200 mL), then saturated aqueous sodium chloride (200 mL) and dried over magnesium sulfate before evaporation in vacuo to give an amorphous colourless solid, $[\alpha]_D^{20}$ + 65°(*c* = 1, ethanol), lit. [11]. +64 °(34.84 g, 92%) of sufficient purity to use without further purification in subsequent steps. ^{1}H NMR ($CDCl_3$): δ_H 5.68 (d, 1H, $J_{1,2}$ 8.0, H-1), 5.30 (d, 1H, $J_{1',2'}$ 4.0, H-1'), 5.28–5.20 (cm, 2H, H-3, H-3'), 5.01 (t, 1H, $J_{3',4'}$, $J_{4',5'}$,10.0, H-4'), 4.91 (dd, 1H, $J_{2,3}$ 9.0, H-2), 4.80 (dd, 1H, $J_{2',3'}$, 10.0, H-2'), 4.37 (dd, 1H, $J_{5,6a}$ 2.0 $J_{5,6b}$ 5.0, H-6a), 4.24–4.13

(cm, 2H, H-6b, H-6a,), 4.03–3.95 (cm, 2H, H-4, H-6b,), 3.90–3.85 (cm, 1H, H-5,), 3.81–3.75 (cm, 1H, H-5), 2.07–1.93 (cm, 8×$COCH_3$), ^{13}C NMR ($CDCl_3$): δ_C 170.3–168.5 (8×$COCH_3$), 95.5, (CH), 91.0, (CH), 75.0 (CH), 72.8 (CH), 72.3 (CH), 70.7, (CH), 69.8 (CH), 69.1 (CH), 68.4 (CH), 67.8 (CH), 62.3 (CH_2), 61.2 (CH_2), 20.8–20.2 (8×$COCH_3$).

Maltose 2,3,6,2′,3′,4′,5′-heptaacetate (**3α** *and* **3β**).—β-Maltose octaacetate **2β**, 20.00 g, 29.5 mmol) was added at −78 °C to a mixed solvent (methanol:tetrahydrofuran 3:7, 450 mL) through which ammonia had been bubbled vigorously over a 25 min period. After stirring for 10 min, the reaction was allowed to warm to room temperature. When TLC (ethyl acetate:cyclohexane 4:1) had indicated the complete consumption of the starting material and the formation of a single, more polar fraction, the solvent and excess ammonia were removed by evaporation in vacuo to yield a pale yellow syrup which solidified on standing to a glass. Although not essential, this glass may be recrystallised slowly from ethanol:water (9:1) to provide **3α** solely, or as an anomeric mixture of **3α** and **3β** from *iso*-propanol to yield an amorphous solid (15.61 g, 82%). α-form ^1H NMR ($CDCl_3$): δ_H 5.52 (dd, 1H, $J_{2,3}$ 9.0, $J_{3,4}$ 10.0, H-3), 5.37 (d, 1H, $J_{1',2'}$, 4.0, H-1′), 5.30 (d, 1H, $J_{1,2}$ 4.0, H-1), 5.22 (t, 1H, $J_{2',3'}$, 9.0, $J_{3',4'}$, 9.0, H-3′), 5.00 (dd, 1H, $J_{4',5'}$, 10.0, H-4′), 4.70 (dd, 2H, $J_{2,3}$ 10.0, H-2, H-2,), 4.43 (dd, 1H, $J_{5,6a}$ 3.0, $J_{6a,6b}$ 13.0, H-6a), 4.26-4.14 (cm, 3H, H-5, H-6a, H-6b), 3.99, (dd, 1H, $J_{5',6a'}$, 3.5, $J_{6a',6b'}$, 12.0, H-6a′), 3.99–3.89 (cm, 2H, H-4, H-5′), 2.08–1.94 (21H, 7×CH_3); ^{13}C NMR ($CDCl_3$): δ_C 170.5–169.3 (7×$COCH_3$), 95.3 (CH), 89.7 (CH), 72.5 (CH), 72.1 (CH), 71.4 (CH), 69.8 (CH), 69.2 (CH), 68.2 (CH), 67.8 (CH), 67.4 (CH), 62.6 (CH_2), 61.2 (CH_2), 20.7–20.3 (7×$COCH_3$). β-form ^1H NMR ($CDCl_3$): δ_H 5.37 (d, 1H, $J_{1',2'}$ 4.0, H-1′), 5.30 (t, 1H, J2,3 9.0, $J_{3,4}$ 9.0, H-3), 5.22 (t, 1H, $J_{2',3'}$ 9.0, $J_{3',4'}$ 9.0, H-3′), 5.00 (dd, 1H, $J_{4',5'}$ 10.0, H-4′), 4.81 (dd, 1H, H-2′), 4.72–4.65 (cm, 2H, H-1, H-2), 4.43 (dd, 1H, $J_{5,6a}$ 3.0, $J_{6a,6b}$ 13.0, H-6a), 4.26–4.14 (cm, 2H, H-6b′, H-6a′), 3.99 (dd, 1H, $J_{5',6a'}$ 3.5, $J_{6a',6b'}$ 12.5, H-6a′), 3.99–3.89 (cm, 2H, H-5′, H-4), 3.75–3.66 (cm, 1H, H-5), 2.08-1.95 (21H, 7×$COCH_3$). ^{13}C NMR ($CDCl_3$): δ_C 170.5–169.3 (7×$COCH_3$), 95.3 (CH), 94.6 (CH), 74.8 (CH), 73.5 (CH), 72.5 (CH), 69.8 (CH), 69.2 (CH), 68.2 (CH), 67.8 (CH), 67.4 (CH), 62.6 (CH_2), 61.2 (CH_2), 20.7–20.3 (7×$COCH_3$).

Methyl α/β-D-*heptaacetyl-maltoside* (**4α** *and* **4β**).—To a Soveril-joint ampoule containing aldose **3** (1.01 g, 1.6 mmol) suspended in acetonitrile (7 mL) was added silver oxide (0.44 g, 1.9 mmol) and the mixture was stirred for 5 min. with the vessel protected from light. After this time, iodomethane (0.15 mL, 1.9 mmol, freshly filtered through a plug of neutral aluminium oxide) was added, the vessel sealed and immersed in an oil bath at ca. 90 °C for 90 min. Upon cooling to room temperature, the reaction mixture was diluted with dichloromethane (20 mL), filtered through a plug of celite and evaporated in vacuo to give a faintly yellow crystalline foam which was recrystallised from ethanol as a colourless amorphous solid (0.86 g, 81%, α : β 8:1 by ^1H NMR spectroscopy). α-form ^1H NMR ($CDCl_3$): δ_H 5.35 (d, 1H, $J_{1,2}$ 4.0, H-1), 5.30–5.11 (cm, 2H, H-3, H-3′), 4.99 (t, 1H, $J_{3',4'}$ 10.0, $J_{4',5'}$ 10.0, H-4′), 4.82 (d, 1H, $J_{1',2'}$ 4.0, H-1′), 4.75 (dd, 1H, $J_{2,3}$ 9.0, H-2), 4.41 (cm, 1H, H-2′), 4.30–4.16 (cm, 3H, H-5, H-6a′, H6b′), 4.01–3.75 (cm, 3H, H-4, H-6a′, H-6b′), 3.66–3.57 (cm, 1H, H-5′), 3.43 (s, 3H, OCH_3), 2.09–1.94 (cm, 21H, 7×$COCH_3$). ^{13}C NMR ($CDCl_3$): δ_C 170.3–169.2 (7×$COCH_3$), 100.9 (CH), 95.3 (CH), 75.2 (CH), 72.5 (CH), 71.9 (2×CH), 69.8 (CH), 69.1 (CH), 68.3 (CH), 67.8 (CH), 62.6 (CH2), 61.3 (CH2), 56.8 (OCH_3), 20.7–20.4 (7×$COCH_3$).

Methyl α-D-*heptaacetyl-maltoside* (**4α**).—To an anomeric mixture of aldose **3** (1.01 g, 1.6 mmol) suspended in acetonitrile (7 mL) in the dark, was added silver oxide (0.77 g, 3.3 mmol) with stirring. After 15 min, iodomethane (0.21 mL, 3.3 mmol, freshly filtered through a plug of neutral aluminium oxide) was added and the mixture left to stir over a 72 h period. Afterwards, the reaction mixture was diluted with dichloromethane (20 mL), filtered through a plug of celite, and evaporated in vacuo to a crystalline foam which was recrystallised from *iso*-propanol to yield **4α** (vide supra) as colourless needles (0.86 g, 83%).

Methyl α-D-*maltoside* (**5α**).—To a rapidly stirred solution of **4α** (4.53 g, 7.0 mmol) in methanol (25 mL) was added freshly ground sodium hydroxide (0.98 g, 24.4 mmol). After 10 min, TLC (ethyl acetate) showed complete consumption of starting material and the presence of only one very polar fraction. The reaction mixture was neutralised by the addition of Dowex MR-3 ion exchange resin, and evaporated in vacuo to a crystalline foam $[\alpha]_D^{20} + 176°$ ($c = 1$, water), lit. + 174° [6] (2.48 g, 100%). 1H NMR (D_2O): δ_H 5.20 (d, 1H, $J_{1,2}$ 4.0, H-1), 4.29 (d, 1H, $J_{1',2'}$ 8.0, H-1′), 4.10–3.22 (cm, 12H, ring protons), 3.46 (s, 3H, OCH_3); ^{13}C NMR (CD_3OD): δ_C 101.4 (CH), 100.1 (CH), 78.5 (CH), 74.8 (CH), 74.0 (CH), 73.6 (CH), 72.7 (CH), 72.0

(CH), 71.3 (CH), 70.0 (CH), 61.8 (CH_2), 61.6 (CH_2), 55.6 (OCH_3).

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