Synthesis of Functionalised Biodegradable Polyesters

By

Anita Haider

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry

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Acknowledgements

I cannot overstate my gratitude to my PhD supervisor, Dr. Charlotte K. Williams, for the opportunity to conduct this research and work within her group. This would not have been possible without her immeasurable inspiration, encouragement and support. I would also like to thank the EPSRC for the funding towards this research and extend my gratitude to Imperial College, London and the University of London.

Thanks to colleagues and staff at Imperial College for their guidance throughout my time at Imperial. Thanks to Dick Sheppard and Pete Haycock for the countless NMR experiments and thanks to the Mass Spectrometry department.

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Finally, and most importantly, my love and admiration goes to my husband, Rob. Thank you for believing in me and for your endless support and patience. I could not have done this without you - thank you. Special thanks to my parents for surmounting all obstacles to ensure that nothing stood in the way of my success. Muito obrigada por tudo - sem vocês aqui nunca chegaria. Thanks to Walid, Katia, Adel and Nara for being there for me. Thanks to all my family, friends as well as the Beck family for their enduring support.

To my grandfather on his 90th birthday.

Publications

The following publication has arisen from the work described in this thesis:

1. Haider, A. F.; Williams, C. K., *J. Polym Sci Part A: Polym Chem.* **2008,** 46, (8), 2891-2896.
2. Haider, A. F.; Williams, C. K., *J. Carb. Chem.* **2007,** 26, (7-9), 411-418.
3. Tang, M.; Haider, A. F.; Minelli, C.; Stevens, M. M.; Williams, C. K., *J. Polym Sci Part A: Polym Chem.* **2008,** 46, (13), 4352-4362.

Declaration

The work performed in this thesis was carried out in The Chemistry Department, Imperial College, London, between October 2004 and September 2007 and is the work of the author unless otherwise stated.

Abstract

This thesis describes the synthesis and characterisation of novel, biodegradable polyesters derived from carbohydrates. These were prepared from hexose and pentose derivatives. Acetyl-protected 1,5-lactones were prepared *via* per-acetylation, bromination, hydrolysis and Swern oxidation in up to 72 % overall yield. These were used to prepare novel aldaric esters *via* a ring-opening reaction with butan-1-ol or 1,4-butanediol in the presence of *p*-TSA.

Aldaric esters were used to prepare highly functionalised polyesters *via* polycondensation with adipoyl chloride, oxalyl chloride and terephthalic chloride with M_n of up to 86,600 gmol^{-1}.

A glucose-derived oligomer was used as a macro-initiator in the ring opening polymerisation (ROP) of *rac*-lactide to form a block-copolymer comprising of 12 to 250 lactide units attached to the oligoester blocks of up to 3 carbohydrate repeat units. The aldaric esters were used as co-initiators in the controlled ROP of $[L,L]$-lactide and *rac*-lactide with M_n of 6,300 gmol^{-1}. The observed rate constant, k_{obs} using mono-functional aldaric esters was half that observed in bi-functional ones (diols) due to transesterification. Hydrolytic degradation of PLA with these carbohydrate-derived moieties indicated that their introduction enhanced degradation.

Outline

Chapter 1 presents a review of background and current research related to this subject. It covers degradable polymers, polymerisation methods and catalytic/initiating systems explored in this research.

Chapter 2 describes the synthesis and characterisation of acetyl- and methyl-protected 1,5-lactones derived from hexose and pentose sugars. These were prepared *via* acetylation, bromination, hydrolysis and oxidation.

Chapter 3 describes the synthesis and characterisation of aldaric esters derived from 1,5-lactones prepared *via* a ring-opening reaction using *para*-toluenesuphonic acid and either 1,4-butanediol or butan-1-ol.

Chapter 4 describes the synthesis and characterisation of highly-functionalised polyesters *via* polycondensation the carbohydrate-derived aldaric esters. It also covers the use of aldaric esters as co-initiators in the ring opening polymerisation of lactide and subsequent hydrolytic degradation of this modified poly(lactide).

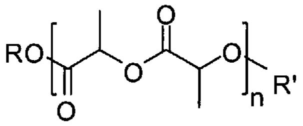
Chapter 5 describes ring opening polymerisation investigations of functionalised 1,5-lactones.

Chapter 6 summarises the major conclusions drawn from this work and future prospects.

Chapter 7 details the experimental procedures used in this research.

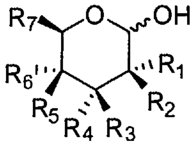
Table of Compounds

General



[1]
poly(lactide)

Starting Materials



[2]

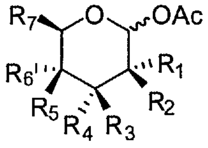
[2a]
R_1 = OH, R_2 = H, R_3 = OH, R_4 = H, R_5 = OH, R_6 = H, R_7 = CH_2OH
D-(+)-Galactopyranose

[2b]
R_1 = H, R_2 = OH, R_3 = OH, R_4 = H, R_5 = H, R_6 = OH, R_7 = CH_2OH
D-(+)-Mannopyranose

[2c]
R_1 = OH, R_2 = H, R_3 = OH, R_4 = H, R_5 = H, R_6 = OH, R_7 = H
D-(+)-Xylopyranose

[2d]
R_1 = OH, R_2 = H, R_3 = OH, R_4 = H, R_5 = OH, R_6 = H, R_7 = H
L-(+)-Arabinoopyranose

Glycosyl Acetates

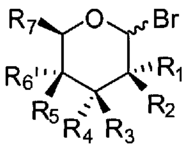
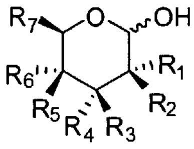


[3]

[3a]
R_1 = OAc, R_2 = H, R_3 = OAc, R_4 = H, R_5 = OAc, R_6 = H, R_7 = CH_2OAc
1,2,3,4,6-Penta-*O*-acetyl-*α*-D-galactopyranose

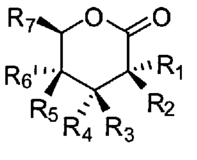
[3b]
R_1 = H, R_2 = OAc, R_3 = OAc, R_4 = H, R_5 = H, R_6 = OAc, R_7 = CH_2OAc
1,2,3,4,6-Penta-*O*-acetyl-*α*-D-mannopyranose

[3c]
R_1 = OAc, R_2 = H, R_3 = OAc, R_4 = H, R_5 = H, R_6 = OAc, R_7 = H
1,2,3,4-Tetra-*O*-acetyl-*α*/*β*-D-xylopyranose

[3d] **R_1 = OAc, R_2 = H, R_3 = OAc, R_4 = H, R_5 = OAc, R_6 = H, R_7 = H** 1,2,3,4-Tetra-*O*-acetyl-*α*/*β*-L-arabinopyranose
Glycosyl Bromides
 **[4]**
[4a] **R_1 = OAc, R_2 = H, R_3 = OAc, R_4 = H, R_5 = OAc, R_6 = H, R_7 = CH_2OAc** 2,3,4,6-Tetra-*O*-acetyl-*α*-D-galactopyranosyl bromide
[4b] **R_1 = H, R_2 = OAc, R_3 = OAc, R_4 = H, R_5 = H, R_6 = OAc, R_7 = CH_2OAc** 2,3,4,6-Tetra-*O*-acetyl-*α*-D-mannopyranosyl bromide
[4c] **R_1 = OAc, R_2 = H, R_3 = OAc, R_4 = H, R_5 = H, R_6 = OAc, R_7 = H** 2,3,4-Tri-*O*-acetyl-*α*-D-xylopyranosyl bromide
[4d] **R_1 = OAc, R_2 = H, R_3 = OAc, R_4 = H, R_5 = OAc, R_6 = H, R_7 = H** 2,3,4-Tri-*O*-acetyl-*α*-L-arabinopyranosyl bromide
Functionalised Pyranoses
 **[5]**
[5a] **R_1 = OAc, R_2 = H, R_3 = OAc, R_4 = H, R_5 = OAc, R_6 = H, R_7 = CH_2OAc** 2,3,4,6-Tetra-*O*-acetyl-*α*-D-galactopyranose
[5b] **R_1 = H, R_2 = OAc, R_3 = OAc, R_4 = H, R_5 = H, R_6 = OAc, R_7 = CH_2OAc** 2,3,4,6-Tetra-*O*-acetyl-*α*-D-mannopyranose
[5c] **R_1 = OAc, R_2 = H, R_3 = OAc, R_4 = H, R_5 = H, R_6 = OAc, R_7 = H** 2,3,4-Tri-*O*-acetyl-*α*/*β*-D-xylopyranose

[5d]
R_1 = OAc, R_2 = H, R_3 = OAc, R_4 = H, R_5 = OAc, R_6 = H, R_7 = H
2,3,4-Tri-*O*-acetyl-*α*/*β*-L-arabinopyranose

1,5-lactones



[6]

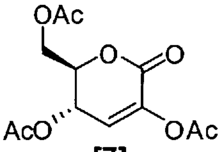
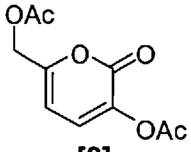
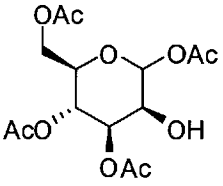
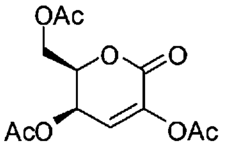
[6a]
R_1 = OAc, R_2 = H, R_3 = OAc, R_4 = H, R_5 = OAc, R_6 = H, R_7 = CH_2OAc
2,3,4,6-Tetra-*O*-acetyl-D-galactono-1,5-lactone

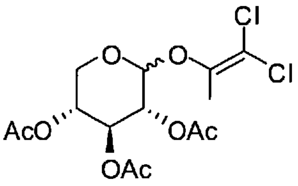
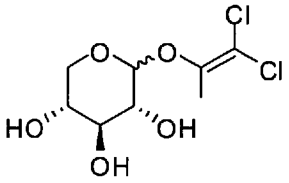
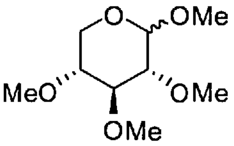
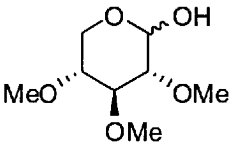
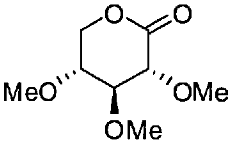
[6b]
R_1 = H, R_2 = OAc, R_3 = OAc, R_4 = H, R_5 = H, R_6 = OAc, R_7 = CH_2OAc
2,3,4,6-Tetra-*O*-acetyl-D-mannono-1,5-lactone

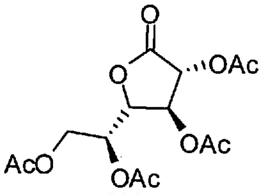
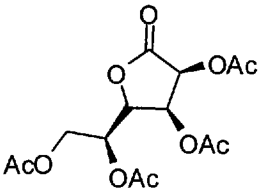
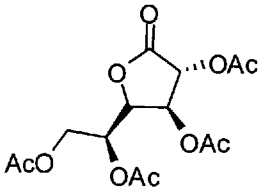
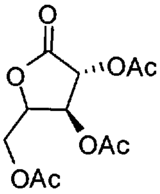
[6c]
R_1 = OAc, R_2 = H, R_3 = OAc, R_4 = H, R_5 = H, R_6 = OAc, R_7 = H
2,3,4-Tri-*O*-acetyl-D-xylono-1,5-lactone

[6d]
R_1 = OAc, R_2 = H, R_3 = OAc, R_4 = H, R_5 = OAc, R_6 = H, R_7 = H
2,3,4-Tri-*O*-acetyl-D-arabinono-1,5-lactone

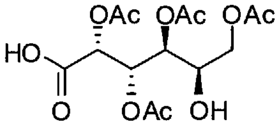
[6e]
R_1 = OAc, R_2 = H, R_3 = OAc, R_4 = H, R_5 = OH, R_6 = OAc, R_7 = CH_2OAc
2,3,4,6-Tetra-*O*-acetyl-D-glucono-1,5-lactone

Decomposition Products
 **[7]** (2*R*,3*S*)-2-(acetoxymethyl)-6-oxo-3,6-dihydro-2*H*-pyran-3,5-diyl diacetate (derived from galactose)
 **[8]** (3-Acetoxy-2-oxo-2H-pyran-6-yl)methyl (derived from galactose)
 **[9]** 1,3,4,6-Tetra-*O*-acetyl-*α*-D-mannopyranose
 **[10]** (2*R*,3*R*)-2-(acetoxymethyl)-6-oxo-3,6-dihydro-2*H*-pyran-3,5-diyl diacetate (derived from mannose and glucose)

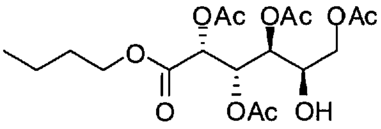
Methyl protected D-(+)-xylopyranose derivatives
 **[11]** 2,3,4-Tri-*O*-acetyl-(2',2'-Dichloro-1'-methyl)ethenyl-D-xylopyranoside
 **[12]** (2',2'-Dichloro-1'-methyl)ethenyl-D-xylopyranoside
 **[13]** 1,2,3,4-Tetra-*O*-methyl-α/β-D-xylopyranose
 **[14]** 2,3,4-Tri-*O*-methyl-α/β-D-xylopyranose
 **[15]** 2,3,4-Tri-*O*-methyl-D-xylono-1,5-lactone

1,4-lactones
 **[16]** 2,3,4,6-Tetra-*O*-acetyl-D-galactono-1,4-lactone
 **[17]** 2,3,4,6-Tetra-*O*-acetyl-D-mannono-1,4-lactone
 **[18]** 2,3,4,6-Tetra-*O*-acetyl-D-glucono-1,4-lactone
 **[19]** 2,3,4-Tri-*O*-acetyl-D-xylono-1,4-lactone

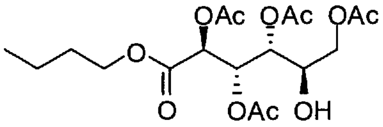
Aldaric esters and Oligomers



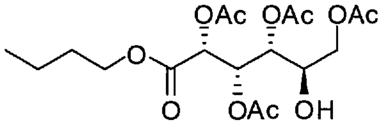
[20]
2,3,4,6-Tetra-*O*-acetyl-D-galactonic acid



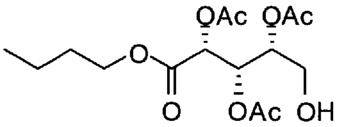
[21]
Butyl 2,3,4,6-tetra-*O*-acetyl-D-galactonate



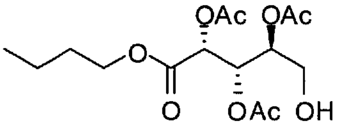
[22]
Butyl 2,3,4,6-tetra-*O*-acetyl-D-mannonate



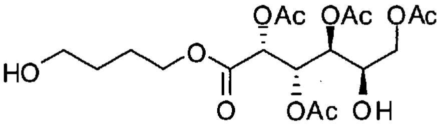
[23]
Butyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate



[24]
Butyl 2,3,4-tri-*O*-acetyl-D-xylononate

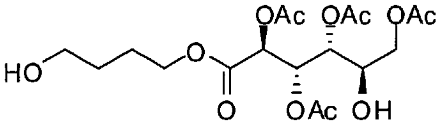


[25]
Butyl 2,3,4,6-tri-*O*-acetyl-L-arabinonate



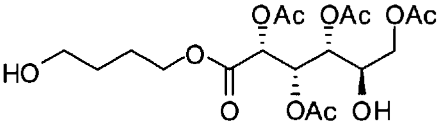
[26]

4-Hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-galactonate



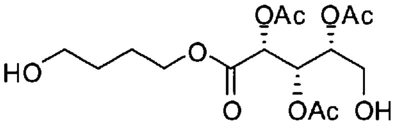
[27]

4-Hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-mannonate



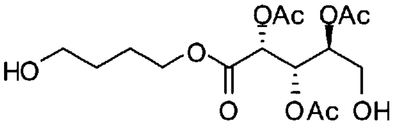
[28]

4-Hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate



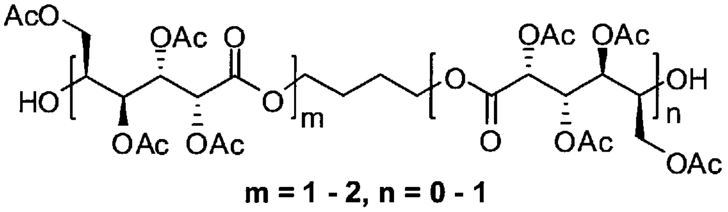
[29]

4-Hydroxybutyl 2,3,4-tri-*O*-acetyl-D-xylononate



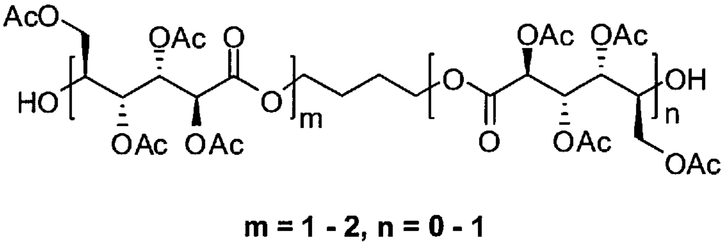
[30]

4-Hydroxybutyl 2,3,4,6-tri-*O*-acetyl-L-arabinonate



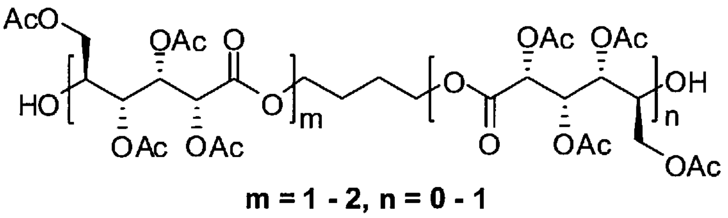
[31]

Oligomer derived from 4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-galactonate [26]



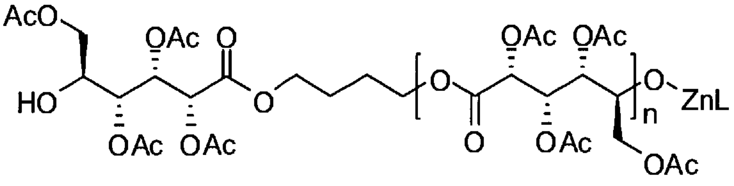
[32]

Oligomer derived from 4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-mannonate **[27]**

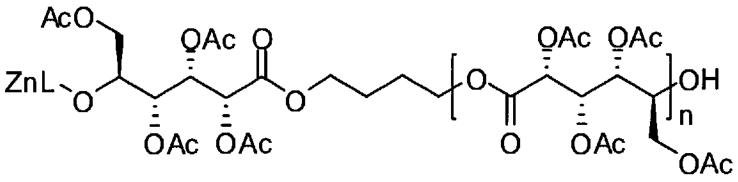


[33]

Oligomer derived from 4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate **[28]**



or

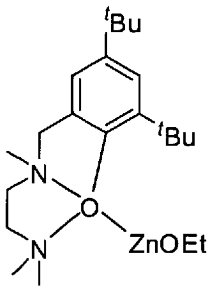


[34]

n = 0 - 2

Initiating species derived from 4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate, **[28]**

Initiator



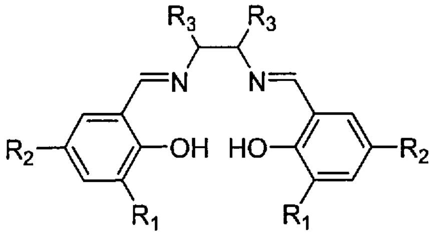
LZnOEt

[35]

Abbreviations used in the text

DSC	differential scanning calorimetry
DXO	1,5-dioxepan-2-one
EA	elemental analysis
eq.	Equivalents
FAB	fast atom bombardment (mass spectrometry)
FDA	Food and Drug Administration
GPC	gel permeation chromatography
H	hour(s)
HMBC	Heteronuclear Multiple Bond Coherence
HMQC	Heteronuclear Multiple Quantum Coherence
M	mol dm^{-3}
MALDI-TOF	matrix assisted laser desorption ionisation-time of flight
m-CPBA	*meta*-chloroperbenzoic acid
Min	Minutes
M_n	number average molecular weight
M_w	weight average molecular weight
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
PCL	poly(ε-caprolactone)
PDI	polydispersity index
PEG	poly(ethylene glycol)
PEI	poly(ethylene isophthalate)
PET	poly(ethylene terephthalate)
PHA	poly(hydroxyalkanoate)
PLA	poly(lactide)
p-TSA	*para*-toluenesulphonic acid
r.t.	room temperature
RI	refractive index
ROH	general alcohol
ROMP	ring-opening metathesis polymerisation
ROP	ring opening polymerisation
s	Seconds

Abbreviations used in the text

Salen ligand	 abbreviation for compounds derived from salicylic aldehyde and 1,2 diamines
$Sn(II)Oct_2$	tin(II)2-ethylhexanoate
T	Time
TLC	thin layer chromatography

CHAPTER 1:

INTRODUCTION

1.1 The need for degradable polymers from renewable resources

The synthesis of renewable, degradable polymers is becoming increasingly attractive largely owing to growing social and political pressure to move towards sustainable materials and to reduce the environmental impact of petrochemical-based polymers.[1]

Petroleum-derived polymers dominate the plastics market. This is a concern as they are non-sustainable and derived from depleting feedstocks. The limited supply of oil also puts substantial economic pressure on petroleum and its derivatives due to the supply-demand balance shifting towards the latter. This is being made evident at present due to current high oil prices.[2] Consequently, the cost of commodity plastics is increasing making those derived from alternative feedstocks more economically viable. Also contributing to high prices of plastics feedstocks are legislative measures imposed by governments to tackle climate change. An example of this is the introduction of carbon-credits. This translates as the cost of producing CO_2 and is ultimately borne by the consumer.

Petroleum-derived plastics are also associated with numerous environmental concerns. The routes to obtaining their raw materials are energy intensive and not to mention highly polluting. Their failure to degrade means that they themselves are sources of pollution. Whilst landfill is a potential solution, this is becoming increasingly challenging due to limited landfill availability. This is particularly pronounced in densely populated areas such as the UK and much of Western Europe. The consumer's market in which we live is dominated by considerable amounts of trivial plastic packaging. Recycling and incineration are alternative methods for the disposal of unwanted plastics. However, these techniques are expensive as well as energy intensive resulting in the production of toxic waste.[3] Governments have also realised that there is reason for concern and are beginning to put pressure on suppliers to shift to degradable and sustainable materials.

Advances in biomedical science also fuel the need for, not only biodegradable polymers, but also biocompatible and bioassimilable materials for medical applications.[4] Biocompatible polymers also require non-toxic synthetic routes and biodegradation products. Biodegradable polymers are widely used as the matrices for tissue engineering such as that of bones. They are also found in surgical fixation materials such as sutures, clips, bone pins and plates.[3] Furthermore, they have been used as the excipent for the controlled release of pharmacologically active ingredients.[4] In fact, this application extends beyond medicine to veterinary and agrochemical disciplines.[3]

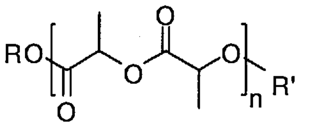
1.2 Types of degradable and biodegradable polymers

Biodegradation can be defined as occurring through the action of biological organisms including enzymes, bacteria or fungi. Nonetheless, and in particular to address environmental concerns, it is important to address abiotic degradation such as hydrolysis.[3] There are several types of biodegradable polymers which can be grouped into the following categories:[3]

a) Polyesters
b) Polyamides
c) Polyurethanes
d) Polyureas
e) Polyethers
f) Polyanhydrides
g) Poly(orthoester)s
h) Polypeptides and proteins
i) Polysaccharides

Polyesters are the most widely explored sustainable and degradable polymers. These include poly(lactide), poly(glycolic acid), poly(hydroxyl alkanoate)s and other poly(lactone)s such as poly(caprolactone) and poly(valerolactone). This research focuses on the synthesis of polyesters derived from lactide and functionalised carbohydrates.

1.2.1 Poly(lactide)



[1]

Poly(lactide)

One of the most comprehensively defined bioderived polymers, in terms of its chemical, physical, biological and degradation properties, is poly(lactide) (PLA) **[1]**.[5] PLA is derived from corn or sugar beet which is fermented to produce lactic acid. Lactic acid is polymerised to yield a low molecular weight oligomer. This is subsequently thermally degraded to produce the cyclic dimer of lactic acid: lactide. Lactide is polymerised by ring opening polymerisation (ROP) to yield PLA. It is produced commercially, by several smaller companies in the EU and Japan and on a larger scale in the USA, for both commodity (e.g. packaging) and medical applications.[4] Nonetheless its hydrophobicity can be a drawback with respect to both environmental and medical applications as this contributes to slow and uncontrolled degradation rates. The lack of chemical functionality along its backbone also hinders its potential as a biomaterial; for example PLA scaffolds do not allow for seeded cell mass and protein recognition.[6]

The aim of this research is to address these drawbacks by increasing the hydrophilicity of PLA and by creating new highly functionalised polyesters. Therefore, the natural choice would be to move from hydrocarbons to carbohydrates as a starting point. Carbohydrates meet two essential criteria; they are highly functionalised and are a renewable resource. Furthermore, carbohydrates are relatively inexpensive with raw sugar currently priced at $200 per tonne.[7] By contrast, the market price for methyl methacrylate, the precursor to an alternative polymer, is about $2,000 per tonne.[8]

1.3 Monomer synthesis

In this research, monomer synthesis plays an important role in order to increase the range of polymers produced and to fine-tune their physical, chemical and biological properties. Generally, when biodegradable polymers are investigated, little attention is given to the monomer synthesis and can thus be a limiting factor. Carbohydrates make suitable candidates as precursors for monomers in the preparation of sustainable biodegradable polymers as they are highly abundant, renewable resources. Not only are carbohydrates naturally abundant, they exist in numerous forms which are manifested in different degrees of substitution and stereochemistry. Thus the preparation of substrates from carbohydrates forms part of an exhaustive area of chemistry. The highly functionalised nature of carbohydrates such as D-(+)-galactopyranose, D-(+)-mannopyranose, D-(+)-glucopyranose, D-(+)-xylopyranose and L-(+)-arabinopyranose often makes simple chemical transformations non-trivial due to competition for selectivity.

1.4 Methods of polymerisation and their catalysts

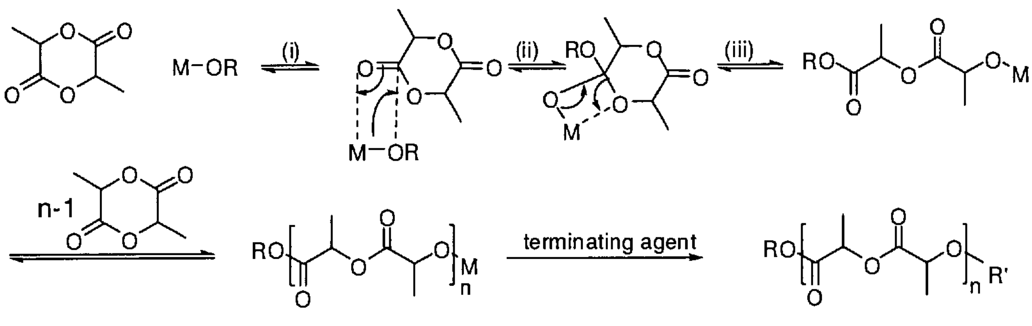
The most widespread route to biodegradable polyesters is *via* ROP of anhydrosulphites, anhydrocarboxylates and lactones/dilactones.[3] The benefits of this method *versus* polycondensation are the potential for controlled polymerisation, the mild conditions which can be used and the shorter reaction times.

1.4.1 Mechanism

There are four mechanisms associated with ROP and are largely determined by the initiator used. These are coordination-insertion, anionic, nucleophilic and cationic polymerisation.

Coordination-insertion

Coordination-insertion is by far the most widely investigated mechanism for ROP of lactones.[9] This three-step mechanism is initiated by a metal centre and is illustrated by Scheme 1.1, using lactide initiated by a metal alkoxide as an example. It should be noted that the metal complex is strictly speaking an initiator for the polymerisation process and not a catalyst, however the terms are both widely used in the field and will both be used interchangeably in this thesis. According to the coordination-insertion mechanism, the metal centre coordinates to the carbonyl group of the lactone ring thus activating it (i). The lactone subsequently inserts into the metal alkoxide bond (ii) and the intermediate undergoes acyl bond cleavage and ring opening to yield a new metal alkoxide species (iii).[4] This process repeats itself until all the monomer is consumed or a terminating agent is introduced.



M =Al, Sn, Y, Zn; R = $(CH_2)_4OH$, $OiPr_3$, $(CH_2)_2OH$; R' depends on the terminating agent

Scheme 1.1 - Coordination-insertion ROP mechanism of lactide

Many metals are known to initiate ROP. Here we will examine key developments and initiators based on tin, aluminium, zinc and yttrium. An exhaustive review of all initiators will not be given, instead the reader is referred to the recent literature.[4,10]

Tin(II)-2-ethylhexanoate ($Sn(II)Oct_2$) in combination with alcohols is the most commonly used ROP initiator on account of its good activity, tolerance of impurities, ease of handling and commercial availabilty.[11] Its success as an initiator in the ROP of lactide is manifested by its use in the industrial production of PLA.[5] Furthermore, it has been approved by the American Food and Drug Administration (FDA) for use as a catalyst.[12] Ever since Leenslag and Pennings first reported the successful synthesis of PLA using $Sn(II)Oct_2$ in 1987,[13] the mechanism of this reaction has been extensively researched and the subject of intense debate.[4] Although $Sn(II)Oct_2$ can be used on its own as an initiator for lactide ROP, it is faster and much better controlled when used in combination with an alcohol (ROH).[4] It is proposed that there are various equilibria present in solution between $Sn(II)Oct_2$, $Sn(II)OR_2$, and $ROSn(II)Oct$, $Sn(II)OR_2$ (Scheme 1.2) and octanoic acid, however the precise role of these species is still debated.[14]

$$Sn(II)Oct_2 + ROH \rightleftharpoons OctSn(II)OR + OctH$$

$$OctSn(II)OR + ROH \rightleftharpoons Sn(II)(OR)_2 + OctH$$

Scheme 1.2 - Equilibrium of $Sn(II)Oct_2$ alcohol species[15]

Penczek and co-workers have dedicated several years to determining the active species in the $Sn(II)Oct_2/ROH$ initiating system.[14-20] They have recently established that the active species is the metal alkoxide and that the metal carboxylate does not play an active role in the ROP of either lactide of ε-caprolactone.[14,15,17] This study was also extended to zinc(II)octoate ($Zn(II)Oct_2$) and aluminium(III)acetate ($Al(III)(Acac)_3$).[15] They used MALDI-TOF mass spectrometry to observe Sn alkoxide end groups in polymer samples which had been carefully prevented from exposure to moisture. The presence of the tin alkoxide propagating groups and the ester end groups at the other end of the polymer chain (from the alcohol co-initiator) led to the conclusion that the true initiator was a Sn alkoxide species, They also isolated $Sn(II)(OBu)_2$ and compared the polymerisation kinetics of $Sn(II)(OBu)_2$ + 2 2-ethylhexanoic acid with the kinetics using $Sn(II)(Oct)_2$ + 2 BuOH. They obtained identical rates of reaction and thus concluded that the active species in the tin octoate/butanol system was the tin butoxide.[16]

In early work, Kricheldorf and co-workers showed that a number of metal alkoxides are active towards ROP of lactones. These include simple alkoxides based on magnesium, aluminium, zinc, titanium and zirconium.[21] Of these, aluminium *iso*-propoxide ($Al(O^iPr)_3$) became a popular initiator owing to its good polymerisation control. For example the polydispersity index (PDI) of PLA obtained using this catalyst was usually less than 1.2. However, such homoleptic alkoxides are well known to form clusters or aggregates which affect the reaction rates[20,22] and complicate the analysis of the reaction mechanism.[4] A common strategy to prevent aggregation is to isolate a single site catalyst. That is, a metal complex of the form LMOR where L is a bulky ancillary ligand, M is the metal, and OR is the initiating group. Many well defined complexes have been examined and shown to be active initiators for lactide polymerisation. A particularly common and useful ancillary ligand is the salen. Pioneering work by Spassky and co-workers established that aluminium salen complexes produced stereoblock PLA from *rac*-lactide.[23] Subsequently, many groups have studied aluminium salen complexes and made some improvements to the stereocontrol. Recently titanium salen complexes (Figure 1.1) have also been shown to be viable initiators for lactide ring opening polymerisation.[24,25]

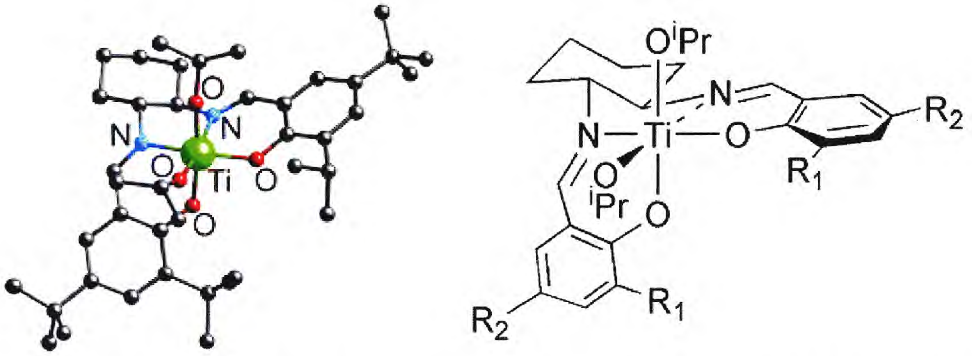


Figure 1.1 - Example of a titanium–salen complex which is a successful initiator for the ROP of *rac*-lactide[25]

Single site initiators have also been developed with zinc and yttrium metal centres. Chisholm[26] prepared trispyrazolylborate zinc alkoxide complexes as the first example of single site zinc catalysts. These species did not prove to be highly active, but showed good polymerisation control.[10] Stereocontrol is important in the synthesis of PLA as it determines the polymer's properties, such as its tensile strength, which are characterised by the degree of crystallinity. Isotactic PLA gives rise to a crystalline polymer whereas syndiotactic PLA yields an amorphous material. A good example of complexes which exhibited much greater polymerisation rates and also excellent stereocontrol are zinc β-diiminate complexes developed by Coates *et al.* Key to these outstanding results are bulky ligands which increase the influence of the stereogenic centre of the last inserted monomer, thus determining the relative sequence of stereocentres in the polymer chain.[27]

In addition to stereocontrol, activity is also an important criterion in the selection of the lactide polymerisation initiator. One of the most active complexes to this end was reported by Williams *et al.*; a zinc-based phenolate (Figure 1.2). Not only did this complex exhibit remarkable activity, but also good molecular weight control with relatively narrow molecular weight distribution. This extended to low catalyst loadings of <0.1 % yielding a number average molecular weight (M_n) as high as 130 kg mol^{-1}.[28]

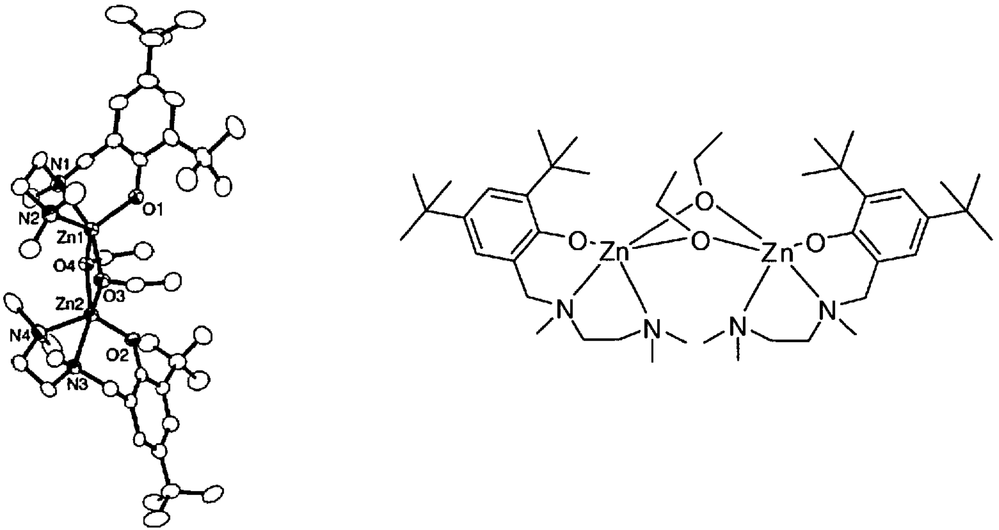


Figure 1.2 - A highly active zinc alkoxide for the ROP of lactide [28]

Yttrium complexes are among some of the most active towards lactide polymerisation. The first yttrium complexes were prepared from the reaction of an alcohol with the yttrium *iso*-propoxide cluster compound. This formed a homoleptic complex which is still one of the most active initiators in addition to good polymerisation control. Recently, our group has prepared a highly active yttrium complex using an ancillary ligand with soft thio donor atoms (Figure 1.3).[22] Unlike the original yttrium complex, it is a heteroleptic one. The advantage of such initiators include the reproducibility of their syntheses as well as enhanced polymerisation rates and improved control.[10]

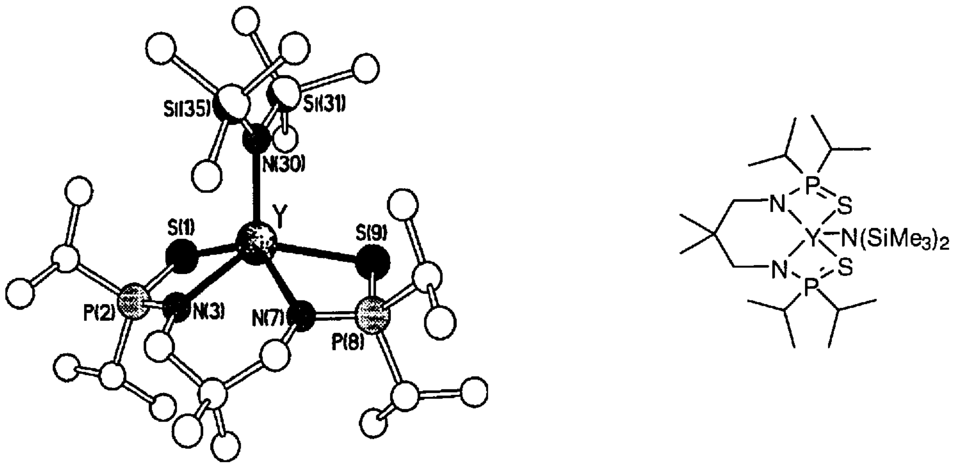


Figure 1.3 - A highly active bis(thiophosphinicamido)yttrium complex for the ROP of lactide[22]

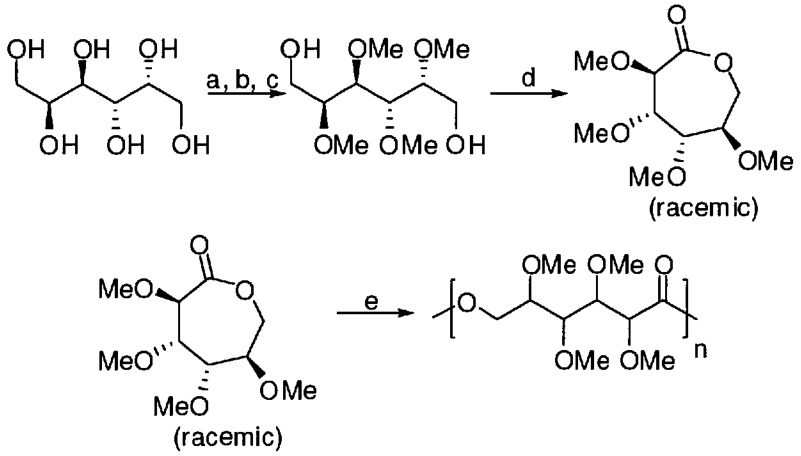
1.4.2 Reaction conditions

Lactones are normally polymerised in the bulk or in a solvent such as THF, methylene chloride or toluene.[11,19,28] Bulk polymerisation is carried out at temperatures ranging from 80 to 175 °C, depending on the melting temperature of the monomer.[29] Temperatures for ROP in solution are kept as low as possible in order to maximise the free-energy of the reaction. These are generally carried out between, 0 °C and 25 °C.[20,23,28,30] The use of low temperatures is often limited by the poor solubility of the initiators, monomers and/or resulting polymers. Therefore temperatures of up to 70 °C are occasionally necessary.[20] Higher temperatures are also avoided to minimise intermolecular and intramolecular transesterification side reactions.[11,31]

1.4.3 Carbohydrate-derived biodegradable polymers

Guan *et al.* have shown that highly functionalised aliphatic polyesters can be successfully prepared by both ROP and polycondensation methods. They have recently reported the synthesis of methyl ether substituted polyesters derived from D-dulcitol .[32-34]

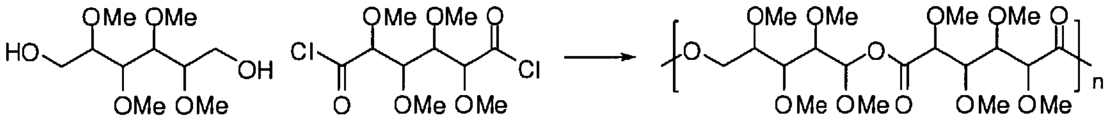
The controlled ROP of a methyl protected ε-caprolactone was initiated by yttrium(III)isopropoxide as shown in Scheme 1.3. This efficient synthesis yielded degradable protein-resistant polymers with M_n of up to 40,000 gmol^{-1}. The narrow PDIs (1.1 - 1.2) as well as the linear dependence of Ln{([LA]$_0$ - [LA]$_{eq}$)/([LA]$_t$ - [LA]$_{eq}$)} with time and the linear correlation between M_n and monomer conversion indicated good polymerisation control. However, the most significant limitation is the monomer synthesis. It requires a series of protection and deprotection steps followed by a ring closing reaction using the epimerisation catalyst, Shvo's catalyst (Scheme 1.3). In summary, the monomer synthesis is low yielding (27 %) and with poor atom economy.[32,33]



a) TrCl, pyridine, reflux, 14 h (78 %); b) MeI, NaOH, rt, 14 h (89 %); c) p-TSA, MeOH, CH_2Cl_2, r.t., 14 h (75 %); d) Shvo's catalyst, Na_2CO_3, $CHCl_3$, 100 °C, 40 h, (60 %); e) $Y(O^iPr)_3$, toluene, r.t., 12 h, (85 %).

Scheme 1.3 - Synthesis and ROP of a methyl protected ε-caprolactone initiated by yttrium(III)isopropoxide[32]

Guan *et al.* have also reported the synthesis of a closely related polymer *via* the polycondensation of an activated, protected aldaric chloride with a protected alditol (Scheme 1.4). The resulting polymers are promising materials as degradable alternatives to PEG with M_n of 29,000 gmol^{-1} and a PDI of 1.5. However, as with the ε-caprolactone-derived polymer, this synthetic methodology is also accompanied by low overall monomer yields (20 to 30 %) requiring 6 synthetic steps.[34]



Scheme 1.4 - Synthesis of permethoxy polyesters[34]

Galbis *et al.* have reported the synthesis and characterisation of aromatic homo- and copolyesters based on L-arabinitol and xylitol. Thus they produced bioderived materials related to poly(ethylene terephthalate) (PET) and poly(ethylene isophthalate) (PEI).[35] These polymers were obtained by a polycondensation reaction of 2,3,4-tri-*O*-methyl-L-arabinitol or 2,3,4-tri-*O*-methyl-xylitol, or their mixtures, with ethylene glycol and with either terephthaloyl chloride or isophthaloyl chloride.

In order to address the requirements of biomedical science, carbohydrate-derived compounds have also been used as grafts on PET. Most striking is the use of the Nobel-prize winning chemistry;[36] ring-opening metathesis polymerisation (ROMP) using Grubbs catalyst. Kiessling *et al.* have reported the ROMP of carbohydrate-substituted bridged cyclohexenes to yield polymers with high selectin activity.[37] Whilst these polymers are successful in the area of biological activity, they are not biodegradable and thus their applications are limited. Similarly, carbohydrate-grafting has also been reported *via* aminolysis[38] as well as using UV-reactive carbohydrates.[39]

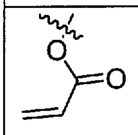
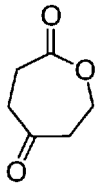
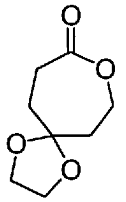
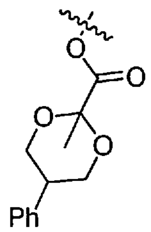
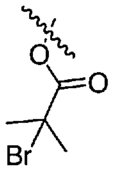
Finally, Minami *et al.* have reported in a patent the ROP of 2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone **[6e]** using $Al(O^iPr)_3$ and $Sn(II)Oct_2$ with seemingly successful results. However, experimental details and characterisation is limited.[40]

1.4.4 Functionalised ε-caprolactones

Functionalised aliphatic polyesters have also been prepared by ring opening polymerisation of ε-caprolactone substituted at the γ- or α-position by a variety functional groups.[11] Generally, the monomers were prepared from the corresponding cyclohexanone which is treated with *meta*-chloroperbenzoic acid (*m*-CPBA) to produce the substituted ε-caprolactone *via* Baeyer-Villiger oxidation.[30,41-45] Homopolymerisation of these monomers was normally carried out at elevated temperatures in the bulk, in the presence of $Sn(II)Oct_2$ and an alcohol or between 0 - 25 °C with $Al(O^iPr)_3$ in toluene. The resulting polymers exhibited reasonable molecular weights with narrow PDIs (Table 1.1).

One of the major drawbacks of these functionalised poly(ε-caprolactone)s is the limited number of functional groups present per repeat unit. A high degree of functionality is favourable for biomedical applications to encourage cell-binding. Moreover, functionalised poly(ε-caprolactone)s are not self-sustaining as the starting materials are not derived from renewable resources.

Table 1.1 - Functionalised poly(ε-caprolactone)s

R/monomer =	i	Functional group description and polymer characteristics	Initiator(s)
	γ	Acrylate[42] Mw's of up to 20,500 gmol^{-1} achieved with narrow PDI (1.22)	$Al(O^iPr)_3$
	γ	Ketone[41] PDI of *ca.* 1.7	BnCH(OH)Me-Sn(II)Oct$_2$
	γ	Ketal[41]	
OBn	γ	Protected Alcohol[30] Mw from 5,000 to 15,000 and PDI's of 1.20 to 1.35	BnOC(O)CMe(CH$_2$OH)$_2$-Sn(II)Oct$_2$ or $Al(O^iPr)_3$
	γ	Protected carboxylic acid[30] Mw from 5,000 to 15,000 and PDI's of 1.20 to 1.35	BnOC(O)CMe(CH$_2$OH)$_2$-Sn(II)Oct$_2$ or $Al(O^iPr)_3$
Br	γ	Halogen[46] that than be subjected to subsequent modification. Mw of up to 15,600 with PDI's from 1.15 to 1.35	$Al(O^iPr)_3$
	γ	Pendant-activated alkyl bromide for a combination of ROP and ATRP graft copolymers[45]	$Al(O^iPr)_3$
Cl	α	Halogen that can be subsequently functionalized to hydroxyl, carboxylic acid and epoxide by atom transfer radical polymerisation.[43]	

^{i}*Substituent position.*

1.4.5 Modifying PLA

A common approach to addressing the limitations of PLA is by modifying it rather than using alternatives. This can be achieved by chemical modification or by blending.

Copolymerisation

Lactide copolymerisation is the most common form of chemically modifying PLA and has received much attention with a wide range of co-monomers and especially with ε-caprolactone.[33,38,51-57] Aluminium alkoxides[47,48] and Sn(II)Oct$_2$[49,50] have widespread use as initiators for this purpose. Whilst copolymerisation of lactide with ε-caprolactone *per se* does not address its poor hydrophilicity, ε-caprolactone can readily be functionalised at the α or γ positions.[30,41-45,47,51] This in turn may serve to begin to overcome the hydrophobicity of PLA. This was taken a step further by Albertsson *et al.* where 1,5-dioxepan-2-one (DXO) was used to tailor the hydrophilicity of the PLA copolymer by changing the relative ratios of co-monomers.[50] Nonetheless, the most successful method of enhancing hydrophilicity in PLA is by the introduction of poly(ethylene glycol) (PEG) which serves to bring about continuous drug release; a property which is not inherent to the PLA homopolymer.[52] One of the most striking advantages of PEG is its biocompatibility and hydrophilicity.[5] However, PEG is not susceptible to hydrolytic degradation.

Amass and co-workers have elegantly addressed the limitations of controlled drug release intrinsic to PLA *via* the synthesis of linear and star-shaped PEG-block-PLA copolymers.[52,53] Their research not only served to increase drug release rates as well as to prolong them,[52,53] but also to increase the degradation rate of the biomaterial by using star poly(ε-caprolactone)-block-poly(ethylene glycol) initiators.[52] In addition to this, they also addressed the challenge of using biologically safer initiators based on potassium rather than the traditional tin compounds.[52,53]

Naturally occurring and occasionally, modified carbohydrates have also been used as initiators in lactide polymerisation.[54-59] The introduction of carbohydrate moieties was found to affect the glass transition temperature[54,56] as well as enhance the hydrophilicity of the PLA copolymer.[57,58] The presence of sugar units introduced important biochemical properties critical for biomedical applications as specific recognition of lectin proteins with the sugar molecules was observed. [54,55,57]

Blending

Blending polymers is also an attractive method of fine-tuning a material's properties whilst reducing its overall cost.[3] Poly(hydroxyalkanoate)s (PHAs) are natural polymers produced in plant cells but that can also be synthesised either chemically or biochemically.[3] Several researchers have observed promising results on blending PHA with PLA.[3] They found that these blends are miscible and degrade by enzymatic as well as non-enzymatic hydrolysis, erosion and degradation.

PLA blends have been reported with numerous other co-monomers in order to enhance biological, physical and mechanical properties of the resulting polymers. As with copolymerisation, the most common blends are with PCL[60] and PEG.[61,62] Where PCL blends were used, PLA was blended with the copolymer, poly(lactide-co-ε-caprolactone) (PLA-PCL) to further fine-tune the copolymer's properties where synthetic restrictions arise. PLA has also been blended with co-polymers derived from terephthalates,[38,39,61,63] vinyl alcohol[64] as well as with polyurethane.[65] Wan and co-workers have also shown that PLA can be blended with the carbohydrate, chitosan[66] which created a porous material with greater tensile strength than chitosan alone.

1.5 Conclusion

From analysis of literature precedent and our current environment, it is evident that although significant progress has been made in the area of synthesis of biomaterials and degradable polymers, there is still much to be explored. We have also found that there is a significant gap in research in carbohydrate-derived degradable material yet the little literature precedent available indicates that there is a great deal of potential in this area. Hence this research seeks to address this gap by using high yielding polymerisation methods and catalysts in order to optimise the use of carbohydrates in biocompatible materials and degradable polymers. In order to achieve this, it was necessary to explore numerous areas of chemistry; from organic synthesis to catalyst preparation and not to mention polymer synthesis and characterisation.

1.6 References

1. Clover, C., [Gordon] Brown urges ban on plastic bags. *Telegraph.co.uk* **20/11/2007, 2007.**

2. www.nymex.com

3. Amass, W.; Amass, A.; Tighe, B., *Polym. Int.* **1998,** 47, (2), 89-144.

4. Dechy-Cabaret, O.; Martin-Vaca, B.; Bourissou, D., *Chem. Rev.* **2004,** 104, (12), 6147-6176.

5. Uhrich, K. E.; Cannizzaro, S. M.; Langer, R. S.; Shakesheff, K. M., *Chem. Rev.* **1999,** 99, (11), 3181-3198.

6. Wan, Y. T., Chifeng; Yang, Jian; Bei, Jianzhong; Wang, Shenguo. , *Biomaterials* **2006,** 27, (13), 2699-2704.

7. Bloomberg Market Data - Commodities' futures prices. http://www.bloomberg.com/markets/commodities/cfutures.html

8. ICIS chemical pricing. http://www.icis.com/v2/chemicals/9076048/methyl-methacrylate/pricing.html

9. Dittrich, W.; Schulz, R. C., *Angew. Makromol. Chem.* **1971,** 15, 109-&.

10. Hodgson, L. M.; Williams, C. K.; Platel, R. H., *Polymer Reviews* **2008,** 48, 11-63.

11. Albertsson, A. C.; Varma, I. K., *Biomacromolecules* **2003,** 4, (6), 1466-1486.

12. Code of Federal Regulations. In 2005; Vol. 3; 21CFR175.300.

13. Leenslag, J. W.; Pennings, A. J., *Makromol. Chem.* **1987,** 188, (8), 1809-1814.

14. Kowalski, A.; Duda, A.; Penczek, S., *Macromolecules* **2000,** 33, (3), 689-695.

15. Kowalski, A.; Libiszowski, J.; Majerska, K.; Duda, A.; Penczek, S., *Polymer* **2007,** 48, (14), 3952-3960.

16. Kowalski, A.; Libiszowski, J.; Duda, A.; Penczek, S., *Macromolecules* **2000,** 33, (6), 1964-1971; Kowalski, A.; Duda, A.; Penczek, S., *Macromol. Rapid Commun.* **1998,** 19, (11), 567-572.

17. Kowalski, A.; Duda, A.; Penczek, S., *Macromolecules* **2000,** 33, (20), 7359-7370; Kowalski, A.; Libiszowski, J.; Biela, T.; Cypryk, M.; Duda, A.; Penczek, S., *Macromolecules* **2005,** 38, (20), 8170-8176; Penczek, S.; Duda, A.; Kowalski, A.; Libiszowski, J.; Majerska, K.; Biela, T., *Macromol. Symp.* **2000,** 157, 61-70.

18. Libiszowski, J.; Kowalski, A.; Duda, A.; Penczek, S., *Macromol. Chem. Phys.* **2002,** 203, (10/11), 1694-1701; Duda, A.; Penczek, S.; Kowalski, A.; Libiszowski, J., *Macromol. Symp.* **2000,** 153, 41-53.

19. Duda, A.; Kowalski, A.; Libiszowski, J.; Penczek, S., *Macromol. Symp.* **2005,** 224, 71-83.

20. Duda, A.; Penczek, S., *Macromolecules* **1995,** 28, (18), 5981-5992.

21. Kricheldorf, H. R.; Berl, M.; Scharnagl, N., *Macromolecules* **1988,** 21, (2), 286-293.

22. Hodgson, L. M.; White, A. J. P.; Williams, C. K., *J. Polym Sci Part A: Polym Chem* **2006,** 44, (22), 6646-6651.

23. Spassky, N.; Simic, V.; Montaudo, M. S.; Hubert-Pfalzgraf, L. G., *Macromol. Chem. Phys.* **2000,** 201, (17), 2432-2440.

24. Wu, J.-C.; Huang, B.-H.; Hsueh, M.-L.; Lai, S.-L.; Lin, C.-C., *Polymer* **2005,** 46, (23), 9784-9792; Chisholm, M. H.; Gallucci, J. C.; Quisenberry, K. T.; Zhou, Z., *Inorg. Chem.* **2008,** 47, (7), 2613-2624; Nobuyoshi Nomura, R. I. Y. Y. T. K., *Chem. Eur. J.* **2007,** 13, (16), 4433-4451; Cameron, P. A.; Jhurry, D.; Gibson, V. C.; White, A. J. P.; Williams, D. J.; Williams, S., *Macromol. Rapid Commun.* **1999,** 20, (12), 616-618; Atkinson, R. C. J. G., Kathryn; Gibson, Vernon C.; Long, Nicholas J.; Marshall, Edward L.; West, Lara J., *Organometallics* **2007,** 26, (2), 316-320; Gregson, C. K. A.

G., Vernon C.; Long, Nicholas J.; Marshall, Edward L.; Oxford, Phillip J.; White, Andrew J. P. , *J. Am. Chem. Soc* **2006,** 128, (23), 7410-7411.

25. Gregson, C. K. A.; Blackmore, I. J.; Gibson, V. C.; Long, N. J.; Marshall, E. L.; White, A. J. P., *Dalt. Trans.* **2006,** 25, 3134-3140.

26. Chisholm, M. H.; Eilerts, N. W., *Chem. Comm.* **1996**, (7), 853-854.

27. Chamberlain, B. M.; Cheng, M.; Moore, D. R.; Ovitt, T. M.; Lobkovsky, E. B.; Coates, G. W., *J. Am. Chem. Soc* **2001,** 123, (14), 3229-3238.

28. Williams, C. K.; Breyfogle, L. E.; Choi, S. K.; Nam, W.; Young, V. G.; Hillmyer, M. A.; Tolman, W. B., *J. Am. Chem. Soc.* **2003,** 125, 11350-11359.

29. Storey, R. F.; Sherman, J. W., *Macromolecules* **2002,** 35, 1504-1512; Trimaille, T.; Moller, M.; Gurny, R., *J. Polym Sci Part A: Polym Chem* **2004,** 42, (17), 4379-4391; Huang, M.-H.; Li, S.; Vert, M., *Polymer* **2004,** 45, (26), 8675-8681.

30. Trollsas, M.; Lee, V. Y.; Mecerreyes, D.; Lowenhielm, P.; Moller, M.; Miller, R. D.; Hedrick, J. L., *Macromolecules* **2000,** 33, (13), 4619-4627.

31. Dubois, P.; Jacobs, C.; Jerome, R.; Teyssie, P., *Macromolecules* **1991,** 24, (9), 2266-2270.

32. Urakami, H.; Guan, Z., *Biomacromolecules* **2008,** 9, (2), 592-597.

33. Metzke, M.; Guan, Z., *Biomacromolecules* **2008,** 9, (1), 208-215.

34. Metzke, M.; Bai, J. Z.; Guan, Z., *J. Am. Chem. Soc* **2003,** 125, (26), 7760-7761.

35. Zamora, F.; Hakkou, K.; Muñoz-Guerra, S.; Galbis, J. A., *Polymer Degradation and Stability* **2006,** 91, (11), 2654-2659; Zamora, F.; Hakkou, K.; Alla, A.; Rivas, M.; Roffé, I.; Mancera, M.; Muñoz-Guerra, S.; Galbis, J. A., *J. Polym Sci Part A: Polym Chem* **2005,** 43, (19), 4570-4577; Zamora, F.; Hakkou, K.; Alla, A.; Espartero, J. L.; Muñoz-Guerra, S.; Galbis, J. A., *J. Polym Sci Part A: Polym Chem* **2005,** 43, (24), 6394-6410.

36. The Nobel Prize in Chemistry 2005 for the development of the metathesis method in organic synthesis. http://nobelprize.org/nobel_prizes/chemistry/laureates/2005/

37. Mortell, K. H.; Weatherman, R. V.; Kiessling, L. L., *J. Am. Chem. Soc* **1996,** 118, (9), 2297-2298; Owen, R. M.; Gestwicki, J. E.; Young, T.; Kiessling, L. L., *Org. Lett.* **2002,** 4, (14), 2293-2296; Manning, D. D.; Strong, L. E.; Hu, X.; Beck, P. J.; Kiessling, L. L., *Tetrahedron* **1997,** 53, (35), 11937-11952.

38. Bech, L.; Meylheuc, T.; Lepoittevin, B.; Roger, P., *J. Polym Sci Part A: Polym Chem* **2007,** 45, (11), 2172-2183.

39. Renaudie, L.; LeNarvor, C.; Lepleux, E.; Roger, P., *Biomacromolecules* **2007,** 8, (2), 679-685.

40. Minami, M.; Shinya, K. Eur Patent 2001-128072, 20011126, 1211274, 2002.

41. Latere, J. P.; Lecomte, P.; Dubois, P.; Jerome, R., *Macromolecules* **2002,** 35, (21), 7857-7859.

42. Mecerreyes, D.; Humes, J.; Miller, R. D.; Hedrick, J. L.; Detrembleur, C.; Lecomte, P.; Jérôme, R.; Roman, J. S., *Macromol. Rapid. Commun.* **2000,** 21, (11), 779-784.

43. Riva, R.; Lenoir, S.; Jerome, R.; Lecomte, P., *Polymer* **2005,** 46, (19), 8511-8518.

44. Detrembleur, C.; Mazza, M.; Lou, X.; Halleux, O.; Lecomte, P.; Mecerreyes, D.; Hedrick, J. L.; Jerome, R., *Macromolecules* **2000,** 33, (21), 7751-7760; Tian, D.; Dubois, P.; Grandfils, C.; Jerome, R., *Macromolecules* **1997,** 30, (3), 406-409.

45. Mecerreyes, D.; Atthoff, B.; Boduch, K. A.; Trollsas, M.; Hedrick, J. L., *Macromolecules* **1999,** 32, (16), 5175-5182.

46. Detrembleur, C. M., M.; Halleux, O.; Lecomte, P.; Mecerreyes, D.; Hedrick, J. L.; Jerome, R., *Macromolecules* **2000,** 33, (1), 14-18.

47. Jacobs, C.; Dubois, P.; Jerome, R.; Teyssie, P., *Macromolecules* **1991,** 24, (11), 3027-3034.

48. Tian, D.; Dubois, P.; Jerome, R., *Macromolecules* **1997,** 30, (9), 2575-2581.

49. Veld, P.; Velner, E. M.; VanDeWitte, P.; Hamhuis, J.; Dijkstra, P. J.; Feijen, J., *J. Polym Sci Part A: Polym Chem* **1997,** 35, (2), 219-226; Zhang, X.; MacDonald, D. A.; Goosen, M. F. A.; McAuley, K. B. J., *J. Polym Sci Part A: Polym Chem* **2000,** 35, (2); Barakat, I.; Dubois, P.; Grandfils, C.; Jerome, R., *J. Polym Sci Part A: Polym Chem* **2001,** 39, (2), 294-306.

50. Ryner, M.; Albertsson, A. C., *Biomacromolecules* **2002,** 3, (3), 601-608.

51. Niamsa, N.; Baimark, Y., *J. App. Polym. Sci.* **2007,** 106, (5), 3315-3320.

52. Lemmouchi, Y.; Perry, M. C.; Amass, A. J.; Chakraborty, K.; Schacht, E., *J. Polym Sci Part A: Polym Chem* **2007,** 45, (17), 3966-3974.

53. Lemmouchi, Y.; Perry, M. C.; Amass, A. J.; Chakraborty, K.; Schacht, E., *J. Polym Sci Part A: Polym Chem* **2007,** 45, (17), 3975-3985; Lemmouchi, Y.; Perry, M. C.; Amass, A. J.; Chakraborty, K.; Schué, F., *J. Polym Sci Part A: Polym Chem* **2007,** 45, (11), 2235-2245.

54. Kumar, R.; Gao, W.; Gross, R. A., *Macromolecules* **2002,** 35, (18), 6835-6844.

55. Nagasaki, Y.; Yasugi, K.; Yamamoto, Y.; Harada, A.; Kataoka, K., *Biomacromolecules* **2001,** 2, (4), 1067-1070; Yasugi, K.; Nakamura, T.; Nagasaki, Y.; Kato, M.; Kataoka, K., *Macromolecules* **1999,** 32, (24), 8024-8032.

56. Marcincinova-Benabdillah, K.; Boustta, M.; Coudane, J.; Vert, M., *Biomacromolecules* **2001,** 2, (4), 1279-1284.

57. Lu, C. H.; Shi, Q.; Chen, X. S.; Lu, T. C.; Xie, Z. G.; Hu, X. L.; Ma, J.; Jing, X. B., *J. Polym Sci Part A: Polym Chem* **2007,** 45, (15), 3204-3217; Ouchi, T.; Kontani, T.; Aoki, R.; Saito, T.; Ohya, Y., *J. Polym Sci Part A: Polym Chem* **2006,** 44, (21), 6402-6409.

58. Satoh, T.; Tamaki, M.; Kitajyo, Y.; Maeda, T.; Ishihara, H.; Imai, T.; Kaga, H.; Kakuchi, T., *J. Polym Sci Part A: Polym Chem* **2006,** 44, (1), 406-413; Ouchi, T.; Kontani, T.; Saito, T.; Ohya, Y., *J. Biomater. Sci. Polym. Ed.* **2005,** 16, (8), 1035-1045.

59. Hao, Q. H.; Li, F. X.; Li, Q. B.; Li, Y.; Jia, L.; Yang, J.; Fang, Q.; Cao, A. M., *Biomacromolecules* **2005,** 6, (4), 2236-2247; Arvanitoyannis, I.; Nakayama, A.; Psomiadou, E.; Kawasaki, N.; Yamamoto, N., *Polymer* **1996,** 37, (4), 651-660; Mahapatro, A.; Kumar, A.; Gross, R. A., *Biomacromolecules* **2004,** 5, (1), 62-68.

60. Maglio, G.; Malinconico, M.; Migliozzi, A.; Groeninckx, G., *Macromol. Chem. Phys.* **2004,** 205, (7), 946-950; Tsuji, H.; Yamada, T.; Suzuki, M.; Itsuno, S., *Polym. Int.* **2003,** 52, (2), 269-275; Tsuji, H.; Yamada, T., *J. Appl. Polym. Sci.* **2003,** 87, (3), 412-419.

61. Chen, Y. W.; Zhu, X. J.; Tan, L. C.; Su, J. Y., *J. App. Polym. Sci.* **2008,** 108, (4), 2171-2179.

62. Gaikwad, A. N.; Wood, E. R.; Ngai, T.; Lodge, T. P., *Macromolecules* **2008,** 41, (7), 2502-2508; Hu, Y.; Hu, Y. S.; Topolkaraev, V.; Hiltner, A.; Baer, E., *Polymer* **2003,** 44, (19), 5711-5720; Zhang, L. L.; Deng, X. M.; Zhao, S. J.; Huang, Z. T., *J. Appl. Polym. Sci.* **1997,** 65, (10), 1849-1856.

63. Liu, T. Y.; Lin, W. C.; Yang, M. C.; Chen, S. Y., *Polymer* **2005,** 46, (26), 12586-12594.

64. Tsuji, H.; Muramatsu, H., *Polym. Degrad. Stabil.* **2001,** 71, (3), 403-413; Shuai, X.; He, Y.; Asakawa, N.; Inoue, Y., *J. Appl. Polym. Sci.* **2001,** 81, (3), 762-772.

65. Hong, Y.; Fujimoto, K.; Hashizume, R.; Guan, J. J.; Stankus, J. J.; Tobita, K.; Wagner, W. R., *Biomacromolecules* **2008,** 9, (4), 1200-1207.

66. Wu, H.; Wan, Y.; Cao, X. Y.; Wu, Q., *Mater. Lett.* **2008,** 62, 330-334; Wan, Y.; Wu, Q.; Wang, S.; Zhang, S. M.; Hu, Z. L., *Macromol. Mater. Eng.* **2007,** 292, (5), 598-607.

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CHAPTER 2:

CARBOHYDRATE-DERIVED 1,5-LACTONES

2.1 Introduction

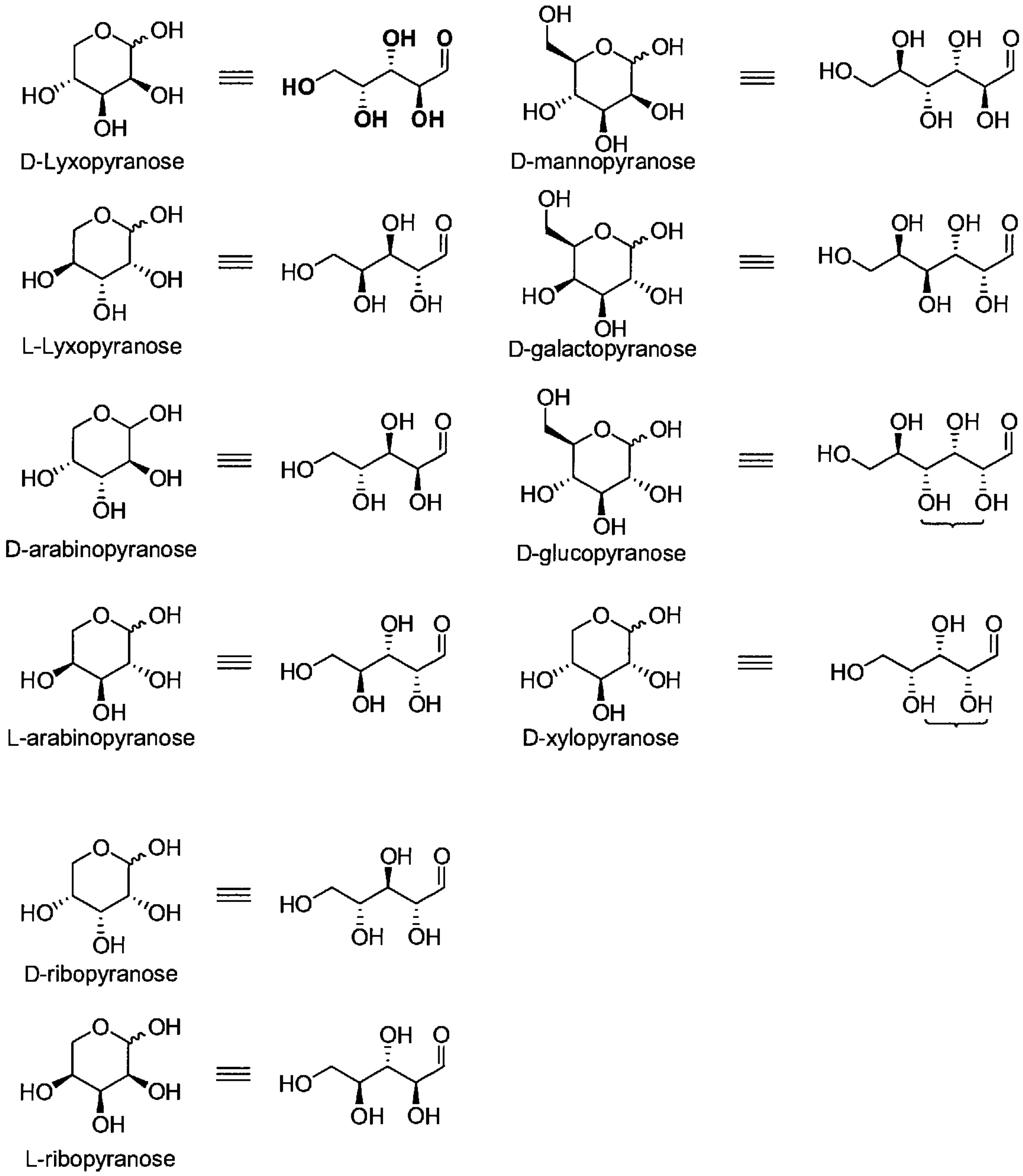
Carbohydrates can be converted to lactones bearing different functional groups with different stereochemistry. The degree of substitution can be modified owing to the availability of hexose and pentose sugars.

Scheme 2.1 shows some of the major pentose and hexose sugars as well as the stereochemistry of the resulting ring opened forms.

The monomers explored to date, derived from D-(+)-glucopyranose and D-(+)-xylopyranose, have similar stereochemistry and differ in their degree of substitution. In their linear, ring opened form, their C-2 and C-4 substituents lie on the same face. Therefore, steric clash may hinder the degree of polymerization. Conversely, D-(+)-mannopyranose and D-(+)-galactopyranose appear to exhibit less steric clash with their substituents on alternating faces. Among the pentose sugars, L-(+)-arabinopyranose and D-(+)-lyxopyranose exhibit this same property, but with one less substituent than the hexose sugars.

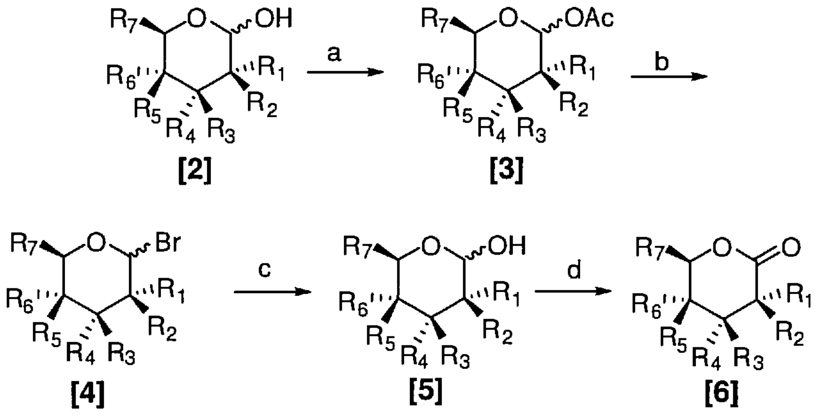
These differences in stereochemistry may not only affect the polymerisation thermodynamics, but also the properties of the resulting oligomer/polymer.

The nature of the substituent may also affect these properties. Two markedly different substituents are the methyl and acetyl groups. The bulkiness of the acetyl groups and its high electron density and electron-withdrawing ability may give rise to properties that differ significantly to the smaller methyl group.



Scheme 2.1 – Comparative stereochemistry of carbohydrates

With the exception of D-glucono-1,5-lactone, non-functionalised 1,5-lactones are not readily commercially available and therefore functionalised lactones were prepared from the corresponding pyranoses or lactols. In exploring protection, the acetyl group was chosen to begin with. The overall route towards synthesis of acetyl-functionalised 1,5-lactones is given in Scheme 2.2.



a) TFA, Ac_2O, r.t., 20 h (for ***[2c]****) or 5 min (for* ***[2d]****); b) HBr (AcOH),*

CH_2Cl_2*, 0 °C - r.t., overnight; c)* Ag_2CO_3*, acetone, water, 0 °C - r.t., overnight; d) i) 7 eq.* $(COCl)_2$*, 13 eq. DMSO, -78 °C, 2 h ii) 5 eq. NEt3, -78 °C, 30 min*

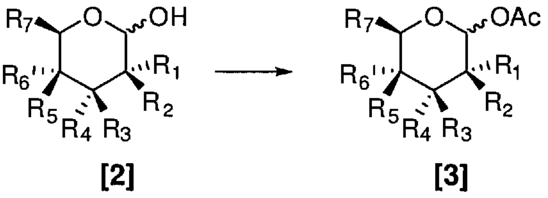
Scheme 2.2 – Overall synthesis of the acetyl-protected 1,5-lactones, [6]
Substituents are identified in the Table of Compounds

The initial step was a per-acetylation to form the glycosyl acetates, **[3]**. There are two possible routes towards attaining the functionalised lactols, **[5]**. These are the hydrolysis of glycosyl acetates using an amino alcohol and acid hydrolysis of glycosyl bromides. However, this chapter will show that the most effective route towards functionalised lactols is *via* the glycosyl bromides which can be prepared from their parent glycosyl acetates.

The final step towards the synthesis of functionalised 1,5-lactones is the oxidation of the lactols. In principle there are several oxidation methods which could be used. However, the sensitivity of acetyl-protected carbohydrate derivatives limits those which can be applied. For example, the use of aqueous reaction conditions such as the Jones' reagent would not be suitable due to subsequent formation of the aldaric acid from the 1,5-lactones. Literature precedence indicates that oxidation with CrO_3 would be ideal as it has been applied to 2,3,4-tri-*O*-acetyl-*α*/*β*-D-xylopyranose. However, toxicity of Cr(VI) presents a limitation particularly with respect to large-scale syntheses. Swern oxidation would address the toxicity issue although the use of NEt_3 in the work-up could present a challenge as NEt_3 is known to catalyse the formation of the unsaturated 1,5-lactone.[1]

2.2 Synthesis of glycosyl acetates

Starting from commercially available pyranoses, acetylation was carried out in the presence of acetic anhydride (Ac_2O) and trifluoroacetic acid (TFA) to yield the per-acetylated glycosides in quantitative yield.



*TFA, Ac_2O, r.t., 20 h (for **[2c]**) or 5 min (for **[2d]**) (quantitative)*

Scheme 2.3 – Synthesis of glycosyl acetates [3]
Substituents are identified in the Table of Compounds

Table 2.1 – Stereochemical configuration of the products in Scheme 2.3

Starting Material	R_1	R_2	R_3	R_4	R_5	R_6	R_7
D-(+)-galactopyranose **[2a]**	OAc	H	OAc	H	OAc	H	CH_2OAc
D-(+)-mannopyranose **[2b]**	H	OAc	OAc	H	H	OH	CH_2OAc
D-(+)-xylopyranose **[2c]**	OAc	H	OAc	H	H	OAc	H
L-(+)-arabinopyranose **[2d]**	OAc	H	OAc	H	OAc	H	H

*The starting materials from which **[3]** are derived (**[2]**) have the same stereochemistry as their derivative where OAc is replaced by OH*

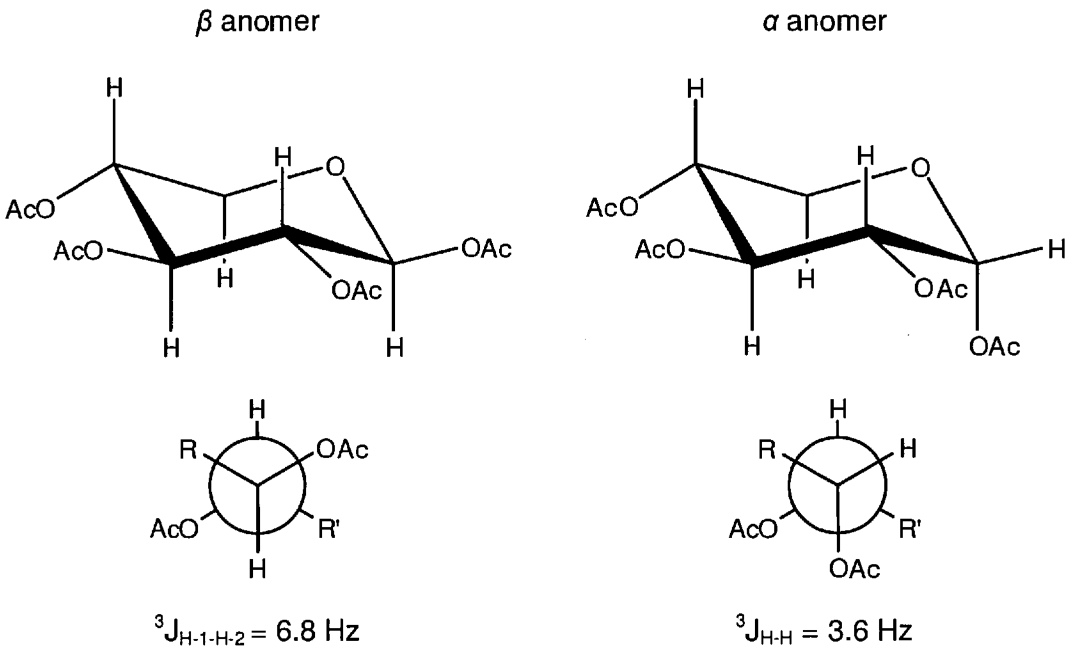
These materials were fully characterised. This was in close agreement with the literature where comparisons were available. Hexoses selectively formed the *α* anomer, whereas an equal mixture of *α* and *β* anomers were observed for the pentoses. The *α* anomer adopts the more sterically hindered axial position due to the anomeric or Edward-Lemieux effect.[2] In the presence of an electronegative anomeric substituent, X, the anti-periplanar configuration of the lone pairs on the oxygen and the anti-bonding orbital of the C-X bond stabilises the *α* anomer.[3]

Distinction between *α* and *β* anomers was made possible using ^{13}C NMR as well ^{1}H NMR. Bock *et al.*[4] established that anomeric configuration of pyranoses has a characteristic influence on the coupling constant between ^{13}C-1 and ^{1}H-1 (J_{C1-H1}). The *β* anomer of the pyranose has a J_{C1-H1} of about 10 Hz lower than the corresponding *α* anomer.[4] Similarly, by applying the Karplus equation (Equation (2.1),[5] a relative comparison of the $^{3}J_{H-H}$ coupling constants at the anomeric centres, can also be used to ascertain the identities of the *α*- and *β* anomers.

$$J(\phi) = A\cos^2\phi + B\cos\phi + C \text{ (Karplus Equation)} \tag{2.1}$$

where J = ^3J coupling constant; ϕ = dihedral angle; A, B, and C are empirically-derived parameters whose values depend on the atoms and substituents involved.[5]

The Karplus equation relates the dihedral angle, ϕ between the proton at the anomeric centre and that at C-2 to the coupling constant associated with them.[5] The greater the dihedral angle, ϕ the greater the coupling constant (assuming that A, B and C are similar for pairs of anomers). Figure 2.1 graphically illustrates the dihedral angles (ϕ) in 1,2,3,4-tetra-*O*-acetyl-*α*/*β*-D-xylopyranose. The *β* anomer, with the larger dihedral angle, has a $^3J_{H\text{-}1\text{-}H\text{-}2}$ coupling constant of 6.8 Hz whereas the analogous coupling constant for the *α* anomer is 3.6 Hz.



$^3J_{H\text{-}1\text{-}H\text{-}2} = 6.8$ Hz

$^3J_{H\text{-}H} = 3.6$ Hz

Figure 2.1 – Dihedral angles in the *α* and *β* anomers 1,2,3,4-tetra-*O*-acetyl-D-xylopyranose, [3c]

α Anomers are also characterised by a chemical shift for H-1, in the ^1H NMR spectrum, between 6.2 and 6.3 ppm with $^3J_{H1\text{-}H2}$ of 2 – 4 Hz. In $^{13}C\{^1H\}$ NMR, the chemical shift for C-1 is in the region of 89 to 90 ppm.

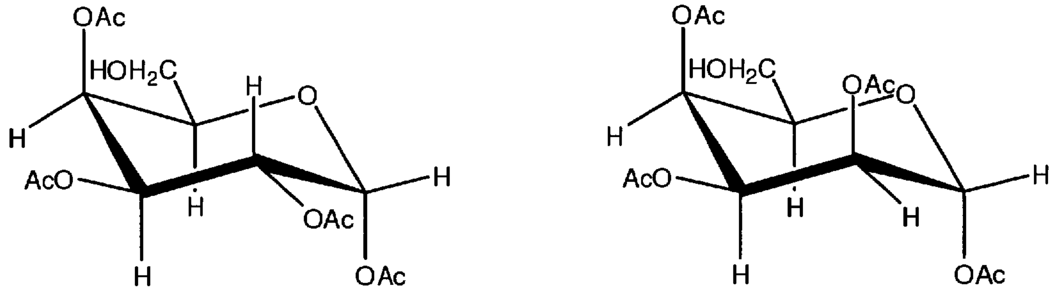
Table 2.2 – Significant NMR characteristics of glycosyl acetates

Compound	**[3a]** α anomer	**[3b]** α anomer	**[3c]** α anomer	**[3c]** β anomer	**[3d]** α anomer	**[3d]** β anomer
Derived From	D-(+)-galactopyranose	D-(+)-mannopyranose	D-(+)-xylopyranose		L-(+)-arabinopyranose	
δ H-1 (ppm)	6.34 *(lit. 6.35)*[6]	6.06 *(lit. 6.06)*[6]	6.18 *(lit. 6.25)*[6]	5.66	6.33 *(lit. 6.32)*[6]	5.68
$^3J_{H1\text{-}H2}$ (Hz)	2.3	4.5	3.6 *(lit. 3.7)*[6]	6.8	2.9 *(lit. 2.6)*[6]	6.9
δ C-1 (ppm)	89.68 *(lit. 90.3)*[6]		88.96 *(lit. 89.9)*[6]	91.74	89.49 *(lit. 90.8)*[6]	91.71

*The β anomer was not formed in the hexose derivatives **[3a]** and **[3b]***

Table 2.2 shows the characteristic chemical shifts for the β anomers of the pentoses. The chemical shift for H-1, in the ^1H NMR spectrum, is around 5.7 ppm, with a $^3J_{H1\text{-}H2}$ value of about 7 Hz. H-1 in β anomers resonate at about 0.5 ppm upfield *versus* the analogous α anomers. The coupling constants, $^3J_{H1\text{-}H2}$ in β anomers are up to 4 Hz greater than those in the analogous α anomers. The larger dihedral angle, ϕ in β anomers explains the greater coupling constants observed. Furthermore, the configuration of the β anomers of the D-(+)-galactopyranose-, D-(+)-xylopyranose- and L-(+)-arabinopyranose-derived products is such that orbital overlap occurs between the oxygen atom within the ring with that on C-1 and H-1. Consequently, this results in greater shielding and thus a lower resonating frequency for H-1 in the ^1H NMR.

Characteristic to the D-(+)-mannopyranose derivatives is the configuration of the substituent at C-2. Unlike the other analogues, it has an axial C-2 substituent rather than an equatorial one as observed in the other compounds (Figure 2.2). Consequently the anti-periplanar arrangement of the acetyl groups at C-1 and C-2 results in good orbital overlap and hence increased shielding at C-1. Thus H-1 resonates at 6.06 ppm; 0.2 - 0.3 ppm upfield *versus* the other analogues.



1,2,3,4,6-penta-*O*-acetyl-*α*-D-galactopyranose, **[3a]**

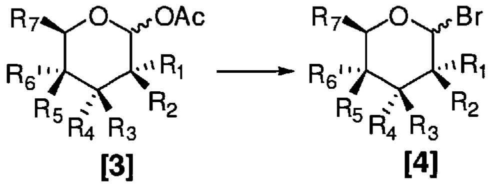
1,2,3,4,6-penta-*O*-acetyl-*α*-D-mannopyranose, **[3b]**

Figure 2.2 - Comparison of configuration of the D-(+)-galactopyranose and D-(+)-mannopyranose derivatives

The presence of 5 acetyl signals in the ^{1}H NMR for the hexoses and 4 acetyl signals for the pentoses also served to confirm of the formation of the target compounds. These acetyl resonances lie between 2.2 and 2.0 ppm.

2.3 Synthesis of gylcosyl bromides

The per-acetylated glycosides were subsequently brominated using HBr and acetic acid at r.t. (Scheme 2.4) adapted from procedure described by Mitchell *et al.*[7]



HBr (AcOH), CH_2Cl_2, *0 °C – r.t., 24 h, 76 - 95 %*

Scheme 2.4 – Bromination of glycosyl acetates to form glycosyl bromides, [4]
Substituents are identified in the Table of Compounds

Reactions were monitored by TLC and allowed to proceed for 24 h to ensure complete bromination to the glycosyl bromide. Good to excellent yields were obtained in all cases ranging from 95 % in the syntheses of 2,3,4,6-tetra-*O*-acetyl-*α*-D-mannopyranosyl bromide **[4b]** and 2,3,4-tri-*O*-acetyl-*α*-D-xylopyranosyl bromide **[4c]**, to 76 % in the synthesis of 2,3,4,6-tetra-*O*-acetyl-*α*-D-galactopyranosyl bromide **[4a]**, as shown in Table 2.3.

Table 2.3 – Yields for bromination of glycosyl acetates

Product	Yield
2,3,4,6-tetra-*O*-acetyl-*α*-D-galactopyranosyl bromide **[4a]**	76 %
2,3,4,6-tetra-*O*-acetyl-*α*-D-mannopyranosyl bromide[8] **[4b]**	95 %
2,3,4-tri-*O*-acetyl-*α*-D-xylopyranosyl bromide[9] **[4c]**	85 %
2,3,4-tri-*O*-acetyl-*α*-L-arabinopyranosyl bromide[10] **[4d]**	95 %

Glycosyl bromides were characterised by ^{1}H and $^{13}C\{^{1}H\}$ NMR spectroscopy and found to be in agreement with the literature where previously reported data was available.[8-10] H-1 in these compounds is characterised by a downfield shift *versus* the parent glycosyl acetates as shown in Table 2.4.

Table 2.4 – Significant NMR characteristics of glycosyl acetates and glycosyl bromides

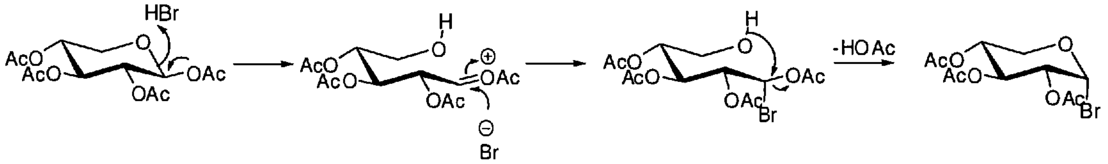
Glycosyl Acetate	**[3a]** *α* anomer	**[3b]** *α* anomer	**[3c]** *α* anomer	**[3c]** *β* anomer	**[3d]** *α* anomer	**[3d]** *β* anomer
Derived From	D-(+)-galactopyranose	D-(+)-mannopyranose	D-(+)-xylopyranose		L-(+)-arabinopyranose	
δ H-1 (ppm)	6.34 (lit. 6.35)[6]	6.06 (lit. 6.06)[6]	6.18 (lit. 6.25)[6]	5.66	6.33 (lit. 6.32)[6]	5.68
$^3J_{H1-H2}$ (Hz)	2.3	4.5	3.6 (lit. 3.7)[6]	6.8	2.9 (lit. 2.6)[6]	6.9
δ C-1 (ppm)	89.68 (lit. 90.3)[6]	91.2[6]	89.0 (lit. 89.9)[6]	91.74	89.49 (lit. 90.8)[6]	91.71
δ H-2 (ppm)	5.31 (lit. 5.31)[6]	5.28[6]	4.96 (lit. 5.02)[6]	4.96	5.03 (lit. 5.30 (m))[6]	5.30

Glycosyl Bromide	**[4a]** *α* anomer	**[4b]** *α* anomer	**[4c]** *α* anomer	**[4c]** *β* anomer	**[4d]** *α* anomer	**[4d]** *β* anomer
Derived From	D-(+)-galactopyranose	D-(+)-mannopyranose	D-(+)-xylopyranose		L-(+)-arabinopyranose	
δ H-1 (ppm)	6.68	6.29 (lit. 6.29)[8]	6.60	Not formed	6.69	Not formed
$^3J_{H1-H2}$ (Hz)	3.9	-	4.0		3.8	
δ C-1 (ppm)	88.07	-	87.59		89.6	
δ H-2 (ppm)	5.03	5.44	5.06		5.07	

The electron-withdrawing bromine atom deshields the H-1 proton in the glycosyl bromide, *versus* its parent glycosyl acetate, resulting in a downfield shift.

Mass spectrometry was also used to confirm the presence of glycosyl bromides. The hexoses produced signals at 428 and 430 amu in approximately equal intensity. These correspond to the molecular ions with Br-79 and Br-81 respectively. Similarly, the pentoses gave rise to signals at 356 and 358 amu, corresponding to the molecular ions with Br-79 and Br-81 respectively.

For all the derivatives, only the *α* anomer was observed even where the starting material comprised of a mixture of *α* and *β* anomers. From this it can be concluded that the reaction mechanism for this bromination reaction involves the opening of the ring, as shown in Scheme 2.5.

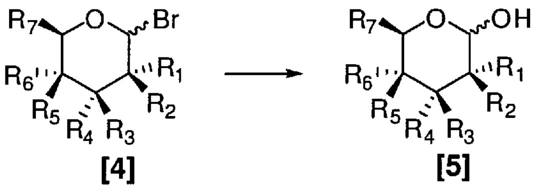


Scheme 2.5 – Reaction mechanism for the bromination of 1,2,3,4-tetra-*O*-acetyl-*β*-D-xylopyranose, [3c]

Using 1,2,3,4-tetra-*O*-acetyl-*α*/*β*-D-xylopyranose **[3c]** as an example, the pyranose ring is opened as the oxygen within the ring is activated by HBr and facilitated by neighbouring group participation from the acetate group. The resulting bromide ion attacks at C-1 from the *α* face. This allows the larger acetate group to adopt the equatorial position thus minimising steric hindrance. As this intermediate collapses to reform the pyranose ring, acetic acid is eliminated. The anomeric effect serves to stabilise the axial configuration of the bulky Br substituent.

2.4 Synthesis of lactols

A Koenigs-Knorr type reaction was used to convert the glycosyl bromides to their respective lactols (Scheme 2.6). Glycosyl bromides were hydrolysed using Ag_2CO_3, in aqueous acetone.



Ag_2CO_3, acetone (aq), 0 °C, 20 h (77 % - 100 %)

Scheme 2.6 – Hydrolysis of glycoside bromides[11]
Substituents are identified in the Table of Compounds

The conditions used were adapted from a procedure reported by Grummitt *et al.*[11] The reactions proceeded for 24 h and the products were isolated in excellent yields ranging from 77 % to 100 % as shown in Table 2.5. These compounds were characterised by NMR and some characteristic chemical shifts are compared in Table 2.6.

Table 2.5 – Yields for the hydrolysis of glycoside bromides

Product	Yield
2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranose **[5a]**	100 %
2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranose **[5b]**	88 %
2,3,4-tri-*O*-acetyl-α/β-D-xylopyranose **[5c]**	88 %
2,3,4-tri-*O*-acetyl-α/β-L-arabinopyranose **[5d]**	77 %

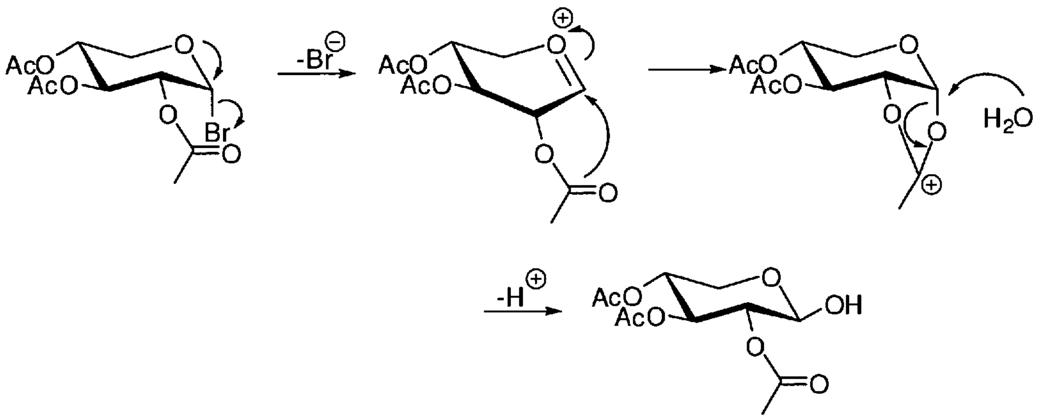
Table 2.6 – Significant NMR characteristics of glycosyl bromides and their respective lactols

Glycosyl Bromide	**[4a]** α anomer	**[4b]** α anomer	**[4c]** α anomer	**[4c]** β anomer	**[4d]** α anomer	**[4d]** β anomer
Derived From	D-(+)-galactopyranose	D-(+)-mannopyranose	D-(+)-xylopyranose		L-(+)-arabinopyranose	
δ H-1 (ppm)	6.68	6.29 (lit. 6.29)[8]	6.60	Not formed	6.69	Not formed
$^3J_{H1\text{-}H2}$ (Hz)	3.9	-	4.0		3.8	
δ C-1 (ppm)	88.07	-	87.59		89.6	
δ H-2 (ppm)	5.03	5.44	5.06		5.07	

Lactol	**[5a]** α anomer	**[5b]** α anomer	**[5c]** α anomer	**[5c]** β anomer	**[5d]** α anomer	**[5d]** β anomer
Derived From	D-(+)-galactopyranose	D-(+)-mannopyranose	D-(+)-xylopyranose (α/β ratio 2:1)		L-(+)-arabinopyranose (α/β ratio 2:1)	
δ H-1 (ppm)	5.50	5.25	5.41	4.70	5.47 *(lit. 5.47)*[11]	4.61 *(lit. 4.61)*[11]
$^3J_{H1\text{-}H2}$ (Hz)	3.4	-	3.5	7.7	3.4 *(lit. 3.4)*[11]	7.2 *(lit. 7.5)*[11]
δ C-1 (ppm)	89.6	91.9	90.30	95.91	90.82	96.05
δ H-2 (ppm)	5.46	5.26	4.90 - 4.80	4.88 - 4.77	5.18	5.08

The transformation from glycosyl bromides to their respective lactols is marked by a sharp upfield shift in the H-1 resonance *versus* their parent lactols. The coupling constants associated with these protons did not change significantly. The magnitude of the coupling constants however, was used to identify the anomeric configuration. *α* anomers have a coupling constant at H-1 between 3 - 4 Hz whereas the analogous coupling constant in the *β* anomers lie between 7 - 8 Hz. Therefore, from NMR analysis, it was apparent that both *α* and *β* anomers were formed for the pentoses.

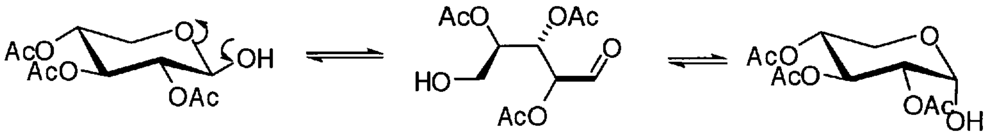
One of the possible reaction mechanisms for the hydrolysis of these glycosyl bromides, using 2,3,4-tri-*O*-acetyl xylopyranose as an example, is given in Scheme 2.7.[12]



Scheme 2.7 – Mechanism for the hydrolysis of 2,3,4-tri-*O*-acetyl-*α*/*β*-D-xylopyranose[12]

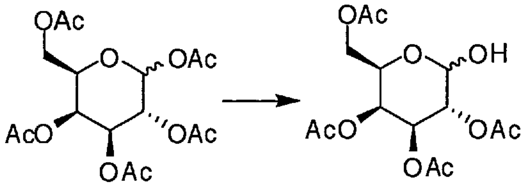
The anomeric centre is activated by the decomposition of the glycosyl bromide. Neighbouring participation of the acetyl group at C-2 protects the *α* face and is followed by the nucleophilic attack of water at the anomeric centre. This yields the *β* anomers and the reaction is thought to occur on the surface of Ag_2CO_3.[13]

The *α* anomer is formed exclusively in the hexoses. The presence of water enables mutarotation, which allows conversion of the *β* anomers to *α* anomers, as shown in Scheme 2.8. The anomeric effect[2] is the driving force behind the formation of the more sterically hindered *α* anomers.



Scheme 2.8 – Mutarotation between both anomers of 2,3,4-tri-*O*-acetyl-*α*/*β*-D-xylopyranose

Two alternative procedures for the hydrolysis of per-acetylated glycosides have been reported and were explored.[14,15] The first method was reported by Tosin *et al.* for the hydrolysis of 1,2,3,4,6-penta-*O*-acetyl-*α*-D-galactopyranose **[3b]** using aminoethanol in ethyl acetate as shown in Scheme 2.9.[14]

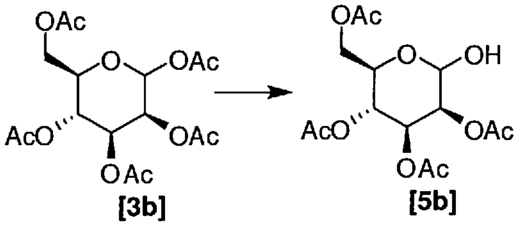


[3a] **[5a]**

$NH_2(CH_2)_2OH$, EtOAc, r.t. 60 h (60 %)

Scheme 2.9 – Synthesis of 2,3,4,6-tetra-*O*-acetyl-*α*-D-galactopyranose using ethanolamine[2]

Similarly Namchuk *et al.* reported the synthesis of 2,3,4,6-tetra-*O*-acetyl-*α*-D-mannopyranose, from its parent glycosyl pentaacetate using benzylamine in ethyl acetate, as shown in Scheme 2.10.[15]



BnNH$_2$, THF, r.t., 20 h (50 %)

Scheme 2.10 – Synthesis of 2,3,4,6-tetra-*O*-acetyl-*α*-D-mannopyranose using benzylamine[15]

However, these reactions required in excess of 60 h and resulted in a mixture of unidentified products which could only be separated by column chromatography. Conversely, the procedure of choice, *via* the glycoside bromide, resulted in pure products in high yields. This is essential to maximise the yields for the synthesis of these compounds as they are prepared on large scales of 20 g.

Table 2.7 – Yields for the syntheses of the pyranoses [5a] to [5d]

Starting Sugar	**Direct hydrolysis with amino alcohol**	**Overall yield *via* glycosyl bromide**
2,3,4,6-tetra-*O*-acetyl-*α*-D-galactopyranose **[5a]**	59 %	67 %
2,3,4,6-tetra-*O*-acetyl-*α*-D-mannopyranose **[5b]**	50 %	73 %
2,3,4-tri-*O*-acetyl-*α*/*β*-D-xylopyranose **[5c]**	n/a	75 %
2,3,4-tri-*O*-acetyl-*α*/*β*-L-arabinopyranose **[5d]**	n/a	73 %

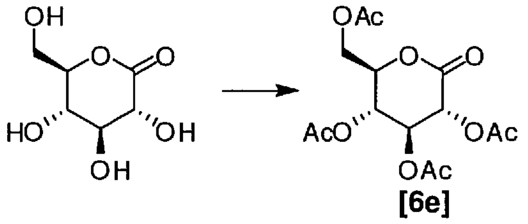
2,3,4,6-Tetra-*O*-acetyl-*α*-D-galactopyranose **[5a]** was isolated in 59 % yield when prepared using the amino alcohol catalysed hydrolysis of the glycosyl acetate.

However, the overall yield for the synthesis of this compound from the same starting material *via* the glycosyl bromide was 67 % as shown in Table 2.7. Similarly, 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranose **[5b]** was isolated in 50 % yield when prepared using the amino alcohol catalysed hydrolysis of the pentaacetate. However, it was isolated in 73 % overall yield from the two-step route involving reaction of the glycosyl acetate **[3b]** to glycosyl bromide **[4b]** and its subsequent hydrolysis. Similarly, the pentose derivatives were isolated in 73 – 75 % overall yield *via* their glycolsyl bromides. Therefore, a combination of shorter reaction times, enhanced purity, better practicality with regards to large-scale synthesis and significantly improved yields, led to the choice of this two-step synthesis over the single-step amino alcohol route.

2.5 1,5-Lactone synthesis

2.5.1 Literature precedence

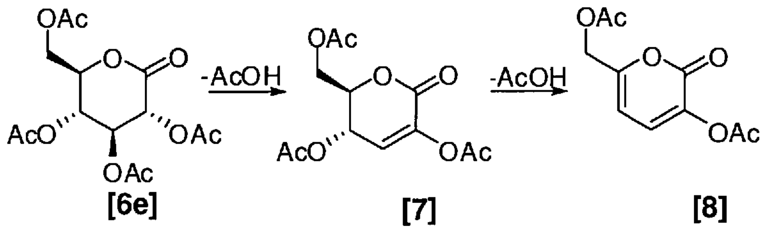
2,3,4,6-Tetra-*O*-acetyl-D-glucono-1,5-lactone **[6e]** was prepared from the commercially available D-glucono-1,5-lactone, following the procedure reported by Joseph *et al.*[16] As shown in Scheme 2.11, the starting material was treated with TFA, in acetic anhydride, and the reaction was complete in 3 h.



TFA, Ac_2O, r.t., 3 h (quantitative)

Scheme 2.11 — Synthesis of 2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone [6e]

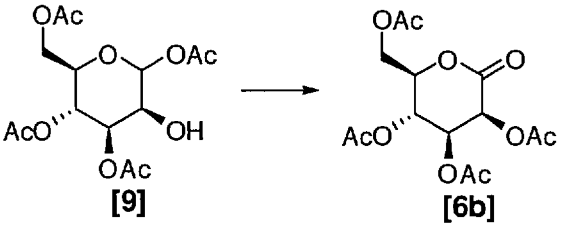
The product was isolated as a syrup in quantitative yield, after washing with water to remove the excess acetic acid. Alternative purification attempts, including column chromatography and distillation, were unsuccessful as the lactone generally decomposed. It was later discovered that this lactone is acid-sensitive and formed the more stable 1,4-lactone. Distillation, or indeed heating beyond 80 °C, resulted in elimination of one or two molecules of acetic acid to form the more stable, conjugated lactones as shown in Scheme 2.12. A more detailed investigation of decomposition products is discussed later (Chapter 5).



Scheme 2.12 – Decomposition of 2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone [6e]

The remaining lactones were prepared from their respective pyranoses by oxidation, as the non-functionalised 1,5-lactones were not commercially available. Oxidation of alcohols to carbonyls is a well-established area of chemistry and consequently there are many methods to choose from. However, only a small number of these methods have literature precedence as oxidants of lactols. In order to choose the most suitable oxidation method several factors had to be considered, notwithstanding the requirement for high-yielding reactions. One of the prevailing issues is that these reactions have to be carried out on a relatively large scale. A major issue on scale-up is the ease of temperature control and also the availability and cost of the oxidising agents. Finally, in keeping with the aim of this research in producing biodegradable and biocompatible materials, the oxidation step should also be as efficient and clean as possible. Therefore, the use and production of toxic materials should ideally be eliminated. It should be noted however, that in these early stages of research, it is often difficult to meet all these criteria. Nonetheless, after extensive research, these were in fact met and the steps leading to these results are described herein.

The Jones reagent and potassium permanganate are common oxidising agents, but are unsuitable due to the need for aqueous conditions. Under these conditions, over-oxidation of the pyranoses to the aldaric acids would be observed. Therefore, these and other oxidation methods under aqueous conditions were not given further consideration. Ruthenium has received a great deal of attention as an oxidant, in part due to its versatility as a transition metal whose oxidation state can vary from –II to +VIII.[17] Applications of ruthenium as an oxidant are included in the oxidation of lactols.[18-20] The dominant ruthenium-based oxidant used in the conversion of lactols to lactones is tetra-*n*-propyl ammonium perruthenate (TPAP). This reagent has received attention recently in the synthesis of both 1,4- and 1,5-lactones,[19,20] with the first reports carried out by Benhaddou *et al.* in the synthesis of benzyl and allyl protected 1,5-lactones.[20] Furthermore, 2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone **[5b]** was prepared from 1,3,4,6-tetra-*O*-acetyl-*α*-D-mannopyranose **[9]** by Lichtenthaler *et al.* using RuO_2 in the presence of $NaIO_4$, as shown in Scheme 2.13.[18] However, this reaction requires a period of 10 days to achieve a 35% yield. Furthermore, the synthesis of this unusual precursor, where the hydroxyl is at the C-2 position, requires several low-yielding steps.



RuO_2, $NaIO_4$, H_2O, CH_2Cl_2, *r.t., 10 days (35 %)*

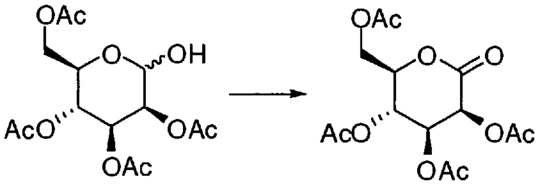
Scheme 2.13 – Synthesis of 2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone [6b] using RuO_2[18]

The syntheses of 2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone **[6b]** and 2,3,4,6-tetra

O-acetyl-D-glucono-1,5-lactone **[6e]** were also reported by Senni *et al.*[21] from the parent glycosyl azide *via* a photo-induced reaction in the presence of *N*-bromosuccinimide (NBS). The reaction comprises of 5 steps and an overall yield of

30 %. An alternative approach was also employed by oxidation of the glycosyl azide with light to yield 2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone **[6e]** in only 45 % yield. Therefore, a combination of low yields, several steps and the use of toxic solvents clearly renders this an unfavourable synthetic route.

Also reported by Senni *et al.*, is the oxidation of 2,3,4,6-tetra-*O*-acetyl-*α*-D-mannopyranose **[5b]** using N-iodosuccinimide and tetra-*n*-butylammonium iodide. This was reported in 56 % yield but did require a 10-day reaction, as shown in Scheme 2.14.[21] This long reaction time and the low overall yield makes this an unattractive synthetic route.

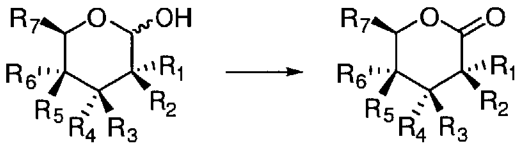


N-iodosuccinimide, tetra-n-butylammonium iodide, CH_2Cl_2, *r.t., 10 days (56 %)*

Scheme 2.14 – Oxidation of 2,3,4,6-tetra-*O*-acetyl-*α*-D-mannopyranose [5b] using *N*-iodosuccinimide and tetra-*n*-butylammonium iodide[21]

2.5.2 Oxidation using CrO_3

Literature precedence revealed that CrO_3 was used in the oxidation of 2,3,4-tri-*O*-acetyl-*α*/*β*-D-xylopyranose **[5c]** to the 1,5-lactone. Nelson reported this reaction using 8 equivalents of chromium (VI) oxide (CrO_3) in glacial acetic acid at r.t.[22] These reaction conditions were applied in the oxidation of 2,3,4,6-tetra-*O*-acetyl-*α*-D-galactopyranose **[5a]** as well as 2,3,4-tri-*O*-acetyl-*α*/*β*-D-xylopyranose **[5c]**. A pentose as well as a hexose were chosen to explore this reaction so as to ascertain if the difference in substitution significantly affects the outcome of the reaction. This is illustrated by Scheme 2.15.



[5a], [5c] **[6a], [6c]**

8 or 2.5 eq. CrO_3, glacial acetic acid, r.t. 10 – 20 min.(8 % - 17 %)

Scheme 2.15 – Oxidation of lactols using CrO_3

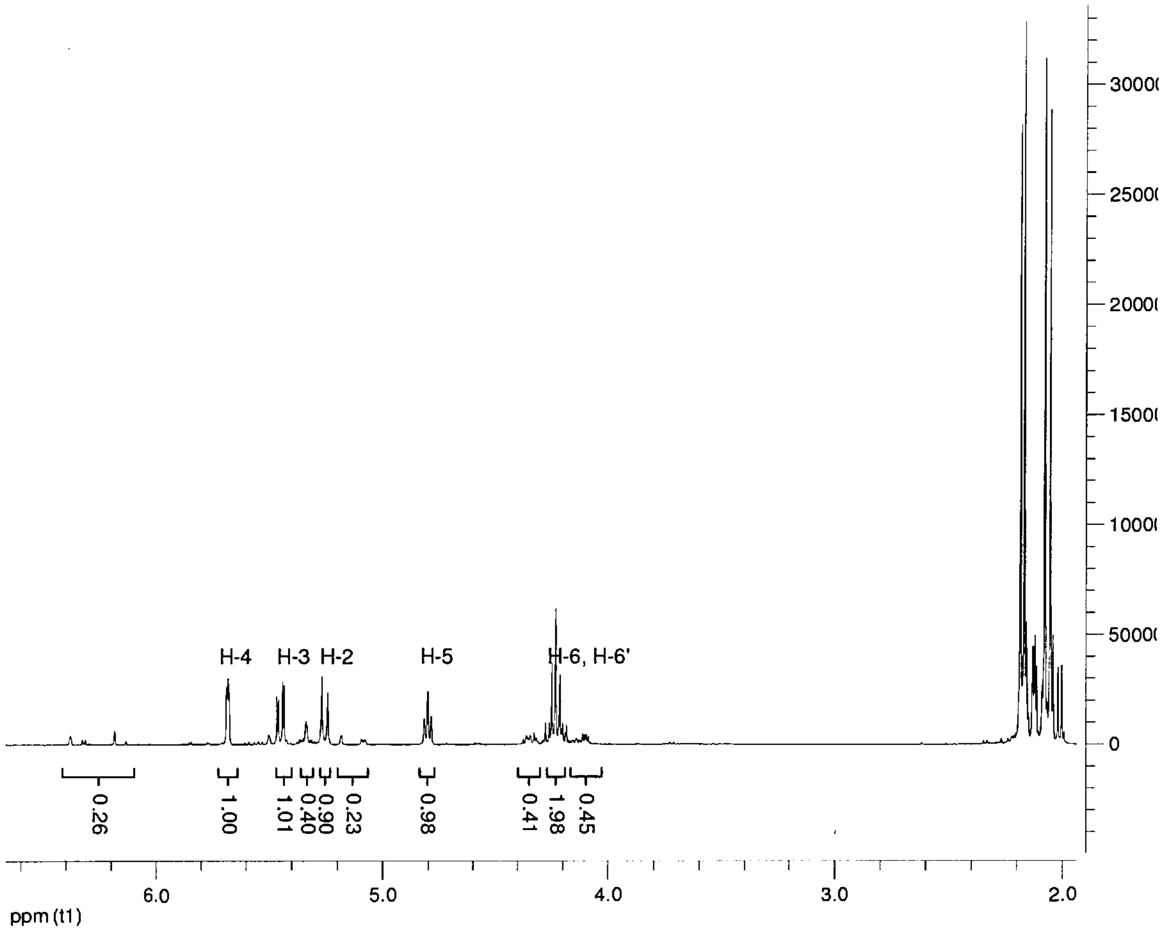
2,3,4,6-Tetra-*O*-acetyl-D-galactono-1,5-lactone **[6a]** and 2,3,4-tri-*O*-acetyl-D-xylono-1,5-lactone **[6c]** were prepared in 8 and 17 % yield respectively (Table 2.8). In order to remove the majority of chromium compounds from the reaction mixture, 9 cycles of washing with water were employed, as specified in the literature.[22] This raised the possibility of the lactone being lost in the aqueous washings. However, reducing the number of wash cycles did not serve to improve product recovery.

Table 2.8 – Oxidation Attempts using CrO_3

Substrate	Yield
2,3,4,6-tetra-*O*-acetyl-D-galactono-1,5-lactone **[6a]**	8 %^{i}
2,3,4-tri-*O*-acetyl-D-xylono-1,5-lactone **[6c]**	17 %^{ii}

^{i}*using 2.5 eq.* CrO_3; ^{ii}*using 8 eq.* CrO_3

Figure 2.3 shows the ^1H NMR spectrum of crude 2,3,4,6-tetra-*O*-acetyl-D-galactono-1,5-lactone. Outside the acetyl region, the lactone shows resonances assigned to H-2 to H-6/6'. The impurity on the other hand, makes up less than 2 protons in this region. Thus, there are no significant traces of starting material which could account for the 80 – 90 % loss in mass observed.



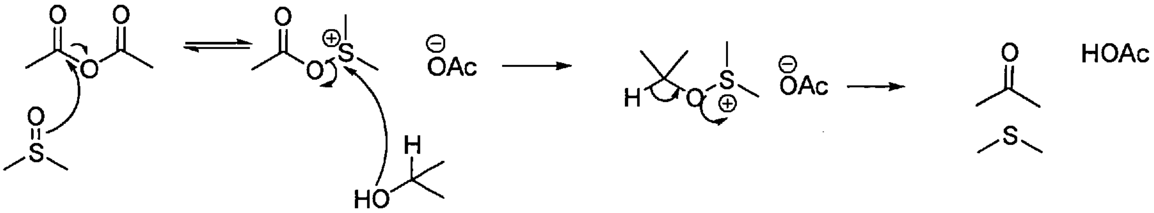
$CDCl_3$, 400 MHz

Figure 2.3 – ^{1}H NMR spectrum of crude 2,3,4,6-tetra-*O*-acetyl-D-galactono-1,5-lactone [6a]

Thus it was concluded that there are side reactions which result in water soluble by-products. It is possible that the reaction conditions may deacetylate the substrate leading to water-soluble, unprotected carbohydrates. In summary, the oxidation of these pyranoses using CrO_3 is characterised by very poor yields, high levels of toxic waste and difficulty in purification. Furthermore, the oxidation with chromium has also been explored by Kuzuhara *et al.*[23] However, they found that chromic anhydride-pyridine with oxygen in the presence of a platinum catalyst failed to oxidise partially benzylated aldoses.[23]

2.5.3 Oxidation using DMSO-acetic anhydride

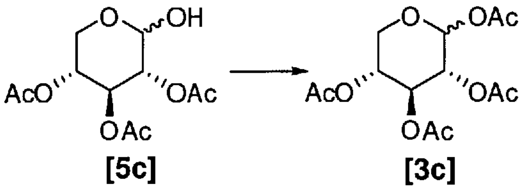
Overkleeft *et al.*[24] reported the oxidation of 2,3,4,6-tetra-*O*-benzyl gluco-, manno-, and galactopyranoses to their corresponding lactones, with DMSO in acetic anhydride. The mechanism for this oxidation is shown in Scheme 2.16.



Scheme 2.16 – Oxidation mechanism using DMSO and acetic anhydride[23]

Kuzuhara[23] and Goldman[25] suggest that DMSO interacts with acetic anhydride, as shown in Scheme 2.16, to give α-alkoxy sulphoxides, in the rate-determining step. This interacts with the pyranose to form a salt, which collapses to form the lactone, with formation of acetic acid and dimethylsulphane as by-products.

However, when we treated **[5c]** with DMSO, in acetic anhydride, using the conditions described by Overkleeft *et al.*[24], this resulted in the formation of its parent glycosyl acetate **[3c]**, as shown in Scheme 2.17. This is not altogether surprising since, as shown in Scheme 2.16, acetic acid is formed as a by-product which subsequently serves to acetylate at the anomeric position. Furthermore, Senni *et al.* have discovered that the analogous reaction with 2,3,4,6-tetra-*O*-acetyl-*α*-D-mannopyranose also results in the formation of the peracetylated derivative.[21]

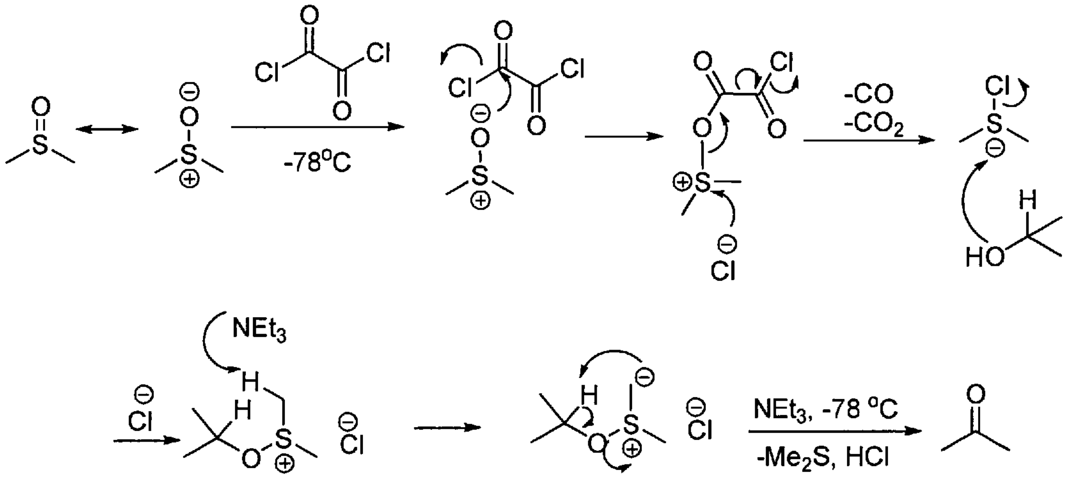


Ac_2O, DMSO, r.t., overnight

Scheme 2.17 – Reaction of 2,3,4-tri-*O*-acetyl-*α*/*β*-D-xylopyranose [5c] with acetic anhydride-DMSO

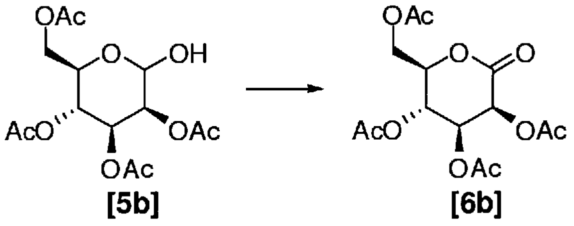
2.5.4 Swern oxidation

Another common oxidation route is the Swern oxidation.[26] However, it has not been investigated in the oxidation of partially functionalised pyranoses. The mechanism for this reaction is given in Scheme 2.18.



Scheme 2.18 – Mechanism for the Swern oxidation[26]

In fact, the Swern oxidation is related to the oxidation using acetic anhydride-DMSO reported above. However, in the Swern oxidation acetic anhydride is replaced by oxalyl chloride thus overcoming the issue of acetylation at the anomeric position. The Swern oxidation is also characterised by the activation of DMSO with oxalyl chloride at very low temperatures (-78 °C). After loss of CO and CO_2, the resulting intermediate is attacked by an alcohol at the nucleophilic sulphur centre to form the dimethylalkoxysulphonium salt. The reaction of this salt with triethylamine results in the formation of the carbonyl product and dimethyl sulphide.[26]

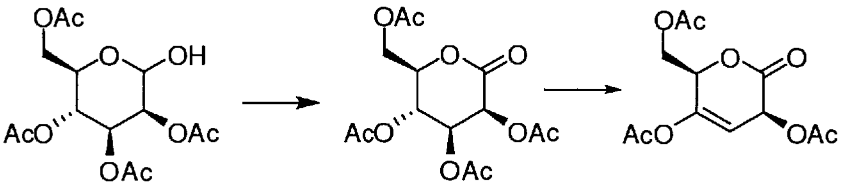


i) $(COCl)_2$, DMSO, -78 °C, 30 min

ii) NEt_3, 30 min

Scheme 2.19 – Swern oxidation of 2,3,4,6-tetra-*O*-acetyl-*α*-D-mannopyranose [5b]

Thus the oxidation of 2,3,4,6-tetra-*O*-acetyl-*α*-D-mannopyranose **[5b]** was investigated using the Swern oxidation. The same conditions used to oxidise (1R,5R)-6-oxabicyclo[3.2.1]octane-4,7-dione were applied (Scheme 2.20).[27] These conditions required 7 equivalents of oxalyl chloride, 13 equivalents of DMSO and 16 equivalents of triethylamine for the work-up. However, when these reaction conditions were applied to the oxidation of 2,3,4,6-tetra-*O*-acetyl-*α*-D-mannopyranose **[5b]**, complications arose. It was discovered that after the formation of 2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone **[6b]**, subsequent elimination of acetic acid was observed, resulting in the formation of the unsaturated lactone as shown in Scheme 2.20. Pedersen *et al.*[1,28] have reported the elimination of acetic acid from 2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone **[6e]** in the presence of triethylamine. Therefore, it was deduced that triethylamine had the same effect on the mannose derivative under these conditions.



i) 7 eq. $(COCl)_2$, 13 eq. DMSO, -78 °C, 30 min

ii) 16 eq. NEt_3, 30 min (< -30 °C)

Scheme 2.20 – Swern oxidation of 2,3,4,6-tetra-*O*-acetyl-*α*-D-mannopyranose [5b] under conditions reported by Su *et al.*[27]

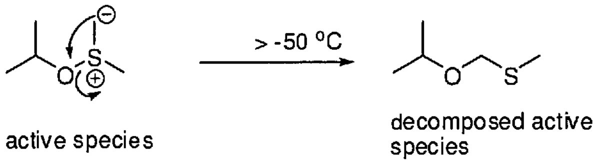
Several experiments were carried out to optimise the yield and purity of the products of this reaction. These results are presented in Table 2.9.

Table 2.9 - Optimisation of the Swern Oxidation to 2,3,4,6-tetra-*O*-acetyl mannono-1,5-lactone [6b]

Entry	Conditions	Remarks
1	7 eq. $(COCl)_2$, 13 eq. DMSO, -78 °C, 30 min work up: 16 eq. NEt_3, -78 °C, 30 min, -78 °C to r.t. concentration of reaction mixture followed by filtration to remove $HNEt_3Cl$ then concentration.	32 % yield Mixture of lactone and unsaturated lactone (ratio 2:3). Traces of $HNEt_3Cl$ present in crude.
2	7 eq. $(COCl)_2$, 13 eq. DMSO, -78 °C, 30 min work up: 16 eq. NEt_3, -78 °C, 30 min, warm to r.t. Single brine washing	72 % yield Mixture of lactone and unsaturated lactone (ratio 1:6). Traces of $HNEt_3Cl$ present in crude.
3	7 eq. $(COCl)_2$, 13 eq. DMSO, -78 °C, 30 min work up:	76 % yield No decomposition and no

Entry	**Conditions**	**Remarks**
	5 eq. NEt_3, -78 °C, 30 min, -30 °C washing with water, 1 M HCl, $NaHCO_3$, brine. Recrystallisation at low temperature.	traces of DMSO or $HNEt_3Cl$ present.

Attention was given to the reaction work up as it is where the target lactone was exposed to materials it is sensitive to; triethylamine and water. As it is known that water readily opens the lactone ring, water washing was omitted in an attempt to increase the yield. Instead, the reaction mixture was concentrated and filtered to remove $HNEt_3Cl$ (Table 2.9, Entry 1). However, this resulted in a low yield (32 %) and a mixture of 2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone **[6b]** and the unsaturated lactone **[10]**, in the ratio 2:3. As triethylamine is known to catalyse the formation of the unsaturated lactone, it was deduced that triethylammonium chloride has the same affect. Hence, the reaction mixture was washed once with brine. This resulted in a greater yield of 72 % with respect to 2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone **[6b]** and significantly less unsaturated lactone. The ratio of 2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone **[6b]** to the unsaturated lactone **[10]** was 1:6 (Table 2.9, Entry 2). Nonetheless, significant traces of triethylammonium chloride were present in the crude. Elimination of $HNEt_3Cl$ can only be effectively achieved after several washing cycles, as shown by Keyworth *et al.*,[29] where a simple aliphatic alcohol was oxidised to an aldehyde. Furthermore, they also report the use of only 5 equivalents of triethylamine in the work up. Thus the triethylamine loading was reduced and washing with water, aqueous HCl and $NaHCO_3$ and finally brine was carried out so as to remove all traces of triethylammonium chloride. Additional challenges were faced with regards to temperature control of these reactions on a large scale. An essential aspect of the Swern oxidation is the formation of the active species, shown in Scheme 2.21. If the temperature is allowed to rise above -50 °C, decomposition is observed.



Scheme 2.21 – Mechanism for the decomposition of the Swern oxidation active species

To prevent DMSO from freezing, it was dissolved in CH_2Cl_2, cooled to -78 °C prior to its addition. Neat DMSO freezes within the reaction vessel at the tip of the cannula as it is being introduced. Once the solid DMSO falls into the reaction vessel, it dramatically increases the reaction temperature. The starting pyranose was treated in the same manner to ensure good temperature control. In order to obtain high yields of the target lactone, the reaction mixture's temperature was constantly monitored and never allowed to rise beyond -60 °C. Due to the effects of triethylamine on these compounds, after its addition, it was allowed to react for 30 min at -78 °C followed by warming to only -30 °C before being swiftly worked up. It was observed that prolonged exposure to triethylamine, even with the use of only 5 equivalents, led to partial decomposition to the unsaturated lactone. As a result of these optimisations, 2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone **[6b]** was obtained, pure by NMR and elemental analysis, and in 76 % yield (Table 2.9, Entry 3). The ^{1}H NMR spectrum of 2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone **[6b]** lactone is shown in Figure 2.4.

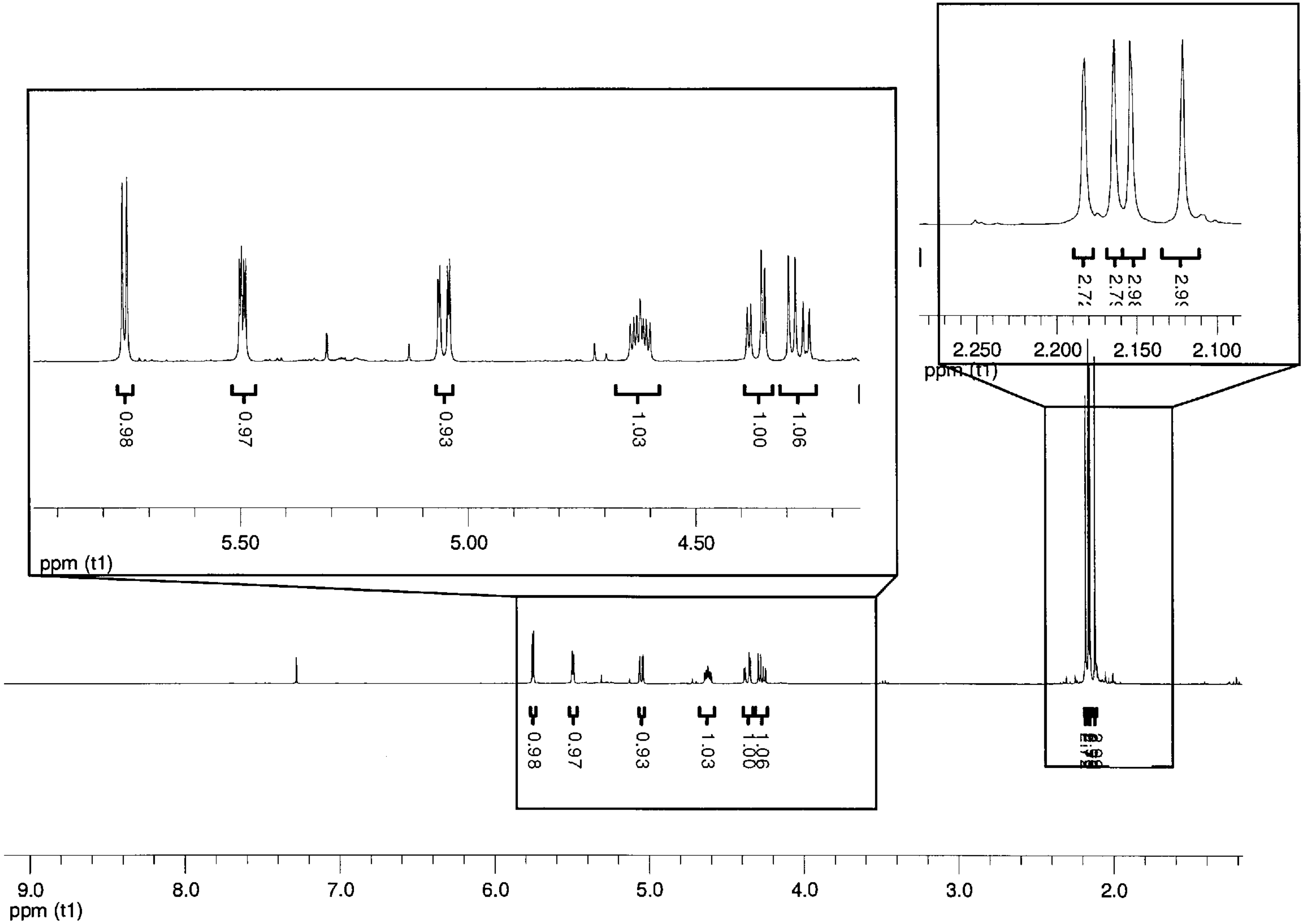
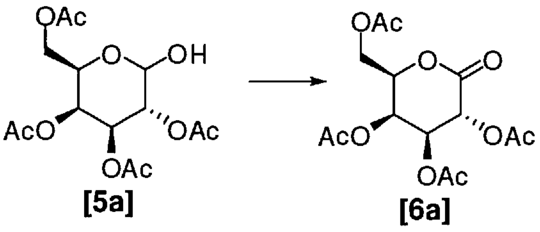


Figure 2.4 - ^{1}H NMR spectrum of 2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone [6b]



[5a] **[6a]**

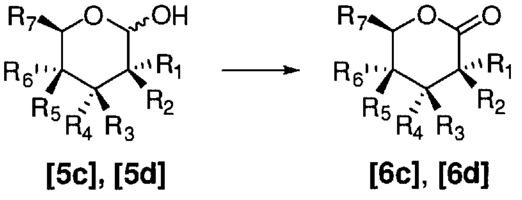
i) 7 eq. $(COCl)_2$, 13 eq. DMSO, -78 °C, 30 min

ii) 5 eq. NEt_3, -78 °C, 30 min (83%)

Scheme 2.22 – Synthesis of 2,3,4,6-tetra-*O*-acetyl-D-galactono-1,5-lactone, [6a]

Following the success achieved with 2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone **[6b]**, the same conditions were applied to the galactose derivative **[5a]**, with even better results. 2,3,4,6-Tetra-*O*-acetyl-D-galactono-1,5-lactone **[6a]** was prepared in 83 % yield under the same conditions, and was also pure by elemental analysis. However, it was noted that this compound was particularly sensitive to temperature during the reaction. Whereas the mannose derivative **[6b]** withstood temperatures up to -40 °C during work up, reaction with the galactose derivative **[6a]** had to strictly be maintained below -60 °C.

The pentose derivatives, 2,3,4-tri-*O*-acetyl-D-xylono-1,5-lactone **[6c]** and 2,3,4-tri-*O*-acetyl-L-arabinono-1,5-lactone **[6d]**, were prepared using the optimised reaction conditions, as shown in Scheme 2.23.



[5c], [5d] **[6c], [6d]**

i) 7 eq. $(COCl)_2$, 13 eq. DMSO, -78 °C, 2 h

ii) 5 eq. NEt_3, -78 °C, 30 min (52 % - 64 %)

Scheme 2.23 – General Conditions for the Swern oxidation of lactols
Substituents are identified in the Table of Compounds

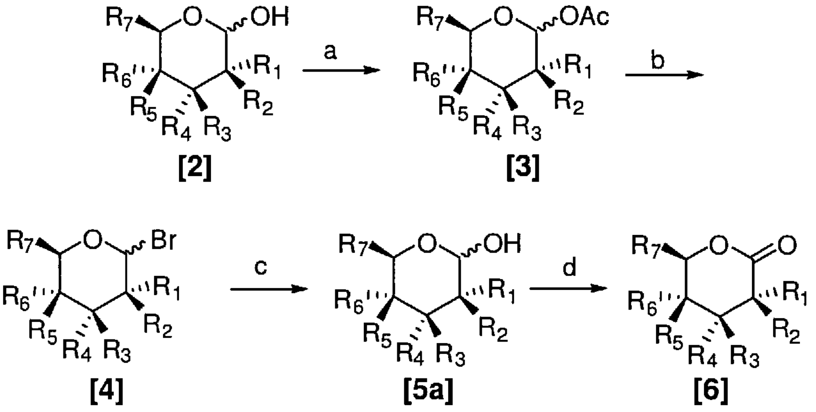
2,3,4-tri-*O*-acetyl-D-xylono-1,5-lactone **[6c]** and 2,3,4-tri-*O*-acetyl-L-arabinono-1,5-lactone **[6d]** were prepared in 64 % and 52 % yields respectively, as shown in Table 2.10.

Table 2.10 – Yields for the synthesis of acetyl-protected 1,5-lactones corresponding to Scheme 2.23

Product	**Yield from acetyl-protected lactol**	**Overall Yield from starting unprotected pyranose**
2,3,4,6-tetra-*O*-acetyl-D-galactono-1,5-lactone **[6a]**	83 %	55 %
2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone **[6b]**	76 %	72 %
2,3,4-tri-*O*-acetyl-D-xylono-1,5-lactone **[6c]**	64 %	48 %
2,3,4-tri-*O*-acetyl-L-arabinono-1,5-lactone **[6d]**	52 %	68 %

Conditions: i) 7 eq. $(COCl)_2$, 13 eq. DMSO, -78 °C, 2 h; ii) 5 eq. NEt_3, -78 °C, 30 min, < -30 °C

Thus, the Swern oxidation has been optimised to effectively synthesise acetyl-protected 1,5-lactones. By fine-tuning the reaction conditions, side reactions were successfully eliminated without compromising on product purity and, in most cases, whilst achieving good yields. Unlike previously reported routes to these materials which require a significant number of steps,[21,30] the overall synthesis of the acetyl-protected 1,5-lactones can be prepared *via* a 4-step synthesis in good to excellent overall yields (48 % to 72 %). Literature precedence was not found to reveal overall yields which surpassed those reported herein. Furthermore, the steps employed are simple and well-established using readily available reagents which, on the most part, do not require or generate toxic materials.



a) TFA, Ac_2O, r.t., 20 h (for ***[2c]****) or 5 min (for* ***[2d]****); b) HBr (AcOH), CH_2Cl_2, 0 °C - r.t., overnight; c) Ag_2CO_3, acetone, water, 0 °C - r.t., overnight; d) i) 7 eq. $(COCl)_2$, 13 eq. DMSO, -78 °C, 2 h ii) 5 eq. NEt3, -78 °C, 30 min*

Scheme 2.24 – Overall synthesis of the acetyl-protected 1,5-lactones, [6]
Substituents are identified in the Table of Compounds

Owing to the poor availability of characterisation of these 1,5-lactones, and in some cases this being the first reports of their synthesis, complete characterisation was carried out. The most useful tool was NMR spectroscopy, as the chemical shift and coupling constants are very characteristic and provide a clear "fingerprint" for these compounds. ^1H and $^{13}C\{^1H\}$ NMR chemical shifts are reported in Table 2.11 and Table 2.12.

The most characteristic mark of the conversion of lactols to 1,5-lactones is the loss of the stereoisomerism due to the loss in chirality at the anomeric centre. This was evident in the pentose derived carbohydrates where a mixture of α and β lactols were present in the starting reaction mixture.

Table 2.11 – ^{1}H NMR data for carbohydrate-derived 1,5-lactones [6]

Product	δ H-2 (*J*)	δ H-3 (*J*)	δ H-4 (*J*)	δ H-5 (*J*)	δ H-5' (*J*)	δ H-6 (*J*)	δ H-6' (*J*)
2,3,4,6-tetra-*O*-acetyl-D-galactono-1,5-lactone **[6a]**	5.28 (10.3)	5.47 (10.3, 2.9)	5.70 (2.8, 1.5)	4.82	-	4.25	
2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone **[6b]**	5.75 (3.9)	5.49	5.05	4.62 (8.6, 5.8)	-	4.37 (12.4, 3.1)	4.27 (12.5, 5.8)
2,3,4-tri-*O*-acetyl-D-xylono-1,5-lactone **[6c]**	5.52 (8.7)	5.20	5.13	4.60 (13.0, 2.2)	4.48 - 4.39	-	-
2,3,4-tri-*O*-acetyl-L-arabinono-1,5-lactone **[6d]**	5.34 (10.2)	5.48 (10.2, 3.0)	5.56 (4.7, 2.1)	4.53 (13.1, 1.6)	4.46 (13.1, 2.3)	-	-
2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone[16] **[6e]**	5.10 (9.1)	5.44	5.25	4.56 - 4.44	-	4.28 (12.7, 3.7)	4.14 (12.7, 2.3)

δ = chemical shift (reported in ppm). J = coupling constant (reported in Hz).

Unreported coupling constants could not be resolved.

The H-2 protons have characteristic chemical shifts between 5.1 and 5.8 ppm. With the exception of the galactose derivative **[6a]**, the transformation from the lactol to the 1,5-lactone is associated with a decrease in the chemical shift, ranging from 0.3 to 0.7 ppm. An increase of 0.2 ppm is observed in the chemical shift at H-2 on transformation of 2,3,4,6-tetra-*O*-acetyl-*α*-D-galactopyranose **[5a]** to 2,3,4,6-tetra-*O*-acetyl-D-galactono-1,5-lactone **[6a]**. H-2 is also characterised by the coupling constant associated with it. With the exception of the mannose derivative **[6b]**, the coupling constants are between 9 and 10 ppm. The mannose derivative, **[6b]** has a much smaller coupling constant at H-2 of only 3.9 ppm. This marked difference in magnitude of this coupling constant is associated with the stereochemistry. In all but the mannose derivative, H-2 and H-3 are anti-periplanar. This brings about the large coupling constant. H-2 and H-3 in the mannose derivative are synplanar.

The chemical shifts for H-3 lie between 5.2 and 5.5 ppm. With the exception of the *α* anomers of the pentose derivatives, these are similar to the parent lactols. The H-3 resonances generally have two coupling constants associated with them; a larger coupling constant due to coupling with H-2 and a smaller one due to coupling with H-3. The chemical shifts for H-4 lie between 5.1 and 5.7 ppm, with relatively small coupling constants. This is where the most significant change in chemical shift is observed when compared with their parent lactols. H-5 is characterised by a chemical shift between 4.5 and 4.8 ppm. The pentoses have a geminal coupling constant of 13 Hz.

Table 2.12 – $^{13}C\{^1H\}$ NMR data for carbohydrate-derived 1,5-lactones [6]

Product	δ C-1	δ C-2	δ C-3	δ C-4	Δ C-5	δ C-6
2,3,4,6-tetra-*O*-acetyl-D-galactono-1,5-lactone **[6a]**	164.46	68.44	69.16	66.22	74.71	60.98
2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone **[6b]**	168.41	66.53	70.38	69.1	75.37	62.26
2,3,4-tri-*O*-acetyl-D-xylono-1,5-lactone **[6c]**	165.46	68.59	72.93	70.51	66.47	-
2,3,4-tri-*O*-acetyl-L-arabinono-1,5-lactone **[6d]**	165.7	68.72	67.02	68.78	67.99	-

δ = chemical shift (reported in ppm). J = coupling constant (reported in Hz).

Table 2.12 shows the $^{13}C\{^1H\}$ NMR chemical shifts for all the 1,5-lactones prepared. $^{13}C\{^1H\}$ NMR is an invaluable tool in confirming the transformation of the lactol to the lactone, due to the characteristic carbonyl signal. A standard carbonyl carbon resonates at ~ 170 ppm, however, C-1 in 1,5-lactones, resonates at about 165 ppm. This is a result of the strain present in the ring resulting in increased electron density at this carbon centre and subsequent deshielding *versus* a standard carbonyl.

Infra-red spectroscopy is often a useful tool in the characterisation of 1,5-lactones due to the presence of the carbonyl which should absorb in the region of 1750 cm^{-1}. However, the carbonyl signals in the acetyl-protected 1,5-lactones are masked by the absorbances due to the acetyl carbonyl groups. The infra-red spectrum for 2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone is shown in Figure 2.5.

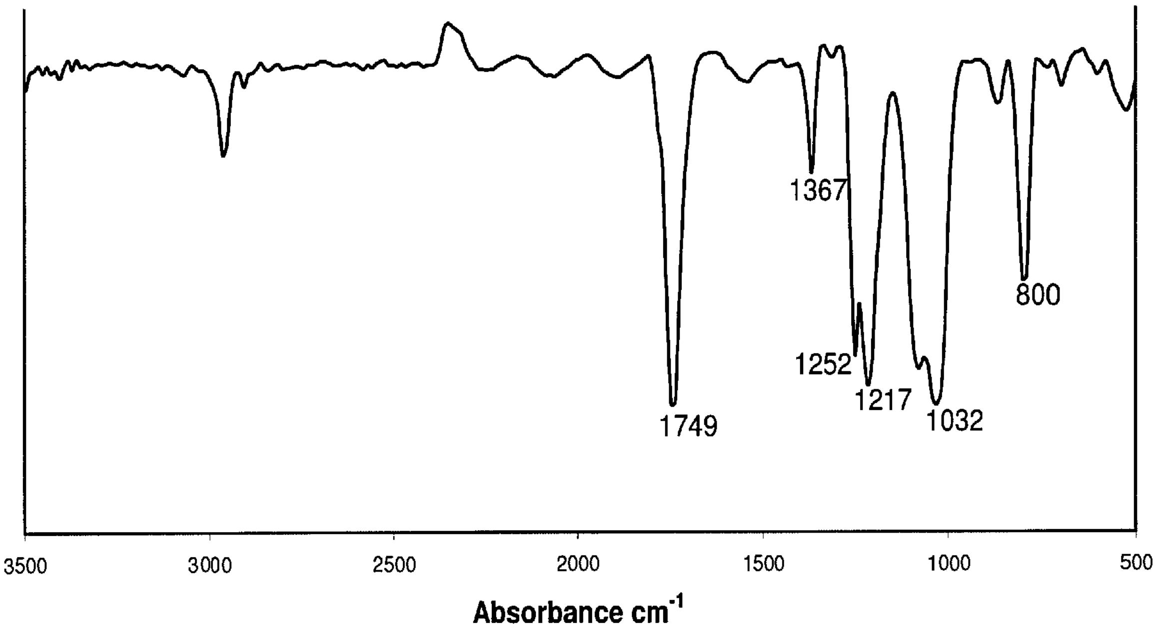


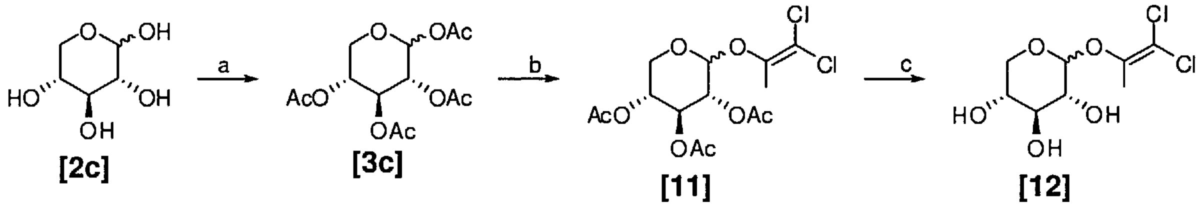
Figure 2.5 – Infra-red spectrum of 2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone [6b]

2.6 2,3,4-Tri-*O*-methyl-D-xylono-1,5-lactone

2,3,4-Tri-*O*-methyl-D-xylono-1,5-lactone was also considered as a monomer. The nature of the methyl protecting group required a rather different synthetic procedure. Thus it was prepared from D-(+)-xylopyranose protected at the anomeric position as a dichlorovinyl glycoside **[11]**.

2.6.1 Anomeric-protected lactone precursor

Scheme 2.25 illustrates the synthetic route to anomeric protected lactone precursor. This was adapted from a method applied to the glucose analogue reported by Figueiredo *et al.*[31]



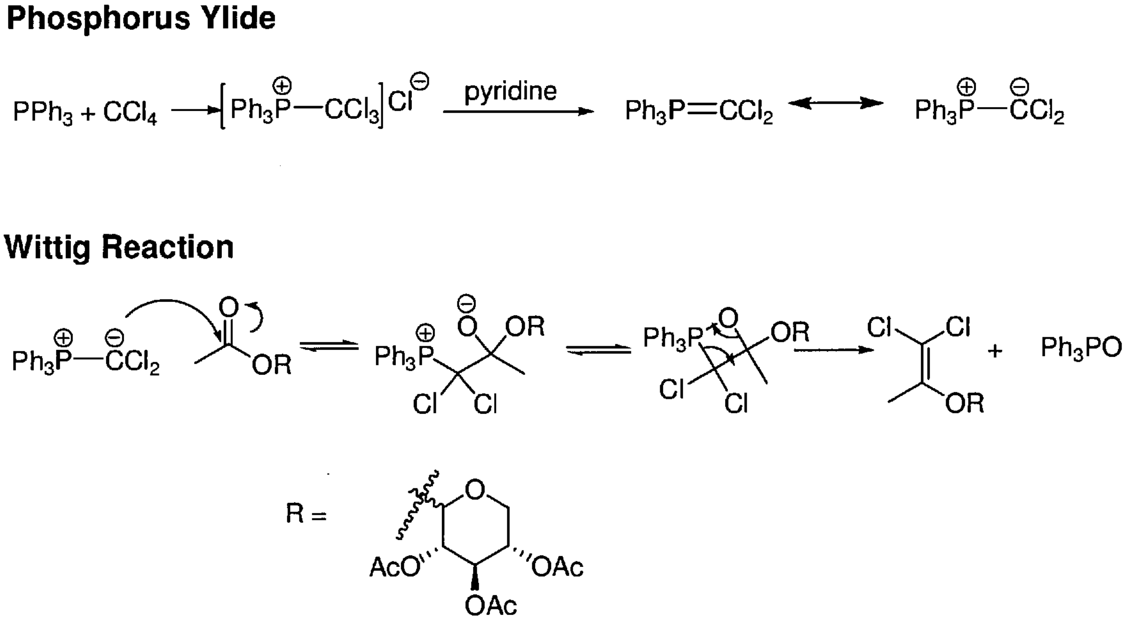
(i) TFA, Ac_2O, r.t., 20 h; b) 2 eq. PPh_3, CCl_4, 7 eq. KCl, 90 °C, 50 mins;

c) 0.5 eq. MeONa, MeOH, r.t., 1 h

Scheme 2.25 – Synthesis of (2',2'-dichloro-1'-methyl)ethenyl-D-xylopyranoside [3]

The first step involved the complete and quantitative acetylation of D-(+)-xylopyranose **[2c]**, under acidic conditions. A Wittig-type reaction yielded **[11]**, the dichlorovinyl oside selectively at the anomeric centre. This reaction was complete in under an hour at 90 ºC. It poses a challenging work-up, owing to the removal of the by-product, PPh_3O. To optimise the yield, it was necessary to extract the maximum amount of product from the reaction mixture which takes the form of a slurry. This was done by dissolution in a mixture of CH_2Cl_2, EtOAc and hexane (2:1:1) followed by filtration through a pad of silica gel. PPh_3O was removed by the addition of a minimum amount of EtOAc and hexane (1:1), followed by filtration to remove the majority of PPh_3O present which did not dissolve in the mixture. Subsequently, column chromatography (silica gel, Ethyl Acetate-Hexane, 1:1) enabled isolation of the pure product as a yellow semi-solid.

A proposed reaction mechanism for the introduction of the anomeric group is given in Scheme 2.26. The phosphorus ylide is formed from PPh_3 with CCl_4. Reaction of the ylide with the anomeric acetyl yields the dichlorovinyl glycoside.



Scheme 2.26 – Reaction mechanism for introduction of the anomeric protecting group

Deacetylation under Zemplén[43] conditions[31] yields the anomeric protected species, **[12]** in good yield. The use of weakly acidic ion exchange resin renders the reaction work-up facile by efficiently removing NaOH and NaOMe. The crude product was washed with acetone to remove further impurities. The elemental analysis was in excellent agreement with that expected. Figure 2.6 shows the $^{13}C\{^{1}H\}$ NMR chemical shifts of the anomeric protected xylose **[12]**. The characteristic signals are those observed at *ca.* 148, 104 and 14 ppm corresponding to the C-1', C-2' and C-3' environments respectively. The chemical shifts for the analogous glucose-derived environments are similar at 150, 107 and 15 ppm for the C-1', C-2' and C-3' environments respectively.[31]

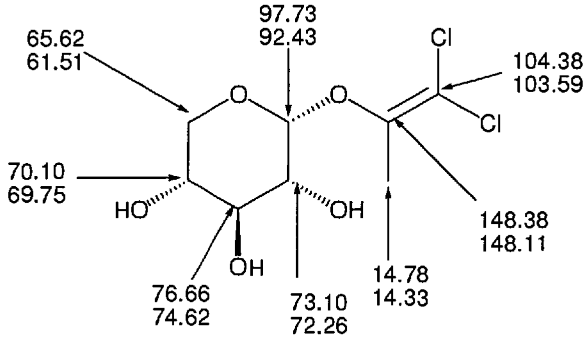
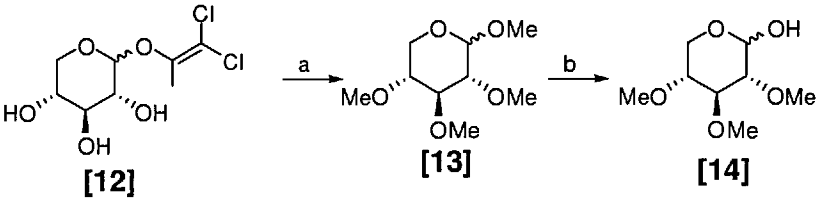


Figure 2.6 – (2',2'-Dichloro-1'-methyl)ethenyl-D-xylopyranoside [12] showing $^{13}C\{^{1}H\}$ NMR shifts for α and β anomers



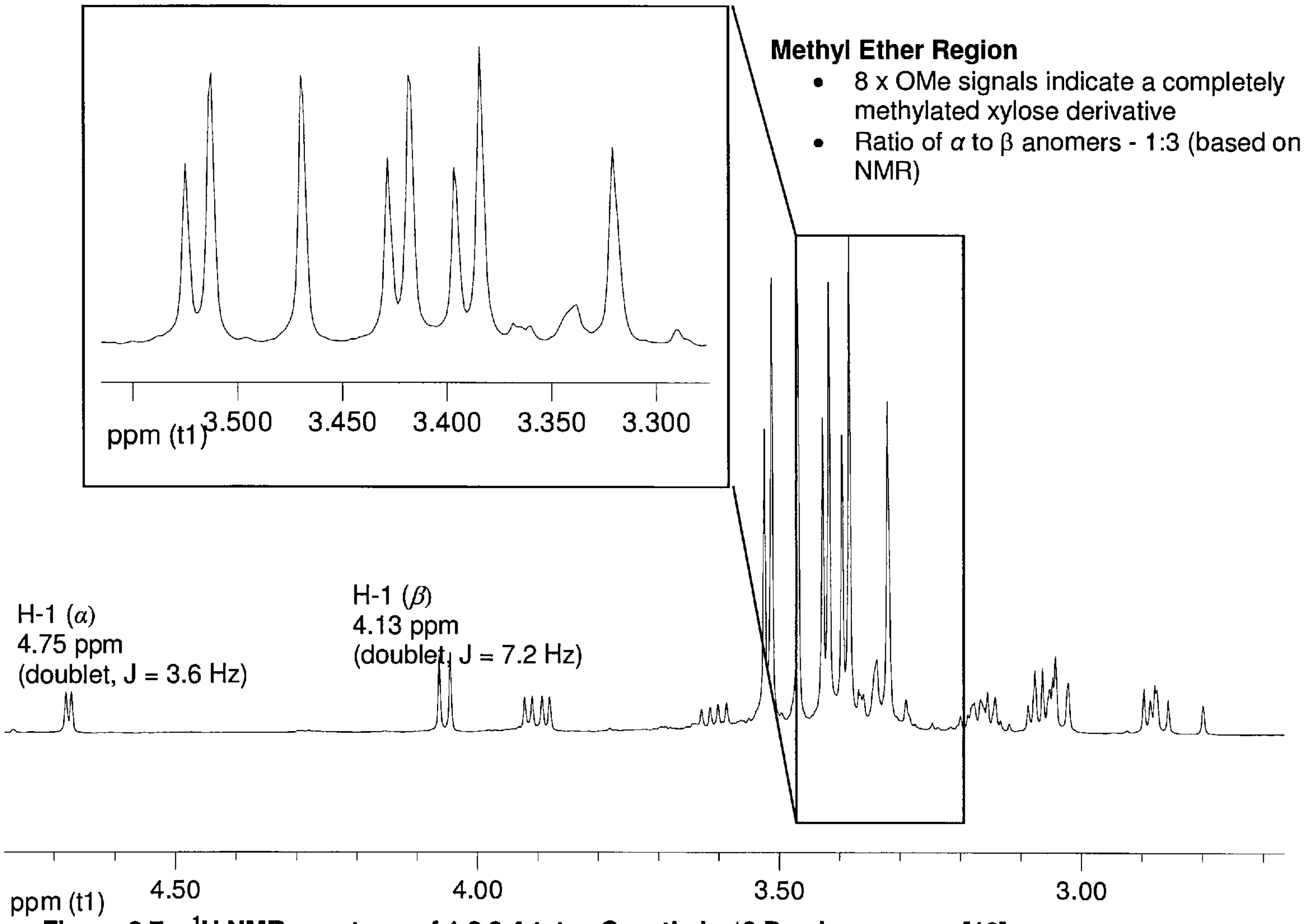
a) 13 eq. NaH, 8 eq. MeI, DMF, 0 °C - r.t, 4 h, b) TFA, H_2O, 65 °C, 4 h; c) PCC,

CH_2Cl_2, *reflux, 7 h*

Scheme 2.27 – Synthetic route to 2,3,4-tri-*O*-methyl-*α*/*β*-D-xylopyranose [14]

The vinyl glycoside **[12]** was methylated by treatment with excess sodium hydride, to deprotonate the hydroxyl groups. This was followed by the addition of methyl iodide to afford 1,2,3,4-tetra-*O*-methyl-D-xylopyranoside **[13]**, in reasonable yield (Scheme 2.27). Complete methylation was achieved in only 4 h and at temperatures not exceeding r.t.

Figure 2.7 shows the ^{1}H NMR of the per-methylated xylose, **[13]**. The presence of 8 clearly defined methyl resonances in Figure 2.7; 4 for each of the anomers, confirms the presence of only the completely methylated species, without contamination from partially methylated compounds.



Methyl Ether Region

- 8 x OMe signals indicate a completely methylated xylose derivative
- Ratio of α to β anomers - 1:3 (based on ^{1}H NMR)

Figure 2.7 – ^{1}H NMR spectrum of 1,2,3,4-tetra-*O*-methyl-α/β-D-xylopyranose [13]

The $^{13}C\{^1H\}$ NMR spectrum of **[13]**, in Figure 2.8 clearly shows 9 distinctive carbon environments for each of the anomers. The signals at 104.7 and 97.59 ppm correspond to the C-1 environments for the *α* and *β* anomers respectively. Due to their proximity to the electronegative oxygen atom in the ring, they experience the least shielding.

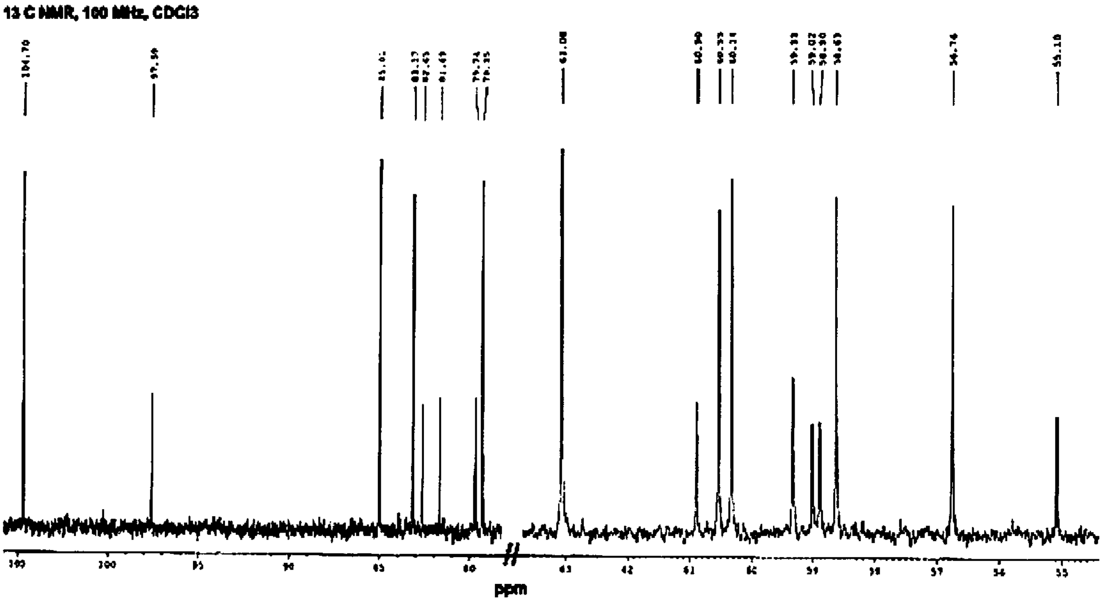
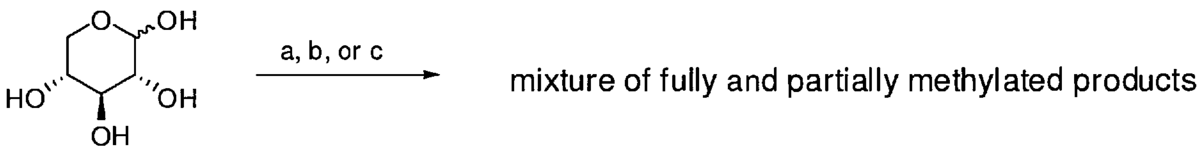


Figure 2.8 – $^{13}C\{^1H\}$ NMR spectrum of 1,2,3,4-tetra-*O*-methyl-*α*/*β*-D-xylopyranose [13]

From the NMR spectrum, it is clear that there are two anomers present in the ratio 3:1. It is concluded that *β* anomer is in greater abundance due to a comparison of the coupling constants on the H-1 protons (with the H-2 protons). In general *β anomers* have a greater coupling constant than α anomers. *β* anomers of methyl glycosides are favoured due to the anomeric effect.

2.6.2 Attempted direct methylation of D-(+)-xylopyranose

Several reports of the direct methylation of carbohydrates are present in the literature. However, characterisation of the products is often limited. In some cases, this is due to the work having been carried out prior to the availability of modern spectroscopic tools.[32-35] Nonetheless, several attempts were made at direct methylation of D-(+)-xylopyranose (Scheme 2.28).



[2c]

a). 12 eq. $(MeO)_2SO_2$, 27 eq. NaOH(aq), 30 - 100 °C, 2 h; 2. 11 eq. MeI, 5 eq. Ag_2O, MeOH, r.t. to 65 °C, 20 h; b)1 eq. MeI, 5 eq. Ag_2O, DMF, r.t., 20 h; c)7 eq. NaH, 10 eq. MeI, DMF, 0 °C to 60 °C, 4 h

Scheme 2.28 – Attempted direct methylation of D-(+)-xylopyranose [2c]

The first method attempted followed the first reports of the methylation of D-(+)-xylopyranose **[2c]** by Carruthers[32] and Purdie.[33] The first step involved the use of NaOH, to deprotonate the hydroxyl moieties, followed by dimethyl sulphate as the methylating agent. At the end of 2 h, with temperatures of up to 100 °C, a mixture of partially and fully methylated D-(+)-xylopyranose derivatives was obtained, as identified by ^1H NMR spectroscopy.

The subsequent step involved treating the methylated xylose products with MeI and Ag_2O. This reaction proceeded for 20 h at temperatures up to 65 °C. This second step yielded some of the target compound although complete methylation was not achieved. However, this methylation route was inefficient, with a yield less than 10%, largely due to the first step in the series. Dimethyl sulphate is also a very toxic reagent and is considered more harmful than MeI. Furthermore, Ag_2O is expensive, difficult to handle, and the removal of silver salts are sometimes problematic, requiring a hazardous cyanide extraction.[34]

In the more recent literature, Walker and co-workers claimed that the complete methylation of carbohydrates was achieved using MeI and Ag_2O in DMF as DMF is known to accelerate alkylation reactions.[34] However, despite following the procedure employed by Walker and co-workers, only partially methylated xylose derivatives were isolated, again in very low yield.

The final attempted procedure for the direct methylation of D-(+)-xylopyranose was based on the conditions which worked for the anomeric protected xylose. Treatment of D-(+)-xylopyranose with NaH and MeI in DMF for 24 h failed to result in complete methylation. As with all the other attempted methylation reactions, a low yield of partially methylated xylose derivatives resulted. Anomeric protection of D-(+)-xylopyranose prior to methylation appears to be the only route to high yielding, completely methylated carbohydrates.

The importance of the anomeric protection in complete methylation of carbohydrates can be rationalised by the relative stabilities of the intermediates as illustrated in Figure 2.9.

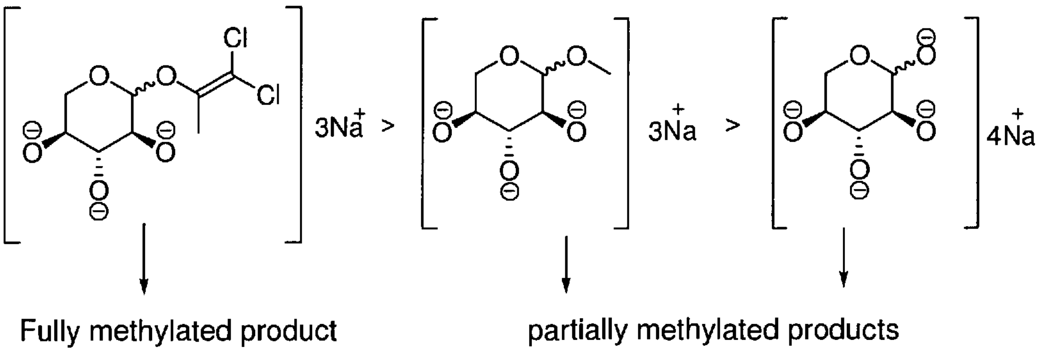
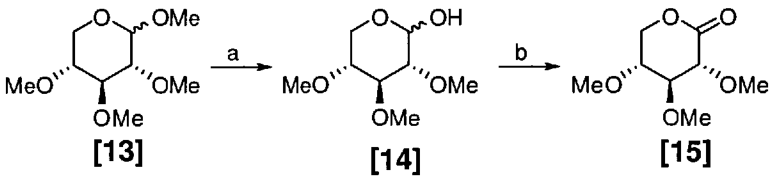


Figure 2.9 – Relative stabilities of the intermediates of the methylation reaction

The reaction proceeds *via* deprotonation with sodium hydride, followed by methylation with methyl iodide. The electron withdrawing nature of the protecting group is likely to stabilise the intermediate as it draws electron density from the anionic centres, thus delocalising the charge density.

2.6.3 Hydrolysis and oxidation

In the final steps of the preparation of the protected xylonolactones hydrolysis using aqueous TFA cleaved the anomeric ether group yielding the methyl-protected lactol, **[14]**. The oxidation was accomplished using pyridinium chlorochromate (PCC) and yielded 2,3,4-tri-*O*-methyl-D-xylono-1,5-lactone **[15]** (Scheme 2.29). It should be noted that these experiments were conducted prior to Swern oxidation investigations. Based on the results obtained with the acetyl-protected derivatives, it is expected that this could be applied to the methyl-protected ones.



a) TFA, H_2O, 65 °C, 4 h; b) PCC, CH_2Cl_2*, reflux, 7 h*

Scheme 2.29 – Hydrolysis and oxidation leading to the synthesis of 2,3,4-tri-*O*-methyl-D-xylono-1,5-lactone [15]

Figure 2.10 shows the ^1H NMR spectrum of 2,3,4-tri-*O*-methyl-D-xylono-1,5-lactone **[15]**. The 3 strong signals corresponding to the 3 methoxy environments are well defined. The loss of chirality at the anomeric centre results in the presence of a single species and is confirmed by the NMR spectroscopy.

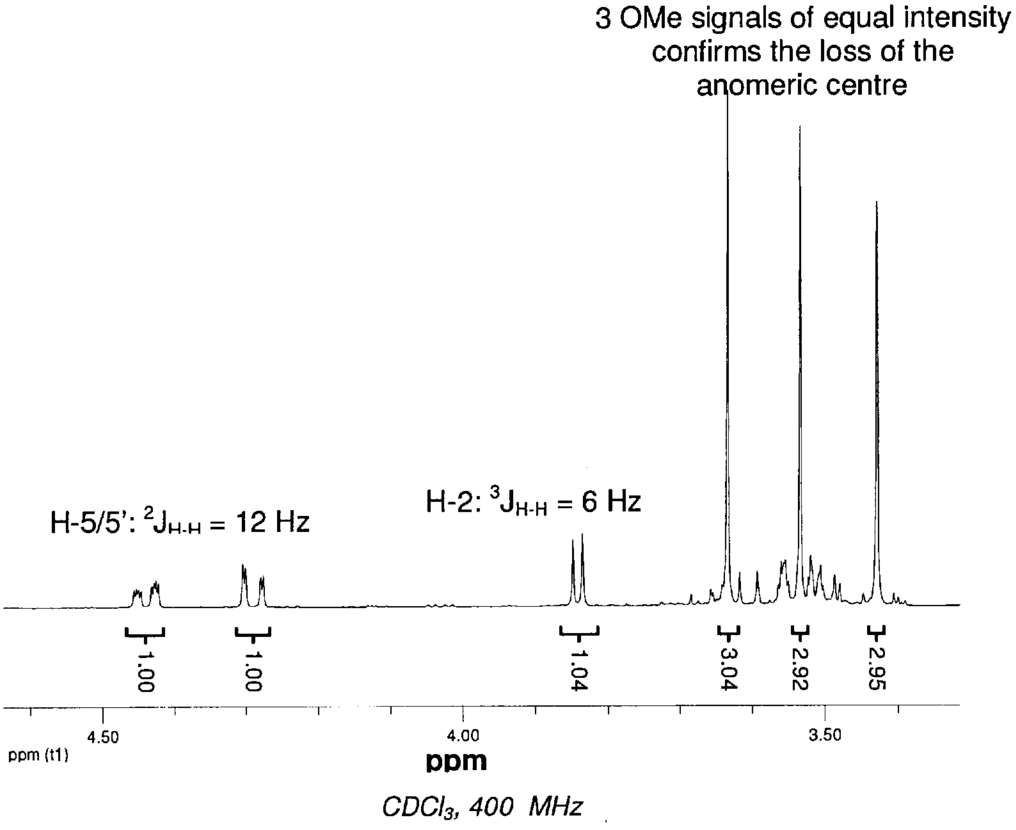
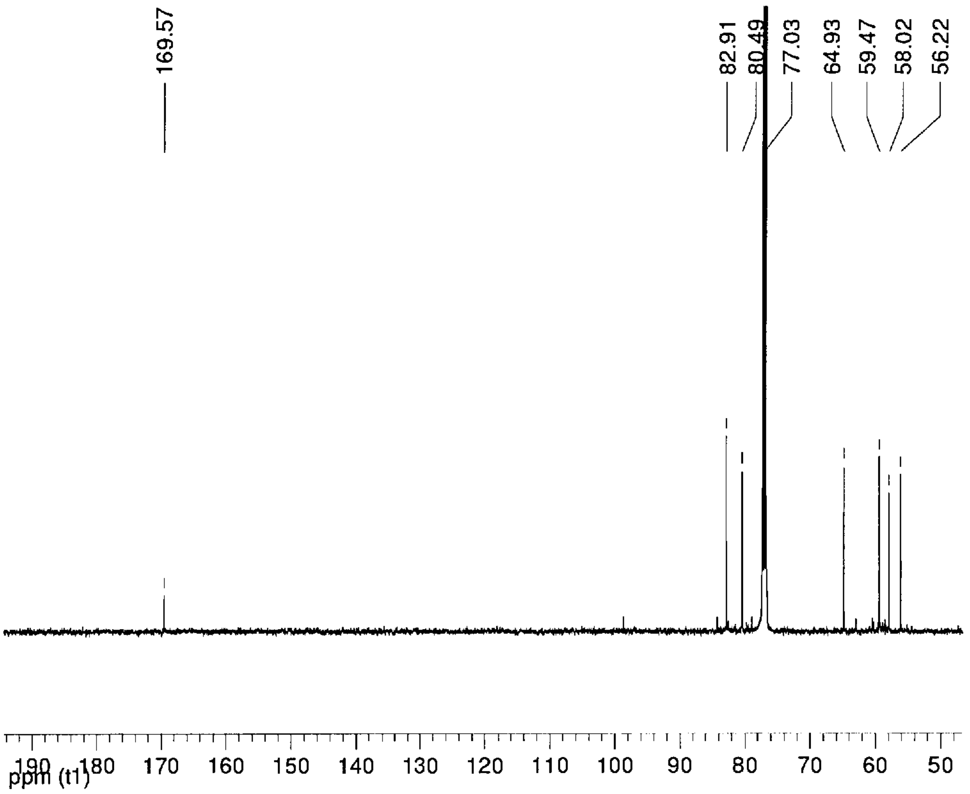


Figure 2.10 – ^1H NMR spectrum of 2,3,4-tri-*O*-methyl-D-xylono-1,5-lactone [15]

Figure 2.11 shows the $^{13}C\{^1H\}$ NMR spectrum of the lactone **[15]** . The signal at 169.57 ppm confirms the presence of the carbonyl group. The remaining 7 signals are attributed to C-2, C-3, C-4, C-5 and the three OMe carbon atoms.



CDCl₃, 125 MHz

Figure 2.11 – $^{13}C\{^1H\}$ NMR spectrum of 2,3,4-tri-*O*-methyl-D-xylono-1,5-lactone [15]

2.7 Conclusion

Acetyl-protected 1,5-lactones, derived from hexose and pentose sugars, were prepared as monomers for ROP as well as precursors for monomers suitable for polycondensation. Derivatives of D-(+)-galactopyranose, D-(+)-mannopyranose, D-(+)-xylopyranose and L-(+)-arabinopyranose were prepared *via* a 4-step procedure in overall yields of up to 72 %. Intermediary and target compounds were completely characterised. Particular attention was drawn to NMR as this provided critical information which alluded to the anomeric and conformational structures. Furthermore, where available, this was in agreement with the literature.

The first step was the per-acetylation using TFA in acetic anhydride in quantitative yield. This was followed by bromination using HBr in acetic acid to form the corresponding glycosyl bromides in excellent yields between 76 % and 95 %. These were subsequently converted to their respective lactols *via* a Koenigs-Knorr type hydrolysis reaction using Ag_2CO_3, in aqueous acetone. Excellent yields were obtained which ranged from 77 % to 100 %. Whilst alternative methods were reported in the literature which enabled the direct synthesis of lactols from their parent glycosyl acetates using amino alcohols, it was found that these are relatively low-yielding with difficult isolation of the target products. For example, 2,3,4,6-tetra-*O*-acetyl-*α*-D-galactopyranose **[5a]** was prepared in an overall 95 % yield *via* the glycosyl bromide whereas a mere 50 % isolated yield was achieved when prepared using the amino alcohol. Therefore, despite the introduction of an additional step, the simplicity and high-yielding glycosyl bromide route was optimal for the synthesis of the lactols.

The critical step and least-developed area towards the monomer synthesis is the oxidation to achieve the 1,5-lactones. This was not applicable to the D-(+)-glucopyranose derivative as its 1,5-lactone is commercially available. Thus a simple per-acetylation served to yield this acetylated derivative in quantitative yield.[16] The remainder of the acetyl-protected 1,5-lactones had to be obtained by oxidation of their parent pyranoses. There is limited literature precedence with respect to the oxidation of pyranoses and in particular acetyl-protected ones. Several oxidation methods were considered taking into consideration environmental impacts as well as ease of scale-up. Literature precedence revealed some routes to acetyl-protected 1,5-lactones such as the synthesis of 2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone **[6b]** using RuO_2.[18] **[6b]** and 2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone **[6e]** were prepared from the parent glycosyl azide *via* a photo-induced reaction in the presence of NBS.[21] However, the final step towards the 1,5-lactones were low-yielding. Furthermore, the synthesis of the precursors required several low-yielding steps.

The most promising route appeared to be oxidation of pyranoses using CrO_3 as this was reported in the synthesis of 2,3,4-tri-*O*-acetyl-D-xylono-1,5-lactone **[6c]**.[22] This involved the use of 8 equivalents of CrO_3 which immediately raised concern due to toxicity of Cr(VI) and the large scale of the reactions. Attempts were made to optimise this reaction but the greatest yield obtained was 17 %. Thus alternative routes were sought.

This led to oxidation using DMSO in acetic anhydride which was reported in the synthesis of benzyl protected 1,5-lactones.[24] This appeared to be ideal owing to the non-toxic nature of the reagents compared to heavy metals. However, when applied to acetyl-protected lactols, acetylation at the anomeric position was observed leading to per-acetylated glycosyl acetates. These results led to the consideration of the related oxidation route; the Swern oxidation. Despite its widespread use in organic chemistry, this simple yet robust oxidation method had not been reported as the oxidant of such lactols. Thus, it was applied to the oxidation of our acetyl-protected lactols with remarkable results after several optimisation steps. The most critical optimisation related to temperature control. The Swern oxidation requires the reaction, which is carried out at -78 °C, to be quenched using triethylamine and generally accompanied by warming to r.t. However, triethylamine readily catalyses elimination of acetic acid to yield the unsaturated 1,5-lactone. However, it was observed that if the reaction temperature was not allowed to warm beyond -30 °C after addition of triethylamine, subsequent elimination was not observed. This was achieved by washing the reaction mixture with iced water once the reaction temperature reached -30 °C. This procedure could be applied to all the protected lactols in yields of up to 83 %. As the acetyl group is considered a sensitive protecting group, it is likely that this procedure can be applied to other protecting groups such as benzyl and methyl. This robustness and flexibility makes it an invaluable synthetic procedure. Furthermore, owing to the ease of the reaction and non-hazardous reagents and by-products, this makes it a particularly useful method for large-scale syntheses.

The synthesis of the methyl protected xylose-derivative 2,3,4-tri-*O*-methyl-D-xylono-1,5-lactone **[15]** was also explored to allow for an alternative set of carbohydrate-derived polyesters. In so doing, a new synthesis of this 1,5-lactone was achieved in five steps from D-(+)-xylopyranose. The synthesis applied a novel C-1 protecting group strategy, previously described for hexoses,[31] to facilitate the synthesis and purification of permethylated xylose. The anomeric methyl group was cleaved in reasonable yield using a dilute trifluoroacetic acid solution and the oxidation of the permethylated xylopyranose was accomplished in excellent yield by using PCC.

Thus after establishing and optimising invaluable synthetic procedures we were armed with a comprehensive library of compounds which would serve as useful tools for further chemical manipulation as well as for polymerisation reactions.

2.8 References

1. Pedersen, C., *Carb. Res.* **1999,** 315, 192-197.

2. Juaristi, E.; Cuevas, G., *Tetrahedron* **1992,** 48, (24), 5019-5087.

3. Kirby, A. J., *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen.* Springer-Verlag: 1983.

4. Bock, K.; Lundt, I.; Pedersen, C., *Tet. Lett.* **1973,** 14, (13), 1037-1040; Bock, K.; Pedersen, C., *J. Chem. Soc., Perkin Trans II* **1974,** 3, 293-297.

5. Karplus, M., *J. Chem. Phys.* **1959,** 30, (1), 11-15.

6. Wahlera, D.; Boujarda, O.; Lefèvre, F.; Reymond, J.-L., *Tetrahedron* **2004,** 60, (3), 703-710.

7. Mitchell, S. A.; Pratt, M. R.; Hruby, V. J.; Polt, R., *J. Org. Chem.* **2001,** 66, (7), 2327-2342.

8. Nobrega, C.; Vazquez, J. T., *Tet. Asymm.* **2003,** 14, 2793-2801.

9. Yu, W.; Jin, Z., *J. Am. Chem. Soc.* **2002,** 124, (23), 6576-6583.

10. Alcaro, S.; Arena, A.; Neri, S.; Ottana, R.; Ortuso, F.; Pavone, B.; Vigorita, M. G., *Bioorg. Med. Chem.* **2004,** 12, (7), 1781- 1791.

11. Grummitt, Annaleise R.; Harding, Margaret M.; Anderberg, Pia I.; Rodger, A., *Eur.J. Org. Chem.* **2003**, (1), 63-71.

12. Hanessian, s., *Preparative Carbohydrate Chemistry.* Marcel Dekker: 1997; p 283-285.

13. Lindhorst, T. K., *Essentials of Carbohydrate Chemistry and Biochemistry.* Wiley-VCH: 2007.

14. Tosin, M.; Murphy, P. V., *J. Org. Chem.* **2005,** 70, (10), 4107-4117.

15. Namchuk, M. N.; McCarter, J. D.; Becalski, A.; Andrews, T.; Withers, S. G., *J. Am. Chem. Soc* **2000,** 122, (7), 1270-1277.

16. Joseph, C. C.; Regeling, H.; Zwanenburg, B.; Chittenden, G. J. F., *Tetrahedron* **2002,** 58, 6907-6911.

17. Pagliaro, M.; Campestrini, S.; Ciriminna, R., *Chem. Soc. Rev.* **2005,** 34, 837-845.

18. Lichtenthaler, F. W.; Jarglis, P., *Chem. Ber.* **1980,** 113, (2), 489-510.

19. El-Badri, M. H.; Willenbring, D.; Tantillo, D. J.; Gervay-Hague, J., *J. Org. Chem.* **2007,** 72, (13), 4663-4672; Brüns, A.; Wibbeling, B.; Fröhlich, R.; Hoppe, D., *Synthesis* **2006,** 18, 3111-3121; Zanoni, G.; Porta, A.; Brunoldi, E.; Vidari, G., *J. Org. Chem.* **2006,** 71, (22), 8459-8466.

20. Benhaddou, R.; Czernecki, S.; Farid, W.; Ville, G.; Xie, J.; Zegar, A., *Carb. Res.* **1994,** 260, (2), 243-250.

21. Senni, D.; Praly, J.-P., *Synth. Comm.* **1998,** 28, (3), 433-441.

22. Nelson, C. R., *Carb. Res.* **1979,** 68, (1), 55-60.

23. Kuzuhara, H. F., Hewitt G., Jr., *J. Org. Chem.* **1967,** 32, (8), 2531-2534.

24. Overkleeft, H. S. v. W., Jim; Pandit, Upendra K;, *Tetrahedron* **1994,** 50, (14), 4215- 4224.

25. Albright, D.; Goldman, L., *J. Am. Chem. Soc* **1965,** 87, (18), 4214-4216.

26. Omura, K.; Swern, D., *Tetrahedron* **1978,** 34, (11), 1651-1660.

27. Su, Z.; Paquette, L. A., *J. Org. Chem* **1995,** 60, (3), 764-766.

28. Bock; Lundt; Pedersen, *Acta Chem. Scand.* **1981**, (B35), 155-162.

29. Keyworth, C. 4th Year Undergraduate Project. 2006.

30. Praly, J.-P.; Senni, D.; Faureb, R.; Descotes, G., *Tetrahedron* **1995,** 51, (6), 1697-1708.

31. Figueiredo, R. M. d.; Baillieza, V.; Dubreuilb, D.; Oleskera, A.; Cleophax, J., *Synthesis* **2003**, 2831-2835.

32. Carruthers, A.; Hirst, E. L., *J. Chem. Soc.* **1922,** 121, 2299-2308.

33. Purdie, T.; Irvine, J., *J. Chem. Soc.* **1903,** 83, 1021-1041.

34. Walker, H. G.; Gee, M.; McCready, R. M., *J. Org. Chem* **1962,** 27, 2100-2102.

35. Haworth, W. N.; Westgarth, G. C., *J. Chem. Soc.* **1926**, 880-887; Wintersteiner, O.; Klingsberg, A., *J. Am. Chem. Soc* **1949,** 71; Pacsu, E.; Trister, S. M., *J. Am. Chem. Soc* **1939,** 61, 2442-2444; West, E. S.; Holden, R. F., *Org. Synth. Coll.* **1955,** 3, 800.

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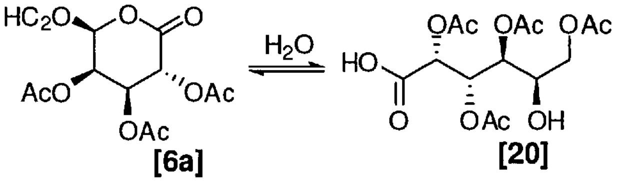
CHAPTER 3:

ACETYL-PROTECTED ALDARIC ESTERS

3.1 Introduction

After the successful synthesis of functionalised, carbohydrate-derived 1,5-lactones **[6]**, further manipulation was considered to increase the range of monomers and potential polymerisation techniques. Thus, the natural choice was to open the 1,5-lactone ring. This enabled the synthesis of substrates with multiple applications. Not only could they be used as co-initiators in the ring opening polymerization (ROP) of lactide, these compounds are potential monomers in polycondensation reactions by careful selection of the ring-opening agent.

Aldonolactones are commonly associated with their ring-opened forms. In fact, in solution unprotected aldonolactones are in equilibrium with their aldonic acids, as residual water acts as the ring-opening agent. The same was found when acetyl-protected lactones were exposed to moisture. In principle, this should be advantageous as it forms an AB-type monomer (Scheme 3.1) for polycondensation. However, it has been well established that aldonic acids do not readily undergo polycondensation. The ring-closed form is more stable and aldonic acids readily cyclise under most reactions conditions (eg. heat, solution) and in the presence of catalysts.



Scheme 3.1 - Equilibrium between 2,3,4,6-tetra-*O*-acetyl-D-galactono-1,5-lactone [6a] and its aldonic acid

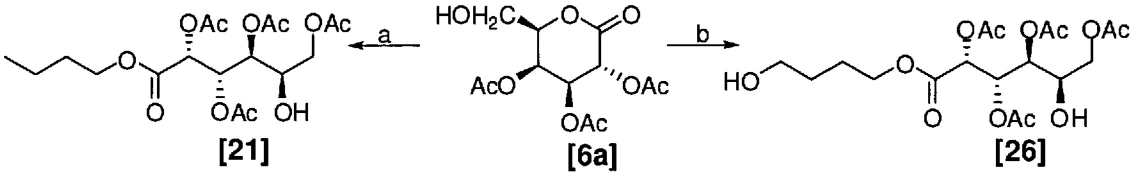
Joseph *et al.* had shown that methanol can be used to open 2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone **[6e]** to form a stable ring-opened methyl ester.[1] Thus alternative alcohols were explored which could introduce the functionality required to prepare suitable monomers for polycondensation. Therefore, 1,4-butanediol, a bi-functional alcohol, was investigated using a method derived from that reported by Joseph *et al.*[1] It was necessary to choose an alcohol which would result in an alkyl ester with a back-bone containing more than 7 atoms so as to hinder cyclisation. It was also noted that in this form, these compounds are also potential co-initiators for lactide ROP due to the presence of their hydroxyl groups. This brings about an elegant manner of introducing carbohydrate moieties to poly(lactide) (PLA). They were also modified by using butan-1-ol as the ring-opening agent to produce carbohydrate esters with a single hydroxyl group. This allowed us to investigate the effect this change has on polymerisation activity as well as in the resulting polymers. The successful synthesis of derivatives of the large number of hexoses and pentoses also enabled us to study how the parent carbohydrate affects polymerisability.

It should also be noted that we have prepared a large library of well-characterised compounds which may also have applications in other areas of chemistry. Biological chemistry in particular, is always in search of compounds derived from naturally-occurring materials with sugars playing an important role. Finally, this chapter will also show how this reproducible synthetic procedure can be successfully applied to a wide range of substrates.

3.2 Synthesis

Novel aliphatic esters derived from acetyl-protected 1,5-lactones were prepared *via* a ring-opening reaction, catalyzed by *para*-toluenesulphonic acid (*p*-TSA) in the presence of one of two aliphatic alcohols; butan-1-ol or 1,4-butanediol.

The purpose for synthesising these esters was two-fold. The ring-opening reaction with butan-1-ol or 1,4-butanediol yielded a compound suitable as an initiator for the ROP of lactide. This would serve to increase the functionality of the resulting PLA end-group. In addition to this, it was expected to increase its hydrophilicity due to the presence of hydrophilic acetyl groups. Furthermore, the ring-opening reaction with 1,4-butanediol yields a novel diol, a BB-type monomer, suitable for polycondensation reactions.



a) 0.1 eq. p-TSA, 1.0 eq. butan-1-ol, $CHCl_3$, 0 °C or r.t.

b) 0.1 eq. p-TSA, 1.0 eq. 1,4-butandiol, CH_2Cl_2, 0 °C or r.t.

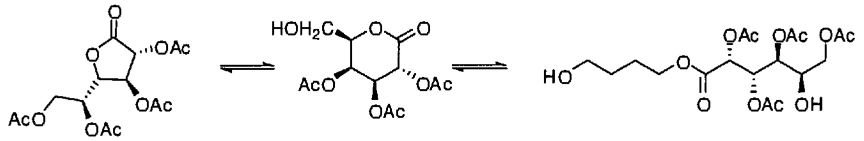
Scheme 3.2 - Synthesis of monoesters and diesters derived from acetyl-protected 1,5-lactones with butan-1-ol and 1,4-butanediol shown using 2,3,4,6-tetra-*O*-acetyl-D-galactono-1,5-lactone [6a]

Scheme 3.2 illustrates the syntheses of the aliphatic esters derived from acetyl-protected 1,5-lactones **[6]**. The procedure employed in the synthesis of these esters was an adaptation of a similar method reported by Joseph *et al.*,[1] where the methyl ester of 2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone was prepared using methanol. However, unlike in the procedure reported by Joseph *et al.*,[1] the alcohols could not be used as solvents for two reasons. Firstly, the high boiling points of the alcohols would make it difficult to remove them. Secondly, in the case of 1,4-butanediol, possible uncontrolled oligomerisation may result due to the presence of two alcohol moieties.

Thus using either butan-1-ol or 1,4-butanediol, 10 equivalents of the starting 1,5-lactone **[6]** were used with a single equivalent of *p*-TSA. The alcohol was first dissolved in the reaction solvent and then treated with *p*-TSA. The 1,5-lactone **[6]** was then introduced. The alcohol must first be activated with the acid. Failure to do so, results in irreversible decomposition of the 1,5-lactone to the 1,4-lactone before ring-opening is observed. The same observation was made when the ring opening reaction in methanol was carried out.

Several experiments were conducted to optimise yields. During the course of these experiments, there was a distinctive difference in the rates of reactions depending on the stereochemistry of the 1,5-lactones. It was found that the D-(+)-galactopyranose derivative was the most reactive, requiring the shortest reaction times, whereas the pentose derivatives were the least reactive.

As part of the kinetics studies, carried out at room temperature and for prolonged reaction times, it was observed that the reaction proceeded through the products illustrated in Scheme 3.3 shown using 2,3,4,6-tetra-*O*-acetyl-D-galactono-1,5-lactone **[6a]** as an example.



[16] Thermodynamic product

[6a]

[26] Kinetic product

Scheme 3.3 - Reaction of 2,3,4,6-tetra-*O*-acetyl-D-galactono-1,5-lactone [6a] in the presence of *p*-TSA and an aliphatic alcohol over long reaction times at r.t.

The formation of the monoester required between 20 mins and 2 h, depending on the starting 1,5-lactone **[6]**. This is a reversible reaction resulting in the reformation of the starting material if the reaction was not stopped after formation of the ring-opened ester. Further exposure of **[6]** to acid with prolonged reaction times, catalysed its conversion to the 1,4-lactone (**[16]** - **[18]**). This suggests that the monoester is the kinetic product whereas the 1,4-lactone is the thermodynamic one (Scheme 3.3). This claim is further supported by the information presented in Figure 3.1 to Figure 3.3 and in Table 3.1. These show the relative ratios of isolated compounds for reactions with 1,4-butanediol at r.t. Similar results were obtained when using butan-1-ol.

Table 3.1 - Molar ratios observed on monitoring the synthesis of 4-hydroxybutyl terminated monoesters

Starting 1,5-Lactone	15 mins 1,5-lactone : monoester : 1,4-lactone	1 h 1,5-lactone : monoester : 1,4-lactone	2 h 1,5-lactone : monoester : 1,4-lactone	48 h 1,5-lactone : monoester : 1,4-lactone
2,3,4,6-tetra-*O*-acetyl-D-galactono-1,5-lactone **[6a]**	0 : 1 : 0	1 : 4 : 2	1 : 5 : 4	0 : 0 : 1
2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone **[6b]**	1 : 2 : 0	0 : 1 : 0	1 : 3 : 0	2: 2 : 1
2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone **[6e]**	-	1 : 0 : 0	0 : 1 : 0	-
2,3,4-tri-*O*-acetyl-D-xylono-1,5-lactone **[6c]**	-	4 : 1 : 0	0 : 1 : 0	0 : 1 : 1
2,3,4-tri-*O*-acetyl-L-arabinono-1,5-lactone **[6d]**	-	-	0 : 1 : 0	-

Reaction conditions: 1 eq. 1,5-*lactone, 1.0 eq. 1,4-butanediol, 0.1 eq. p-TSA,*

CH_2Cl_2, r.t.

To effectively illustrate the course of the reaction described in Scheme 3.3, Figure 3.1 to Figure 3.3 show how the proportions of lactones and 4-hydroxybutyl ester derived from D-(+)-galactopyranose **[26]** varied with reaction time in the presence of *p*-TSA.

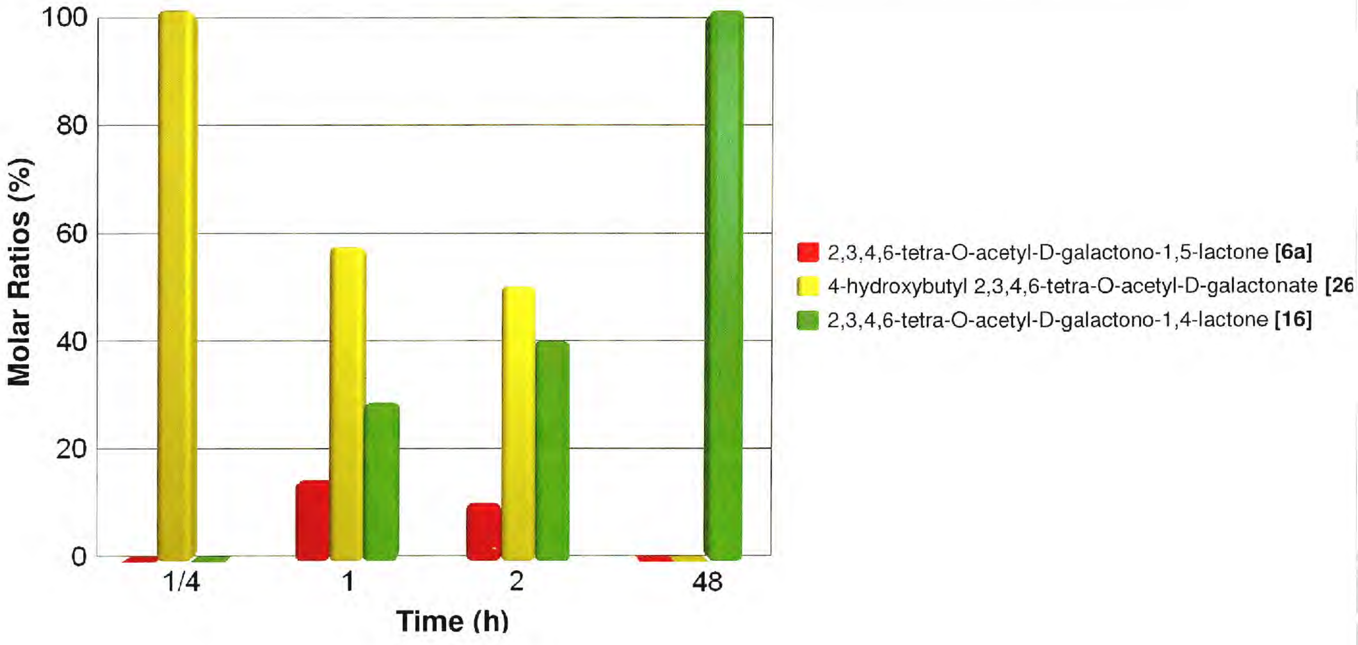


Figure 3.1 - Molar ratios of lactones ([6a], [16]) and 4-hydroxyl ester [26] in the D-(+)-galactopyranose-derived reaction

The formation of 4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-galactonate **[26]** was complete in under 15 mins with no traces of either lactones as shown in Figure 3.1. However, at the end of 1 h, 15 mol % of the reaction mixture was comprised of the 1,5-lactone **[6a]**, and 29 mol % was attributed to the 2,3,4,6-tetra-*O*-acetyl-D-galactono-1,4-lactone **[16]**. As the reaction time was increased, the proportions of 1,5-lactone **[6a]** and 4-hydroxybutyl ester decreased **[26]**. The proportion of 1,4-lactone **[16]** continuously increased until at the end of 48 hours, it was the only carbonyl product left in the reaction mixture.

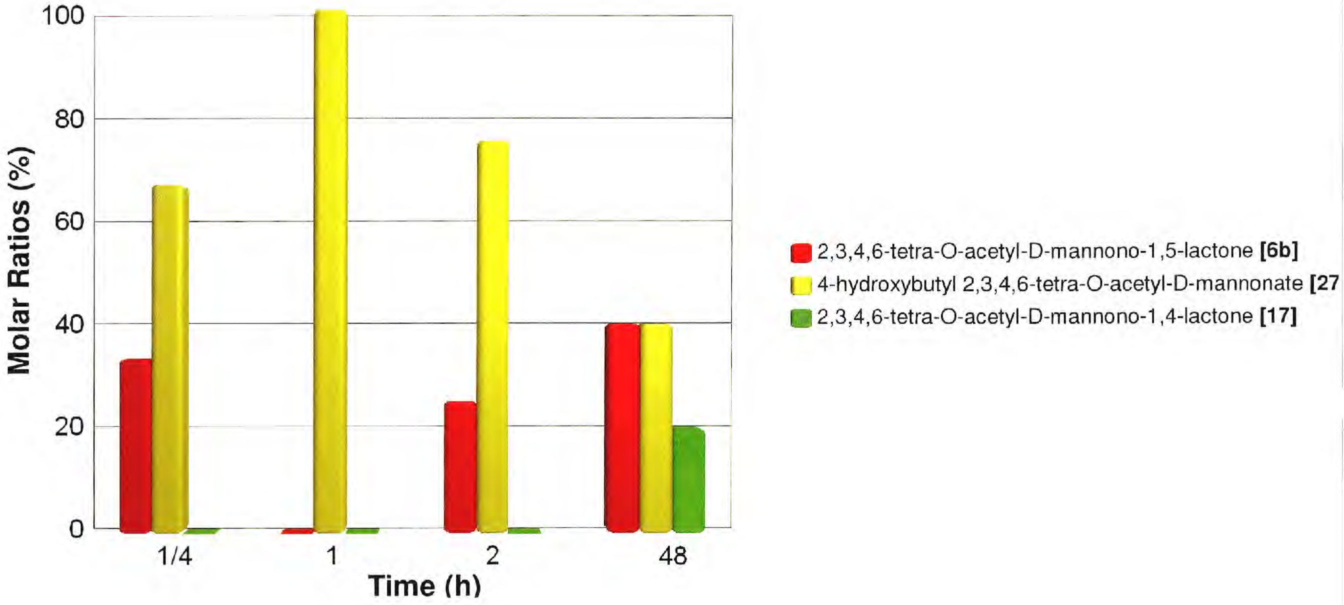


Figure 3.2 - Molar ratios of lactones ([6b], [17]) and 4-hydroxyl ester [27] in the D-(+)-mannopyranose-derived reaction

A similar trend was observed with the D-mannose derivatives and is illustrated by Figure 3.2. As the reaction proceeds, the 1,5-lactone **[6b]** is consumed at the end of an hour where the 4-hydroxybutyl ester **[27]** is the only product present. Although the trend observed here is similar to that observed for the galactose derivative. The rate of the reaction is slower for the derivative. Whereas complete conversion to 4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-galactonate was observed in 15 mins, the analogous derivative was observed in an hour, taking 4 times as long.

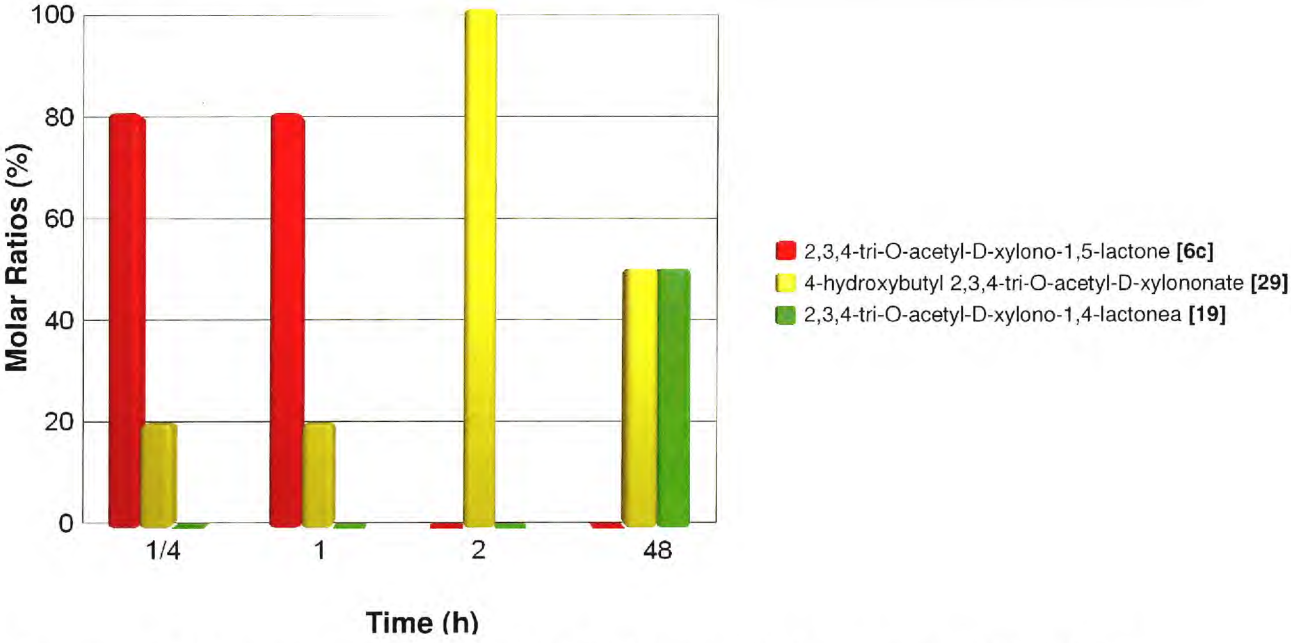


Figure 3.3 - Molar ratios of lactones ([6c], [19]) and 4-hydroxyl ester [29] in the D-(+)-xylopyranose-derived reaction

Figure 3.3 illustrates how the same trend is observed for the D-(+)-xylopyranose derivative. However, the rate was even slower than that observed for the D-(+)-mannopyranose derivative. Only at the end of 2 h was complete conversion to the 4-hydroxybutyl ester **[29]** observed, with the exclusion of the formation of both the lactones. Similar results were observed for the L-(+)-arabinopyranose derivative. By stopping the reactions at the times where the 4-hydroxyl ester was the exclusive product, the esters were isolated cleanly and in good yield. The reaction with the D-(+)-galactopyranose derivative however, was carried out at 0 °C in order to slow the reaction and isolate the 4-hydroxyl ester. When butan-1-ol was used, the reaction kinetics did not alter and the same conditions were used to isolate the target products.

Table 3.2 – Yields for the syntheses of esters derived from acetyl-protected 1,5-lactones

Product	Yield	Product	Yield
butyl 2,3,4,6-tetra-O-acetyl-D-galactonate **[21]**	49 %	4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-galactonate **[26]**	60 %
butyl 2,3,4,6-tetra-*O*-acetyl-D-mannonate **[22]**	21 %	4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-mannonate **[27]**	76 %
butyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate **[23]**	77 %	4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate **[28]**	95 %
butyl 2,3,4-tri-*O*-acetyl-D-xylononate **[24]**	67 %	4-hydroxybutyl 2,3,4-tri-*O*-acetyl-D-xylononate **[29]**	73 %
butyl 2,3,4,6-tri-*O*-acetyl-L-arabinonate **[25]**	79 %	4-hydroxybutyl 2,3,4,6-tri-*O*-acetyl-L-arabinonate **[30]**	39 %

The yields for these reactions are given in Table 3.2. These range from 21 % to 95 % and the new esters were all pure by elemental analysis. Attempts were made at monitoring the reaction by TLC. However, it was observed that they decomposed to the starting 1,5-lactones **[6]** and starting alcohol on the TLC plate.

3.3 Characterisation

Once isolated, these novel compounds were characterised by NMR spectroscopy, IR spectroscopy, optical rotation and elemental analysis. Table 3.3 to Table 3.6 show the ^{1}H and 13C{^{1}H} NMR resonances for the 4-hydroxybutyl and butyl-terminated esters **[21]** to **[30]** In order to arrive at these assignments derivatives were also analysed by HMQC and HMBC 2-dimensional NMR.

Table 3.3 - ^{1}H NMR data for 4-hydroxybutyl terminated monoesters derived from acetyl-protected 1,5-lactones

Product	**δ H-2 (*J*)**	**δ H-3 (*J*)**	**δ H-4 (*J*)**	**δ H-5 (*J*)**	**δ *H-5' (*J*)**	**δ H-6/H-6' (*J*)**
4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-galactonate **[26]**	5.78 (9.8, 2.0)	5.21 - 5.16	4.22 - 4.06			
4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-mannonate **[27]**	5.17 (7.8)	5.66 (8.6, 2.2)	5.27 (9.1, 2.1)	4.29 - 4.07		
4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate **[28]**	5.29 (3.9)	5.74 (3.7, 3.7)	5.20 (8.3, 3.6)	3.89 - 3.80	-	4.15 - 4.11
4-hydroxybutyl 2,3,4-tri-*O*-acetyl-D-xylononate **[29]**	5.70 (8.0)	5.64 (7.8, 7.8)	5.02 (7.6, 2.9)	4.40 (12.8, 2.9)	4.28 (12.8, 3.0)	-
4-hydroxybutyl 2,3,4,6-tri-*O*-acetyl-L-arabinonate **[30]**	5.57 (6.9)	5.45 (6.8, 6.8)	4.55 (6.6, 4.9, 2.9)	4.47 (12.6, 4.9)	4.27 (12.6, 4.9)	-

1,5 = *chemical shift (reported in ppm). J = coupling constant (reported in Hz). * only applies to pentose-derived carbohydrates.*

Unreported coupling constants are those which were not resolved.

Table 3.4 - $^{13}C\{^1H\}$ NMR data for 4-hydroxybutyl terminated monoesters derived from acetyl-protected 1,5-lactones

Product	δ C-1 (*J*)	δ C-2 (*J*)	δ C-3 (*J*)	δ C-4 (*J*)	δ C-5 (*J*)	*δ C-6 (*J*)
4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-galactonate **[26]**	168.03	69.71	68.53	68.21	68.29	68.21 - 63.51
4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-mannonate **[27]**	169.00	69.55	66.44	69.55	64.21	62.87 - 61.96
4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate **[28]**	166.76	71.81	69.50	70.56	68.41	64.35
4-hydroxybutyl 2,3,4-tri-*O*-acetyl-D-xylononate **[29]**	168.45	70.44	72.48	75.53	60.27	-
4-hydroxybutyl 2,3,4,6-tri-*O*-acetyl-L-arabinonate **[30]**	168.27	72.00	72.56	77.43	62.11	-

1,5 = *chemical shift (reported in ppm). J = coupling constant (reported in Hz). * only applies to hexose-derived carbohydrates.*

Unreported coupling constants could not be resolved.

Table 3.5 - ^1H NMR data for butyl terminated monoesters derived from acetyl-protected 1,5-lactones

Product	δ H-2 *(J)*	Δ H-3 *(J)*	δ H-4 *(J)*	δ H-5 *(J)*	δ *H-5' *(J)*	δ H-6/H-6' *(J)*
butyl 2,3,4,6-tetra-*O*-acetyl-D-galactonate **[21]**	5.76	5.16	5.30 (3.9, 2.0)	3.97 (11.5, 7.4)	-	4.14 - 4.06
butyl 2,3,4,6-tetra-*O*-acetyl-D-mannonate **[22]**	5.28 (9.1, 2.4)	5.67 (8.5, 2.2)	5.09 (8.5)	3.80	-	4.11 (11.0, 5.3)
butyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate **[23]**	5.30 (3.9)	5.73 (3.7)	5.20 (8.3, 3.6)	3.89 - 3.80	-	4.23 - 4.02
butyl 2,3,4-tri-*O*-acetyl-D-xylononate **[24]**	5.69 (8.0)	5.63 (7.8, 7.8)	5.02	4.50 - 4.08		-
butyl 2,3,4,6-tri-*O*-acetyl-L-arabinonate **[25]**	5.56 (6.9)	5.45 (6.8, 6.8)	4.54 (6.8, 4.9, 2.9)	4.46 (12.6, 3.0)	4.26 (12.6, 5.0)	-

1,5 = *chemical shift (reported in ppm). J = coupling constant (reported in Hz). *only applies to pentose-derived carbohydrates.*

Unreported coupling constants could not be resolved.

Table 3.6 - $^{13}C\{^1H\}$ NMR data for butyl terminated monoesters derived from acetyl-protected 1,5-lactones

Product	δ C-1 *(J)*	δ C-2 *(J)*	δ C-3 *(J)*	δ C-4 *(J)*	δ C-5 *(J)*	*δ C-6 *(J)*
butyl 2,3,4,6-tetra-*O*-acetyl-D-galactonate **[21]**	167.76	70.58	69.62	68.65	67.71	62.75
butyl 2,3,4,6-tetra-*O*-acetyl-D-mannonate **[22]**	167.76	69.55	68.97	69.59	67.62	64.78
butyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate **[23]**	166.87	71.75	69.51	70.78	68.41	65.94
butyl 2,3,4-tri-*O*-acetyl-D-xylononate **[24]**	168.45	70.42	72.91	75.35	69.28	-
butyl 2,3,4,6-tri-*O*-acetyl-L-arabinonate **[25]**	168.26	72.06	72.63	77.37	62.10	-

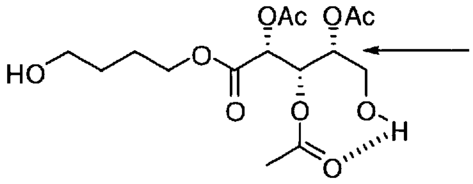
1,5 = chemical shift (reported in ppm). J = coupling constant (reported in Hz). *only applies to hexose-derived carbohydrates. Unreported coupling constants could not be resolved.

3.3.1 ^{1}H NMR Characterisation

^{1}H NMR analysis revealed several similarities as well as some differences between the alcohol terminated esters. It was observed that H-2 resonated between 5.6 and 5.8 ppm for all the ring-opened esters, except from those derived from D-(+)-mannopyranose and D-(+)-glucopyranose. On the whole this resonance did not differ greatly from the starting 1,5-lactones **[6]**. H-2 for the D-(+)-mannopyranose-derived esters (**[22]**, **[27]**) and D-(+)-glucopyranose-derived esters (**[23]**, **[28]**) resonated at lower frequencies, between 5.2 and 5.3 ppm. This is not surprising for the D-(+)-glucopyranose-derived esters (**[23]**, **[28]**) as H-2 resonates close to the analogous proton 1,5-lactone. However H-2 in the D-(+)-mannopyranose derivatives (**[22]**, **[27]**) resonates at a frequency of 0.5 ppm below the analogous proton in the starting material **[6b]**. This marked difference, is attributed to the unique stereochemistry that the D-(+)-mannopyranose derivative possesses at this position. Its derivatives possess *S* stereochemistry at C-2 whereas the remaining library of compounds possess *R* stereochemistry at this position.

H-4 resonates between 4.6 and 5.3 ppm for all the esters, except for those derived from D-(+)-galactopyranose where the resonating frequency is between 4.1 and 4.2 ppm. This is again due to the different stereochemistry of these derivatives at C-4 compared to the other compounds.

The most striking NMR characteristic of these compounds is the resonating frequency for H-5. The chemical shift at this position is between 3.8 and 4.5 ppm for all the esters. For those derived from the hexoses, this is about 1 ppm upfield *versus* the parent 1,5-lactones **[6]**. However, H-5 resonances in the pentose derivatives do not differ greatly from their parent lactones. Furthermore, H-5 and H-5' are still distinguishable from one another. This is surprising as once the ring is opened one would expect free rotation about the C4–C5 bond. Thus H-5 and H-5' should be magnetically equivalent. However, the ^{1}H NMR signals associated with H-5 and H-5' in a 4-hydroxybutyl 2,3,4-tri-*O*-acetyl-D-xylononate appear as 2 well-defined doublet of doublets at 4.40 and 4.28 ppm. Associated with these resonances are geminal coupling constants of 13 Hz as well as $^3J_{H\text{-}H}$ coupling constants of 3 Hz resulting from coupling with H-4. This suggests that there is no free rotation about the C-5–C-5 bond. This can be explained by hydrogen bonding between the hydroxyl end group at C-5 and the acetyl group at C-3 as illustrated in Figure 3.4.



rotation about this bond is restricted

Figure 3.4 - Intramolecular hydrogen-bonding in 4-hydroxybutyl 2,3,4-tri-*O*-acetyl-D-xylononate [29]

A study by López de la Paz *et al.*[2] showed that intra-molecular hydrogen bonding in carbohydrates influences the magnitude of coupling constants as a result of fixing the confirmation of the carbohydrate as is observed here. Lommerse *et al.*[3] have also confirmed these results with an investigation of the hydrogen bonding between carbonyl and hydroxyl groups.

The H-6 protons resonate between 4.1 and 4.3 ppm for all the hexose derivatives and are not distinguishable from one another. There is no well-defined hydrogen bonding between the unprotected hydroxyl group at C-5 and the acetyl group at C-3. This is most likely hindered by the presence of the acetyl group at C-6. The unprotected hydroxyl group at C-5-may hydrogen bond with the acetyl groups at C-3 as well as at C-6 (illustrated in Figure 3.5 using 4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-galactonate **[6a]** as an example). This is thought to occur rapidly and thus only an averaged signal is observed in the ^{1}H NMR spectrum.

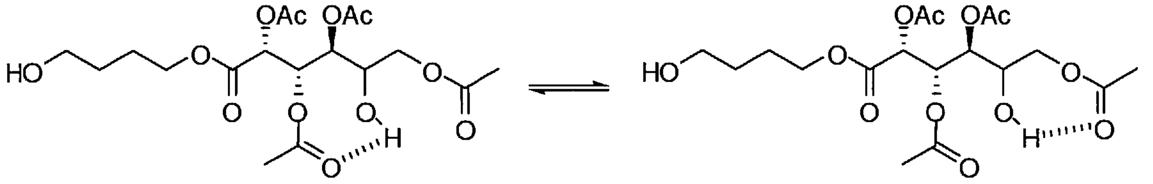


Figure 3.5 - Possible intramolecular hydrogen bonding in 4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-galactonate [6a]

3.3.2 $^{13}C\{^1H\}$ NMR Characterisation

$^{13}C\{^1H\}$ NMR revealed that C-1 resonates between 167 and 169 ppm. This was consistent for all the esters. When compared to the parent 1,5-lactones **[6]**, an increase in the resonating frequency of 2 - 3 ppm, on average, was observed. This is in agreement with a decrease in the strain of the carbonyl on ring-opening.

The chemical shift of C-2 was observed between 70 and 72 ppm for all derivatives and when compared to the 1,5-lactones, again an increase of 2 - 3 ppm was observed. This difference is also likely to be associated with the relief in ring strain.

C-3 resonates at slightly lower frequency than C-2; between 66 and 73 ppm. When compared to their parent lactones this is a downfield shift of 5 ppm for the D-(+)-mannopyranose derivative and a downfield shift of 6 ppm for the L-(+)-arabinopyranose derivatives.

The resonating frequency for C-4 was observed between 68 ppm for the D-(+)-galactopyranose derivatives (**[21]**, **[26]**) and at 77 ppm for the L-(+)-arabinopyranose ones (**[25]**, **[30]**). The chemical shift for C- 4 in the D-(+)-xylopyranose (**[24]**, **[29]**) and L-(+)-arabinopyranose (**[25]**, **[30]**) derivatives is 3 to 5 ppm above the average of 72 ppm. This is attributed to the hydrogen bonding observed between the free hydroxyl at C-5 and the acetyl group at C-3.

C-5 and C-6 resonate between 60 and 69 ppm for all ring-opened derivatives. However, when compared to the parent 1,5-lactones **[6]** this was shifted downfield by up to 11 ppm. The most significant difference was attributed to 4-hydroxybutyl 2,3,4,6-tetra-*O*-

acetyl-D-mannonate **[27]**. A downfield shift in the resonating frequency suggests that there is a decrease in electron density at these carbon centres. In the 1,5-lactones **[6]**, C-5 and C-6 are adjacent to the ester group where there is overlap of the sp^2 and sp^3 orbitals increasing electron density. Once the ring is opened, this extensive delocalisation is lost and with it electron density.

Also characteristic to the ring-opened esters, was the presence of the 4-hydroxybutyl and butyl end groups. Both possess similar resonances apart from the terminal hydroxyl group in the 4-hydroxybutyl terminated esters. Indeed, both the ^1H and $^{13}C\{^1H\}$ chemical shifts for the end groups are similar. The protons on the methylene group adjacent to the ester, resonate between 3.9 and 4.2 ppm. The protons in the methylene group adjacent to the terminal hydroxyl resonate at about 3.6 ppm; 0.3 to 0.6 ppm upfield of their resonance in the free alcohols. This is consistent with deshielding at these centres due to the presence of the electron-withdrawing carbonyls. Similar trends are observed in the $^{13}C\{^1H\}$ NMR chemical shifts. The same methylene carbons resonate between 63 and 68 ppm; up to 5 ppm downfield when compared to the parent alcohols.

3.3.3 Other characterisation

Figure 3.6 shows the IR spectra of 4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate compared with its parent 1,5-lactone, **[6e]**. Absorbances below 3000 cm^{-1} are essentially identical in both compounds, with a characteristic feature being an absorbance at 1749 cm^{-1} as a result of the carbonyl stretching frequencies. Confirmation of the synthesis of 4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate is given by the presence of a broad absorbance at about 3500 cm^{-1} attributed to the terminal hydroxyl groups.

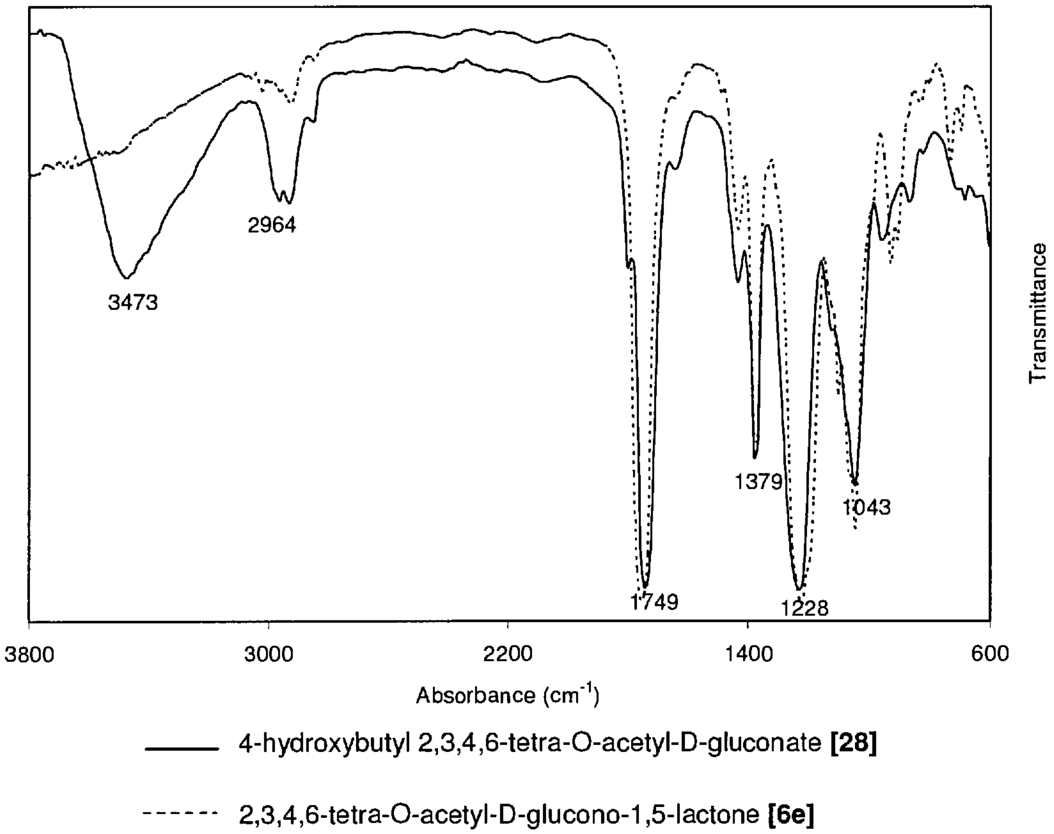


Figure 3.6 - IR spectrum of 4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate [28] compared with the parent 1,5-lactone [6e]

Figure 3.7 compares the IR spectra of the butyl and 4-hydroxyl terminated esters derived from D-(+)-glucopyranose **[23]** and **[28]**. As expected, the spectra are also very similar. Absorbances at about 3500 cm^{-1} attributed to the terminal hydroxyl groups are observed in both spectra. However, this absorbance for the butyl terminated ester **[23]** is significantly weaker. This is in agreement with the presence of 2 terminal hydroxyl groups in **[28]**, *versus* one in **[23]**. Fewer hydroxyl groups result in less inter-molecular hydrogen bonding and thus a weaker, sharper absorbance is observed.

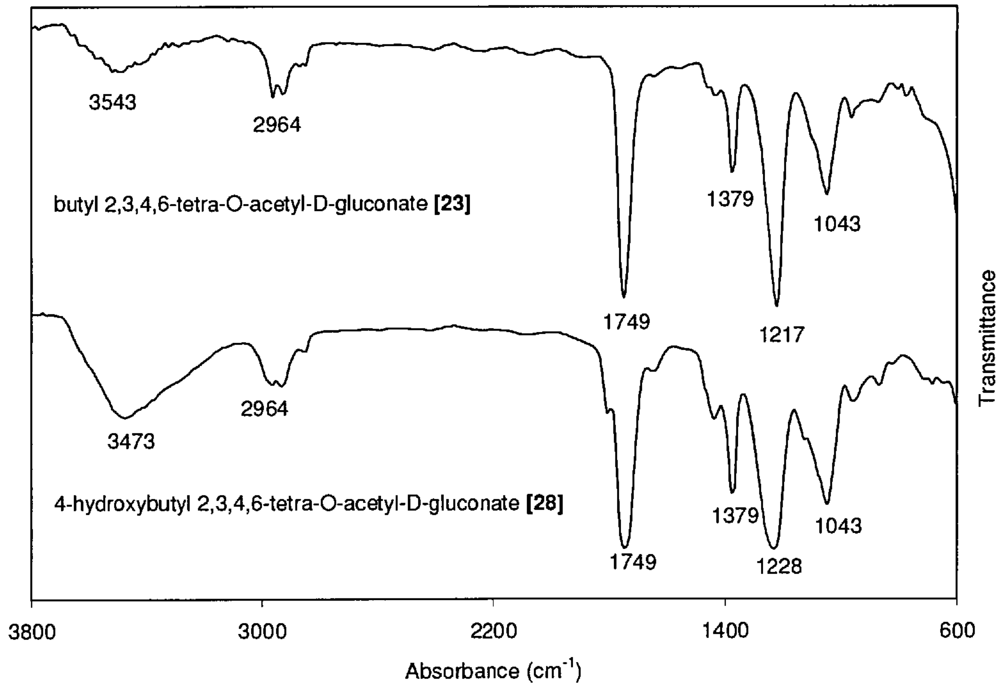


Figure 3.7 - IR spectra of the butyl and 4-hydroxyl terminated esters derived from D-(+)-glucopyranose [23] and [28]

Other tools used to characterise these compounds were mass spectrometry and elemental analysis. The optimum mass spectrometric technique is chemical ionisation; a soft technique which does not break up the compound and allows the molecular ion to be observed. Using this technique, the hexose-derived 4-hydroxybutyl terminated esters for example, gave rise to peaks at 454 amu. This corresponds to a molecular ion associated with NH_4^+ and in most cases was present in 100 % abundance. Table 3.7 shows the molecular ion peaks observed for the remaining compounds. In all cases the molecular ion associated with NH_4^+ was observed. Elemental analysis was found to be in agreement with the calculated values for all compounds and is given in the experimental section.

Table 3.7 - Molecular ion peaks observed in the mass spectrometry of the ring-opened esters

Product	$[M+NH4]^+$ (abundance)	Product	$[M+NH4]^+$ (abundance)
butyl 2,3,4,6-tetra-*O*-acetyl-D-galactonate **[21]**	438 (100 %)	4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-galactonate **[26]**	454 (100 %)
butyl 2,3,4,6-tetra-*O*-acetyl-D-mannonate **[22]**	438 (100 %)	4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-mannonate **[27]**	454 (29 %)
butyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate **[23]**	438 (100 %)	4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate **[28]**	454 (25 %)
butyl 2,3,4-tri-*O*-acetyl-D-xylononate **[24]**		4-hydroxybutyl 2,3,4-tri-*O*-acetyl-D-xylononate **[29]**	382 (15 %)
butyl 2,3,4,6-tri-*O*-acetyl-L-arabinonate **[25]**	366 (20 %)	4-hydroxybutyl 2,3,4,6-tri-*O*-acetyl-L-arabinonate **[30]**	382 (20 %)

Peaks observed are quoted in atomic mass units. Abundance is relative to the maximum.

3.4 Conclusion

Novel aliphatic aldaric esters derived from acetyl-protected 1,5-lactones were prepared *via* a ring-opening reaction with either butan-1-ol or 1,4-butanediol catalysed by *p*-TSA. This enabled us to achieve mono-functional alkyl esters suitable as co-initiators for the ROP of lactide as well as bi-functional ones. The latter is an AA-type monomer with potential applications in polycondensation reactions as well as a co-initiator for ROP. The synthetic procedure can be generally applied to all the 1,5-lactones. However, in order to optimise yields, it was necessary to adjust the reaction time in order to minimise the formation of by-products. As the reaction progressed it was found that after formation of the alkyl esters, these subsequently reformed the 1,5-lactone after prolonged exposure to acid. This then resulted in the formation of the 1,4-lactone; the stable thermodynamic product. The relative rates for the formation of these products varied with the parent carbohydrate. Thus it can be concluded that stereochemistry of the substituents influenced the relative reaction rates. 2,3,4,6-tetra-*O*-acetyl-D-galactono-1,5-lactone **[6a]** was found to be the most reactive starting 1,5-lactone. It selectively formed the 4-hydroxybutyl ester at the end of 15 mins at r.t. The D-(+)-glucopyranose, D-(+)-xylopyranose and L-(+)-arabinopyranose derivatives on the other hand required 2 h to selectively form the analogous compounds under the same conditions. Butyl aldaric esters were isolated in up to 79 % yield and the 4-hydroxybutyl ones in up to 95 % yield.

These novel compounds were comprehensively characterised with NMR being a critical tool in confirming the identity of these substances. A combination of 1-dimensional NMR (^{1}H NMR, $^{13}C\{^1H\}$ NMR) and 2-dimensional NMR (COSY, HMQC, HMBC) methods were used to resolve this. As expected, there were no significant differences in the chemical shifts in the back-bone regions of the aldaric esters derived from the same parent carbohydrate. The key differences observed were related to the end group. Owing to the presence of the methyl group in the butyl terminus, a resonance at about 0.9 ppm was observed.

NMR served to reveal interesting conformational behaviours of these compounds. In the hexose derivatives it was observed that H-6 and H-6' were indistinguishable from each other by ^{1}H NMR. This is owing to free rotation about the C-5–O bond. Thus it was expected that in the pentose derivatives, the same would be true with respect to H-5 and H-5'. However, it was discovered that these gave rise to two distinguishable doublets of doublets with coupling constants of 13 and 3 Hz, in each of the pentose-derived aldaric esters. This large coupling constant was an indicator of geminal coupling much like that observed in the parent 1,5-lactones. Thus it was concluded that hydrogen-bonding between the acetyl group at C-3 and the terminal hydroxyl at C-5 restricted free rotation about the C-4–C-5 bond giving rise to distinguishable resonances for H-5 and H-5'.

^{13}C{^{1}H} NMR served to confirm that the ring had been opened as the resonating frequency for C-1 was found to be 167 and 169 ppm; an increase in 2 - 3 ppm *versus* the parent 1,5-lactones. This downfield shift is consistent with relief in ring strain.

Thus the versatile synthetic procedure enabled the synthesis of compounds suitable as co-monomers in polycondensation as well as novel initiators for ROP.

3.5 References

1. Joseph, C. C.; Regeling, H.; Zwanenburg, B.; Chittenden, G. J. F., *Tetrahedron* **2002,** 58, 6907-6911.

2. López de la Paz, M.; Vicent, C., *Chem. Comm.* **1998**, 465-466.

3. Lommerse, J. P. M.; Price, S. L.; Taylor, R., *J. Comp. Chem.* **1997,** 18, (6), 757-774.

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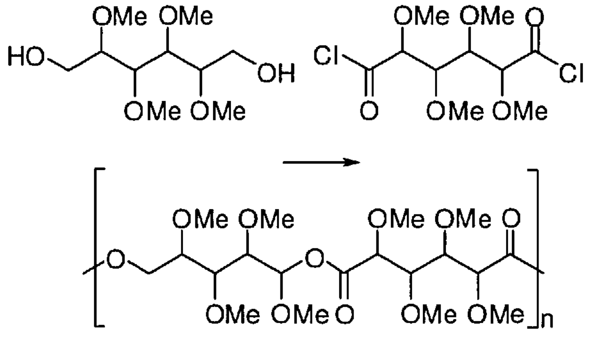
CHAPTER 4:

POLYMERISATION STUDIES 1: USING ALDARIC ESTERS

4.1 Introduction

The carbohydrate-derived aliphatic esters can be applied in both polycondensation and ring opening polymerisation (ROP). The presence of two terminal hydroxyl groups in the aliphatic esters derived from 1,4-butanediol formed AA-type monomers suitable for polycondensation with carboxylic acids or acid chlorides.

Polycondensation reactions of carbohydrate-derived monomers have been elegantly described by Guan[1] and Galbis.[2] Guan *et al.*[1] reported polyesters produced *via* polycondensation with M_n and M_w values of 29,000 gmol^{-1} and 44,000 gmol^{-1} respectively and with a polydispersity index (PDI) of 1.5 (Scheme 4.1).

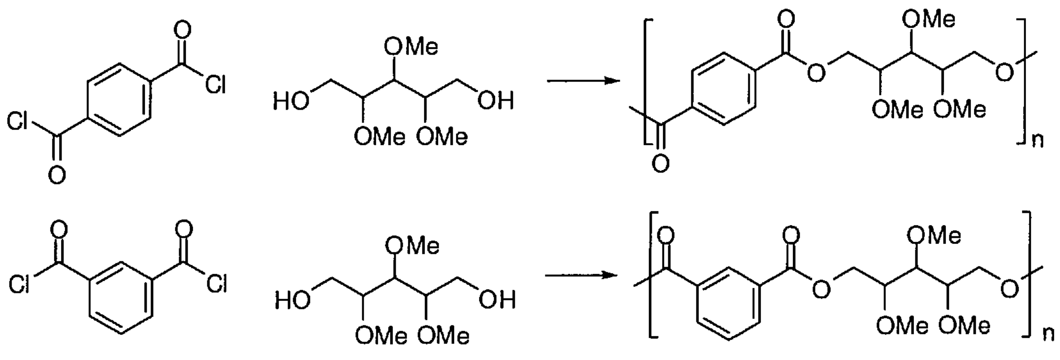


NEt_3, CH_2Cl_2, r.t., 24 h

M_n: 29,000; M_w: 44,000; PDI: 1.5

Scheme 4.1 - Synthesis of the permethoxy polyesters *via* polycondensation[1]

Galbis *et al.*[2] reported polyesters obtained by the polycondensation reaction of the 2,3,4-tri-*O*-methyl-arabinitol or 2,3,4-tri-*O*-methylxylitol, or their mixtures with ethylene glycol, with terephthaloyl chloride or isophthaloyl chloride. The reactions were carried out in the melt. M_w values ranged between 11,500 and 46,500, with PDIs from 1.5 to 2.3 (Scheme 4.2).



o-$C_6H_4Cl_2$, tetrabutyl titanate, r.t. to 200 °C, 4 h

M_w: 11,500 - 46,500; PDI: 1.5 - 2.3

Scheme 4.2 - Synthesis of carbohydrate-derived permethoxy aromatic copolymers *via* polycondensation[2]

These conditions were not suitable for peracetylated derivatives due to their intolerance of high temperatures. However, if conditions and reagents which are tolerant to the acetyl protecting groups could be applied, this would prove to be ideal.

Thus we applied reaction conditions employed by Guan[1] with commercially available acid chlorides. This narrowed the choice down to oxalyl chloride and adipoyl chloride. The former was of particular interest owing to the short chain length thus creating a polymer with a greater weighting of the carbohydrate derivative. The use of terephthalic acid would also serve to produce a material which could serve as modified poly(ethylene terephthalate) (PET); a widely used commodity plastic. In order to preserve the acetyl groups, reactions with terephthalic chloride, which is insoluble in DCM, were successfully carried out in toluene at 60 °C.

The presence of hydroxyl groups in both sets of aliphatic polyesters derived from butal-1-ol and 1,4-butanediol, makes them suitable candidates as co-initiators in the

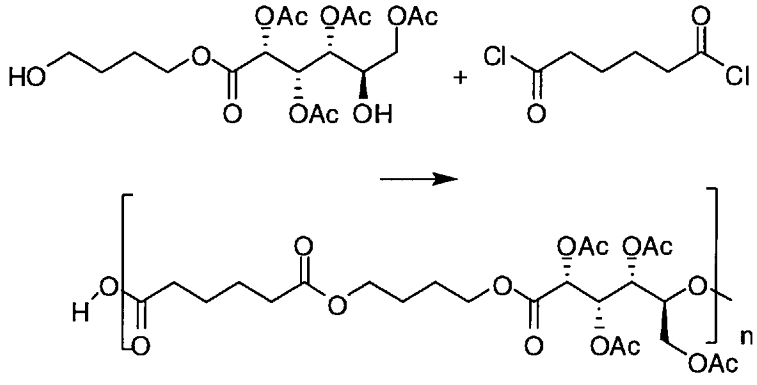
ROP of lactide. ROP of lactide generally requires a metal complex with a co-initiator such as an alcohol. Thus this is an elegant way of introducing functionalised carbohydrate moieties including a carbohydrate-derived oligomer **[33]** (whose synthesis is discussed in Chapter 5) to form a block copolymer. A similar approach was report by Arvanitoyannis *et al.* where sorbitol was used as a co-monomer in the ROP of *rac*-lactide using Sn(II)Oct$_2$ in varying sorbitol to lactide ratios, carried out in the bulk at high temperatures (130 °C). This enabled the synthesis of copolymers of about M_n 10, 000 gmol^{-1} (SEC) and PDIs between 1.3 and 2.0 and in up to 98 % yield. They also found that the content of carbohydrate moieties increased the crystallinity of the resulting copolymer.[3] Nonetheless, the main limitation of this method is poor polymerisation control. Furthermore, acetyl-protected carbohydrate esters would not withstand the high temperatures required.

Lactide ROP has been the subject of much research and is generally carried out under mild reaction conditions.[4] Thus a zinc complex which was found to be highly active towards the ROP of lactide[5] was investigated as a co-initiator in the ROP of lactide with the carbohydrate-derived aliphatic esters. ROP has the advantage over polycondensation of being a controlled method of polymerisation affording high molecular weight polymers with narrow molecular weight distributions.

4.2 Copolymers *via* polycondensation

Polycondensation was explored as a synthetic route to highly functionalised, carbohydrate-derived copolymers. In principle, aldonic acids derived from the carbohydrate lactones are suitable monomers for polycondensation reactions. In fact, these were successfully prepared in good yields. However, it was observed that the peracetylated gluconic acid was unstable and readily cyclised to its parent 1,5-lactone in solution and in the presence of acids, bases and catalysts used in polycondensations, such as scandium triflate. Thus the functionalised diols **[26]** - **[30]** were more suitable monomers for polycondensations as the introduction of the alkyl chain inhibited cyclisation. These AA-type monomers **[26]** - **[30]** were treated with diacid chlorides to successfully yield novel, highly-functionalised polyesters. Each diol was independently treated with adipoyl chloride, oxalyl chloride and terephthalic chloride in the presence of 2 equivalents of triethylamine, in either CH_2Cl_2 or toluene. Toluene at 60 °C was used with terephthalic chloride due to the poor solubility of this acid chloride. Reactions were carried out at a concentration of 0.1 M in each monomer. Triethylamine was found to be critical to the success of these reactions. Where they were conducted in the absence of triethylamine resulted in degradation of the oligomeric products, possibly due to acidic by-products/acid chloride monomers.

Reactions were carried out using dry reagents and quenched at the end of 3 days by addition of aqueous HCl. This was followed by washing with aqueous $NaHCO_3$ and water. This was an adaptation of a method reported by Guan *et al.* described above.[1] An aliquot was taken at the end of 1 day, quenched and analysed by SEC (polystyrene standards, $CHCl_3$) before the reactions were stopped at the end of 3 days. From this, it was concluded that the highest molecular weights were obtained at the end of 1 day. Prolonged reaction times did not improve molecular weight. Reactions in CH_2Cl_2 were started at 0 °C to optimise the thermodynamic effects. Scheme 4.3 illustrates the reaction using **[28]** with adipoyl chloride as an example.

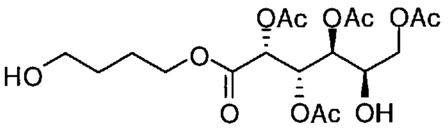
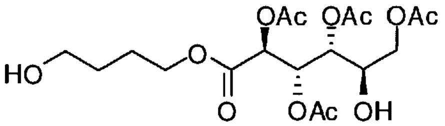
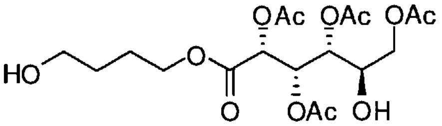
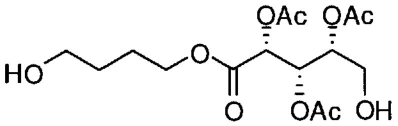
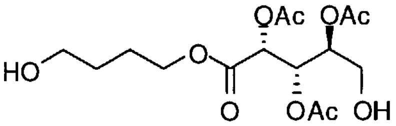


2 eq. NEt₃, dry DCM, 0 °C - r.t., 3 days

Scheme 4.3 - Synthesis of a highly functionalised polyester produced *via* polycondensation

Whilst analysis of these polymers was attempted using MALDI-TOF, this was undetectable due to the failure of these polymers to "fly". Nonetheless, analysis by SEC revealed polymers with approximately 100 repeat units, M_n between 41,000 and 56,000 and M_w between 69,800 and 94,100 gmol^{-1}. PDIs ranged between 1.5 and 2.8 (Table 4.1).

Table 4.1 - Highly functionalised, carbohydrate-derived polyesters produced *via* polycondensation

Entry	Monomer	Acid Chloride	M_n	M_w	PDI
1	 **[26]** 4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-galactonate	adipoyl chloride	52,700	86,600	1.64
2		oxalyl chloride	45,300	72,300	1.60
3		terephthalic chloride*	45,900	86,300	1.88
4	 **[27]** 4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-mannonate	adipoyl chloride	47,900	82,900	1.73
5		oxalyl chloride	26,100	74,000	2.84
6		terephthalic chloride*	31,600	71,800	2.27
7	 **[28]** 4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate	adipoyl chloride	45,100	78,300	1.73
8		oxalyl chloride	47,200	78,700	1.67
9		terephthalic* chloride	39,700	81,400	2.05
10	 **[29]** 4-hydroxybutyl 2,3,4-tri-*O*-acetyl-D-xylononate	adipoyl chloride	64,100	94,100	1.47
11		terephthalic chloride*	32,900	80,300	2.44
12	 **[30]** 4-hydroxybutyl 2,3,4,6-tri-*O*-acetyl-L-arabinonate	oxalyl chloride	38,500	76,300	1.98
13		terephthalic chloride*	37,400	69,800	1.87

*Conditions: 2 eq.NEt_3, dry CH_2Cl_2, r.t., 3 days. * 2 eq.NEt_3, dry toluene, 60 °C, 3 days*

SEC also indicated the presence of low molecular weight oligomers. Residual water is the most likely contributor to low conversions despite distillation of the starting acid chlorides and the use of dry solvents. Reprecipitation of the polymer from DCM-hexane resulted in fractionation of high molecular weight polymer chains thus narrowing PDIs.

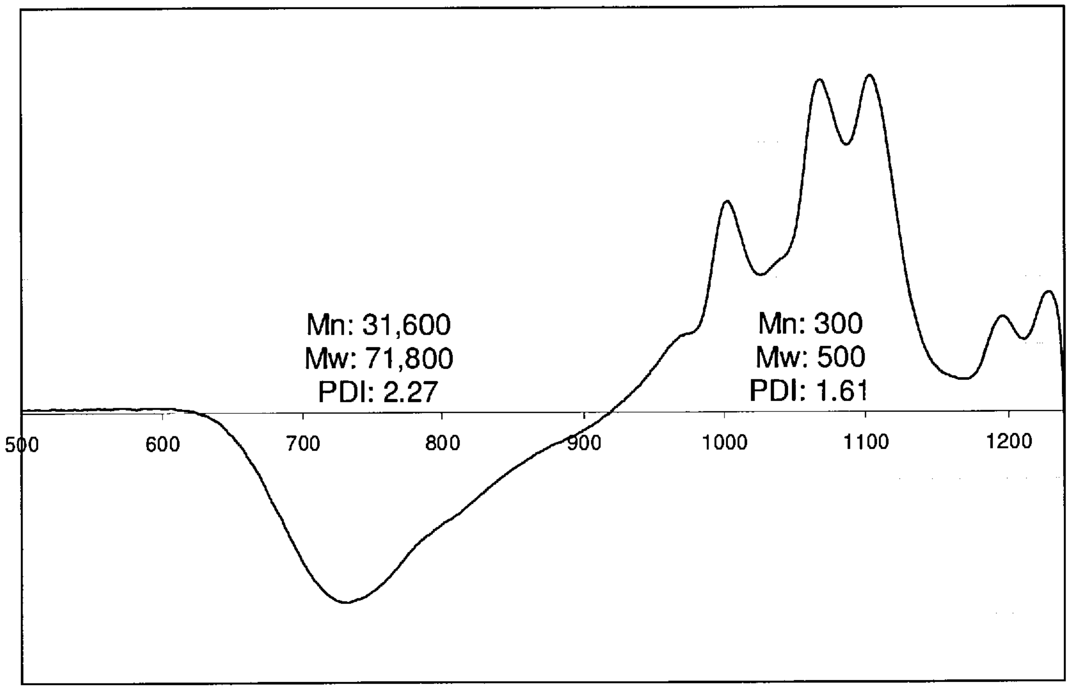


Figure 4.1 - SEC for PET-[27]-copolymer

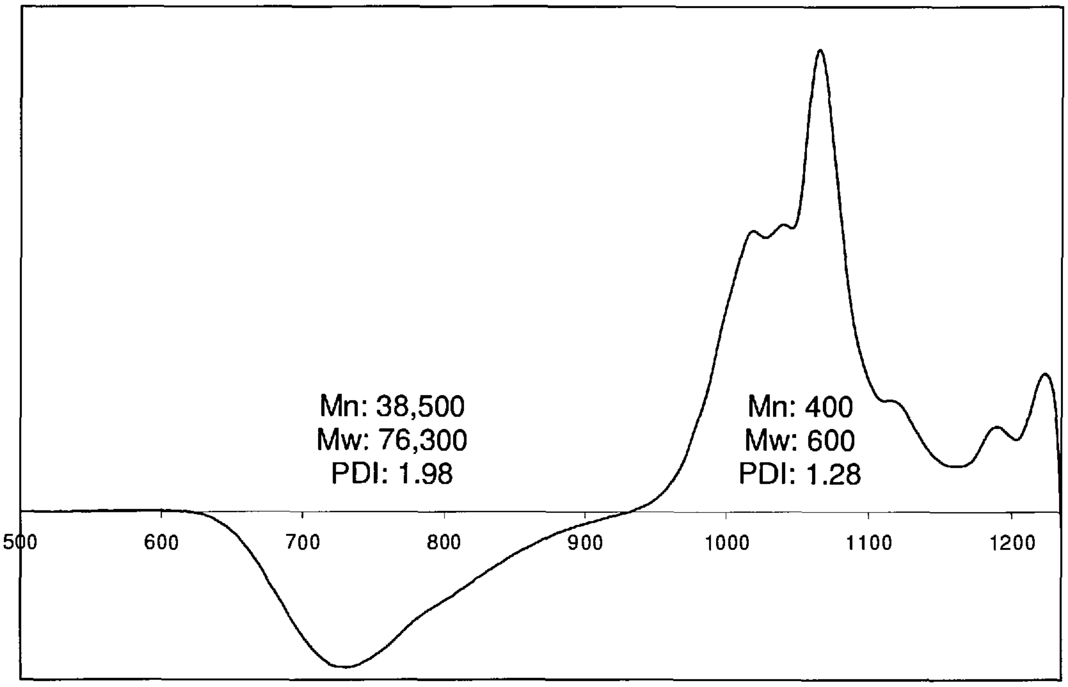
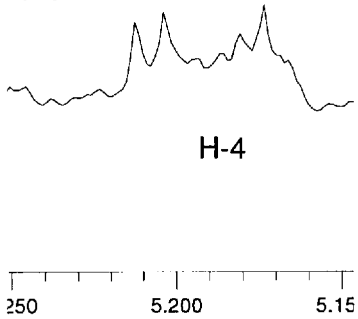


Figure 4.2 - SEC for copolymer of [30] with oxalyl chloride

These polymers were compared with related methyl protected ones derived from xylose and arabinose reported by Guan[1] and Galbis.[2] Guan reported that methyl protected polyesters derived from xylose achieved polymers with M_n and M_w values of 29,000 gmol^{-1} and 44,000 gmol^{-1} respectively with PDIs of 1.5 (*ca.* 70 repeat units). Those reported by Galbis, which were methyl protected polyesters prepared from pentose derivatives, a diol and an aromatic acid chloride, were characterised by M_w values between 11,500 and 46,500 gmol^{-1} and PDIs from 1.5 to 2.3 (*ca.* 100 units). By contrast, the copolymers we prepared had comparable PDIs (1.5 – 2.8) and degrees of polymerisation (*ca.* 100 units). However, the significantly higher molecular weights (M_n 41,000 and 56,000 gom^{-1}) are attributed to the heavier repeat units owing to the bulkier acetyl groups *versus* methyl ones.

Acetyl-protected polyesters derived from **[26]** - **[30]** were also analysed by ^{1}H NMR and ^{13}C{^{1}H} NMR. ^{1}H NMR of the polymers was characterised by broadening of signals. Using the copolymer of **[28]** with adipoyl chloride as an example, Figure 4.3 shows that the resonating frequency of H-4 in the polymer is centred around 5.2 ppm, similar to that observed in the carbohydrate monomer, **[28]**. However, the polymeric signal showed a much more complex multiplicity/overlap of signals and was significantly broadened.

(a)
copolymer of [28] with adipoyl chloride



(b)
4-hydroxybutyl 2,3,4,6-tetra-O-acetyl-D-gluconate [28]

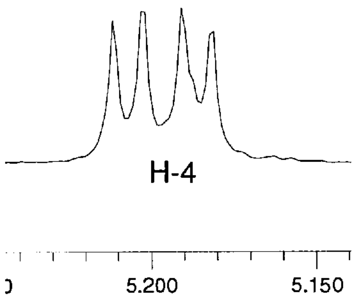


Figure 4.3 - ^{1}H NMR resonances for the copolymer of [28] with adipoyl chloride (a) monomer [28] alone (b) for H-4 resonances.

Similarly, broadening was observed in the region between 4.5 and 4.0 ppm in the polymer as shown in Figure 4.4. This also shows another characteristic observation which is the downfield shift of the H-5 resonance from 3.85 ppm in the monomer to between 4.5 and 4.0 ppm in the polymer. This is as expected as the adipic group adjacent to H-5 increases its electronegativity.

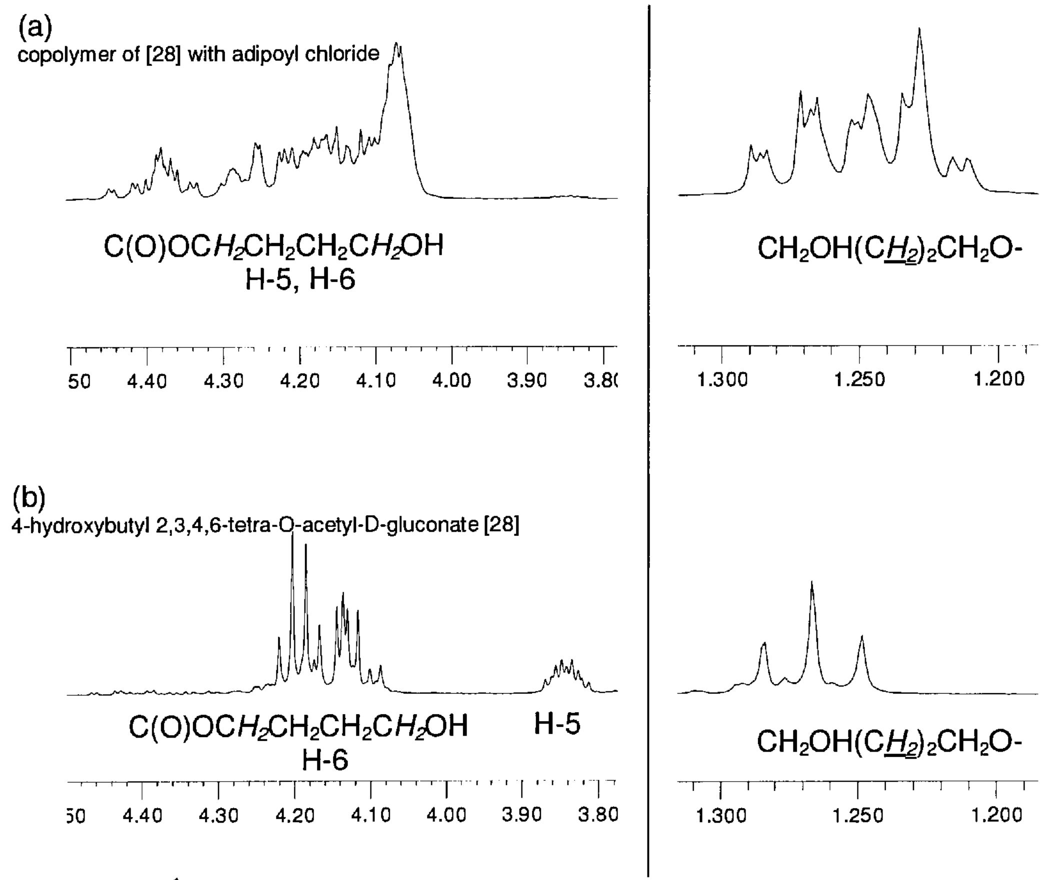


Figure 4.4 - ^{1}H NMR resonances for the copolymer of [28] with adipoyl chloride (a) and starting monomer, [28] alone (b) in the regions between 4.5 - 3.8 ppm and 1.3 and 1.2 ppm

The methylene protons in the adipic repeat units also resonated at 2.90 ppm and 1.70 ppm (Figure 4.5). Whilst the former was comparable to the resonating frequency of adipoyl chloride, the latter is shifted upfield from 1.8 ppm from the equivalent resonances in adipoyl monomer. Moreover, the ^{1}H NMR resonances of adipoyl chloride have a characteristic shape due to the symmetry of the molecule. The symmetry of the adipic unit is lost in the polymer and so the multiplicity of the resonances is much more complex. This is accompanied by broadening of these respective signals (Figure 4.5).

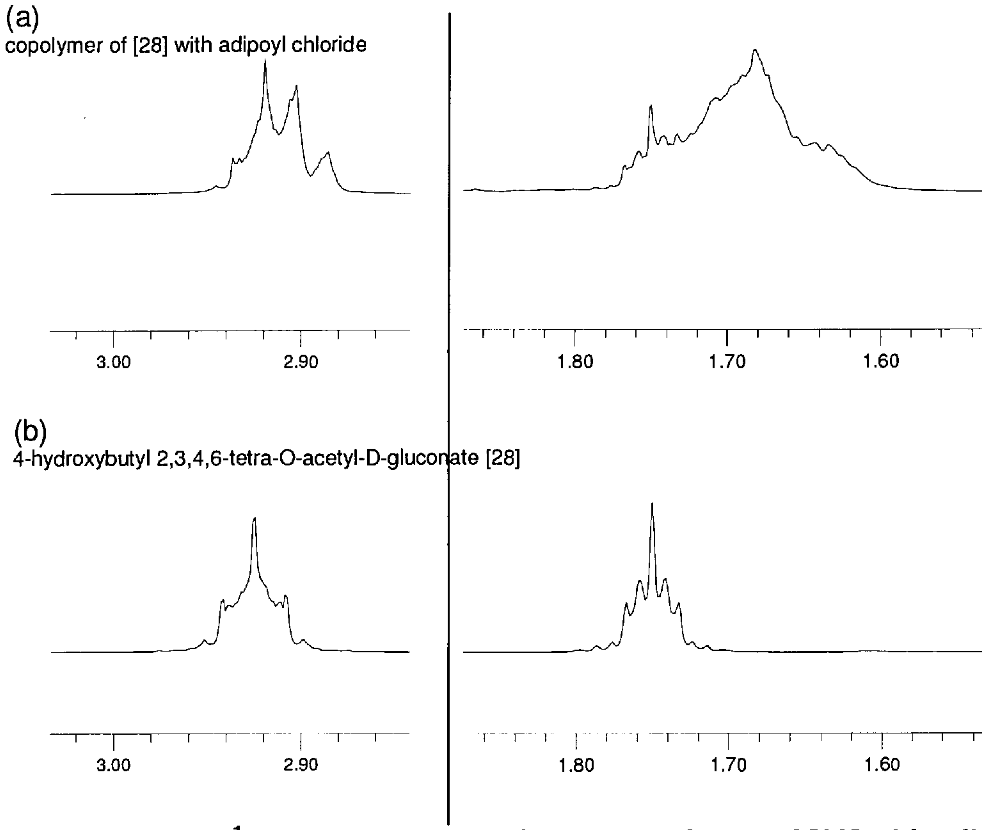


Figure 4.5 - Adipic ^{1}H NMR resonances for the copolymer of [28] with adipoyl chloride (a) and adipoyl chloride alone (b).

The unsubstituted butyl area of the polymer chain was also at a similar chemical shift to the monomer **[28]** (1.30 - 1.20 ppm) but was broadened.

$^{13}C\{^1H\}$ NMR of the polymer resembled that of the starting carbohydrate-derived monomer, as expected and is shown in Figure 4.6. The carbonyl resonances in the polymer were observed between 171 and 170 ppm. The absence of adipoyl chloride in the polymer was confirmed by the absence of the carbonyl resonance at 173 ppm. Carbohydrate resonances were observed between 72 and 68 ppm, and were unchanged compared to the starting monomer, **[28]**. The characteristic adipic resonance at 46 ppm due to the α-carbon in adipoyl chloride, was shifted to 64 - 63 ppm in the polymer. This chemical shift is comparable to the analogous butyl resonances. This change is attributed to the loss of the electronegative chloride atom resulting in deshielding of the α-carbon. The complexity of the resonances centred at 25 ppm was increased as β-carbon resonances were observed for both the adipic and butyl carbons. Acetyl resonances were observed between at 21 and 20 ppm, as was seen in the starting monomer.

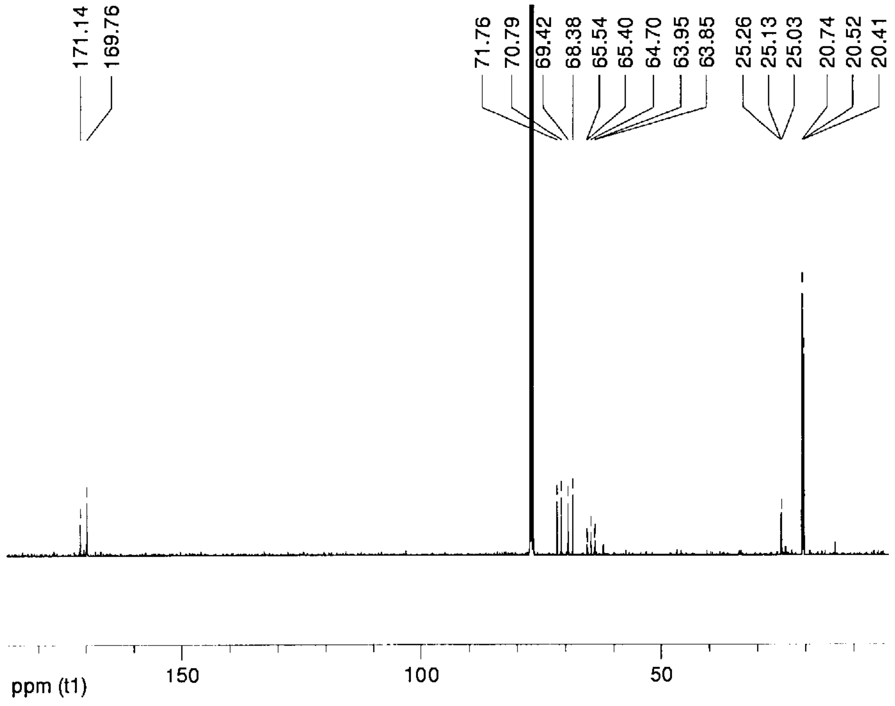
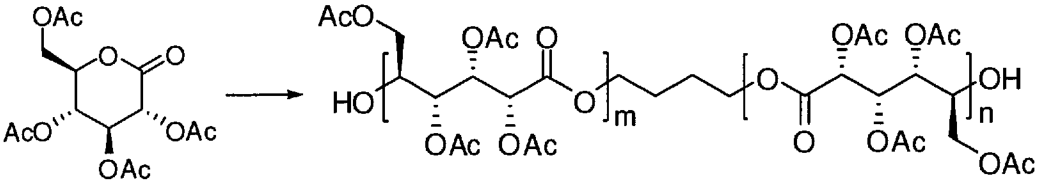


Figure 4.6 - $^{13}C\{^1H\}$ NMR of the copolymer of [28] with adipoyl chloride

4.3 α-4-Hydroxybutyl-ω-hydroxyl-oligo(2,3,4,6-tetra-*O*-acetyl-D-gluconate)-block-poly(lactide)

The highly functionalised oligomer α-4-hydroxybutyl-ω-hydroxyl-oligo(2,3,4,6-tetra-*O*-acetyl-D-gluconate), **[33]** was prepared *via* ring-opening polymerisation of 2,3,4,6-tetra-*O*-acetyl-D-galactono-1,5-lactone in the presence of Sn(II)Oct$_2$ and 1,4-butanediol (discussed in Chapter 5).



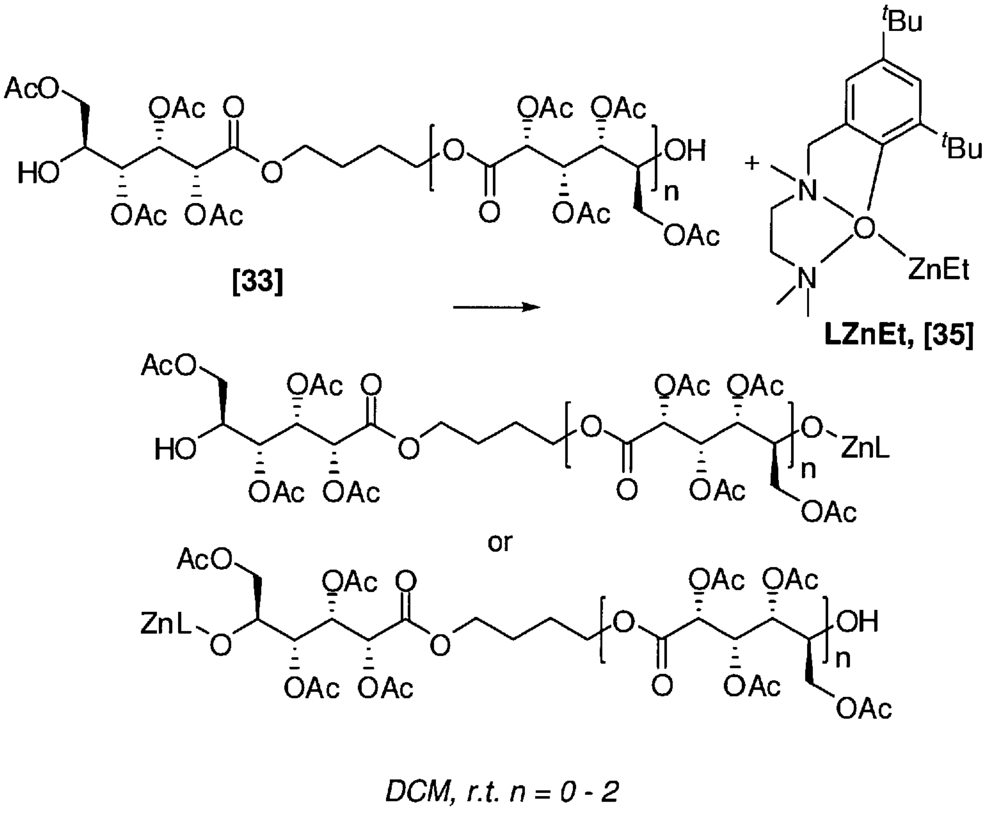
m = 1 - 2, n = 0 – 1

[33]

Sn(II)Oct$_2$, alcohol, 80 °C, bulk

Scheme 4.4 – Synthesis of α-4-hydroxybutyl-ω-hydroxyl-oligo(2,3,4,6-tetra-*O*-acetyl-D-gluconate), [33]

[33] was used as a macro-initiator in the ring opening polymerisation of *rac*-lactide. This co-polymerisation was investigated using an alkyl zinc co-initiator, **[35]**[5] by preparation of the initiating species in *situ* as shown in Scheme 4.5.



Scheme 4.5 - Synthesis of glucose-derived initiator, [34]

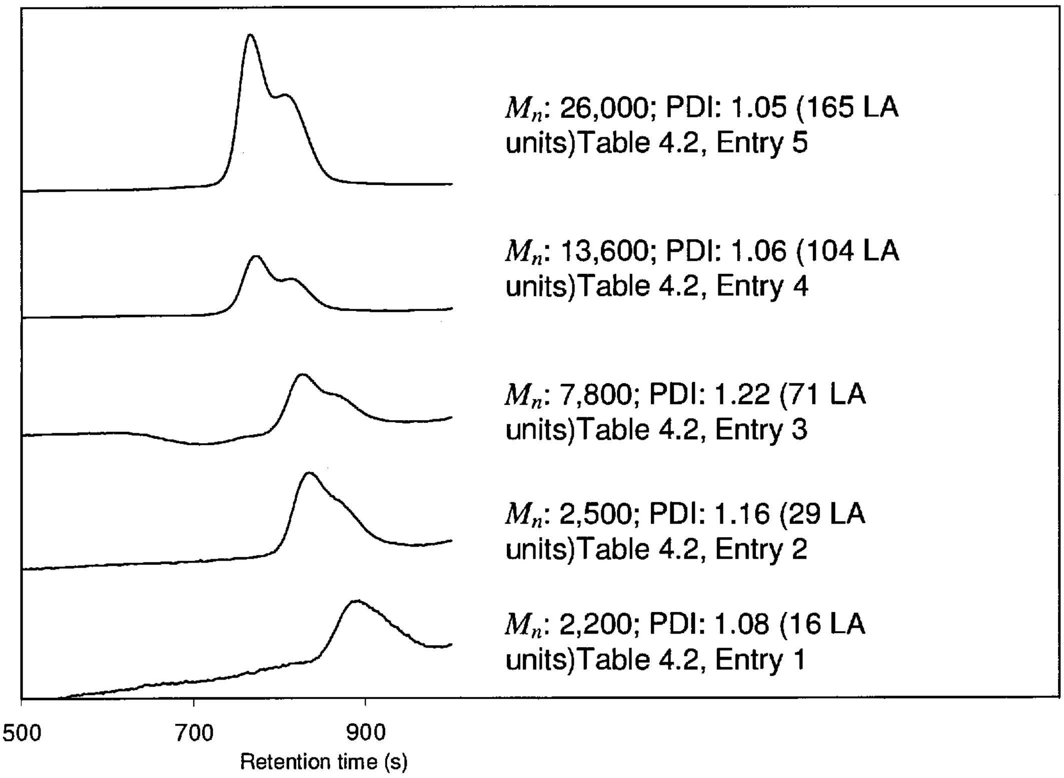
After the addition of *rac*-lactide, aliquots were regularly withdrawn to monitor the reaction's conversion and the polymer's M_n. This enabled the successful synthesis of triblock ABA copolymers comprising lactide blocks of 12 to 250 repeat units attached to the oligoester blocks of up to 3 repeat units. The copolymers' M_n were determined by size exclusion chromatography (SEC) and by end group analysis from the ^{1}H NMR spectrum (Table 4.2). Integration of the PLA methyne protons' signal at 5.20 ppm versus the oligomer acetyl methyls' signal at 2.07 ppm, provided an approximation of the DP and from this the copolymers' M_n. The M_n from NMR, SEC (polystyrene standard, $CHCl_3$), and the calculated M_n based on the percentage conversion and the reaction stoichiometry were in excellent agreement. Thus for a lactide loading of 25 equivalents and 63 % lactide conversion, the calculated M_n is 2,700 gmol^{-1}. This was in agreement with M_n determined by SEC (2,200 gmol^{-1}) as well as by ^{1}H NMR (2,900 gmol^{-1}). The polymerisation was therefore, well controlled, further reinforced by the narrow PDIs between 1.05 and 1.22 for the copolymers.

Table 4.2 - Copolymers prepared using the macro-initiator [33] for the ROP of lactide

Entry	Initiator:Lactide loading	Lactide Conversion[a]	Number of lactide units	M_n Calc.[b]	M_n NMR[c]	M_n SEC[d] (PDI)
1	1:25	63 %	16	2,700	2,900	2,200 (1.08)
2	1:50	58 %	29	4,600	4,000	2,500 (1.16)
3	1:100	71 %	71	11,000	8,600	7,800 (1.22)
4	1:200	52 %	104	15,400	15,800	13,600 (1.06)
5	1:500	33 %	165	24,200	18,800	26,000 (1.05)

[a] Determined by normalization of the integrals for the CH resonances in lactide (5.00 ppm) and polylactide (5.20 ppm). Reactions were quenched prematurely and hence conversions beyond 90 % as expected in a controlled polymerisation are not reported. [b] M_n calc = (144 × DP) + 436. [c] Determined by integration of the CH signal in polylactide (5.20 ppm) versus the acetyl signal in the oligoester (2.10 ppm). [d] Determined by SEC, using polystyrene standards to calibrate the instrument and with a correction factor of 0.58.[5]

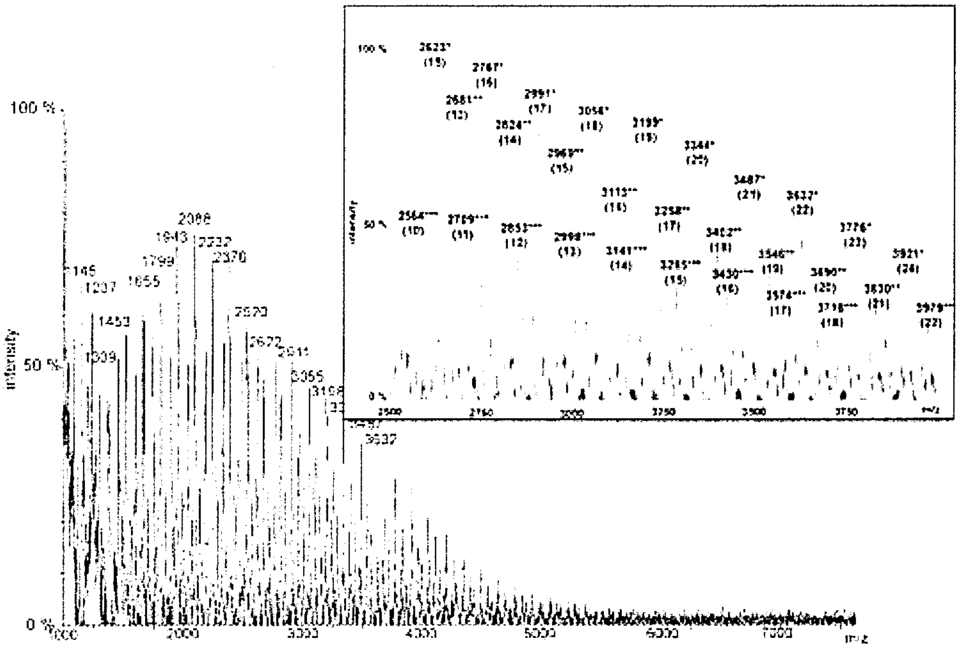
Figure 4.7 shows the SEC traces of the lactide copolymers synthesized with the macro-initiator **[33]**. For lower molecular weight polymers (*ca.* 2,000 gmol^{-1}) a mono-modal distribution is observed. However, longer chains exhibit a bi-modal distribution. This reflects the fact that the macro-initiator contains a mixture of monomer (**[33]**, n = 1), dimer (**[33]**, n = 2) and trimer (**[33]**, n = 3) with respect to its carbohydrate derivative. Unlike the monomer, the dimer and trimer do not possess a primary hydroxyl end group (Scheme 4.5). Therefore, initiation rates will differ and this becomes more prevalent in higher molecular weight polymers.



Using polystyrene standards to calibrate the instrument and M_n corrected with a factor of 0.58.[5]

Figure 4.7 - SEC traces for copolymers produced using the macro-initiator [34] for ROP of lactide

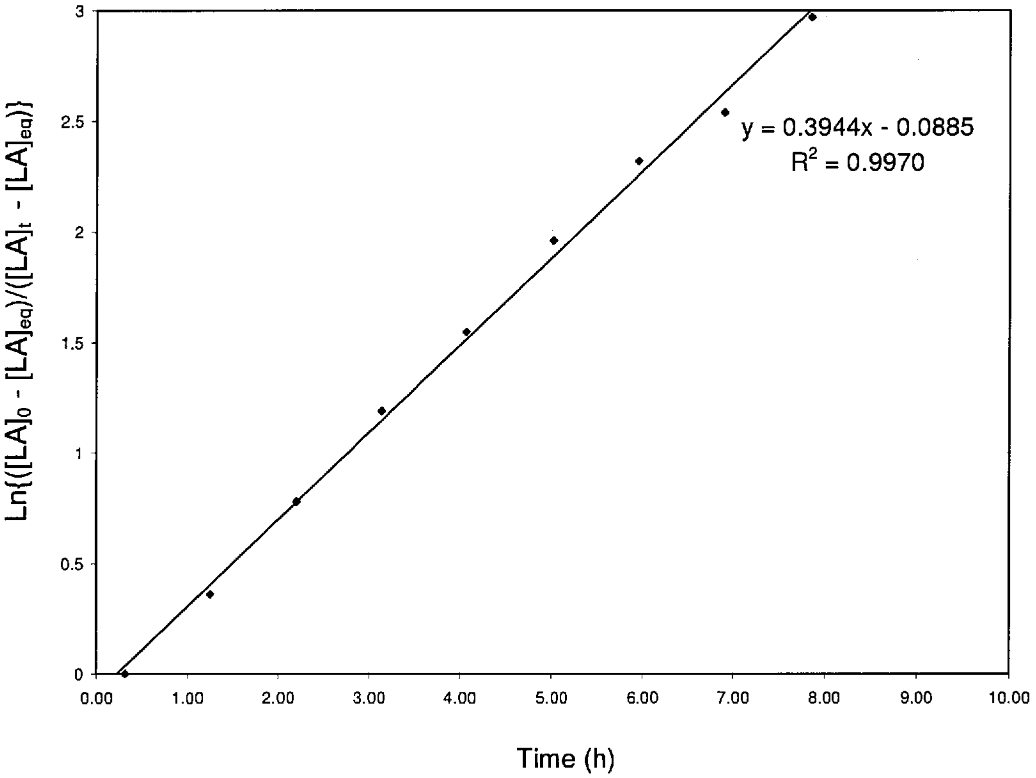
The sodium cationised MALDI mass spectrum for the copolymer, with 25 lactide units, is shown in Figure 4.7. There are three series of peaks, each containing peaks separated by 144 units (corresponding to the lactide repeat unit) and separated from one another by 346 units (corresponding to the 2,3,4,6-tetra-*O*-acetyl-D-gluconate repeat unit). These series of peaks are assigned to the different oligoester initiators, for example, mono- (*), di- (**), and triester (***) initiating groups. The relative intensity of the series by MALDI is mono > di > tri. However this is likely due to the improved ionization of the monoester compared with the triester. There was no evidence for lactide polymerisation initiated by other groups, for example, water, 1,4-butanediol or for the formation of cyclic products.



*The peaks corresponding to monoester, diester, and triester end groups are marked with *, **, and ***, respectively, and for each series the degrees of polymerisation*

Figure 4.8 - MALDI spectrum of the copolyester initiated by [34] with a loading of *rac*-lactide:macro-initiator of 25:1

The polymerisation kinetics were monitored in *situ* by ^1H NMR spectroscopy which enabled determination of the percentage conversion and from that the concentration of monomer. The semi-logarithmic plot, $Ln\{([LA]_0 - [LA]_{eq})/([LA]_t - [LA]_{eq})\}$ against time is shown in Figure 4.9 (where $[LA]_0$ = initial lactide concentration, in this case 1M, $[LA]_{eq}$= concentration of lactide at equilibrium, a very low amount which cannot be detected by ^1H NMR spectroscopy and is thus not considered and $[LA]_t$ = concentration of lactide at time t). The plot shows a linear fit, consistent with a well-controlled polymerisation. It also indicates that the concentration of the active species is invariable during the polymerisation process at least up to about 90 % [*L*,*L*]-lactide conversion. The pseudo first order rate constant, k_{obs}, (the gradient of the line in Figure 4.9) is 0.39 h^{-1} (6.57×10^{-3} min^{-1}) which compares well with other lactide polymerisation initiators.[5,6] There is an initiation time of *ca.*14 min; it is proposed that this is required for the zinc alkoxide initiator to form by the reaction between the oligoester hydroxyl groups and **[35]**.



Polymerisation conditions: $[LA]_0$ = 0.7 M, $[\mathbf{[33]}]_0$ = 0.028 M, CD_2Cl_2, r.t.

Figure 4.9 - Plot of Ln{$[LA]_0/[LA]_t$} versus time for the polymerisation of [*L*,*L*]-lactide.

The initiation was studied by the stoichiometric reaction between the oligoester and **[35]**, using ^1H NMR spectroscopy. On addition of **[35]** to the carbohydrate-derived initiator, a diminution of the zinc ethyl peak at 0.42 ppm was observed. This is consistent with the formation of an LZnOR species.

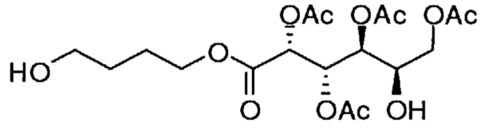
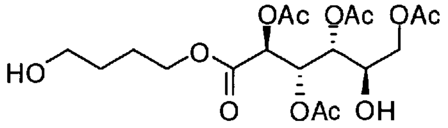
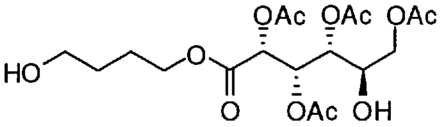
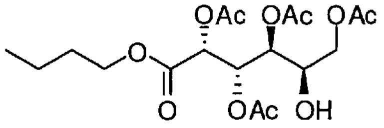
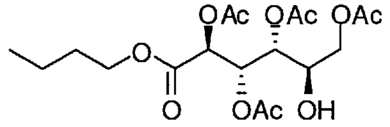
4.4 Carbohydrate-derived alcohols as initiators for lactide polymerisation

Aldaric esters derived from the reaction of 1,4-butanediol (**[26]**, **[27]**, **[28]**) and butan-1-ol (**[21]**, **[22]**) were investigated as co-initiators in the ROP of lactide in conjunction with the alkyl zinc initiator, **[35]**.[5] Kinetic experiments were conducted by investigating the hexose-derived co-initiators. Pentose-derived co-initiators were also used to explore tacticity control.

4.4.1 Synthesis

Polymerisations were carried out in a Youngs tap NMR tube using dry $CDCl_3$ at room temperature with an initiator to lactide ratio of 1:50 and at a concentration of 0.7 M in [*L*,*L*]-lactide. The initiating species was generated *in situ* by a stoichiometric reaction between the hydroxyl groups on the aldaric esters and **[35]**. The polymerisation reaction was monitored *in situ* by ^{1}H NMR spectroscopy. This resulted in the synthesis of a range of polymers with end groups derived from the various protected carbohydrates containing 30 - 50 repeat units of lactide. These carbohydrate-terminated PLA samples were treated in the same manner as the carbohydrate copolymer derived from **[33]**. M_n from NMR and SEC, and M_n calculated from the percentage conversion and reaction stoichiometry were all in excellent agreement. Table 4.3 summarises the percentage conversions achieved and M_n data for these polymers, where the starting initiator to lactide loading was 1:50. Entry 1 shows that for a conversion of 94 % and thus 47 lactide units, the calculated M_n of 7,200 gmol^{-1} was in agreement with the M_n determined by SEC (6,300 gmol^{-1}) and that determined by ^{1}H NMR (6,700 gmol^{-1}).

Table 4.3 - Conversion and M_n data for PLA produced using carbohydrate-derived co-initiators

Entry	Co-Initiator	% conv[a]	M_n Calc.[b]	M_n NMR[c]	M_n SEC[d] (PDI)
1	 **[26]** 4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-galactonate	94	7,200	6,700	6,300 (1.24)
2	 **[27]** 4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-mannonate	98	7,500	6,600	8,300 (1.66)
3	 **[28]** 4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate	95	7,300	8,300	7,400 (1.52)
4	 **[21]** butyl 2,3,4,6-tetra-*O*-acetyl-D-galactonate	62[e]	4,900	4,900	5,300 (1.31)
5	 **[22]** butyl 2,3,4,6-tetra-*O*-acetyl-D-mannonate	82	6,300	6,500	5,900 (1.33)

*[a]Determined by normalization of the integrals for the CH resonances in lactide (5.00 ppm) and polylactide (5.20 ppm). [b]M_n calc = (144 × % conv. * 50) + M_n(co-initiator). [c]Determined by integration of the CH signal in polylactide (5.20 ppm) versus the acetyl signal in the initiator (2.10 ppm). [d]Determined by SEC, using polystyrene standards to calibrate the instrument and with a correction factor of 0.58.[5] [d]Reaction was quenched before complete conversion could be attained.*

Figure 4.10 shows the SEC traces for PLA initiated by **[26]**, **[27]**, **[28]**, **[21]**, **[22]**. Unlike SEC traces from copolymers derived from the carbohydrate oligomer, **[33]**, mono-modal distributions were observed. This confirms the presence of a single initiating species.

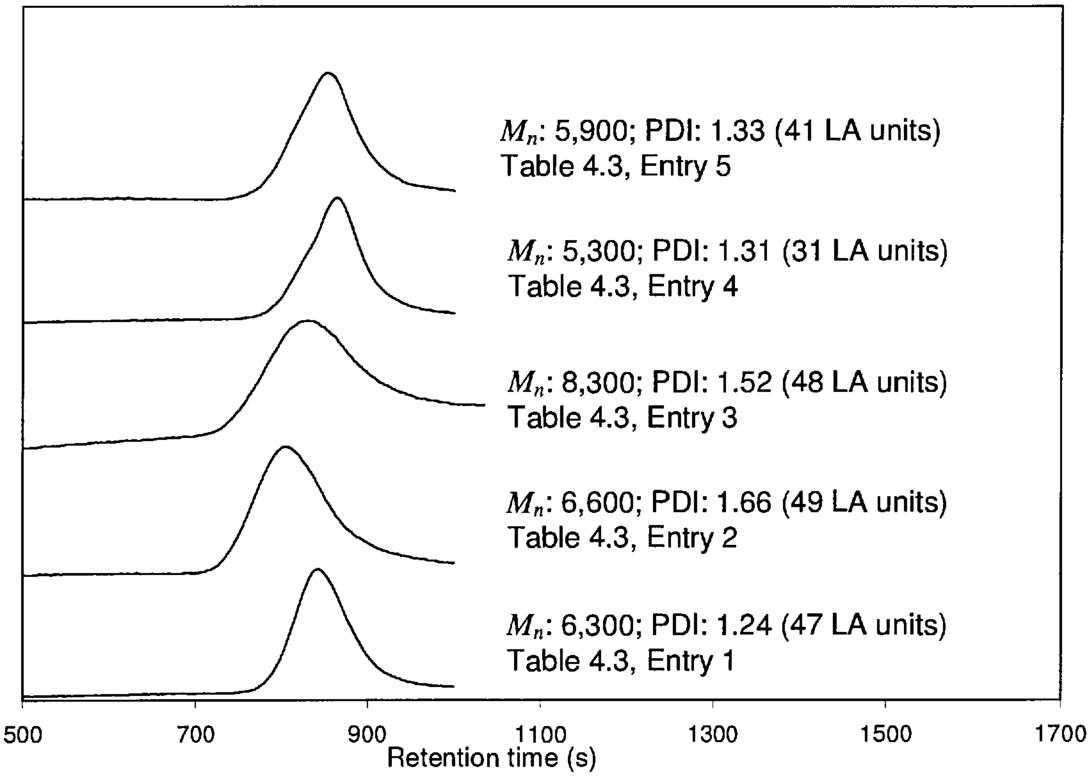
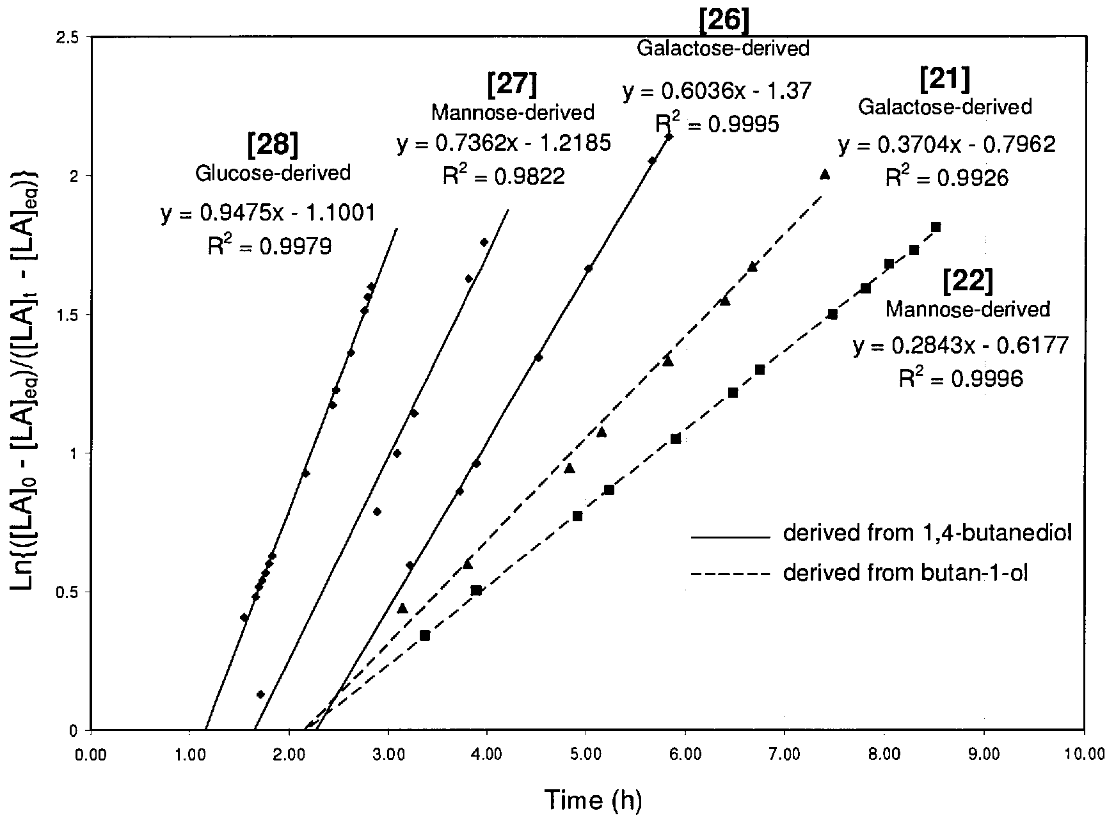


Figure 4.10 - SEC traces for [*L,L*]-PLA initiated by [26], [27], [28], [21], [22]

These traces are associated with narrow PDIs which ranged from 1.24 to 1.66 showing the well-controlled nature of these polymerisations. This control is further supported by the linear fit of the semi-logarithmic plot, $\mathrm{Ln}\{([LA]_0 - [LA]_{eq})/([LA]_t - [LA]_{eq})\}$ against time (Figure 4.11).

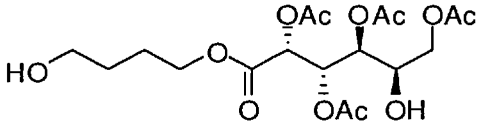
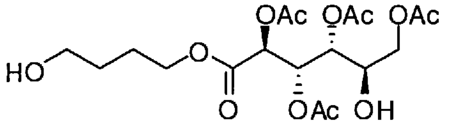
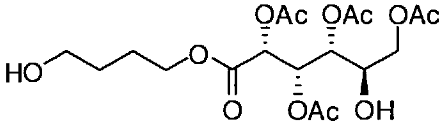
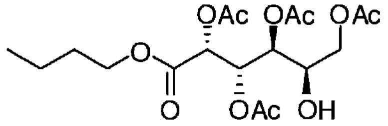
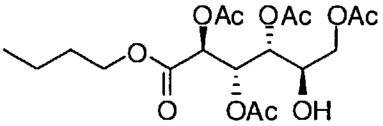


Conditions: anaerobic, r.t., initiator to lactide ratio of 1:50, 0.7M in lactide, dry $CDCl_3$

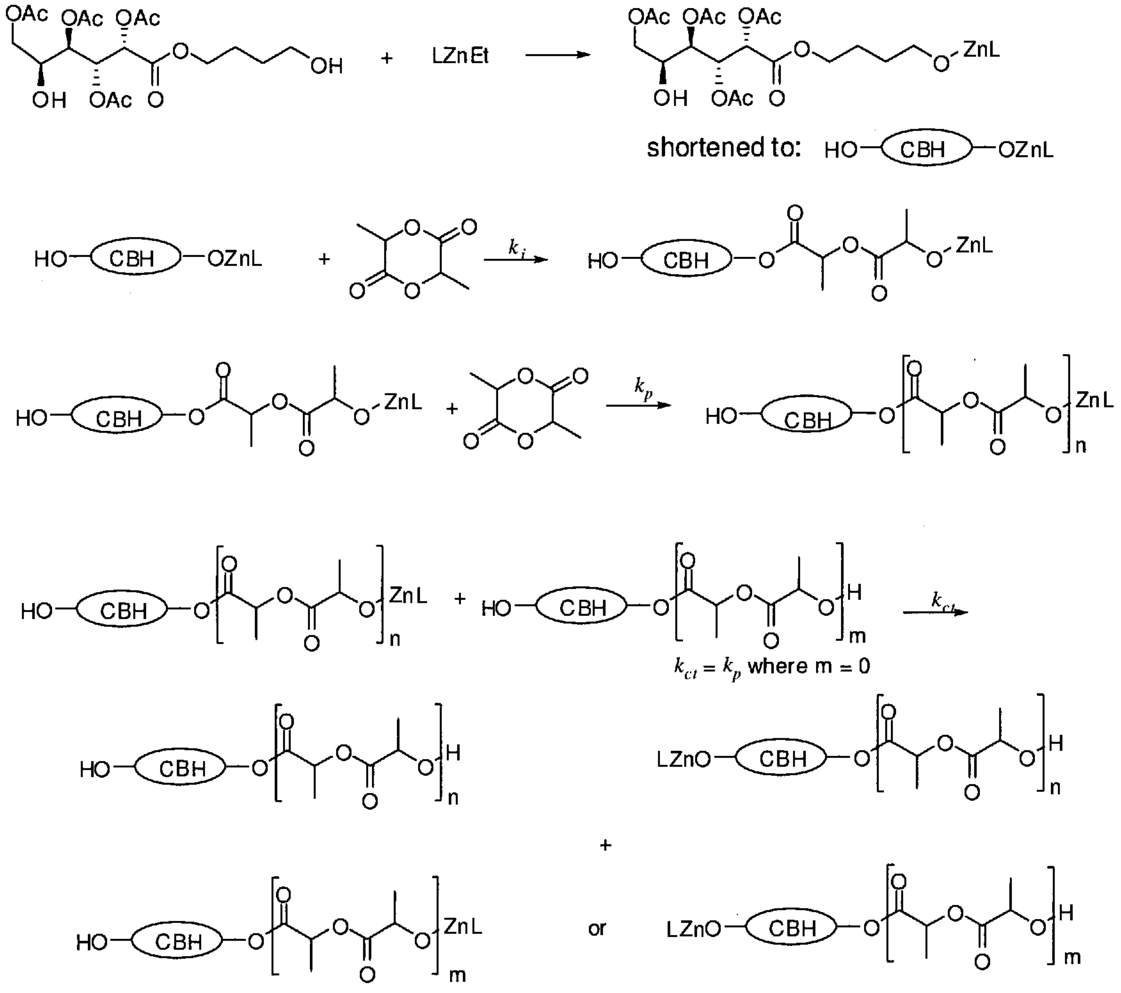
Figure 4.11 - Kinetics for Ring Opening Polymerisation of [*L,L*]-Lactide initiated by [26], [27], [28], [21], [22]

Pseudo-first order rate constants, k_{obs} were determined from these plots (Table 4.4) with the observation that those derived from 1,4-butanediol and are hence bi-functional (**[26]** - **[28]**) were between 0.60 and 0.95 h^{-1}. On average k_{obs} for those with a single hydroxyl group (**[21]**, **[22]**) was about half, ranging from 0.28 and 0.37 h^{-1}.

Table 4.4 - Kinetic data for of [*L*,*L*]-Lactide initiated by [26], [27], [28], [21], [22]

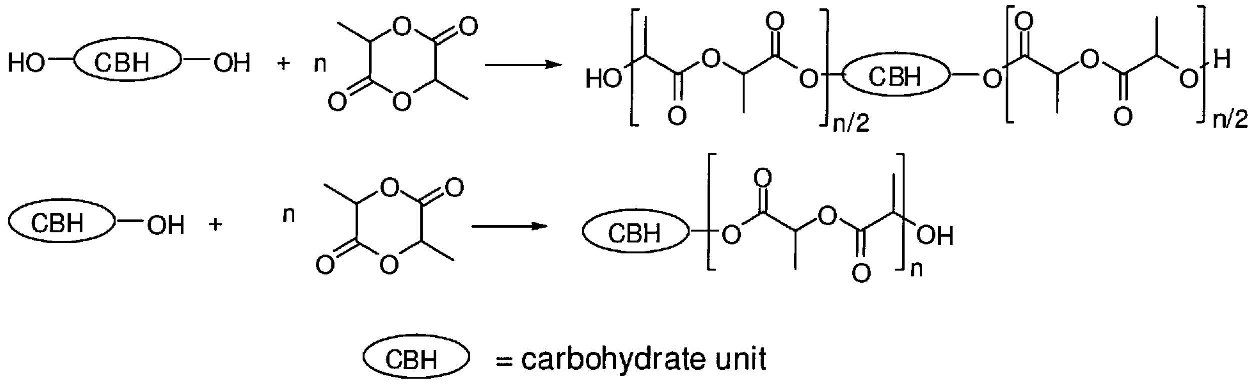
Entry	Co-Initiator	k_{obs} (h^{-1})	induction period (h^{-1})
1	 **[26]** 4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-galactonate	0.60	2.3
2	 **[27]** 4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-mannonate	0.74	1.7
3	 **[28]** 4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate	0.95	1.2
4	 **[21]** butyl 2,3,4,6-tetra-*O*-acetyl-D-galactonate	0.37	2.2
5	 **[22]** butyl 2,3,4,6-tetra-*O*-acetyl-D-mannonate	0.28	2.2

This difference can be rationalised by the active species present in the polymerisation reaction. Scheme 4.6 shows the mechanism and active species in the ROP of lactide initiated by carbohydrates bearing two terminal hydroxyl groups. The initiator is formed *in situ* by reaction between LZnEt, **[35]** and the alcohol moieties to form a zinc alkoxide. This is followed by initiation and propogation as with a standard ROP reaction with the associated rate constants k_i and k_p respectively. However, it is not only zinc alkoxides which are involved in the polymerisation. Free alcohol groups are significant as they can act as chain transfer agents. Chisholm *et al.* have established that chain transfer occurs significantly faster than propagation in lactide polymerisation.[7] Thus, the latter is the rate determining step and governs the observed rate constant, $\boldsymbol{k_{obs}}$. Furthermore, this dictates that $\boldsymbol{k_{obs}}$ is a function of the initial hydroxyl group concentration. Thus the reaction rate is doubled on account of the initial hydroxyl concentration being twice that in the 1,4-butandiol-derived co-initiators compared to those derived from butan-1-ol.



Scheme 4.6 - Active species and reaction mechanism of the ROP of lactide by initiators derived from 1,4-butanediol

This also suggests that the structure of the resulting PLA derived from bifunctional co-initiators is inherently different from that initiated by the mono-functional ones. Chain transfer allows the polymer chain to grow from both ends of the molecule. Thus the carbohydrate unit is no longer an end group but is centred within the polymer chain as shown in Scheme 4.7.



Scheme 4.7 - PLA structure initiated by mono- and bi-functional carbohydrate initiators

Another characteristic of these polymerisation reactions is the observed induction period which is manifested by a non-zero *x*-intercept in the semi-logarithmic plot, $\mathrm{Ln}\{([LA]_0 - [LA]_{eq})/([LA]_t - [LA]_{eq})\}$ against time (Figure 4.11). The induction period ranges between 1 and 2 h for the initiators investigated (Table 4.4) and presumably reflects the time taken for the carbohydrate alcohols to react with the alkyl zinc co-initiator.

Tacticity

Co-initiators were also investigated to determine whether they exhibited any control over the tacticity of the resulting polymers derived from *rac*-lactide. Polymers prepared using co-initiators **[28]**, **[30]**, **[23]** and **[25]** were examined. This was also compared with ^{i}PrOH as a control alcohol. The tacticity was determined from the homonuclear decoupled ^{1}H NMR spectrum. P_s (P_i) is the probability of syndiotactic (isotactic) linkages between monomer units and $P_s + P_i = 1$.[8]

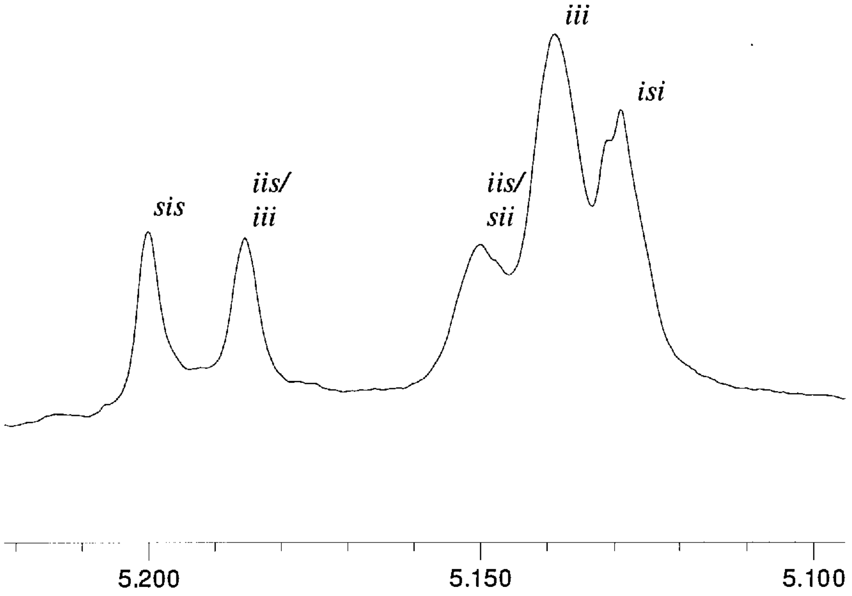


Figure 4.12 - Homonuclear decoupled ^{1}H NMR spectrum of poly(lactide) initiated by [23] (methyne region, $CDCl_3$, 400 MHz)

The polymers analysed were found to be atactic with the probability of a racemic enchainment, $P_i = 0.5$[9] (Table 4.5). This is consistent with the control experiment, where *i*-propanol was used as the co-initiator. As expected, the carbohydrate co-initiators do not influence with tacticity of the polymer as stereocontrol occurs by either an enantiomorphic site control mechanism (chiral metal centre) or *via* a chain end control mechanism (stereochemistry of the last inserted monomer unit). Neither of which are affected by the initiating group.

Table 4.5 - Tacticity Control

Co-initiator	**P_r**	**Tacticity**
^{i}PrOH (control)	0.5	Atactic
4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate **[28]**	0.5	atactic
butyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate **[23]**	0.5	atactic
butyl 2,3,4,6-tri-*O*-acetyl-L-arabinonate **[25]**	0.5	atactic

4.4.2 Hydrolytic degradation

Preliminary experiments were conducted to investigate the effect of the carbohydrate unit on the hydrolytic degradation of [*L,L*]- and *rac*-poly(lactide). There are a multitude of methods used to analyse the degradation in the literature.[10,11] These include among others *in vitro* degradation and bulk degradation. The method we chose involved the acid catalysed degradation because it allowed degradation of small quantities of polymer samples to be investigated efficiently and relatively quickly (under standard aqueous conditions the degradation can take months). It should be noted that degradation conditions are acidic and thus do not represent neither soil (compost) nor *in vivo* degradation conditions. The polymer sample was instead dissolved in TFA(aq.)/$CHCl_3$ (2 % v/v) to form a 3 mg/mL solution. Polymer samples were analysed by SEC (polystyrene standards, $CHCl_3$) on a daily basis over a 1 week period.

Theoretical Considerations[10]

Analysis of the degradation of PLA was based on the assumption that degradation occurs in a random chain scission mechanism. This is widely accepted in the acid catalysed degradation of PLA.[10-12].

Based on this, Liu *et al.*[10] have shown the relationship between the number average degree of polymerisation at time, t (X_t) and the rate constant k_x can be simplified as follows:

$$(X_t-1)/X_t=[(X_0-1)/X_0]\exp(-k_x t)$$

Where X_0 is the initial number average degree of polymerisation

This can also be expressed as:

$$\mathrm{Ln}[(X_t-1)/X_t]=\mathrm{Ln}[(X_0-1)/X_0]-k_x t$$

As per the property of the logarithmic function the following approximation can be drawn:

$$\mathrm{Ln}(1-1/X_t)=-1/X_t-(1/X_t)^{1/2}/2-\ldots-(1/X_t)^{1/n}/n-\ldots\approx-1/X_t$$

Thus Liu *et al.*[10] have shown that this can be simplified to:

$$M_0/M_t-1=-M_0k_dt$$

Where M_0 and M_t are the molecular weight of the polymer at time 0 and t, respectively, k_d is the apparent rate constant.

Analysis of hydrolytic degradation

Plots of M_n against time revealed a logarithmic relationship consistent with random chain scission.[10] The plot of $[M_0/M_t - 1]$ *versus* time is a linear one and also supports a random chain scission degradation pathway. The gradient of these linear relationships gives the degradation rate constant, k_d and are summarised in Table 4.6.

Table 4.6 - Degradation of PLA

Figure	**Co-Initiator**	**Starting LA stereochemistry *rac*- or [*L*,*L*]-**	**k_d (days^{-1})**	**R^2 (correlation coefficient)**
Figure 4.13	^{i}PrOH	*rac*-	0.07	0.9925
Figure 4.13	**[23]**	*rac*-	0.21	0.9884
Figure 4.14	**[28]**	*rac*-	1.21	0.9806
Figure 4.14	**[28]**	[*L*,*L*]-	0.38	0.9420
Figure 4.15	**[27]**	*rac*-	0.28	0.9577
Figure 4.15	**[22]**	*rac*-	0.71	0.9609
Figure 4.16	**[26]**	[*L*,*L*]-	0.56	0.9835
Figure 4.16	**[27]**	[*L*,*L*]-	0.35	0.9994

Figure 4.13 shows the change of M_n with time for *rac*-poly(lactide) initiated by **[23]**, the carbohydrate co-initiator derived from glucose and butan-1-ol and is compared with *rac*-poly(lactide) initiated by ^{i}PrOH. From the logarithmic plots, the gradients reveal that *rac*-poly(lactide) initiated with the functionalised carbohydrate-derived moiety degrades faster that a PLA homopolymer (0.21 day^{-1} *versus* 0.07 day^{-1}).

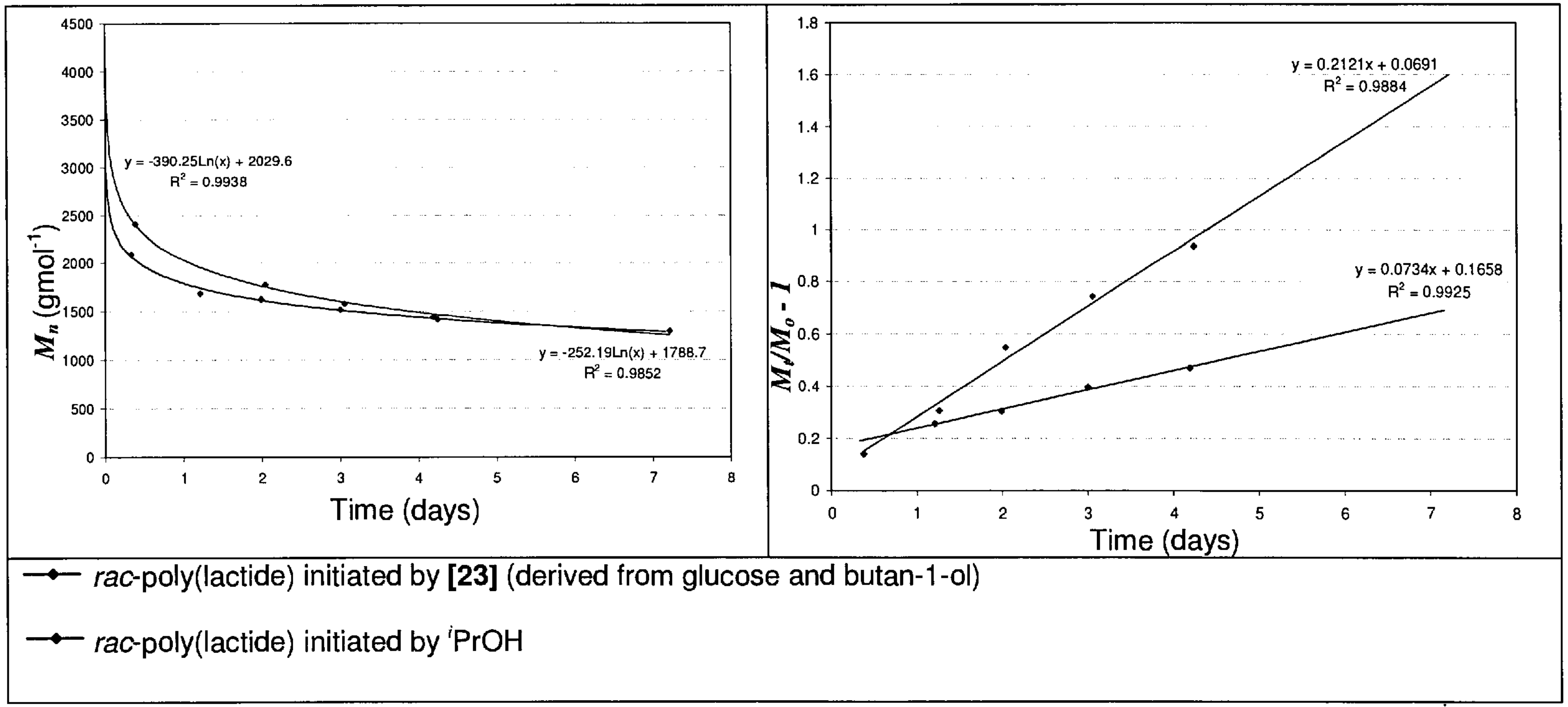


Figure 4.13 - Hydrolytic degradation of *rac*-poly(lactide) initiated by [23] and *rac*-poly(lactide) initiated by ^{i}PrOH

Investigations were conducted to determine the behaviour of *rac*-poly(lactide) *versus* [*L*,*L*]-poly(lactide) towards hydrolytic degradation where the carbohydrate moiety was unchanged. In Figure 4.14 this is illustrated using **[28]** and shows that *rac*-poly(lactide) degrades faster than [*L*,*L*]-poly(lactide). This is as expected as the greater crystallinity of [*L*,*L*]-poly(lactide) hinders its degradation rate. The carbohydrate moiety is not expected to alter this trend.

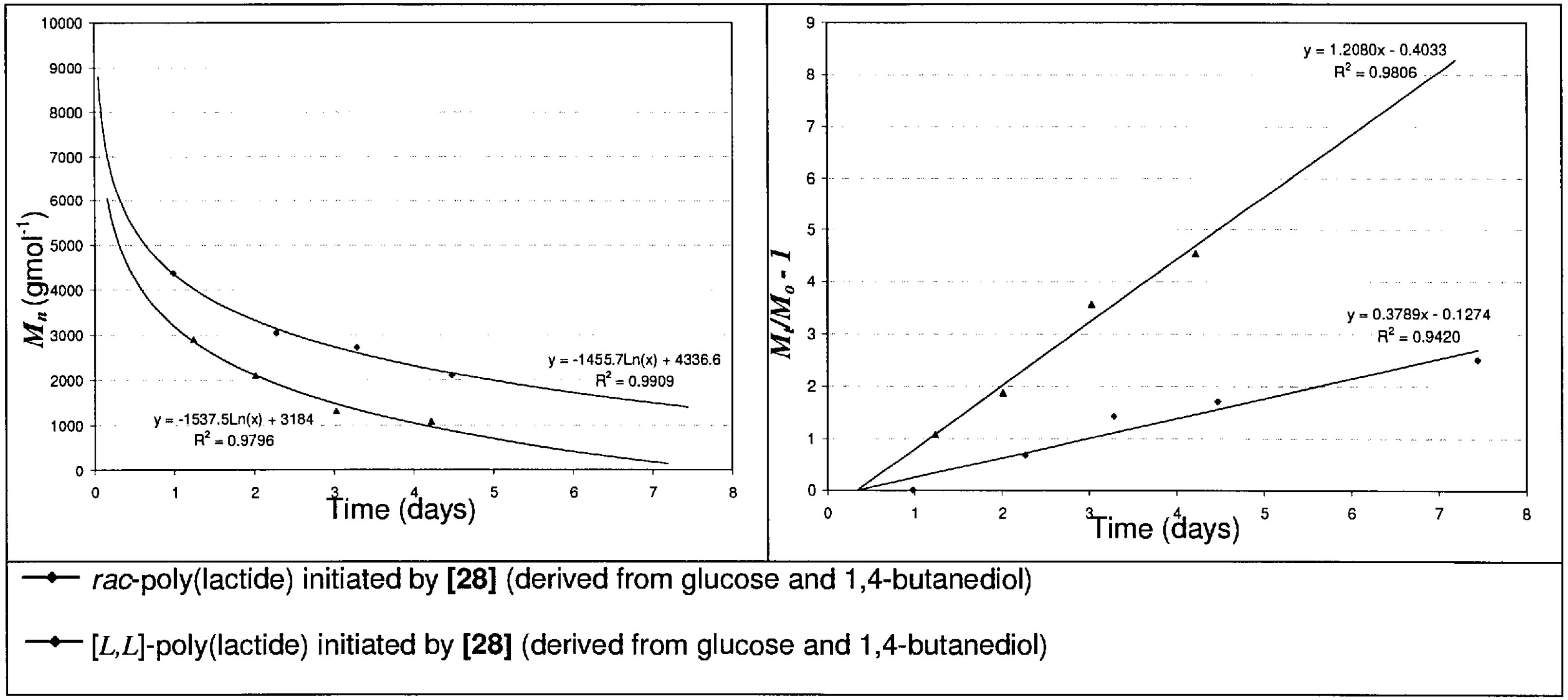


Figure 4.14 - Hydrolytic degradation of *rac*-poly(lactide) and [*L*,*L*]-poly(lactide) initiated by [28]

Carbohydrate co-initiators derived from 1,4-butanediol were compared with those derived from butan-1-ol. Using the mannose derivatives as examples, Figure 4.15 shows that degradation is marginally enhanced in those derived from butan-1-ol.

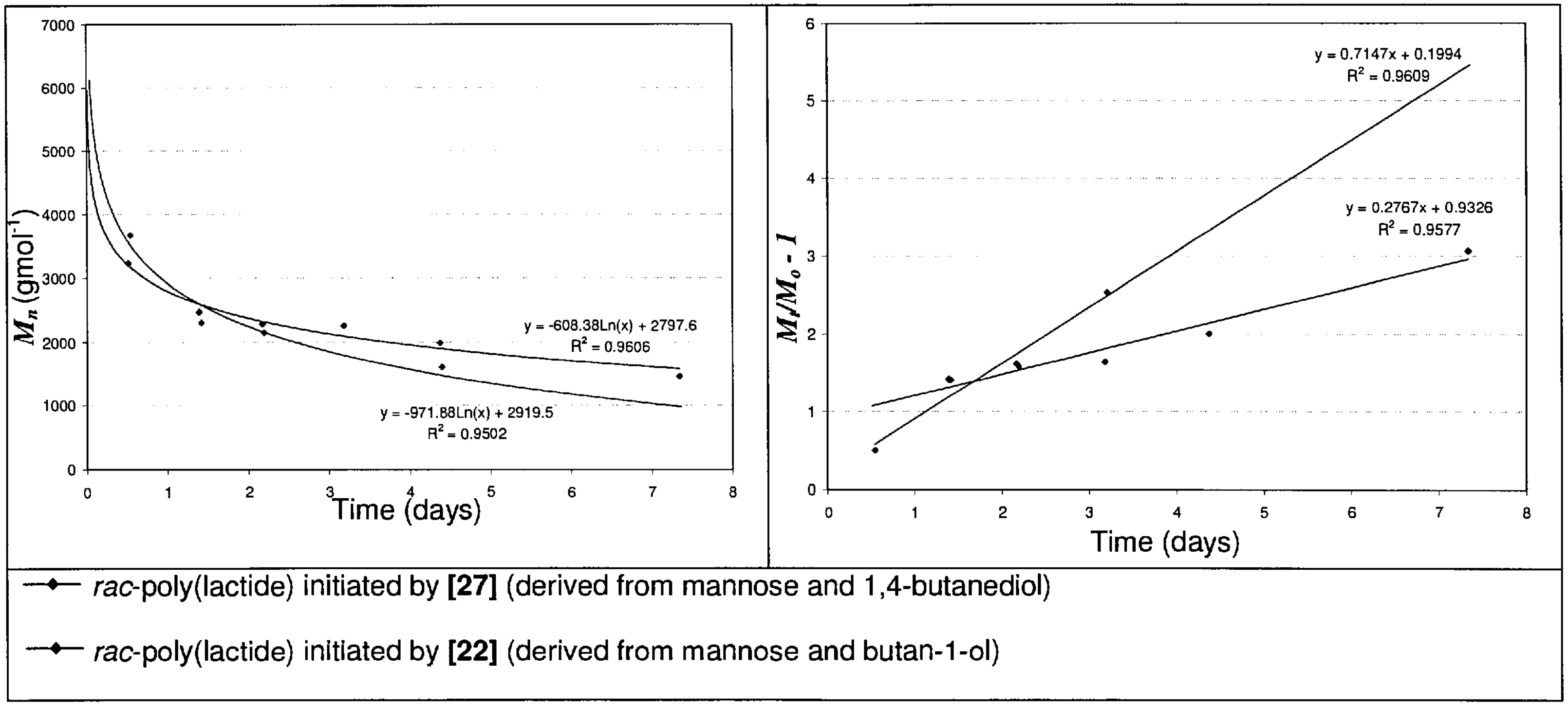


Figure 4.15 - Hydrolytic degradation of *rac*-poly(lactide) initiated by [27] and *rac*-poly(lactide) initiated by [22]

Investigations were also conducted to determine the effect of changing the parent carbohydrate. Using galactose and mannose derivatives to illustrate this, it was observed that modifying the carbohydrate (whilst keeping the parent alcohol constant) does not significantly alter the degradation rate. Figure 4.16 shows that the degradation rates for these were between 0.4 and 0.6 day^{-1}.

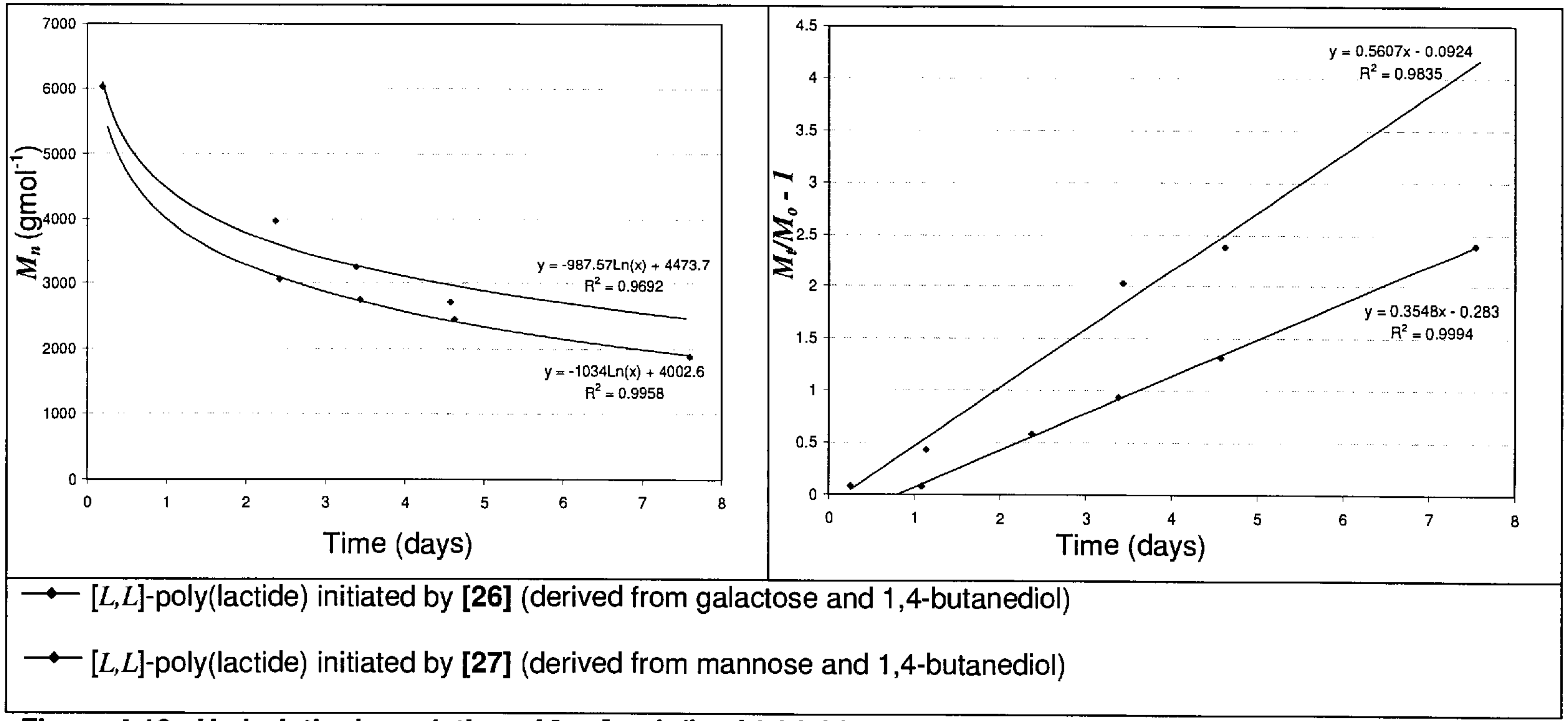


Figure 4.16 - Hydrolytic degradation of [*L*,*L*]-poly(lactide) initiated by [26] and [*L*,*L*]-poly(lactide) initiated by [27]

4.5 Conclusion

Polycondensation was explored as a synthetic route to novel, highly functionalised polyesters. Acetyl-protected, carbohydrate-derived diols **[26]** - **[30]** were treated with various acid chlorides in DCM or toluene, in the presence of NEt_3 and under mild conditions. Mild conditions were critical to ensure tolerance towards the sensitive acetyl protecting groups. Copolymers of all 5 carbohydrate derivatives were afforded with acid chlorides with up to 100 repeat units and M_n between 41,000 and 56,000 $gmol^{-1}$ (SEC). PDIs ranged between 1.5 and 2.8. The former limit is not generally associated with polycondensation reactions which are characterised by broad molecular weight distributions. In this instance, work-up and purification is likely to have caused fractionation. In addition to SEC, the polymers were characterised by NMR. The structural similarity of the monomers and resulting polymer as well as the complexity of carbohydrate NMR prevents clear distinction between monomer and polymer signals. However, a common observation made was broadening of ^1H NMR signals which are characteristic of polymers. This is applicable to the carbohydrate as well as acid chloride moieties. In polyesters with adipic units, the loss of symmetry within this unit resulted in the appearance of an asymmetrical NMR signal in the polymer compared to adipoyl chloride. The most conclusive NMR evidence which pointed to the reaction between the acid chloride and the diol, was the shift of the H-5 resonance from 3.85 ppm in the carbohydrate monomer to between 4.5 and 4.0 ppm in the polymer. This is brought about by the proximity to the carbonyl group of the acid chloride which increases electron-withdrawal. Similarly, $^{13}C\{^1H\}$ NMR revealed that the characteristic adipic resonance at 46 ppm due to the α-carbon in adipoyl chloride was shifted to 64 - 63 ppm in the polymer. In this case, loss of the chloride atom results in deshielding of the α-carbon.

A highly functionalised, carbohydrate-derived oligomer, **[33]** was used as a macro-initiator in the ring opening polymerisation of *rac*-lactide, investigated using an alkyl zinc co-initiator, **[35]**.[13] This resulted in the successful synthesis of triblock ABA copolymers comprising of lactide blocks of 12 to 250 repeat units attached to the oligoester blocks of up to 3 repeat units. The copolymers were analysed by ^{1}H NMR and SEC. M_n determined using both methods were in close agreement with one another. MALDI also confirmed the polymers' M_n as well as the presence of three series corresponding to the different oligoester initiators (mono-, di- and triester). Narrow polydispersity indices (PDIs) between 1.05 and 1.22 suggested good polymerisation control. This was supported by the linear relationship between $\mathrm{Ln}\{([LA]_0 - [LA]_{eq})/([LA]_t - [LA]_{eq})\}$ and time from which a pseudo first order rate constant, $k_{obs,}$ of 0.39 h^{-1} (6.57×10^{-3} min^{-1}) was derived ($[LA]_0 = 0.7$ M, $[\mathbf{[33]}]_0 = 0.028$ M, CD_2Cl_2).

Highly functionalised aldaric esters derived from the reaction of 1,4-butanediol (**[26]**, **[27]**, **[28]**) and butan-1-ol (**[21]**, **[22]**) were investigated as co-initiators in the ROP of lactide in conjunction with the alkyl zinc initiator, **[35]**. This afforded polymers with 30 - 50 repeat units of lactide and M_n (SEC) from 5,300 and 8,300 $gmol^{-1}$. This was accompanied by narrow PDIs from 1.24 to 1.66 as well as linear relationships between $\mathrm{Ln}\{([LA]_0 - [LA]_{eq})/([LA]_t - [LA]_{eq})\}$ and time. This was all evidence of well-controlled polymerisations. Bi-functional initiators (**[26]** - **[28]**) were associated with k_{obs} 0.60 and 0.95 h^{-1}; twice the rate of the mono-functional analogues (**[21]**, **[22]**) where k_{obs} was between 0.28 and 0.37 h^{-1}. This is attributed to the concentration of hydroxyl groups in the bi-functional initiators being twice that in the mono-functional ones. This allows chain transfer to take place in the former which is faster than the rate of propagation. Hence k_{obs} is doubled whilst the polymer chain length remains comparable to where mono-functional initiators are used. This suggests that the bi-functional aldaric ester unit is not necessarily an end-group but is instead within the polymer chain.

Preliminary experiments were conducted to investigate the effect of the carbohydrate unit on the hydrolytic degradation of [*L,L*]- and *rac*-poly(lactide). This was carried out using an aqueous solution of TFA in $CHCl_3$. Theoretical considerations shown by Liu *et al.*[10] shows that degradation occurs *via* a random chain scission pathway as expected. The degradation studies showed that the introduction of a carbohydrate moiety enhances the degradation rate. Polymers prepared with a mono-functional initiator do degrade faster than those prepared with a bi-functional one. Finally, changing the carbohydrate moiety does not significantly influence the rate of degradation.

4.6 References

1. Metzke, M.; Bai, J. Z.; Guan, Z., *J. Am. Chem. Soc.* **2003,** 125, (26), 7760-7761.

2. Zamora, F.; Hakkou, K.; Muñoz-Guerra, S.; Galbis, J. A., *Polymer Degradation and Stability* **2006,** 91, (11), 2654-2659; Zamora, F.; Hakkou, K.; Alla, A.; Rivas, M.; Roffé, I.; Mancera, M.; Muñoz-Guerra, S.; Galbis, J. A., *J. Polym Sci Part A: Polym Chem* **2005,** 43, (19), 4570-4577; Zamora, F.; Hakkou, K.; Alla, A.; Espartero, J. L.; Muñoz-Guerra, S.; Galbis, J. A., *J. Polym Sci Part A: Polym Chem* **2005,** 43, (24), 6394-6410.

3. Arvanitoyannis, I.; Nakayama, A.; Psomiadou, E.; Kawasaki, N.; Yamamoto, N., *Polymer* **1996,** 37, (651).

4. Platel, R. H.; Hodgson, L. M.; Williams, C. K., *Polymer Reviews* **2008,** 48, 11-63.

5. Williams, C. K.; Breyfogle, L. E.; Choi, S. K.; Nam, W.; Young, V. G.; Hillmyer, M. A.; Tolman, W. B., *J. Am. Chem. Soc.* **2003,** 125, 11350-11359.

6. Dechy-Cabaret, O.; Martin-Vaca, B.; Bourissou, D., *Chem. Rev.* **2004,** 104, (12), 6147-6176.

7. Chisholm, M. H.; Delbridge, E. E.; Gallucci, J. C., *New J. Chem.* **2004,** 28, (1), 145-152.

8. Kricheldorf, H. R.; Boettcher, C.; Tonnes, K. U., *Polymer* **1992,** 33, (13), 2817-2824; Jensen, T. R.; Breyfogle, L. E.; Hillmyer, M. A.; Tolman, W. B., *Chem. Comm.* **2004**, 2504-2505; Chamberlain, B. M.; Cheng, M.; Moore, D. R.; Ovitt, T. M.; Lobkovsky, E. B.; Coates, G. W., *J. Am. Chem. Soc.* **2001,** 123, (14), 3229-3238.

9. Method for determining tacticity is described in the appendix.

10. Liu, X. B.; Zou, Y. B.; Li, W. T.; Cao, G. P.; Chen, W. J., *Polym. Degrad. Stab.* **2006,** 91, (12), 3259-3265.

11. Kulkarni, A.; Reiche, J.; Lendlein, A., *Surface and Interface Analysis* **2007,** 39, (9), 740-746; Vey, E.; Miller, A. F.; Claybourn, M.; Saiani, A., *Macromol. Symp.* **2007,** 251, 81-87; Sivalingam, G.; Madras, G., *Polym. Degrad. Stab.* **2004**, 84, (3), 393-398; Nugroho, P.; Mitomo, H.; Yoshii, F.; Kume, T., *Polymer Degradation and Stability* **2001,** 72, (2), 337-343; Zong, X. H.; Wang, Z. G.; Hsiao, B. S.; Chu, B.; Zhou, J. J.; Jamiolkowski, D. D.; Muse, E.; Dormier, E., *Macromolecules* **1999,** 32, (24), 8107-8114; Li, Y. X.; Volland, C.; Kissel, T., *Polymer* **1998,** 39, (14), 3087-3097.

12. Belbella, A.; Vauthier, C.; Fessi, H.; Devissaguet, J. P.; Puisieux, F., *Int. J. Pharm.* **1996,** 129, (1-2), 95-102; Shih, C., *J. Control. Rel.* **1995,** 34, (1), 9-15; Shih, C., *Pharm. Res.* **1995,** 12, (12), 2036-2040.

13. Williams, C. K., *Chem. Soc. Rev.* **2007,** 36, 1573-1580.

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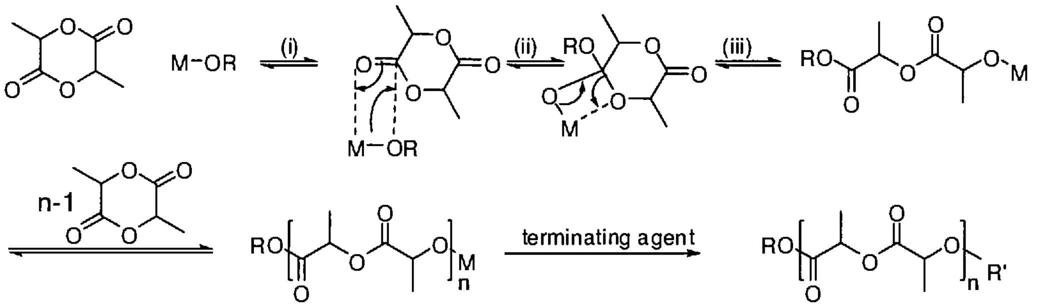
CHAPTER 5:

POLYMERISATION STUDIES 2: USING 1,5-LACTONES

5.1 Introduction

Following the successful preparation of 1,5-lactones, their ring opening polymerisation (ROP) activity was investigated. ROP are equilibrium reactions and are controlled by two key criteria: the initiating group and the reaction conditions.

Firstly, a suitable catalytic or initiating system for ring-opening polymerisation was needed. For lactide ROP, metal alkoxide complexes are frequently used, these species are proposed to operate via a coordination-insertion mechanism.[1-3] Scheme 5.1 illustrates the coordination-insertion mechanism and the role of the initiator.



M =Al, Sn, Y, Zn; R = $(CH_2)_4OH$, $OiPr_3$, $(CH_2)_2OH$; R' depends on the terminating agent

Scheme 5.1 - Coordination-insertion ROP mechanism of lactide

Well established initiating systems are based on Sn(II), Al(III) and Zn(II) alkoxide complexes.[1] Tin(II) bis[2-ethylhexanoate] ($Sn(II)Oct_2$, tin octoate) and alcohols are probably the most widely used initiating systems for the ROP of cyclic esters.[3-10] In these instances, the actual initiating system, $Sn(II)(OR)_2$ is frequently formed *in situ* by reaction between $Sn(II)(Oct)_2$ and an additional alcohol co-initiator. This system has previously been successfully applied as an initiator in the polymerisation of lactide[3,4,6,11,12] and ε-caprolactone.[7,9,10,12,13] More significant, however, is its application in the commercial production of poly(lactide) (PLA) on a 140,000 tonne scale annually.[14] Despite the poor understanding of its mechanism, the popularity of tin-based systems are largely attributed to its robustness as well as effectiveness. However, the reaction mechanism is poorly understood and has been the subject of investigation for over 20 years.[15] Whilst both activated monomer and cationic mechanisms have been postulated, it is becoming increasingly accepted that coordination-insertion mechanism prevails in the ROP with Sn(II)$(Oct)_2$.[15-17] Further details regarding the activity of Sn(II)Oct_2 are given in the introduction.

The reaction conditions can be controlled by varying the concentration and temperature. However, these are often two variables which oppose each other. The nature of polymerisation reactions is such that the entropy change is unfavourable with respect to the Gibbs free energy. Therefore, ideally the reaction temperature should be as low as possible to favour the long polymer chains, whilst keeping the concentration of monomer as high as possible. However, the temperature has to be high enough to provide sufficient activation energy for both the initiation and propagation reactions.

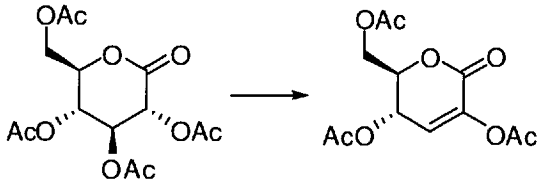
This chapter covers our investigations of ROP of carbohydrate-derived 1,5-lactones using tin systems as well as other initiators and the associated the limitations.

5.2 Investigations using Sn(II)Oct$_2$ initiating systems

Sn(II)Oct$_2$ was used as an initiator in the ring opening polymerisation of protected 1,5-lactones with a variety of alcohols. It is important to note that successful reactions were observed only when Sn(II)Oct$_2$ which had not been purified, and was therefore contaminated by octanoic acid (the significance of this finding is explained later). Reactions were carried out in the melt and at temperatures ranging from 80 °C to 160 °C.

High concentrations (i.e. melt reactions) were chosen to minimise the unfavourable entropic effects of the polymerization reaction. Butan-1-ol, 1,4-butanediol, and benzyl alcohol were used as the co-initiators, chosen because of their high boiling points and thus their ability to withstand the reaction conditions. Butan-1-ol and benzyl alcohol were chosen as co-initiators with a single hydroxyl group. Butan-1-ol provided a direct comparison to 1,4-butanediol due to their structural similarity. Reactions were monitored by ^{1}H NMR spectroscopy, size exclusion chromatography (SEC) as well as mass spectrometry (MALDI-TOF, chemical and electron spray ionisation).

To determine the optimal reaction conditions, 2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone, **[6e]** was treated with 1,4-butanediol and Sn(II)Oct$_2$ initially at temperatures between 100 and 160 °C in the melt. This is the standard procedure for the ring opening polymerisation of lactide and ε-caprolactone.[1,6,8,18,19,20] High temperatures are a requirement for Sn(II)Oct$_2$ where it has been established that monomer conversion is strongly dependent on temperature. Storey *et al.* have also shown that ε-caprolactone conversions above 80 % were only obtained at temperatures above 120 °C.[19] However, under these conditions, the reaction led to the formation of the *α,β*-unsaturated 1,5-lactone **[33]** as shown in Scheme 5.2.



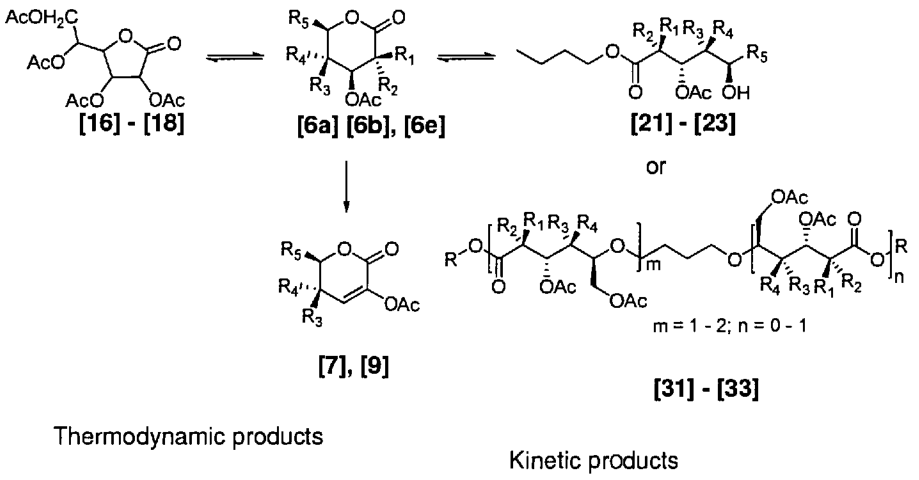
[6e] **[10]**

*1 eq. 1,4-butanediol, 2 eq. Sn(II)Oct$_2$, 6 eq. 2,3,4,6-tetra-O-acetyl-D-glucono-1,5-lactone, **[6e]** bulk, 100 - 160 ℃*

Scheme 5.2 - Product of the reaction of 2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone with Sn(II)Oct$_2$ at 120 ℃

The *α,β*-unsaturated 1,5-lactone **[10]** has a characteristic chemical shift at 6.4 ppm with a coupling constant of 4 Hz corresponding to H-3. The presence of this olefinic group was also confirmed by a bromine water test. The presence of only 3 acetyl resonances in the ^{1}H NMR spectrum also identified this compound. Furthermore, the ^{1}H NMR spectrum was consistent with that reported in the literature.[21] It has been previously reported to form by reaction between **[6e]** and triethylamine at r.t.[21,22] The optimal reaction temperature was 80 ℃, as this temperature allowed formation of the true initiator (the Sn(II) alkoxide complex)[19] whilst minimising the elimination reaction.

The same temperature (80 ℃) was used to investigate the ROP of the 1,5-lactones derived from D-(+)-galactopyranose and D-(+)-mannopyranose, **[6a]** and **[6b]**. Due to the bi-functional nature of 1,4-butanediol, reactions were carried out using 6 equivalents of the lactone with 1 equivalent of diol and Sn(II)Oct$_2$. On the other hand, 2 equivalents of butan-1-ol and benzyl alcohol were used in the respective reactions. Aliquots were taken at timed intervals and analysed by ^{1}H NMR, mass spectrometry and SEC to monitor the progress of the reaction. As the reaction progressed, ring-opened esters of 1 to 3 repeat units were formed in a reversible reaction. These were detected by ^{1}H NMR primarily by monitoring the resonating frequency for H-2 in the monomer and ring-opened esters. SEC showed monomers, dimers and trimers were formed. In addition to the oligoesters, two other products formed in irreversible reactions: the 1,4-lactones (**[16]** - **[18]**) and the *α,β*-unsaturated 1,5-lactones (**[7]**, **[9]**). The relative proportions of these were also monitored using ^{1}H NMR spectroscopy. The general reaction pathway is illustrated by Scheme 5.3. The relative proportions of the different species present depended on the nature of the carbohydrate lactone, the reaction time and the alcohol co-initiator used.



Sn(II)Oct$_2$, alcohol, 80 °C, bulk

Scheme 5.3 - Oligomerisation of acetyl-protected 1,5-lactones using Sn(II)Oct$_2$ in the presence of an alcohol

Figure 5.1 to Figure 5.3 show the % composition of products of the oligomerisations of 2,3,4,6-tetra-*O*-acetyl-D-galactono-1,5-lactone **[6a]** in the presence of butan-1-ol, benzyl alcohol and 1,4-butandiol respectively. In all cases, a mixture of the desired ring opened products, the starting lactone, the 1,4-lactone **[16]** and the *α,β*-unsaturated 1,5-lactone **[7]** formed immediately. After 1 to 2 h, the relative proportion of ring opened product reached a maximum. Over time, the proportion of 1,4-lactone increased as the starting material was depleted. However, the proportion of *α,β*-unsaturated 1,5-lactone remained largely constant throughout the experiment after its initial formation.

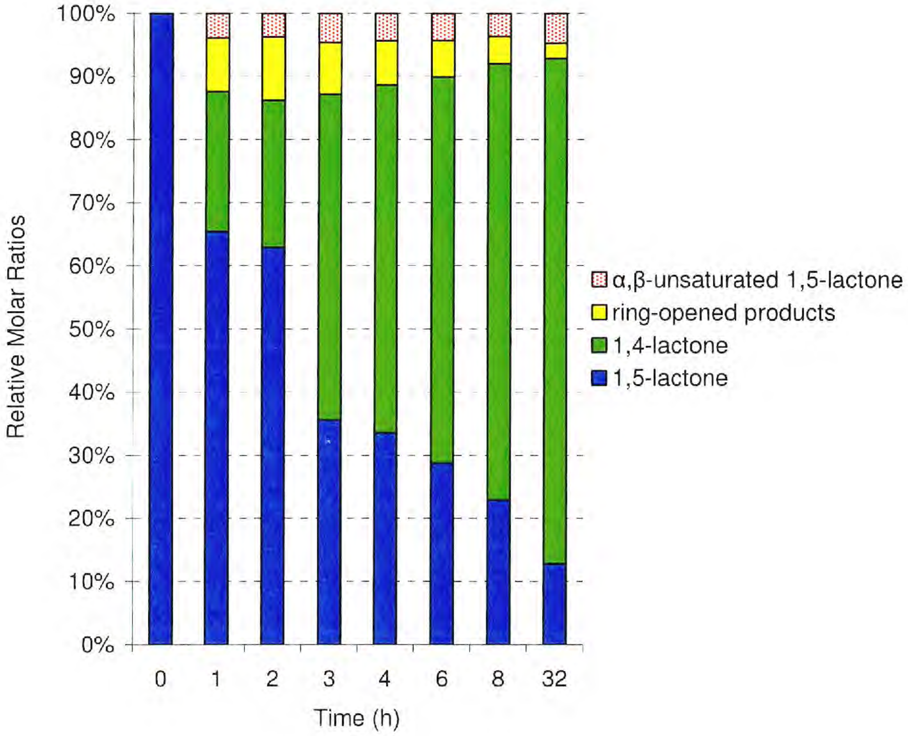


Figure 5.1 - Relative molar ratios of the oligomerisation of 2,3,4,6-tetra-*O*-acetyl-D-galactono-1,5-lactone [6a] with butan-1-ol using Sn(II)Oct$_2$

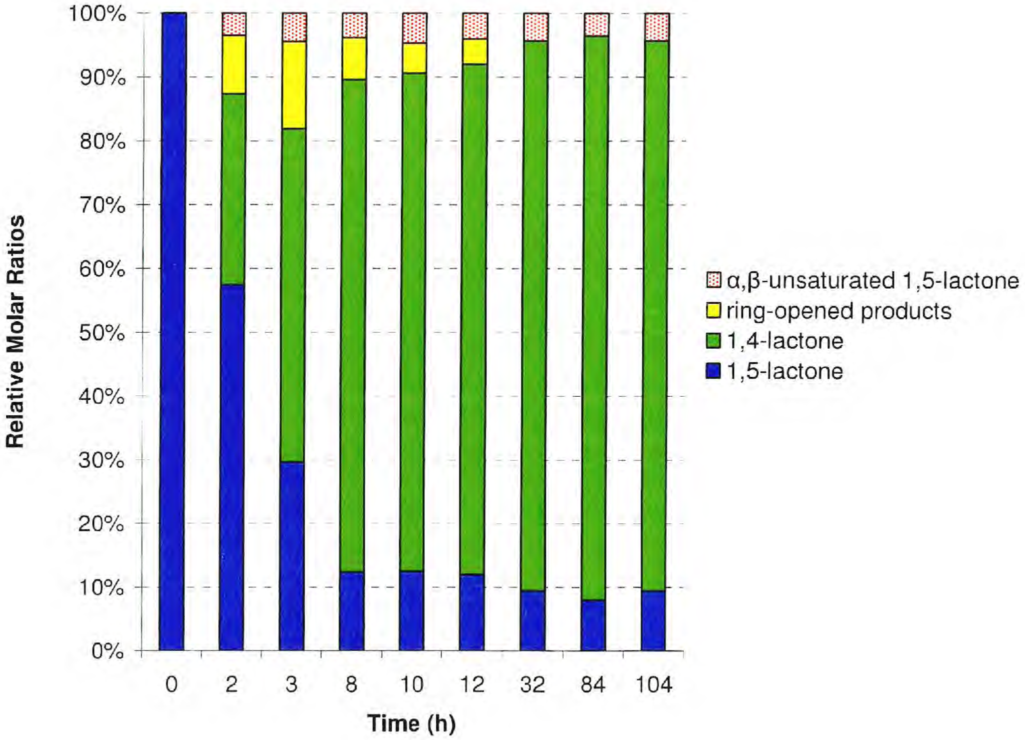


Figure 5.2 - Relative molar ratios of the oligomerisation of 2,3,4,6-tetra-*O*-acetyl-D-galactono-1,5-lactone [6a] with benzyl alcohol using Sn(II)Oct$_2$

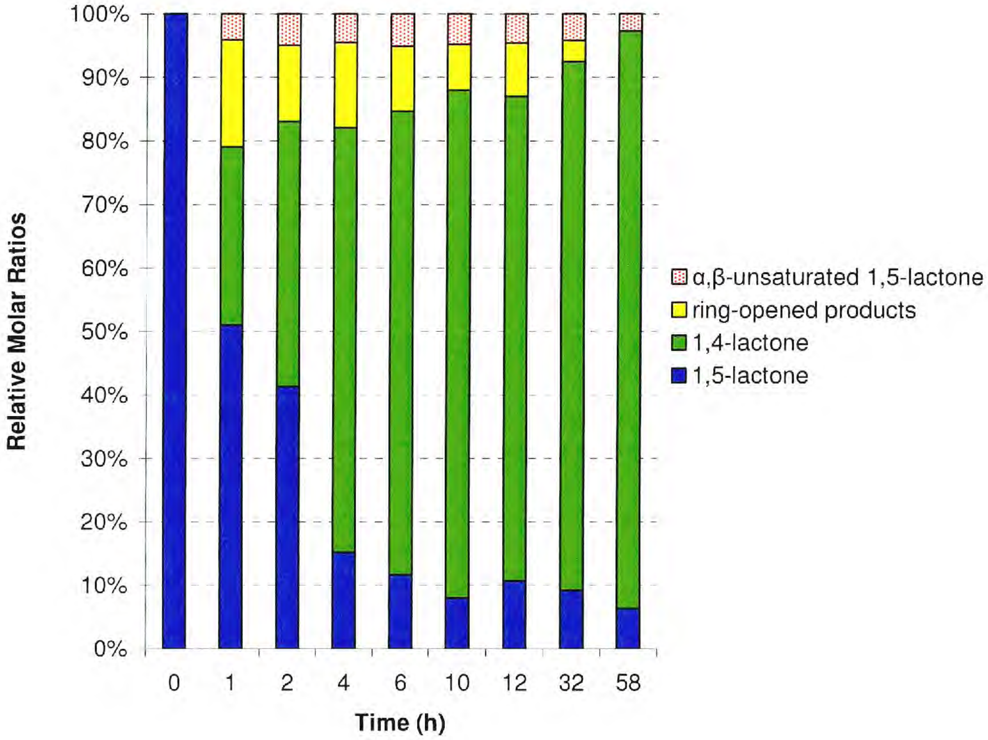


Figure 5.3 - Relative molar ratios of the oligomerisation of 2,3,4,6-tetra-*O*-acetyl-D-galactono-1,5-lactone [6a] with 1,4-butandiol using Sn(II)Oct$_2$

When the mannose derivative was tested under the same conditions, similar results were observed. However, it was noted that the molar ratio of the ring-opened product falls then rises, before it is completely depleted. Using the experiment with butan-1-ol as an example (Figure 5.4), the maximum molar ratio of ring opened product of 18 % is achieved after 6 h. Subsequently, the molar ratio falls to 6 mol % at 32 h and then rises to 9 mol % at 58 h.

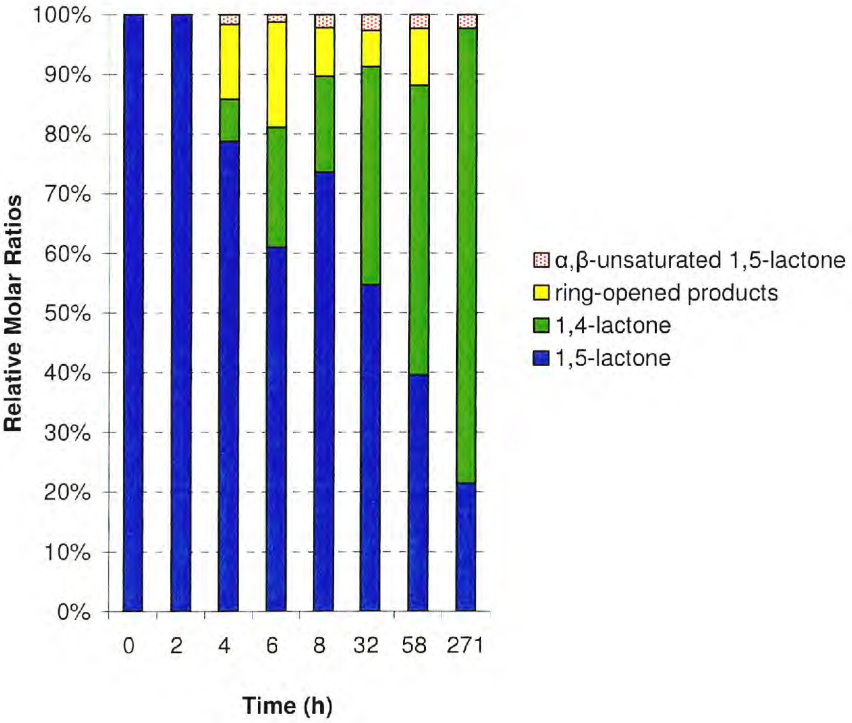


Figure 5.4- Relative molar ratios of the oligomerisation of 2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone [6b] with butan-1-ol using Sn(II)Oct$_2$

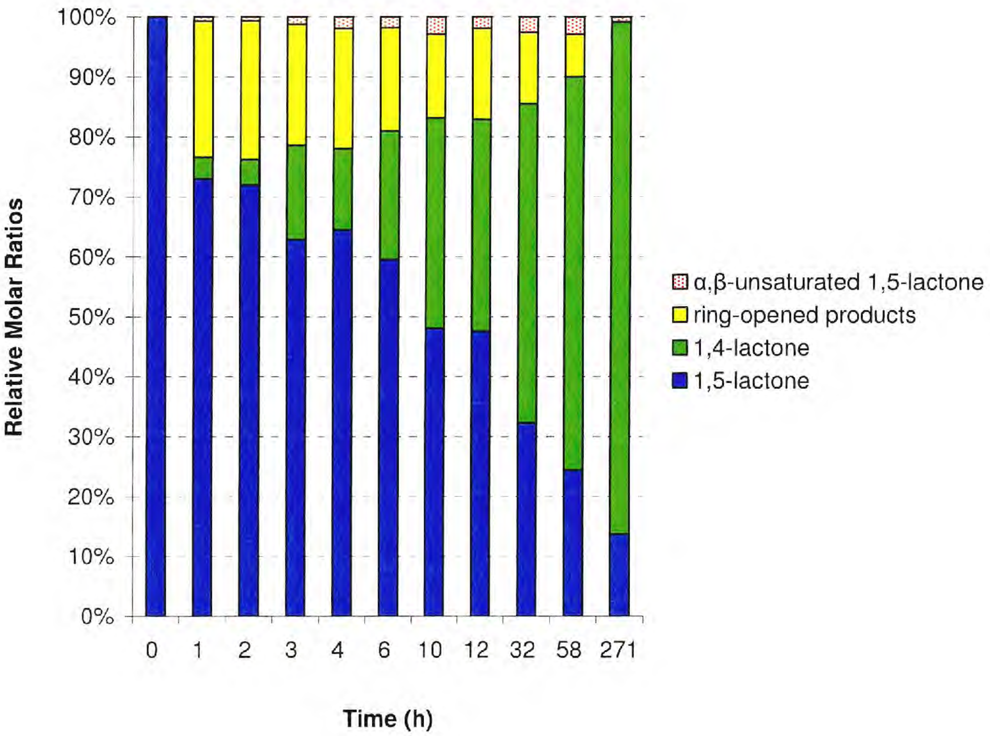


Figure 5.5 - Relative molar ratios of the oligomerisation of 2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone [6b] with benzyl alcohol using Sn(II)Oct$_2$

The reaction of the mannose derivative with 1,4-butanediol was the most successful, as the maximum molar ratio for the ring-opened product was 52 mol %; this was the maximum molar ratio obtained in any experiment. Furthermore, the molar ratio of the ring-opened product fluctuated before becoming depleted. This is in fact a characteristic feature of several of these reactions, but is more pronounced in this experiment due to the large molar ratios of this ring-opened ester. After 3 h 52 mol % of the reaction mixture was composed of this product. This is likely to be attributed to the stability of **[6b]** and its resistance to decomposition. This is probably due to the difference in stereochemistry of **[6b]** at C-2 *versus* the other carbohydrate derivatives.

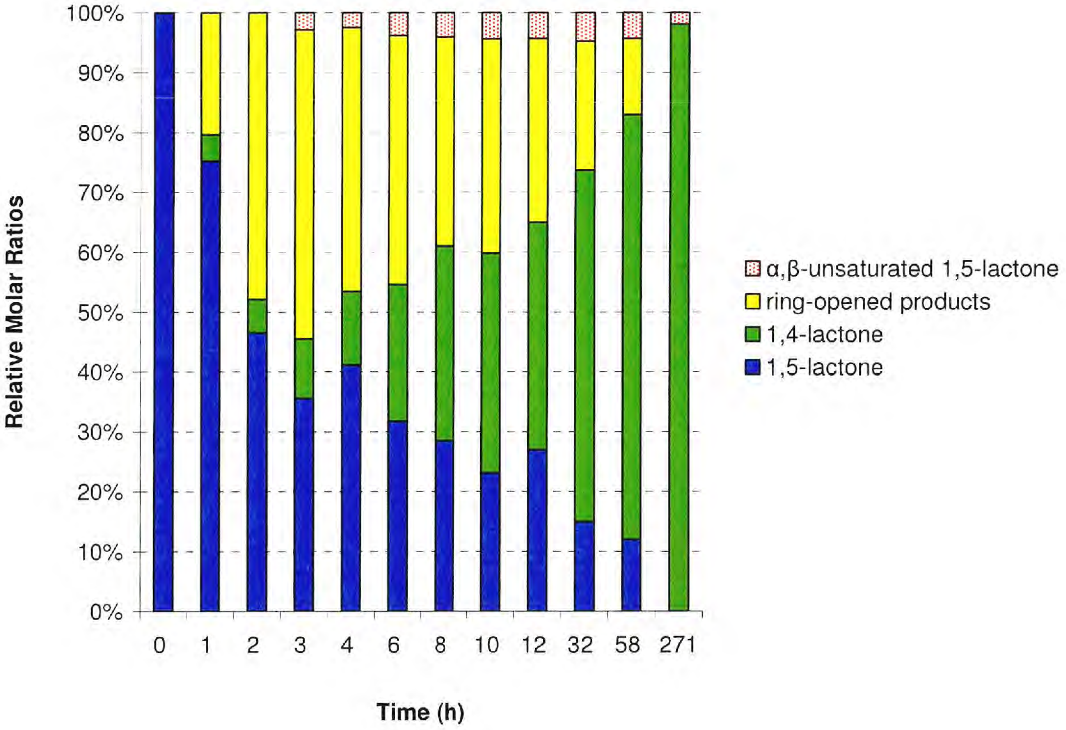


Figure 5.6 - Relative molar ratios of the oligomerisation of 2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone [6b] with 1,4-butanediol using Sn(II)Oct$_2$

The D-(+)-glucopyranose experiments were similar to the D-(+)-galactopyranose experiments. The formation of the ring-opened product was suppressed as it decomposed to the starting material which itself was converted to the 1,4-lactone and some *α,β*-unsaturated 1,5-lactone.

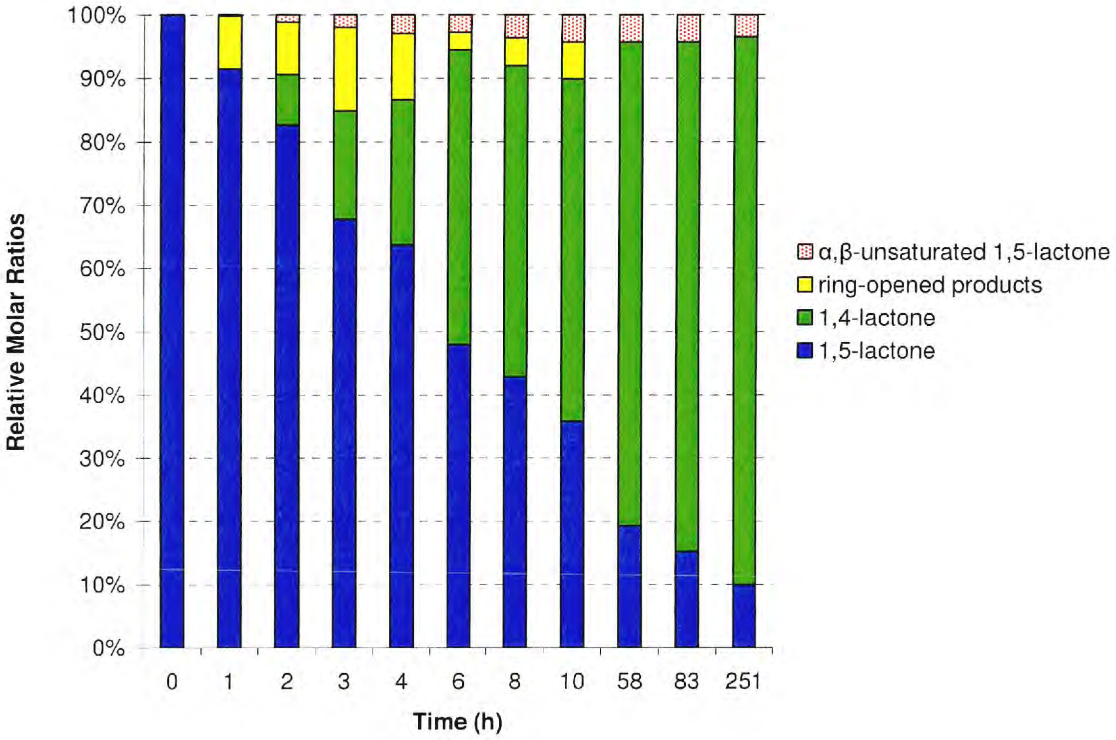


Figure 5.7 - Relative molar ratios of the oligomerisation of 2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone [6e] with butan-1-ol using Sn(II)Oct$_2$

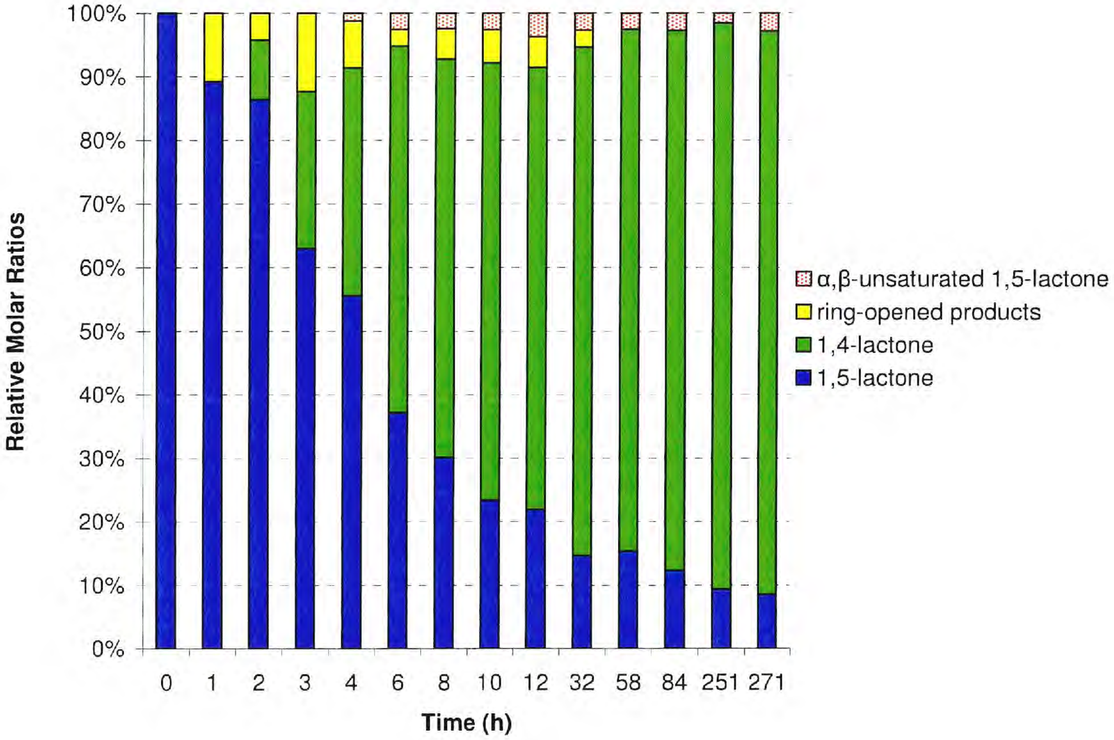


Figure 5.8 - Relative molar ratios of the oligomerisation of 2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone [6e] with benzyl alcohol using Sn(II)Oct$_2$

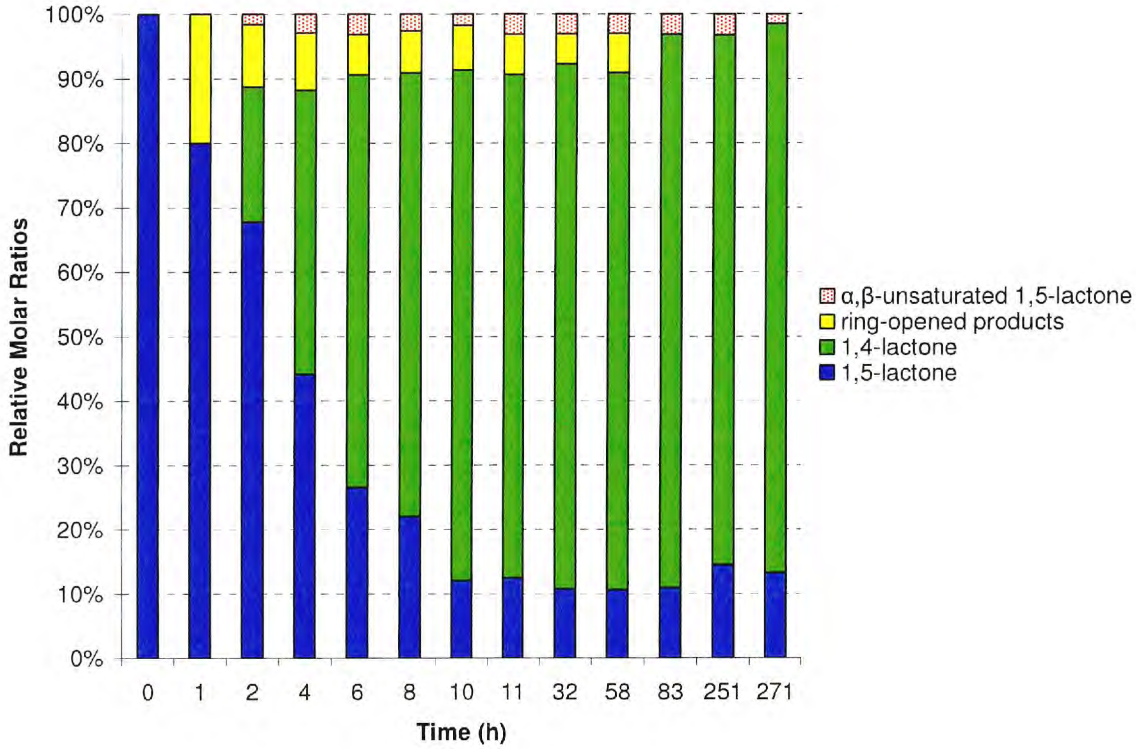


Figure 5.9 - Relative molar ratios of the oligomerisation of 2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone [6e] with 1,4-butanediol using Sn(II)Oct$_2$

Table 5.1 shows the proportions of the ring-opened esters achieved for each functionalised 1,5-lactone with the different co-initiating alcohols. Comparing the alcohols shows that 1,4-butanediol was the most successful as it led to the highest proportions of the ring-opened esters. On average, the percentage of the ring-opened esters was 30 %, compared to 14 to 16 % obtained using butan-1-ol and benzyl alcohol respectively. On comparing the functionalised 1,5-lactones, the mannose derivative consistently out-performed its D-(+)-galactopyranose and D-(+)-glucopyranose analogues owing to its unique stereochemistry at C-2. This was most notable when using 1,4-butanediol, where half of the reaction mixture was the ring-opened esters. The initial concentration of hydroxyl groups was kept constant across all experiments. Half as much 1,4-butanediol was used *versus* the primary alcohols. Nonetheless, the bi-functional nature of this alcohol appears to enhance the activity of this tin system. There was little difference in the performance of the D-(+)-galactopyranose and D-(+)-glucopyranose derivatives, where the maximum molar proportions of the ring-opened products did not exceed 20 %.

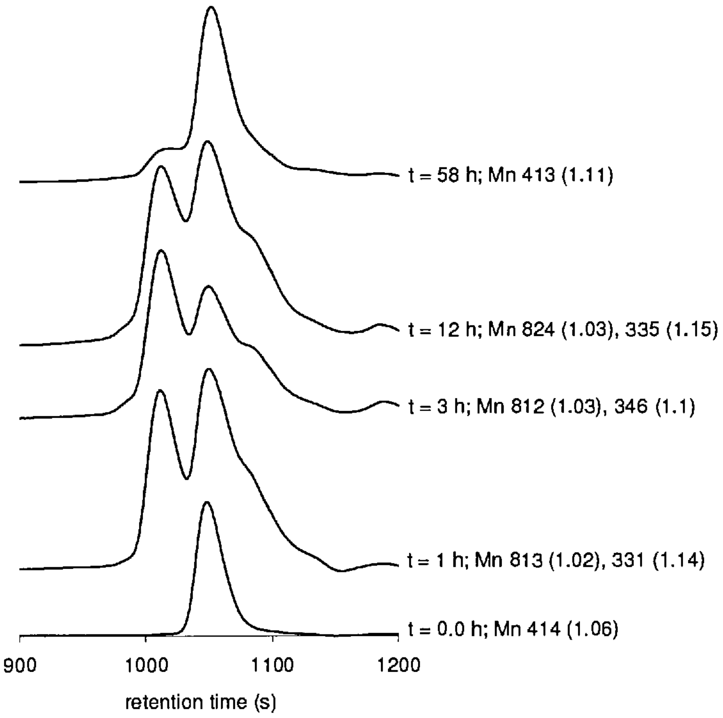
Table 5.1 also shows the M_n results obtained using SEC. From this it is evident that where ring-opened esters were formed, the reactions with the mono-functional alcohols yielded only those bearing a single carbohydrate unit. However, when 1,4-butanediol was used, dimers were formed with all of the functionalised 1,5-lactones used.

Table 5.1 - Summary of performance of the functionalised 1,5-lactones with respect to the ring-opened species, its M_n (by SEC) and co-initiating alcohol

	Starting Material	% Molar Composition	Max Mn (PDI)
	Co-initiator: Butan-1-ol		
	2,3,4,6-tetra-*O*-acetyl-D-galactono-1,5-lactone **[6a]**	10	438 (1.05)
	2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone **[6b]**	18	461 (1.03)
	2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone **[6e]**	13	446 (1.08)
	Average	*14*	
	Co-initiator: Benzyl Alcohol		
	2,3,4,6-tetra-*O*-acetyl-D-galactono-1,5-lactone **[6a]**	14	440 (1.05)
	2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone **[6b]**	23	484 (1.11)
	2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone **[6e]**	12	470 (1.06)
	average	*16*	
	Co-initiator: 1,4-Butanediol		
	2,3,4,6-tetra-*O*-acetyl-D-galactono-1,5-lactone **[6a]**	17	831 (1.01), 370 (1.11)
	2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone **[6b]**	52	824 (1.03), 335 (1.14)
	2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone **[6e]**	20	867 (1.03), 417 (1.07)
	average	*30*	

Results for reactions with starting 1,5-lactones in the presence of Sn(II)Oct$_2$ and 80 °C

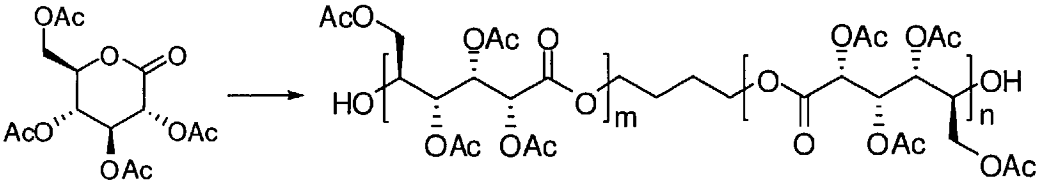
This is further illustrated by Figure 5.10 which shows the SEC signals for the oligomerisation of of 2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone with 1,4-butanediol using Sn(II)Oct$_2$. Between reaction times of 1 and 12 h a bimodal distribution is observed where the peak corresponding to a higher M$_n$ is attributed to a dimeric species. This is confirmed by a M$_n$ of about 800 gmol^{-1}.



PDI is reported in parentheses adjacent to the respective M$_n$ values

Figure 5.10 - SEC signals of reaction progress of the oligomerisation of of 2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone [6b] with 1,4-butanediol using Sn(II)Oct$_2$

As 2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone **[6e]** is readily accessible due to the commercial availability of its precursor, it was chosen to optimise the oligomerisation reaction with Sn(II)Oct$_2$. 1,4-Butanediol was the co-initiator of choice owing to its success in earlier reactions. This reaction was repeated on a large scale, under the same conditions and a low M$_n$ oligoester **[33]** was produced (Scheme 5.5). The oligomer, **[33]** was purified by dissolution in CH$_2$Cl$_2$ followed by precipitation from hexane. This was subsequently isolated by column chromatography using neutral alumina and isolated in 10 % yield. Silica was not a suitable stationary phase as it caused decomposition to the starting 1,5-lactone **[6e]**.



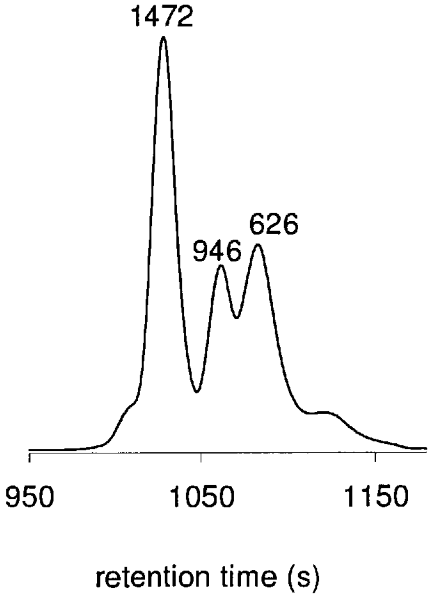
[6e]

m = 1 - 2, n = 0 – 1
[33]

Sn(II)Oct$_2$, alcohol, 80 °C, bulk

Scheme 5.4 – Synthesis of *α*-4-hydroxybutyl-*ω*-hydroxyl-oligo(2,3,4,6-tetra-*O*-acetyl-D-gluconate), [33]

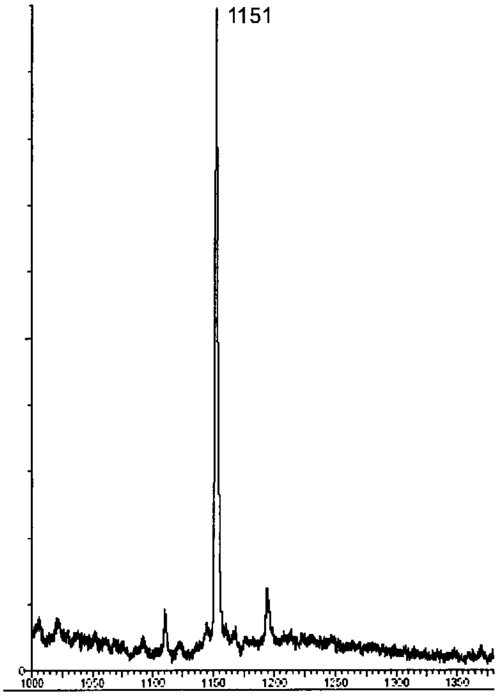
Figure 5.11 shows the SEC signals for **[33]**, the signal corresponding to 1472 gmol^{-1} suggests that a trimer was isolated in greatest proportion. Also present are smaller proportions of dimer (946 gmol^{-1}) and monomers (626 gmol^{-1}).



The SEC was determined using THF as the eluent and calibrated using narrow M_n polystyrene standards. In the SEC trace the peaks are labelled with the M_n (vs. polystyrene)—that is, 1472, 946, and 626 gmol^{-1}, respectively.

Figure 5.11 - SEC signals for [33]

MALDI mass spectrometry confirmed the molecular weight of the trimer **[33]**, as well as its butanediol end group. Figure 5.12 shows the MALDI signals for the sodium cationised trimer, **[33]**$^+$ (where n = 2) at 1151 amu.



The MALDI mass spectrum was determined using a dithranol matrix dissolved in THF with NaOTf as the cationising agent

Figure 5.12 - MALDI mass spectrum for [33]

Figure 5.13 shows the ^{1}H NMR spectrum of the glucose derived oligomer, **[33]**. The broad signals are consistent with oligomers being present. Using 2-D NMR techniques (COSY, HMQC and HMBC) it was possible to assign the resonance due to H-2, H-3 and H-4 between 4.9 and 5.8 ppm. In the oligomer **[33]** H-2, H-3 and H-4 resonate between 5.2 and 5.7 ppm. H-6 resonates between 4.0 and 4.5 ppm together with the methyne protons adjacent to the ester groups. H-5 resonates between 3.6 and 3.7 ppm which is similar to the 1mer, **[28]**.

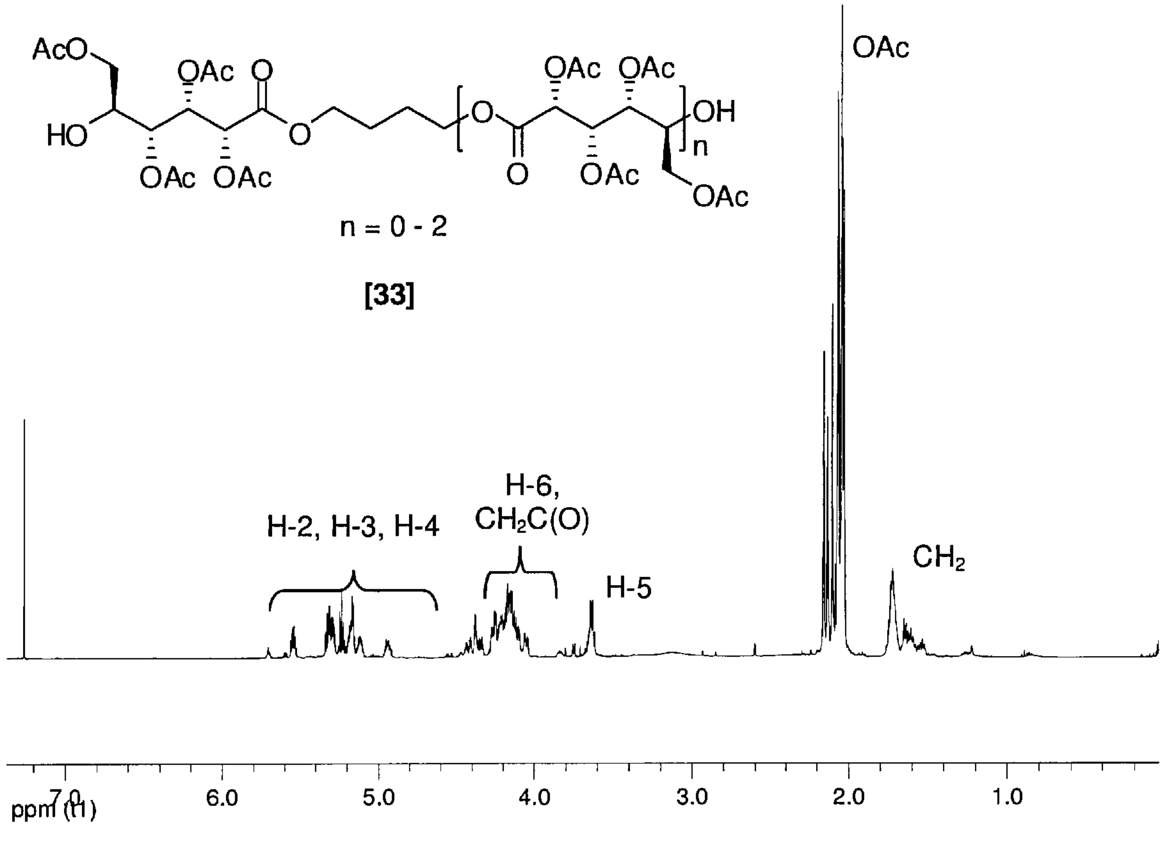


Figure 5.13 - ^{1}H NMR Spectrum of [33]

Unlike other applications of Sn(II)Oct$_2$ in the ring-opening polymerisation of lactones, there is no evidence for the formation of cyclic lactones, carboxylic acid terminated chains, or octanoic ester end groups.[2,23] This emphasises the value of this novel reaction for selectively synthesising linear oligoesters.

5.3 Investigations with alternative initiators

Alternative initiating systems were considered in an attempt to polymerise the lactones. In addition to Sn(II)Oct$_2$, Al(III) and Zn(II) initiating systems are commonly used as initiators the ring-opening polymerization of various lactones including ε-caprolactone and lactide.[2,8,9,15,17,18,20,24] An advantage of these systems is that they can be applied at low temperature. Al(O^{i}Pr$_3$)$_3$ was tested as an initiator in the ROP of the glucose-derivative 1,5-lactone, **[6e]**. Reactions were carried out at temperatures from -30 °C to 130 °C, over up to 3 days with between 1 to 100 equivalents of monomer. However, at temperatures between -30 °C and r.t., there was no reaction. Whilst at temperatures above 80 °C, decomposition to the unsaturated 1,5-lactone **[10]** was observed. Two zinc initiators were investigated: diethyl zinc and a highly active single site system, developed by Williams *et al.*,[25] for ROP opening polymerization of lactide **[35]** (LZnOEt). Both zinc initiators behaved in the same manner as Al(O^{i}Pr$_3$)$_3$. The aluminium and zinc based systems investigated are known to polymerize lactide *via* a coordination-insertion mechanism (i.e. this requires the co-ordination of the lactone carbonyl group to the metal centre). In the carbohydrate-derived lactones, there are 4 of 5 carbonyl groups which could coordinate to the metal centre. However, for the coordination-insertion mechanism to operate the metal complexes would be required to distinguish between the ring carbonyl with those on the protecting groups, which perhaps explains the lack of polymerisation using these initiators.

The ring-opening of the glucose derivative **[6e]** was only possible when crude Sn(II)Oct$_2$ was used. Crude Sn(II)Oct$_2$ contains significant amounts of 2-ethylhexanoic acid, clearly identified by the acidic proton resonance in the ^{1}H NMR spectrum at 11.5 ppm.[7] The unique reactivity of crude Sn(II)Oct$_2$ suggests that the acidic impurities activate the monomer **[6e]** leading to cleavage of the acyl bond by the alcohol co-initiator. Such a reaction is closely related to the ring-opening of **[6e]** in the presence of *p-TSA* and an alcohol to form the monoester. The formation of oligomers of up to three units can be rationalised by the excess of monomer and also by Sn(II)Oct$_2$ catalysing intermolecular transesterification reactions. Indeed, Sn(Oct)$_2$ has good precedence as a transesterification catalyst.

5.4 Factors limiting chain length

Although it was not possible to initiate ROP of **[6e]** using metal initiators, oligomerisation was possible using crude Sn(II)Oct$_2$. In principle, it should be possible to create higher oligomers by changing the monomer loading. However, all attempts to increase the chain length failed. The maximum chain length obtained was three repeat units. Therefore, there must be factors limiting long chain lengths which are intrinsic to the monomer structure. One of these limiting factors is undoubtedly the formation of thermodynamic by-products (*vide supra*). The second factor is the position of the polymerisation equilibrium. There are three main factors that limit the molecular weights of polyesters: the ring strain, a low polymer ceiling temperature and intra-molecular transesterification or back-biting reactions.

5.4.1 Ring Strain

In general, the entropy decreases in polymerisation reactions (this can crudely be rationalised by the decrease in the number of molecules occurring on polymerisation) and hence the enthalpy controls the polymerisation. A measure of ring strain can be given by the negative of the enthalpy of polymerisation.[26] Ring strain is controlled by bond angle distortions, conformational strain, steric hindrance and non-bonded interactions in the ring.[27-29] Table 5.3 shows values for the ring strain in some cyclic ethers and esters. Considerable ring strain is present in 3-, 4- and 7-membered rings (30 to 90 kJmol^{-1}). Therefore, these are readily polymerisable. On the other hand, 5- and 6-membered rings possess little or no ring strain. Six-membered rings can be polymerised but in 5-membered rings, such as γ-butyrolactone, ring strain is decreased due to the envelope-like arrangement adopted by the ring, thus preventing polymerisation.

Table 5.2 - Dependence of ΔH_p on the ring size for cyclic ethers and esters (lactones)

Ring Size (no. atoms)	Ether[27]	$-\Delta H_p$ (kJmol^{-1})	Lactone[28]	$-\Delta H_p$ (kJmol^{-1})
3	ethylene oxide	95	-	-
4	trimethylene oxide	81	-	-
5	tetrahydrofuran	15	γ-butyrolactone	7
6	tetrahydropyran	~0	δ-valerolactone	27
6	1,4-dioxane	~0	-	-
7	hexamethylene oxide	34	ε-caprolactone	29

Although similar data is not available for **[6e]**, it is likely that the ring strain is lower than δ-valerolactone due to degree of substitution. Substitution decreases ring strain due to the Thorpe-Ingold effect.[26] Although this effect is commonly used to rationalise behaviour of complexes with geminal dialkyl carbon centres, it also applies to the introduction of single substituents to rings, as is illustrated by the data in Table 5.3.

Table 5.3 – Effect of substitution on ring strain

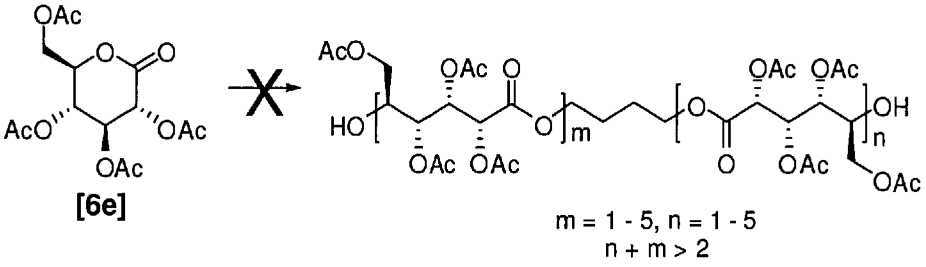
No. of substituents	Cyclic ester[35]	$-\Delta H_p$ (kJmol^{-1})
0	glycolide	23
2	lactide	21
4	tetramethyl glycolide	14

The Thorpe-Ingold effect has been used to explain the formation of cyclic products and thus failure to polymerise certain carbosiloxadienes.[30] 1,5-lactones derived from D-(+)-galactopyranose (**[6a]**), D-(+)-mannopyranose (**[6b]**) and D-(+)-glucopyranose (**[6e]**) are highly functionalised. Therefore, the Thorpe-Ingold effect is expected to be very pronounced in these compounds. This was one of the primary reasons for investigating the pentose-derived carbohydrates, 2,3,4-tri-*O*-acetyl-D-xylono-1,5-lactone **[6c]** and 2,3,4-tri-*O*-acetyl-L-arabinono-1,5-lactone **[6d]**. However, preliminary experiments did not show any improvement in polymerisability of these lactones. Another effect of increased substitution is the steric hindrance of the active site, which may adversely affect the polymerisation rate.[27] This will be more pronounced in the hexose-derived carbohydrates due to the large and flexible C-6 substituent.

5.4.2 Ceiling Temperatures

The ceiling temperature, T_c is that at which polymerisation and depolymerisation occur at the same rate, i.e. $Tc = \frac{\Delta H_P}{\Delta S_P + R\,ln\,[M]_{eq}}$;[26,29] where $[M]_{eq}$ = equilibrium monomer concentration; ΔS_P = entropy change for polymerisation at [M] = 1 moldm^{-3}

Although oligomers may be formed at the ceiling temperature, polymerisation to high molecular weight species is not possible above this temperature.[31] A higher weight polymer formed below its ceiling temperature will degrade so as to restore its equilibrium conditions, as the temperature rises above its T_c. An example of a polymer with a low ceiling temperature is poly-α-(methylstyrene).[32] Monomers with low ring strain are often synonymous with producing polymers with low ceiling temperatures.[27] Having determined that Sn(II)Oct$_2$ is required for the ring-opening reaction and that it requires elevated temperatures before it becomes active, it was not possible to carry out the reaction below the ceiling temperature of these oligomers. However, experiments were carried out based on the same conditions used to selectively prepare the 4-hydroxybutyl terminated esters using *p*-TSA in CH_2Cl_2 at r.t as shown in Scheme 5.5. This experiment involved the use of 10 monomer units and a single 1,4-butanediol unit. However, when monitored by ^{1}H NMR and GPC, chains bearing more than 2 monomer units were not observed.

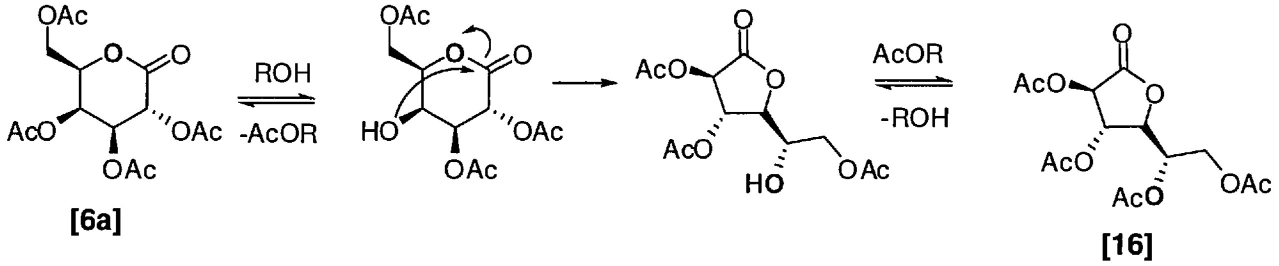


2 eq. p-TSA, 1 eq. 1,4-butanediol, 10 eq. **[6e]**, CH_2Cl_2, *r.t.*

Scheme 5.5 - Polymerisation attempt using *p*-TSA at r.t.

5.5 Characterisation of by-products

As previously discussed, 1,4-lactones, **[16]**, **[17]** and **[18]** were formed as by-products during the polymerisation attempts. Synthesis and characterisation of these species has limited or no literature precedence. Thus attention was given to their synthesis and characterisation. A possible (simplified) mechanism for the 1,4-lactone formation is shown in Scheme 5.6, using 2,3,4,6-tetra-*O*-acetyl-D-galactono-1,5-lactone **[6a]** as an example. The transformation is only possible if the acetyl groups are labile, however, in the presence of water, acid or an alcohol this is feasible. Thus, a reversible reaction allows nucleophilic attack at C-1 by a hydroxyl group at C-4 and formation of a 5-membered ring. The hydroxyl group formed during ring opening can be acetylated to form the product.



ROH = alcohol or water

Scheme 5.6 - Possible mechanism for the conversion of an acetyl functionalised 1,5-lactone to the corresponding 1,4-lactones using 2,3,4,6-tetra-*O*-acetyl-D-galactono-1,5-lactone [6a] as an example

All the acetyl groups are labile, however, the selectivity for the 5-membered ring (and overall irreversibility of the reaction), is the high thermodynamic stability of the 1,4-lactone. Therefore, the 1,4-lactone is selectively formed due to its envelope-like configuration resulting in low ring-strain and making it the most stable compound.

The 1,4-lactones were analysed by mass spectrometry, IR and NMR spectroscopy. Mass spectrometry showed that the mass of the products was identical to that of the starting material, 364 amu. IR confirmed the decrease in ring strain as all the 1,4-lactones have absorbances at *ca.* 1810 cm^{-1} as shown in Figure 5.14.

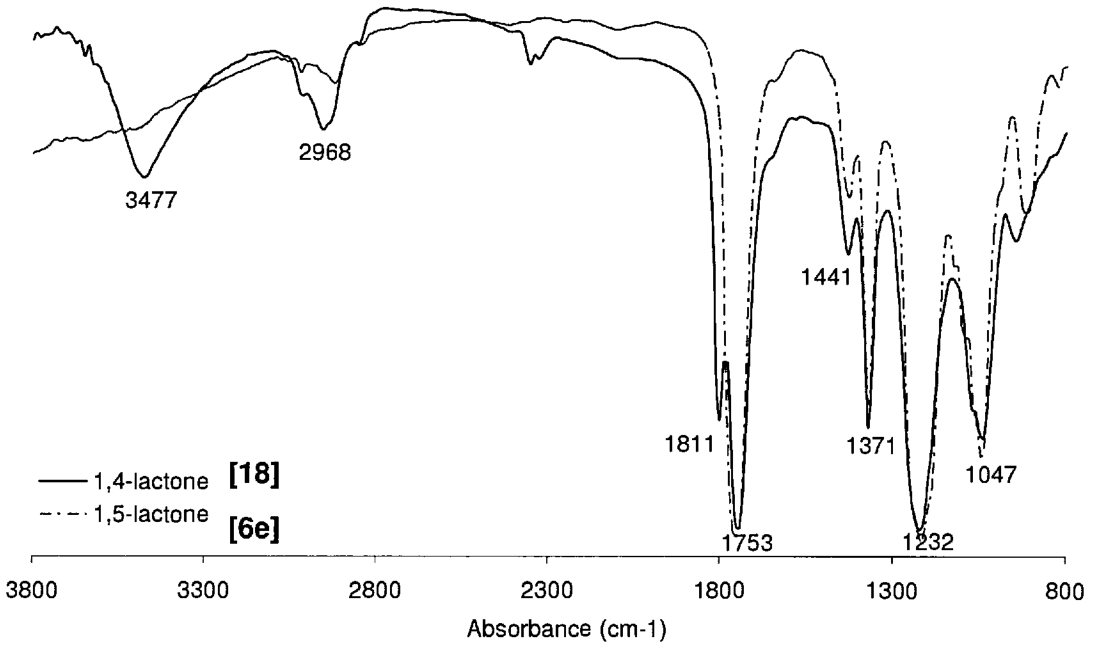


Figure 5.14 - IR spectra of the acetyl functionalised 1,4- and 1,5-lactones derived from D-(+)-glucopyranose [18] and [6e]

Table 5.4 and Table 5.5 show the ^{1}H and ^{13}C{^{1}H} NMR data for the functionalised 1,4-lactones and their parent 1,5-lactones. From NMR analysis, it is clear that each parent 1,5-lactone forms a different 1,4-lactone. This confirms that acetyl migration rather than C-C bond cleavage is responsible for the decomposition reaction. It also confirms that the 1,4-lactones are formed from the residual starting material present in the reactions and not by decomposition of the oligoester products (as these oligoesters would be expected to form mixtures of various stereoisomers of the 1,4-lactones). When compared to the 1,5-lactones, the most pronounced change in the ^{1}H NMR was at H-4 and H-5 in the 1,4-lactones. Whereas in the 1,5-lactone C-5 forms part of the ring, in the 1,4-lactone it becomes a substituent. The remaining chemical shifts were similar to the analogous parent 1,5-lactones. In general, H-2 resonates between 5.3 and 5.7 ppm in the 1,4-lactones. With the exception of the D-mannose derivative, it is also the most deshielded proton due to its proximity to the ester functional group within the ring. The ^{13}C{^{1}H} NMR also confirmed the decrease in ring strain in the 1,4-lactone: C-1 resonates at a higher frequency in the 1,4-lactone, between 168 and 170 ppm. A similar effect is observed with all the carbon centres still contained within the ring; C-2, C-3 and C-4 resonate from 4 to 11 ppm downfield in the 1,4-lactone. This is true for all sets of compounds with the exception of the D-(+)-mannopyranose derivative.

Table 5.4 – ^{1}H NMR Data for Carbohydrate-Derived 1,5-Lactones and 1,4-Lactones

Product	δ H-2 ($^3J_{2,3}$)	δ H-3 ($^3J_{2,3}$, $^3J_{3,4}$)	δ H-4 ($^3J_{3,4}$, $^3J_{4,5}$)	δ H-5 ($^3J_{4,5}$, $^3J_{5,6}$, $J_{5,6'}$)	δ H-6 ($J_{6,6'}$, $J_{5,6}$)	δ H-6' ($J_{6,6'}$, $J_{5,6'}$)
2,3,4,6-tetra-*O*-acetyl-D-galactono-1,5-lactone **[6a]**	5.28 (10.3)	5.47 (10.3, 2.9)	5.70 (2.8, 1.5)	4.82 (*)	4.25 (*)	
2,3,4,6-tetra-*O*-acetyl-D-galactono-1,4-lactone **[16]**	5.60 (7.2)	5.42 (7.0, 7.0)	4.58 (6.9, 2.9)	5.33 (*)	4.33 (11.7, 5.4)	4.24 (11.7, 6.5)
2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone **[6b]**	5.75 (3.9)	5.49 (*)	5.05 (*)	4.62 (8.6, *, 5.8)	4.37 (12.4, 3.1)	4.27 (12.5, 5.8)
2,3,4,6-tetra-*O*-acetyl-D-mannono-1,4-lactone **[17]**	5.70 (4.9)	5.75 (4.9, 3.0)	4.75 (3.0, 9.5)	5.35 (9.5, 4.0, 2.3)	4.63 (12.6, 2.3)	4.16 (12.6, 4.1)
2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone **[6e]**	5.10 (9.1)	5.44 (9.1, 9.1)	5.25 (9.0, 9.0)	4.56 - 4.44 (8.8, 3.0, 3.0)	4.28 (12.7, 3.7)	4.14 (12.7, 2.3)
2,3,4,6-tetra-*O*-acetyl-D-glucono-1,4-lactone **[18]**	5.25 (3.3)	5.65 (3.4, 5.6)	4.98 (5.8, 8.0)	5.40 - 5.35 (8.1, 3.3, 4.7)	4.60 (12.4, 3.1)	4.18 (12.4, 4.9)

δ = chemical shift (reported in ppm). J = coupling constant (reported in Hz).
**Unreported coupling constants could not be resolve*

Table 5.5 – $^{13}C\{^1H\}$ NMR data for Carbohydrate-Derived 1,5-Lactones and 1,4-Lactones

Product	δ C-1	δ C-2	δ C-3	δ C-4	δ C-5	δ C-6
2,3,4,6-tetra-*O*-acetyl-D-galactono-1,5-lactone **[6a]**	164.46	68.44	69.16	66.22	74.71	60.98
2,3,4,6-tetra-*O*-acetyl-D-galactono-1,4-lactone **[16]**	167.98	71.94	77.23	77.40	68.25	61.62
2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone **[6b]**	168.41	66.53	70.38	69.10	75.37	62.26
2,3,4,6-tetra-*O*-acetyl-D-mannono-1,4-lactone **[17]**	170.32	67.95	68.28	74.69	66.70	61.92
2,3,4,6-tetra-*O*-acetyl-D-glucono-1,4-lactone **[18]**	170.40	72.01	70.98	76.64	67.53	62.13

δ = chemical shift (reported in ppm).

Estimates of the dihedral angles, assuming a Karplus-type dependence, are consistent with that the assumption that the 1,5-lactones adopt the half-chair confirmation in solution.[33-35] Table 5.6 and Table 5.7 show the estimated dihedral angles and the proposed structures for these compounds.

Table 5.6 – Estimated dihedral angles Carbohydrate-Derived 1,5-Lactones and 1,4-Lactones in °

Product	$\phi_{2,3}$	$\phi_{3,4}$	$\phi_{4,5}$	$\phi_{5,6}$	$\phi_{5,6'}$
2,3,4,6-tetra-*O*-acetyl-D-galactono-1,5-lactone **[6a]**	~180	51	62		
2,3,4,6-tetra-*O*-acetyl-D-galactono-1,4-lactone **[16]**	152	151	51	140	147
2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone **[6b]**	45		165	50	143
2,3,4,6-tetra-*O*-acetyl-D-mannono-1,4-lactone **[17]**	38	51	~180	131	132
2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone **[6e]**	173	173	171	125	125
2,3,4,6-tetra-*O*-acetyl-D-glucono-1,4-lactone **[18]**	49	33	159	49	39

ϕ solved for the Karplus equation where A = 4.22, B = -0.5, C = 4.5[34,36]

R =

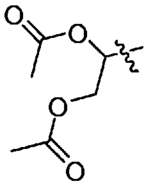
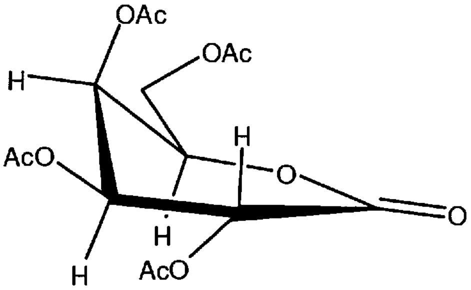
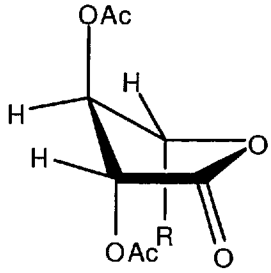
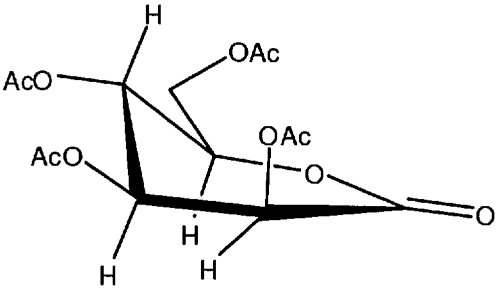
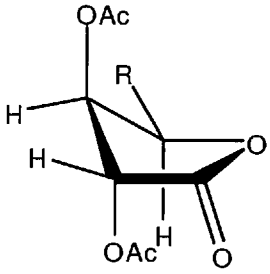
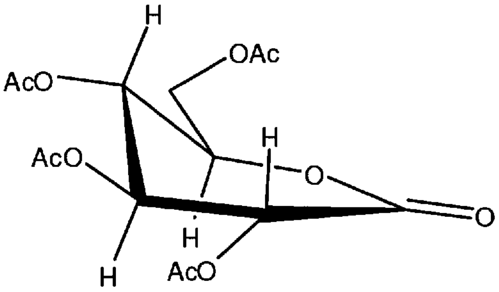
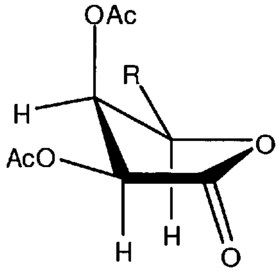


Table 5.7 – Most stable conformation of 1,5- and 1,4-lactones based on estimated dihedral angles

2,3,4,6-tetra-*O*-acetyl-D-galactono-1,5-lactone **[6a]**  	2,3,4,6-tetra-*O*-acetyl-D-galactono-1,4-lactone **[16]** 
2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone **[6b]**  	2,3,4,6-tetra-*O*-acetyl-D-mannono-1,4-lactone **[17]** 
2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone **[6e]**  	2,3,4,6-tetra-*O*-acetyl-D-glucono-1,4-lactone **[18]** 

2,3,4,6-Tetra-*O*-acetyl-D-galactono-1,5-lactone **[6a]** possesses a large $^3J_{2,3}$ coupling constant (10 Hz), suggesting that the associated dihedral angle ($\phi_{2,3}$) is *anti*-periplanar. The $\phi_{3,4}$ and $\phi_{4,5}$ angles are between 50 and 60°, indicating gauche interactions between these substituents. Therefore, the substituents **[6a]** must be equatorial except at C-4. In 2,3,4,6-tetra-*O*-acetyl-D-mannono-1,5-lactone **[6b]**, the $^2H_3$ interaction is gauche, whereas the $^3H_4$ and $^4H_5$ interactions are *anti*-periplanar. All the substituents in this molecule are equatorial except that at C-2. 2,3,4,6-Tetra-*O*-acetyl-D-glucono-1,5-lactone **[6e]** also adopts the half-chair conformation but with all its substituents equatorial minimising steric hindrance, in agreement with the findings reported by Nelson.[35] Therefore in **[6e]** the $^2H_3$, $^3H_4$, and $^4H_5$ interactions are all *anti*-periplanar.

Whereas interactions varied significantly amongst the 1,5-lactones, 1,4-lactones formed rings which were far more rigid with similar dihedral interactions throughout. The dihedral angles calculated, using the Karplus equation, confirmed that all the 1,4-lactones adopt an envelope conformation and that the dihedral interactions were generally gauche. In the galactose derivative **[16]**, all the substituents are axial. Therefore, $^2H_3$ and $^3H_4$ have similar interactions with dihedral angles of about 150°. Although there is free bond rotation about the C-4/C-5 bond, the magnitude of the $^4H_5$ interaction gives an indication of the most stable configuration of the pendant arm. A dihedral angle of 125° suggests that the axial pendant group is positioned away from the ring. This avoids the formation of a sandwich-type structure and minimises steric hindrance. In 2,3,4,6-tetra-*O*-acetyl-D-mannono-1,4-lactone **[17]**, $^2H_3$ and $^3H_4$ show gauche interactions and small dihedral angles ranging from 49° in the former, to 33° in the latter. Consequently the substituents at C-2 and at C-3 are equatorial. H-4 is *anti*-periplanar to H-5 as shown by the large coupling constant ($^3J_{4,5}$) of 9.5 Hz. This suggests that the most stable conformation of the pendant arm is one where it forms a *quasi* planar structure as shown in Figure 5.15.

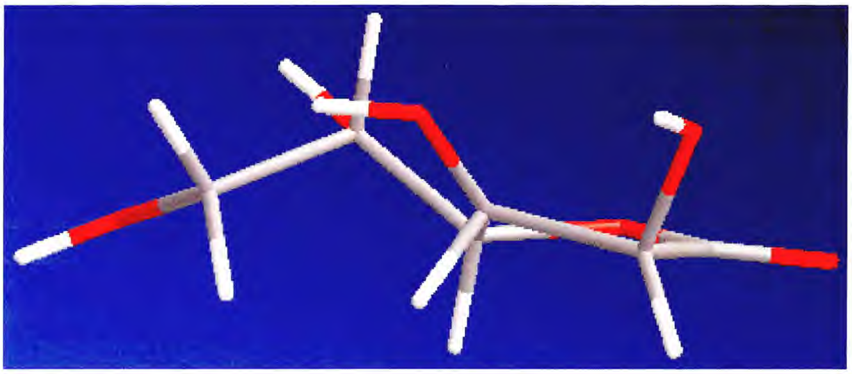


Figure 5.15 - Conformation of 2,3,4,6-tetra-*O*-acetyl-D-mannono-1,4-lactone [17]
shown with acetyl groups replaced by hydroxyl groups for simplicity

A unique aspect to the transformation from the 1,5-lactone to the 1,4-lactone for the D-(+)-mannopyranose derivative is that C-3 becomes more electron rich in the 1,4-lactone. This is manifested by an upfield shift in the C-3 resonance from 70.38 ppm in the 1,5-lactone to 68.28 ppm in the 1,4-lactone. The acetyl groups move from having gauche interactions in the 1,5-lactone to having *syn*-planar interactions in the 1,4-lactone.This results in greater electron delocalisation and increased electron density at C-3. The most stable conformation of 2,3,4,6-tetra-*O*-acetyl-D-glucono-1,4-lactone **[18]** is similar to that of the D-(+)-mannopyranose derivative, except the acetyl group at C-2 is axial in the D-(+)-glucopyranose derivative.

5.6 Conclusion

After the successful synthesis of acetyl-protected 1,5-lactones **[6]**, they were tested as substrates in ROP using metal co-initiators such as Sn(II)Oct$_2$ and the zinc-based complex **[35]** and aluminium *iso*-propoxide. It was found that neither the zinc nor the aluminium systems were active towards the ROP of the 1,5-lactones **[6]**. This is probably due to competition for co-ordination with the acetyl groups. However, when the 1,5-lactones **[6]** were treated with an Sn(II)Oct$_2$ and an alcohol some activity was observed although it required significant optimisation.

The most critical learning from these experiments was the discovery that the 1,5-lactones **[6]** were very heat sensitive. This proved challenging as Sn(II)Oct$_2$ requires high temperatures (> 80 °C) for optimal activity. At temperatures above 100 °C decomposition to the unsaturated 1,5-lactone was observed. When temperatures were lowered to 80 °C, some success was observed towards ring-opening reactions. However, over long reaction times (> 24 h) decomposition to the 1,4-lactones was observed. The reaction conditions were optimised by conducting the experiment at 80 °C for 3 h using 2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone **[6e]** and 1,4-butanediol to yield an oligomer of up to 3 repeat units and a M_n (SEC) of 1,472 gmol^{-1} which was confirmed by MALDI-TOF (1151 amu). It was also discovered that residual octanoic acid in Sn(II)Oct$_2$ was critical to the successful synthesis of the oligomer. This oligomer was characterised by ^{1}H NMR and from this it was deduced that the 1,4-butanediol unit was centred within the chain with carbohydrate-derived units on either end. It was deduced that the chain length was limited to 3 units due to the polymer's low ceiling temperature brought about by low ring strain and thus an unfavourable enthalpy of polymerisation. This is in part attributed to the high degree of substitution on the lactone rings.

Attention was drawn to the by-products of the attempted prolonged polymerisation products; in particular to the 1,4-lactones. These are interesting compounds in themselves which may serve other applications in organic synthesis. Furthermore, they had previously been poorly characterised. We report the complete characterisation of these compounds and suggest a reaction mechanism to their formation. Compared to the starting 1,5-lactones, the 1,4-lactones showed an absorbance of 1811 cm^{-1} in the infra-red region attributed to the carbonyl stretch at C-1 compared to 1753 cm^{-1} in the 1,5-lactone. This was not present in the 1,5-lactones and is indicative of a relief in strain associated with 1,4-lactones. By comparing ^1H NMR coupling constants and application of the Karplus equation it was confirmed that all the 1,4-lactones adopt an envelope-like conformation which is intrinsic to 5-membered rings with and sp^2 carbon.

5.7 References

1. Dechy-Cabaret, O.; Martin-Vaca, B.; Bourissou, D., *Chem. Rev.* **2004,** 104, (12), 6147-6176.

2. Kricheldorf, H. R.; Berl, M.; Scharnagl, N., *Macromolecules* **1988,** 21, (2), 286-293.

3. Ryner, M.; Stridsberg, K.; Albertsson, A. C.; von Schenck, H.; Svensson, M., *Macromolecules* **2001,** 34, (12), 3877-3881.

4. Kowalski, A.; Duda, A.; Penczek, S., *Macromolecules* **2000,** 33, 7359-7370; Kowalski, A.; Libiszowski, J.; Biela, T.; Cypryk, M.; Duda, A.; Penczek, S., *Macromolecules* **2005,** 38, (20), 8170-8176; Arvanitoyannis, I.; Nakayama, A.; Psomiadou, E.; Kawasaki, N.; Yamamoto, N., *Polymer* **1996,** 37, (4), 651- 660; Leenslag, J. W.; Pennings, A. J., *Makromol. Chem.* **1987,** 188, 1809-1814; Trimaille, h.; Moller, i.; Gurny, o., *J. Polym. Science, Part A* **2004,** 42, (17), 4379-4391; Zhang, X.; MacDonald, D. A.; Goosen, M. F. A.; McAuley, K. B., *J. Polym. Sci., Part A: Polymer. Chem.* **1994,** 32, 2965-2970.

5. Kowalski, A.; Duda, A.; Penczek, S., *Macromolecules* **2000,** 33, (3), 689-695; Choi, I. S.; Langer, R., *Macromolecules* **2001,** 34, (16), 5361-5363; Dechy-Cabaret, O.; Martin-Vaca, B.; Bourissou, D., *Chemical Reviews* **2004,** 104, (12), 6147-6176; Mecerreyes; Humes; Miller, D.; Hedrick, L.; Detrembleur; Lecomte; Jerome; Roman, S., *Macromol. Rapid. Commun.* **2000,** 21, (11), 779-784; Pack, J. W.; Kim, S. H.; Park, S. Y.; Lee, Y. W.; Kim, Y. H., *Macromolecules* **2003,** 36, (20), 7884-7886; Stjerndahl, A.; Wistrand, A. F.; Albertsson, A. C., *Biomacromolecules* **2007,** 8, (3), 937-940; Storey, o. F.; Sherman, o. W., *Macromolecules* **2002,** 35, 1504-1512.

6. Cai, Q.; Zhao, Y.; Bei, J.; Xi, F.; Wang, S., *Biomacromolecules* **2003,** 4, (3), 828-834.

7. Kowalski, A.; Duda, A.; Penczek, S., *Macromol. Rapid Commun.* **1998,** 19, (11), 567-572.

8. Kowalski, A.; Libiszowski, J.; Duda, A.; Penczek, S., *Macromolecules* **2000,** 33, (6), 1964-1971.

9. Libiszowski, J.; Kowalski, A.; Duda, A.; Penczek, S., *Macromol. Chem. Phys.* **2002,** 203, (10/11), 1694-1701.

10. Rieger, J.; Coulembier, O.; Dubois, P.; Bernaerts, K. V.; DuPrez, F. E.; Jerome, R.; Jerome, C., *Macromolecules* **2005,** 38, (26), 10650-10657.

11. Zhang, X.; Wyss, U. P.; Pichora, D.; Goosen, M. F. A., *Polym. Bull. (Berlin)* **1992,** 27, (6), 623-629.

12. Zhang, X.; MacDonald, D. A.; Goosen, M. F. A.; McAuley, K. B. J., *J. Polym Sci Part A: Polym Chem* **2000,** 35, (2).

13. Pappalardo, a.; Annunziata, i.; Pellecchia, I.; Biesemans, o.; Willem, u., *Macromolecules* **2007,** 40, (6), 1886-1890; Kowalski, d.; Libiszowski, a.; Biela, a.; Cypryk, a.; Duda, n.; Penczek, t., *Macromolecules* **2005,** 38, (20), 8170-8176.

14. http://www.cargill.com/about/citizenship/developingproducts.htm ; Gruber, P.; O'Brien, M., *Biopolymers.* WILEY-VCH: 2004.

15. Platel, R. H.; Hodgson, L. M.; Williams, C. K., *Polymer Reviews* **2008,** 48, 11-63.

16. Nijenhuis, A. J.; Grijpma, D. W.; Pennings, A. J., *Macromolecules* **1992,** 25, 6414-6424.

17. Schwach, G.; Coudane, J.; Engel, R.; Vert, M., *J. Polym. Chem., Part A: Polym. Chem.* **1997,** 35, (16), 3431-3440.

18. Mecerreyes, D.; Humes, J.; Miller, R. D.; Hedrick, J. L.; Detrembleur, C.; Lecomte, P.; Jérôme, R.; Roman, J. S., *Macromol. Rapid. Commun.* **2000,** 21, (11), 779-784.

19. Storey, R. F.; Sherman, J. W., *Macromolecules* **2002,** 35, 1504-1512.

20. Kowalski, A.; Duda, A.; Penczek, S., *Macromolecules* **2000,** 33, (20), 7359-7370.

21. Plantier-Royon, R.; Cardona, F.; Anker, D.; Condemine, G.; Nasser, W.; Robert-Baudouy, J., *J. Carb. Chem.* **1991,** 10, (5), 787 - 811.

22. Pedersen, C., *Carb. Res.* **1999,** 315, 192-197; Mackie, D. M.; Perlin, A. S., *Carb. Res.* **1972,** 24, (1), 67-85.

23. Duda, A.; Florjanczyk, Z.; Hofman, A.; Slomkowski, S.; Penczek, S., *Macromolecules* **1990,** 23, (6), 1640-1646.

24. Kricheldorf, H. R.; Boettcher, C.; Tonnes, K. U., *Polymer* **1992,** 33, (13), 2817-2824; Duda, A.; Penczek, S.; Kowalski, A.; Libiszowski, J., *Macromol. Symp.* **2000,** 153, 41-53; Penczek, S.; Duda, A.; Kowalski, A.; Libiszowski, J.; Majerska, K.; Biela, T., *Macromol. Symp.* **2000,** 157, 61-70; Ovitt, T. M.; Coates, G. W., *J. Am. Chem. Soc* **2002,** 124, (7), 1316-1326; Gregson, C. K. A.; Blackmore, I. J.; Gibson, V. C.; Long, N. J.; Marshall, E. L.; White, A. J. P., *Dalt. Trans.* **2006,** 25, 3134-3140.

25. Williams, C. K.; Breyfogle, L. E.; Choi, S. K.; Nam, W.; Young, V. G.; Hillmyer, M. A.; Tolman, W. B., *J. Am. Chem. Soc.* **2003,** 125, 11350-11359.

26. Goethals, E. J., *Telechelic Polymers: Synthesis and Applications.* 1989; p 116.

27. Cowie, J. M. G., *Polymers.* CRC Press: 1991.

28. Saiyasombat, W.; Molloy, R.; Nicholson, T. M.; Johnson, A. F.; Ward, I. M., *Polymer* **1998,** 39, (23), 5581-5585.

29. Dainton, F. S.; Ivin, K. J., *Q. Rev. Chem. Soc.* **1958,** 12, 61-92.

30. Rogers, M. E.; Long, T. E., *Synthetic Methods in Step-Growth Polymers.* 2003; p 605.

31. Elias, H.-G., *An Introduction to Plastics.* Wiley-VCH: 2003; p 34.

32. Alger, M., *Polymer Science Dictionary.* Springer: 1996; p 640.

33. Pocker, Y.; Green, E., *J. Am. Chem. Soc* **1973,** 95, (1), 113-119.

34. Nelson, C. R., *Carb. Res.* **1979,** 68, (1), 55-60.

35. Nelson, C. R., *Carb. Res.* **1982,** 106, (1), 155-159.

36. Karplus, M., *J. Am. Chem. Soc* **1963,** 85, (18), 2870-2871; Coxon, B., *Carb. Res.* **1968,** 8, (2), 125-134.

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CHAPTER 6:

CONCLUSIONS AND OUTLOOK

Acetyl-protected 1,5-lactones derived from carbohydrates were prepared *via* a 4-step procedure in excellent overall yields of up to 72 %. The oxidation of acetyl-protected lactols was comprehensively investigated and reaction conditions were optimised to achieve a route that would suit a large-scale, environmentally friendly procedure. Thus the Swern oxidation was found to accommodate these factors *versus* oxidation using CrO_3. The latter resulted in poor yields likely due to de-acetylated by-products in addition to its high toxicity.

These lactones were subsequently converted to aldaric esters by reaction with *para*-toluenesulphonic acid (*p*-TSA) and an alcohol. By using butan-1-ol and 1,4-butanediol the successful synthesis of mono-functional and bi-functional aldaric esters was achieved. However, owing to the sensitivity of these compounds, it was necessary to control the reaction time to prevent decomposition. These novel esters were completely characterised by NMR where similar chemical resonances were observed between all compounds. However, due to hydrogen-bonding between the acetyl group at C-3 and the terminal hydroxyl at C-5, restricted free rotation about the C-5–O bond gave rise to distinguishable resonances for H-5 and H-5'.

The overall procedure to 1,5-lactones as well as the aldaric esters has proven to be versatile when protected with an acetyl group. The only other protection investigated in the synthesis of carbohydrate-derive polyesters is methylation.[1] There are however, numerous simple protecting groups which could be investigated and give rise to alternative polymers. Research in this area has already started in our group using benzyl protection although this presents synthetic limitations.[2] Thus an attractive alternative would be benzoylation.

Polycondensation experiments were carried out using the bi-functional aldaric esters with commercially available acid chlorides; oxalyl chloride, adipoyl chloride and terephthaloyl chloride. This afforded high molecular weight polyesters with M_n between 41,000 and 56,000 gmol^{-1} (100 repeat units) and polydispersity indices (PDIs) between 1.5 and 2.8. These polymers were also characterised by ^{1}H and ^{13}C{^{1}H} NMR. However isolation of the high-molecular weight polymer from its oligomers merits further attention. The yields could also be optimised by ensuring strictly dry reagents and reaction conditions to avoid premature quenching of the reaction. Further investigation would be carried out to determine whether any competing cyclisation was apparent as well as any limitations to chain length. Once the polymer synthesis is well established and reproducible, its physical properties would be investigated. That is, properties such as its tensile strength, hydrophilicity as well as glass-transition and melting temperatures using differential scanning calorimetry (DSC). This would also provide some information on its degree of crystallinity. This is important to determine its potential as a commodity plastic. In addition to this, it would also be tested for its degradation properties; both biotic and abiotic. Its biocompatibility would also be addressed such as its interaction with proteins. This would determine its suitability for biomedical applications such as matrices for tissue engineering or for surgical fixation.

Functionalised 1,5-lactones were also explored as monomers for ROP. Zn and Al initiators were found to be inactive towards these compounds. This is likely due to competition with the acetyl protecting groups. However, using Sn(II)Oct$_2$ and 1,4-butanediol, a trimer derived from 2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone was successfully prepared. It was observed that the presence of residual octanoic acid in Sn(II)Oct$_2$ was critical to the success of this reaction. However, further attempts to optimise this reaction failed to result in longer chain lengths. Instead prolonged reaction times and elevated temperatures resulted in decomposition. This limitation to the chain length is likely to be attributed to the degree of substitution of these 1,5-lactones which reduces ring-strain. Thus the free-energy associated with their ROP is not favourable. In most instances decomposition to two sets of thermodynamic products was observed: functionalised 1,4-lactones were observed at temperatures below 100 °C and *α,β*-unsaturated 1,5-lactones were attained at higher temperatures.

Copolymerisation with lactide was investigated to introduce functionality to poly(lactide) thus addressing its limitations with regards to hydrolytic degradation and use in biomaterials. Therefore, the carbohydrate-derived oligomer as well as the aldaric esters were used as co-initiators in the ROP of lactide with the alkyl zinc co-initiator, **[35]**.[3] Kinetic experiments revealed a linear relationship between $\mathrm{Ln}\{([LA]_0 - [LA]_{eq})/([LA]_t - [LA]_{eq})\}$ and time, indicating that the polymerisation was controlled. This was supported by mono-modal molecular weight distributions and narrow PDIs. Bi-functional initiators, however, were associated with a rate constant which was twice that observed with the mono-functional aldaric esters. This is attributed to the concentration of hydroxyl groups in the bi-functional aldaric esters being twice that in the mono-functional ones. This allows chain transfer to occur which takes place at a much faster rate than propagation. From this it can be deduced that the bi-functional aldaric ester forms part of the polymer chain and is not merely an end-group.

Preliminary experiments showed that the introduction of a carbohydrate moiety enhances the degradation rate of poly(lactide) *via* a random chain scission pathway. Based on these promising results, degradation conditions which mimic either soil or biological environments would be investigated to determine whether the same trend is observed. As with the polycondensation products, physical and biological properties would be investigated to assess their potential applications.

The major limitation in the ROP of highly functionalised 1,5-lactones is the degree of substitution. To date, research has been carried out in our group to this effect with promising results. A polyester of up to 60 repeat units was prepared from a saturated, di-substituted 1,5-lactone derived from the hydrogenation of the unsaturated 1,5-lactone, **[8]**.[2] This confirms that our proposal that chain length was limited by the degree of substitution.

References

1. Urakami, H.; Guan, Z., *Biomacromolecules* **2008,** 9, (2), 592-597; Metzke, M.; Guan, Z., *Biomacromolecules* **2008,** 9, (1), 208-215; Metzke, M.; Bai, J. Z.; Guan, Z., *J. Am. Chem. Soc.* **2003,** 125, (26), 7760-7761; Zamora, F.; Hakkou, K.; Muñoz-Guerra, S.; Galbis, J. A., *Polymer Degradation and Stability* **2006,** 91, (11), 2654-2659; Zamora, F.; Hakkou, K.; Alla, A.; Rivas, M.; Roffé, I.; Mancera, M.; Muñoz-Guerra, S.; Galbis, J. A., *J. Polym Sci Part A: Polym Chem.* **2005,** 43, (19), 4570-4577; Zamora, F.; Hakkou, K.; Alla, A.; Espartero, J. L.; Muñoz-Guerra, S.; Galbis, J. A., *J. Polym Sci Part A: Polym Chem.* **2005,** 43, (24), 6394-6410.

2. Tang, M.; Williams, C. K., Functionalised Biodegradable Polyesters. In Imperial College: London, 2008.

3. Williams, C. K.; Breyfogle, L. E.; Choi, S. K.; Nam, W.; Young, V. G.; Hillmyer, M. A.; Tolman, W. B., *J. Am. Chem. Soc.* **2003,** 125, 11350-11359.

CHAPTER 7:

EXPERIMENTAL PROCEDURES

7.1. General methods and procedures

The table below indicates how chemical and solvents were treated prior to their use as well as their supplier. Where no mention of supplier, purification or drying is made, it can be assumed that solvents were purchased from VWR, chemicals from Aldrich and that these were used as received. However, only solvents referred to as "dry" can be assumed to have been treated in the manner indicated below.

Table 7.1 - Chemical supplier and purification/drying

Chemical	**Supplier**	**Purification/ Drying**
1,4-BD	Aldrich	Distilled from CaH_2
Absolute MeOH	Aldrich	Used as received
Adi[pyl Chloride	Aldrich	Distillation under vacuum
CCl_4	VWR	Dried over Molecular sieves and degassed
CH_2Cl_2	VWR	Distilled from CaH_2 and degassed
NEt_3	VWR	Distilled from CaH_2, degassed and stored over molecular sieves
Oxalyl Chloride	Aldrich	Distillation under vacuum
Pyridine	VWR	Distilled from CaH_2, degassed and stored over molecular sieves
$Sc(OTf)_3$	Strem	used as received (packed under argon) and handled anaerobically
$Sn(II)Oct_2$	Aldrich	Distilled twice under reduced pressure (unless otherwise specified)
THF	VWR	Distilled from Na-Benzophenone and degassed
Toluene	VWR	Distilled from Na-Benzophenone and

Chemical	Supplier	Purification/ Drying
		degassed

7.2. Measurements

^{1}H NMR spectroscopy was performed on a 400 MHz Bruker AV400 instrument at Imperial College, London. All other NMR experiments were either carried out on a 500 MHz Bruker AV500 instrument by the Imperial College NMR service or on a 400 MHz Bruker AV400. $CDCl_3$ was used as the NMR solvent and reference compound. GPC measurements were performed on a *PolyLabs PCL-50* instrument using THF as the eluting solvent at Imperial College, London. Ammonia gas chemical ionisation mass spectrometry was carried by the mass spectrometry service at Imperial College, London. The SEC measurements were performed on a Polymer labs GPC 60 instrument with two Polymer labs mixed B columns and THF at a flow rate of 1mlmin^{-1} as the eluent. Narrow molecular weight polystyrene standards were used to calibrate the instrument. The MALDI- TOF mass spectrometry was performed by the Imperial College Mass Spectrometry Service with a Micromass MALDI micro MX mass spectrometer equipped with a UV (337nm) laser. All mass spectra recorded in linear mode. An average of 40 spectra from random positions on the target, each spectrum averaged from 10 laser shots. 1.2 μL of a mixture of the matrix (dithranol, 30 mg/ml in THF), cationizing agent ($NaCO_2CF_3$, 10 mg/ml in THF), and the sample (~10mg/ml in CH_2Cl_2) in the ratio 3:1:1 respectively was applied to the target and air-dried immediately before use. All TLC was carried out using aluminium plates coated with silica and eluted with a 1:1 mixture of EtOAc:Hexane unless otherwise stated.

7.3. Monomer Synthesis

7.3.1. General acetylation procedure[1]

This acetylation procedure was adapted from the one reported by Joseph *et al.*[2] The starting sugar was charged to a flask and dried *in vacuo* for 1 h. To it, was added the acetylating mixture. The acetylating mixture comprised acetic anhydride and TFA (5:1 v/v). The ratio of the mass of the starting sugar to volume of acetylating mixture was 1:8 (w/v). The mixture was stirred at r.t. for between 3 and 20 h until complete dissolution of the sugar was observed. This was dependent on the starting sugar and is reported in the monomer synthesis results and discussion. The solvents were removed in *vacuo* to yield a syrup which was redissolved in $CHCl_3$ and extracted with water (1:1 v/v). The volume of $CHCl_3$ used was 5 times that of acetic anhydride. The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo* to yield syrups in all cases. The resulting compounds were mixtures of α and β anomers of peracetylated carbohydrates (for all except where glucono-1,5-lactone was used) and obtained in quantitative yield. The products were characterised by mass spectrometry and NMR (^1H, $^{13}C\{^1H\}$, ^{13}C, COSY, DEPT 90, DEPT 135, HMQC). In some cases the products comprised a single anomer. The resulting products were in the form of syrups unless otherwise stated. ^1H and $^{13}C\{^1H\}$ NMR spectroscopy was found to be in agreement with the literature where available.

1,2,3,4,6-Penta-*O*-acetyl-*α*-D-galactopyranose [3a][1]

Quantitative yield. TLC R_f 0.30 (EtOAc:Hexane 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (1 H, d, J = 2.33 Hz, H-1), 5.48-5.45 (1 H, m, H-3), 5.33-5.28 (2 H, m, H-2, H-4), 4.33 (1 H, m, H-6), 4.07 (2 H, m, H-5, H-6'), 2.13 (3 H, s, $COCH_3$), 2.05 (3 H, s, $COCH_3$), 2.02 (3 H, s, $COCH_3$), 1.99 (3 H, s, $COCH_3$), 1.97 (3 H, s, $COCH_3$) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 170.45 ($COCH_3$), 170.19, 170.1, 169.95, 169.45 ($COCH_3$), 89.68 (C-1), 69.25 (C-4), 67.83 (C-3), 67.35 (C-2), 62.56 (C-5), 61.05 (C-6), 20.84 - 20.49 ($COCH_3$) ppm. NMR is in agreement with the literature.[1]

1,2,3,4,6-Penta-*O*-acetyl-*α*-D-mannopyranose [3b][1]

Quantitative yield. TLC Rf 0.28 (EtOAc:Hexane; 1:1). NMR in agreement with the literature.[1]

1,2,3,4-Tetra-*O*-acetyl-*α*/*β*-D-xylopyranose [3c] (*α*/*β* ratio 1:1)[1]

Quantitative yield. TLC R_f 0.30 (EtOAc:Hexane; 1:1). *α*-anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.18 (1 H, d, J = 3.6 Hz, H-1), 5.14 (1 H, m, H-3), 4.99-4.93 (2 H, m, H-2, H-4), 4.08 (1 H, dd, J = 12.0, 4.9 Hz, H-5), 3.65 (1 H, m, H-5), 2.15-1.95 (m, 12 H, $COCH_3$) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 170 (m, $COCH_3$), 88.96 (C-1), 70.64 (C-3), 69.09, 68.39 (C-2, C-4), 60.37 (C-5), 20 (m, $COCH_3$) ppm. *β*-anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.66 (1 H, d, J = 6.8 Hz, H-1), 5.43-5.37 (1 H, m, H-3), 4.99-4.93 (2 H, m, H-2, H-4), 4.08 (1 H, dd, J = 12.0, 4.9 Hz, H-5), 3.48 (1 H, dd, J = 12.1, 8.3 Hz, H-5'), 2.15-1.95 (12 H, m, 12 H, $COCH_3$) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 170 (m, $COCH_3$), 91.74 (C-1), 69.18 (C-3), 69.06, 68.03 (C-2, C-4), 62.47 (C-5), 20 (m, $COCH_3$) ppm. NMR data is in agreement with the literature.[1] MS (CI, ammonia): m/z (%) 336 (100 %, $M+NH_4$).

1,2,3,4-Tetra-*O*-acetyl-*α*/*β*-L-arabinopyranose [3d] (*α*/*β* ratio 1:1)[1]

Quantitative yield. TLC R_f 0.60 (EtOAc:Hexane; 1:1). *β*-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (1 H, d, J = 6.9 Hz, H-1), 5.37 (1 H, m, H-3), 5.32-5.27 (1 H, m, H-2), 5.23 (1 H, m, H-4), 3.87 (1 H, dd, J = 13.2, 1.8 Hz, H-5), 3.79 (1 H, dd, J = 13.1, 1.9 Hz, H-5'), 2.13 (3 H, s, $COCH_3$), 2.11 (3 H, s, $COCH_3$), 2.08 (3 H, s, $COCH_3$), 2.06 (3 H, s, $COCH_3$) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 170.14 - 168.65 ($COCH_3$), 91.71 (C-1), 74.64 (C-4), 66.32 (C-3), 66.96 (C-2), 64.30 (C-5), 21.00 - 18.27 ($COCH_3$) ppm. *α*-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (1 H, d, J = 2.9 Hz, H-1), 5.37 (1 H, m, H-4), 5.09 (1 H, dd, J = 9.1, 3.5 Hz, H-3), 5.03 (1 H, d, J = 2.9 Hz, H-2), 4.07 - 3.99 (2H, m, H-5, H-5'), 2.16 (3 H, s, $COCH_3$), 2.14 (3 H, s, $COCH_3$), 2.12 (3 H, s, $COCH_3$), 2.04 (3 H, s, $COCH_3$) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 170.14 - 168.65 ($COCH_3$), 89.49 (C-1), 76.76 (C-2), 69.48 (C-3), 67.39 (C-4), 60.99 (C-5), 21.00 - 18.27 ($COCH_3$) ppm. NMR data is in agreement with the literature.[1] MS (CI, ammonia): m/z (%) 336 (95 %, $M+NH_4$).

7.3.2. General procedure for the synthesis of glycosyl bromides[3]

The procedure for the synthesis of glycoside bromides from their corresponding peracetylated pyranosides was adapted from the one reported by Mitchell *et al.*[3] The reactions were allowed to proceed for 24 h instead of 1 h at r.t. as reported in the literature. Reactions were monitored by TLC. The resulting glycoside bromides were characterised by mass spectrometry and NMR (^{1}H, ^{13}C{^{1}H}, ^{13}C, COSY, DEPT 90, DEPT 135, HMQC). In some cases the products comprised a single anomer. The resulting products were in the form of syrups unless otherwise stated.

2,3,4,6-Tetra-*O*-acetyl-*α*-D-galactopyranosyl bromide [4a]

76 % yield. TLC R_f 0.50 (EtOAc:Hexane; 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.68 (1 H, d, J = 3.9 Hz, H-1), 5.50 (1 H, m, H-4), 5.39 (1 H, m, H-3), 5.03 (1 H, dd, J = 10.5, 3.9 Hz, H-2), 4.47 (1 H, m, H-5), 4.17 (1 H, dd, J = 11.4, 6.3 Hz, H-6), 4.10 (1 H, dd, J = 11.4, 6.8 Hz, H-6'), 2.14, 2.10, 2.05, 2.00 (4 x 3 H, 4 x s, 4 x ($COCH_3$)). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 170-169 ($COCH_3$), 88.07 (C-1), 71.01 (C-5), 67.95 (C-3), 67.72 (C-2), 66.93 (C-4), 60.81 (C-6), 20.72, 20.62, 20.56, 20.54 ($COCH_3$) ppm. MS (CI, ammonia): m/z (%) 428 (100 %, M+ NH_4, Br-79), 430 (100 %, M + NH_4, Br-81).

2,3,4,6-Tetra-*O*-acetyl-*α*-D-mannopyranosyl bromide [4b]

95 % yield. TLC R_f 0.38 (EtOAc:Hexane 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (1 H, br s, H-1), 5.74 (1 H, dd, J = 10.1, 3.4 Hz, H-3), 5.47 (1 H, dd, J = 3.4, 1.6 Hz, H-2), 5.39 (1 H, apt, J = 10.2 Hz, H-4), 4.36 (1 H, dd, J = 12.4, 4.9 Hz, H-6), 4.25 (1 H, ddd, J = 10.2, 4.9, 2.0 Hz, H-5), 4.16 (1 H, dd, J = 12.5, 2.1 Hz, H-6'), 2.20, 2.13, 2.10 (3 H, s, ($COCH_3$)), 2.03 (3 H, s, ($COCH_3$)) ppm. NMR data in agreement with literature data.[4]

2,3,4-Tri-*O*-acetyl-*α*-D-xylopyranosyl bromide [4c]

85 % yield. TLC R_f 0.50 (EtOAc:Hexane 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (1 H, d, J = 4.0 Hz, H-1), 5.59 (1 H, t, J = 9.8 Hz, H-3), 5.06 (1 H, ddd, J = 10.8, 9.7, 6.0 Hz, H-2), 4.79 (1 H, dd, J = 9.9, 4.0 Hz, H-4), 4.08 (1 H, dd, J = 11.4, 6.0 Hz, H-5), 3.90 (1 H, t, J = 11.1 Hz, H-5'), 2.12 (3 H, s, ($COCH_3$)), 2.08 (6 H, apt s, 2 x ($COCH_3$)) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 130.18, 128.33, 121.20 ($COCH_3$), 87.59 (C-1), 70.88 (C-2), 69.56 (C-3), 68.10 (C-4), 62.54 (C-5), 20.65 ($COCH_3$) ppm.

2,3,4-Tri-*O*-acetyl-*α*-L-arabinopyranosyl bromide [4d]

95 % yield. TLC *R*$_f$ 0.80 (EtOAc:Hexane 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (1 H, d, J = 3.8 Hz, H-1), 5.42-5.35 (2 H, m, H-3, H-4), 5.07 (1 H, dd, J = 10.9, 3.1 Hz, H-2), 4.18 (1 H, d, J = 13.4 Hz, H-5), 3.92 (1 H, dd, J = 13.4, 1.6 Hz, H-5'), 2.14, 2.10, 2.02 (3 x 3 H, 3 x s, 3 x $COCH_3$) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 170 -169 ($COCH_3$), 89.60 (C-1), 68.92 (C-4), 67.95 (C-3), 67.90 (C-2), 63.45 (C-5), 20.55 ($COCH_3$) ppm. *m/z* (CI, NH_3): 356 (81 %, M (Br-79 + NH_4)); 358 (79 %, M (Br-81 + NH_4)).

7.3.3. General procedure for the hydrolysis of glycoside bromides[5]

The procedure for the hydrolysis of glycoside bromides to their corresponding pyranoses was adapted from one reported by Grummitt *et al.*[5] using Ag_2CO_3.The reactions were allowed to proceed for 24 h instead of 4 h at r.t. as reported in the literature. Reactions were monitored by TLC. The resulting pyranoses were characterised by mass spectrometry and NMR (^{1}H, $^{13}C\{^1H\}$, ^{13}C, COSY, DEPT-90, DEPT-135, HMQC). In some cases the products comprised of a single anomer. The resulting products were in the form of syrups unless otherwise stated.

2,3,4,6-Tetra-*O*-acetyl-*α*-D-galactopyranose [5a]

88 % yield. TLC *R*$_f$ 0.20 (EtOAc:Hexane 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 (1 H, d, J = 3.4 Hz, H-1), 5.46 (1 H, m, H-2), 5.39 (1 H, m, H-3), 5.13 (1 H, dd, J = 10.8, 3.6 Hz, H-4), 4.46 (1 H, m, H-5), 4.15 (2 H, m, H-6, H-6'), 2.14, 2.13, 2.09, 2.08 (4 x 3 H, s, ($COCH_3$)) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 170-169 ($COCH_3$), 90.67 (C-1), 68.24 (C-4), 68.15 (C-2), 67.18 (C-3), 62.54 (C-5), 61.81 (C-6), 20.82-20.55 (4 x ($COCH_3$)) ppm. MS (CI, ammonia): m/z (%) 366 (M+NH_4, 100 %).

2,3,4,6-Tetra-*O*-acetyl-*α*-D-mannopyranose [5b][6]

Quantitative yield. TLC *R*$_f$ 0.22 (EtOAc:Hexane 1:1). ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.39 (1 H, dd, J = 10.1, 3.3 Hz, H-3), 5.28 (1 H, d, J = 9.88, H-4), 5.26 (1H, dd, J = 3.3, 2.0 Hz, H-2), 5.25 (1H, br, H-1), 4.28 - 4.16 (2 H, m, H-5, H-6), 4.15 - 4.08 (1 H, m, H-6'), 2.14, 2.08, 2.03, 1.98 (4 x 3 H, 4 x s, 4 x (COC*H$_3$*)) ppm. ^{13}C{^{1}H} NMR (400 MHz, CDCl$_3$) δ 170.8, 170.1, 170.0, 169.8 (4 x *C*OCH$_3$), 91.9 (C-1), 70.1, 68.8, 68.1, 66.1, (C-2 to C-5), 62.5 (C-6), 20.9, 20.8, 20.6, (CO*C*H$_3$) ppm. MS (CI, ammonia): m/z (%) 366 (M+NH$_4$, 100 %). ^{1}H NMR data in agreement with the literature.[6]

2,3,4-Tri-*O*-acetyl-*α*/*β*-D-xylopyranose [5c] (*α*/*β* ratio 2:1)

88 % yield. TLC *R*$_f$ 0.20 (EtOAc:Hexane 1:1). *α*-anomer: ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 5.54 (1 H, m, H-3), 5.41 (1 H, d, J = 3.47 Hz H-1), 5.02 – 4.89, (1 H, m, H-4), 4.90 - 4.80 (1 H, m, H-2), 4.15 (1 H, dd, J = 11.68, 5.50 Hz, H-5), 3.44-3.33 (1 H, m, H-5'), 2.09 (12 H, m, C*H$_3$*) ppm. ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 170.08, 170.02 (*C*OCH$_3$), 90.30 (C-1), 71.23 (C-2), 69.29 (C-3), 69.06 (C-4), 62.71 (C-5), 20.71 (CO*C*H3) ppm. *β*-anomer: ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 5.25 (1 H, m, H-3), 5.02 – 4.89, (1 H, m, H-4), 4.88-4.77 (1 H, m, H-2), 4.70 (1 H, d, J = 7.65 Hz, H-1), 3.94-3.79 (2 H, m, H-5), 2.09 (12 H, m, COC*H$_3$*). ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 170.86, 170.21, 169.91 (3 x *C*OCH$_3$), 95.91 (C-1), 73.1 (C-2), 71.52 (C-3), 69.2 (C-4), 58.52 (C-5), 20.72 (CO*C*H$_3$) ppm. MS: (CI - NH$_3$) m/z: 294 (M+NH$_4$, 100 %).

2,3,4-Tri-*O*-acetyl-*α*/*β*-L-arabinopyranose [5d] (*α*/*β* ratio 2:1)

α-anomer: ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.47 (1 H, d, J = 3.4 Hz, H-1), 5.40 (1 H, dd, J = 10.4, 3.6 Hz, H-3), 5.38-5.34 (1 H, m, H-4), 5.18 (1 H, dd, J = 10.5, 3.4 Hz, H-2), 4.25-4.17 (1 H, m, H-5), 3.70 (1 H, dd, J = 13.0, 2.3 Hz, H-5', overlapping with *β*-equivalent), 2.16, 2.13, 2.09 (3 x 3 H, 3 x s, 3 x COC*H$_3$*) ppm. ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 170 - 168 (*C*OCH$_3$), 90.82 (C-1), 69.02 (C-2), 68.58 (C-4), 66.83 (C-

3), 60.25 (C-5), 21 - 20 (CO*C*H$_3$) ppm. *β*-anomer: ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.27 (1 H, m, H-4), 5.08 (2 H, m, H-2, H-3), 4.61 (1 H, d, J = 7.2 Hz, H-1), 4.02 (1 H, dd, J = 13.3, 2.4 Hz, H-5), 3.67 (1 H, dd, J = 13.3, 1.3 Hz, H-5', overlapping with *α* equivalent), 2.14, 2.10, 2.01 (3 x 3 H, 3 x s, COC*H*$_3$) ppm. ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 170 - 168 (*C*OCH$_3$), 96.05 (C-1), 71.12 (C-2), 70.04 (C-3), 67.92 (C-4), 64.06 (C-5), 21 - 20 (CO*C*H$_3$) ppm.MS: (CI - NH$_3$) m/z: 294 (M+NH$_4$, 100 %).

2,3,4,6-Tetra-*O*-acetyl-D-glucono-1,5-lactone [6e][2]

Prepared following procedure reported by Joseph *et al.* Characterisation data in agreement with literature data.[2] $[\alpha]_D^{25}$ = +72.0º (c, 1.75, CHCl$_3$) (lit. $[\alpha]_D^{25}$ = +76.1º). ν_{max}(neat) 1757 cm^{-1} (C=O). ^{1}H NMR (270 MHz, CDCl$_3$) δ 5.44 (1 H, apt t, H-3), 5.25 (1 H, m, H-4), 5.10 (1 H, d, J = 9.10 Hz, H-2), 4.56-4.44 (1 H, m, H-5), 4.28 (1 H, dd, J = 12.71, 3.65 Hz, H-6), 4.14 (1 H, dd, J = 12.74, 2.29 Hz, H-6), 2.04 (3 H, s, COC*H*$_3$), 1.99 (3 H, s, COC*H*$_3$), 1.97-1.95 (6 H, 2 x s, 2 x COC*H*$_3$) ppm.

7.3.4. General procedure for the Swern oxidation of lactols

Oxalyl chloride (3.4 mL, 39 mmol, 7 eq.) was dissolved in dry CH_2Cl_2 (100 mL) and cooled to -78 °C. A solution of DMSO (5.4 mL, 76 mmol, 13 eq.) in CH_2Cl_2 (15 mL) at -78 °C was added dropwise to the oxalyl chloride solution under N_2. After 15 min a solution of the functonalised pyranose (5.7 mmol, 1 eq.) in CH_2Cl_2 (50 mL) at -78 °C was added dropwise. After 30 min NEt_3 (4.0 mL 29 mmol, 5 eq) was slowly introduced and the reaction mixture was stirred at 78 °C for a further 30 min (Until this point, the reaction temperature was not allowed to rise beyond -60 °C). The reaction mixture was then allowed to warm to -30 °C and washed with ice-water (200 mL), 1M HCl (200 mL), saturated $NaHCO_3$ (aq) (200 mL), water (200 mL), brined (200 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to yield the product as a syrup.

2,3,4,6-Tetra-*O*-acetyl-D-galactono-1,5-lactone [6a]

(1.66 g, 4.79 mmol, 83 %). TLC R_f 0.33 (EtOAc:Hexane 1:1). $[\alpha]_D^{25}$ = +43.2º (c, 1.25, $CHCl_3$) ν_{max}(neat) 1766 cm^{-1} (C=O).^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.70 (1 H, dd, J = 2.76, 1.5 Hz, H-4), 5.47 (1 H, dd, J = 10.28, 2.9 Hz, H-3), 5.28 (1 H, d, J = 10.3 Hz, H-2), 4.82 (1 H, m, H-5), 4.25 (2 H, m, H-6, H-6'), 2.20 (3 H, s, $COCH_3$), 2.19 (3 H, s, $COCH_3$), 2.10 (3 H, s, $COCH_3$), 2.08 (3 H, s, $COCH_3$) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 170.18, 170.12, 169.75, 169.46 ($COCH_3$); 164.95 (C-1); 74.71 (C-5); 69.16 (C-3); 68.44 (C-2); 66.22 (C-4); 60.98 (C-6); 20.56, 20.52, 20.44, 20.41 ($COCH_3$) ppm. MS (CI, ammonia): m/z (%) 364 (100 %, M+NH_4). Anal Calcd for $C_{14}H_{18}O_{10}$: C, 48.56 %; H, 5.24 %. Anal Found: C, 48.65 %; H 5.37 %.

2,3,4,6-Tetra-*O*-acetyl-D-mannono-1,5-lactone [6b][7]

(1.50 g, 4.34 mmol, 76 %). TLC R_f 0.25 (EtOAc:Hexane 1:1). $[\alpha]_D^{25}$ = 30.4°(c, 1.25, $CHCl_3$). ν_{max}(neat) 1748 cm^{-1} (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (1 H, d, J = 3.9 Hz, H-2), 5.52-5.46 (1 H, m, H-3), 5.07-5.03 (1 H, m, H-4), 4.62 (1 H, ddd, J = 8.6, 5.8, 3.2 Hz, H-5), 4.37 (1 H, dd, J = 12.4, 3.1 Hz, H-6), 4.27 (1 H, dd, J = 12.5, 5.8 Hz, H-6'), 2.15 (3 H, s, $COC\mathit{H}_3$), 2.16 (3 H, s, $COC\mathit{H}_3$), 2.18 (3 H, s, $COC\mathit{H}_3$), 2.12 (3 H, s, $COC\mathit{H}_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.39, 169.41, 169.04, 168.97 ($\mathit{C}OCH_3$), 164.81 (C-1), 75.37 (C-5), 70.38 (C-3), 69.10 (C-4), 66.53 (C-2), 62.26 (C-6), 20.63 - 20.38 ($CO\mathit{C}H_3$) ppm. MS:(CI - NH_3) *m/z*: 364 (M+NH_4, 60 %). Anal Calcd. for $C_{14}H_{18}O_{10}$: C, 48.56 %; H, 5.24 %. Found: C, 48.70 %; H, 5.12 %.

2,3,4-Tri-*O*-acetyl-D-xylono-1,5-lactone [6c][8]

(3.87 g, 14.11 mmol, 64 %). TLC R_f 0.38 (EtOAc:Hexane 1:1). $[\alpha]_D^{25}$ = -64.0°(c, 0.19, $CHCl_3$). ν_{max}(neat) 1747 cm^{-1} (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52 (1 H, d, J = 8.7 Hz, H-2), 5.23-5.17 (1 H, m, H-3), 5.15-5.11 (1 H, m, H-4), 4.60 (1 H, dd, J = 13.00, 2.23 Hz, H-5), 4.48-4.39 (1 H, m, H-5'), 2.20 (3 H, s, $COC\mathit{H}_3$), 2.13 (3 H, s, $COC\mathit{H}_3$), 2.12 (3 H, s, $COC\mathit{H}_3$) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 169.65, 169.47, 169.21 ($\mathit{C}OCH_3$), 165.46 (C-1), 72.93 (C-3), 70.51 (C-4), 68.59 (C-2), 66.47 (C-5), 66.27 (C-5), 20.64, 20.38, 19.59 ($CO\mathit{C}H_3$) ppm. NMR data is in agreement with the literature.[8] [8,9] MS: (CI - NH_3) *m/z*: 292 (M+NH_4, 100 %). Anal Calcd. for $C_{11}H_{14}O_8$ C, 48.18 %; H, 5.15 %. Anal Found: C, 48.09 %; H, 5.07 %.

2,3,4-Tri-*O*-acetyl-L-arabinono-1,5-lactone [6d][9]

(0.93 g, 3.39 mmol, 47 %). TLC R_f 0.50 (EtOAc:Hexane 1:1). $[\alpha]_D^{25}$ = +54.4°(c, 1.25, $CHCl_3$). ν_{max}(neat) 1751 cm^{-1} (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (1 H, dd, J = 4.7, 2.1 Hz, H-4), 5.48 (1 H, dd, J = 10.2, 3.0 Hz, H-3), 5.34 (1 H, d, J = 10.2 Hz, H-2), 4.53 (1 H, dd, J = 13.1, 1.6 Hz, H-5), 4.46 (1 H, dd, J = 13.1, 2.3 Hz, H-5), 2.09 (1

H, s, COC*H*$_3$), 2.18 (1 H, s, COC*H*$_3$), 2.19 (1 H, s, COC*H*$_3$) ppm.^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 170.13 (*C*OCH$_3$), 169.82 (*C*OCH$_3$), 169.7 (*C*OCH$_3$), 165.69 (C-1), 68.78 (C-4), 68.72 (C-2), 67.99 (C-5), 67.02 (C-3), 20.75 (CO*C*H$_3$), 20.63 (CO*C*H$_3$), 20.46 (CO*C*H$_3$), ppm. NMR data is in agreement with the literature.[9] [9] MS: (Cl - NH$_3$) *m/z*: 292 (M+NH$_4$, 100 %).

7.3.5. Methyl protected D-(+)-xylopyranose derivatives

(2',2'-Dichloro-1'-methyl)ethenyl-*α/β*-D-xylopyranoside [12]

1,2,3,4-Tetra-O-acetyl-α/β-D-xylopyranose **[2c]** (20.00 g, 62.80 mmol, 1 eq), PPh$_3$ (49.40 g, 189 mmol, 3 eq), and KCl (42.20 g, 566 mmol, 9 eq) were dried in *vacuo* for 1 h and suspended in dry toluene (55 mL), dry pyridine (30 mL), and dry CCl$_4$ (45 mL) and stirred at 90°C for 50 min. The resulting black heterogeneous mixture was filtered through a plug of silica gel eluted with CH$_2$Cl$_2$-EtOAc (1:1) and concentrated to dryness to yield a yellow semi-solid, which was purified by column chromatography (EtOAc:Hexane, 1:1, R$_f$=0.6) to yield a yellow semi-solid (2,3,4-Tri-*O*-acetyl-(2',2'-Dichloro-1'-methyl)ethenyl-*α/β*-D-xylopyranoside [11]) (15.25 g, 40.82 mmol, 63%). To a solution of 2,3,4-Tri-*O*-acetyl-(2',2'-Dichloro-1'-methyl)ethenyl-*α/β*-D-xylopyranoside [11](5.00 g, 13 mmol, 1 eq.) in absolute MeOH (50 mL) was added MeONa (0.37 g, 6.90 mmol, 0.5 eq). After 2 h, the solution was neutralized with ion exchange resin (Amberlite IRC 50 S H$^+$ form). The reaction mixture was concentrated and washed with acetone (30 mL) to yield the product as a semi-solid (2.49 g, 9.60 mmol, 80%). ^{13}C{^{1}H}NMR (75 MHz, DMSO-d$_6$) δ 148.38, 148.11 (C-1'), 104.38, 103.59 (C-2'), 97.73, 92.43 (C-1), 76.66, 74.62 (C-3), 73.1, 72.26 (C-2), 70.1, 69.75 (C-4), 65.62, 61.51 (C-5), 14.78, 14.33 (C-3'). MS (CI, ammonia): m/z (%) 276 (100) [M+NH$_4^+$, ^{35}Cl), 278 (65), [M+NH$_4^+$,^{35}Cl, ^{37}Cl], 280 (15) [M+NH$_4^+$, ^{37}Cl]. Anal. Calcd. for C$_8$H$_{12}$Cl$_2$O$_5$: C, 37.09; H, 4.67. Found: C, 37.05; H, 4.70.

1,2,3,4-Tetra-*O*-methyl-*α*/*β*-D-xylopyranose [13][10]

(2',2'-Dichloro-1'-methyl)ethenyl-*α*/*β*-D-xylopyranoside **[12]** (0.74 g, 2.90 mmol, 1 eq) was dissolved in dry DMF (15 mL), under nitrogen. NaH (1.5 g, 60% dispersion in mineral oil, 31 mmol, 13 eq) was added at 0°C with stirring, followed by MeI (1.42 mL, 23 mmol, 8 eq). After 4 h at room temperature, the reaction was quenched by addition of MeOH (20 mL). The mixture was diluted with CH_2Cl_2 (50 mL) and water (50 mL). The organic phase was separated and the aqueous layer extracted with $CHCl_3$ (350 mL). The organic layer was dried ($MgSO_4$) and concentrated in *vacuo* and residual DMF was removed by distillation under vacuum (5 mbar, 35°C). The resulting residue was purified by flash chromatography (EtOAc-Hexane; 1:1) to yield the product as a mixture of the *α*- and *β*-anomers in the ratio 1:3, respectively (0.36 g, 1.74 mmol, 60%). Mp 44-45°C [lit.[10] Mp 46-48°C, *β*-anomer].$[\alpha]_D^{25}$ -16.1 ° (c, 0.31, $CHCl_3$) [lit. $[\alpha]_D^{25}$ -66°, *β*-anomer (c, 1.16, MeOH)[10]].

α anomer: ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.75 (1H, d, $^3J_{HH}$=3.5 Hz, H-1), 3.98 (1H, dd, $^2J_{HH}$=11.5 Hz, $^3J_{HH}$=4.7 Hz, H-2), 3.61 (3H, s, OMe), 3.50 (3H, s, OMe), 3.47 (3H, s, OMe), 3.40 (3H, s, OMe), 3.62-2.93 (4H, m, H-3, H-4, H-5). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ=97.59 (C-1), 82.65 (C-2), 81.69 (C-3), 79.74 (C-4), 60.90 (C-5), 59.33, 59.02, 58.90 (OMe), 55.1 (C-1 - OMe).

β anomer: ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.13 (1H, d, $^3J_{HH}$=7.2 Hz, H-1), 3.69 (1H, dd, $^2J_{HH}$=10.90 Hz, $^3J_{HH}$=5.60 Hz, H-2), 3.59 (3H, s, OMe), 3.55 (3H, s, OMe), 3.50 (3H, s, OMe), 3.46 (3H, s, OMe), 3.62-2.93 (4H, m, H-3, H-4, H-5). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 104.70 (C-1), 85.01 (C-2), 83.17 (C-3), 79.35 (C-4), 63.03 (C-5), 60.55, 60.34, 58.63 (OMe), 56.76 (C-1- OMe).

MS (CI, ammonia): m/z (%) 224 (100) $[M+NH_4^+]$. Anal. Calcd. for $C_9H_{18}O_5$: C 52.43, H 8.74. Found: C, 53.43; H, 8.84.

2,3,4-Tri-*O*-methyl-*α*/*β*-D-xylopyranose [14][10]

1,2,3,4-Tetra-*O*-methyl-*α*/*β*-D-xylopyranose **[13]** (0.26 g, 1.26 mmol) was dissolved in a solution of trifluoroacetic acid (2.5 mL) and water (1.0 mL) and heated at 65℃ for 4 h. The mixture was concentrated to yield the product as an oil (0.16 g, 0.83 mmol, 66%). The oil was composed of a 2:1 ratio of *α*:*β* anomers. $[\alpha]_D^{25}$ +18.8° (c, 0.64, $CHCl_3$) [lit $[\alpha]_D^{25}$ +20.1° (c, 1.095, MeOH)[10]].

α-anomer (66%): ^1H NMR (400 MHz, $CDCl_3$) δ 5.24 (1 H, d, $^3J_{HH}$=3.44 Hz, H-1), 3.76-3.72 (1 H, m, H-5), 3.62 (3 H, s, OMe), 3.55 (3 H, s, OMe), 3.49 (3 H, s, OMe), 3.45 (1 H, d, $^3J_{HH}$=8.44 Hz, H-3), 3.28-3.16 (2 H, m, H-2, H-4). $^{13}C\{^1H\}$ (125 MHz, $CDCl_3$) δ 90.90 (C-1), 81.45 (C-2 or C-4), 81.36 (C-3), 79.01 (C-2 or C-4), 60.67 (OMe), 59.89 (C-5), 58.93, 58.71 (OMe).

β-anomer (33%): ^1H NMR (400 MHz, $CDCl_3$) δ 4.62 (1 H, d, $^3J_{HH}$=6.83 Hz, H-1), 4.02 (1 H, dd, $^2J_{HH}$=11.09, $^3J_{HH}$=4.23 Hz, H-5), 3.62 (6 H, s, OMe), 3.46 (3 H, s, OMe), 3.31-3.17 (2 H, m, H-3, H-4), 2.99 (1 H, dd, $^3J_{H2H3}$=8.01 Hz, $^3J_{H1H2}$=6.91 Hz, H-2). $^{13}C\{^1H\}$ (125 MHz, $CDCl_3$) δ 97.10 (C-1), 84.17 (C-3 or C-4), 83.46 (C-2), 78.80 (C-3 or C-4), 62.64 (C-5), 60.52, 60.36, 58.65 (OMe).

MS (CI, ammonia): *m/z* (%) 210 (100) $[M+NH_4^+]$. Anal. Calcd. for $C_8H_{16}O_5$: C, 50.00; H, 8.33. Found: C, 50.08; 7.24.

2,3,4-Tri-*O*-methyl-D-xylono-1,5-lactone [15][11]

Pyridinium chlorochromate (0.36 g, 1.70 mmol, 2.0 eq) in dichloromethane (3 mL) was added to 2,3,4-Tri-*O*-methyl-*α*/*β*-D-xylopyranose **[14]** (0.20 g, 1 mmol) dissolved in CH_2Cl_2 (3 mL), and the mixture was refluxed for 7 h. It was then cooled, diluted with diethyl ether (30 mL), decanted, filtered through celite, and concentrated to yield the product as an oil (0.15 g, 0.80 mmol, 95%). $[\alpha]_D^{25}$ +16.8° (c, 0.95, CH_2Cl_2). IR ($CDCl_3$): 1765 cm^{-1} (C=O).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.44 (1 H, ddd, $^{2}J_{HH}$=12.26, $^{3}J_{HH}$=2.99, 1.66 Hz, H-5 axial), 4.29 (1 H, dd, $^{2}J_{HH}$=12.41, $^{3}J_{HH}$=1.75 Hz, H-5 equatorial), 3.84 (1 H, d, $^{3}J_{HH}$=6.53 Hz, H-2), 3.63 (3 H, s, CH_3), 3.53 (3 H, s, CH_3), 3.43 (3 H, s, CH_3), 3.57-3.55 (1 H, m, H-4), 3.50 (1 H, m, H-3).

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ=169.57 (C-1), 82.91 (C-3), 80.49 (C-2), 77.00 (C-4), 64.93 (C-5), 59.47, 58.02, 56.22 (3 x CH_3). MS (CI, ammonia): *m/z* (%) 208 (100), [$M+MH_4^+$].

Anal Calcd. for $C_8H_{14}O_5$: C 50.52, H 7.42. Found: C 50.68, H 7.51.

7.3.6. General procedure for synthesis of aldaric esters

The 1,5-lactone (300 mg) was dissolved in $CHCl_3$ (15 mL) and to it was added a 1.0 M solution of the alcohol (1 eq.) containing *p*-TSA (0.1 eq.) After between 15 mins and 2 h the reaction was quenched with $NaHCO_3$ (aq) (50 mL), washed with water (2 x 50 mL) and dried ($MgSO_4$). The organic layer was concentrated *in vacuo* to yield the aldaric ester as a syrup. Butyl aldaric esters were prepared using butan-1-ol and 4-hydroxybutyl aldaric ester were prepared using 1,4-butanediol.

Butyl 2,3,4,6-tetra-*O*-acetyl-D-galactonate [21]

(0.15 g, 0.35 mmol, 49 % yield). TLC: decomposes on silica. $[\alpha]_D^{25}$ = +6.7° (c, 1.8, $CHCl_3$). ν_{max}(neat) 3430 cm^{-1} (OH), 1751 cm^{-1} (C=O). ^1H NMR (400 MHz, $CDCl_3$) δ 5.76 (1 H, m, H-2), 5.30 (1 H, dd, J = 3.9, 2.0 Hz, H-4), 5.16 (1 H, m, H-3), 4.25 - 4.15 - 4.06 (4 H, m, $C(O)OCH_2CH_2CH_2CH_3$, H-6), 3.97 (1 H, dd, J = 11.5, 7.4 Hz, H-5), 2.15 (3 H, s, $COCH_3$), 2.11 (3 H, s, $COCH_3$), 2.07 (3 H, s, $COCH_3$), 2.06 (3 H, s, $COCH_3$), 1.72 - 1.52 (2 H, m, $C(O)OCH_2CH_2CH_2CH_3$), 1.45 - 1.20 (2 H, m, $C(O)OCH_2CH_2CH_2$CH3), 0.88 (3 H, m, $C(O)OCH_2CH_2CH_2CH_3$) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 170.99, 170.51, 170.18, 169.36 ($COCH_3$), 167.76 (C-1), 69.62 (C-2, C-4), 68.65 (C-3), 67.71 (C-5), 66.01 ($C(O)OCH_2CH_2CH_2CH_3$), 65.86 (C-6), 30.3 ($C(O)OCH_2CH_2CH_2CH_3$), 20.74, 20.71, 20.55, 20.43 ($COCH_3$) 18.95 ($C(O)OCH_2CH_2CH_2CH_3$) 13.6 ($C(O)OCH_2CH_2CH_2CH_3$) ppm. MS: (CI - NH_3) *m/z*: 438 (M+NH_4, 100 %). Anal. Calcd. for $C_{18}H_{28}O_{11}$: C, 51.42 %; H, 6.71 %. Anal. Found: C, 51.33 %; H, 6.60 %.

Butyl 2,3,4,6-tetra-*O*-acetyl-D-mannonate [22]

(0.13 g, 0.30 mmol, 21 % yield). TLC: decomposes on silica. ν_{max}(neat) 3406 cm^{-1} (OH), 1749 cm^{-1} (C=O). ^1H NMR (400 MHz, $CDCl_3$) δ 5.67 (1 H, dd, J = 8.5, 2.2 Hz, H-3), 5.28 (1 H, dd, J = 9.1, 2.2 Hz, H-2), 5.09 (1 H, d, J = 8.5 Hz, H-4), 4.29 - 4.14 (2

H, m, $\mathrm{C(O)OC}H_2\mathrm{CH_2CH_2CH_3}$), 4.11 (2 H, td, J = 11.0, 5.3 Hz, H-6/H-6’), 3.80 (1 H, ddd, J = 11.6, 8.1, 3.4 Hz, H-5), 2.15, 2.13, 2.09 (12 H, 4 x $\mathrm{COC}H_3$), 1.69 - 1.52 (2 H, m, $\mathrm{C(O)OCH_2C}H_2\mathrm{CH_2CH_3}$), 1.38 (2 H, td, J = 15.0, 7.4, Hz, $\mathrm{C(O)OCH_2CH_2C}H_2\mathrm{CH_3}$), 0.94 (3 H, t, J = 7.4 Hz, $\mathrm{C(O)OCH_2CH_2CH_2C}H_3$) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, CDCl3) δ 171.14, 170.85, 169.64, 169.55 ($C\mathrm{OCH_3}$), 167.57 (C-1), 69.59 (C-4), 69.55 (C-2), 68.97 (C-3), 67.62 (C-5), 64.78 (C-6), 65.91 ($\mathrm{C(O)O}C\mathrm{H_2CH_2CH_2CH_3}$), 30.36 ($\mathrm{C(O)OCH_2}C\mathrm{H_2CH_2CH_3}$), 20.77, 20.62, 20.39 ($\mathrm{CO}C\mathrm{H_3}$), 18.94 (30.36 ($\mathrm{C(O)OCH_2CH_2}C\mathrm{H_2CH_3}$)) 13.6 (30.36 ($\mathrm{C(O)OCH_2CH_2CH_2}C\mathrm{H_3}$)) ppm. MS: (CI - NH_3) *m/z*: 438 (M+NH_4, 100 %).

Butyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate [23]

(0.28 g, 0.66 mmol, 67 % yield). TLC: decomposes on silica. $[\alpha]_D^{25}$ = +24.9° (c, 1.85, $CHCl_3$). ν_{max}(neat) 3523 cm^{-1} (OH), 1741 cm^{-1} (C=O). ^1H NMR (400 MHz, $CDCl_3$) δ 5.73 (1 H, apt t, J = 3.7 Hz, H-3), 5.30 (1 H, d, J = 3.9 Hz, H-2), 5.20 (1 H, dd, J = 8.3, 3.6 Hz, H-4), 4.23 - 4.02 (4 H, m, H-6. H-6', $\mathrm{C(O)OC}H_2\mathrm{CH_2CH_2CH_3}$), 3.89 - 3.80 (1 H, m, H-5), 2.16 (3 H, s, $\mathrm{COC}H_3$), 2.13 (3 H, s, $\mathrm{COC}H_3$), 2.09 (6 H, s, 2 x $\mathrm{COC}H_3$), 1.66 - 1.57 (2 H, m, $\mathrm{C(O)OCH_2C}H_2\mathrm{CH_2CH_3}$), 1.45 - 1.31 (2 H, m, $\mathrm{C(O)OCH_2CH_2C}H_2\mathrm{CH_3}$), 0.93 (3 H, apt t, J = 7.4 Hz, $\mathrm{C(O)OCH_2CH_2CH_2C}H_3$) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 171.13, 170.51, 169.73, 166.87 ($C\mathrm{OCH_3}$, C-1), 71.75 (C-2), 70.78 (C-4), 69.51 (C-3), 68.41 (C-5), 65.94, 64.66 (C-6, $\mathrm{C(O)O}C\mathrm{H_2CH_2CH_2CH_3}$) 30.39 ($\mathrm{C(O)OCH_2}C\mathrm{H_2CH_2CH_3}$), 20.74, 20.54, 20.44 ($\mathrm{CO}C\mathrm{H_3}$), 18.93 ($\mathrm{C(O)OCH_2CH_2}C\mathrm{H_2CH_3}$), 13.61 ($\mathrm{C(O)OCH_2CH_2CH_2}C\mathrm{H_3}$) ppm. MS: (CI - NH_3) *m/z*: 438 (M+NH_4, 100 %). Anal. Calcd. for $C_{17}H_{26}O_{11}$: C, 51.42 %; H, 6.71 %. Anal. Found: C, 51.33 %; H, 6.78 %.

Butyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate [24]

(0.09 g, 0.32 mmol, 67 % yield). TLC: decomposes on silica. $[\alpha]_D^{25}$ = +25.5° (c, 0.85, $CHCl_3$). ν_{max}(neat) 3508 cm^{-1} (OH), 1749 cm^{-1} (C=O). ^1H NMR (400 MHz, $CDCl_3$) δ 5.69 (1 H, d, J = 8.0 Hz, H-2), 5.63 (1 H, t, J = 7.8 Hz, H-3), 5.02 (1 H, m, H-4), 4.50 - 4.08 (4 H, m, H-5, H-5', $C(O)OC\mathit{H_2}CH_2CH_2CH_3$), 2.15 (3 H, s, $COC\mathit{H_3}$), 2.14 (3 H, s, $COC\mathit{H_3}$), 2.10 (3 H, s, $COC\mathit{H_3}$), 1.67 - 1.60 (2 H, m, $C(O)OCH_2C\mathit{H_2}CH_2CH_3$), 1.31 - 1.28 (2 H, m, $C(O)OCH_2CH_2C\mathit{H_2}CH_3$), 1.00 - 0.88 (3 H, m, $C(O)OCH_2CH_2CH_2CH_3$) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 179.03, 169.76 ($COCH_3$), 168.45 (C-1), 75.35 (C-4), 72.91 (C-3), 70.42 (C-2), 69.28 (C-5), 61.17 ($C(O)O\mathit{C}H_2CH_2CH_2CH_3$), 30.20 ($C(O)OCH_2\mathit{C}H_2CH_2CH_3$), 20.51, 20.57, 20.67 ($CO\mathit{C}H_3$), 18.95 ($C(O)OCH_2CH_2\mathit{C}H_2CH_3$) 14.06 ($C(O)OCH_2CH_2CH_2\mathit{C}H_3$) ppm.

Butyl 2,3,4-tri-*O*-acetyl-L-arabinonate [25]

(0.05 g, 0.14 mmol, 79 % yield). TLC: decomposes on silica. $[\alpha]_D^{25}$ = -20.0° (c, 0.30, $CHCl_3$). ν_{max}(neat) 3566 cm^{-1} (OH), 1749 cm^{-1} (C=O). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 5.56 (1 H, d, J = 6.9 Hz, H-2), 5.45 (1 H, apt t, J = 6.8, 6.8 Hz, H-3), 4.54 (1 H, ddd, J = 6.8, 4.9, 2.9 Hz, H-4), 4.46 (1 H, dd, J = 12.6, 3.0 Hz, H-5), 4.26 (1 H, dd, J = 12.6, 5.0 Hz, H-5'), 4.22 - 4.09 (2 H, m, $C(O)OC\mathit{H_2}CH_2CH_2CH_3$), 2.17 (3 H, s, $COC\mathit{H_3}$), 2.12 (3 H, s, $COC\mathit{H_3}$), 2.10 (3 H, s, $COC\mathit{H_3}$), 1.40 – 1.24 (4 H, m, $C(O)OCH_2C\mathit{H_2}C\mathit{H_2}CH_3$), 1.05 - 0.64 (3 H, m, $C(O)OCH_2CH_2CH_2C\mathit{H_3}$). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 170.28, 169.84, 169.48 ($COCH_3$), 168.26 (C-1), 77.37 (C-4), 72.63 (C-3), 72.06 (C-2), 65.00 ($C(O)O\mathit{C}H_2CH_2CH_2CH_3$), 62.1 (C-5), 30.36 ($C(O)OCH_2\mathit{C}H_2CH_2CH_3$), 20.75, 20.53, 20.34 ($CO\mathit{C}H_3$), 18.96 ($C(O)OCH_2CH_2\mathit{C}H_2CH_3$), 14.09 ($C(O)OCH_2CH_2CH_2\mathit{C}H_3$) ppm. MS: (CI - NH_3) *m/z*: 366 ($M+NH_4$, 20 %).

4-Hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-galactonate [26]

(0.76 g, 1.11 mmol, 60 % yield). TLC: decomposes on silica. $[\alpha]_D^{25}$ = +8.00°(c, 0.5, $CHCl_3$). ν_{max}(neat) 3519 cm^{-1} (OH), 1749 cm^{-1} (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (1 H, dd, J = 9.8, 2.0 Hz, H-2), 5.21-5.16 (1 H, m, H-3), 4.22 - 4.06 (4 H, m, H-4, H-5, H-6, H-6'), 4.03-3.82 (2 H, m, $C(O)OC\mathit{H}_2CH_2CH_2OH$), 3.72-3.63 (2 H, m, $C(O)OCH_2CH_2C\mathit{H}_2OH$), 2.18 (3 H, s, $COCH_3$), 2.14 (3 H, s, $COCH_3$), 2.13 (3 H, s, $COCH_3$), 2.09 (3 H, s, $COCH_3$), 1.81 - 1.68 (2 H, m, $C(O)OCH_2C\mathit{H}_2CH_2CH_2OH$), 1.32 - 1.23 (2 H, m, $C(O)OCH_2CH_2C\mathit{H}_2CH_2OH$) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, CDCl3) δ 170.98 - 169.35 ($\mathit{C}OCH_3$), 168.03 (C-1), 69.709 (C-2), 68.531 (C-3), 68.21, 68.29, 68.21, 63.51 (C-4, C-5, C-6, C-6'), 68.27 ($C(O)O\mathit{C}H_2CH_2CH_2\mathit{C}H_2OH$), 25.38 ($C(O)OCH_2\mathit{C}H_2CH_2CH_2OH$), 21.08 - 19.66 ($CO\mathit{C}H_3$), 12.97 ($C(O)OCH_2CH_2\mathit{C}H_2CH_2OH$) ppm. MS: (CI - NH_3) *m/z*: 454 ($M+NH_4$, 100 %). Anal. Calcd. for $C_{18}H_{28}O_{12}$ C, 49.54 %; H, 6.47 %. Anal. Found: C, 49.50 %; H, 6.57 %.

4-Hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-mannonate [27]

(0.96 g, 2.20 mmol, 76 % yield). TLC: decomposes to lactone on silica. $[\alpha]_D^{25}$ = +13.09°(c, 2.75, $CHCl_3$). ν_{max}(neat) 1761 cm^{-1} (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (1 H, dd, J = 8.6, 2.2 Hz, H-3), 5.27 (1 H, dd, J = 9.1, 2.1 Hz, H-4), 5.17 (1 H, d, J = 7.8 Hz, H-2), 4.29 - 4.07 (3 H, m, H-5, H-6, H-6'), 4.01 (2 H, m, $C(O)OC\mathit{H}_2CH_2CH_2CH_2OH$), 3.68 (2 H, m, $C(O)OCH_2CH_2CH_2C\mathit{H}_2OH$), 2.15 (3 H, s, $COC\mathit{H}_3$), 2.13 (3 H, s, $COC\mathit{H}_3$), 2.09 (6 H, 2 x s, $COC\mathit{H}_3$), 1.75 (2 H, m, $C(O)OCH_2C\mathit{H}_2CH_2CH_2OH$), 1.27 (2 H, m, $C(O)OCH_2CH_2C\mathit{H}_2CH_2OH$) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 171-169 ($\mathit{C}OCH_3$, C-1), 66.44 (C-3), 69.55 (C-4), 69.55 (C-2), 64.21, 62.87, 61.96 (C-5, C-6, C-6'), 64.65 ($C(O)O\mathit{C}H_2CH_2CH_2CH_2OH$), 61.96 ($C(O)OCH_2CH_2CH_2\mathit{C}H_2OH$), 25.42 ($C(O)OCH_2CH_2\mathit{C}H_2CH_2OH$), 20.02 ($CO\mathit{C}H_3$), 20.02 ($CO\mathit{C}H_3$), 20.48 ($CO\mathit{C}H_3$), 20.48 ($CO\mathit{C}H_3$), 13.78 ($C(O)OCH_2CH_2\mathit{C}H_2CH_2OH$), ppm. MS: (CI - NH$_3$) *m/z*: 454 (M+NH$_4$, 29 %). Anal Calcd for $C_{18}H_{28}O_{12}$ C, 49.54 %; H, 6.47 %. Anal Found C, 49.68 %; H, 6.39 %.

4-Hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate [28]

Reaction time: 2 h. (0.37 g, 0.89 mmol, 95 %). TLC *R*$_f$ 0.43 – some decomposes to lactone on TLC plate (EtOAc:Hexane 1:1). $[\alpha]_D^{25}$ = + 45.2 ° (c, 1.15, CHCl$_3$). ν_{max}(neat) 3485 cm^{-1} (OH), 1738 cm^{-1} (C=O). ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.74 (1 H, m, H-2), 5.29 (1 H, m, H-3), 5.20 (1 H, dd, J = 8.3, 3.6 Hz, H-4), 4.22 - 4.12 (6 H, m, J = 14.3, 7.2 Hz, C(O)OC*H*$_2$CH$_2$CH$_2$C*H*$_2$OH, H-6), 3.84(1 H, m, H-5), 3.01 (1 H, d, J = 5 Hz, OH), 2.16 (3 H, s, COC*H*$_3$), 2.14 (3 H, s, COC*H*$_3$), 2.10 (6 H, s, 2xCOC*H*$_3$), 1.27 (4 H, m, C(O)OCH$_2$C*H*$_2$C*H*$_2$CH$_2$OH) ppm. ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 171.15, 170.58, 169.76, 166.76 (*C*OCH$_3$, C-1), 71.81 (C-3), 70.56 (C-4), 69.50 (C-2), 68.41 (C-5), 64.65, 62.16 (C(O)O*C*H$_2$CH$_2$CH$_2$*C*H$_2$OH, C-6), 20.78, 20.58, 20.47 (COC*H*$_3$), 14.00 (C(O)OCH$_2$*C*H$_2$*C*H$_2$CH$_2$OH) ppm. MS: (CI - NH$_3$) *m/z*: 454 (M+NH$_4$, 25 %). Anal Calcd. for $C_{18}H_{28}O_{12}$: C, 49.54 %; H, 6.47 %. Anal Found: C, 49.62 %; H, 6.38 %.

4-Hydroxybutyl 2,3,4-tri-*O*-acetyl-D-xylononate [29]

(0.87 g, 2.34 mmol, 73 % yield). TLC: decomposes on silica gel. $[\alpha]_D^{25}$ = +22.2° (c, 0.45, CHCl$_3$). ν_{max}(neat) 1749 cm^{-1} (C=O). ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.70 (1 H, d, J = 8.0 Hz, H-2), 5.64 (1 H, m H-3), 5.02 (1 H, m, H-4), 4.40 (1 H, dd, J = 12.8, 2.9 Hz, H-5), 4.28 (1 H, dd, J = 12.8, 3.0 Hz, H-5'), 4.17 - 4.07 (4 H, m, C(O)OC*H*$_2$CH$_2$CH$_2$C*H*$_2$OH), 3.08 (1 H, d, J = 7.5 Hz, OH), 2.20 (3 H, s, COC*H*$_3$), 2.15 (3 H, s, COC*H*$_3$), 2.13 (3 H, s, COC*H*$_3$), 1.78 - 1.70 (2 H, m, C(O)OCH$_2$C*H*$_2$CH$_2$CH$_2$OH), 1.35 - 1.25 (2 H, m, C(O)OCH$_2$CH$_2$C*H*$_2$CH$_2$OH) ppm. ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 170 - 169 (*C*OCH$_3$), 168.45 (C-1), 70.44 (C-2), 72.48 (C-3), 75.53 (C-4), 62.82 (C(O)O*C*H$_2$CH$_2$CH$_2$CH$_2$OH), 60.27 (C-5), 25.72

($C(O)OCH_2\mathit{C}H_2CH_2CH_2OH$), 20.64 ($CO\mathit{C}H_3$), 13.01 ($C(O)OCH_2CH_2\mathit{C}H_2CH_2OH$) ppm. MS: (CI - NH_3) *m/z*: 382 ($M+NH_4$, 15 %). Anal. Calcd for $C_{15}H_{24}O_{10}$ C, 49.45 %; H, 6.64 %. Anal Found C, 49.34 %; H, 6.48 %.

4-Hydroxybutyl 2,3,4,6-tri-*O*-acetyl-L-arabinonate [30]

(0.52 g, 1.42 mmol, 39 % yield). TLC: decomposes on silica. $[\alpha]_D^{25}$ = -16.36° (c, 1.1, $CHCl_3$). ν_{max}(neat) 3519 cm^{-1} (br, OH), 1749 cm^{-1} (C=O). ^1H NMR (400 MHz, $CDCl_3$) δ 5.57 (1 H, d, J = 6.9 Hz, H-2), 5.45 (1 H, t, J = 6.8 Hz, H-3), 4.55 (1 H, ddd, J = 6.6, 4.9, 2.9 Hz, H-4), 4.47 (1 H, dd, J = 12.6, 2.9 Hz, H-5), 4.27 (1 H, dd, J = 12.6, 4.9 Hz, H-5'), 4.23 - 4.10 (4 H, m, $C(O)OC\mathit{H_2}CH_2CH_2C\mathit{H_2}OH$), 2.18 (3 H, s, $COC\mathit{H_3}$), 2.12 (3 H, s, $COC\mathit{H_3}$), 2.11 (3 H, s, $COC\mathit{H_3}$), 1.31 - 1.23 (4 H, m, $C(O)OCH_2C\mathit{H_2}C\mathit{H_2}CH_2OH$) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 170.31, 169.84 169.52 ($\mathit{C}OCH_3$), 168.27 (C-1), 72.00 (C-2), 72.56 (C-3), 77.43 (C-4), 62.11 (C-5), 64.88 ($C(O)O\mathit{C}H_2CH_2CH_2\mathit{C}H_2OH$), 29.65 ($C(O)OCH_2CH_2\mathit{C}H_2CH_2OH$), 20.6, 21.55, 21.08 ($CO\mathit{C}H_3$), 14.39 ($C(O)OCH_2CH_2\mathit{C}H_2CH_2OH$) ppm. MS: (CI - NH_3) *m/z*: 382 ($M+NH_4$, 20 %). Anal Calcd for $C_{18}H_{28}O_{11}$ C, 51.42 %; H, 6.71 %. Anal Found C, 45.03 %; H, 6.03 %.

7.3.7. General polycondensation procedure

All reagents and reactants were dried prior to use and dissolved in dry CH_2Cl_2. A solution of the acid chloride (1 eq.) and NEt_3 (2 eq.) was added dropwise to the aldaric ester. After 20 h the reaction was quenched by washing with HCl (aq) and water. The organic layer was dried ($MgSO_4$) and concentrated to yield the polyer as a solid (average 90 % yield.) The crude polymer was analysed by SEC and NMR. It was subsequently re-precipitated from CH_2Cl_2-hexane but this failed to isolate the high molecular weight species.

7.3.8. General ring opening polymerisation procedure

LZnEt **[35]** was kindly prepared by and received from Min Tang. It was prepared according to the literature.<Williams, 2003 #177>

To a solution of LZnEt **[35]** (1.0 mL of 0.007 M solution in CH_2Cl_2 or $CHCl_3$, 7.00 μmol, 1 eq.) the aldaric ester or oligoester (0.44 mL of 0.016 M solution in CH_2Cl_2 or $CHCl_3$, 7.00 μmol,, 1 equiv) was added lactide (known volume of 0.7 M solution in CH_2Cl_2 or $CHCl_3$ depending on the desired chain length). Aliquots were taken at regular intervals, quenched with hexane, and dried *in vacuo* where the oligoesters was used. Experiments conducted with the monoesters were carried out in a Young's tap NMR tube and monomer conversion was monitored by ^1H NMR. Monomer conversion was determined from the crude copolymer sample using ^1H NMR. The copolymer was then isolated by repeated precipitation from CH_2Cl_2-hexane (isolated yield = 90%) and was analyzed by SEC and MALDI.

Characterisation of **[34]**: ^1H NMR (500 MHz, $CDCl_3$) δ 5.66 – 5.34 (6 H, m, C*H*), 5.21 – 5.18 (44 H, q, CH(C*H*$_3$)O), 5.00 – 4.97 (1 H, m, C*H*(CH$_3$)O), 4.62 – 4.11 (20 H, m, C*H*, C*H*$_2$), 2.14 – 2.08 (36 H, m, OC*H*$_3$), 1.61 – 1.55 (127 H, d, CH(C*H*$_3$)O), 1.53 – 1.45 (10 H, m, C*H*$_2$C*H*$_2$).

7.3.9. General Sn(II)Oct$_2$ oligomerisation procedure

The lactone (3.00 g) was charged to an oven-dried flask with a magnetic stirrer and dried *in vacuo* for 2 h. Sn(II)Oct$_2$ (1 equiv) and 1,4-butanediol (2 equiv) were added and the reaction mixture was stirred at 80 °C for up to 7 days. Aliquots were taken regularly and analysed by ^1H NMR. To isolate the oligomer **[33]**, the reaction was quenched at the end of 8 h by dissolving in CH_2Cl_2 and excess hexane to precipitate the product. It was subsequently purified by column chromatography (neutral alumina, CHCl$_3$ followed by MeOH) to yield the product as a white solid (1.00 g, 30%). Characterisation for **[33]**: ν_{max} (neat, cm^{-1}): 3472 (OH), 2950 (CH, CH$_2$, CH$_3$), 1744 (CO), 1436 (CH$_3$), 1371 (CH$_3$), 1222 (COC), 1046 (CH2, CCH$_3$), 905 (COO). ^{1}H NMR (500 MHz, CDCl3) δ 5.70 – 4.85 (3 H, m, H-2, H-3, H-4), 4.46 – 4.07 (6 H, m, H-6, C(O)OCH_2CH$_2$CH$_2$CH_2OH), 4.06 – 3.65 (1 H, m, H-5), 2.17 – 1.95 (15 H, m, OC(O)CH_3), 1.73 – 1.53 (4 H, m, C(O)OCH$_2$CH_2CH_2CH$_2$OH) ppm. ^{13}C{^{1}H} NMR (500 MHz, CDCl3) δ 171.82 – 167.53 (C(O)O), 73.23 – 67.96 (C-2, C-3, C-4, C-5), 65.78 – 61.47 (C-6, C(O)OCH$_2$CH$_2$CH$_2$$CH_2$OH) 29.66 – 24.93 (C(O)OCH$_2$$CH_2$$CH_2CH_2$OH), 20.85 – 20.30 ($CH_3$). MALDI (dithranol, THF, NaOTf) 1151 (3 + Na)+. SEC (THF, Polystyrene standards) 626, 946 and 1472.

7.3.10. Degradation protocol

The polymer sample (20 mg) which had previously been dried *in vacuo* was dissolved in CHCl$_3$ to form a 3 mg/mL solution. To this was added TFA(aq.)/CHCl$_3$ (2 % v/v) (0.1 mL per mL of polymer solution). Aliquots were taken on a daily basis and analysed by GPC (CHCl$_3$, polystyrene standards).

7.3.11. Functionalised 1,4-lactones

After prolonged exposure to the reaction conditions described in 7.3.9, 1,4-lactones were isolated by reprecipitation from CH$_2$Cl$_2$-hexane.

2,3,4,6-Tetra-*O*-acetyl-D-galactono-1,4-lactone [16]

ν_{max}(neat) *ca.* 1810 cm^{-1} (C=O). ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 5.60 (1 H, d, J = 7.2 Hz, H-2), 5.42 (1 H, dd, J = 7.0 Hz, H-3), 5.33 (1 H, m, H-5), 4.58 (1 H, dd, J = 6.9, 2.9 Hz, H-4), 4.33 (1 H, dd, J = 11.7, 5.4 Hz, H-6), 4.24 (1 H, dd, J = 11.7, 6.5

Hz, H-6), 2.18 (3 H, s, COC*H*$_3$), 2.12 (3 H, s, COC*H*$_3$), 2.12 (3 H, s, COC*H*$_3$), 2.08 (3 H, s, COC*H*$_3$) ppm. ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 170 - 169 (*C*O*C*H$_3$); 167.98 (C-1); 77.40 (C-4); 77.23 (C-3); 71.94 (C-2); 68.25 (C-5); 61.62 (C-6); 21 - 20 (CO*C*H$_3$) ppm. MS (CI, ammonia): m/z (%) 364 (100 %, M+NH$_4$).

2,3,4,6-Tetra-*O*-acetyl-D-mannono-1,4-lactone [17]

v_{max}(neat) *ca.* 1810 cm^{-1} (C=O). ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 5.75 (1 H, dd, J = 4.9, 3.0 Hz, H-3), 5.70 (1 H, d, J = 4.9 Hz, H-2), 5.35 (1 H, ddd, 9.5, 4.0, 2.3 Hz, H-5), 4.75 (1 H, dd, J = 3.0, 9.5 Hz, H-4), 4.63 (1 H, dd, J = 12.6, 2.3 Hz, H-6), 4.16 (1 H, dd, J = 12.6, 4.1 Hz, H-6), 2.2 - 2.1 (12 H, 4 x s, 4 x COC*H*$_3$) ppm. ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 170 - 169 (*C*O*C*H$_3$); 170.32 (C-1); 74.69 (C-4); 68.28 (C-3); 67.95 (C-2); 66.70 (C-5); 61.92 (C-6); 21 - 20 (CO*C*H$_3$) ppm. MS (CI, ammonia): m/z (%) 364 (100 %, M+NH$_4$).

2,3,4,6-Tetra-*O*-acetyl-D-glucono-1,4-lactone [18]

v_{max}(neat) *ca.* 1810 cm^{-1} (C=O). ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 5.65 (1 H, dd, J = 3.4, 5.6 Hz, H-3), 5.25 (1 H, d, J = 3.3 Hz, H-2), 5.40 - 5.35 (1 H, m, H-5), 4.98 (1 H, dd, J = 5.8, 8.0 Hz, H-4), 4.60 (1 H, dd, J = 12.4, 3.1 Hz, H-6), 4.18 (1 H, dd, J = 12.4, 4.9 Hz, H-6), 2.2 - 2.1 (12 H, 4 x s, 4 x COC*H*$_3$) ppm. ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 170 - 169 (*C*O*C*H$_3$); 170.40 (C-1); 76.694(C-4); 72.01 (C-2); 70.98 (C-3); 67.53 (C-5); 62.13 (C-6); 21 - 20 (CO*C*H$_3$) ppm. MS (CI, ammonia): m/z (%) 364 (100 %, M+NH$_4$).

7.4. References

1. Wahlera, D.; Boujarda, O.; Lefèvre, F.; Reymond, J.-L., *Tetrahedron* **2004,** 60, (3), 703-710.

2. Joseph, C. C.; Regeling, H.; Zwanenburg, B.; Chittenden, G. J. F., *Tetrahedron* **2002,** 58, 6907-6911.

3. Mitchell, S. A.; Pratt, M. R.; Hruby, V. J.; Polt, R., *J. Org. Chem.* **2001,** 66, (7), 2327-2342.

4. Nobrega, C.; Vazquez, J. T., *Tet. Asymm.* **2003,** 14, 2793-2801.

5. Grummitt, A. R.; Harding, M. M.; Anderberg, P. I.; Rodger, A., *Eur. J. Org. Chem.* **2003,** (1), 63-71.

6. Tosin, M.; Murphy, P. V., *J. Org. Chem.* **2005,** 70, (10), 4107-4117.

7. Senni, D.; Praly, J.-P., *Synth. Comm.* **1998,** 28, (3), 433-441.

8. Nelson, C. R., *Carb. Res.* **1979,** 68, (1), 55-60.

9. Somsák, L.; Papp, E.; Batta, G.; Farkas, I., *Carb. Res.* **1991,** 211, (1), 173-178.

10. Carruthers, A.; Hirst, E. L., *J. Chem. Soc.* **1922,** 121, 2299-2308.

11. Drew, J. D. K.; Goodyear, E. H.; Haworth, W. N., *J. Chem. Soc.* **1927,** 1237-1245.

APPENDIX

Tacticity in PLA[1]

Tacticity in PLA was determined using homonuclear decoupled ^{1}H NMR as described by Coates *et al.*[1] This was carried out by analysis of the methyne region of the polymer's homonuclear decoupled ^{1}H NMR. This region shows 5 tetrads whose intensities are related to the probability of a syndiotactic enchainment (P_s) and that of an isotactic enchainment (P_i). An example of such an NMR is given in Figure App.1.

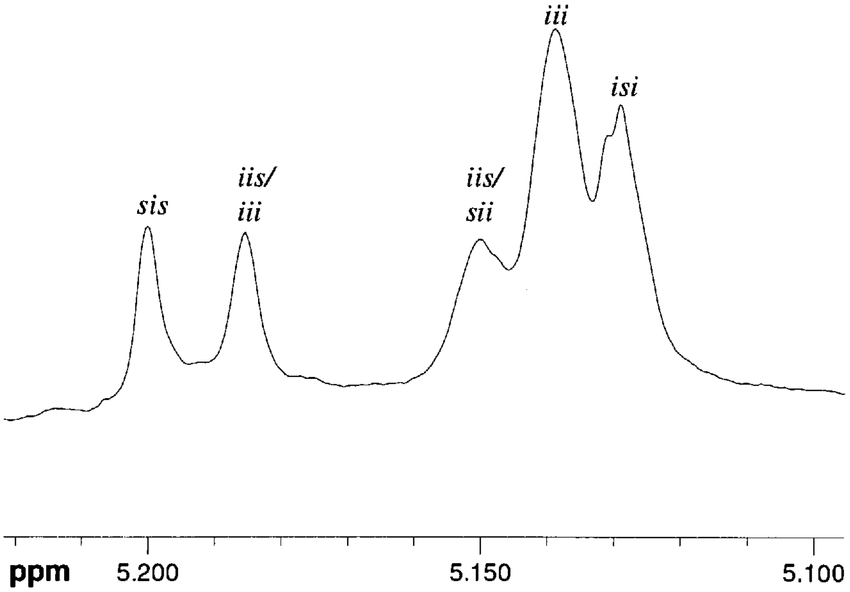

Figure App.1 - Homonuclear decoupled ^{1}H NMR spectrum of poly(lactide) initiated by [23] (methyne region, $CDCl_3$, 400 MHz)

The first indication that tacticity control was not observed is the presence of 5 tetrad sequences in this NMR. The relationship between these intensities and probabilities is given in **Table App. 1**.

Table App. 1 - *rac*- Lactide tetrad probabilities based on Bernoullian statistics[1]

Tetrad	Probability
[*iii*]	$P_i^2 + P_sP_i/2$
[*iis*]	$P_sP_i/2$
[*sii*]	$P_sP_i/2$
[*sis*]	$P_s^2/2$
[*isi*]	$(P_s^2 + P_sP_i)/2$

P_s = probability of a syndiotactic linkage between monomer units

P_i = probability of an isotactic linkage between monomer units

$P_s + P_i = 1$

Given that $P_s + P_i = 1$, the probability associated with the [*sis*] tetrad can be rearranged to; $P_s = \sqrt{2[sis]}$. P_s was hence determined by normalising the methyne region of the spectrum in Figure App.1 and evaluating the intensity associated with the [*sis*] tetrad. This tetrad was chosen as it is clearly defined in the spectrum. However, this procedure could be applied to the other tetrads. The magnitude of the either P_s or P_i indicates the bias towards syndiotactic and isotactic enchainment respectively. A probability of 0.5, which was observed in this research, suggests that tacticity was controlled.

Publications arisen from the work described in this thesis

a) Haider, A. F.; Williams, C. K., *J. Polym Sci Part A: Polym Chem* **2008,** 46, (8), 2891-2896.

b) Haider, A. F.; Williams, C. K., *J. Carb. Chem.* **2007,** 26, (7-9), 411-418.

c) Tang, M.; Haider, A. F.; Minelli, C.; Stevens, M. M.; Williams, C. K., *J. Polym Sci Part A: Polym Chem* **2008,** 46, (13), 4352-4362.

References

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1. Chamberlain, B.M., Cheng, M., Moore, D.R., Ovitt, T.M., Lobkovsky, E.B., and Coates, G.W., *J. Am. Chem. Soc.*, 123, 14, 3229 - 3238, 2001

NOTE

Synthesis of Highly Functionalized Oligo- and Copolyesters from a Carbohydrate Lactone

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INTRODUCTION

The use of biomass as a feedstock material for polymer synthesis is attracting attention because of concerns associated with the cost, supply, environmental footprint, and biocompatibility of petrochemicals.[1] One of the most successful bio-derived polymers is polylactide, a degradable polyester manufactured from corn or sugar beet on a large scale in United States and on a smaller scale elsewhere.[2] It is applied as a degradable and renewable material in packaging, tissue engineering matrices, drug delivery excipients and implants. A significant limitation of PLA is its lack of chemical functionality and its hydrophobicity, which results in slow degradation.[3] We are investigating methods to increase its hydrophilicity and/or synthesize new functionalized aliphatic polyesters from renewable resources. Therefore, carbohydrates are attractive as they are highly functionalized renewable monomers. Carbohydrates are also abundant being the major constituent of terrestrial biomass and relatively inexpensive, illustrated by D-glucose production at 5 million metric tonnes per annum and a cost of $\$0.76\ \mathrm{kg}^{-1}$ which compares with methyl methacrylate production at 2.1 million tonnes per annum and a cost of $\$1.32\ \mathrm{kg}^{-1}$.[4] Previously carbohydrate derived polyesters have been synthesized by condensation polymerizations of alditols and/or aldaric acids using lipase catalysis or protected alditols and activated aldaric esters or acyl chlorides.[5–9] The ring opening polymerization of carbohydrate functionalized lactones has been limited to 1,4-dioxane-2,5-diones substituted at position 3 with protected D-gluconic acids, tetra-*O*-methy-D-glucono-1,6-lactone, and cyclic carbonate monomers derived from D-xylose.[10–12] Furthermore, the lactone syntheses are lengthy and of moderate yield. Carbohydrate 1,5-lactones, on the other hand, are synthesized in quantitative yield by the oxidation of glycosides and are attractive monomers which have received very little attention. The only reports are restricted to an observation by Haworth and Drew, in 1927, that tri-*O*-methyl-D-arabonolactone solidified to a crystalline "polymeride" in the presence of acid, and a patent from Minami and Shinya, at Canon in 2002, claiming the polymerization of D-glucono-1,5-lactones.[13,14] In both reports the experimental details and characterization are extremely limited.

EXPERIMENTAL

Methods

[*R*,*S*]-Lactide was donated by Purac Plc, it was purified by recrystalization from hot toluene followed by repeated sublimations *in vacuo* (3 times). Stannous octanoate, Sn(Oct)$_2$, and 1,4-butanediol were purchased

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from Aldrich and used as received. Tetra-*O*-acetyl-D-glucono-1,5-lactone was prepared according to the literature and used without further purification.[15] The zinc ethyl complex (LZnEt, L = 2,4-di-*tert*-butyl-6-{[(2′-dimethylaminoethyl)methylamino]methyl}phenolate, Fig. S1) was prepared and used according to the literature.[16] Methylene chloride was dried by distillation from calcium hydride. Glassware used for polymerizations was treated with a silanizing agent (Me_2SiCl_2 in CH_2Cl_2, 1 M) and dried for 4 h before use. All manipulations were carried out using standard anaerobic techniques under a dry nitrogen atmosphere or in an MBraun nitrogen filled glove box.

Measurements

NMR spectra collected at 400 MHz were performed on a Bruker AV400 instrument. NMR spectra collected at 500 MHz, as well as $^{13}C\{^1H\}$ NMR, were carried out on a Bruker AV500 instrument. $CDCl_3$ was used as the NMR solvent and reference compound. The GPC measurements were performed on a Polymer labs GPC 60 instrument with two Polymer laboratories mixed D columns and using $CHCl_3$ or THF, at a flow rate of 1 mL min^{-1}, as the eluent. Narrow molecular weight polystyrene standards were used to calibrate the instrument and a correction factor of 0.58 was applied to the M_n according to the literature.[17] The MALDI-TOF mass spectrometry was performed with a Micromass MALDI micro MX mass spectrometer equipped with a UV (337 nm) laser. All mass spectra recorded in linear mode. An average of 40 spectra was collected from random positions on the target, each spectrum averaged from 10 laser shots. 1.2 μL of a mixture of the matrix (dithranol, 30 mg/mL in THF), cationizing agent ($NaCO_2CF_3$, 10 mg/mL in THF), and the sample ($\sim$10 mg/mL in CH_2Cl_2) in the ratio 3:1:1, respectively, was applied to the target and air-dried immediately before use.

Oligomer/Polymer Syntheses

4-Hydroxybutyl 2,3,4,6-tetra-O-acetyl-D-gluconate 1

1,4-Butanediol (0.90 mL of a 1.0 M solution in $CHCl_3$), 0.90 mmol, 1.0 equiv) was diluted in $CHCl_3$ (15 mL), and *p*-toluenesulfonic acid monohydrate (0.02 g, 0.09 mmol, 0.1 equiv) was added and stirred for 15 min. Tetra-*O*-acetyl-D-glucono-1,5-lactone (0.30 g, 0.88 mmol, 1.0 equiv) was then added and the solution stirred for 3 h. It was neutralized (IRA 400, HCO_3^- form) and concentrated to yield the title compound as a colorless syrup (0.37 g, 0.89 mmol, 95%).

TLC R_f 0.43 (EtOAc:Hexane 1:1). $[\alpha]_D^{25} = +45.2\,°$ (c, 1.15, $CHCl_3$). ν_{max}(neat) 3485 cm^{-1} (OH), 1738 cm^{-1} (C=O). ^1H NMR (400 MHz, $CDCl_3$) δ 5.74 (1 H, m, H-3), 5.29 (1 H, m, H-2), 5.20 (1 H, dd, J = 8.3, 3.6 Hz, H-4), 4.22–4.12 (6 H, m, J = 14.3, 7.2 Hz, $\mathrm{C(O)O}\mathit{CH_2}\mathrm{CH_2CH_2}\mathit{CH_2}\mathrm{OH}$, H-6), 3.84 (1 H, m, H-5), 3.01 (1 H, d, J = 5 Hz, OH), 2.16 (3 H, s, $\mathrm{CO}\mathit{CH_3}$), 2.14 (3 H, s, $\mathrm{CO}\mathit{CH_3}$), 2.10 (6 H, s, 2 x $\mathrm{CO}\mathit{CH_3}$), 1.27 (4 H, m, $\mathrm{C(O)OCH_2}\mathit{CH_2CH_2}\mathrm{CH_2OH}$) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 171.15, 170.58, 169.76, 166.76 ($\mathit{C}\mathrm{OCH_3}$, C-1), 71.81 (C-2), 70.56 (C-4), 69.50 (C-3), 68.41 (C-5), 64.65, 62.16 ($\mathrm{C(O)O}\mathit{C}\mathrm{H_2CH_2CH_2}\mathit{C}\mathrm{H_2OH}$, C-6), 20.78, 20.58, 20.47 ($\mathrm{CO}\mathit{C}\mathrm{H_3}$), 14.00 ($\mathrm{C(O)OCH_2}\mathit{C}\mathrm{H_2}\mathit{C}\mathrm{H_2CH_2OH}$) ppm. MS: (CI-$NH_3$) *m/z*: 454 ($M+NH_4$, 25%). Anal Calcd. for $C_{18}H_{28}O_{12}$: C, 49.54%; H, 6.47%. Anal Found: C, 49.62%; H, 6.38%.

α-4-Hydroxybutyl-ω-hydroxyl-oligo(2,3,4,6-tetra-O-acetyl-D-gluconate) 1,2,3

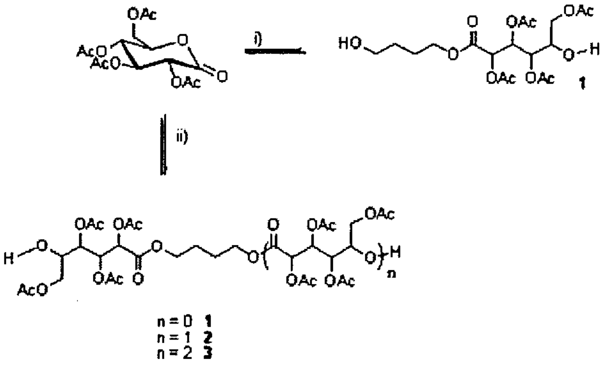
Tetra-*O*-acetyl-D-glucono-1,5-lactone (3.00 g, 8.70 mmol, 6 equiv) was charged to an oven-dried flask with a magnetic stirrer and dried *in vacuo* for 2 h. $Sn(Oct)_2$ (0.50 mL, 1.50 mmol, 1 equiv) and 1,4-butanediol (0.30 mL, 3.40 mmol, 2 equiv) were added and the reaction mixture was stirred at 80 °C for 8 h. The resulting oligomer was dissolved in CH_2Cl_2 and excess hexane was used to precipitate the product. It was subsequently purified by column chromatography (neutral alumina, $CHCl_3$ followed by MeOH) to yield the product as a white solid (1.00 g, 30%).

ν_{max} (neat, cm^{-1}): 3472 (OH), 2950 (CH, CH_2, CH_3), 1744 (CO), 1436 (CH_3), 1371 (CH_3), 1222 (COC), 1046 (CH_2, CCH_3), 905 (COO). ^1H NMR (500 MHz, $CDCl_3$) δ ppm 5.70–4.85 (3H, m, H-2, H-3, H-4), 4.46–4.07 (6H, m, H-6, $\mathrm{C(O)O}\mathit{CH_2}\mathrm{CH_2CH_2}\mathit{CH_2}\mathrm{OH}$), 4.06–3.65 (1H, m, H-5), 2.17–1.95 (15 H, m, $\mathrm{OC(O)C}\mathit{H_3}$), 1.73–1.53 (4H, m, $\mathrm{C(O)OCH_2}\mathit{CH_2CH_2}\mathrm{CH_2OH}$). $^{13}C\{^1H\}$ NMR (500 MHz, $CDCl_3$) δ ppm 171.82–167.53 ($\mathit{C}\mathrm{(O)O}$), 73.23–67.96 (C-2, C-3, C-4, C-5), 65.78–61.47 (C-6, $\mathrm{C(O)O}\mathit{C}\mathrm{H_2CH_2CH_2}\mathit{C}\mathrm{H_2OH}$) 29.66–24.93 ($\mathrm{C(O)OCH_2}\mathit{C}\mathrm{H_2}\mathit{C}\mathrm{H_2CH_2OH}$), 20.85–20.30 ($\mathit{C}\mathrm{H_3}$). MALDI (dithranol, THF, NaOTf) 1151 (3 + Na)$^+$. SEC (THF, Polystyrene standards) 626, 946 and 1472.

α-Hydroxyl-ω-hydroxyl polylactide-block-*oligo(2,3,4,6-tetra-O-acetyl-D-gluconate)-block-polylactide*

To a solution of LZnEt (1.0 mL of 0.007 M solution in CH_2Cl_2, 7.00 μmol, 1 equiv) and α-4-hydroxybutyl-ω-hydroxyl-oligo(2,3,4,6-tetra-*O*-acetyl-D-gluconate) (0.44 mL of 0.016 M solution in CH_2Cl_2, 7.00 μmol, 1 equiv), was added [*R,S*]-lactide (0.25 mL of 0.7 M solution in CH_2Cl_2, 0.35 mmol, 25 equiv). Aliquots were taken at regular intervals, quenched with hexane, and dried *in vacuo*. Monomer conversion was determined from the crude copolymer sample using ^1H NMR (see Fig. S6). The copolymer was then isolated by repeated precipitation from CH_2Cl_2-hexane (isolated yield = 90%) and was analyzed by SEC (Fig. S7) and MALDI. The representative ^1H NMR spectrum for an initiator:monomer ratio of 1:25 at 97% conversion is presented. By ^1H NMR the degree of polymerization was 23, in good agreement with the expected value.

^1H NMR (500 MHz, $CDCl_3$) δ ppm: 5.66–5.34 (6H, m, CH), 5.21–5.18 (44H, q, $\mathit{CH}\mathrm{(CH_3)O}$), 5.00–4.97 (1H, m, $\mathit{CH}\mathrm{(CH_3)O}$), 4.62–4.11 (20H, m, CH, $\mathit{CH_2}$),



Scheme 1. Synthesis of a novel oligoester (**1**, **2**, **3**) and copolyesters from tetra-*O*-acetyl-D-gluconolactone, (**1**). Reagents and conditions: (i) TsOH, 1,4-butanediol, r.t, 3 h, 95%. (ii) Sn(Oct)$_2$ (0.17 equiv), 1,4-butanediol (0.3 equiv), neat, 80 °C, 8 h, 80%.

2.14–2.08 (36H, m, OCH_3), 1.61–1.55 (127H, d, CH(CH_3)O), 1.53–1.45 (10H, m, CH_2CH_2).

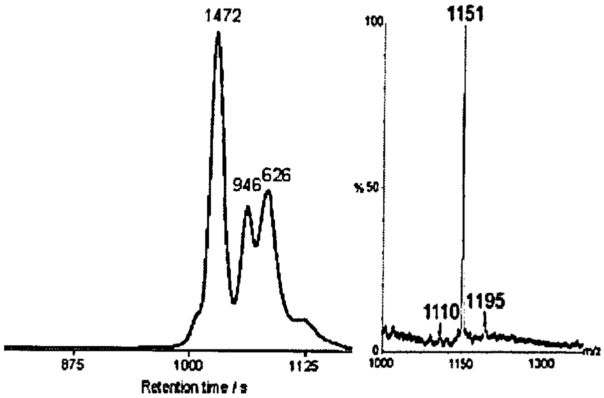


Figure 1. SEC signals and MALDI mass spectrum for **2**. The SEC was determined using THF as the eluent and calibrated using narrow M_n polystyrene standards. In the SEC trace the peaks are labeled with the M_n (vs. polystyrene)—that is, 1472, 946, and 626, respectively. The MALDI mass spectrum was determined using a dithranol matrix dissolved in THF with NaOTf as the cationizing agent.

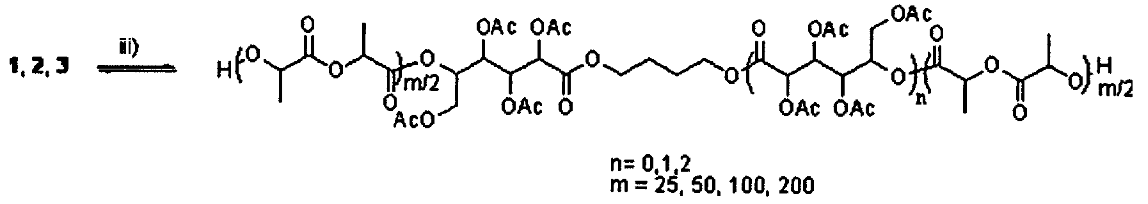
RESULTS AND DISCUSSION

Ring Opening of Tetra-*O*-acetyl-D-glucono-1,5-lactone

The ring opening of a carbohydrate derived 1,5-lactone with 1,4-butanediol yielded either a well-defined mono aldaric ester (**1**) or an oligomer comprising mono-, di-, and tri aldaric ester groups (**1**, **2**, **3**), depending on the reaction conditions (Scheme 1). These novel aldaric esters were used as bifunctional initiators for controlled lactide polymerization (Scheme 2).

The lactone monomer, tetra-*O*-acetyl-D-glucono-1,5-lactone, was synthesized in a single step by the acetylation of commercially available D-glucono-1,5-lactone and isolated in 90% yield as a sticky oil with good analytical purity.[15] The ring opening of carbohydrate 1,5-lactones with alcohols have scarcely been examined.[15] Therefore, we investigated the stoichiometric reaction between the lactone and acidified 1,4-butanediol which yielded a novel aldaric ester, 4-hydroxybutyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate, **1** isolated in 95% yield. Its ^{1}H and ^{13}C{^{1}H} NMR spectra (Figs. S2, S3) confirmed the structure, the integrals for the backbone carbohydrate protons, at 5.70, 5.29, 5.20 ppm, versus the methylene protons of the end group, at 4.18 and 1.27 ppm, respectively, were as expected for ring opening occurring at only one of the two 1,4-butanediol hydroxyl groups. Further confirmation of the structure was provided by the mass spectrum and the elemental analysis results which matched the calculated values.

Having established that the lactone could be opened by stoichiometric reaction with an alcohol, we next investigated whether it could be oligomerized/polymerized by a metal alkoxide initiator. Stannous octanoate (Sn(Oct)$_2$) and alcohol, including diol, initiating systems have been widely studied for polymerization of other lactones, for example, lactide or ε-caprolactone, and are attractive due to their tolerance of functionality, high activity, and ease of use.[18] Tetra-*O*-acetyl-D-gluconolactone reacted with 1,4-butanediol and Sn(Oct)$_2$, at 80 °C, to produce a low M_n oligoester, in 8 h. The oligoester was isolated by column chromatography, which removed the initiator residues but resulted in some decomposition, in 30% yield. The oligoester comprised a mixture of compound **1** and dialdaric ester, **2**, and trialdaric ester, **3** as established



Scheme 2. The oligoester as a macroinitiator for [*R*,*S*]-lactide polymerization. Reagents and conditions: m [*R*,*S*]-lactide, LZnEt (L = 2,4-di-*tert*-butyl-6-{[(2′-dimethylaminoethyl)methylamino]methyl}phenolate, Figure S1 illustrates the structure of LZnEt), CH$_2$Cl$_2$, room temperature, 20 h.

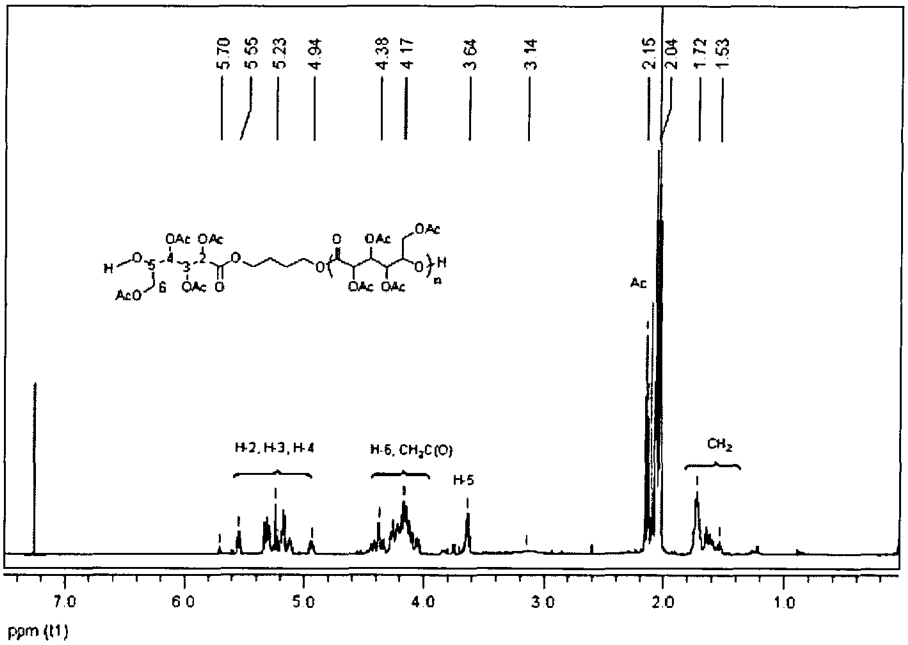


Figure 2. ^1H NMR spectrum of the oligoester (**1**, **2**, **3**).

by SEC (Scheme 1, Fig. 1). The SEC showed signals for **1**, **2**, and **3** corresponding to M_n (vs. polystyrene) of 1472, 946, and 626 (Fig. 1). The MALDI mass spectrum showed a single peak consistent with a sodium cationized trimer, [**3**+Na$^+$], at 1151 (Fig. 1). There was no evidence for formation of cyclic lactones, carboxylic acid terminated chains, or octanoic ester end groups—highlighting the utility of this novel reaction for selective oligoester synthesis.

The oligomerization was also monitored by ^1H NMR spectroscopy, where loss of the well resolved signals due to **1** and the growth of broadened resonances were observed. The reaction was judged to have gone to completion when the signal due to the H-3 protons at 5.44 ppm in **1** disappeared. The ^1H NMR spectrum of the oligomer (Fig. 2) showed multiplets for the carbohydrate methyne protons (H-2, H-3, H-4) at 5.70–4.94 ppm and 3.64 ppm (H-5). The methylene groups, H-6, and the butanediyl protons attached to ester and hydroxyl groups, gave a multiplet between 4.38 and 4.17 ppm. The acetyl methyl groups showed multiple peaks between 2.15 and 2.04 ppm and the butanediyl methylene groups resonated at 1.72–1.53 ppm. Although the hydroxyl end groups were not clearly observed, the broadened peak at 3.14 ppm is tentatively assigned to a hydroxyl moiety. The $^{13}C\{^1H\}$ NMR spectrum (Fig. S4) showed multiple peaks but in the correct regions for a mixture of compound **1**, **2**, and **3**.

The IR spectrum of the oligoester (Fig. S5) showed a resonance at 1744 cm^{-1} for the carbonyl groups which was at a lower frequency than the carbonyl resonances of tetra-*O*-acetyl-D-glucono-1,5-lactone at

Table 1. Copolyesters Produced Using the Macroinitiator **2** for Lactide Polymerization

Degree of Polymerization (DP)[a]	M_n Calc.[b]	M_n NMR[c]	M_n SEC[d] (PDI)
16	2,700	2,900	2,200 (1.08)
29	4,600	4,000	2,500 (1.16)
71	11,000	8,600	7,800 (1.22)
104	15,400	15,800	13,600 (1.06)
165	24,200	18,800	26,000 (1.05)

[a] Determined by normalization of the integrals for the CH resonances in lactide (5.00 ppm) and polylactide (5.20 ppm).

[b] M_n calc = (144 × DP) + 436.

[c] Determined by integration of the CH signal in polylactide (5.20 ppm) versus the acetyl signal in the oligoester (2.10 ppm).

[d] Determined by SEC, using polystyrene standards to calibrate the instrument and with a correction factor of 0.58.[16]

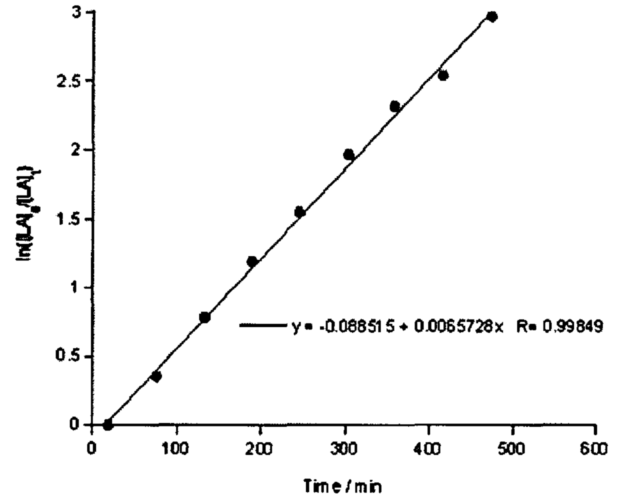


Figure 3. Plot of ln{[LA]$_0$/[LA]$_t$} versus time for the polymerization of lactide. Polymerization conditions: [LA]$_0$ = 0.7 M, [oligoester]$_0$ = 0.028 M, CD_2Cl_2, room temperature.

1760 cm^{-1}, consistent with a slight reduction in ring strain. In addition, there was a very broadened resonance at 3472 cm^{-1} assigned to the hydroxyl end groups and an increase in the intensity of the resonance at 2950 cm^{-1} because of the methylene groups in the 1,4-butanediol end group.

The loading of Sn(Oct)$_2$ and 1,4-butanediol was an important factor; a loading of 3:1:0.5 for lactone:1,4-butanediol:Sn(Oct)$_2$ yielded quantitative conversion to the series of oligomers. The use of lower diol and metal loadings led to the same product distributions, as determined by SEC, but in reduced yield with significant quantities of **1** being unreacted. The chain length is presumably limited by the four acetyl groups attached to the backbone, which stabilize the ring conformation.[19] The reaction mechanism could be either a coordination-insertion ring-opening oligomerization or a Sn(Oct)$_2$ catalyzed transesterification.[20] Other common ring-opening polymerization initiators of increased Lewis acidity, for example, Al(O^{i}Pr)$_3$ and a well defined zinc alkoxide complex, LZnOEt (Fig. S1), did not open the lactone but rather catalyzed the formation of a known α,β-unsaturated lactone.[21]

Lactide Polymerization

The novel esters **1**, **2**, **3** were interesting products in their own right but the two hydroxyl end groups were also used as macroinitiators for [*R*,*S*]-lactide polymerization (Scheme 2).

The copolymerization with [*R*,*S*]-lactide was investigated using an alkyl zinc initiator (LZnEt, Fig. S1) that had previously shown good precedence for high activity and control for lactide polymerization using ethanol or benzyl alcohol.[16] Thus, the oligoester (**1**, **2**, **3**) was added to a solution of LZnEt and [*R*,*S*]-lactide and aliquots were regularly withdrawn to monitor the reaction's conversion and the polymer's M_n. The oligoesters were successful macroinitiators and enabled the synthesis of triblock ABA copolymers comprising lactide

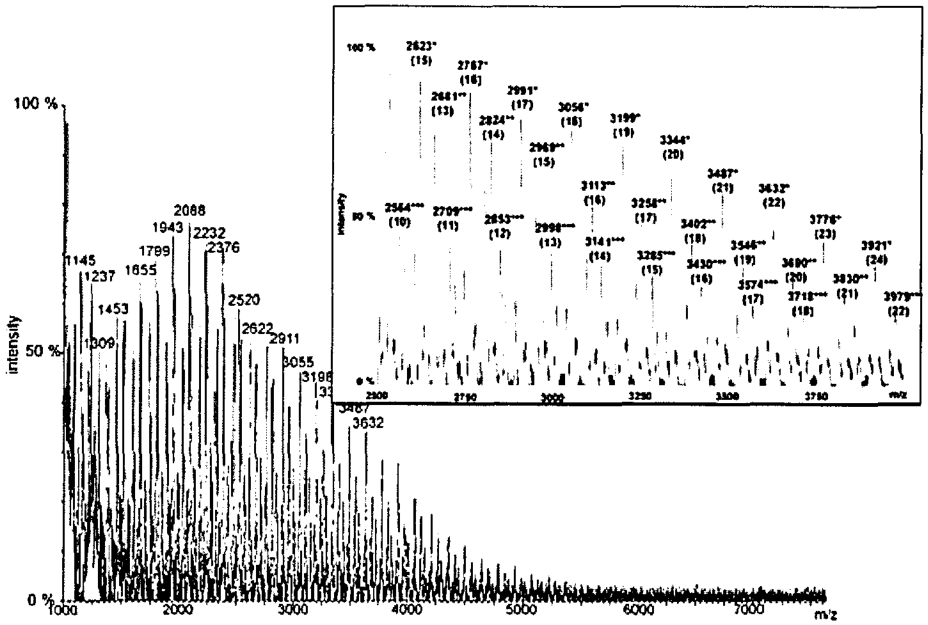


Figure 4. MALDI spectrum of the copolyester **2** with a loading of monomer:macroinitiator of 25:1. The peaks corresponding to monoester, diester, and triester end groups are marked with *, **, and ***, respectively, and for each series the degrees of polymerization are shown in parentheses.

blocks of chain length from 12 to 250 repeat units and oligoester blocks of up to three repeat units. The copolymers' M_n were determined by SEC (vs. polystyrene standards) and by end group analysis from the ^{1}H NMR spectrum (Table 1, Fig. S6). Integration of the polylactide methyne protons' signal at 5.20 ppm versus the oligomer acetyl methyls' signal at 2.07 ppm provided an estimation of the M_n. The M_n from NMR, SEC, and the calculated M_n from the DP were in excellent agreement, thus for a DP of 16, the M_n determined by ^{1}H NMR was 2900, by SEC was 2200, and the calculated value was of 2700. The polymerization was, therefore, well controlled, further reinforced by the narrow PDI values (1.05–1.22) for the copolymers.

The polymerization kinetics were monitored *in situ* by ^{1}H NMR spectroscopy and the plot of $\ln\{[LA]_0/[LA]_t\}$ is shown in Figure 3. The plot shows a linear fit, consistent with a well-controlled polymerization. The pseudo first order rate constant, k_{app}, (the gradient of the linear fit) is 6.57×10^{-3} min^{-1} which compares well with other lactide polymerization initiators.[16,18] There is an initiation time of ~14 min; it is proposed that this is required for the zinc alkoxide initiator to form by the reaction between the oligoester hydroxyl groups and LZnEt. The initiation was studied by the stoichiometric reaction between the oligoester and LZnEt, using ^{1}H NMR spectroscopy, and a diminution of the zinc ethyl peak at 0.42 ppm was observed, consistent with the formation of LZnOR, and the liberation of ethane.

The sodium cationized MALDI mass spectrum for the copolymer, with DP of 25, is shown in Figure 4. There are three series, each containing peaks separated by 144 units (corresponding to the lactide repeat unit) and separated from one another by 346 units (corresponding to the 2,3,4,6-tetra-*O*-acetyl-D-gluconate repeat unit). These series of peaks are assigned to the different oligoester initiators, for example, mono-(*), di (**), and triester (***) initiating groups. The relative intensity of the series by MALDI is mono > di > tri, however this is likely due to the improved ionization of the monoester compared with the triester. There was no evidence for lactide polymerization initiated by other groups, for example, water, 1,4-butanediol or for the formation of cyclic products.

In conclusion, the reaction of an easily accessible sugar lactone, derived from renewable resources, with $Sn(Oct)_2$ and 1,4-butandiol provided a viable route to a novel highly functionalized oligoester. It was a macroinitiator for the controlled [*R*,*S*]-lactide ring-opening polymerization, producing ABA type copolymers. Currently, detailed studies of the physical properties, degradation behavior, and medical applications for these novel polyesters are underway and will be reported in due course.

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REFERENCES AND NOTES

1. Ragauskas, A. J.; Williams, C. K.; Davison, B. H.; Britovsek, G.; Cairney, J.; Eckert, C. A.; Fredrick, W. J., Jr.; Hallett, J. P.; Leak, D. J.; Liotta, C. L.; Mielenz, J. R.; Murphy, R.; Templer, R.; Tschaplinski, T. Science 2006, 311, 484–489.
2. http://www.cargilldow.com, http://www.hycail.com, http://www.mitsui-chem.co.jp/e/index.htm
3. Lunt, J. Polym Degrad Stab 1998, 59, 142–152.
4. Lichtenthaler, F. W. Acc Chem Res 2002, 35, 728–737.
5. Kumar, A.; Kulshrestha, A. S.; Gao, W.; Gross, R. A. Macromolecules 2003, 36, 8219–8221.
6. Fu, H. Y.; Kulshrestha, A. S.; Gao, W.; Gross, R. A.; Baiardo, M.; Scandola, M. Macromolecules 2003, 36, 9804–9808.
7. Hu, J.; Gao, W.; Kulshrestha, A.; Gross, R. A. Macromolecules 2006, 39, 6789–6792.
8. Alla, A.; Hakkou, K.; Zamora, F.; de Ilarduya, A. M.; Galbis, J. A.; Muñoz-Guerra, S. Macromolecules 2006, 39, 1410–1416.
9. Metzke, M.; Bai, J. Z.; Guan, Z. J Am Chem Soc 2003, 125, 7760–7761.
10. Marcincinova-Benabdillah, K.; Boustta, M.; Coudane, J.; Vert, M. Biomacromolecules 2001, 2, 1279–1284.
11. Kumar, R.; Gao, W.; Gross, R. A. Macromolecules 2002, 35, 6835–6844.
12. Pinilla, I. M.; Martinez, M. B.; Galbis, J. A. Carbohydr Res 2003, 338, 549–555.
13. Drew, H. D. K.; Haworth, W. N. J Chem Soc 1927, 775–779.
14. Minami, M.; Shinya, K. Eur Patent 2001-128072, 20011126, 1211274 (2002).
15. Joseph, C. C.; Regeling, H.; Zwanenberg, B.; Chittenden, G. J. F. Tetrahedron 2002, 58, 6907–6911.
16. Williams, C. K.; Breyfogle, L. E.; Choi, S. K.; Nam, W. W.; Young, V. G., Jr.; Hillmyer, M. A.; Tolman, W. B. J Am Chem Soc 2003, 123, 11350–11359.
17. Kowalski, A.; Duda, A.; Penczek, S. Macromolecules 1998, 31, 2114–2122.
18. Cabaret, O. D.; Vaca, B. M.; Bourissou, D. Chem Rev 2004, 104, 6147–6176.
19. Carothers, W. H.; Dorough, G. L.; Van Natta, F. J. J Am Chem Soc 1932, 54, 761–772.
20. The transesterification mechanism could operate if adventitious water opened the lactone ring to yield the gluconic acid. Detailed mechanistic studies are currently in progress and will be reported in due course.
21. Nelson, C. R.; Gratzl, J. S. Carbohydr Res 1978, 60, 267–273.

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Application of Dichlorovinyl Xyloside for the Novel Synthesis of 2,3,4-Tri-O-methyl-D-xylono-1,5-lactone

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A novel synthesis of 2,3,4-tri-*O*-methyl-D-xylopyranose, **4**, and its oxidation product 2,3,4-tri-*O*-methyl-D-xylono-1,5-lactone, **5**, are reported. The new synthesis applies a regioselective Wittig-like reaction of tetra-O-acetyl-D-xylopyranase, **1**, with triphenylphosphine and carbon tetrachloride to yield an *O*-dichlorovinyl xyloside protected at C-1, **2**. The protecting group facilitates the permethylation of xylose and is removed under the methylation conditions, to yield tetra-O-acetyl-D-xylopyranase, **3**. The anomeric methyl group was removed under mildly acidic conditions to give 2,3,4-tri-*O*-methyl-D-xylopyranose, **4**, in good yield. Compound **4** was oxidized using pyridinium chlorochromate to give the title compound, **5**, in 95% yield.

Keywords Carbohydrates, Protecting groups, Wittig reactions, Lactones, Oxidations

INTRODUCTION

Carbohydrates are important in many biological processes and structures. They regulate intercellular interactions and play essential roles in cell–cell, cell–pathogen, and cell-signaling events. Their use in therapeutics or as model compounds to study biological processes is attracting much attention. Carbohydrates are also abundant and inexpensive renewable resources but have received much less attention as alternative reagents to petrochemicals, for example, in polymer synthesis. As an example of their potential, it is noteworthy that glucose is produced at 5 million metric tons per annum and at a cost of $\$0.76\,\mathrm{kg}^{-1}$, which compares with methyl methacrylate production at 2.1 million tons per annum and a cost of $\$1.32\,\mathrm{kg}^{-1}$.[1,2] Two major challenges

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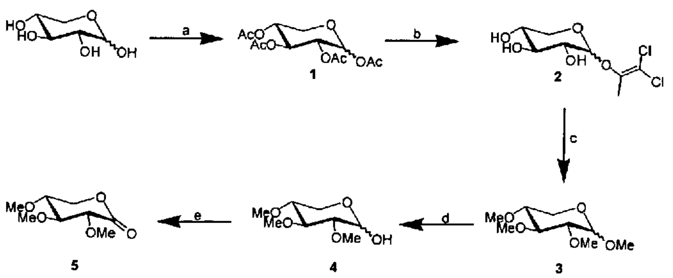
for polymer applications are the development of efficient and selective protection strategies for the hydroxyl functionalities and the selection of a monomer class that will undergo general, high-yielding polymerizations. Carbohydrate δ-lactones are attractive precursors due to the reactivity of the lactone, for example, in selective ring-opening reactions, although to date they have received limited attention as monomers themselves.[3,4] Galbis and coworkers have carried out extensive investigations using carbohydrate-derived diacids, diols, and diamines to make condensation polyamides, polyesters, and polycarbonates.[5–11] Their syntheses sometimes use carbohydrate δ-lactones as starting materials in the diacid or diamine synthesis.[12,13] Fleet et al. have also recently reported a number of routes starting from δ- and γ-lactones to make tetrahydroxylated 6-amino hexanoic acids or 4-aminomethyl-tetrahydrofuran-2-carboxylates, which were subsequently transformed into well-defined oligoamides.[14–16] We are researching the synthesis of aliphatic polyesters directly from carbohydrate-derived lactones.[17] Therefore, the efficient, selective, and scaleable synthesis of hydroxyl-protected carbohydrate 1,5-lactones is required; herein we present a novel synthesis of 2,3,4-tri-*O*-methyl-D-xylono-1,5-lactone and full analytical data.

RESULTS AND DISCUSSION

The synthesis of 2,3,4-tri-*O*-methyl-D-xylonolactone has been known since the 1920s when both the δ- and γ-lactones were prepared as part of studies to elucidate the structure of carbohydrates.[18,19] As part of these studies, Haworth reported the first synthesis by bromine oxidation of 2,3,4-tri-*O*-methyl-D-xylose. Although the yield for the oxidation was excellent, the method to prepare the xylose precursors was low yielding and inefficient.[20] Furthermore, the analytical data presented were limited to specific rotations and melting points. Galbis has reported an alternative synthesis from benzyl-α-D-xylopyranoside, by methylation, selective hydrogenolysis, and oxidation, producing the title compound in excellent yield.[13] However, the synthesis of benzyl-α-D-xylopyranoside itself is low yielding.[21] The alternative synthetic scheme applied here is outlined in Scheme 1 and takes advantage of a protecting group recently identified by Cleophax et al. for selective anomeric protection of hexoses.[22]

Tetra-*O*-acetyl-D-xylopyranose 1 was prepared according to the literature procedure by reaction of D-xylose with acetic anhydride and a catalytic quantity of trifluoroacetic acid.[23] The second step involved a Wittig-type condensation between the anomeric acetyl group of 1 and carbon tetrachloride to yield an *O*-dichlorovinylxylopyranoside. This reaction has been previously used by Cleophax et al. to prepare 2,3,4,6-tetra-*O*-benzyl-glycopyranosides.[22] The condensation was highly regioselective, and only occurred at the anomeric acetyl group. The 1-*O*-dichlorovinyl-2,3,4-tri-*O*-acetyl-D-xylopyranoside was



Scheme 1: Synthesis of 2,3,4-tri-O-methyl-D-xylono-1,5-lactone Reagents and conditions: (a) CF_3CO_2H, $(CH_3CO)_2O$, 20 h, 25°C, 100%; (b) (i) 3 KCl, CCl_4, py, 1 h, 90°C; (ii) NaOMe, MeOH, 2 h, 25°C, (i) and (ii) 50%; (c) NaH, MeI, DMF, 4 h, 0°C, 60%; (d) CF_3CO_2H (aq), 4 h, 65°C, 65%; (e) PCC, CH_2Cl_2, 12 h, 50°C, 95%.

not isolated but was reacted in situ under the Zemplen deacetylation conditions, with sodium methoxide in methanol, to yield 1-*O*-dichlorovinyl-D-xylopyranose **2** in 50% yield as a mixture of anomers. The compound showed elemental analysis in good agreement with calculated values and an isotope distribution pattern for the molecular ion consistent with two chlorides being present. Furthermore, the ^{13}C {1H} NMR spectrum showed characteristic signals at 148, 104, and 14 ppm, indicative of the *O*-dichlorovinyl group. Compound **2** was methylated by reaction with sodium hydride in DMF, followed by the addition of methyl iodide, and this produced tetra-*O*-methyl-D-xylopyranose **3** in 60% yield and as a mixture of anomers. Compound **3** showed analytical values in agreement with the literature,[20] its ^1H and $^{13}C\{^1H\}$ NMR spectra were also fully assigned. The removal of the anomeric methyl group was accomplished in improved yield by heating **3** with trifluoroacetic acid for 4 h to produce 2,3,4-tri-*O*-methyl-D-xylopyranose **4** in 66% yield, as a mixture of anomers. Compound **4** showed analytical values in agreement with the literature,[20] and was further characterized using NMR spectroscopy, mass spectrometry, and elemental analysis. The route to **4** was accomplished in straightforward steps and in 20% overall yield from D-xylose. The route is an improvement over alternative permethylation and selective anomeric *O*-methyl hydrolysis routes, which only yielded **4** in 10% from D-xylose.[20] Compound **4** was oxidized to 2,3,4-tri-*O*-methyl-D-xylono-1,5-lactone **5** in 95% yield by reaction with pyridinium chlorochromate. Compound **5** showed analytical data in agreement with the literature[19] and in addition was fully characterized, including by NMR spectroscopy, with the characteristic carbonyl C-1 resonance at 169.57 ppm and by IR spectroscopy where absorption at 1765 cm^{-1} was characteristic of the carbonyl group in a δ-lactone.

In conclusion, a new synthesis of 2,3,4-tri-*O*-methyl-D-xylono-1,5-lactone was achieved in five steps from D-xylose in an overall yield of 15%. The synthesis applied a novel C-1 protecting group strategy, previously described for the hexoses, to facilitate the synthesis and purification of permethylated xylose.

The anomeric methyl group was cleaved in reasonable yield using a dilute trifluoroacetic acid solution and the oxidation of the permethylated xylopyranose was accomplished in excellent yield by using pyridinium chlorochromate.

EXPERIMENTAL SECTION

Toluene and THF were dried by distillation over sodium metal; methylene chloride was dried by distillation from calcium hydride. All other reagents and chemicals were purchased from Aldrich Chemical Co. and used as received. All manipulations were carried out under a dry nitrogen atmosphere. NMR spectra collected at 400 MHz were performed on a Bruker AV400 instrument. NMR spectra collected at 500 MHz and $^{13}C\{^1H\}$ NMR spectra were carried out on a Bruker AV500 instrument. $CDCl_3$ was used as the NMR solvent and reference compound. Chemical ionization mass spectrometry was performed on a Fison's VG Platform, a quadrapole mass spectrometer. The ionization gas was ammonia and the source temperature was 150°C. IR absorbances were determined using a Satellite FTIR instrument using KBr plates and processed using WinFIRST lite 1.02. Specific rotations were measured using an Optical Activity Ltd Instrument with a cell path length of 0.5 dm. Melting points were measured using a Reichert instrument and are uncorrected. Elemental analyses were determined by Mr Stephen Boyer at London Metropolitan University.

Tetra-*O*-acetyl-D-xylopyranose (α- and β-anomers) (1)

D-(+)-Xylose (9.38 g, 62.50 mmol, 1 eq) was suspended in a solution of trifluoroacetic acid (6 mL) in acetic anhydride (120 mL) for 3 h and until all the solid had been consumed. The reaction mixture was filtered and concentrated in vacuo, and toluene (3 × 20 mL) was then distilled from the residue to form a white semi-solid, that was dissolved in methanol and washed with hexane (3 × 20 mL). The solvent was removed in vacuo to form the product as a pale yellow semi-solid and as a mixture of α- and β-anomers in the ratio 1:0.8, respectively (19.80 g, 62.20 mmol, quantitative).

α-anomer: ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.18$ (d, $^3J_{HH} = 3.63$ Hz, 1H, H-1), 5.14 (m, 1H, H-3), 4.99–4.93 (m, 2H, H-2, H-4), 4.08 (dd, $^2J_{HH} = 11.97$, $^3J_{HH} = 4.88$ Hz, 1H, H-5), 3.65 (m, 1H, H-5), 2.15–1.95 (4 × s, 12H, OAc). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): $\delta = 170.00$ (m, 4 × C=O), 88.96 (C-1), 70.64 (C-3), 69.09, 68.39 (C-2, C-4), 60.37 (C-5), 20 (m, 4 × CH_3).

β-anomer: ^1H NMR (500 MHz, $CDCl_3$) $\delta = 5.66$ (d, $^3J_{HH} = 6.76$ Hz, 1H, H-1), 5.43–5.37 (m, 1H, H-3), 4.99–4.93 (m, 2H, H-2, H-4), 4.08 (dd, $^2J_{HH} = 11.97$, $^3J_{HH} = 4.88$ Hz, 1H, H-5), 3.48 (dd, $^2J_{HH} = 12.06$, $^3J_{HH} = 8.33$ Hz, 1H, H-5), 2.15–1.95 (4 × s, 12H, OAc).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) : $\delta = 170.00$ (m, 4 × C=O), 91.74 (C-1), 69.18 (C-3), 69.06, 68.03 (C-2, C-4), 62.47 (C-5), 20 (m, 4 × CH_3).

MS (CI, ammonia): m/z (%): 336 (100) $[M + NH_4^+]$.
Anal. Calcd. for $C_{13}H_{18}O_9$: C, 49.06; H, 5.70; Found: C, 48.88; H, 5.63.

(2′,2′-Dichloro-1′-methyl)-ethenyl-D-xylopyranoside (α- and β-anomers) (2)

Tetra-*O*-acetyl-D-xylopyranose (20.00 g, 62.80 mmol, 1 eq), PPh_3 (49.40 g, 189 mmol, 3 eq), and KCl (42.20 g, 566 mmol, 9 eq) were dried in vacuo for 1 h and suspended in dry toluene (55 mL), dry pyridine (30 mL), and dry CCl_4 (45 mL) and stirred at 90°C for 50 min. The resulting black heterogeneous mixture was filtered through a plug of silica gel eluted with CH_2Cl_2-EtOAc (1:1) and concentrated to dryness to yield a yellow semi-solid, which was purified by column chromatography (EtOAc:Hexane, 1:1, $R_f = 0.6$) to yield a yellow semi-solid (2′,2′-dichloro-1′-methyl)-ethenyl-D-xylopyranose (15.25 g, 40.82 mmol, 63%). To a solution of (2′,2′-dichloro-1′-methyl)-ethenyl-2,3,4-tri-*O*-acetyl-D-xylopyranoside (5.00 g, 13 mmol, 1 eq.) in absolute MeOH (50 mL) was added MeONa (0.37 g, 6.90 mmol, 0.5 eq). After 2 h, the solution was neutralized with ion exchange resin (Amberlite IRC 50 S H^+ form). The reaction mixture was concentrated and washed with acetone (30 mL) to yield the product as a semi-solid (2.49 g, 9.60 mmol, 80%).

$^{13}C\{^1H\}$NMR (75 MHz, DMSO-d_6): $\delta = 148.38$, 148.11 (C-1′), 104.38, 103.59 (C-2′), 97.73, 92.43 (C-1), 76.66, 74.62 (C-3), 73.1, 72.26 (C-2), 70.1, 69.75 (C-4), 65.62, 61.51 (C-5), 14.78, 14.33 (C-3′).

MS (CI, ammonia): m/z (%) = 276 (100) $[M + NH_4^+$, $^{35}Cl)$, 278 (65), $[M + NH_4^+, ^{35}Cl, ^{37}Cl]$, 280 (15) $[M + NH_4^+, ^{37}Cl]$.
Anal. Calcd. for $C_8H_{12}Cl_2O_5$: C, 37.09; H, 4.67. Found: C, 37.05; H, 4.70.

Tetra-*O*-methyl-D-xylopyranose (3)$^{(20)}$

(2′,2′-Dichloro-1′-methyl)ethenyl-D-xylopyranoside [**2**] (0.74 g, 2.90 mmol, 1 eq) was dissolved in dry DMF (15 mL), under nitrogen. NaH (1.5 g, 60% dispersion in mineral oil, 31 mmol, 13 eq) was added at 0°C with stirring, followed by MeI (1.42 mL, 23 mmol, 8 eq). After 4 h at room temperature, the reaction was quenched by addition of MeOH (20 mL). The mixture was diluted with CH_2Cl_2 (50 mL) and water (50 mL). The organic phase was separated and the aqueous layer extracted with $CHCl_3$ (350 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo and residual DMF was removed by distillation under vacuum (5 mbar, 35°C). The resulting residue was purified by flash chromatography (EtOAc-Hexane; 1:1) to yield the product as a mixture of the α- and β-anomers in the ratio 1:3, respectively (0.36 g, 1.74 mmol, 60%).

Mp 44–45°C [lit.[20] Mp 46–48°C, β-anomer].
$[\alpha]_D^{25}$ −16.1° (c, 0.31, $CHCl_3$) [lit. $[\alpha]_D^{20}$ −66°, β-anomer (c, 1.16, MeOH)[20]].

α-anomer: ^1H NMR (270 MHz, $CDCl_3$): $\delta = 4.75$ (1H, d, $^3J_{HH} = 3.5$ Hz, H-1), 3.98 (1H, dd, $^2J_{HH} = 11.5$ Hz, $^3J_{HH} = 4.7$ Hz, H-2), 3.61 (3H, s, OMe), 3.50 (3H, s, OMe), 3.47 (3H, s, OMe), 3.40 (3H, s, OMe), 3.62–2.93 (4H, m, H-3, H-4, H-5).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta = 97.59$ (C-1), 82.65 (C-2), 81.69 (C-3), 79.74 (C-4), 60.90 (C-5), 59.33, 59.02, 58.90 (OMe), 55.1 (C-1 - OMe).

β-anomer: ^1H NMR (270 MHz, $CDCl_3$): $\delta = 4.13$ (1H, d, $^3J_{HH} = 7.2$ Hz, H-1), 3.69 (1H, dd, $^2J_{HH} = 10.90$ Hz, $^3J_{HH} = 5.60$ Hz, H-2), 3.59 (3H, s, OMe), 3.55 (3H, s, OMe), 3.50 (3H, s, OMe), 3.46 (3H, s, OMe), 3.62–2.93 (4H, m, H-3, H-4, H-5).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta = 104.70$ (C-1), 85.01 (C-2), 83.17 (C-3), 79.35 (C-4), 63.03 (C-5), 60.55, 60.34, 58.63 (OMe), 56.76 (C-1- OMe).

MS (CI, ammonia) m/z (%) = 224 (100) $[M + NH_4^+]$.
Anal. Calcd. for $C_9H_{18}O_5$: C 52.43, H 8.74. Found: C, 53.43; H, 8.84.

2,3,4-Tri-*O*-methyl-D-xylopyranoside (4)[(20)]

Tetra-*O*-methyl-D-xylopyranose [3] (0.26 g, 1.26 mmol) was dissolved in a solution of trifluoroacetic acid (2.5 mL) and water (1.0 mL) and heated at 65°C for 4 h. The mixture was concentrated to yield the product as an oil (0.16 g, 0.83 mmol, 66%). The oil was composed of a 2:1 ratio of α:β anomers.
$[\alpha]_D^{25}$ +18.8° (c, 0.64, $CHCl_3$) [lit $[\alpha]_D^{25}$ +20.1° (c, 1.095, MeOH)[20]].

α-anomer (66%): ^1H NMR (400 MHz, $CDCl_3$) $\delta = 5.24$ (1 H, d, $^3J_{HH} = 3.44$ Hz, H-1), 3.76–3.72 (1 H, m, H-5), 3.62 (3 H, s, OMe), 3.55 (3 H, s, OMe), 3.49 (3 H, s, OMe), 3.45 (1 H, d, $^3J_{HH} = 8.44$ Hz, H-3), 3.28–3.16 (2 H, m, H-2, H-4).

$^{13}C\{^1H\}$ (125 MHz, $CDCl_3$) $\delta = 90.90$ (C-1), 81.45 (C-2 or C-4), 81.36 (C-3), 79.01 (C-2 or C-4), 60.67 (OMe), 59.89 (C-5), 58.93, 58.71 (OMe).

β-anomer (33%): ^1H NMR (400 MHz, $CDCl_3$) $\delta = 4.62$ (1 H, d, $^3J_{HH} = 6.83$ Hz, H-1), 4.02 (1 H, dd, $^2J_{HH} = 11.09$, $^3J_{HH} = 4.23$ Hz, H-5), 3.62 (6 H, s, OMe), 3.46 (3 H, s, OMe), 3.31–3.17 (2 H, m, H-3, H-4), 2.99 (1 H, dd, $^3J_{H2H3} = 8.01$ Hz, $^3J_{H1H2} = 6.91$ Hz, H-2).

$^{13}C\{^1H\}$ (125 MHz, $CDCl_3$) $\delta = 97.10$ (C-1), 84.17 (C-3 or C-4), 83.46 (C-2), 78.80 (C-3 or C-4), 62.64 (C-5), 60.52, 60.36, 58.65 (OMe).

MS (CI, ammonia): m/z (%) = 210 (100) $[M + NH_4^+]$.
Anal. Calcd. for $C_8H_{16}O_5$: C, 50.00; H, 8.33. Found: C, 50.08; 7.24.

2,3,4-Tri-O-methyl-D-xylono-1,5-lactone (5)[19]

Pyridinium chlorochromate (0.36 g, 1.70 mmol, 2.0 eq) in dichloromethane (3 mL) was added to 2,3,4-tri-*O*-methyl-D-xylopyranoside [4] (0.20 g, 1 mmol) dissolved in CH_2Cl_2 (3 mL), and the mixture was refluxed for 7 h. It was then cooled, diluted with diethyl ether (30 mL), decanted, filtered through celite, and concentrated to yield the product as an oil (0.15 g, 0.80 mmol, 95%).

$[\alpha]_D^{25}$ +16.8° (c, 0.95, CH_2Cl_2).

IR ($CDCl_3$): 1765 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.44$ (1 H, ddd, $^2J_{HH} = 12.26$, $^3J_{HH} = 2.99$, 1.66 Hz, H-5 axial), 4.29 (1 H, dd, $^2J_{HH} = 12.41$, $^3J_{HH} = 1.75$ Hz, H-5 equatorial), 3.84 (1 H, d, $^3J_{HH} = 6.53$ Hz, H-2), 3.63 (3 H, s, CH_3), 3.53 (3 H, s, CH_3), 3.43 (3 H, s, CH_3), 3.57–3.55 (1 H, m, H-4), 3.50 (1 H, m, H-3).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): $\delta = 169.57$ (C-1), 82.91 (C-3), 80.49 (C-2), 77.00 (C-4), 64.93 (C-5), 59.47, 58.02, 56.22 (3 × CH_3).

MS (CI, ammonia): m/z (%) = 208 (100), $[M + MH_4^+]$.

Anal Calcd. for $C_8H_{14}O_5$: C 50.52, H 7.42. Found: C 50.68, H 7.51.

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REFERENCES

[1] Ragauskas, A.J.; Williams, C.K.; Davison, B.H.; Britovsek, G.; Cairney, J.; Eckert, C.A.; Fredrick, W.J., Jr.; Hallett, J.P.; Leak, D.J.; Liotta, C.L.; Mielenz, J.R.; Murphy, R.; Templer, R.; Tschaplinski, T. The path forward for biofuels and biomaterials. Science **2006**, *311*, 484.

[2] Lichtenthaler, F.W. Unsaturated O- and N-Heterocycles from carbohydrate feedstock. Acc. Chem. Res. **2002**, *35*, 728.

[3] Drew, H.D.K.; Haworth, W.N. Studies in polymerization. Part 1. 2,3,4-trimethyl-L-arabonolactone. J. Chem. Soc. **1927**, 775–779.

[4] Masato, M. Japan, **2002**, JP 2002167430 A2 20020611.

[5] Zamora, F.; Bueno, M.; Molina, I.; Iribarren, J.I.; Muñoz-Guerra, S.; Galbis, J.A. Stereoregular copolyamides derived from D-xylose and L-arabinose. Macromolecules **2000**, *33*, 2030–2038.

[6] Mancera, M.; Roffé, I.; Rivas, M.; Silva, C.; Galbis, J.A. Synthesis of D-mannitol and L-iditol derivatives as monomers for the preparation of new regioregular AABB-type polyamides. Carbohydr. Res. **2002**, *337*, 607–611.

[7] Mancera, M.; Roffé, I.; Al-Kass, S.S.J.; Rivas, M.; Galbis, J.A. Synthesis and characterization of new stereoregular AABB-type polyamides from carbohydrate-based

monomers having D-manno and L-ido configurations. Macromolecules **2003**, *36*, 1089–1097.

[8] Mancera, M.; Zamora, F.; Roffé, I.; Bermúdez, M.; Alla, A.; Muñoz-Guerra, S.; Galbis, J.A. Synthesis and properties of poly(D-mannaramide)s and poly(galactaramide)s. Macromolecules **2004**, *37*, 2779–2783.

[9] Garcia-Martin, M.D.G.; Hernandez, E.B.; Perez, R.R.; Alla, A.; Muñoz-Guerra, S.; Galbis, J.A. Synthesis and characterisation of linear polyamides derived from L-arabinitol and xylitol. Macromolecules **2004**, *37*, 5550–5556.

[10] Garcia-Martin, M.G.; Perez, R.R.; Hernandez, E.B.; Espartero, J.L.; Muñoz-Guerra, S.; Galbis, J.A. Carbohydrate based polycarbonates. Synthesis, structure and biodegradation studies. Macromolecules **2005**, *38*, 8664–8670.

[11] Zamora, F.; Khalid, H.; Abdelilah, A.; Espartero, J.L.; Muñoz-Guerra, S.; Galbis, J.A. Aromatic homo- and copolyesters from naturally occuring monosaccharides: PET and PEI analogs derived from L-arabinitol and xylitol. J. Polym. Sci. Polym. Chem. **2005**, *43*, 6394–6410.

[12] Zamora, F.; Galbis, J.A. Synthesis of 3-deoxy-2,4-di-O-methyl-D-erythro-pentono-1,5-lactone and of its L enantiomer by stereoselective hydrogenation of alpha,-beta-unsaturated aldono-1,5-lactones. Carbohydr. Res. **1996**, *293*, 251–258.

[13] Garcia-Martin, M.G.; Perez, R.R.; Hernandez, E.B.; Galbis, J.A. Synthesis of L-arabinitol and xylitol monomers for the preparation of polyamides. Preparation of an L-arabinitol-based polyamide. Carbohydr. Res. **2001**, *333*, 95–103.

[14] Hunter, D.F.A.; Fleet, G.W.J. Towards hydroxylated nylon 6: oligomers from a protected 6-amino-6-deoxy-D-allonate. Tetrahedron Asymm. **2003**, *14*, 3831–3839.

[15] Edwards, A.A.; Sanjayan, G.J.; Hachisu, S.; Soengas, R.; Stewart, A.; Tranter, G.E.; Fleet, G.W.J. Synthesis of 4-aminomethyl-tetrahydrofuran-2-carboxylates with 2,4-cis and 2,4-trans relationships. Tetrahedron **2006**, *62*, 4110–4119.

[16] Edwards, A.A.; Sanjayan, G.J.; Hachisu, S.; Tranter, G.E.; Fleet, G.W.J. A novel series of oligomers from 4-aminomethyl-tetrahydrofuran-2-carboxylates with 2,4-cis and 2,4-trans stereochemistry. Tetrahedron **2006**, *62*, 7718–7725.

[17] Haider, A.F.; Williams, C.K. Synthesis of highly functionalised oligoesters and copolyesters from a carbohydrate lactone. J. Poly. Sci. Part A Poly. Chem. **2007**, Submitted manuscript.

[18] Haworth, W.N.; Westgarth, G.C. Synthesis of derivatives of gamma-xylose. J. Chem. Soc. **1926**, 880–887.

[19] Drew, J.D.K.; Goodyear, E.H.; Haworth, W.N. The study of lactones derived from simple sugars. J. Chem. Soc. **1927**, 1237–1245.

[20] Carruthers, A.; Hirst, E.L. Methylation of xylose. J. Chem. Soc. **1922**, 2299–2308.

[21] Ballou, C.E.; Roseman, S.; Link, K.P. Reductive cleavage of benzyl glycosides for relating anomeric configurations. Preparation of some new benzyl pentosides. J. Am. Chem. Soc. **1951**, *73*, 1140–1144.

[22] de Figueiredo, R.M.; Bailliez, V.; Dubreuil, D.; Olesker, A.; Cleophax, J. O-dichlorovinyl osides: a new anomeric protecting group. Synthesis **2003**, *18*, 2831–2834.

[23] Wolfrom, M.L.; Thompson, A. Methods Carbohydr. Chem. **1963**, *2*, 211–215.

Lactide Polymerization Co-initiated by Carbohydrate Esters and Pyranoses

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ABSTRACT: The polymerization of [*S*]-lactide was accomplished using an initiating system comprising an alkyl zinc complex and a series of well defined carbohydrate co-initiators derived from D-glucose, D-xylose, and 2-deoxy-D-ribose. The monosaccharide co-initiators were aldonate esters and pyranoses, they were all prepared in high yield and had only a single alcohol co-initiating group; the remaining carbohydrate hydroxyl functionalities were protected as acetyl, benzyl ether and isopropylidene acetal groups. The polymerizations were all well controlled, illustrated by the linear increase in poly(*S*-lactide) M_n with percentage conversion of lactide, the increase in poly(*S*-lactide) M_n with $[\text{lactide}]_0$-$[\text{lactide}]_t$/[co-initiator] and the narrow polydispersity indices of the polylactides. Thus, the novel initiating systems were used to produce poly(*S*-lactides) end functionalized with a variety of different aldonate ester and pyranose groups and with degrees of polymerization from 10 to 250. The polyesters were fully characterized, including by NMR spectroscopy, size exclusion chromatography (SEC), matrix-assisted laser deposorption/ionization (MALDI) mass spectrometry and by static water contact angle measurements. © 2008 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 46: 4352–4362, 2008

Keywords: biomaterials; initiators; kinetics (polym.); polyesters; ring opening polymerization

INTRODUCTION

Aliphatic polyesters have been attracting considerable attention as sustainable alternatives to commodity plastics such as polypropylene. The most widespread and commercially viable of which is polylactide (PLA), produced by the ring opening polymerization of lactide, which itself derives from biomass. It is used in disposable consumer articles as well as in fiber applications, a key advantage being its hydrolysis to lactic acid, a metabolite in the carboxylic acid cycle.[1–3] PLA is biocompatible and an FDA-approved polymer for use in therapy. It has been used for some time in biomedical applications such as sutures, stents, dental implants, vascular grafts, bone screws, and pins. It has also been investigated as a vector for drug delivery, for example in the long-term delivery of antimicrobial drugs, contraceptives and prostate cancer treatments.[4] PLA has been widely used in the field of tissue engineering as a scaffold material to support cell and tissue growth.[5–7]

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However, it is unsuitable for some applications due to its high hydrophobicity which leads to a slow degradation rate. It is therefore important to develop strategies and syntheses of functionalized PLA materials and in particular to develop routes to functionalize it with biologically relevant and compatible molecules.

Cell surface carbohydrates are involved in numerous biological functions, including cellular recognition, adhesion, growth regulation, inflammation, and cancer cell metastasis. However, the natural glycopolymers displaying these cell surface carbohydrates are heterogeneous and their structures are ill-defined. Synthetic carbohydrate based polymers are emerging as useful tools for investigating carbohydrate based interaction processes as well as interesting materials for biomedical applications.[8] However, their biomedical applications require the design and efficient synthesis of materials incorporating well defined carbohydrate moieties and degradable, biocompatible backbones. A solution to this challenge is the synthesis of biodegradable polyesters incorporating carbohydrate groups. Our solution was to use a carbohydrate hydroxyl group to co-initiate the controlled polymerization of *S*-lactide, thereby introducing functionalized carbohydrate end groups to the PLA.

D-glucopyranosides and D-galactopyranosides protected with alkyl ether, benzyl ether, or isopropylidene acetal groups have precedent as co-initiators for cyclic ester ring opening polymerization in combination with either lipases, metal complexes or Bronsted acids.[9–16] Also, Kricheldorf and Stricker used stannylenated glycopyranosides as cyclic initiators for ε-caprolactone polymerization and the synthesis of biodegradable network polymers.[17] However, the previous studies were limited to hexose co-initiators and few were controlled polymerizations. Furthermore, the materials produced had M_n limited to 20,000, which means the polymer will be restricted to nonload bearing applications.

Here, we report the application of a series of carbohydrates as co-initiators for the controlled polymerization of lactide producing PLA end-capped with highly functionalized groups. This is a sustainable route to polymers synthesized from renewable resources as well as yielding novel materials for applications in tissue engineering. Different types of carbohydrate co-initiators were investigated including aldonate esters and pyranoses. The co-initiation using monosaccharides was known as some hexoses had been investigated previously,[9–17] however pentoses, for example, D-xylopyranose and 2-deoxy-D-ribopyranose, and aldonate esters were not previously researched. The use of different co-initiators yielded PLA end capped with a range of carbohydrates and illustrated the influence of the initiator structure on the polymerization rate. All the monosaccharide co-initiators were well defined compounds which were synthesized in high yield from natural carbohydrates. They each had one free hydroxyl group to initiate the lactide polymerization and the remaining hydroxyl groups were protected by acetyl, *O*-benzyl ether and isopropyl acetal groups.

EXPERIMENTAL

Materials

[*S*]-Lactide was donated by Purac Plc, it was purified by recrystallization from hot toluene followed by repeated sublimations *in vacuo* (three times). The co-initiators: methyl-2,3,4,6-tetra-*O*-acetyl-D-gluconate **1**,[18] 2,3,4-tri-*O*-acetyl-D-xylopyranose **3**,[19,20] 2,3,4-tri-*O*-benzyl-D-xylopyranose **4**,[21] and 3,4-isopropylidene acetal-2-deoxy-D-ribopyranose **5**[22] were prepared in excellent analytical purity and good yield according to the literature. Methyl-2,3,4-tri-*O*-benzyl-D-xylonate **2** was prepared from 2,3,4-tri-*O*-benzyl-1,5-lactone, the lactone was itself prepared according to the literature protocols.[23–25] The zinc ethyl complex (LZnEt, Fig. S1) was prepared and used according to the literature.[26] Methylene chloride was dried by distillation from calcium hydride. All other reagents and chemicals were purchased from Aldrich Chemical and used as received. All manipulations were carried out under a dry nitrogen atmosphere.

Measurements

NMR spectra collected at 400 MHz were performed on a Bruker AV400 instrument. NMR spectra collected at 500 MHz, as well as $^{13}C\{^1H\}$ NMR spectra, were carried out on a Bruker AV500 instrument. $CDCl_3$ was used as the NMR solvent and reference compound. The SEC measurements were performed on a Polymer labs SEC 60 instrument with two Polymer labs mixed D columns and $CHCl_3$ at a flow rate of 1 mL min^{-1} as the eluent. Narrow molecular weight polystyrene standards were used to calibrate the instrument and a correction factor of 0.58 was applied to the M_n obtained as outlined in the literature.[27] The MALDI-TOF mass spectrometry was performed with a Micromass MALDI micro MX mass spectrometer equipped with a UV (337 nm) laser. All mass spectra were recorded in linear mode. Forty spectra were collected from random positions on the target, each spectrum averaged from 10 laser shots. About 1.2 μL of a mixture of the matrix (dithranol, 30 mg/mL in THF), cationizing agent ($NaCO_2CF_3$, 10 mg/mL in THF), and the sample (~ 10 mg/mL in CH_2Cl_2) in the ratio 3:1:1 respectively, was applied to the target and air-dried immediately before use. Polymer films were coated on clean glass slides (13 mm diameter, VWR International, PA) using a dip coater (KSV Instrument, Finland). The slides were completely dipped into a 5 mg/mL solution of polymer in chloroform at a velocity of 85 mm/min and withdrawn at 5 mm/min to allow the formation of a thin polymer film on the glass slide. Film roughness was measured using a microscope-based interferometer (New View 200, Zygo, CT). The measurements were performed on three different areas of each slide and repeated on two slides for each kind of polymer film. The roughness for each film is expressed as the average root mean square (RMS). Static water contact angles were measured using a Drop Shape Analysis System (EasyDrop, Krüss, Germany). A 30 μL drop of ultra-pure water (MilliQ water, Millipore, MA) was placed on the film surfaces and static water contact angle was measured. The measurements were performed on three different areas of each slide, repeated on two slides for each kind of polymer film and the values averaged.

Methyl-2,3,4-tri-O-Benzyl-D-Xylonate (2,3,4-Tris-benzyloxy-5-hydroxy-pentanoic acid methyl ester)

Para-toluene sulfonic acid (*p*-TSA) (7.6 mg) was dissolved in MeOH (10 mL) to make a stock solution. The 2,3,4-tri-*O*-benzyl-1,5-lactone (42 mg, 0.1 mmol) was added to a dry flask, followed by *p*-TSA solution in methanol (1 mL). As the lactone has poor solubility in MeOH, CH_2Cl_2 was added dropwise (ca. 1.5 mL) to dissolve it. The solution was stirred for 20 h at room temperature. TLC (toluene/ethyl acetate = 2:1) analysis revealed the presence of a new compound in the reaction mixture (R_f = 0.47). The R_f for the starting material was 0.66. The product was pre-absorbed on silica and purified by column chromatography (silica gel, toluene/ethyl acetate = 2:1) and isolated as a white powder (30 mg, 0.06 mmol, 60%).

Yield: 60%. Purity (HPLC) > 99%. $R_f = 0.47$ (SiO_2, toluene/ethyl acetate = 2:1). MPt. 111–112°C. Anal. Calc. for $C_{27}H_{30}O_6$, C, 71.98, H, 6.71%. Found, C, 71.87, H, 6.82%. ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 7.36–7.20 (m, 15H, Ar—*H*), 4.84 (d, $^3J_{H-H}$ = 11.56 Hz, 1H, O—CH_2—Ar), 4.46 (d, $^3J_{H-H}$ = 11.57 Hz, 1H, O—CH_2—Ar), 4.74 (d, $^3J_{H-H}$ = 11.62 Hz, 1H, O—CH_2—Ar), 4.58 (d, $^3J_{H-H}$ = 11.45 Hz, 1H, O—CH_2—Ar), 4.66 (d, $^3J_{H-H}$ = 10.48 Hz, 2H, O—CH_2—Ar), 4.24. (d, $^3J_{H-H}$ = 3.94 Hz, 1H, H-2), 4.08 (dd, $^3J_{H-H}$= 3.99 Hz, $^2J_{H-H}$ = 6.39 Hz, 1H, H-3), 3.79 (m, 1H, H-4), 3.73 (dd, $^3J_{H-H}$ = 4.03 Hz, $^2J_{H-H}$ = 12.00 Hz,1H, H-5), 3.50 (dd, $^3J_{H-H}$= 4.75 Hz, $^2J_{H-H}$ = 11.93 Hz, 1H, H-5), 3.64 (s, 3H, —OCH_3). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, δ ppm): 171.07 (C-1), 138.02 (ArC), 137.85 (ArC), 136.81 (ArC), 128.58-127.89 (ArC), 79.29 (C-4), 79.10 (C-3), 78.09 (C-2), 74.53 (O—*C*H_2—Ar), 73.06 (O—*C*H_2—Ar), 61.37 (C-5), 51.97 (—O—*C*H_3). *m*/*z* (CI-ammonia gas): 468 [$M+NH_4^+$].

General Lactide Polymerization Protocol (Initiator 2)

Methyl-2,3,4-tri-*O*-benzyl-D-xylonate (0.036 g, 0.08 mmol) was dissolved in CH_2Cl_2 (3.30 mL) to make a stock solution. [*S*]-lactide (0.432 g, 3 mmol) was added into an oven dried vial, followed by the zinc complex, LZnEt, (0.0055 g, 0.013 mmol). Then CH_2Cl_2 (2.5 mL) and the stock solution (0.5 mL) were added, so as to make a solution of concentration 1 M in lactide. The polymerization was conducted at 25°C. Aliquots were withdrawn at regular intervals and were quenched by addition into wet hexane. The PLA was purified by dissolving it in CH_2Cl_2 and precipitation into hexane. The purification was carried out three times and the PLA was dried *in vacuo* for 4 h prior to analysis (0.39 g, 91%).

^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 7.34–7.31 (m, 15H, Ar—*H*), 5.18 (q, $^3J_{H-H}$ = 7.10 Hz, 2nH, COC*H*(CH_3)O), 4.81–3.76 (m, 12H, —OCH_2Ar, —C*H*(CH_3)OH, H-2, H-3, H-4, H-5, H-5′), 3.61 (s, 3H, OCH_3), 1.59 (d, 6nH, CHCH_3).

Methyl-2, 3, 4, 6-Tetra-O-Acetyl-D-Gluconate-Poly(*S*-Lactide)

Prepared according to general polymerization protocol on the following scale: Methyl-2,3,4,6-

tetra-*O*-acetyl-D-gluconate **1** (0.0138 g, 0.05 mmol), [*S*]-lactide (1.8 g, 12.5 mmol), LZnEt, (0.023 g, 0.055 mmol) and CH_2Cl_2 (12.5 mL) and yielded methyl-2, 3, 4, 6-tetra-*O*-acetyl-D-gluconate-poly(*S*-lactide) (1.62 g, 91%).

^1H NMR (400 MHz, $CDCl_3$, δ ppm): 5.50–5.10 (m, 4H, H-2, H-3, H-4, H-5), 5.21–5.16 (m, 2nH, $COCH(CH_3)O$), 4.40–4.20 (m, 3H, H-6, H-6′, $CH(CH_3)OH$), 3.76 (s, 3H, OCH_3), 2.14-2.07 (m, 12H, $COCH_3$), 1.59 (d, 6nH, $CHCH_3$).

2,3,4-Tri-O-Acetyl-D-Xylopyranose-Poly(*S*-Lactide)

Prepared according to general polymerization protocol on the following scale: 2,3,4-Tri-O-acetyl-D-xylose **3** (0.0138 g, 0.05 mmol), *S*-lactide (1.80 g, 12.5 mmol), LZnEt (0.023 g, 0.055 mmol) and CH_2Cl_2 (12.5 mL) and yielded 2,3,4-tri-*O*-acetyl-D-xylopyranose-poly(*S*-lactide) (1.63 g, 91%).

^1H NMR (500 MHz, $CDCl_3$, δ ppm): 6.30 and 5.76 (d, 1H, H-1 α and β anomers), 5.18 (q,$^3J_{H-H}$ = 7.10 Hz, 2nH, $COCH(CH_3)O$), 4.80–5.60 (m, 3H, H-2, H-3, H-4), 4.38 (m, 1H, $CH(CH_3)OH$), 3.50-4.20 (m, 2H, H-5, H-5′), 2.11-2.07 (m, 9H, $COCH_3$), 1.59 (d, 6nH, $CHCH_3$).

2,3,4-Tri-O-Benzyl-D-Xylopyranoside-Poly(*S*-Lactide)

Prepared according to general polymerization protocol on the following scale: 2, 3, 4-tri-*O*-benzyl-D-xylose **4** (0.021 g, 0.05 mmol), *S*-lactide (1.80 g, 12.5 mmol), LZnEt (0.025 g, 0.06 mmol) and CH_2Cl_2 (12.5 mL) and yielded 2,3,4-tri-*O*-benzyl-D-xylopyranoside-poly(*S*-lactide) (1.65 g, 92%).

^1H NMR (500 MHz, $CDCl_3$, δ ppm): 7.34-7.31 (m, 15H, Ar—*H*), 6.2 and 5.6 (d, 1H, H-1 α and β anomers), 5.18 (q,$^3J_{H-H}$ = 7.10 Hz, 2nH, $COCH(CH_3)O$), 4.90–4.60 (m, 6H, OCH_2Ar), 4.38 (m, 1H, $CH(CH_3)OH$), 3.70–3.60 (m, 4H, H-2, H-3, H-5), 2.70 (m, 1H, H-4), 1.59 (d, 6nH, $CHCH_3$).

3,4-O-Isopropylidene-2-Deoxy-D-Ribopyranoside-Poly(s-Lactide)

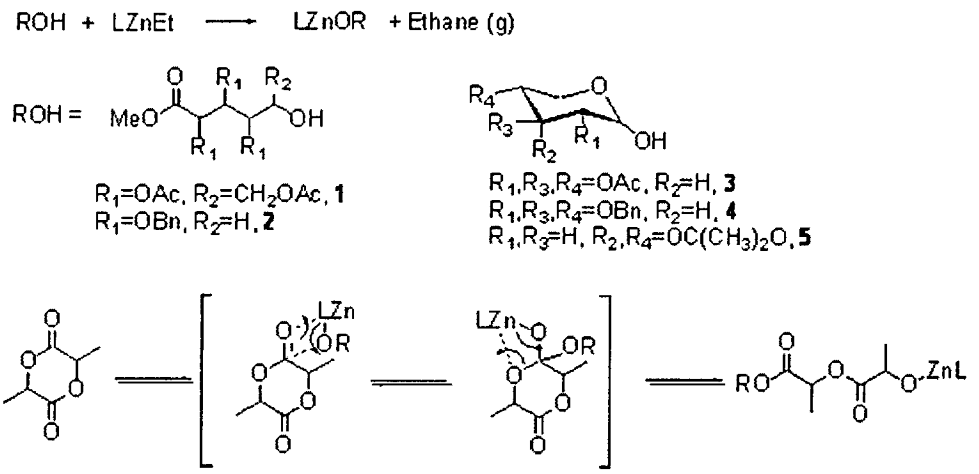
Prepared according to general polymerization protocol on the following scale: 2-deoxy-3, 4-*O*-isopropylidene-D-ribose **5** (0.021 g, 0.012 mmol), *S*-lactide (0.432 g, 3 mmol), LZnEt (0.0055 g, 0.0132 mmol) and CH_2Cl_2 (3 mL) and yielded 3,4-*O*-isopropylidene-2-deoxy-D-ribopyranoside-poly(*S*-lactide) (0.40 g, 93%).

^1H NMR (500 MHz, $CDCl_3$, δ ppm): 6.22 and 6.00 (dd, 1H, H-1 α and β anomers), 5.18 (q,$^3J_{H-H}$ = 7.10 Hz, 2nH, $COCH(CH_3)O$), 4.50–4.20 (m, 3H, $CH(CH_3)OH$, H-3, H-4), 3.84 (d,$^3J_{H-H}$ = 7.07 Hz, 2H, H-5), 2.47–2.22 (m, 1H, H-2), 1.88 (m, 1H, H-2′), 1.59 (d, 6nH, $CHCH_3$) 1.35 (m, 6H, $C(CH_3)_2$).

RESULTS AND DISCUSSION

The controlled lactide polymerization and end group functionalization of the PLA was achieved using an initiating system comprising an alkyl zinc complex (LZnEt where L = 2,4-di-*tert*-butyl-6-{[(2′-dimethylaminoethyl)methylamino]-methyl}phenolate) and a range of carbohydrate alcohol co-initiators. The alkyl zinc (Fig. S1)/alcohol initiating system had previously shown very high rates and excellent control in lactide ring opening polymerization (ROP) using "simple" alcohols, for example, ethanol or benzyl alcohol.[26] The key to its success was the ancillary ligand (L) coordinated to the zinc center which prevented aggregation of the zinc alkoxide initiator. In this study, functionalized alcohol co-initiators were used, either aldonate esters or pyranoses derived from D-glucose, D-xylose and 2-deoxy-D-ribose. The alkyl zinc complex and the carbohydrate alcohol reacted *in situ* to form the zinc alkoxide, which is the true initiator; the polymerization subsequently occurred via the coordination-insertion reaction mechanism (Scheme 1). Support for these notions came from the end group analysis which showed exclusive initiation by carbohydrate alcohols; the M_n for each polymer being in excellent agreement with that predicted from alcohol loadings. Furthermore, a 1:1 reaction between the zinc complex (LZnEt) and co-initiator **5** was monitored by ^1H NMR. This showed a decrease in the resonances assigned to the zinc ethyl protons and a downfield shifting and broadening of the peaks assigned to **5**, consistent with the formation of a zinc alkoxide complex and the elimination of ethane.

The coordination-insertion mechanism involved the lactide being activated and ring opened by the zinc alkoxide complex. The ring opening led to formation of a novel ring opened metal alkoxide and enabled chain propagation to occur. The alcohol co-initiator became an ester end group on one end of the polymer chain. The advantage



Scheme 1. The coordination-insertion mechanism for the ring opening polymerization of lactide using alkyl zinc (LZnEt)/carbohydrate initiating system. L = 2,4-di-*tert*-butyl-6-{[(2′-dimethylaminoethyl)methylamino]methyl}phenolate, Fig. S1 illustrates the structure of LZnEt.

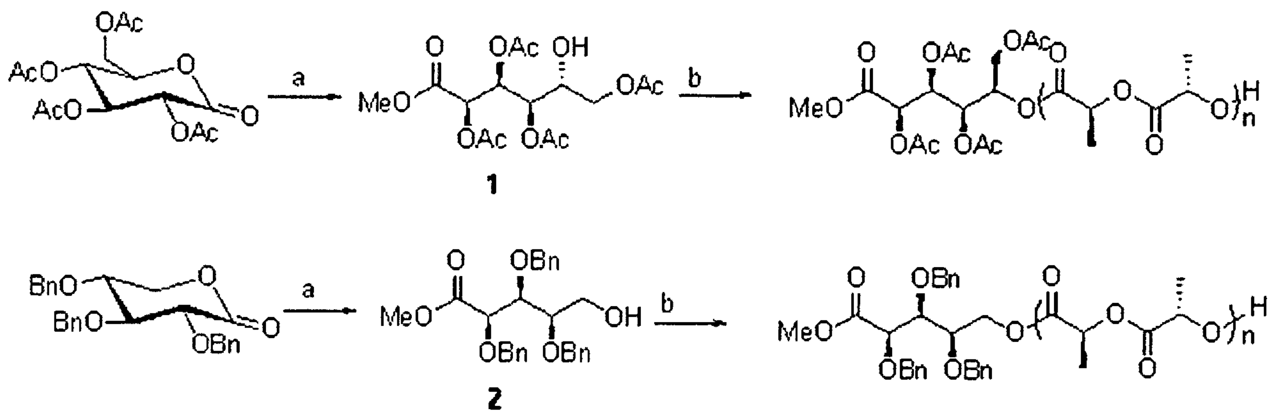
of the zinc/carbohydrate alcohol initiating system was that it enabled controlled lactide polymerization and therefore very tight control over the polymer properties, for example, M_n, PDI.

Aldonate Esters

The lactide polymerizations, using the zinc/carbohydrate alcohol initiating system, were investigated using the aldonate esters **1** and **2** (Scheme 2).

The aldonate esters **1** and **2** were prepared from 2,3,4,6-tetra-*O*-acetyl-D-gluconolactone and 2,3,4-tri-*O*-benyl-D-xylonolactone respectively, by reaction with acidified methanol and were isolated in excellent yield (60% for **1**, 86% for **2**) and analytical purity as white solids.[18] They were then used as co-initiators, with the alkyl zinc complex, in the ROP of lactide at room temperature in methylene chloride. To establish the properties and degree of control exerted by the carbohydrate alcohol co-initiators, detailed investigations were carried out using **1**. The polymerizations were conducted using a range of **1**: lactide loadings and enabled the preparation of PLA of controlled M_n (Table 1).

The percentage conversions were determined from the ^{1}H NMR spectrum by integration of the methine signals due to lactide (5.00 ppm)



Scheme 2. (*S*)-Lactide polymerization using co-initiators derived from D-gluconolactone (**1**) and D-xylonolactone (**2**). Reagents and conditions: (a) MeOH, TsOH, DCM, 20 h, 30°C. (b) n [*S*]-LA, LZnEt (Fig. S1), CH_2Cl_2, 25 °C. *n* = 25–250.

Table 1. PLA Synthesized Using Co-initiator 1

Initiator	LZnEt:1:Lactide[a]	Time/Min	% Conversion[b]	M_n Calculated[c]	M_n SEC[d] (PDI)
1	1:1:10	15	100	1800	1770 (1.15)
1	1:1:50	210	90	6840	6000 (1.12)
1	1:1:100	210	80	11,800	11,300 (1.15)
1	1:1:250	960	87	31,700	33,200 (1.13)

[a] Polymerization conditions: $[LA]_0 = 1$ M, CH_2Cl_2, 25 °C.

[b] Determined by ^1H NMR by integration of the methine signals at 5.20 ppm for PLA and 5.00 ppm for lactide.

[c] Calculated from $M_n = (144 \times DP) + 378$.

[d] Determined by SEC using $CHCl_3$ and versus narrow M_n polystyrene standards, a correction factor of 0.58 was applied according to the literature.[27]

and PLA (5.20 ppm). The initiating system exerted good polymerization control and therefore by varying the loading of **1** it was possible to produce PLA of predictable and controllable M_n (Fig. 1). It was also notable that the M_n obtained for the polyesters by SEC was in reasonable agreement with the M_n calculated from the reaction stoichiometry, for example using **1** at a concentration of 2 mM and at 90% conversion, resulted in an expected M_n of 6840 and a SEC value of 6000. The close agreement between calculated and experimental values of the M_n confirmed the controlled nature of the polymerization and this was reinforced by the relatively narrow polydispersity indices. The polymerization control was further illustrated by the linear increase in the M_n with the polymerization percentage conversion (Fig. 2). It was also notable that the initiator enabled the preparation of high M_n PLA, a limitation with previously used carbohydrate initiators.[9–17]

The polymerizations with **1** demonstrated the high degree of control exerted by the initiating system at room temperature. The same conditions were therefore used with all the other carbohydrate co-initiators and the results for the aldonate ester **2** derived from D-xylose (at 4 mM concentration) are shown in Table 2. As for **1**, these show that excellent control is also exerted using **2** as illustrated by the close agreement between the calculated and experimental SEC results and also the narrow PDI values.

The MALDI mass spectra were obtained for all the novel initiators, these provided further evidence for the control of M_n and also confirmed the end groups. In each case only two

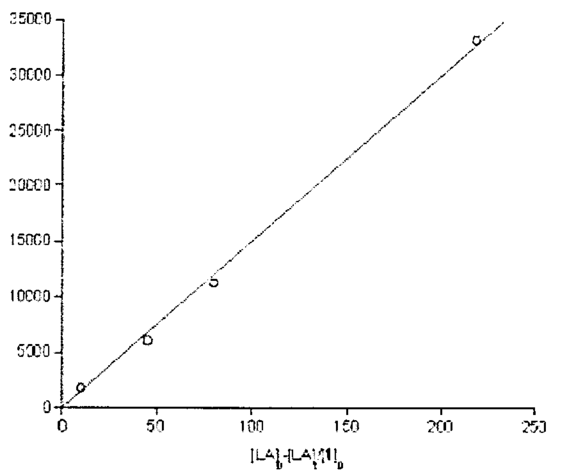


Figure 1. Plot showing the evolution of PLA M_n against $[LA]_0 - [LA]_t/[1]_0$. The M_n was determined by SEC in $CHCl_3$ versus polystyrene standards and a correction factor of 0.58 was applied according to the literature.[27]

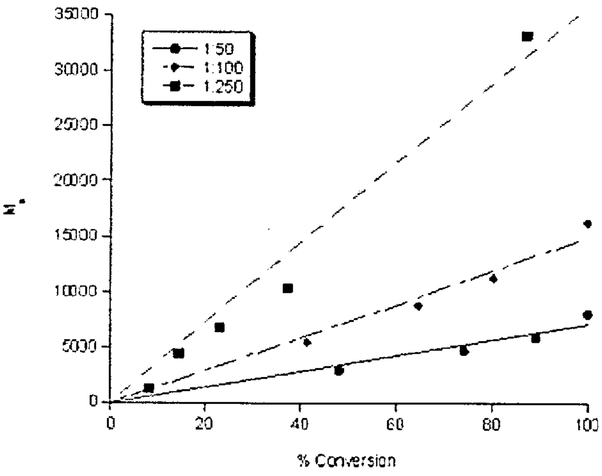


Figure 2. Plot showing the PLA M_n versus the lactide percentage conversion using **1**. The ratios refer to the concentrations of **1**:LA. The M_n was determined by SEC in $CHCl_3$ versus polystyrene standards and a correction factor of 0.58 was applied according to the literature.[27] The % conversion was determined by integration of the methine region of the ^1H NMR.

Table 2. Polymerizations Conducted with Co-initiator 2

Co-initiator[a]	% Conversion[b]	Time/Min	M_n Calculated[c]	M_n SEC[d] (PDI)
2	16	93	6200	5250(1.08)
2	31	163	11800	12700(1.04)
2	59	250	21600	24000(1.04)
2	90	425	33000	42000(1.07)

[a] Polymerization conditions: $[LA]_0 = 1$ M, $[2] = 4$ mM, CH_2Cl_2, 25 °C.

[b] Determined by ^1H NMR by integration of the methine signals at 5.20 ppm for PLA and 5.00 ppm for lactide.

[c] Calculated using the percentage conversion determined by ^1H NMR: $M_n = (144 \times DP) + 450$.

[d] Determined by SEC using $CHCl_3$ and versus narrow M_n polystyrene standards, a correction factor of 0.58 was applied according to the literature.[27]

major series of peaks were observed: one due to the sodium cationized and the other due to the doubly sodium cationized polymers with the carbohydrate ester end groups, as expected from a coordination-insertion polymerization mechanism. The MALDI mass spectrum for co-initiator **2** with a degree of polymerization of 10 is shown in Figure 3. There are three series of peaks in the spectrum and these correspond to the [**2**-PLA + Na] (marked with * in Fig. 3), [**2**-PLA + 2Na] (** in Fig. 3) and a very small series assigned to cyclic PLA. The cyclic PLA formed during transesterification reactions which occurred more rapidly at this low degree of polymerization than they did at higher degrees of polymerization.

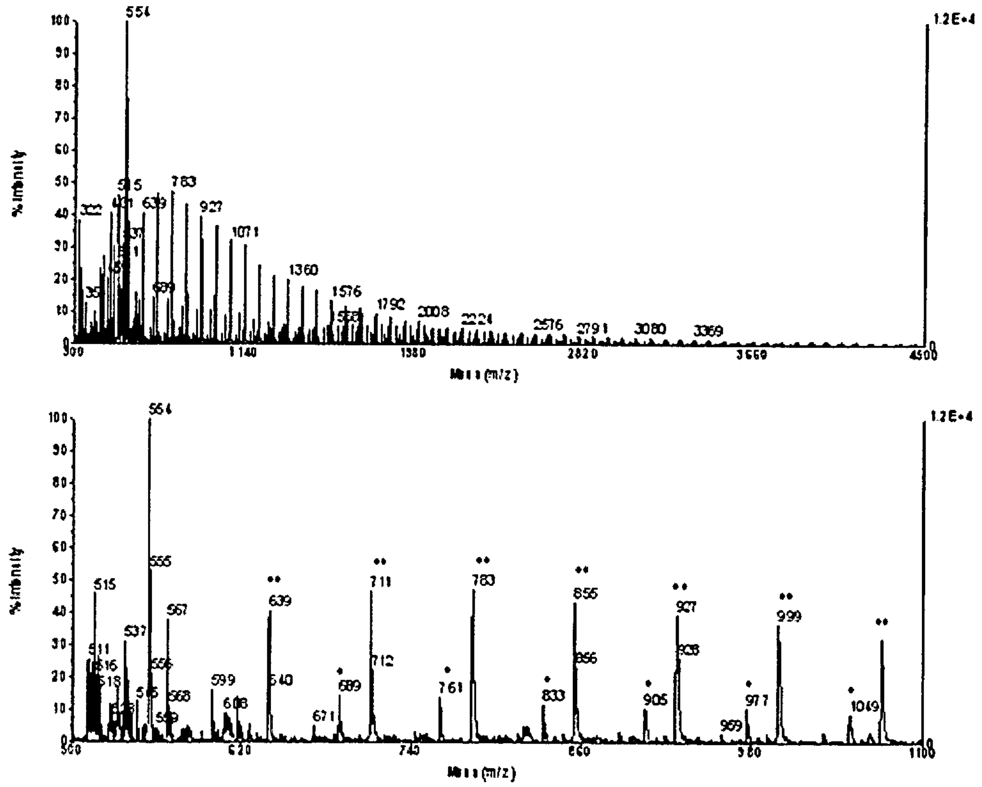
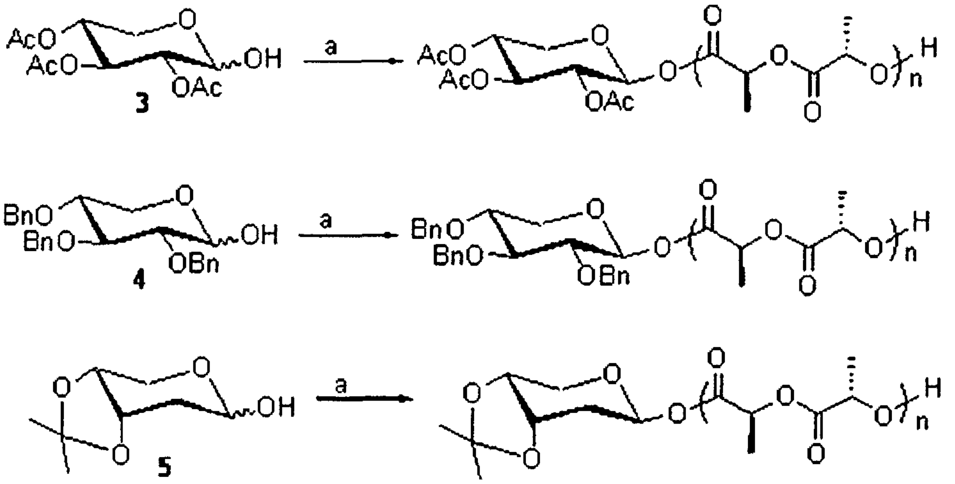


Figure 3. The MALDI mass spectrum for PLA produced from co-initiator **2**, with a degree of polymerization of 10. The peaks marked with * correspond to [**2**-PLA-Na]$^+$ and the peaks marked with ** correspond to [**2**-PLA-2Na]$^+$.



Scheme 3. Synthesis and structure of PLA prepared using 2,3,4-tri-*O*-acetyl-D-xylopyranose **3**, 2,3,4-triO-benzyl-D-xylopyranose **4**, and 2-deoxy-3,4-isopropylidene acetal-D-ribose **5** co-initiators. Where *n* = 10–250. Reagents and conditions: a) n [*S*]-lactide (1 M), LZnEt, CH_2Cl_2, 25 °C.

Pyranoses Derived from D-Xylose and 2-Deoxy-D-Ribose

To probe the scope of the initiating system and the utility of carbohydrate end capped PLA, a range of other pyranose co-initiators were tested (Scheme 3). Pyranoses are the most prevalent form of most simple carbohydrates and are therefore abundant, inexpensive chiral compounds with a multitude of hydroxyl groups. Previous investigations using pyranoses have focused exclusively on the hexoses D-glucose or D-galactose.[9–17] Therefore, there was scope for an examination of an initiating system using pentoses. D-Xylose is the pentose with the same stereochemistry as D-glucose but without substitution at C-5 and 2-deoxy-D-ribose has only two ring hydroxyl substituents; they were targeted as useful materials for biomedical studies to elucidate the influence of ring substitution. Furthermore, D-xylose is a major constituent of hemicellulose and is therefore easily accessible and inexpensive, 2-deoxy-D-ribose is a constituent of nucleic acids and therefore ubiquitous in biology.[2] The polymerization conditions were the same as used for the aldonate esters **1** and **2**; the initiating system required the synthesis of pyranoses with only one free hydroxyl group. The co-initiators 2,3,4-tri-*O*-acetyl-D-xylopyranose **3**, 2,3,4-tri-*O*-benzyl-D-xylopyranose **4** and 2-deoxy-3,4-isopropyl acetal-D-ribopyranose **5** were prepared from D-xylose and 2-deoxy-D-ribose, respectively, using literature methods which were straightforward and high yielding, this was important due to the complexity of some carbohydrate functionalization strategies.[19,20,22,28] All of the co-initiators had the initiating hydroxyl moiety at the anomeric position (C-1) and were isolated in anomeric ratios (α:β) of 10:7, 5:2 and 3:2 for **3**, **4**, and **5**, respectively.

The properties of the PLA produced at 4 mM concentration of co-initiator **3**, **4**, or **5** are shown in Table 3, it is notable that all the polymerizations occurred rapidly and with good control. There was close agreement between calculated and experimental M_n, for example using **4** at 80% conversion of lactide, the calculated M_n was 30,000 and that obtained by SEC was 29,800. The polymerizations occurred more rapidly than with aldonate ester co-initiators, for example at 4 mM concentration of **1** the polymerization required 960 min to reach 87% conversion whereas with **3** only 80 min were needed.

The ^1H NMR spectrum of the PLA indicated only the expected carbohydrate ester end group resonances, as illustrated in Figure 4 and Figures S1-5. Figure 4 shows the ^1H NMR spectrum of the PLA end capped with **5**, the α and β anomers are most clearly distinguished by the two H-1 signals at 6.22 and 6.00 ppm, respectively. Furthermore, the integrals for the end-groups versus those for the PLA methylene groups are in excellent agreement with the polymerization stoichiometry. In Figure 4, the polymerization was conducted using 50 equivalents of lactide to **5**, the relative integrals of the H-1

Table 3. PLA Synthesized Using Co-initiators **3**, **4** and **5**

Co-initiator[a]	% Conversion[b]	Time/Min	M_n Calculated	M_n SEC[c] (PDI)
3	12	20	4300	3800 (1.17)
3	63	50	22,800	25,000 (1.17)
3	87	80	31,700	30,700 (1.14)
3	91	110	33,000	33,700 (1.10)
3	95	170	34,400	37,100 (1.46)
4	10	80	3900	3920 (1.15)
4	20	110	7620	7300 (1.17)
4	44	140	16,300	15,000 (1.10)
4	62	210	22,700	21,200 (1.04)
4	82	360	30,000	29,800 (1.28)
5	16	94	5900	5200 (1.05)
5	30	150	11,000	10,900 (1.04)
5	51	215	18,600	20,600 (1.02)
5	89	393	32,200	41,900 (1.09)

[a] Polymerization conditions: $[LA]_0 = 1$ M, [co-initiator] = 4 mM, CH_2Cl_2, 25 °C.

[b] Determined by ^1H NMR by integration of the methine signals at 5.20 ppm for PLA and 5.00 ppm for lactide.

[c] Determined by SEC using $CHCl_3$ and versus narrow M_n polystyrene standards and with a correction factor applied.[27]

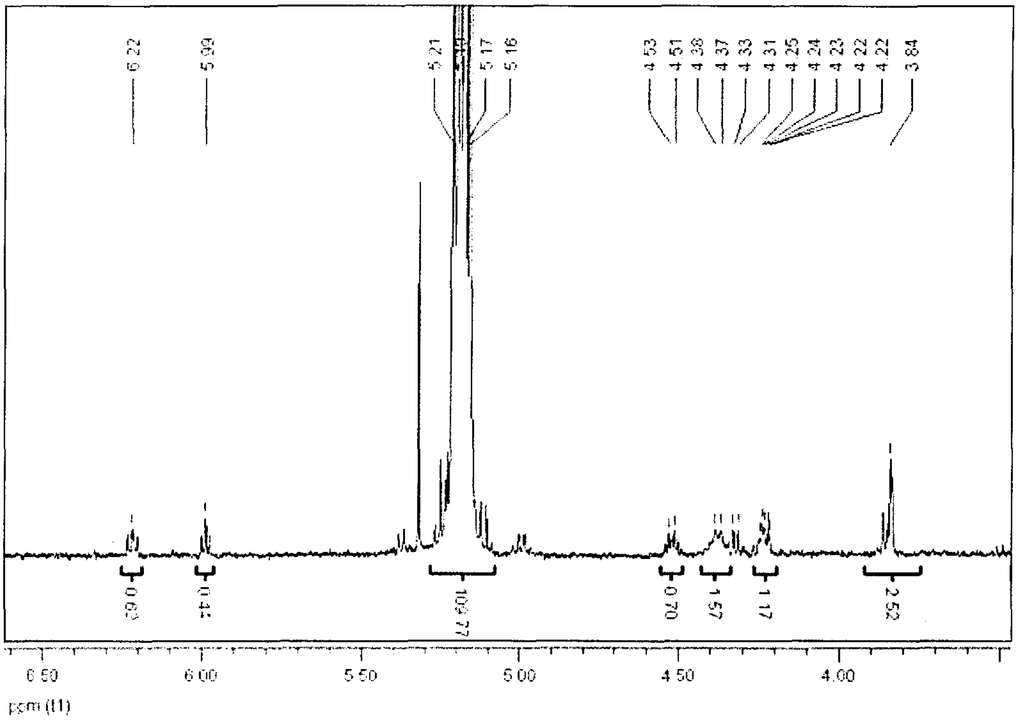


Figure 4. ^1H NMR spectrum showing PLA synthesized using co-initiator **5** to illustrate the two anomeric signals at 6.22 and 6.00 ppm (for full spectrum see Figure S5). Polymerization conditions: $[\mathbf{5}]_0 = 0.02$ M, $[LA]_0 = 1$ M, CH_2Cl_2, 25 °C. The polymerization went to complete conversion and the polymer was purified (see experimental section). The ratio of the anomers is indicated by the ratio of the integrals for the signals at 6.20 and 6.00 ppm.

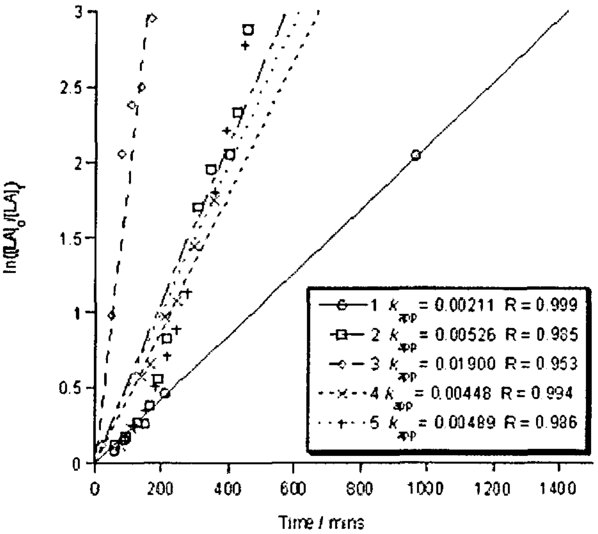


Figure 5. Plot of ln{$[LA]_0/[LA]_t$} versus time for co-initiators **1–5**. Polymerization conditions: $[LA]_0 = 1$ M, [co-initiator] = 4 mM, CH_2Cl_2, 25 °C. $[LA]_t$ was determined from the percentage conversion by ^{1}H NMR.

signals, at 6.22 and 6.00 ppm, to the lactide methylene signals, at 5.18 ppm, indicate a degree of polymerization of 52.

Polymerization Kinetics

The co-initiators showed significant differences in the polymerization rate, presumably reflecting differences in the rate of initiation between the different initiators. The plots of ln{$[LA]_0/[LA]_t$} versus time, for 4 mM concentration of co-initiator and 1 M concentration of lactide, are illustrated in Figure 5.

In Figure 5, the gradient of the lines corresponds to the pseudo first order rate constant, k_{app}, for the various co-initiators. A comparison of the k_{app} values for the initiators shows an order: **3** > **2** > **5** > **4** > **1**. The relative rates of the co-initiators relate to the type of hydroxyl group initiating the polymerization with secondary anomeric hydroxyl groups (e.g., on **3–5**) showing significantly enhanced rates compared to the secondary hydroxyl group on **1**. It is postulated that the reason for the greater rate of secondary anomeric hydroxyl initiators is due to their reduced steric hindrance and higher acidity compared to open chain secondary hydroxyl initiator **1**. The primary hydroxyl group on **2** showed a rate comparable to the secondary anomeric hydroxyl groups on **3–5**. Thus, the nature of the hydroxyl group had a significant influence over the polymerization rate and this was controlled predominantly by steric factors.

Water Contact Angle

For biomedical applications it is important to reduce the hydrophobicity of PLA and it is proposed that end group functionalization may help achieve this. To establish the hydrophilicity of the series of end-capped PLAs, the static contact angles with water were measured (Table 4). Investigation of the polymer films using a microscope-based interferometer showed that the films were homogeneously coated on the glass slides and their surface roughness values comparable (Table 4). Therefore, the differences of surface wettability among the films can be entirely attributed to differences of the chemical composition of the film/water interface. The initiator was found to reduce the contact angles of the poly(*S*-lactide) compared to poly(*S*-lactide) initiated from ethanol which a contact angle of 82°, in reasonable agreement with literature values.[29] The carbohydrate initiators all resulted in films with reduced contact angles, with the order of increasing hydrophilicity being: **4**-PLA ~ **5**-PLA < **2**-PLA < **3**-PLA < **1**-PLA. Both the nature of the carbohydrate substituents and the type of carbohydrate, pyranose versus aldonate ester, influence the contact angle. Acetyl groups are more hydrophilic than benzyl or isopropylidene acetal groups therefore poly(*S*-lactide) initiated with **3** has a lower contact angle than that initiated using **4**. Also, increasing the number of substituents increases the hydrophilicity, thus poly(*S*-lactide) endcapped with substituted D-glucose is more hydrophilic than D-xylose or

Table 4. The Surface Roughness and Static Water Contact Angles of Films of Polylactide Initiated Using Compounds 1–5

Initiator	RMS (nm)[a]	Water contact angle[b]
1-PLA	3.7 ± 0.8	64.2° ± 1.0°
2-PLA	4.3 ± 1.9	76.0° ± 3.0°
3-PLA	4.2 ± 0.8	66.2° ± 1.8°
4-PLA	3.0 ± 2.0	79.7° ± 0.2°
5-PLA	5.0 ± 5.0	79.4° ± 0.3°
PLA	2.3 ± 0.8	82.1° ± 0.3°

[a] Determined using a microscope-based interferometer expressed as the average root mean square (RMS) value.

[b] Determined by deposition of 30 μL of ultra-pure water to the surface of the films and using a drop shape analysis system to determine the contact angle.

2-deoxy-D-ribose. Finally, the aldonate esters have lower contact angles than their pyranose counterparts, thus poly(S-lactide) initiated with **2** is more hydrophilic than with **4**. Although, the decreases in contact angle are quite modest, they do show the potential for these initiators to increase the hydrophilicy of the polylactide films.

CONCLUSIONS

The controlled S-lactide polymerization using a range of different carbohydrate co-initiators has been established. The novel co-initiators were pyranoses and aldonate esters derived from D-gluconolactone, D-xylose, D-xylonolactone, and 2-deoxy-D-ribose. The polymerizations were all well controlled, as illustrated by the good correlation between calculated and experimental M_n, the linear increase in the M_n with percentage conversion, the correlation between M_n and [lactide]$_0$-[lactide]$_t$/[co-initiator] and the narrow polydispersity indices. Polylactides with a controllable degree of polymerization were synthesized for each different co-initiating group, thereby providing a viable route to PLA end functionalized with biologically compatible and derived molecules. The polyesters were fully characterized, including by NMR spectroscopy, SEC and mass spectrometry. Thin films of the polymer had lower water contact angles than poly(S-lactide), indicating that the carbohydrate initiators were useful for increasing the hydrophilicity, an important parameter for improving biocompatibility. We are currently exploring the utility of these polyesters as matrices for tissue engineering and this will be the subject of a future report.

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REFERENCES AND NOTES

1. Amass, W.; Amass, A.; Tighe, B. Polym Int 1998, 47, 89–144.
2. Ragauskas, A. J.; Williams, C. K.; Davison, B. H.; Britovsek, G.; Cairney, J.; Eckert, C. A.; Fredrick, W. J., Jr.; Hallett, J. P.; Leak, D. J.; Liotta, C. L.; Mielenz, J. R.; Murphy, R.; Templer, R.; Tschaplinski, T. Science 2006, 311, 484–489.
3. Drumwright, R. W.; Gruber, P. R.; Henton, D. E. Adv Mater 2000, 12, 1841–1846.
4. Albertsson, A.-C.; Varma, I. K. Biomacromolecules 2003, 4, 1466–1486.
5. Langer, R.; Vacanti, J. Science 1993, 260, 920–926.
6. Stevens, M. M.; George, J. Science 2005, 310, 1135–1138.
7. Bonanzi, I.; George, J.; Stevens, M. M. Curr Opin Chem Biol 2006, 10, 568–575.
8. Wang, Q.; Dordick, J. S.; Linhardt, R. J. Chem Mater 2002, 14, 3232–3244.
9. Bisht, K. S.; Deng, F.; Gross, R. A.; Kaplan, D. L.; Swift, G. J Am Chem Soc 1998, 120, 1363–1367.
10. Deng, F.; Bisht, K. S.; Gross, R. A.; Kaplan, D. L. Macromolecules 1999, 32, 5159–5161.
11. Yasugi, K.; Nakamura, T.; Nagasaki, Y.; Kato, M.; Kataoka, K. Macromolecules 1999, 32, 8024–8032.
12. Nagasaki, Y.; Yasugi, K.; Yamamoto, Y.; Harada, A.; Kataoka, K. Biomacromolecules 2001, 2, 1067–1070.
13. Ouchi, T.; Uchida, T.; Ohya, Y. Macromol Biosci 2001, 1, 371–375.
14. Persson, P. V.; Schröder, J.; Wickholm, K.; Hedenström, E.; Iversen, T. Macromolecules 2004, 37, 5889–5893.
15. Córdova, A.; Iversen, T.; Hult, K. Macromolecules 1998, 31, 1040–1045.
16. Bernard, K.; Degeé, P.; Dubois, P. Polym Int 2003, 52, 406–411.
17. Kricheldorf, H. R.; Stricker, A. Macromolecules 2000, 33, 696–701.
18. Joseph, C. C.; Regeling, H.; Zwanenberg, B.; Chittenden, G. J. F. Tetrahedron 2002, 58, 6907–6911.
19. Mitchell, S. A.; Pratt, M. R.; Hruby, V. J.; Polt, R. J Org Chem 2001, 66, 2327–2342.
20. Grummitt, A. R.; Harding, M. M.; Anderbert, P. I.; Rodger, A. Eur J Org Chem 2003, 63–71.
21. Decoster, E.; Lacombe, J. M.; Strebler, J. L.; Ferrari, B.; Pavia, A. A. J Carbohydr Chem 1983, 2, 329–341.
22. Corey, E. J.; Marfat, A.; Goto, G.; Brion, F. J Am Chem Soc 1980, 102, 7984–7985.
23. Nishizawa, M.; Komana, S.; Yamane, Y.; Kayano, K.; Hatakeyama, S.; Yamada, Y. Chem Pharm Bull 1994, 42, 982–984.
24. Kluger, R.; Song, Y. H. J Org Chem 1994, 59, 733–736.
25. Bessmertnykh, A.; Henin, F.; Muzart, J. Carbohydr Res 2004, 339, 1377–1380.
26. Williams, C. K.; Breyfogle, L. E.; Choi, S. K.; Nam, W. W.; Young, V. G, Jr.; Hillmyer, M. A.; Tolman, W. B. J Am Chem Soc 2003, 123, 11350–11359.
27. Kowalski, A.; Duda, A.; Penczek, S. Macromolecules 1998, 31, 2114–2122.
28. Tejima, S.; Ness, R. K.; Kaufman, R. L.; Fletcher, H. G, Jr. Carbohydr Res 1968, 7, 485–490.
29. Hu, Y.; Winn, S. R.; Krajbich, I.; Hollinger, J. O. J Biomed Mater Res 2003, 64A, 583–590.