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Novel Regioselective Syntheses of Carbohydrate Clusters and β-Cyclodextrin Derivatives and Studies of the Reactions of Dialkylstannylene Acetals of Carbohydrate-Derived *cis*-1,2-Diols

by

Hassan Namazi

Submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy

at

Dalhousie University
Halifax, Nova Scotia
February, 1997

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by Hassan Namazi

in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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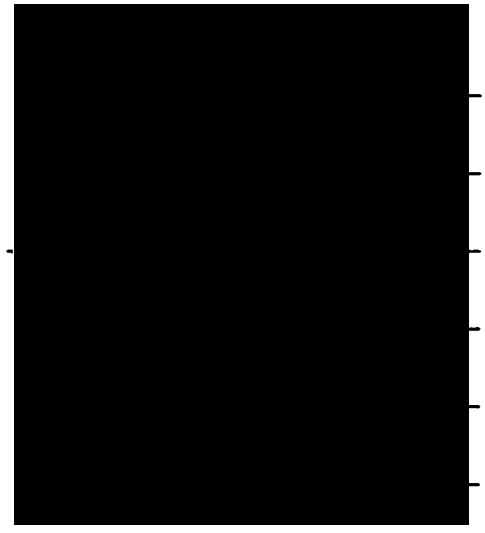

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Dedicated to my family and parents

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Abstract

Dialkylstannylene acetals are known to be very useful intermediates for the regioselective preparation of monosubstituted derivatives of diols and polyols and are widely used during syntheses of complex carbohydrates. The factors that influence the regioselectivity of reactions of different dialkylstannylene acetals of three *cis*-1,2-diols on pyranose rings, namely methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (**34**) and methyl 4,6-*O*-benzylidene- α- and β- D-allopyranoside (**54** and **60**), were investigated in detail. Dialkylstannylene acetals of compound **34** react at O-2 or O-3 depending on reaction conditions, while those of compounds **54** and **60** react only at O-2. It was shown by ^{119}Sn NMR spectroscopy that dialkylstannylene acetals of compound **34** exist in chloroform-*d* solutions mainly as mixtures of a dimer and a trimer, those of compound **54** are mixtures of two dimers, while those of compound **60** are mainly one dimer. The structures of these species were determined. The factors influencing reaction regioselectivity for these intermediates include the nature of the species present in solution and the reactivities of the oxygen atoms in the different species present.

Clustering of oligosaccharide molecules on cell surfaces are important for their biological activity. Methodology was developed for the regioselective preparation of small non-glycosidically linked clusters in high yields from dibutylstannylene acetal intermediates. Many different small clusters were formed by linking a number of different monosaccharides *via* ester linkages formed by reaction with a wide variety of di- or tri- functional electrophiles.

Cyclodextrins are very useful as complexing agents for drugs and other biologically active molecules and there has been intense interest in preparing modified derivatives. Methods have been developed that give by far the highest yields known of two substituted derivatives that have been widely used in syntheses, namely heptakis-(6-*O*-*tert*-butyldimethylsilyl)-2-*O*-*p*-toluenesulfonyl-β-cyclodextrin (**114**) and heptakis-(6-*O*-*tert*-butyldimethylsilyl-2-*O*-*p*-toluenesulfonyl)-β-cyclodextrin (**118**). Dimeric silylated β-cyclodextrins (**119-121**) were also prepared but broadening in their NMR spectra limited precise determination of their structures. Evidence was obtained from variable temperature ^{1}H NMR spectra that the hydrogen bonding in compound **118** is very unusual. The two different types of hydroxyl hydrogens are both extremely reluctant to exchange with each other and, at the same time, are involved in rapid exchange between "flip-flop" hydrogen-bonding sites.

List of Abbre*via*tions and Symbols

Å	angstrom
Ac	Acetyl
All	Allyl
Anal	Analysis
APCI	atmospheric pressure chemical ionization
Ar	aromatic
ax	axial
br	broad signal in NMR
Bn	benzyl
Bz	benzoyl
c	concentration
calc.	calculated
CBZ	benzyloxycarbonyl
CD (s)	cyclodextrin (s)
COSY	Proton correlated NMR spectroscopy
CP/MAS	cross polarization/magic angle spining
d	doublet signals in NMR and day (s) in reaction time
dd	doublet of doublets
ddd	doublet of doublets of doublets
DIPEA	diisopropylethylamine
DMF	*N,N*-dimethylformamide

DMAP	4-*N,N*-dimethylaminopyridine
DMSO	dimethylsulfoxide
2D	two dimensional NMR
eq.	equatorial
EI	electron ionization
Eq.	equation
ES	electrospray
Exp.	experimental
FABMS	Fast Atom Bombardment Mass Spectrometry
Fig.	figure
g	gram
G	Gibb's free energy
GC	gas chromatography
h	hour
H	enthalpy
HETCOR	Heteronuclear Correlated 2D NMR Spectroscopy
HMQC	Heteronuclear Multiple Quantum Correlation
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectroscopy
ibu	isobutyl
ipr	isopropyl
IR	Infrared spectroscopy

J	coupling constant in NMR spectroscopy
JMD	J-Modulated Spin-Echo
lit.	literature
m	multiplet in NMR, and meta position in benzene
Me	methyl
MHz	megahertz
min	minute
M^+	molecular ion
m/z	mass-to-charge ratio in MS
mp	melting point
mL	millilitre
mmol	millimole
MS	Mass Spectrometry
NMI	*N*-methylimidazole
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Spectroscopy
pent	pentet in NMR
ph	phenyl
ppm	parts per million
q	quartet in NMR
R_f	fractional migration distance of a compound on TLC

s	singlet signal in NMR
S	entropy
t	triplet signal in NMR
td	triplet of doublets in NMR
t	tertiary
TBDMS	*tert*-butyldimethylsilyl
TEA	triethylamine
TLC	Thin Layer Chromatography
TMS	tetramethylsilane
TOCSY	Total correlation spectroscopy
Ts	*p*-toluenesulfonyl
δ	chemical shift in ppm
$[\alpha]_D^t$	specific rotation measured at temperature t °C (D = 589 nanometer)

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Chapter 1

Synthesis and regioselective substitution of carbohydrate derived *cis*-1,2-diols *via* dialkylstannylene acetals

1.1 Introduction

In a multistep synthesis, performing reactions on polyfunctional molecules is difficult because it is likely that multiple products will be obtained. Carbohydrates, with their several hydroxyl groups of approximately the same reactivity, are among the most difficult. For synthetic organic chemists, particularly those who are working with carbohydrates, a major consideration in designing any synthesis is the protection of functional groups. The process of protection and deprotection requires choosing a protecting group or groups that can be added in high yield and removed in high yield without affecting the remainder of the molecule. Also, the protecting groups must be stable during the other reactions in the synthetic sequence. These requirements are difficult to satisfy.

Primary hydroxyls in carbohydrates are more reactive than secondary hydroxyls toward electrophiles, whereas the secondary hydroxyls have very similar reactivity. Consequently, substitution at a secondary hydroxyl of a carbohydrate in the presence of a free primary hydroxyl usually requires the prior protection of the primary hydroxyl group. Similarly, substitution of one of the secondary hydroxyls in the presence of other secondary hydroxyls requires a regioselective protecting procedure.

Several methods have been introduced for the regioselective substitution of sugar molecules, but most, with some exceptions, are limited to the selective substitution of

primary hydroxyls in the presence of secondary hydroxyls. For many years, there was not an effective and general method for the regioselective substitution of secondary hydroxyls in the presence of primary and/or other secondary hydroxyls.

A relatively new procedure, in which dibutylstannylene derivatives were used for the selective activation of *vicinal cis*-OH groups of nucleosides was introduced by Moffatt and coworkers[1] in 1974. This approach avoids the above problems and can be used directly for the regioselective monosubstitution of secondary hydroxyls in the presence of primary and other secondary hydroxyls. This methodology has been widely adopted and has become one of the most used methods for the regioselective monofunctionalization of diols and polyols.[2] The discovery of tin-containing intermediates opened a wide area for chemists to regioselectively manipulate hydroxyl groups in diols and polyols.[2,3]

Ogawa and Matsui[4] were the first to apply bis(tributyltin) oxide to obtain regioselective enhancement of the nucleophilicity of polyols by the formation of tributylstannyl ethers. The tin atoms in these intermediates coordinate with neighbouring oxygen atoms in particular stereochemical relationships and increase the nucleophilicity of the tin-ether oxygen atoms.

In this chapter, some synthetic applications of dialkylstannylene acetals for the regioselective monofunctionalization of diols and polyols in carbohydrates will be described. In general, the regioselectivity obtained depends on different factors such as solvent, structure of substrate, the presence or absence of additional nucleophiles, the structure of the alkyl groups on the tin atom, the concentration, and the temperature. The most common reactions which are carried out *via* these intermediates are alkylation,

acylation, tosylation and oxidation. Also, organotin intermediates have been used extensively in the synthesis of macrocyclic lactones and lactams.[5] Activation using tin-containing intermediates has been applied to oligosaccharide synthesis.[6]

Dibutylstannylene acetals are easily prepared by refluxing a diol with one equivalent of dibutyltin oxide in benzene or toluene with azeotropic removal of water (Figure 1.1). Dialkylstannylene acetals may also be prepared by refluxing diols with dialkyltin oxides in methanol *via* the soluble intermediate, dibutyltin dimethoxide, or directly using commercial dibutyltin dimethoxide.[7,8] Tributylstannyl ethers are prepared from alcohols in the same way using half of an equivalent of bis(tributyltin) oxide.

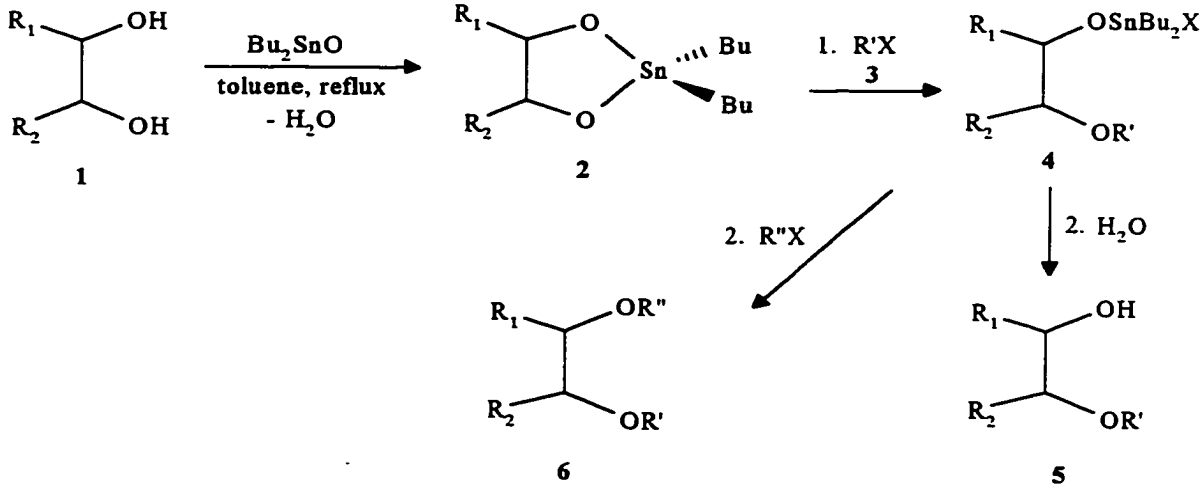


Figure 1.1. Synthesis of dialkylstannylene acetals and their derivatives

These types of reactions are not limited only to 1,2-diols; dialkylstannylene acetals can also be formed from 1,3-diols. The subsequent treatment of these intermediates with electrophiles gives the corresponding monosubstituted derivatives after hydrolysis.

Heterodisubstituted compounds can be obtained by adding a second electrophile to the reaction before the hydrolysis step. Fortunately, the second substitution reaction is much slower than the first, which makes selective monosubstitution easy to achieve.

Reactions involving dialkylstannylene acetal intermediates can be performed immediately after formation without purification or separation, or, alternatively, the stannylation solvent can be removed and another solvent added. A few workers have purified the intermediate before reaction.[9]

The employment of dialkylstannylene acetal intermediates brings three distinct advantages over other methods for substitution that have led to their general use. They give monosubstituted products, usually in high yield and high selectivity under mild conditions. The rates of reactions with these intermediates are enhanced in comparison with reactions performed directly on diols. Finally, and most importantly, the monosubstitution reactions are often highly regioselective.

IUPAC nomenclature for dialkylstannylene acetals is as follows. Five-membered ring dialkylstannylene acetals are called 2,2-dialkyl-1,3,2-dioxastannolanes and the six-membered ring acetals are termed 2,2-dialkyl-1,3,2-dioxastannanes.

1.1.1 Structures of dialkylstannylene acetals and their regioselectivity

The most common techniques that have been applied to the study of the structure of tin intermediates are ^{119}Sn, ^{1}H, and ^{13}C NMR spectroscopy, X-ray crystallography, molecular weight estimation and mass spectrometry.

^{119}Sn NMR spectroscopy is a powerful technique for obtaining information about

structure, reaction, and tin-coordination status. It has been shown that ^{119}Sn NMR chemical shifts for different coordination states of dialkyldialkoxytin atoms range from +100 to -350 ppm. For compounds containing tetracoordinate tin atoms bearing primary alkyl groups, the tin nuclei absorb between +100 and -40 ppm, while pentacoordinate tin nuclei absorb between -90 and -170 ppm.[10,11] Hexacoordinate tin atoms absorb between -200 and -350 ppm relative to the position of the tetrametyltin signal. The cause of this large shielding is attributed to the reduction in the paramagnetic component of shielding which is affected by the valence orbitals on the tin atom.[11] Secondary and tertiary alkyl substituents on tin cause the above ranges to be about 50 and 100 ppm more shielded, respectively.

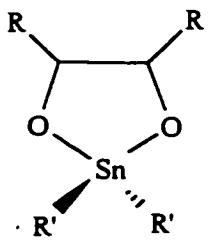
1.1.1.1 Structures of dialkylstannylene acetals derived from simple diols

1.1.1.1.1 In the solid state

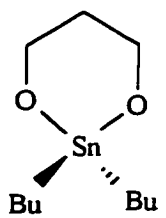
X-ray crystallographic studies of dibutylstannylene acetals derived from simple diols, such as 2,2-dibutyl-1,3,2-dioxastannolane (7), and 2,2-dibutyl-1,3,2-dioxastannane (10) (see Fig 1.2) indicate that these compounds are infinite ribbon polymers in the solid, having the individual monomer units joined together by two Sn-O bonds[12,13] to give hexacoordinate tin atoms.

^{119}Sn NMR CP/MAS (Cross Polarization Magic Angle Spinning) spectra of these compounds contain isotropic peaks at about -231 ppm for 7 and -279 and -281.8 ppm for 10. Compound 8 absorbs in this region at -205 ppm, also consistent with an infinite ribbon polymer. X-ray crystallography of 2,2-di-*t*-butyl-1,3,2-dioxastannolane (9) showed

that it was a dimer in the solid.[14] Its ^{119}Sn NMR chemical shift from both solution and the solid state was -225 ppm, consistent with pentacoordinate tin since *t*-butyl groups on tin cause the absorption to be shielded by about 100 ppm. The large substituents on the tin atoms apparently prevent a higher degree of association than the dimer.



7 R = H, R' = Bu
8 R = Me, R' = Bu
9 R = H, R' = *t*-Bu



10

Figure 1.2 Structures of dialkylstannylene acetals derived from simple diols

X-ray crystallography of dibutylstannylene acetals determined that the O-Sn-O bond angles for five- and six-coordinate tin atoms are 78-80° in five-membered rings. This bond angle for a six-coordinate tin atom in a six-membered ring is 93.2°.[13] These bond angles are much smaller than that predicted for tetrahedral geometry with four-coordinate tin atoms. However, they are close to 90°, the ideal value for the angle between apical and equatorial substituents at five- or six- coordinate tin atoms in trigonal bipyramidal or octahedral geometry. The trigonal bipyramidal geometry is distorted in five-membered ring dialkylstannylene acetals and the intermolecular Sn-O bond lengths are longer (2.23-2.27 Å) than the intramolecular bond lengths (1.98-2.13 Å).[13]

1.1.1.1.2 In solution

Structural studies of liquid acyclic dialkyltin dialkoxides with simple substituents neat or in solution by molecular weight and NMR methods indicate that these compounds exist as dimers. Compounds with bulky substituent groups, e.g., *t*-butyl, exist as monomers, whereas compounds with intermediate-sized substituents, e.g., isopropyl, are mixtures of dimers and monomers in solution.[10]

Dibutylstannylene acetals derived from simple primary or secondary diols exist as complex mixtures in solution in non-polar solvents.[15] These mixtures contain dimers, trimers, tetramers, and pentamers (see Figure 1.3) in exchange with each other at room temperature. The oligomeric composition depends strongly on concentration and temperature. Dimeric species are minor at low temperatures (-50 °C) but become increasingly favoured at temperatures from 0-100 °C.[15] In the ^{119}Sn NMR spectra of dimeric species, only one signal is present at -100 to -150 ppm, whereas the spectra of trimers, tetramers, and other oligomers contain signals of the hexacoordinate tin atom at -200 to -300 ppm (see ^{119}Sn NMR spectra of **7** in Figure 1.4). The absence of signals in the region related to tetracoordinate tin atoms in the ^{119}Sn NMR spectra of all of these compounds indicates that negligible amounts of these species are present under the conditions of examination. Thus, in comparison to the solid state (Section 1.1.1.1.1), in solution, these compounds are much less aggregated.

The greater tendency of cyclic stannylene acetals to dimerize in comparison with acyclic stannylene acetals is attributed to the bond angle imposed on tin by the geometrical constraints of closing a ring containing two long Sn-O bond lengths. The bound angles at

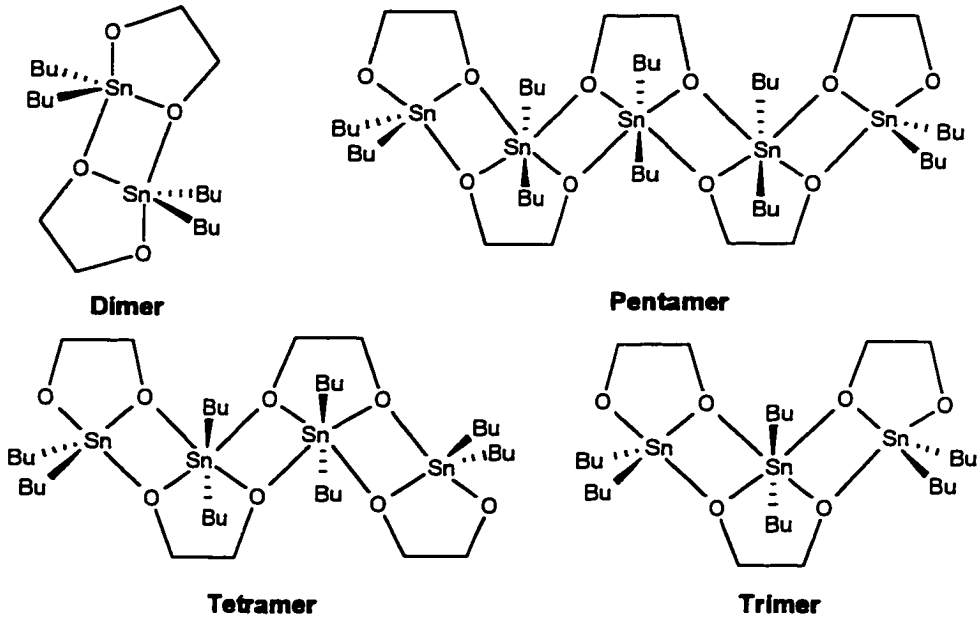


Figure 1.3 Structures of different oligomeric species of compound 7 in solution

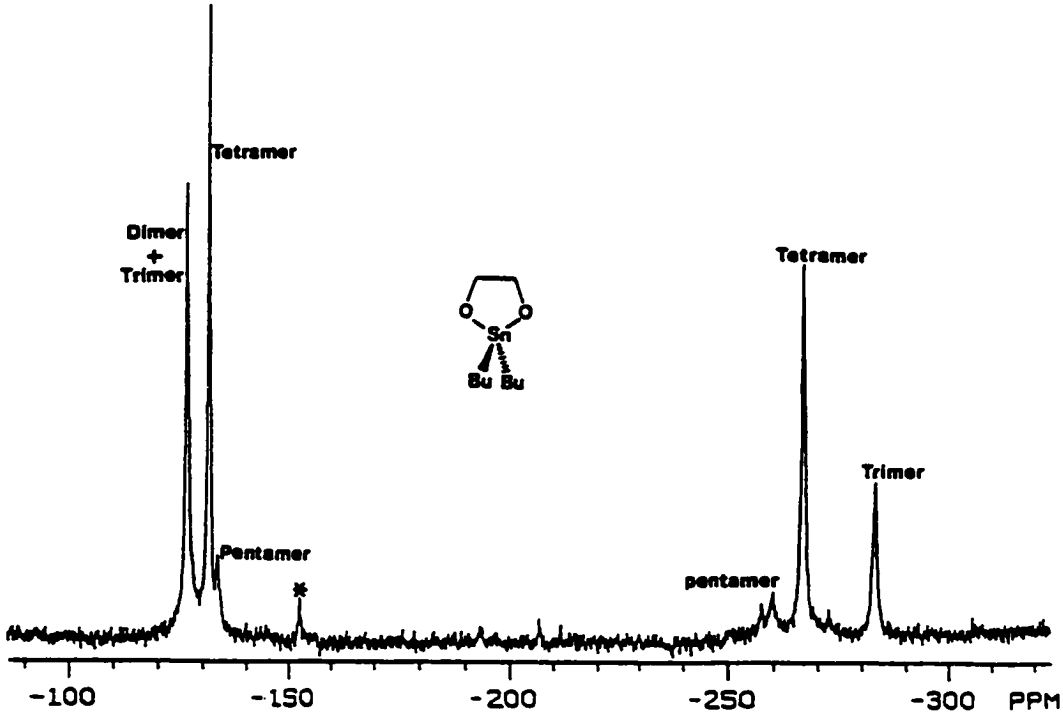


Figure 1.4 134.6 MHz ^{119}Sn NMR spectrum of 0.5 M solution of 7 in chloroform-*d* / dichlorofluoromethane, 3:1 at -80 °C[15]

tin observed in the solid state of ~79° for 1,3,2-dioxastannolanes and ~93° for dioxastannonanes are close to or less than the ideal values of angles for pentacoordinate or hexacoordinate tin but would strain a tetracoordinate tin atom, which prefers a bond angle of about 109.5°.[16]

For dialkylstannylene acetals derived from nonsymmetric parent diols where the oxygen atoms are diastereotopic, three possible dimers, of which two have C_2 symmetry, can be formed in solution. The population of each dimer in solution depends on several factors such as solvent, temperature, concentration and steric effects which can be affected by substituent groups on the tin atom or on the parent diols.[17] The structure of the three possible dimers for dialkylstannylene acetals derived from *vicinal* 1,2-diols are illustrated in Figure 1.5. The formation of a dimeric structure requires that one of the oxygen atoms from each monomer unit becomes tricoordinate and that the tin atoms become pentacoordinate. Dimers have been named by using the positional numbers of the oxygen atoms that are tricoordinate in the structures.[17]

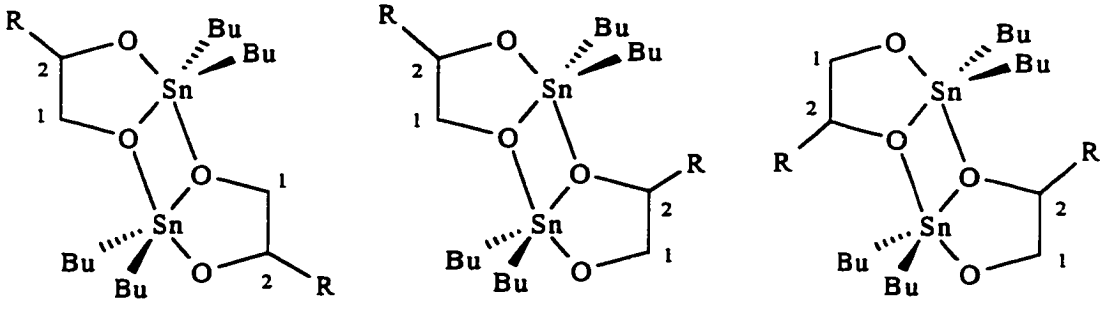


Figure 1.5 Dimeric structures of dialkylstannylene acetals derived from *vicinal* 1,2-diols.

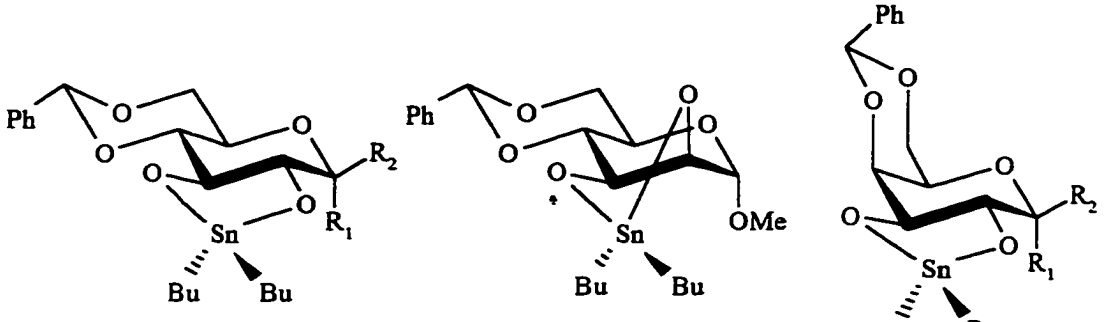
1.1.1.2 Structures of dialkylstannylene acetals derived from carbohydrates

1.1.1.2.1 Isolated secondary-secondary 1,2-diols in the solid state

The structures of dibutylstannylene acetals discussed in this section are shown in Figure 1.6. X-ray diffraction studies of crystals of methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-glucopyranoside (**11a**) showed its structure to be a single dimer.[16,18] The structure is composed of seven fused rings with two monomer units joined together by a central 1,3-dioxa-2,4-distannetane ring. The tin atoms are in the center of trigonal bipyramids with butyl groups occupying two of the equatorial positions. In each monomer unit, one of the oxygen atoms assumes an apical position of the trigonal bipyramid at tin and is dicoordinate, while the other oxygen atom is tricoordinate in the remaining equatorial position.[16,18] Three different dimer structures are possible for **11a**. The dimer observed in both X-ray studies was the 3,3-dimer, which has a C_2 axis of symmetry perpendicular to the plane of the central 1,3-dioxa-2,4-distannetane ring.[16,18]

An X-ray diffraction study of methyl 4,6-*O*-benzylidene-2,4-*O*-dibutylstannylene-α-D-mannopyranoside (**13**) revealed a pentamer structure. In this structure, the metal is pentacoordinate in the two terminal moieties and hexacoordinate in the three internal units.[19] The lengths of intermonomer Sn-O bonds where the oxygen atoms are connected to the hexacoordinate tin atoms is on average 2.48 Å, longer than the intermonomer Sn-O bond lengths to pentacoordinate tin in **13** and in **11a** which are ~ 2.27 Å. Intramonomer Sn-O bond lengths are shorter, averaging 2.12 Å in **13**. The results of solid state ^{119}Sn CP/MAS NMR studies of compounds **11a** and **13** are in agreement with the X-ray

observations.[20] For **11a**, two isotropic peaks are present at -126.8 and -128.6 ppm, consistent with two five-coordinate tin atoms in a dimeric structure that is slightly distorted from C_2 symmetry. The spectra of compound **13** contained two isotropic peaks at -119 and -127 ppm in the region of pentacoordinate tin and two isotropic peaks at -223 and -224 ppm in the region expected for hexacoordinate tin atoms. These observations are in agreement with the pentameric structure of **13**, if it is assumed that two of the hexacoordinate tin atoms have the same shift.



11a R_1 = OMe, R_2 = H

11b R_1 = OBn, R_2 = H

12 R_1 = H, R_2 = OBn

13

14 R_1 = OBn, R_2 = H

15 R_1 = H, R_2 = OBn

Figure 1.6 Structures of dibutylstannylene acetals derived from carbohydrates

The solid state ^{119}Sn CP/MAS NMR spectra of benzyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-β-D-galactopyranoside (**14**) showed an isotropic peak at -141 ppm indicating a dimeric structure.[20] Similar signals were observed[17] for **14** in solution at -138.4 and -143.8 in toluene-d_8 and chloroform-*d*, respectively, in agreement with the same dimeric structure in solution as in the solid state.

1.1.1.2.2. Isolated secondary-secondary 1,2-diols in solution

The structures of dibutylstannylene acetals derived from isolated *trans*-diols in pyranoside carbohydrates have been studied by Grindley *et al.*[17] by a combination of ^{119}Sn, ^{1}H and ^{13}C NMR experiments. For this study, methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-glucopyranoside (**11a**), benzyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α- and β-D-glucopyranoside (**11b** and **12**), and benzyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α- and β-D-galactopyranoside (**14** and **15**), which have different stereochemistries adjacent to the diols, were chosen. These compounds were found to be present predominantly as dimers, in contrast to the stannylene acetals of simple diols. It was found that in non-polar solvents, which of the three possible dimeric structure is adopted by the dialkylstannylene acetal is determined by the orientation of the adjacent substituents on the pyranose rings. For instance, when one adjacent substituent is in an axial orientation and the other is in an equatorial orientation as in **11a**, **11b** or **15**, the dialkylstannylene acetal is present as a single symmetric dimer with the two dicoordinate oxygen atoms adjacent to the axial substituents. For **11a**, the ^{119}Sn NMR spectra in chloroform-*d* contained a single peak in the region where pentacoordinate tin atoms are expected to absorb and the chemical shift from solution was similar to that from the solid state. On this evidence, and on the similarity of the solution and solid state ^{13}C NMR spectra, it was concluded that compound **11a** existed as the same single dimer in solution as in the solid state. It was concluded that steric interactions between the axial substituents and the butyl groups on tin force the tricoordinate oxygen atom to be distant from the axial oxygen atom.[17] Dialkylstannylene acetals with two adjacent equatorial substituents,

such as **12**, exist as mixtures of dimers that do not interconvert on the NMR timescale at accessible temperatures. If there are two adjacent axial substituents as in **14**, the dialkylstannylene acetal exists as a rapidly interconverting mixture of dimers, trimers, and tetrameric species.[17] The dibutylstannylene acetal derived from compound **14** is present as a mixture of species in solution and a mixture of products were obtained without positional preference.[17]

The ^{119}Sn NMR spectra of **13**, the dibutylstannylene acetal of a *cis*-diol, showed the presence of different species ranging in size from dimers to pentamers in solution. Depending on the temperature and solvent, the populations of these species changed. In chloroform-*d*, dimers and trimers are dominant and in toluene-d_8, the species present includes tetramers and pentamers. On lowering the temperature of the solutions, the populations of higher oligomers increase.[20] For a 0.2 M solution of compound at -55 °C, the ^{119}Sn NMR spectra showed one major signal at -123.4 ppm, and three other peaks with lesser intensities at -117.4, -122.5 and -283.3 ppm. On increasing the concentration, the intensities of the latter three signals increased relative to that of the major signal. From the observation of the signal in the hexacoordinate region of the spectrum (-220 to -300 ppm for dibutylstannylene acetals), these signals have been assigned to a trimer. Therefore, at lower temperatures in chloroform-*d*, the major species are dimers and trimers. The ^{119}Sn NMR spectrum of **13** in toluene-d_8 at room temperature contained three peaks, two in the pentacoordinate region at -117.0 and -145.3 ppm and one peak in the hexacoordinate region at -298 ppm. On lowering the temperature, a new signal appeared in the hexacoordinate region, which indicated that a second oligomer larger than

a dimer was now present. The solid state ^{119}Sn NMR spectrum of **13** showed two isotropic peaks in the hexacoordinate region and two of the pentacoordinate region. These results are consistent with the X-ray studies which showed a pentameric structure for the stannylene acetal derived from this carbohydrate if two hexacoordinate tin signals occur at the same chemical shift.[21]

1.1.1.3. Structures of dialkylstannylene acetals derived from primary-secondary (terminal) 1,2-diols on carbohydrates

^{119}Sn NMR studies on a variety of dialkylstannylene acetals derived from carbohydrates containing primary-secondary diols showed one sharp peak in the range of -92.8 to -186.4 ppm at room temperature in each stannylene acetal.[22] These chemical shifts are typical of pentacoordinate tin atoms and indicate that these compounds exist predominantly as single dimers in solution. The chemical shifts of tin atoms for hexamethylenestannylene acetals lie in a narrow range, -93 to -100 ppm. The reason for this more deshielded range of shifts than for other primary alkyl tin derivatives is the C-Sn-C bond angle. This bond angle (122.3 °) is smaller than in acyclic alkyl acetals (128.4 ° and 132.5 °).[23] Similar changes in chemical shifts have been observed for tin atoms in stannacycloalkanes when results for five- and six-membered rings are compared.[24] It has been shown that steric effects are the most important factors in determining which of the three possible dimers will be populated.[22] Therefore, it was concluded that the populated dimers were the ones that kept the tricoordinate oxygen atoms as far as possible from the substituent on the secondary carbon, that is, the dimers with both primary oxygen atoms tricoordinate.

1.1.2 The cause of regioselectivity with dibutylstannylene acetals

Considerable advances have been made in understanding the causes of the regioselectivity obtained in reactions of dibutylstannylene acetals. The rate enhancement in comparison with the direct reaction of diols presumably arises from the greater polarization of the Sn-O rather than the H-O bond.

David *et al.*[25] suggested the formation of dimeric species in general for diols to explain regioselectivity with dibutylstannylene acetals. In their proposal, dimeric structures are formed from two monomers giving a Sn_2O_2 parallelogram. In the four-membered ring, the apical oxygen atoms are dicoordinate and sterically less hindered, whereas, the equatorial oxygen atoms are relatively protected by threefold coordination in the dimeric structure. As a result, the regioselectivity was attributed to the reactivity of the apical dicoordinate oxygen atoms. However, they did not discuss which of the three possible dimers formed.

Later studies by Grindley and Thangarasa[17] pointed out that three dimers could be formed and that an important factor in the regioselectivity is the structure and population of the dominant species. Monomers, dimers, and higher oligomers are in theory possible structures for these species. The population of monomers is negligible; those of higher oligomers are usually much lower than that of the dimers and they are not expected to influence the regioselectivity significantly.

In a dimer, reactivity with electrophiles is greater at the dicoordinate oxygen atom because of its enhanced nucleophilicity compared to that of the tricoordinate oxygens. Another factor which influences the enhanced reactivity of the dicoordinate oxygen atom

is evident from the X-ray study of **11a**.[16,18] In the dimeric structure, two butyl groups on each tin atom extend perpendicular to the plane of four-membered distannetane ring. These highly mobile groups on both sides shield the tricoordinate oxygen atoms from electrophiles more than the dicoordinate oxygens, which are only attached to a single dibutyltin group.

In the case of terminal 1,2-diols, the two oxygen atoms in primary and secondary positions have quite different reactivities. Since steric effects are most important in determining which dimers are populated, it is expected that the most populated dimers would have the substitutent at the secondary centre away from the tricoordinate oxygen, that is, the primary oxygen will be tricoordinate preferentially. If the primary oxygen atoms become tricoordinate, the dicoordinate oxygen atoms, which are at secondary positions, will be more nucleophilic and substitution might be expected to occur mainly on the secondary oxygen. However, substitution was found to occur mainly on the primary oxygen atoms with dibutylstannylene acetals although reactivity at the secondary oxygen atom was enhanced in comparison with reaction directly on the diol. Changing the butyl groups on the tin atom to larger alkyl groups increased the amount of reaction at the secondary oxygen atoms. Altering the two butyl groups to the cyclic hexamethylene group dramatically reversed the regioselectivity from primary to the secondary oxygens.[26] On the basis of this study, it was concluded that two factors, the position of equilibrium among dimers and the reactivity of the oxygen atoms in the individual dimers, compete to determine the regioselectivity.[22]

1.1.3 The effects of added nucleophiles on the regioselectivity of reactions of dibutylstannylene acetals

The mechanism and role of added nuclophiles on the structure of dibutylstannylene acetals in solution is not fully understood. However, some suggestions have been made from indirect evidence derived by analyzing the products. Adding nucleophiles such as tertiary amines, tetrabutylammonium halides and cesium fluoride to the reaction solution increases the reaction rate, and, for some carbohydrates, causes the regioselectivity to be reversed. For instance, acylation of methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-mannopyranoside (**13**) has been investigated in benzene in the presence and absence of added nucleophiles.[27] It was reported that benzoylation of **13** in benzene without any added base or nucleophile resulted in the 2-O and 3-O-benzoylated products in 85% and 15% yields, respectively (from ^{1}H NMR integration). Adding one equivalent of *N*-methylimidazole to the reaction solution in benzene lead to the 3-*O*-benzoyl derivative only in 90% yield. Repeating this reaction in dioxane gave equal amounts of the 2-O and 3-O substituted products. From these observations, the existence of a competitive equilibrium between intermolecular association of a tin-bound oxygen atom from one molecule and the tin atom of another molecule and coordination of polar solvent or added nucleophile to tin atom as shown in Figure 1.7 has been suggested.[27]

It was thought that intermolecular coordination of the tin-bound oxygen atoms occurs through the less hindered oxygen atom of other molecule (equatorial position) and renders the axial oxygen atom more reactive. However, in the monomeric structure when

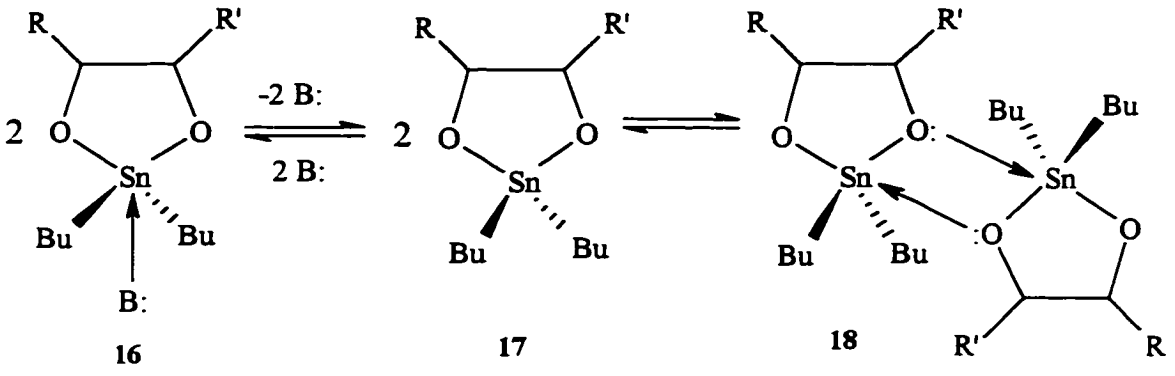


Figure 1.7 Equilibria between coordination of nucleophiles and oxygen to tin atoms[27]

solvent or Lewis base has been coordinated, regioselectivity arises from steric and electronic properties of the molecule.[27]

The effect of added nucleophiles on the structure of dibutylstannylene acetals derived from a variety of *cis*- and *trans*-1,2-diols in carbohydrate molecules has been extensively studied under different conditions by Thangarasa and Grindley[21] using ^{119}Sn NMR spectroscopy. This study showed that upon the addition of a nucleophile to the solution, equilibration occurs between dimers and dimer-mononucleophile adducts that shifts toward the adduct side as the temperature is lowered from ambient. By increasing the concentration of the nucleophile, the equilibrium is shifted more rapidly toward dimer-mononucleophile adducts. However, the changes in regioselecivity cannot br explained in terms of these dimer-monoadducts and it seems likely that monomer-adducts are the likely intermediates in reactions of stannylene acetals in the presence of added nucleophiles. The activation barrier for the interconversion of different dimers is decreased in the presence of nucleophiles and this effect can be seen from the change in the number and intensity of

signals in the ^{119}Sn NMR spectra.

1.1.4 Synthetic applications of dibutylstannylene acetals

In the last two decades, since the first applications of dialkylstannylene acetals, many papers on the synthesis of monosaccharides and oligosaccharide *via* tin intermediates have appeared in the literature. Selective activation of hydroxyl groups on carbohydrates containing primary-secondary or secondary-secondary diols on pyranosides and furanosides is very important for selective acylation, alkylation, and oxidation. Tributylstannyl ethers have also been used for selective substitution and synthesis of oligosaccharides.[28,29,30,31] However, because of the importance of the dibutylstannylene acetals compared to the other dialkylstannylene acetals or tributylstannyl ethers only the application of former will be reviewed here.

1.1.4.1 Macrocyclization *via* dibutylstannylene acetals

It has been shown that the reaction of 2,2-dibutyl-1,3,2-dioxastannolane derived from 1,2-diols with diacyl dichlorides under mild conditions is a convenient, one-pot procedure for the cyclooligomerization or selective synthesis of macrocyclic polyesters.[32,33] A typical example of the reaction in synthesis of macrocyclic oligomers is

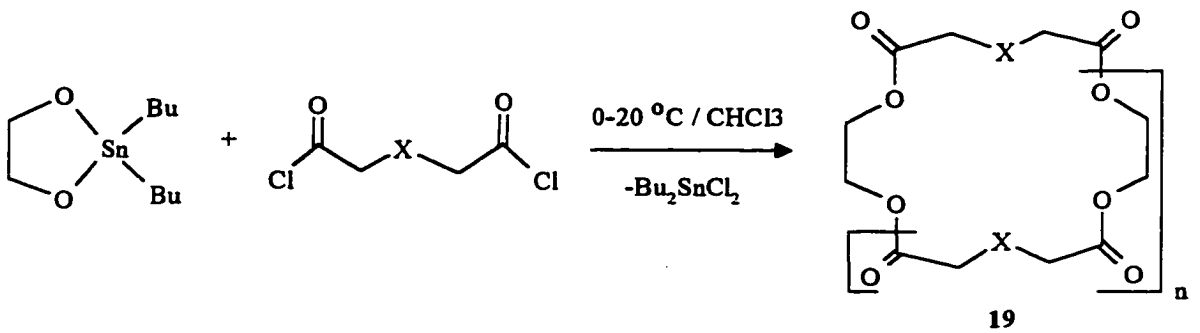


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Figure 1.8 Synthesis of cyclic oligomers using dialkylstannylene acetals

shown in Figure 1.8. In this reaction, the dibutylstannylene acetal derived from 1,2-ethanediol has been reacted with pentanedioyl dichloride (X = CH_2) and the cyclic dimer **19** (n = 1) was the most abundant compound isolated from a mixture of cyclic oligomers.[34]

1.1.4.2. Regioselective oxidation *via* dibutylstannylene acetals

Dibutylstannylene acetals are oxidized regioselectively under mild conditions to α-hydroxyketones. Reactions with bromine are very fast at room temperature; the bromine color disappear almost instantaneously as it is added to the stannylene acetal solution.[35,36,37] Reactions of dibutylstannylene acetals derived from simple diols occur regioselectively in excellent yields. However, for carbohydrates, particularly for terminal 1,2-diols the yields are usually low, probably because of the difficulty of isolating the products, which form mixtures of hemiacetals, which can be monomers, dimers or oligomers. The yields for regioselective oxidation of dibutylstannylene acetals derived from primary-secondary and secondary-secondary 1,2-diols in carbohydrates were improved by using *N*-bromosuccinimide (NBS).[38]

1.1.4.3 Regioselective substitution of carbohydrates *via* dialkylstannylene acetals

1.1.4.3.1 Regioselective substitution of secondary *vicinal cis*-1,2-diols

Dibutylstannylene acetal intermediates have been used extensively for the regioselective acylation and alkylation of *cis*-1,2-diols. A selected collection of some

recent results of regioselective reactions which have been done through these intermediates is shown in Table 1.1. In most cases, reaction occurs regioselectively on equatorial oxygen atoms adjacent to axial oxygen atoms. For example, acylation and alkylation of *cis*-1,2-diols, **20**, **22**, and **28** through dibutylstannylene acetals result in monosubstituted products highly regioselectively on equatorial oxygen atoms. The most prominent exceptions are for reactions of mannopyranoside derivatives protected at O-1, O-4 and O-6, where the regioselectivity varies depending on the reaction conditions. For instance, in the benzoylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (**28**) in benzene in the presence of *N*-methylimidazole, selective substitution is obtained at O-3. The same reaction in dioxane with added triethylamine gave a mixture of monosubstituted products at O-2 and O-3. Highly regioselective monosubstitution at the axial oxygen atom (O-2) has been obtained for the same substrate when the reaction was performed in benzene in the absence of any nucleophiles.[27]

In *p*-methoxybenzylation of 3,4,5,6-tetra-*O*-benzyl-*myo*-inositol (**29**), the 2-*O*-*p*-methoxybenzyl derivative was obtained in high yield *via* the dibutylstannylene acetal.[47] Also, benzylation of benzyl 2-*O*-benzyl-β-D-arabinopyranoside (**30**) occurred on O-3, adjacent to the axial oxygen in 70% yield.[48]

For *cis*-diols, when there is a deoxy centre adjacent to the equatorial hydroxyl preferential, substitution is obtained on the oxygen atom adjacent to the deoxy centre. In the case of 2,6-dideoxy-α-D-*ribo*-hexopyranoside (**31**), a high yield was obtained for reaction on the axial oxygen atom adjacent to the deoxy centre.[39] This result shows that steric effects have a considerable role in determining substitution regioselectivity.

Table 1.1 Regioselectivity with dibutylstannylene acetals derived from pyranoside carbohydrates containing isolated *cis*-1,2-diol units

Diol[a]	Reaction	Solvent	Temp. °C	Selectivity %			Ref.
				O-2	O-3	O-4	
20	benzoylation	dioxane[b]	20	91	-	-	40
21	benzoylation	DMF	20	-	100	-	27
22	benzylation	toluene[c]	100	-	73	-	41
23	benzoylation	dioxane[b]	20	-	81	-	42
	benzylation	DMF	100	-	72	-	42
24	benzoylation	benzene[d]	20	-	74	-	35
25	benzoylation	THF	20	9	67	-	43
26	tosylation	$CHCl_3$[c]	20	-	-	86*	44
27	benzylation	DMF	100	-	62	-	45
28	tosylation	dioxane	20	-	97	-	52
	benzoylation	benzene	-	85	15	-	27
	benzoylation	benzene[e]	-	-	90	-	27
	benzoylation	dioxane[b]	-	50	50	-	27
	benzylation	DMF	100	-	85	-	46
29	PMB	DMF[f]	20	82	-	-	47
30	benzylation	DMF[f]	110	-	82	-	48
31	benzylation	benzene[g]	80	-	60	40	39, 40

[a]For the structures of the diols see Figure 1.9. [b]Added triethylamine. [c]Added Bu_4NBr. [d]Molecular sieves added. [e]Added *N*-methylimidazole. [f]Added CsF. [g]Added Bu_4NI. *O-6.

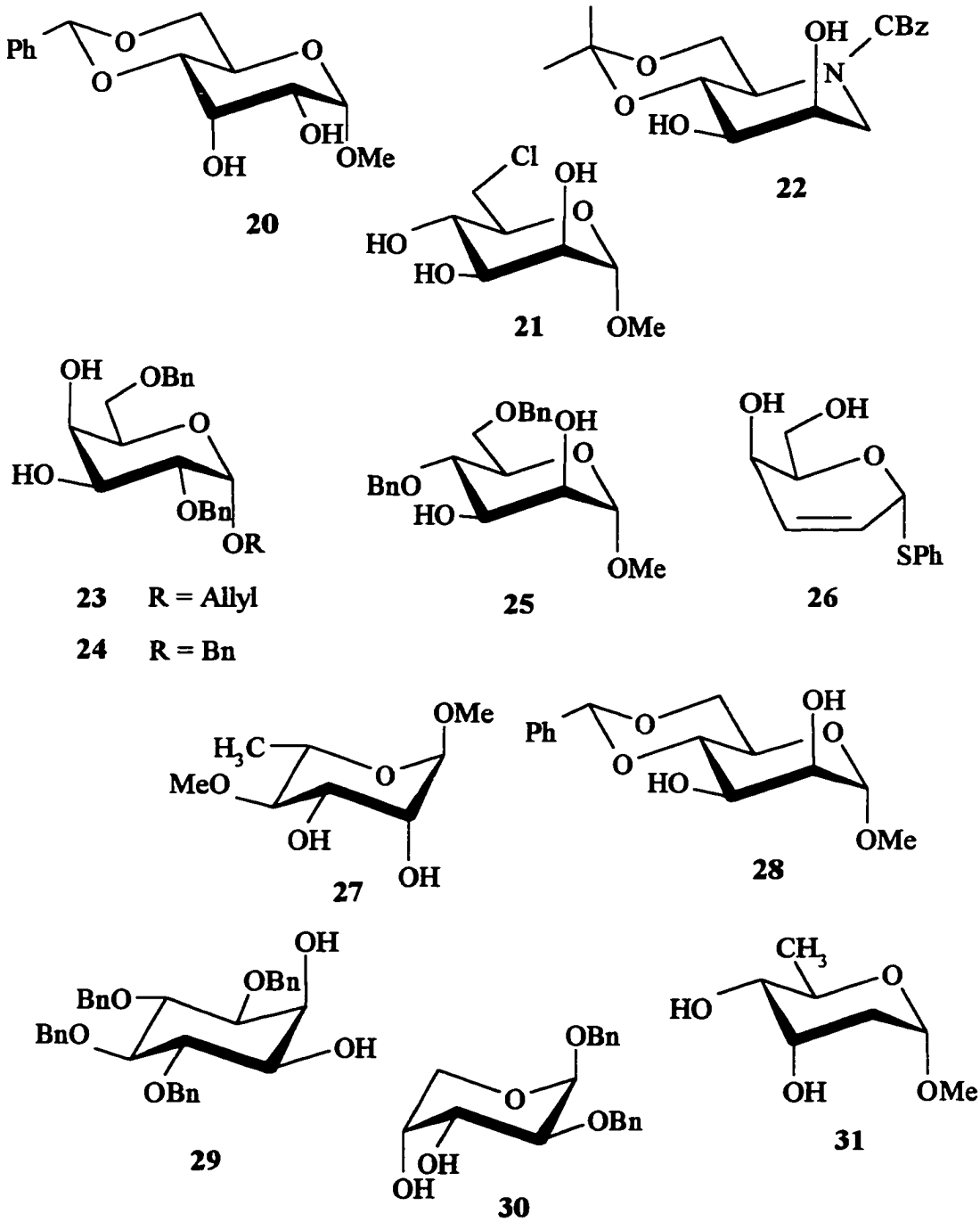


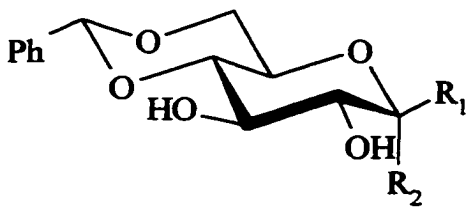
Figure 1.9 Structures of carbohydrates containing *cis*-1,2-diols

1.1.4.3.2 Regioselective substitution of secondary *trans*-1,2 diols

Regioselectivity in reactions of *trans*-1,2-diols, which are usually in diequatorial positions on pyranose rings, can also be obtained *via* dibutylstannylene acetal intermediates. As explained previously (Section 1.1.4.3.1), dibutylstannylene acetals derived from *trans*-1,2-diols adjacent to one axial oxygen form one major dimeric species in solution, that in which the oxygen atom of the stannylene acetal adjacent to the axial substituent is dicoordinate and is more reactive. Indeed, high selectivity is observed when an equatorial position is adjacent to an axial oxygen atom such as in the acylation reactions of dibutylstannylene acetals derived from **32**.[49] Also, *N*-benzyloxycarbonyl 4,6-*O*-benzylidene-1-deoxynojirimycin (**35**) was benzoylated and tosylated selectively *via* a dibutylstannylene acetal at O-2 in yields of 73% and 94%, respectively.[50]

In molecules where the two equatorial hydroxyl groups have two adjacent equatorial substituents, a mixture of products is obtained from substitution reactions. For instance, acylation of the dibutylstannylene acetal derived from methyl 4,6-*O*-benzylidene-β-D-glucopyranoside (**33**) gave a mixture of O-2 and O-3 monosubstituted products.[17] When both adjacent substituents are axial, e.g., in benzyl 4,6-*O*-benzylidene-α-D-galactopyranoside (**37**), benzoylation in benzene gave O-2 and O-3 substituted products in a 1:1 ratio.[17]

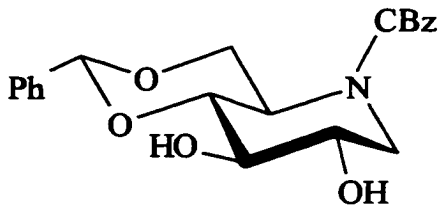
In molecules containing a deoxy centre, high selectivity has been obtained for the reaction at oxygen atom adjacent to the deoxy centre, *e.g.*, for the dibutylstannylene acetal derived from methyl 2,6-dideoxy-α-L-*arabino*-hexopyranoside (**39**), benzoylation in benzene gave a 70% yield at O-3 adjacent to the deoxy centre.[51]



32 $R_1 = H, R_2 = OMe$

33 $R_1 = OMe, R_2 = H$

34 $R_1 = OBn, R_2 = H$



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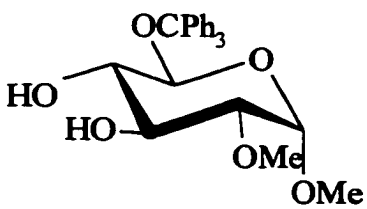

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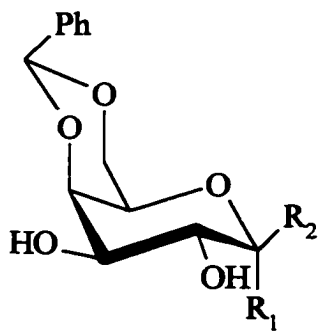
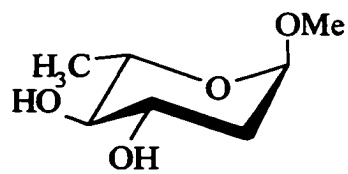


37 $R_2 = H, R_1 = OMe$

38 $R_1 = H, R_2 = OBn$



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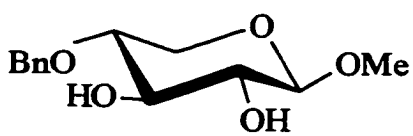

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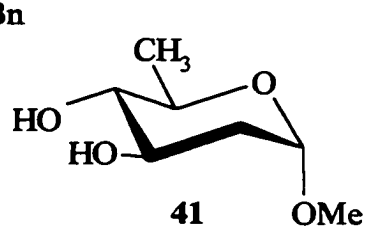

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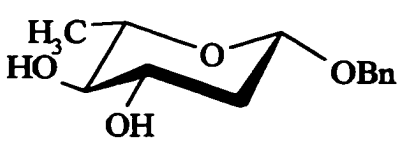

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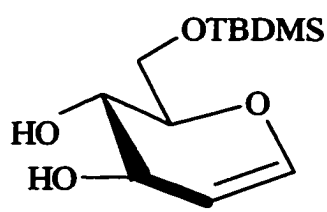

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Figure 1.10 Structures of carbohydrates containing *trans*-1,2-diols

1.1.4.3.3 Regioselective substitution of primary-secondary *vicinal*-diols

Primary hydroxyls are normally more reactive than secondary hydroxyls.[52] In direct electrophilic substitution of 1,2-diols containing primary and secondary hydroxyls in polar solvents such as pyridine, selective acylation and alkylation occurs at the primary position.[53,54] Reactions in polar solvents or in non-polar solvents in the presence of added nucleophiles *via* dibutylstannylene acetals give the same selectivity[35,55,56,57] and enhance the rate of the reaction.[52] For instance, benzoylation of the dibutylstannylene acetal derived from compound **44** (see Figure 1.11) in pyridine gave the primary mono-*O*-benzoylated product in 75% yield.[35]

Substitution of secondary oxygen atoms in the presence of the primary oxygen atoms is highly desirable. Recently, a new approach has been developed by Kong and Grindley.[58] In this method, the reactions of different dialkylstannylene acetals derived from primary-secondary 1,2-diols such as glucofuranose derivatives **44** and **45**, methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside (**46**), allofuranose derivatives **47** and **48**, and mannitol derivative **49** (Figure 1.11) have been studied in different solvents.

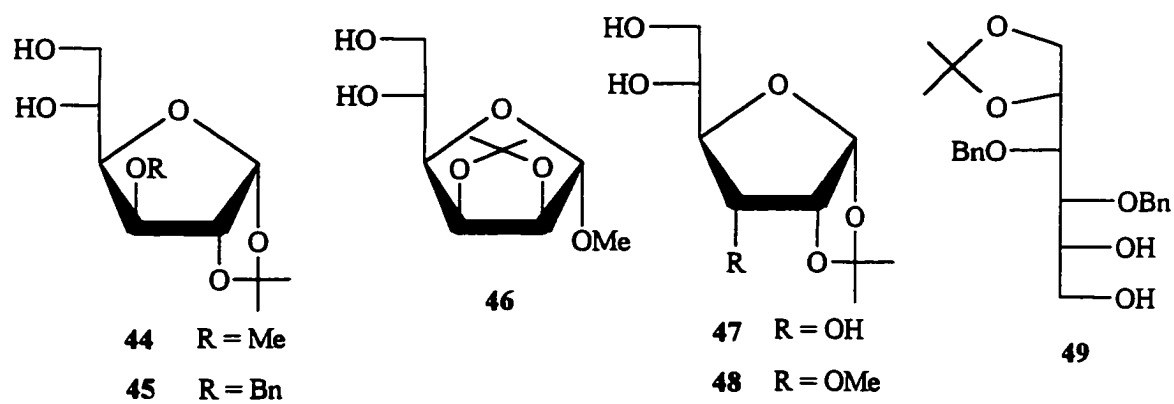


Figure 1.11 Structures of carbohydrates containing terminal 1,2-diols

The nature of the alkyl groups on the tin atom had a large influence on the regioselectivity. It has been found that by increasing the steric bulk of the alkyl substituents on the tin atom, regioselectivity is reversed from a preference for reaction on primary to secondary oxygen atoms but at the expense of longer reaction times.[58] The best selectivity for the secondary oxygen atom in *p*-toluenesulfonylation reactions resulted from use of the hexamethylenestannylene acetal.[58] The yield increased on changing the solvent from toluene to chloroform and also increased on lowering the reaction temperature to 5 °C with prolonged reaction time. The reversal in regioselectivity is attributed to the effect that the hexamethylenestannylene acetal has on the populations of the three possible dimers in solution as outlined following.

Of these three possible dimers, the most populated is the one with the least steric interaction between the alkyl groups on tin and on the diol. Because in terminal 1,2-diols the secondary carbon bears one large substitutent, steric interactions cause the preferential formation of the dimer that has the tricoordinate oxygen atoms as far away from that large substituent as possible. The cyclic hexamethylene group, in which the tin atom is part of a ring, was found[58] to be less able to avoid steric interactions than two separate alkyl groups on tin, e.g., two butyl, isobutyl, isopropyl, neopentyl, or cyclohexyl groups. As a result of the steric effect of the hexamethylene group, the preference for the formation of primary-primary dimer (see Figure 1.5, 1,1-Dimer) is greater.[58]

The secondary oxygen atoms in the primary-primary dimer are dicoordinate and less hindered. Therefore, it was predicted these secondary oxygen atoms would be more nucleophilic in dialkylstannylene acetals than primary oxygen in the terminal 1,2 diols in

the carbohydrates. Indeed, the toluenesulfonylation reaction of the hexamethylenestannylene acetal derived from **45** in chloroform gave mono-*O*-toluensulfonyl product in 91% yield at the secondary position in contrast to the conventional method which gives reaction at the primary position predominantly.

1.2 Results and discussion

1.2.1 Methyl 4,6-*O*-benzylidene-α and β-D-allopyranosides

1.2.1.1 Synthesis of methyl 4,6-*O*-benzylidene-α-D-allopyranoside (54)

In order to investigate the regioselectivity of dibutylstannylene acetals in *cis* 1,2-diol pyranosides, the syntheses of methyl 4,6-*O*-benzylidene-α-D-allopyranoside (**54**) and methyl 4,6-*O*-benzylidene-β-D-allopyranoside (**60**) were planned. Synthetic routes to these compounds are shown in Figures 1.12 and 1.13. These compounds each contain a *cis*-2,3-diol, as does methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (**28**), but the stereochemical relationships to the other functional groups are different. Therefore, it was interesting to compare the regioselectivity of these molecules to that observed for methyl 4,6-*O*-benzylidene-α-D-mannopyranoside which had been extensively studied previously.[27] The regioselectivity obtained with **28** was reexamined here in variety of non-nucleophilic solvents to ensure that identical conditions were employed with all three *cis*-diols.

Methyl 4,6-*O*-benzylidene-α-D-allopyranoside (**54**) was synthesized in five steps starting from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**51**) as shown in Figure 1.12, using a sequence similar to that used previously.[59,60] The only difference between the

structures of compound **54** and compound **51** is the stereochemistry of the hydroxyl group at O-3. One procedure to invert the stereochemistry of a specific secondary hydroxyl group is oxidation[61] followed by stereospecific reduction. Compound **54** was synthesized starting from methyl α-D-glucopyranoside. The OH-4 and OH-6 groups were protected as the 4,6-*O*-benzylidene acetal using benzaldehyde in the presence of Lewis acid catalyst according to the Hall method.[62] To protect the secondary hydroxyl at O-2, compound **51** was treated with one equivalent of dibutyltin oxide in refluxing toluene to give the 2,3-dibutylstannylene acetal intermediate. The activated sugar was treated with one equivalent of benzoyl chloride and after chromatography, methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**52**) was obtained in 93% yield. In the next step, compound **52** was oxidized at -60 °C using Swern oxidation[61] to give a single product (**53**) in excellent yield (94%). The structure of **53** was determined to be methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-*ribo*-hexopyranosid-3-ulose. The ^{1}H NMR spectrum of compound **53** showed two sharp doublets for H-1 and H-2 at 5.34 and 5.63 ppm with J = 4.3 Hz. The simplicity of the coupling pattern confirmed the absence of any proton at C-3 in compound **53**. Additional support was obtained from the ^{13}C NMR spectrum, which showed a signal for the carbonyl carbon at 191.1 ppm. The C-2 and C-4 signals were deshielded by 9 and 8 ppm, respectively, in comparison to their positions in the spectrum of compound **52**, because of their position relative to the carbonyl group in the molecule.

In the final step, the reduction of compound **53** with sodium borohydride in methanol gave a mixture of two products, methyl 4,6-*O*-benzylidene-α-D-allopyranoside

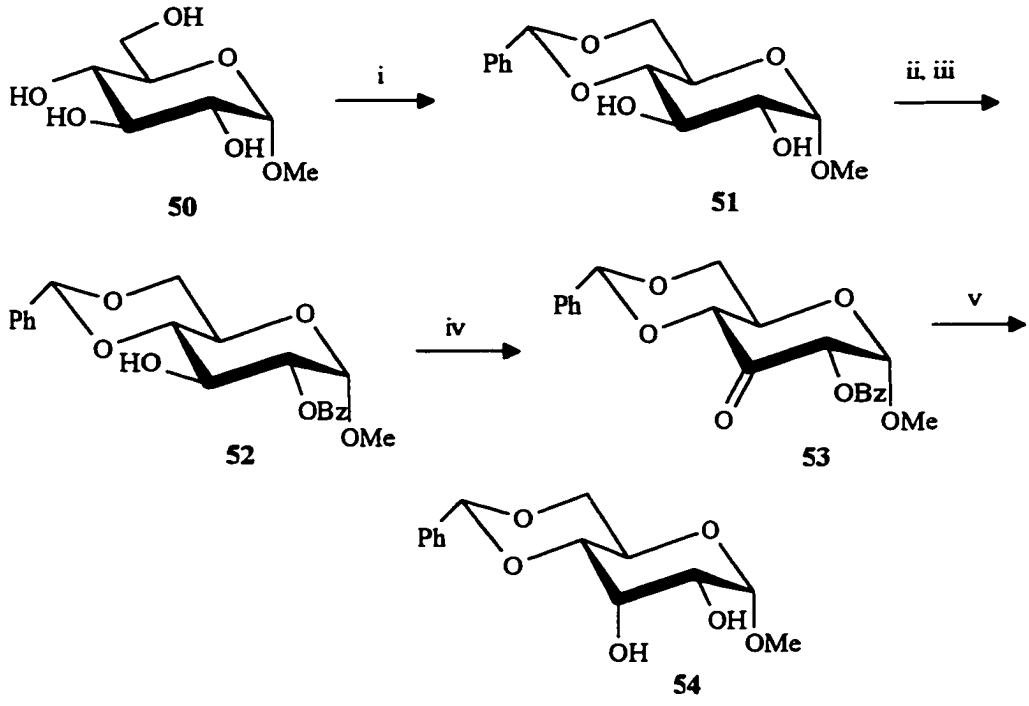


Figure 1.12 The synthetic route to methyl 4,6-*O*-benzylidene-α-D-allopyranoside (**54**). Reaction conditions. i: PhCHO, $ZnCl_2$ reflux. ii: Bu_2SnO, toluene, reflux, azeotropic removal of water. iii: PhCOCl, reflux, iv: DMSO, ClCOCOCl, Et_3N, CH_2Cl_2. v: $NaBH_4$, MeOH.

(**54**) and its epimer **51**, in an approximately 4:1 ratio. Obtaining two compounds was somewhat surprising because it was expected that the hydride ion would attack from the less hindered equatorial side of the carbonyl group to give the allose derivative stereospecifically. It is interesting to note that the reduction of compound **53** was accompanied by removal of the protecting ester group at O-2. The cleavage of the benzoyl group at this stage was a convenient side effect of the reaction conditions that shortened the synthetic route by one step. After the products had been isolated by means of flash column chromatography, compound **54** was recrystallized from ethanol and petroleum ether. The crystals obtained originally had a much lower melting point than

reported for this compound. However, more thorough examination of the literature revealed that a second crystalline form was known, that of the dihydrate. Recrystallization of compound **54** from absolute ethanol gave crystals of the anhydrous form which had the higher melting point.[63]

It was first thought that the reason for obtaining a mixture of compounds in the reduction step was the steric effect of the benzoyl group on O-2. However, examination of TLCs as the reaction progressed suggested that the reduction of ketone and removal of the ester group occur at the same time. The mixture of stereoisomers obtained also suggests that the carbonyl was attacked with hydride ion from both sides of the ketonic centre possibly because of a lack of steric effects on the neighbouring O-2. The previous method using a *p*-toluenesulfonyl group at O-2 yielded only the allopyranoside product but suffered from the need for an extra step, removal of the toluenesulfonyl group.

The structure of **54** was determined by ^{1}H and ^{13}C NMR spectroscopy using 2D NMR experiments to confirm the assignment. The ^{1}H NMR spectrum of **54** contained two sharp doublets at 2.66 and 2.93 ppm with coupling constants of 7.4 Hz (OH-3) and 11.3 Hz (OH-2) caused by the two hydroxyl groups. Karplus equations for OH protons have been established;[64,65] one of the OH protons must be held *anti* to its CH proton. These signals belong to the hydroxyl groups at C-2 and C-3 respectively, and coupling constants in the range of 7- 9.5 Hz for hydroxyls adjacent to the axial oxygens are expected in dry samples.[66] From the size of coupling constants of H-3 with H-2 (3.4 Hz) and H-4 (2.7 Hz), the orientation of the hydroxyl group at C-3 was unambiguously assigned as axial.

1.2.1.2 Synthesis of methyl 4,6-*O*-benzylidene-β-D-allopyranoside (60)

Compound 60 was prepared through a sequence (see Figure 1.13) starting from D-allose, which had been previously prepared in a four-step sequence from D-glucose by a summer student, Richard Tan. Fischer glycosidation of D-allose in acidic methanol at reflux gave a mixture of three isomers. After chromatography, the three compounds were identified as methyl β-D-allofuranoside (59), methyl β-D-allopyranoside (57) and methyl α-D-allopyranoside (56). A trace of another compound, probably methyl α-D-allofuranoside (58), was also obtained, but was not characterized. Methyl β-D-allopyranoside, the required product, was obtained in a modest yield (41%). The configurations of methyl α-D-allopyranoside and methyl β-D-allopyranosides were assigned from the values of the *vicinal* H,H coupling constants of the anomeric protons. Since the chemical shifts of anomeric protons in ^{1}H NMR spectra fall within a distinct region between 4.5 and 5.5 ppm and usually isolated from other proton signals, measurement of the coupling constant of H-1 to H-2 in pyranoside sugars allows one to determine the anomeric configuration. In methyl β-allopyranoside, H-1 and H-2 are *trans* and diaxial and their coupling constant is large. From the ^{13}C NMR spectrum, methyl β-allofuranoside can be easily distinguished from pyranoside isomers. The C-1 signal from allofuranoside is more deshielded by 7-8 ppm compared to the C-1 signals in the pyranosides. Methyl β-allopyranoside had previously been prepared from methyl α-D-allopyranoside,[60] but not directly from D-allose, as far as we know.

Having methyl β-allopyranoside in hand, benzylidenation was attempted. Formation of the 4,6-*O*-benzylidene acetal of tetrol 57 was required to investigate the

regioselectivity of reaction of O-2 and O-3 in the dibutylstannylene acetal. Benzylidenation was carried out by treatment of **57** with α,α-dimethoxytoluene in dimethylformamide (DMF) containing *p*-toluenesulfonic acid as catalyst. The liberated

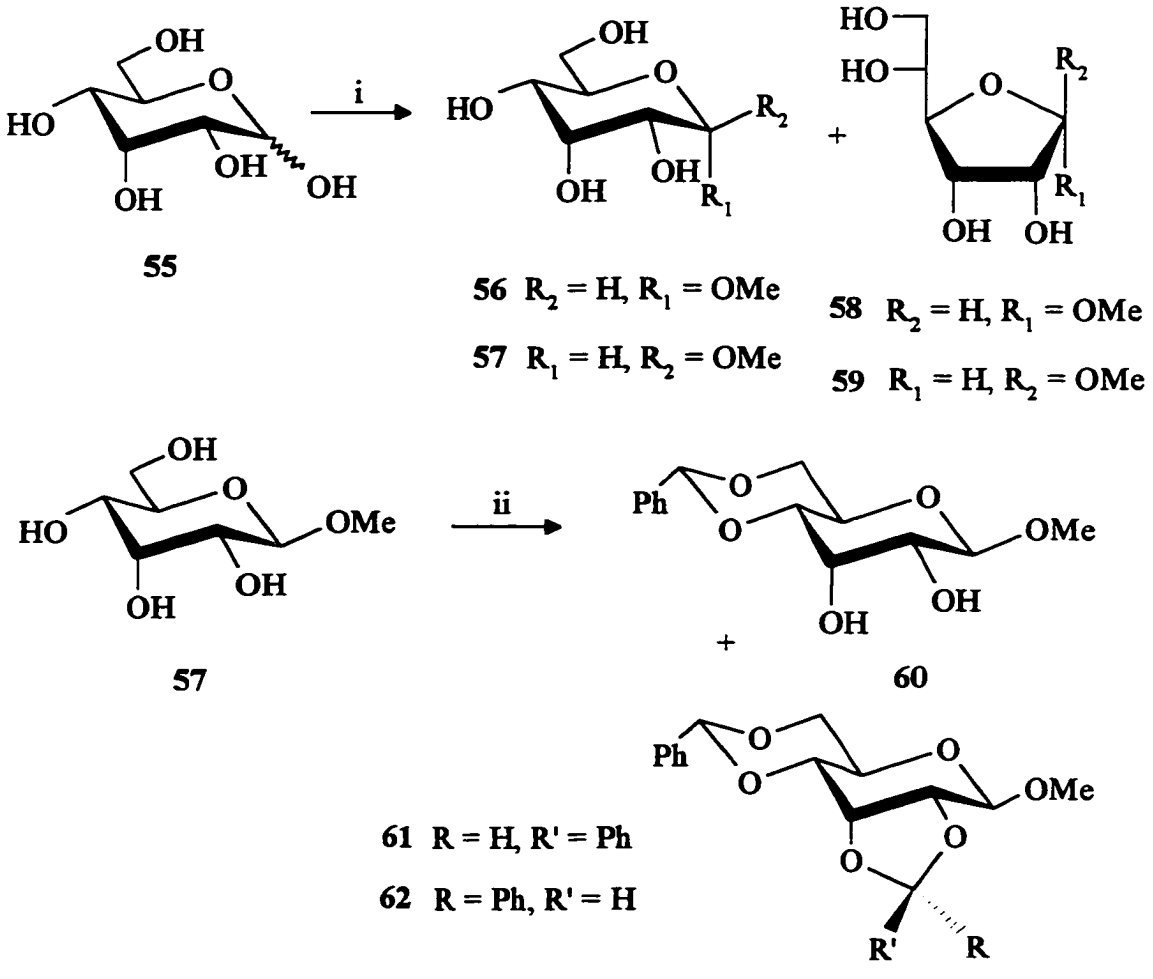


Figure 1.13 The synthetic route to methyl 4,6-O-benzylidene-β-D-allopyranoside (**60**). Reaction conditions i: 2% HCl in methanol, reflux. ii: DMF, *p*-toluenesulfonic acid, α,α-dimethoxytoluene, 100 °C.

methanol in the reaction was removed by passing nitrogen gas through the reaction solution. A small amount of a mixture of the two diastereomers, the *endo* and *exo* isomers

in their 2-phenyl-1,3-dioxolane rings of methyl 2,3:4,6-*O*-dibenzylidene-β-D-allopyranoside, was obtained in addition to the major product, methyl 4,6-*O*-benzylidene-β-D-allopyranoside (**60**). The two stereoisomers were obtained as a mixture from chromatography, then the major isomer was separated by means of fractional crystallization. Formation of six-membered ring (1,3-dioxane) and five membered ring (1,3-dioxolane) acetals from carbohydrates has been extensively studied.[67,68,69] Substituents at the acetal carbon of six-membered ring acetals are much more stable in equatorial than axial orientations so only one stereoisomer of the 4,6-*O*-benzylidene acetal is obtained. Five-membered ring benzylidene acetals are readily formed from *cis*-diols but there is little difference in stability between the stereoisomers so both are obtained under thermodynamic conditions.

The structures of the compounds in the above mentioned series were assigned from their ^{1}H and ^{13}C NMR spectra, using 2D methods. The mono- and di-*O*-benzylidene compounds have characteristic chemical shifts for benzal protons and carbons in their ^{1}H and ^{13}C NMR spectra. Six-membered benzylidene acetal protons give signals at approximately 5.57 ppm. The five-membered benzylidene acetals (*endo* and *exo* isomers) gave signals at 6.42 and 5.98 ppm. These chemical shifts are in the ranges that have been reported for similar molecules.[70] The proton of the *exo*-isomer is about 0.44 ppm more deshielded than its analogous *endo*-isomer. In their ^{13}C NMR spectra, the benzal carbons in the six-membered, and five-membered ring *endo*- and *exo*- acetals, also gave characteristic signals at 102.7, 105.2, and 105.4 ppm, respectively.

1.2.1.3 Regioselective substitution *via* dibutylstannylene acetals

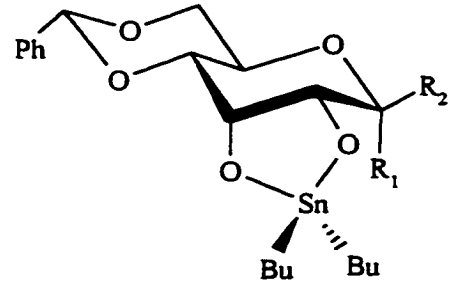
1.2.1.3.1 Regioselective substitution of methyl 4,6-*O*-benzylidene-α-D-allopyranoside (54)

As was outlined in section 1.1.4.3, dibutylstannylene acetals have been used widely in the regioselective mono-*O*-substitution of 1,2-diols.[2,3,6] Acylation and alkylation reactions are the common reactions with stannylene acetals. In order to evaluate regioselectivity with dibutylstannylene acetals derived from the *cis*-1,2-diols in compounds **54** and **60**, these reactions were investigated here.

The two diols were first converted to their 2,3-*O*-dibutylstannylene acetals **63** and **64** by reacting the diols with one equivalent of dibutyltin oxide in toluene with azeotropic removal of water. The products were used directly without any separation or purification for subsequent substitution reactions. The structures of the dibutylstannylene acetals and the isolated products are shown in Figure 1.14.

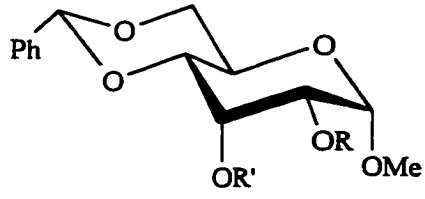
The reaction of the dibutylstannylene acetal derived from **54** with benzoyl chloride was performed in the absence of nucleophiles in toluene at 20 °C. It gave a mono-*O*-substituted product regioselectively in 98% yield after column chromatography. The structure of the product was assigned as methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-allopyranoside (**65**) from its NMR spectra. In the ^{1}H NMR spectrum, the signal of H-2 appeared as a triplet at 5.09 ppm, in which it has been deshielded 1.28 ppm from its position in the starting material **54**, consistent with the presence of an ester on the same carbon. This deshielded signal was unambiguously assigned as H-2 by its correlation in

the COSY spectrum to H-1. From the assigned H-2 signal, the other signals were



63 $R_2 = H, R_1 = OMe$

64 $R_1 = H, R_2 = OMe$

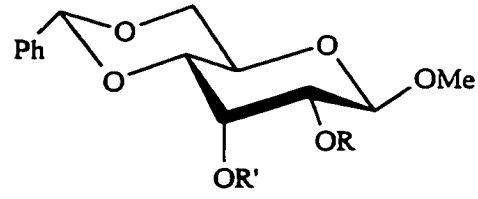


54 R = R' = H

65 R' = H, R = Bz

66 R' = H, R = Ts

67 R' = H, R = Bn



60 R = R' = H

68 R' = H, R = Bz

69 R' = H, R = Ts

70 R' = H, R = Bn

71 R' = Bn, R = H

Figure 1.14 Structures of methyl 4,6-*O*-benzylidene-α- and β-D-allopyranoside and their derivatives *via* dibutylstannylene acetals

assigned using the COSY spectrum. The structural assignment was supported with physical data in accord with those previously reported.[71,72] Because ester groups are known to migrate during substitution under dialkylstannylene acetal conditions, *p*-

toluenesulfonylation reactions were also examined. The *p*-toluenesulfonyl group does not migrate under these conditions. *p*-Toluenesulfonylation reactions were carried out by treatment of activated sugar dibutylstannylene acetal **63** with *p*-toluenesulfonyl chloride in toluene in the absence of nucleophiles.

A mono-*O*-*p*-toluenesulfonyl product was obtained regioselectively in 95% yield

Table 1.2 Regioselectivity with dibutylstannylene acetals derived from methyl 4,6-*O*-benzylidene-α- and β-D-allopyranoside (**54** and **60**)

Entry	Comp.[a]	Reaction	Condition[d]		%Selectivity[b]	
			temp. °C	time	C-2	C-3
1	**54**	benzoylation	20	1 h	93	-
2	**54**	benzoylation	20	0.5 h	98	-
3	**54**	tosylation	20	7 h	95	-
4	**54**	benzylation[c]	130	2 h	81	
5	**60**	benzoylation	20	0.5 h	81	-
6	**60**	tosylation	20	7 h	83	-
7	**60**	benzylation[c]	130	2 h	86	7

[a]For structure of compounds see Figure 1.14. [b]Isolated yields. [c]Added terabutylammonium iodide. [d]All of reactions were performed in toluene.

after chromatography. The structure of the product was determined to be methyl 4,6-*O*-benzylidene-2-*O*-*p*-toluenesulfonyl-α-D-allopyranoside (**66**). The position of substitution was decided from the appearance of a deshielded triplet signal at 4.51 ppm in the ^{1}H NMR spectrum, which again was assigned to H-2. *p*-Toluenesulfonylation in this diol system

was very selective and much faster than for the dibutylstannylene acetal of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (**28**) under the same reaction conditions. When the reaction solvent was changed to the chloroform, the yield improved to 98%. The reaction was finished in a short time (3 h) in comparison to the reaction time with the dibutylstannylene acetal of **28**. Similar results have been obtained for the regioselective substitution of terminal 1,2-diols; when the solvent was changed to chloroform, the yield of the reaction increased.[58]

Alkylation of **63** with benzyl bromide was accomplished in the presence of tetrabutylammonium iodide as the added nucleophile with refluxing in toluene. Alkylation reactions in general are slow and nucleophiles are added to enhance the rate of reaction. The reaction after chromatography gave a mono-*O*-substituted product regioselectively in 81% yield, assigned as methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-allopyranoside (**67**). The structural assignment was based on the COSY spectrum. The OH proton appeared as a doublet coupled to H-3. The assignment of H-3 followed from cross-peaks to H-2 and H-4. The structure was confirmed by comparison of its ^{13}C NMR spectrum with that of its parent **54**; the signal of C-2 was deshielded by 5.6 ppm due to the addition of a β-carbon but that of C-1 and C-3 were shielded by 1.2 and 2.7 ppm, respectively, due to the addition of γ-effects.

1.2.1.3.2 Regioselective substitution of methyl 4,6-*O*-benzylidene-β-D-allopyranoside (60)

Dibutylstannylene acetals derived from methyl 4,6-*O*-benzylidene-β-D-allopyranoside (**60**) similarly afforded regioselective mono-2-*O*-substituted products in benzoylation and *p*-toluenesulfonylation reactions with high yields (see Table 1.2). Benzylation of **64** with benzyl bromide in the presence of tetrabutylammonium iodide gave as the major product, methyl 2-*O*-benzyl-4,6-*O*-benzylidene-β-D-allopyranoside (**70**) in 86% yield and also a minor product methyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-allopyranoside (**71**) in 7% yield.

These regioselective mono-*O*-substitution results obtained with **54** and **60** through their dibutylstannylene acetals (see Table 1.2) clearly showed that the equatorial oxygen atoms in these *cis*-1,2-diol systems are more reactive than axial oxygen atoms. These regioselective results obtained with **54** and **60** are in contrast to the regioselectivity of compound **28** which gave major products by reaction of the axial oxygen atom in nonpolar solvents in the absence of added nucleophiles and under similar conditions. One of the important factors in the regioselectivity of dialkylstannylene acetals derived from 1,2-diols lies in the structure of their major species in the reaction solution.

1.2.1.4 ^{119}Sn NMR spectroscopy and dimerization of dibutylstannylene acetals derived from 54 and 60 in solution

^{119}Sn NMR spectroscopy is a useful technique for study of the structures of tin compounds in the solid state and in solution. Dibutylstannylene acetals derived from

trans-1,2-diols in carbohydrates exist as an equilibrium mixture of three dimers. It was observed that when one major dimer is predominant in solution, substitution reactions gave one mono-*O*-substituted product.[17] Structural studies of methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-mannopyranoside (**74**), which is derived from a *cis*-1,2-diol showed a complicated mixture in solution.[20,21] The regioselectivity observed in the reaction of this compound was very dependant on the reaction conditions.

In order to understand the difference in regioselectivity of these two *cis*-1,2-diol systems, the ^{119}Sn NMR spectral method was employed here to look at the oligomerization of dibutylstannylene acetals **63** and **64**. Their ^{119}Sn NMR spectra were recorded at 20 °, -20 ° and -40 °C.

NMR samples were prepared by distillation of chloroform-*d* through a vacuum line onto the residues of the dialkylstannylene acetals derived from **54** and **60**, that is, **63** and **64**, respectively. The ^{119}Sn NMR spectrum of a 0.2 M solution of compound **63** at 20 °C in chloroform-*d* showed one major signal (65 ± 3%) at -119.4 ppm and two minor signals at -117.0 and -113.2 ppm (see Figure 1.15) with the same intensity (each 17 ± 3%). Lowering the temperature to -20 °C changed the position of the major signal to -121.4 ppm (74% ± 3) and the two minor signals to -117.9 and -115.9 ppm, but did not significantly alter the relative heights of the two latter lines (13 ± 3%). Further lowering to -40 °C again caused the chemical shifts to move, to -122.2 ppm for the major signal and to -117.3 and -117.7 ppm for the minor signals but again the intensities of the latter two signals were very similar. These chemical shifts are all in the region in which pentacoordinate tin atoms are expected to absorb. Because no signal was observed in the

hexacoordinate region, the observed signals are caused by pentacoordinate tin atoms that can only be in dimeric species. In a symmetric dimer, the two tin atoms are identical; however, in unsymmetric dimers, the two tin atoms are in different chemical environments. The observation of two signals with the same intensity at several temperatures must be attributed to the non-symmetric dimer. The three possible dimeric structure for compound **63** are shown in Figure 1.16. The major signal in ^{119}Sn NMR spectrum must belong to either the 2,2- or 3,3-symmetric dimers and the two other signals must result from the 2,3-dimer. Which symmetric dimer is populated is a question that is difficult to answer definitively. If the inherently less reactive oxygen atoms react, as for the analogous mannose derivatives (see later), it can be assumed that the reaction preference must be caused by the presence of a dominant dimer, that in which O-2 is dicoordinate. For **63**, reaction occurs preferentially at the inherently more reactive equatorial oxygen atom. The ^{119}Sn NMR spectra indicate that the mixture present is about 70% symmetric dimer and 30% non-symmetric dimer. Thus, the ratio of populations of dicoordinate oxygens is 85/15, with uncertainty as to which oxygen atom is dicoordinate a greater extent of the time.

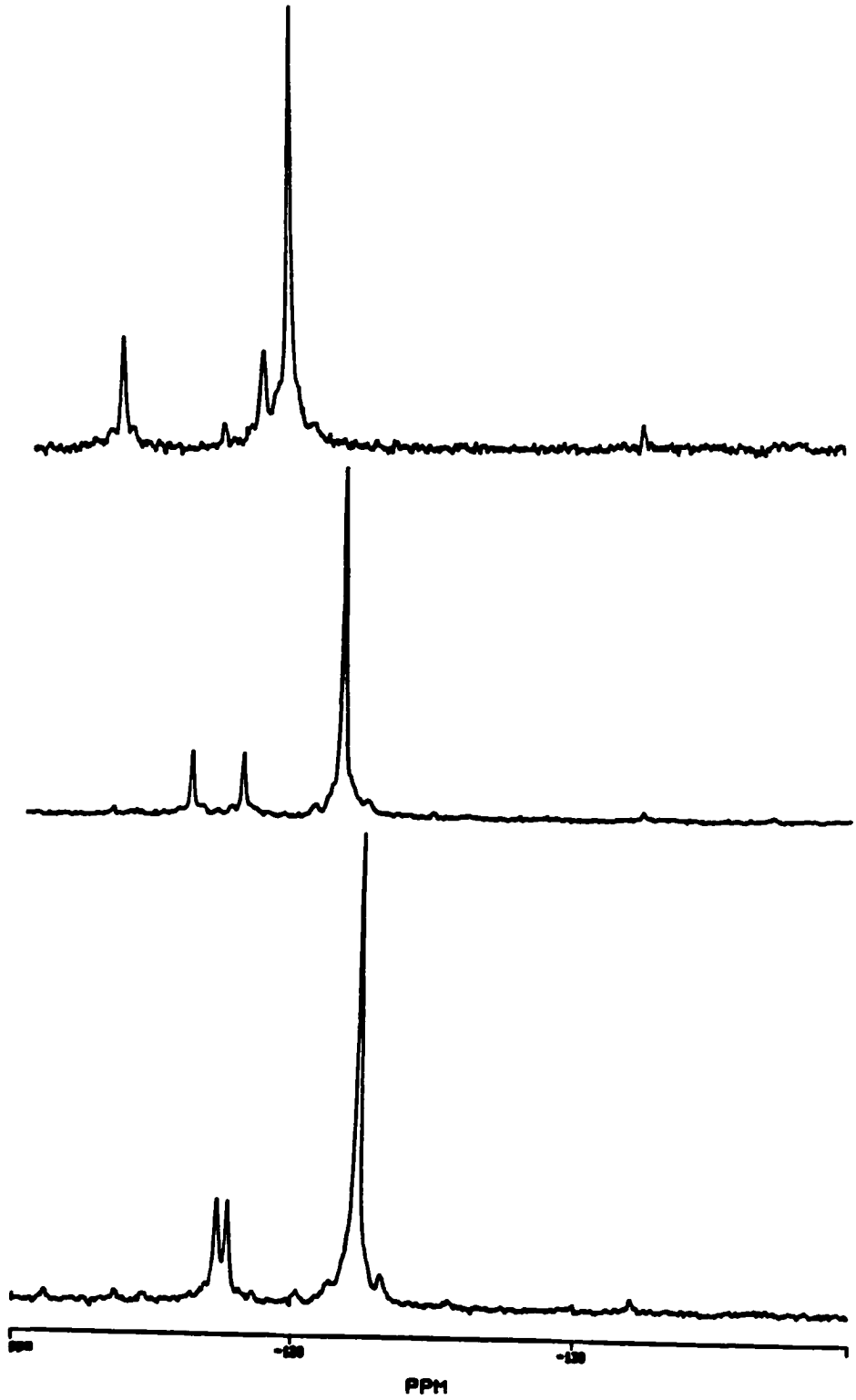


Figure 1.15 149.18 MHz ^{119}Sn NMR spectra of a 0.2 M solution of methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-allopyranosideyranoside (**63**) in $CDCl_3$: from the top, at +20 °C, -20 °C and -40 °C.

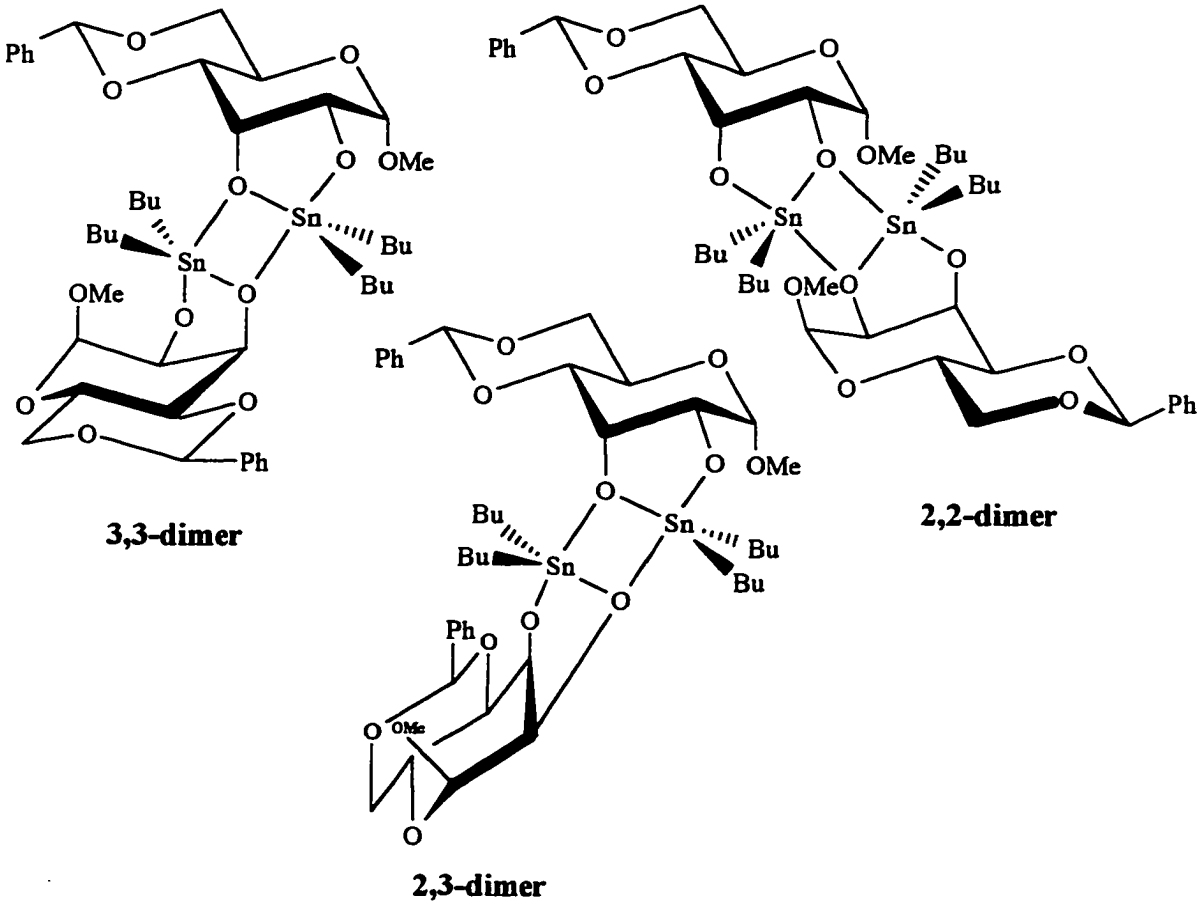


Figure 1.16 The structures of the three dimers possible for **63**

Examination of models suggest that dimers with O-2 tricoordinate have intramolecular interactions between a butyl group on tin and on equatorial β-glycosyl substituents, but to a lesser extent with an axial α-glycosyl substituent. This steric effect with an equatorial substituent is the reverse of the effect noted when both O-2 and O-3 are equatorial.[17]

In similar experiments, the ^{119}Sn NMR spectrum of a 0.1 M solution of dibutylstannylene acetal **64** in chloroform-*d* at 20 °C contained one major signal at -122.6

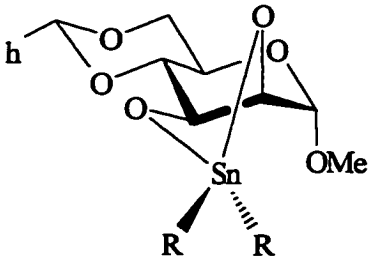
ppm (96%) and more than two minor signals at about -125.9 and -119.0 ppm which have considerably lower intensities (4%) than the minor peaks for the α-anomer. On lowering the temperature to -20 °C and then to -40 °C, the chemical shifts of the signals changed slightly without altering the relative intensities of the peaks. For this compound, one can conclude that one symmetric dimer is the dominant species present and a non-symmetric dimer may be present to a slight extent.

To summarize, the β-isomer is present mainly as one symmetric dimer, and the α-isomer contains a significant amount (30%) of the non-symmetric dimer. It has been suggested on the previous page that an equatorial β-glycosyl substituent destabilizes dimers of 2,3-*O*-dibutylstannylene acetals of allopyranoside derivatives that have O-2 tricoordinate. The observation of an increased amount of a second dimer when the steric destabilization resulting from having O-2 tricoordinate is removed indicates that the major symmetric dimers are the 3,3-dimers. This is in agreement with the very high regioselectivity observed with these compounds, since both the major dimeric structures and the inherent reactivity direct reaction to the same oxygen atom.

1.2.2 Methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (28)

1.2.2.1 Solvent and steric effects on the regioselectivity of dialkylstannylene acetals derived from 28

The effect of changing alkyl groups on the regioselectivity of reaction on secondary-secondary 1,2-diols through dialkylstannylene acetals has not been studied. In order to examine steric effects on the regioselectivity of dialkylstannylene acetals derived from methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (**28**) which contains a 1,2-*cis*-diol, benzoylation and toluenesulfonylation reactions of a variety of dialkylstannylene acetals were studied under different conditions in the absence of added nucleophiles. Dialkyltin oxides such as dibutyltin oxide, diisopropyltin oxide, diisobutyltin oxide, dineopentyltin oxide, dineohexyltin oxide and hexamethylenetin oxide were chosen for this study. Some of the reactions have been studied in several non-nucleophilic solvents such as toluene, benzene, chloroform, dichloromethane, 1,2-dichloroethane, 1,1-dichloromethane, and 1,1,2,2-tetrachloroethane to evaluate solvent effects on the regioselectivity. The results of these reactions are shown in Table 1.3.



74 R = butyl

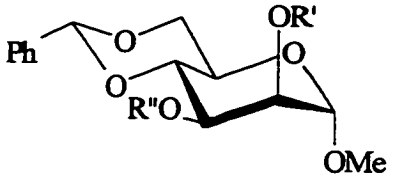
75 R = isopropyl

76 R = isobutyl

77 R = neopentyl

78 R = neohexyl

79 2 R = hexamethylene



28 R = R' = H

80 R' = R" = Bz

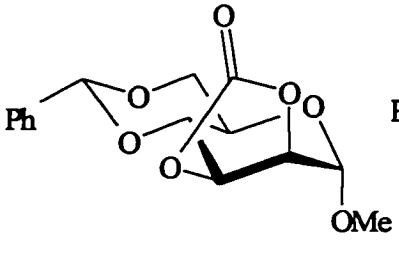
81 R' = Bz, R" = H

82 R' = H, R" = Bz

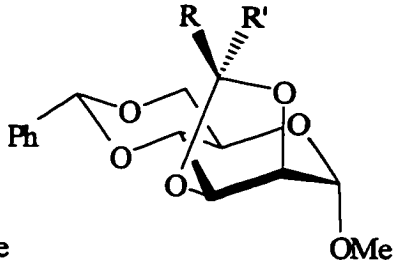
83 R' = Ts, R" = H

84 R' = H, R" = Ts

85 R' = R" = Ts



86



72 R' = H, R = Ph

73 R' = Ph, R = H

Figure 1.17 Structures of dialkylstannylene acetals derived from methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (**28**) and its derivatives

Table 1.3 Selectivity of dialkylstannylene acetals ($R_2Sn(OR')_2$) in different solvents at room temperature

Entry	Acetal[a]	Reaction	Reaction condition[b]		Selectivity(%)[c]			Total%
		Benzoylation	Solvent	Time	C-2	C-3	2,3-Di	
1	74	"	Toluene	3 h	64	16	7	87
2	74	"	$CHCl_3$	3 h	62	21	3	86
3	74	"	CH_2Cl_2	2 h	47	36	11	94
4	74	"	C_6H_6[d]	0.1 h	71	18	-	89
5	75	"	$CHCl_3$	40 h	48	51	-	99
6	76	"	$CHCl_3$	40 h	45	54	1	100
7	77	"	$CHCl_3$	22 h	26	71	-	97
8	78	"	$CHCl_3$	20 h	47	15	37	99
9	79	"	Toluene	48 h	34	62	-	96
10	79	"	$CHCl_3$	24 h	36	51	4	90
11	79	"	CH_2Cl_2	48 h	24	39	28	91
	Toluenesulfonylation							
12	74	"	Toluene	6 d	26	47	-	73
13	74	"	$CHCl_3$	7 d	22	46	3	71
14	74	"	CH_2Cl_2	20 h	24	69	-	93
15	74	"	$ClCH_2CH_2Cl$	6 d	19	73	-	92
16	74	"	$Cl_2CHCHCl_2$	10 d	26	64	-	90
17	79	"	CH_2Cl_2	8 d	27	35	17	79
18	79	"	$ClCH_2CH_2Cl$	3 d	20	58	-	78
19	79	"	$Cl_2CHCHCl_2$	4 d	17	50	16	83

[a]For structures of acetals see Figure 1.17 [b]All of the reactions were performed in room temperature. [c]Isolated yields. [d]Regioselectivity was the same in reactions with one equiv and 10 equiv benzoyl chloride.

1.2.2.1.1 Regioselectivity in benzoylation reactions

For all of the benzoylation reactions, dialkylstannylene acetals were prepared by reaction of **28** with one equivalent of dialkyltin oxide in toluene under conditions of azeotropic removal of water for 12-16 h to give homogenous solutions of the 2,3-*O*-dialkylstannylene acetals. The dialkylstannylene acetals were used directly for the subsequent benzoylation reactions without purification or separation.

The effect of solvent on regioselectivity was investigated first. Benzoylation reaction of the dibutylstannylene acetal of **28** in toluene gave the 2-benzoate, 3-benzoate and 2,3-di-benzoate in 64%, 16%, and 7% yields, respectively. When this reaction was performed under the same conditions in chloroform, almost the same selectivity was obtained, 62%, 21%, and 3% yields, respectively. Repeating the same reaction in dichloromethane resulted in a mixture of products without significant preference for the O-2 or O-3. The reaction of the dibutylstannylene acetal in benzene with one equivalent of benzoyl chloride gave the best regioselectivity; yields of 71% and 18% were obtained for substitution at O-2 and O-3, respectively. It is unclear whether these results are caused by preference for direct reaction at the oxygen atoms or from rearrangement catalyzed by tin compounds or by some combination of these two factors. To evaluate this question, the above reaction was repeated with 10 equivalents of benzoyl chloride at 20 °C in benzene. This reaction gave the same results in a very short time (5 min).

In order to compare the regioselectivity, the above reactions were performed with the hexamethylenestannylene acetal of **28** (**79**) in toluene, dichloromethane and chloroform. It was found that benzoylation of **79** in toluene (entry 9) resulted in a reversal

of reaction preference from O-2 to O-3, giving yields at these two sites of 34% and 62%, respectively. When the same reaction was carried out with the hexamethylenestannylene acetal in chloroform (entry 10), the regioselectivity was the same as in toluene but the preferences for O-3 was less. Benzoylation *via* the hexamethylenestannylene acetal in dichloromethane gave similar preferences but the amount of the di-2,3-benzoate increased to 28% (entry 11). It has been found previously that reactions are faster in dichloromethane.[58]

As can be seen in Table 1.3, changing the alkyl groups on tin from dibutyl to diisopropyl, diisobutyl, or hexamethylene changed the regioselectivity in favour of O-3 instead of O-2 in toluene and chloroform, but also caused the reaction time to increase. Little regioselectivity was observed in the reaction with the diisopropylstannylene acetal **75** in chloroform at 20 °C. The diisobutylstannylene acetal **76** gave very similar regioselectivity. In contrast to other results, the reaction with dineohexylstannylene acetal **78** surprisingly favoured the formation of the di-*O*-substituted product more than the mono-*O*-substituted, although the ratio of O-2 to O-3 product was similar to that observed with butyl.

When the reaction was carried out under the same conditions as for other dialkylstannylene acetals with dineopentylstannylene acetal **77** in chloroform at 20 °C, the best reversed regioselectivity was obtained in 22 h, namely a 71% yield of the 3-benzoate and a 26% yield of the 2-benzoate.

The results of benzoylation reactions in different non-nucleophilic solvents showed that benzene is the best solvent for regioselective substitution of the dibutylstannylene

acetal giving 71% yield at O-2 and 18% at O-3.

1.2.2.1.2 Regioselectivity in *p*-toluenesulfonylation reactions

In order to avoid migration which is known to occur in benzoylation reactions of dialkylstannylene acetals, *p*-toluenesulfonylation reactions were examined with dibutylstannylene acetal **74** and hexamethylenestannylene acetal **79** in different nonpolar solvents (see Table 1.3). *p*-Toluenesulfonyl groups are stable under dialkylstannylene acetal reaction conditions and they have found synthetic applications as leaving groups in nucleophilic reactions. Also, *p*-toluenesulfonyl derivatives can be used as precursors in the formation of epoxides.

In all of the *p*-toluenesulfonylation reactions, the dialkylstannylene acetals were prepared by reacting the diol with one equivalent of dialkyltin oxide in toluene. The dialkylstannylene acetal intermediates were used directly in the next step of *p*-toluenesulfonylation reactions without separation or purification. In these reactions, the tin intermediates (1 mmol) were treated with one equivalent of *p*-toluenesulfonyl chloride in various solvents. *p*-Toluenesulfonylation reactions are slower than benzoylation reactions and depend on the nature of the solvent and the alkyl groups on the tin atom; reaction times varied from 20 h to several days. Dibutylstannylene acetal **74** gave approximately the same preference for O-3 in *p*-toluenesulfonylation reactions in non-nucleophilic solvents such as toluene, chloroform, dichloromethane, 1,2-dichloroethane, and 1,1,2,2-tetrachloroethane (entries 12-19, Table 1.3). The greatest selectivity was obtained in 1,2-dichloroethane, giving reaction at O-3 and O-2 in 73% and 19% yields, respectively. Comparable regioselectivity was obtained with 1,2-dichloroethane (entry 14)

with 69% yield of the 3-*p*-toluenesulfonate and 24% yield of the 2-*p*-toluenesulfonate. The same selectivity was observed for reaction in 1,1,2,2-tetrachloroethane with 64% and 26% yields of the 3-*p*-toluenesulfonate and 2-*p*-toluenesulfonate, respectively. However, the reaction time increased from 20 h in the former reaction to 10 days in the latter. Changing the substituents on tin from dibutyl to hexamethylene not only increased the reaction time but also caused the total yields to decrease slightly. *p*-Toluenesulfonylation reactions performed through **79** in dichloromethane and 1,2-dichloroethane afforded approximately similar regioselectivity in their preferences for O-3. Repeating the toluenesulfonylation reaction with hexamethylenestannylene acetal **79** in dichloromethane gave a mixture of mono- and di- substituted products in a long reaction time. Dichloromethane appears to be the best solvent from the viewpoint of reaction time, and with respect to the regioselectivity and highest total yield, the best solvent was 1,2-dichloroethane through the dibutylstannylene acetal intermediate (entry 15).

p-Toluenesulfonylation reactions in chloroform at 20 °C *via* the diisopropylstannylene acetal **75**, diisobutylstannylene acetal **76**, dineopentylstannylene acetal **77**, and hexamethylenestannylene acetal **79**, failed to give the desired *p*-toluenesulfonate derivative. All of these reactions resulted in the formation of methyl 4,6-*O*-benzylidene-α-*D*-mannopyranoside-2,3-carbonate (**86**) probably via the dichlorocarbene. In these reactions, the tin derivatives probably act as Lewis acids to remove Cl^- from chloroform. Then loss of H^+ gives dichlorocarbene that reacts with oxygen to produce phosgene. Carbonates are an important type of intermediate and protecting group[73] but this is not an efficient method for their preparation.

As shown in Table 1.3, the reaction time for *p*-toluenesulfonylation reactions is very long in comparison with benzoylation reactions. For instance, benzoylation of dibutylstannylene acetal **74** in chloroform is complete in 3 h (entry 2), but performing the *p*-toluenesulfonylation reaction (entry 13) under the same conditions requires seven days for completion. Also, changing the alkyl groups on dialkylstannylene acetals affects the regioselectivity, particularly for benzoylation reactions. These changes could be caused by the changes in the population of the dimer species. Relative dimer populations are influenced by the structure of the alkyl groups on the tin atom and also are different in different solvents. ^{119}Sn NMR spectroscopy was applied to evaluate the dimer population of some dialkylstannylene acetals derivatives of carbohydrates and the results are given in the following section.

1.2.3 ^{119}Sn NMR studies of dialkylstannylene acetals 74, 75, 77 and 79 in solution

Previous ^{119} Sn NMR studies indicated that most dibutylstannylene acetals derived from secondary-secondary *trans*-1,2 diols and primary-secondary 1,2-diols are present predominantly as dimers in solution. Three types of dimer of which two are symmetric can be formed from dialkylstannylene acetals derived from unsymmetric diols.[17,22] Additional support has been obtained by solid state ^{119}Sn NMR spectroscopy and mass spectral studies.[25] However, in the case of 2,3-*O*-dibutylstannylene acetal **74**, ^{119} Sn NMR spectroscopy showed the presence of different oligomeric species from dimer to the pentamer with higher oligomers being favoured in toluene than in chloroform.[20] The observation of different regioselectivities (see Table 1.3) in reactions with different

dialkylstannylene acetals of compound **28** may be related to the structure of species present under the reaction conditions. For this study, dialkylstannylene acetals containing isopropyl, neopentyl and hexamethylene groups were chosen for comparison with the traditional dibutylstannylene acetal.

^{119}Sn NMR samples of dialkylstannylene acetals were prepared as before (see section 1.2.1.5). The ^{119}Sn NMR spectrum of a 0.2 M solution of the 2,3-*O*-dibutylstannylene acetal of **28** in chloroform-*d* showed signals at -282.8, -125.9, -121.0 and -116.3 ppm (see Figure 1.18) with very minor signals at -154.8, -143.3, -136.7 ppm. These chemical shifts are in the regions in which absorption of pentacoordinate and hexacoordinate tin atoms are expected. The signal at -125.9 ppm was by far the most intense signal and the other three major signals have much less but about equal intensity. The peaks at -154.8 and -136.7 ppm have about equal but lower intensity but as noted previously, small signals at -155 ppm and -143 ppm are probably due to hydrolysis products formed during sample preparation. These latter three signals will not be considered further. As noted in the introduction, three dimers are possible, all of which should have signals in the pentacoordinate tin region, that is, -110 to -140 ppm for this type of compound. The C_2 symmetric dimers should give one signal; the non-symmetric dimers, two. Thus, the signal at -125.9 ppm must be due to a symmetric dimer. The signal at -282.8 ppm is due to a hexacoordinate tin atom that must be in a trimer. A trimer must also contain two pentacoordinate tin atoms and these are presumably the signals having very similar intensities at -121.0 and -116.3 ppm. These observations are in agreement with the previous ^{119} Sn NMR studies of **28**.[20]

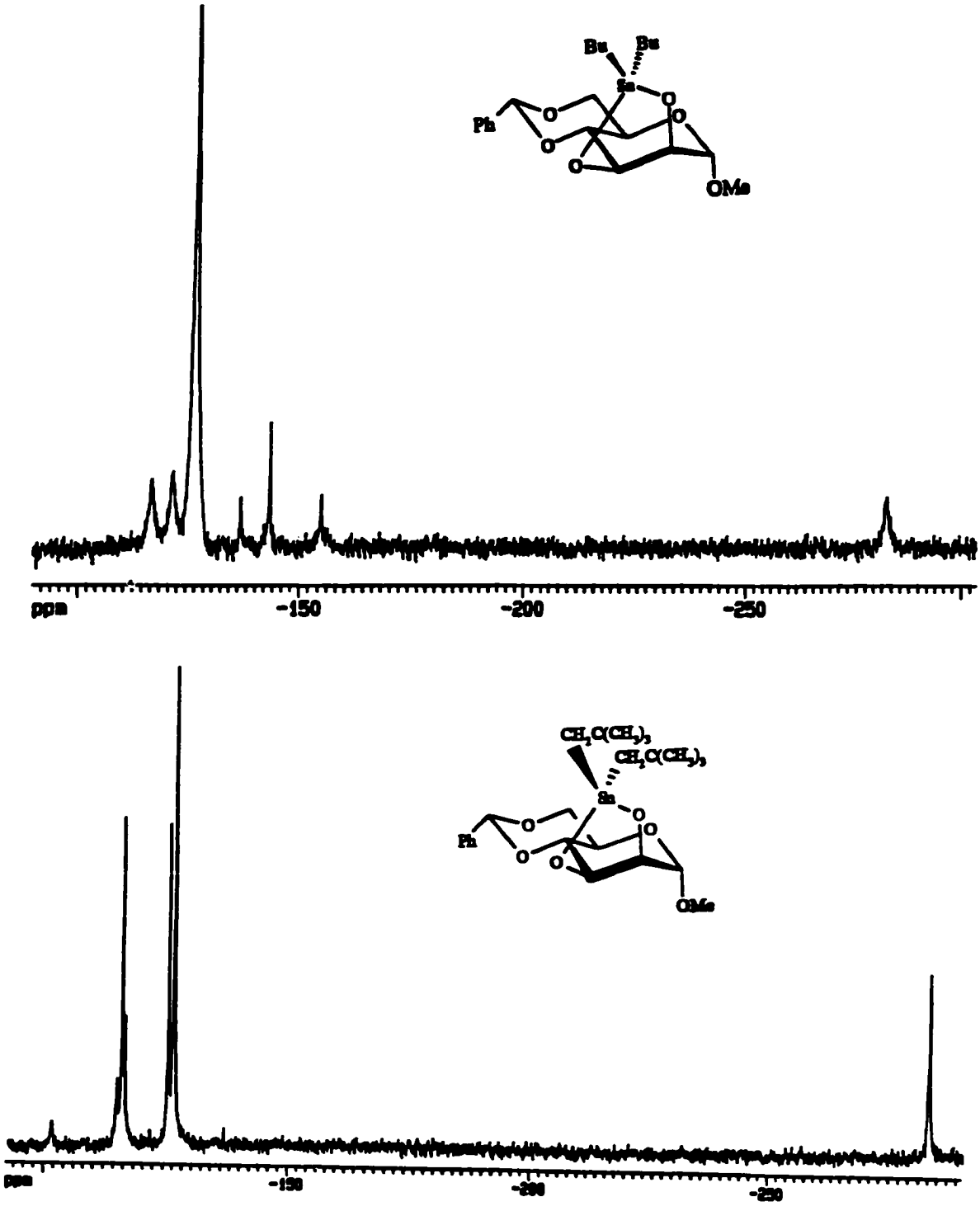


Figure 1.18 149.18 MHz ^{119}Sn NMR spectra of 0.2 M solutions of **74** and **77** in chloroform-*d* at 20 °C

The similar ^{119}Sn NMR experiment for the dineopentylstannylene acetal **77** showed signals at -283.8, -125.9, -124.7, -115.8, -115.3 and -114.3 ppm plus a very minor signal at -101.1 ppm (see Figure 1.18). The signal at -125.9 ppm is largest, consistent with a dominant symmetric dimer, while those at -283.8, -124.7, and -115.3 ppm appear to be of equal intensity consistent with a trimer. The varying line widths of the smaller signals make it uncertain whether the compounds causing these signals have similar correlation times to that of the symmetrical dimer as would be expected for another dimer or different as would be expected for a hydrolysis product that is aggregated through hydrogen bonding. Thus, these small signals are difficult to assign with certainty but it is possible that a much smaller amount of an unsymmetrical dimer is present. Although neopentyl is a sterically hindered group, the chemical shifts are comparable to that of the butyl derivatives because both are primary alkyl groups.

The NMR spectrum of diisopropylstannylene acetal **75** showed one very major sharp signal at -177 ppm (~93% of the total tin based on peak heights) and three very minor signals at -176.6, -175.2 and -172.9 ppm (~2% each based on peak heights). All of these chemical shifts lie in the region expected for pentacoordinate tin atom. However, in comparison with chemical shifts of primary dialkylstannylene acetals, these nuclei have been shielded by approximately 50 ppm. The appearance of one major signal at -174.8 ppm in the pentacoordinate region indicated that one symmetric dimer is the major species present. The other three peaks in low intensity could indicate the presence of low concentrations of the symmetric dimer and the non-symmetric dimer but may also be caused by impurities.

Similar ^{119}Sn NMR experiments on a 0.2 M solution of hexamethylenestannylene acetal 79 in chloroform-*d* showed only one sharp signal at -97.2 ppm indicating the presence of only one symmetric dimer. The deshielding of the signal of the hexamethylenestannylene acetal in comparison with that of the dibutylstannylene acetal may be caused by a change in the size of the bond angle at tin in this compound. It has been found that the C-Sn-C bond angle in hexamethylenestannylene acetals is slightly smaller than in acyclic dialkylstannylene acetals.[23]

To summarize, all four dialkylstannylene acetals contain one major symmetric dimer in chloroform-*d* solutions plus variable amounts of a single trimer. Thangarasa[21] has previously discussed the possible structures of both the dimer and the trimer and assigned to them the 3,3-dimer and 3,2,3,3-trimer structures, respectively (see below). Lower or negligible amounts of trimer were observed for diisopropyl- and hexamethylenestannylene acetals. Both observations are consistent with observations made for simpler diols; the dibutylstannylene acetal of ethylene glycol exists as a complex mixture of dimer, trimer, tetramer, and pentamer,[15] while the di-*t*-butylstannylene acetal of ethylene glycol is present only as a dimer.[14] Substituents branched on the carbon attached to tin hinder assumption of hexacoordination by the tin atom because of steric interactions with two rather than one adjacent monomer units. Replacing two substituents on tin by a cyclic substituent has the same effect as introducing branching because the ring cannot twist to avoid steric effects. Apparently, branching at the β-carbon does not have the same effect because the dineopentylstannylene acetal is present to a greater extent as a trimer than the dibutylstannylene acetal.

If all of the products form through dimeric species, then it might be expected that reaction would take place on the more reactive dicoordinate oxygen atoms and give one monosubstituted compound. However, this is not observed for dialkylstannylene acetals of **28**. The appearance of the second product indicates that dimer populations are not the only controlling factor in the reaction. Electronic effects or the inherent relative reactivity of the oxygen atoms and other factors must have roles in directing the reactions of dialkylstannylene acetals of **28** with electrophiles.

In the terminal sugar units in the pentameric structure of solid **74** in which the tin atoms are pentacoordinate, the axial oxygen atoms are dicoordinate and the equatorial oxygen atoms are tricoordinate. From the X-ray result[19] and from the benzoylation results both here and earlier,[27] it seems most likely that the equatorial oxygen atoms are tricoordinate in the major dimer in solution. But with the hexamethylenestannylene acetal, the major product was obtained with the *p*-toluenesulfonyl group on the equatorial oxygen atom (O-3) and the product on the axial oxygen atom (O-2) was minor. These results indicate that the inherent reactivities of the oxygen atoms play an important role here. As reactions slow, it is to be expected that the rates of reaction from the individual dimers will become more important than the dimers' relative populations.[22] Dicoordinate equatorial oxygen atoms in dimeric structures that are little populated are inherently more reactive than dicoordinate axial oxygen atoms in highly populated dimers. In the toluenesulfonylation reaction, it appears that inherent reactivity is more important in determining the mixture of products than is dimer population. The other dimers are present at concentrations below the limit of detection by ^{119}Sn NMR spectroscopy under

the examination conditions.

1.2.4 Conclusions

The regioselectivities of acylation reactions of dibutylstannylene acetals derived from *cis*-1,2-diols depend on the nature of the carbohydrate and on the reaction conditions. In non-polar solvents without added nucleophiles, dibutylstannylene acetals of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (**28**) react preferentially on the normally less reactive axial oxygen atom O-2 in the benzoylation reaction. Under similar conditions, dibutylstannylene acetals of methyl 4,6-*O*-benzylidene-α- and -β- D-allopyranoside (**54** and **60**) react regioselectively on the equatorial oxygen atom O-2.

On increasing the steric bulk of the alkyl substituents on tin, particularly, with the dineopentylstannylene acetal, regioselectivity reverses to favour reaction at the equatorial oxygen atom, O-3, in benzoylation reactions of dialkylstannylene acetals of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (**28**).

^{119}Sn NMR spectroscopy indicated that dialkylstannylene acetals of **28** having primary alkyl groups on the tin atom exist as mixtures of dimers and a trimer. Branching at the carbon atom attached to tin, as in the isopropyl derivatives, substantially eliminated oligomers higher than dimers. With the hexamethylenestannylene acetal, which has a smaller bond angle at tin, only one symmetric dimer was observed in ^{119}Sn NMR spectra.

^{119}Sn NMR spectroscopy of the dibutylstannylene acetal of methyl 4,6-*O*-benzylidene-α- and β-D-allopyranoside at different temperature only showed the presence of dimers, mainly one symmetric 3,3-dimer for the β-glycoside and two for the α-

glycoside. Monosubstituted products were obtained in high yields and with high regioselectivity in acylation and alkylation reactions with methyl 4,6-*O*-benzylidene-α- and β-D-allopyranoside.

For both of the allopyranosides, the dominant species present was the 3,3'-symmetric dimer. The structure of this species and the inherent reactivity of the oxygen atom both direct reaction to the same oxygen atom. However, for methyl 4,6-O-benzylidene-α-D-mannopyranoside, the structure of the major dimer and the inherently reactivity of the two oxygen atoms compete to direct reactions at O-2 or O-3.

1.4 Experimental

1.4.1 General methods

Melting points were determined using a Fisher-Johns melting point apparatus and were uncorrected. Optical rotations were measured with a Perkin-Elmer 141 polarimeter using the 589 nm sodium line (D). Thin layer chromatography (TLC) was performed on Silica Gel aluminium sheets (60 PF-254, Merck, or Al Sil G/UV, Whatman) cut to be approximately 7 cm long, using solvent mixtures measured on a v/v basis. After chromatography was performed, components were located by examination under UV light and by spraying with 2% ceric sulfate in 2 M sulfuric acid and heating on a hot plate until colouration took place. Purification or separation of compounds was carried out with "dry column" flash chromatography[74,75] on silica gel 60 Å (ave particle size 2-5μ, Aldrich) using hexane-ethyl acetate as an elution gradient unless otherwise stated. Elemental analyses were performed by Canadian Microanalytical Services Ltd., Vancouver, B. C. Unless otherwise noted, ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-250F spectrometer operating at 250.13 and 62.9 MHZ, respectively at ambient temperature on solutions in chloroform-*d*. All ^{119}Sn NMR spectra were recorded on a Bruker AMX-400 spectrometer using 10 mm tubes. The NMR samples were prepared in $CDCl_3$ unless otherwise noted. ^{1}H and ^{13}C NMR chemical shifts were referenced to an internal standard, either TMS (0.03%), or for ^{13}C NMR spectra, the central signal of $CDCl_3$ as a secondary reference at 77.0 ppm. The appearances of signals are indicated using the designations b, s, d, t, q, p, and m for broad, singlet, doublet, triplet, quartet, pentet, and multiplet,

respectively. ^{119}Sn NMR spectra were referenced to external neat tetramethyltin as 0.0 ppm. Assignments and magnitudes of coupling constants were obtained for ^{1}H NMR spectra by first-order analyses and confirmed by COSY experiments. Accurate mass measurements were made on either a Fisons VG ZAB-EQ (FAB) or a Dupont-CEC 21-110 (EI) double focussing mass spectrometer at an accuracy of 3 ppm by voltage scanning using PEG Na and PFK reference ions, respectively. All of the solvents used in the experiments and for chromatography were dried and purified by distillation before use. Benzoyl chloride (150 mL) was purified by washing a benzene (100 mL) solution with %5 sodium bicarbonate (3 x 45 mL). The solution was dried over $CaCl_2$; the solvent was removed, and then benzoyl chloride was distilled under reduced pressure. *p*-Toluenesulfonyl chloride was purified by crystallization from chloroform and petroleum ether.

1.4.1.1 General method for the preparation of dialkylstannylene acetals

The monosaccharide (0.282 g, 1 mmol) was refluxed overnight with dialkyltin oxide (1 mmol) in toluene (20 mL) with continuous removal of water in a Dean-Stark apparatus. Reactions in toluene were performed on this solution. For reactions in other solvents, toluene was removed on a vacuum line and the residue was dried at room temperature under reduced pressure (0.1-0.01 Torr).

1.4.1.2 General procedures for benzoylation and *p*-toluenesulfonylation of dialkylstannylene acetals derived from methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (28)

Method A: The dialkylstannylene acetal of compound **28** was prepared for each experiment by using the standard method outlined in section 1.4.1.1. If the reaction solvent was not toluene, the solvent (20 mL) was added to the residue containing the dried dialkylstannylene acetal. Benzoyl chloride or *p*-toluenesulfonyl chloride (1 equiv) was added at room temperature and the mixture was stirred under a nitrogen atmosphere until TLC showed that all starting material had been consumed. Unless otherwise stated, the substitution reaction was stopped by adding water (5 mL), and the organic layer was diluted with dichloromethane (15 mL). The organic layer was washed with water (15 mL), then dried over sodium sulfate and concentrated on a rotary evaporator to a residue.

Method B: The dialkylstannylene acetal of compound **28** was prepared by the standard method which was outlined in section 1.4.1.1. Toluene was removed on a vacuum line. A solution of benzoyl chloride or *p*-toluenesulfonyl chloride was prepared in the reaction solvent (20 ml) and added to the residue containing the dialkylstannylene acetal. The reaction was continued until TLC showed that all starting material had been consumed. Workup was done in each case as in Method A.

1.4.2 Preparation of methyl 4,6-*O*-benzylidene-α- and β-D-allopyranoside

1.4.2.1 Methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (52)

Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside[76] (**51** or **32**) (22 g, 78 mmol) was refluxed with dibutyltin oxide (21.4 g, 86 mmol) in toluene (480 mL) overnight with continuous removal of water. The reaction mixture was cooled to 5 °C in an ice bath. A solution of freshly distilled benzoyl chloride (9.0 mL, 78 mmol) in toluene (10 mL) was added dropwise and stirred for 1 h. When TLC (ethyl acetate\hexane, 2:1 v/v) showed that all starting material had been consumed, the reaction was quenched by adding water (50 mL). The reaction mixture was diluted with chloroform (220 mL) and the organic layer was separated and washed with dilute hydrochloric acid (0.1 M, 10 mL), water (2 x 100 mL), aqueous saturated sodium bicarbonate (2 x 120 mL), and water (2 x 150 mL), then dried ($MgSO_4$) and concentrated to a colourless solid. Products were separated by dry column flash chromatography with hexane and ethyl acetate as a gradient eluant starting with pure hexane. The title compound, a solid, was recrystallized from ether and petroleum ether to give needle-like crystals, yield 27.8 g (93%); mp 166-168 °C; lit.[77] mp 167-169 ° C; R_f = 0.62 (ethyl acetate\hexane, 2:1 v/v); $[\alpha]_D^{23}$ +105 ° (*c* 0.81, chloroform), lit.[78] $[\alpha]_D^{21}$ + 109.5 °; ^{1}H NMR (DMSO-d_6) δ : 3.32 (s, 3H, OMe), 3.62-3.79 (m, 3H, H-4, H-5 and H-6_{ax}), 3.99 (t, 1H, $J_{2,3} = J_{3,4}$ = 8.9 Hz, H-3), 4.23 (dd, 1H, $J_{5,6eq}$ = 3.1 Hz, $J_{6eq,6ax}$ = 9.3 Hz, H-6_{eq}), 4.84 (dd, 1H, H-2), 4.99 (d, 1H, $J_{1,2}$ = 2.8 Hz, H-1), 5.65 (s, 1H, PhCH), 7.37-7.68 (m, 8H, Ar-H and Ar'-H), 8.00 (d, 2H, J_{ortho} = 7.1 Hz, Ar'-H_{ortho}); ^{13}C NMR (DMSO-d_6), δ : 54.9 (OMe), 62.5 (C-5), 67.5 (C-3), 67.9 (C-6), 74.3 (C-2), 80.9

(C-4), 97.3 (C-1), 101.0 (PhCH), 126.5, 128.1, 128.8, 129.0, 129.4, 129.5 (Ar-C and Ar'-C), 133.7 (Ar'-C_{ipso}), 137.7 (Ar-C_{ipso}), 165.5 (COO).

1.4.2.2 Methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-*ribo*-hexopyranosid-3-ulose (53)

A solution of oxalyl chloride (1.047 mL, 12 mmol) in dry dichloromethane (25 mL) was stirred in a three-necked flask cooled by a bath containing a *N,N*-dimethylformamide and liquid N_2 slurry at -60 °C. Freshly distilled dimethyl sulfoxide (1.8 mL) in dichloromethane (5 mL) and was then added dropwise over 5 min to the cooled stirred reaction mixture. Stirring was continued at -60 °C for 15 min. A solution of methyl 2-*O*-benzoyl 4,6-*O*-benzylidene-α-D-glucopyranoside (4.053 g, 10.5 mmol) in dichloromethane (20 mL) was added dropwise *via* a pressure equalization funnel over 5 min. The reaction was stirred for another 45 min at -60 °C. Triethylamine (6.9 mL, 50 mmol) was added dropwise to the reaction mixture over 10 min and the reaction mixture was stirred at -60 °C for a further 15 min. During addition of the base, formation of a white solid was observed. The reaction mixture was warmed to room temperature and water (30 mL) was added. The colour of the solution changed to yellow after 10 min stirring. The organic phase was separated and washed with dilute cold HCl (250 mL), then with water (3 x 200 mL), dried over calcium chloride, then concentrated to a solid. TLC (ethyl acetate/benzene, 1:1 v/v) showed the formation of one product exclusively. Purification with column chromatography gave the title compound (**53**) as a solid that was recrystallized from dichloromethane and hexane to give colourless needles, yield 3.78 g (94%); mp 208 °C; lit.[77] mp 210-212 ° C; R_f= 0.7 (ethyl acetate/benzene, 1:1), $[\alpha]_D^{24}$ +82 °

(*c* 1.1, chloroform); ^{1}H NMR ($CDCl_3$) δ : 3.50 (s, 3H, OMe), 3.98 (t, 1H, $J_{5,6ax} = J_{6ax,6eq}$ = 10.2 Hz, H-6_{ax}), 4.19 (ddd, 1H, $J_{4,5}$ = 10.0 Hz, $J_{5,6eq}$ = 4.5 Hz, H-5), 4.41-4.48 (m, 2H, H-4 and H-6_{eq}), 5.34 (d, 1H, $J_{1,2}$ = 4.3 Hz, H-1), 5.60 (s, 1H, PhCH), 5.63 (d, 1H, H-2), 7.35-7.60 (m, 8H, Ar-H and Ar'-H), 8.11-8.15 (dd, 2H, J_{ortho} = 9.54 Hz, J_{meta} = 1.52 Hz, Ar-H'$_{ortho}$), ^{13}C NMR ($CDCl_3$), δ : 55.7 (OMe), 65.4 (C-5), 69.4 (C-6), 74.8 (C-2), 82.2 (C-4), 101.4 (C-1), 102.0 (PhCH), 126.4, 128.3, 128.5, 129.4, 130.2 (Ar-H and Ar'-H), 133.7 (Ar'-C_{ipso}), 136.3 (Ar-C_{ipso}), 162.2 (COO), 191.9 (CO).

1.4.2.3 Methyl 4,6-*O*-benzylidene-α-D-allopyranoside (54)

To a solution of compound **53**, (1.15 g, 3 mmol) in DMF (8 mL) was added dried methanol (200 mL). Sodium borohydride (2.0 g) was added in portions to the solution and the mixture was stirred for 1 h. The colour of the solution gradually changed to grey and considerable bubbling was observed. When the reaction mixture was observed by TLC to still contain starting material it was refluxed for 1 h. TLC (ethyl acetate/ hexane, 3:2 v/v) then showed the formation of two products and that all starting material had been consumed. The reaction mixture was concentrated to a solid residue that was fractionated between chloroform and water. The organic layer was concentrated to a residue that was separated by means of dry column flash chromatography using ethyl acetate and hexane as gradient eluant. The first fraction was the title compound (**54**), a solid, that was recrystallized from ethanol and petroleum ether to give needle-like crystals, mp 57-58 °C (hydrated), lit.[79] 58-60 °C. Recrystallization of this compound from absolute ethanol gave crystals of the title compound (**54**); mp 172-174 °C; R_f= 0.24; yield 0.641 g (76%); $[\alpha]_D^{24}$

+125 °(*c* 0.83, chloroform), lit.[80] mp 176-178 °C, $[\alpha]_D$ +126.3 °; ^{1}H NMR ($CDCl_3$), δ : 2.66 (d, 1H, $J_{3,OH-3}$ = 7.4 Hz, OH-3), 2.93 (d, 1H, $J_{2,OH-2}$ = 11.3 Hz, OH-2), 3.49 (s, 3H, OMe), 3.54 (dd, 1H, $J_{3,4}$ = 2.7 Hz, $J_{4,5}$ = 9.7 Hz, H-4), 3.71 (m, 1H, H-2), 3.75 (t, 1H, $J_{5,6ax}$ = $J_{6ax,6eq}$ = 10.3 Hz, H-6_{ax}), 4.08 (ddd, 1H, H-5), 4.27 (pentet, 1H, $J_{2,3}$ = 3.4 Hz, H-3), 4.38 (dd, 1H, $J_{5,6eq}$ = 5.1 Hz, H-6_{eq}), 4.76 (d, 1H, $J_{1,2}$ = 4.0 Hz, H-1), 5.58 (s, 1H, PhCH), 7.35-7.49 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$), δ : 56.4 (OMe), 57.2 (C-5), 68.1 (C-2), 69.2 (C-6), 69.5 (C-3), 78.3 (C-4), 100.7 (C-1), 102.0 (PhCH), 126.2, 128.3, 129.2 (Ar-C), 137.0 (Ar-C_{ipso}).

The second fraction was methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**32** or **51**), yield 0.158 g (19%).

1.4.2.4 Methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-allopyranoside (65)

Compound **54** (0.141 g, 0.5 mmol) and dibutyltin oxide (0.125 g, 0.5 mmol) were refluxed for 8 h in toluene (15 mL) with azeotropic removal of water. The reaction mixture was concentrated to 8 mL, then was cooled to 0 °C in a ice bath. A solution of distilled benzoyl chloride (58 μL, 0.5 mmol) in toluene (1 mL) was added dropwise to the solution under a nitrogen atmosphere. After 0.5 h, TLC (ethyl acetate/cyclohexane, 2:3) showed formation of one product exclusively and consumption of all starting material. The reaction was halted by adding water (2 mL) and worked up as the general method. The residue was purified by means of dry column flash chromatography using ethyl acetate and cyclohexane as the elution gradient. The solvent was removed to give the title compound (**65**), a solid, that was recrystallized from ethyl acetate, yield 0.188 g (98%);

mp 103-104 °C, ; $[\alpha]_D^{32}$ +69.4 ° (*c* 6.62, chloroform), lit.[80] mp 105-107 °C; $[\alpha]_D$ + 73.3 °, R_f =0.55 (ethyl acetate/cyclohexane, 2:3); ^{1}H NMR ($CDCl_3$) δ : 3.48 (s, 3H, OMe), 3.67 (dd, 1H, $J_{3,4}$ = 2.4 Hz, $J_{4,5}$ = 9.7 Hz, H-4), 3.83 (t, 1H, $J_{5,6ax}$ = 10.2 Hz, H-6_{ax}), 4.25 (ddd, 1H, $J_{6ax,6eq}$ = 10.2 Hz, $J_{5,6eq}$ = 5.2 Hz, H-5), 4.42 (dd, 1H, H-6_{eq}), 4.50 (dd, 1H, H-3), 5.05 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1), 5.09 (t, 1H, $J_{2,3}$ = 3.4 Hz, H-2), 5.62 (s, 1H, PhCH), 7.35-7.62 (m, 8H, Ar-H and Ar'-H), 8.14 (dd, 2H, J = 8.0 Hz, J = 0.8 Hz, Ar'-H_{ortho}); ^{13}C NMR ($CDCl_3$) δ : 56.0 (OMe), 57.9 (C-5), 68.2 (C-3), 69.0 (C-6), 69.7 (C-2), 78.5 (C-4), 98.6 (C-1), 101.9 (PhCH), 126.2, 128.2, 128.4, 129.1, 130.0 (Ar-C and Ar'-C), 133.5 (Ar'-C_{ipso}), 137.0 (Ar-C_{ipso}), 165.6 (COO); EI MS for $C_{21}H_{22}O_7$: M^+ (386), 105 (100%), 77 (28%), 154 (25%), 181 (16%), 268 (25%).

1.4.2.5 Preparation of methyl 4,6-*O*-benzylidene-2-*O*-*p*-toluenesulfonyl-α-D-allopyranoside (66) in toluene

Compound **54** (0.141 g, 0.5 mmol) was treated with dibutyltin oxide (0.125 g, 0.5 mmol) in toluene as in the general method to give the dibutylstannylene acetal solution. The stirred reaction mixture was cooled to room temperature and *p*-toluenesulfonyl chloride (0.095 g, 0.5 mmol) was added in portions. After the reaction mixture had been stirred at room temperature for 7 h, TLC (ethyl acetate/hexane, 1:2) showed that all starting material had been consumed. Water (2 mL) was added to the reaction mixture, which was diluted with chloroform (12 mL) and worked up as in the general method. The solid residue was purified by dry column flash chromatography and recrystallized from acetone and hexane to give needle-like crystals of the title compound (**66**), yield 0.206 g,

(95%); mp 163-164 °C; $[\alpha]_D^{24}$ + 60 ° (*c* 0.81, chloroform), lit[80] mp 166-167 °C, $[\alpha]_D$ + 59 °; R_f = 0.35 (ethyl acetate/hexane, 1:2); ^{1}H NMR ($CDCl_3$), δ : 2.46 (s, 3H, tosyl CH_3), 3.06 (d, 1H, $J_{3,OH-3}$ = 7.1 Hz, OH-3), 3.38 (s, 3H, OMe), 3.46 (dd, 1H, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 9.7 Hz, H-4), 3.72 (t, 1H, $J_{5,6ax}$ = $J_{6ax,6eq}$ = 10.2 Hz, H-6_{ax}), 4.12 (ddd, 1H, H-5), 4.15-4.20 (m, 1H, H-3), 4.34 (dd,1H $J_{5,6eq}$ = 5.0 Hz, H-6_{eq}), 4.51 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 3.6 Hz, H-2), 4.80 (d, 1H, Hz, H-1), 5.52 (s, 1H, PhCH), 7.32-7.48 (m, 7H, Ar-H and Ar'-H), 7.84 (d, 2H, J_{ortho} = 8.3 Hz, Ar'-H_{ortho}); ^{13}C NMR ($CDCl_3$), δ : 21.7 (PhOMe), 56.3 (OMe), 57.6 (C-5), 68.3 (C-3), 68.9 (C-6), 74.4 (C-2), 78.2 (C-4), 98.8 (C-1), 102.0 (PhCH), 126.2, 127.8, 128.3, 129.2, 130.0 (Ar-C and Ar'-C), 133.5, 136.7 (Ar'-C_{ipso} and Ar-C_{ipso}), 145.4 (Ar'-$C_{ipso'}$); EI MS for $C_{21}H_{24}O_8S$: M^+ (436, 7%), 91 (80%), 155 (59%), 221 (28%), 242 (47%), 269 (9%), 281 (28%).

1.4.2.6 Preparation of methyl 4,6-*O*-benzylidene-2-*O*-p-toluenesulfonyl-α-D-allopyranoside (66) in chloroform

The dibutylstannylene acetal solution in toluene prepared exactly as in section 1.4.2.5 was concentrated. The residue was dissolved in dry chloroform (12 mL) and *p*-toluenesulfonyl chloride (0.095 g, 0.5 mmol) was added in portions. The reaction mixture was stirred at room temperature for 3 h then worked up as in the general method to give the title compound (66), 0.214 g (98% yield) after column chromatography.

1.4.2.7 Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-allopyranoside (67)

Treatment of compound **54** (0.141 g, 0.5 mmol) with dibutyltin oxide (0.125 g, 0.5 mmol) in toluene gave the dialkylstannylene acetal solution. The reaction mixture was cooled to room temperature and tetrabutylammonium iodide (0.277 g, 0.75 mmol) was added. Then distilled benzyl bromide (66 μL, 0.55 mmol) was added dropwise to the mixture which was refluxed at ~ 130-140 °C under an argon atmosphere. After 2 h, TLC (ethyl acetate/hexane, 1:3) showed that all starting material had been consumed. The reaction mixture was worked up as in the general method. The residue was purified by means of flash column chromatography using an elution gradient from hexane to ethyl acetate, which gave the title compound (**67**) as a syrup, yield 0.152 g (81%); R_f = 0.44 (ethyl acetate-cyclohexane, 1:1); $[\alpha]_D^{29}$ +18° (*c* 3.81, chloroform); ^{1}H NMR ($CDCl_3$) δ : 3.20 (d, 1H, $J_{3,OH-3}$ = 7.0 Hz, OH-3), 3.41 (dd, 1H, $J_{3,4}$ = 3.4 Hz, $J_{4,5}$ = 9.8 Hz, H-4), 3.45 (s, 3H, OMe), 3.50 (t, 1H, $J_{1,2} = J_{2,3}$ = 3.4 Hz, H-2), 3.70 (t, 1H, $J_{5,6ax} = J_{6ax,6eq}$ = 10.2 Hz, H-6_{ax}), 4.15 (ddd, 1H, $J_{5,6eq}$ = 5.2 Hz, H-5), 4.35 (dd, 1H, H-6_{eq}), 4.44 (pentet, 1H, $J_{3,4}$ = 3.4 Hz, H-3), 4.60 (d, 1H, J = 12.51 Hz, 1/2 PhCH), 4.78 (d, 1H, 1/2 PhCH), 4.75 (d, $J_{1,2}$ = 3.7 Hz, H-1), 5.52 (s, 1H, PhCH), 7.32-7.38 (m, 8H, Ar-H and Ar'-H), 7.49-7.53 (m, 2H, Ar'-H_{ortho}); ^{13}C NMR ($CDCl_3$) δ : 55.8 OMe), 57.8 (C-5), 66.8 (C-3), 69.1 (C-6), 70.3 ($PhCH_2$), 73.7 (C-2), 78.8 (C-4), 99.5 (C-1), 101.9 (PhCH), 126.2, 127.9, 128.1, 128.1, 128.5, 129.0 (Ar-C and Ar'-C), 137.1 (Ar-C_{ipso}), 137.1 (Ar'-C_{ipso}); EI MS : M^+ (372, 9%), 340 (35%), 149 (36%), 107 (67%), 105 (64%), 91 (98%).

Anal. calcd. for $C_{21}H_{24}O_6$: C 67.73, H 6.49; found : C 67.07, H 6.48.

2.4.2.8 Methyl β-D-allofuranoside (59), Methyl β-D-allopyranoside (57) and Methyl α-D-allopyranoside (56)

D-Allose (0.6 g) was added to an acidic solution of methanol (about 2% HCl) (12 mL) prepared by bubbling HCl gas through methanol. The solution was refluxed for 3 h. When TLC (ethyl acetate/methanol, 4:1 v/v) showed formation of three products and consumption of all starting material, the reaction mixture was cooled to room temperature, neutralized with saturated aqueous sodium bicarbonate, and then filtered. The solvent was removed under reduced pressure and the white solid residue was separated by means of dry column flash chromatography using ethyl acetate and methanol as gradient eluant starting from pure ethyl acetate. The first fraction was methyl β-D-allofuranoside (**59**) as a syrup, yield 0.05 g, (8%); R_f= 0.54 (ethyl acetate/methanol, 4:1 v/v); $[\alpha]_D^{28}$ -57.4 °(*c* 1.88, methanol), lit.[81] $[\alpha]_D$ -55.3 °; ^{1}H NMR (D_2O, ref. CH_3OH, δ_H = 3.3) δ : 3.34 (s, 3H, OMe), 3.37-3.62 (m, 1H, H-6), 3.68-3.88 (m, 2H, H-5 and H-6'), 3.87 (br t, 1H, $J_{3,4} = J_{4,5}$ = 5.8 Hz, H-4), 4.01 (br d, 1H, $J_{1,2}$ = 5.7 Hz, H-2), 4.30 (br t, 1H, $J_{2,3}$ = 5.5 Hz, H-3), 4.83 (br s, 1H, H-1); ^{13}C NMR (D_2O, ref. CH_3OH, δ_c = 49.0), δ : 55.4 (OMe), 62.8 (C-6), 71.7 (C-3), 72.9 (C-5), 74.6 (C-2), 82.4 (C-4), 108.0 (C-1).

The second fraction was a solid, R_f = 0.45, recrystallized from methanol/ ethyl acetate to give crystals of compound **57**; yield 0.263 g (41%); mp 154-155 °C; $[\alpha]_D^{29}$ -49.2° (*c* 1.23, methanol), lit.[82] mp 154-155 °C, $[\alpha]_D^{20}$ -51.4 ° (water); ^{1}H NMR (D_2O), δ : 3.37 (dd, 1H, $J_{1,2}$ = 8.24 Hz, $J_{2,3}$ = 3.0 Hz, H-2), 3.51 (s 3H, OMe), 3.55 (dd, 1H, $J_{3,4}$ = 2.8 Hz, $J_{4,5}$ = 9.84 Hz, H-4), 3.60-3.76 (m, 2H, H-5 and H-6), 3.86 (bd, 1H, ^2J= 11.7 Hz, H-6'), 4.10 (t, 1H, $J_{3,4} = J_{2,3}$ = 2.8 Hz, H-3), 4.55 (d, 1H, $J_{1,2}$ = 8.24 Hz, H-1), ^{13}C NMR

(D_2O and CD_3OD) δ : 57.24 (OMe), 61.37 (C-6), 67.05 (C-4), 70.50 (C-2), 71.28 (C-3), 73.79 (C-5), 101.28 (C-1).

The third fraction, methyl α-D-allopyranoside (**56**), was not fully characterized.

1.4.2.9 Methyl 4,6-*O*-benzylidene-β-D-allopyranoside (60)

Methyl β-D-allopyranoside (1.8 g, 10 mmol) was dissolved in dry DMF (60 mL) and the solution was heated to 100 °C. *p*-Toluenesulfonic acid (0.040 g, 0.2 mmol) was added to the stirred solution at 100 °C. Then a solution of α,α-dimethoxytoluene (7.2 g, 48 mmol) in DMF (60 mL) was added dropwise under nitrogen. After 12 h, the reaction mixture was cooled to room temperature. A NaOH solution (2 M, 2 mL) was added and the organic layer was washed with water (3 x 60 mL). The solvent was removed under reduced pressure and the residue was chromatographed using ethyl acetate and hexane in an elution gradient. The first fraction was a mixture of the *exo* and *endo* isomers of methyl 2,3:4,6-di-*O*-benzylidene-β-D-allopyranoside as a solid. Fractional crystalization from chloroform gave the *exo* isomer of methyl 2,3:4,6-di-*O*-benzylidene-β-D-allopyranoside, mp 174-175 °C; R_f = 0.82 (ethyl acetate-hexane, 4 : 1); yield 0.209 g (6%); $[\alpha]_D^{30}$ -71 ° (*c* 0.60, chloroform); ^{1}H NMR ($CDCl_3$) δ : 3.56 (s, 3H, OMe), 3.76 (m, 1H, H-6_{ax}), 4.05-4.08 (m, 2H, H-4 and H-5), 4.31 (t, 1H, $J_{1,2} = J_{2,3}$ = 5.4 Hz, H-2), 4.47 (dd, 1H, $J_{5,6eq}$ = 4.3 Hz, $J_{6ax,6eq}$ = 10.1 Hz, H-6_{eq}), 4.57 (dd, 1H, $J_{3,4}$ = 2.4 Hz, H-3), 4.70 (d, 1H, H-1), 5.59 (PhCH), 6.42 (PhCH'), 7.24-7.47 (m, 10H, Ar-H and Ar'-H); ^{13}C NMR ($CDCl_3$) δ : 56.9 (OMe), 62.8 (C-5), 69.7 (C-6), 72.4 (C-3), 76.5 (C-4), 77.5 (C-2), 101.9 (C-1), 102.6 (PhCH, 105.2 (PhCH'), 126.1, 126.4, 128.3, 128.4, 129.0,129.2 (Ar-C and

Ar'-C), 137.00 (Ar-C_{ipso}), 137.74 (Ar'-C_{ipso}).

HRMS (ES) for $C_{21}H_{22}O_6$: calcd. 370.1416, found : 370.1414.

The *endo* isomer of methyl 2,3:4,6-di-*O*-benzylidene-β-D-allopyranoside was isolated in 2% yield from the mother liquor but was not fully characterized.

The second fraction from column chromatography was the title compound (60), a solid that was recrystallized from ethyl acetate and hexane to give colourless needles; R_f = 0.40 (ethyl acetate-hexane 4:1); yield 2.047 g (73%); mp 163-164 °C; $[\alpha]_D^{24}$ - 45.1 °(*c* 1.11, chloroform), lit.[83] mp 173-174 °C; $[\alpha]_D^{24}$ - 43.0 °; ^{1}H NMR ($CDCl_3$) δ : 2.64 (br s, 1H, OH-3), 2.71 (br s, 1H, OH-2), 3.48-3.51 (m, 1H, H-2), 3.58 (s, 3H, OMe), 3.58 (dd, 1H, $J_{3,4}$ = 2.5 Hz, $J_{4,5}$ = 9.8 Hz, H-4), 3.76 (t, 1H, $J_{5,6ax} = J_{6ax,6eq}$ = 10.2 Hz, H-6_{ax}), 4.00 (ddd, 1H, H-5), 4.37 (t, 1H, H-3), 4.39 (dd, 1H, $J_{5,6eq}$ = 4.9 Hz, H-6_{eq}), 4.61 (d, 1H, $J_{1,2}$ = 7.9 Hz, H-1), 5.57 (s, 1H, PhCH), 7.36-7.53 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$), δ : 57.5 (OMe), 63.1 (C-5), 68.8 (C-3), 69.1 (C-6), 71.2 (C-2), 78.7 (C-4), 101.9 (C-1), 102.4 (PhCH), 126.2, 128.4, 129.3 (Ar-C), 136.9 (Ar-C_{ipso}).

1.4.2.10 Methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-β-D-allopyranoside (68)

Compound 60 (57 mg, 0.2 mmol) and dibutyltin oxide (50 mg, 0.2 mmol) were refluxed in toluene (8 mL) with azeotropic removal of water for 12 h. The reaction mixture was cooled to 0 °C in a ice bath. A solution of benzoyl chloride (23 μL, 0.2 mmol) in toluene (1 mL) was added dropwise. After 0.5 h, TLC (ethyl acetate/hexane, 1:2) showed the formation of one product and consumption of all starting material. The reaction mixture was worked up as in the general method to give a residue that was

purified by means of dry column flash chromatography using hexane and ethyl acetate as an elution gradient to yield the title compound (**68**) as a solid. It was recrystallized from ethyl acetate and hexane, yield 0.063 g (81%); mp 149-150 °C; R_f= 0.65 (ethyl acetate/hexane, 1:2), [ ]$_D^{23}$ - 48.6 ° (*c* 2.63, chloroform); ^{1}H NMR (C_6D_6) : 2.95 (dd, 1H, $J_{3,4}$ = 2.2 Hz, $J_{4,5}$ = 9.5 Hz, H-4), 3.22 (s, 3H, OMe), 3.47 (t, 1H, $J_{5,6ax}$ = 10.1 Hz, $J_{6ax,6eq}$ = 10.1 Hz, H-6_{ax}), 4.02 (ddd, 1H, H-5), 4.21 (dd, 1H, $J_{5,6eq}$ = 4.9 Hz, H-6_{eq}), 4.32 (br t, 1H, H-3), 5.03 (d, 1H, $J_{1,2}$ = 8.3 Hz, H-1), 5.20 (s, 1H, PhCH), 5.25 (dd, 1H, $J_{2,3}$ = 3.1 Hz, H-2), 6.94-7.24 (m, 6H, Ar-H, Ar-H), 7.58 (dd, 2H, J_{ortho} = 8.3 Hz, J_{betha} = 1.5 Hz, Ar-H), 8.25 (dd, 2H, Ar-H); ^{13}C NMR ($CDCl_3$) : 59.4 (OMe), 63.2 (C-5), 68.0 (C-3), 69.1 (C-6), 72.2 (C-2), 78.4 (C-4), 100.0 (C-1), 101.8 (PhCH), 126.7, 126.1, 128.3, 129.6, 129.9, 130.2 (Ar-C and Ar-C), 133.6 (Ar-C_{ipso}), 136.9 (Ar-C_{ipso}), 165.5 (COO); EI MS : M^+ (386), 268 (25%), 181 (16%), 154 (25%), 105 (100%).

Anal. calcd. for $C_{21}H_{22}O_7$: C 65.28, H 5.74; found : C 65.09 H 5.56.

1.4.2.11 Methyl 4,6-*O*-benzylidene-2-*O*-p-toluenesulfonyl- -D-allopyranoside (69)

Treatment of compound **60** (0.085 g, 0.3 mmol) with dibutyltin oxide (75 mg, 0.3 mmol) in toluene (12 mL) as Method A gave dibutylstannylene acetal solution. The reaction mixture was cooled to room temperature and a solution of *p*-toluenesulfonyl chloride (33 mg, 0.35 mmol) in toluene (2 mL) was added. Stirring was continued at ambient temperature until no further change was observed by TLC (ethyl acetate, 1 :2) (7 h). The reaction mixture was quenched by adding water (2 mL) and worked up as in the general method. The solid residue was purified by means of dry column flash

chromatography using ethyl acetate and hexane as an elution gradient. The title compound (69) was obtained as solid and recrystallized from ethyl acetate and hexane, mp 142-143 °C; yield 0.109 g (83%); R_f = 0.38; $[\alpha]_D^{30}$ - 55.7 ° (*c* 3.16, chloroform); ^{1}H NMR (C_6D_6) δ : 2.43 (s, 3H, tosyl CH_3), 2.59 (b, 1H, OH-3), 3.26 (s, 3H, OMe), 3.55 (dd, 1H, $J_{3,4}$ = 2.5 Hz, $J_{4,5}$ = 9.15 Hz, H-4), 3.70 (t, 1H, $J_{5,6ax} = J_{6ax,6eq}$ = 10.4Hz, H-6_{ax}), 4.01 (ddd, 1H, H-5), 4.30 (dd, 1H, $J_{1,2}$ = 7.9 Hz, $J_{2,3}$ = 3.1 Hz, H-2), 4.36 (dd, $J_{5,6eq}$ = 4.5 Hz, H-6_{eq}), 4.51 (b, 1H, H-3), 4.71 (d, 1H, H-1), 7.30-7.45 (m, 8H, Ar-H and Ar'-H), 7.81 (dd, 2H, J_{ortho} = 8.6 Hz, J_{meta} = 1.8 Hz, Ar'-H_{ortho}); ^{13}C NMR ($CDCl_3$), δ : 21.6 ($PhCH_3$), 57.3 (OMe), 62.8 (C-5), 68.6 (C-3), 68.8 (C-6), 78.1 (C-4), 78.5 (C-2), 99.2 (C-1), 101.8 (PhCH), 126.1, 128.1, 128.3, 129.3, 129.5 (Ar-C and Ar'-C), 133.6 (Ar'-C_{ipso}), 136.7 (Ar-C_{ipso}), 144.8 (Ar'-$C_{ipso'}$); EI MS : M^+ (436), 28 (100%), 91 (56%), 105 (88%), 221 (31%), 269 (29%).

Anal. calcd. for $C_{21}H_{24}O_8S$: C 57.79, H 5.54; found: C 57.65 H 5.56.

1.4.2.12 Benzylation of methyl 4,6-*O*-benzylidene-β-D-allopyranoside (60)

A dibutylstannylene acetal solution was prepared by treatment of compound 60 (85 mg, 0.3 mmol) and dibutyltin oxide (77 mg, 0.31 mmol) in toluene (12 mL) as in the standard method. The reaction mixture was concentrated to 8 mL and cooled to room temperature. Tetrabutylammonium iodide (0.166 g, 0.45 mmol) was added and the reaction mixture was stirred 0.5 h. A solution of freshly distilled benzyl bromide (42 μL, 0.35 mmol) in toluene (1 mL) was added and the reaction mixture was refluxed at ~ 130-140 °C. After 2 h, TLC (ethyl acetate/hexane, 1:2) showed formation of two products and

consumption of all starting material. The reaction mixture worked up as in the general method to give a yellowish syrup, that was separated by means of dry column flash chromatography using ethyl acetate and hexane in an elution gradient. The first fraction was methyl 2-*O*-benzyl-4,6-*O*-benzylidene-β-D-allopyranoside (**70**) as a solid, yield 0.096 g (86%); mp 114-115 °C; R_f = 0.52 (ethyl acetate/hexane, 1:2); $[\alpha]_D^{24}$ - 48 ° (*c* 1.72, chloroform); ^{1}H NMR ($CDCl_3$),δ : 2.60 (br s, 1H, OH-3), 3.29 (dd, 1H, $J_{1,2}$ = 7.9 Hz, $J_{2,3}$ = 3.1 Hz, H-2), 3.48 (dd, 1H, $J_{3,4}$ = 2.4 Hz, $J_{4,5}$ = 9.2 Hz, H-4), 3.57 (s, 3H, OMe), 3.69 (t, 1H, $J_{5,6ax} = J_{6ax,6eq}$ = 10.4 Hz, H-6_{ax}), 4.01 (ddd, 1H, H-5), 4.27 (br t, 1H, H-3), 4.37 (dd, 1H, $J_{5,6eq}$ = 4.9 Hz, H-6_{eq}), 4.76 (d, 1H, $J_{1,2}$ = 7.9 Hz, H-1), 4.69 (d, 1H, ^2J = 12.2 Hz, 1/2 $PhCH_2$), 4.83 (d, 1H, 1/2 $PhCH_2$), 5.48 (s, 1H, PhCH), 7.23-7.32 (m, 10H, Ar-H and Ar'-H); ^{13}C NMR ($CDCl_3$) δ : 57.2 (OMe), 62.4 (C-5), 68.1 (C-3), 69.0 (C-6), 72.6 ($PhCH_2$), 76.4 (C-2), 78.5 (C-4), 101.7 PhCH), 102.1 (C-1), 126.1, 126.7, 127.7, 127.8, 128.1, 128.3, 128.9 (Ar-C and Ar'-C), 136.9 (Ar-C_{ipso}), 137.7 (Ar'-C_{ipso}).

HRMS (EI) for $C_{21}H_{24}O_6$: calcd. 372.1562; found: 372.1582.

The second fraction from the column was methyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-allopyranoside (**71**) as a syrup, yield 8 mg (7%); R_f = 0.31 (ethyl acetate/hexane, 1:2); $[\alpha]_D^{23}$ -12 ° (*c* 0.20, chloroform); ^{1}H NMR ($CDCl_3$), δ : 2.57 (d, 1H, $J_{2,OH-2}$ = 9.2 Hz, OH-2), 3.52 (dd, 1H, $J_{1,2}$= 7.9 Hz, $J_{2,3}$ = 3.7 Hz, H-2), 3.55 (s, 3H, OMe), 3.68 (dd, 1H, $J_{3,4}$ = 2.4 Hz, $J_{4,5}$ = 9.2 Hz, H-4), 3.77 (t, 1H, $J_{6ax,6eq}$ = 10.4 Hz, H-6_{ax}), 4.06 (ddd, 1H, H-5), 4.23 (br t, 1H, H-3), 4.41 (dd, 1H, $J_{5,6eq}$ = 5.5 Hz, H-6_{eq}), 4.55 (d, 1H, $J_{1,2}$ = 7.9 Hz, H-1), 4.63 (d, 1H, $J_{geminal}$ = 11.0 Hz, 1/2 $PhCH_2$), 5.07 (d, 1H, 1/2 $PhCH_2$), 5.53 (s, 1H, PhCH), 7.33-7.51 (m, 10H, Ar-H and Ar'-H); ^{13}C NMR ($CDCl_3$), δ : 57.4 (OMe), 63.5

(C-5), 69.2 (C-6), 71.0 (C-2), 74.8 (C-4), 80.2 (C-4), 102.2 (C-7), 102.8 (C-1), 126.1, 128.0, 128.1, 128.4, 128.5, 129.2 (Ar-C), 137.3 (Ar-C_{ipso}), 138.0(Ar-C_{ipso}).

HRMS (EI) for $C_{21}H_{24}O_6$: calcd. 372.1562; found: 372.1562.

1.4.3 Methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (28)

1.4.3.1 Preparation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (28)

This preparation is a modification of a literature procedure.[84] Methyl α-D-mannopyranoside (20.0 g, 103 mmol) was dissolved in dry DMF (200 ml) and *p*-toluenesulfonic acid (200 mg, 1.05 mmol) was added. A solution of α,α-dimethoxytoluene (19.8 g, 130 mmol) in DMF (200 ml) was added dropwise to the reaction mixture stirred at 0 °C under nitrogen. The stirred reaction mixture was warmed to 60 °C. After 16 h, when TLC (ethyl acetate, hexane 1:1 v/v) indicated that all starting material had been consumed, water was added (10 mL). Standard workup gave a syrupy residue that was separated by means of dry column flash chromatography by using ethyl acetate and hexane as an gradient eluant. The first fraction (8.27 g) was a mixture of the *exo* (**72**) and *endo* (**73**) isomers of methyl 2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside with $R_f = 0.28$. Fractional crystalization from ethanol gave the pure *exo* isomer of methyl 2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside, $R_f = 0.47$ (ethyl acetate/hexane 1:1); mp 101-102 °C, lit.[85] 96-98 °C

The second fraction was the title compound (**28**) as a gel. Crystallization of the gel from cyclohexane and chloroform gave needles, mp 140-142 °, lit.[84] 141-143 °; $R_f = 0.8$

(ethyl acetate/hexane, 1:1); yield 14.15 g (48.7%); ^{1}H NMR ($CDCl_3$, 250.13 MHz), δ : 2.86 (br, 2H, OH's), 3.40 (s, 3H, OMe), 3.75-3.88 (m, 2H, H-5 and H-6_{ax}), 3.92 (t, 1H, $J_{3,4} = J_{4,5} = 9.1$ Hz, H-4), 4.41 (br s, 1H, H-2), 4.28 (m, 1H, H-6), 4.75 (br s, 1H, H-1), 5.56 (s, 1H, PhCH), 7.25-7.50 (m, 5H, Arom. H's). ^{13}C NMR ($CDCl_3$, 62.89 MHz), δ : 55.2 (OMe), 62.9 (C-5), 68.7 (C-3), 68.9 (C-6), 70.9 (C-2), 78.9 (C-4), 101.2 (C-1), 102.3 (C-7), 126.3, 128.4, 129.4 (Arom. C's).

1.4.3.2 Benzoylation of methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-mannopyranoside (74) in toluene.

A solution of the methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-mannopyranoside (**74**, 1 mmol) was prepared as in the general method. The solution was cooled to room temperature and a solution of freshly distilled benzoyl chloride (115.5 µl, 1 mmol) in toluene (1 mL) was added dropwise to the stirred solution under a nitrogen atmosphere. The progress of the reaction was monitored by TLC (ethyl acetate/hexane 3:1). After 3 h, when all of the starting material had been consumed, the reaction was stopped by adding water (2 mL) and stirring for 0.5 h. The resulting mixture was diluted with dichloromethane (20 mL). The organic layer was separated and washed with cooled dilute aqueous HCl solution (10 mL), water (2 x 100 mL), and saturated $NaHCO_3$, before being dried (magnesium sulfate), and concentrated. The residue was separated by means of dry column flash chromatography using ethyl acetate and hexane as an elution gradient. The first fraction was methyl 2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-α-D-mannopyranoside (**80**) as a syrup; yield 0.026 g (6.7%); $[\alpha]_D^{26}$ -17.6 ° (*c* 0.85, chloroform); R_f= 0.52 (ethyl

acetate/hexane 1: 3); ^{1}H NMR ($CDCl_3$) δ : 3.42 (s, 3H, OMe), 3.96 (t, 1H, $J_{6ax,6eq} = J_{5,6ax}$ = 10.1 Hz, H-6_{ax}), 4.09 (m, 1H, H-5), 4.38 (dd, 1H, $J_{5,6eq}$ = 4.3 Hz, H-6_{eq}), 4.33 (dd, 1H, H-4), 4.81 (d, 1H, $J_{1,2}$ = 1.6 Hz, H-1), 5.66 (s,1H, PhCH), 5.69 (dd, 1H, $J_{2,3}$ = 3.7 Hz, H-2), 5.81 (dd, 1H, $J_{2,3}$ = 3.7 Hz, $J_{3,4}$ = 10.3 Hz, H-3), 7.2-8.1 (m, 15H, Arom. H's); ^{13}C NMR ($CDCl_3$, 62.89 MHz), δ : 55.4 (OMe), 63.8 (C-6), 69.0 (C-5), 70.9 (C-2), 76.8 (C-4), 99.6 (C-1), 101.9 (C-1), 126.2, 128.2, 128.5, 128.6, 128.9, 129.8, 130.3, 130.6, 133.0, 133.6, 133.7, 134.6 Ar-C's), 162.4 (COO), 165.5 (COO).

Further elution gave methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-mannopyranoside **(81)** as a syrup; yield 0.248 g (64.5%); R_f= 0.4 (ethyl acetate / hexane, 1:3); $[\alpha]_D^{29}$ - 22.6 ° (*c* 1.28, chloroform), lit.[27] $[\alpha]_D^{21}$ - 24 °.

The third fraction from column chromatography was methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-mannopyranoside **(82)** as a syrup, yield 0.062 g (16%); R_f= 0.31 (ethyl acetate/hexane 1:3); $[\alpha]_D^{29}$ - 40.2 °(*c* 0.93, chloroform), lit.[27] $[\alpha]_D^{21}$ - 39 °.

1.4.3.3 *p*-Toluenesulfonylation of methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-mannopyranoside (74) in chloroform.

Treatment of compound **28** (0.282 g, 1 mmol) with dibutyltin oxide (0.249 g, 1 mmol) as in the general method gave a solution of **74** which was cooled to room temperature. A solution of *p*-toluenesulfonyl chloride (0.191 g, 1 mmol) in toluene (2 mL) was added dropwise to the stirred reaction mixture. The reaction was continued until TLC showed all of the starting material had been consumed. The reaction was stopped by adding water (10 mL) and worked up as the general method. The residue was

chromatographed using ethyl acetate and hexane as an elution gradient starting from pure hexane. The first fraction was solid methyl 4,6-*O*-benzylidene-2-*O*-p-toluenesulfonyl-α-D-mannopyranoside (**83**), that was recrystallized from ether, yield 0.095 g (22%); mp 80-81 °C; lit.[86] mp 82-84 °C; R_f= 0.19 (ethyl acetate/hexane 1:3); $[\alpha]_D^{29}$ - 23.8 ° (*c* 2.23, chloroform) lit.[87] $[\alpha]_D^{25}$-25 °.

The second fraction was methyl 4,6-*O*-benzylidene-3-*O*-*p*-toluenesulfonyl-α-D-mannopyranoside (**84**), a solid, yield 0.20 g (46%); mp 149-151 °C; $[\alpha]_D^{26}$ 21.8 ° (*c* 1.18, chloroform); lit.[86] mp 151-154 °C; R_f= 0.15 (ethyl acetate/hexane, 1:3); ^{1}H NMR ($CDCl_3$), δ : 2.25 (s, 3H, tosyl Me), 2.88 (br, 1H, OH), 3.31 (s, 3H, OMe), 3.75-3.84 (m, 1H, H-5), 4.03-4.16 (m, 3H, H-5,H-4 and H-6_{ax}), 4.21 (dd, 1H, $J_{6ax,6eq}$ = 8.7 Hz, $J_{5,6eq}$ = 3.3 Hz, H-6_{eq}), 4.32 (dd, 1H, $J_{1,2}$ = 1.7 Hz, $J_{2,3}$ = 3.4 Hz, H-2), 4.77 (dd, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 4.77 (d, 1H, H-1), 7.09-7.74 (m, 9H, Arom. H's); ^{13}C NMR ($CDCl_3$), δ : 21.7 (tosyl Me), 55.1 (OMe), 63.7 (C-5), 68.7 (C-6), 70.6 (C-2), 75.5 (C-4), 78.7 (C-3), 101.4 (C-1), 101.8 (C-7), 126.2, 128.0, 128.1, 129.0, 129.5, 132.9, 136.9, 144.7 (Arom. C's).

1.4.3.4 Benzoylation of dibutylstannylene acetal 74 in chloroform.

Compound **74** (0.249 g, 1 mmol) was prepared in toluene as in Method B. The solvent was removed on the vacuum line, and a solution of freshly distilled benzoyl chloride (1 mmol) in dry chloroform (20 mL) was added to the residue. The reaction mixture was stirred at room temperature until TLC (ethyl acetate/hexane 1:3) showed that all of the starting material had been consumed (3 h). Standard workup followed by dry column flash chromatography of the residue resulted in methyl 2,3-di-*O*-benzoyl-4,6-*O*-

benzylidene-α-D-mannopyranoside (**80**), yield 0.013 g (2.6%), methyl 2-*O*-benzoyl-4,6-*O*-α-D-mannopyranoside (**81**), yield 0.24 g (62%), and methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-mannopyranoside (**82**), yield 0.080 g (21%).

1.4.3.5 Benzoylation of dibutylstannylene acetal 74 in benzene

Compound **74** (1 mmol) was prepared as in Method A. To the above solution residue, a solution of benzoyl chloride (1.16 mL, 10 mmol) was added slowly with stirring at room temperature. After 15 min, TLC showed that all starting compound had been consumed. The reaction was stopped by adding water and the reaction mixture was worked up as in the general method. The residue was separated by column chromatography to give compound **81**, yield 0.274 g (71%), and compound **82**, yield 0.70 g (18%).

This reaction was repeated with one equivalent of benzoyl bromide. The reaction was finished in 15 min and gave the same regioselectivity as before.

1.4.3.6 Benzoylation using hexamethylenestannylene acetal 79 in toluene

Methyl 4,6-*O*-benzylidene-2,3-O-hexamethylenestannylene-α-D-mannopyranoside (**79**) (1 mmol) was prepared by the general method. Then a solution of benzoyl chloride (1 mmol) in toluene (2 mL) was added with stirring at ambient temperature and the reaction was continued until TLC showed all of the starting material had been consumed. The reaction was complete in 48 h and column chromatography of the reaction mixture gave the 2-benzoate **81**, yield 0.13 g (33.7%) and the 3-benzoate **82**, yield 0.24 g (61.6%).

1.4.3.7 Benzoylation using hexamethylenestannylene acetal 79 in chloroform

A solution of hexamethylenestannylene acetal **79** (1 mmol) was prepared as in Method A. Benzoylation was carried out by adding benzoyl chloride (1 mmol) at room temperature. After 24 h, when TLC showed that all of the starting material had been consumed, the reaction was stopped by adding water. Workup as in the general procedure followed by column separation gave the 2,3-di-benzoate **80**, yield 0.022 g (4.4%), the 2-benzoate **81**, yield 0.140 g (36%), and the 3-benzoate **82**, yield 0.198 g (51.3%).

1.4.3.8 Benzoylation using hexamethylenestannylene acetal 79 in dichloromethane

After preparation of the hexamethylenestannylene acetal **79** in toluene using Method B, the substitution reaction was accomplished in dried dichloromethane (20 ml). After workup, column chromatography gave the previous products: 2,3-di-benzoate **80**, yield 0.139 g (28.3%); 2-benzoate 81, yield 0.092 g (29%); and 3-benzoate **82**, yield 0.152 g (39.3%).

1.4.3.9 Benzoylation using diisopropylstannylene acetal 75 in chloroform

Methyl 4,6-*O*-benzylidene-2,3-*O*-diisopropylstannylene-α-D-mannopyranoside (**75**) (1 mmol) was prepared using Method A. A solution of benzoyl chloride (1 mmol) in chloroform (15 mL) was added to the above residue and the reaction mixture was stirred for 40 h at room temperature when TLC showed that all of the starting material had been consumed. Workup and separation by dry column flash chromatography gave the 2-

benzoate **81** and the 3-benzoate **82**, in yields of 0.184g (47.6%) and 0.195g (50.6%), respectively.

1.4.3.10 Benzoylation using diisobutylstannylene acetal 76 in chloroform

A solution of diisobutylstannylene acetal **76** was prepared using Method B. Benzoylation was accomplished as above. When TLC showed all of the starting material was consumed (40 h), the reaction was stopped by adding water. Workup and column chromatography gave the 2-benzoate **81**, yield 0.175 g (45%), the 3-benzoate **82**, yield 0.207 g (53.6%), and the 2,3-di-benzoate **80**, yield 0.005 g (1% yield).

1.4.3.11 Benzoylation using dineopentylstannylene acetal 77 in chloroform

Methyl 4,6-*O*-benzylidene-2,3-O-dineopentylstannylene-α-D-mannopyranoside (**77**) (1 mmol) was prepared using Method B. Benzoyl chloride (1 mmol) in chloroform (20 mL) was added to the dineopentylstannylene acetal residue. The reaction mixture was stirred for 22 h. Resolution of the product mixture by column chromatography gave the 2-benzoate **81**, yield 0.272 g (70.6%) and the 3-benzoate **82**, yield 0.098 g (25.6%).

1.4.3.12 Benzoylation using dineohexylstannylene acetal 78 in chloroform

Methyl 4,6-*O*-benzylidene-2,3-*O*-dineohexylstannylene-α-D-mannopyranoside (**78**) (1 mmol) was prepared using Method B. Benzoylation was carried out in chloroform (20 mL) and was complete in 20 h. Column separation gave the 2,3-di-benzoate **80**, yield 0.185 g (37%), the 2-benzoate **81**, yield 0.183 g (47%) and the 3-benzoate **82**, yield

0.058g, (15%).

1.4.3.13 *p*-Toluenesulfonylation using dibutylstannylene acetal 74 in dichloromethane

The dibutylstannylene acetal **74** (1 mmol) was prepared using Method B. Then *p*-toluenesulfonyl chloride (1 mmol) in dried dichloromethane (20 ml) was added to the dibutylstannylene acetal residue. The reaction mixture was stirred at room temperature for 20 h. After workup, the products were fractionated by dry column flash chromatography to give methyl 4,6-*O*-benzylidene-2-*O*-*p*-toluenesulfonyl α-D-mannopyranoside (**83**) and methyl 4,6-O-benzylidene-3-*O*-*p*-toluenesulfonyl-α-D-mannopyranoside (**84**) in yields of 0.104 g (24%) and 0.302 g (69%), respectively.

1.4.3.14 *p*-Toluenesulfonylation using dibutylstannylene acetal 74 in 1,1,2,2-tetrachloroethane.

A solution of dibutylstannylene acetal **74** (1 mmol) was prepared using Method B. To the residue, *p*-toluenesulfonyl chloride (1 mmol) in 1,1,2,2-tetrachloroethane (20 mL) was added and reaction was allowed to continue for 10 d when it was complete. Fractionation of the product mixture by column chromatography gave compound **83**, yield 0.112 g (26%) and compound **84**, yield 0.281g, (64.4%).

1.4.3.15 *p*-Toluenesulfonylation using dibutylstannylene acetal 74 in 1,2-dichloroethane

Dibutylstannylene acetal **74** (1 mmol) was prepared as in the general method. *p*-Toluenesulfonylation was carried out as previously except in 1,2-dichloroethane (20 mL). The reaction was completed in 6 d and column separation gave **83**, yield 0.084 g (19%) and **84**, yield 0.319 g (73%).

1.4.3.16 *p*-Toluenesulfonylation using hexamethylenestannylene acetal 79 in 1,1-dichloroethane

The hexamethylenestannylene acetal **79** (1 mmol) was prepared in toluene as in the general method. To the residue of the activated sugar, a solution of *p*-toluenesulfonyl chloride (0.191 g, 1 mmol) in 1,1-dichloroethane (20 mL) was added at ambient temperature and the reaction mixture was kept for 4 d until completion. After workup, the compounds separated by column chromatography to give 2,3-di-*O*-*p*-toluenesulfonylate **85** in yield 0.072 g (12%), compound **83**, in yield 0.096 g (22%), and compound **84**, in yield 0.211 g, (48%).

1.4.3.17 p-Toluenesulfonylation using hexamethylenestannylene acetal in 1,2-dichloroethane

A solution of hexamethylenestannylene acetal **79** (1 mmol) was prepared as in the standard method. A solution of *p*-toluenesulfonyl chloride (1 mmol) in 1,2-dichloroethane (20 mL) was added to the residue and the resulting solution was stirred at

room temperature for 3 d. Standard workup and column separation gave **83** and **84**, in yields of 0.089 g (20.5%) and 0.251 g (57.6%), respectively.

1.4.3.18 Methyl 4,6-*O*-benzylidene-α-D-mannopyranoside-2,3-carbonate (86)

Methyl 4,6-*O*-benzylidene-2,3-*O*-isopropylstannylene-α-D-mannopyranoside (**75**) (1 mmol) was prepared as in the general method. *p*-Toluenesulfonyl chloride (1 mmol) in chloroform (20 mL) was added to the above residue. The reaction mixture was stirred at room temperature for 3 d. Workup and column chromatography gave the title compound **86** as a solid; recrystallized from ether and chloroform; yield 0.181 g, (58.7%); mp 124-126 °C; R_f= 0.52 (ethyl acetate / hexane, 1:2); ^{1}H NMR ($CDCl_3$), 3.79-3.85 (m, H-4, H-6 and H-6'), 4.34-4.40 (m, H-5), 4.68 (d, J = 4.3, H-2), 4.20-4.87 (m, H-3) 5.04 (s, H-1); ^{13} C NMR ($CDCl_3$), 55.3 (OMe), 59.3 (C-6), 68.6 (C-5), 75.2 (C-2), 76.4 (C-3), 78.6 (C-4), 96.8 (C-7), 102.0 (C-1), 126.1, 128.3, 129.3 (Ar-C), 136.5 (Ar-C_{ipso}), 153.2 (C=O); EI MS for $C_{15}H_{16}O_7$ (308.0896) M^+ (62%), 265 (20%), 192 (5.3%), 159 (100%), 105 (57%).

Chapter 2

Regioselective synthesis of non-glycosidically linked carbohydrate clusters

2.1 Introduction

Carbohydrate chains on cell surfaces play important roles in biological processes including cellular recognition, adhesion, etc. Recognition of species like bacteria, antibodies and viruses occurs through interaction of the carbohydrate chains with the carbohydrate recognition domains (CRDs) of proteins on the surfaces of the binding species.[88,89] Despite the importance of protein-carbohydrate interactions, the binding of one carbohydrate molecule to a protein is weak. To enhance binding affinity, nature has found it necessary to cluster both the carbohydrates on the cell surfaces and the CRDs in the proteins.

The increasing interest in the application of carbohydrate-protein recognition for medical purposes, provides motivation for trying to develop further understanding of the nature of ligand recognition. Several synthetic methods have been developed for the preparation of clustered carbohydrates including synthesis of complex sialylated oligosaccharides. One recent study describes the synthesis of bivalent Sialyl Lewis x (SLe^x) analogs (see Figure 2.1) using a combination of chemical and enzymatic methodology.[90] In the synthesis of dimeric SLe^x derivatives, the primary acceptor molecules have been attached to each other chemically through different types of spacers. Peripheral sugar residues were anchored enzymatically to the chemically synthesized core molecule. The inhibitory properties of the synthetic bivalent molecules were examined against E-selectin. It was shown that some of them have five-fold increased inhibitory

properties in comparison with univalent SLe^x.[88] The synthesis of dendritic glycosides (glycodentrimers)[91,92] and clustered glycopolymers containing triantennary glycosides of *N*-acetyllactosamine[93] and carbohydrate mimics[94] for the same purposes have been

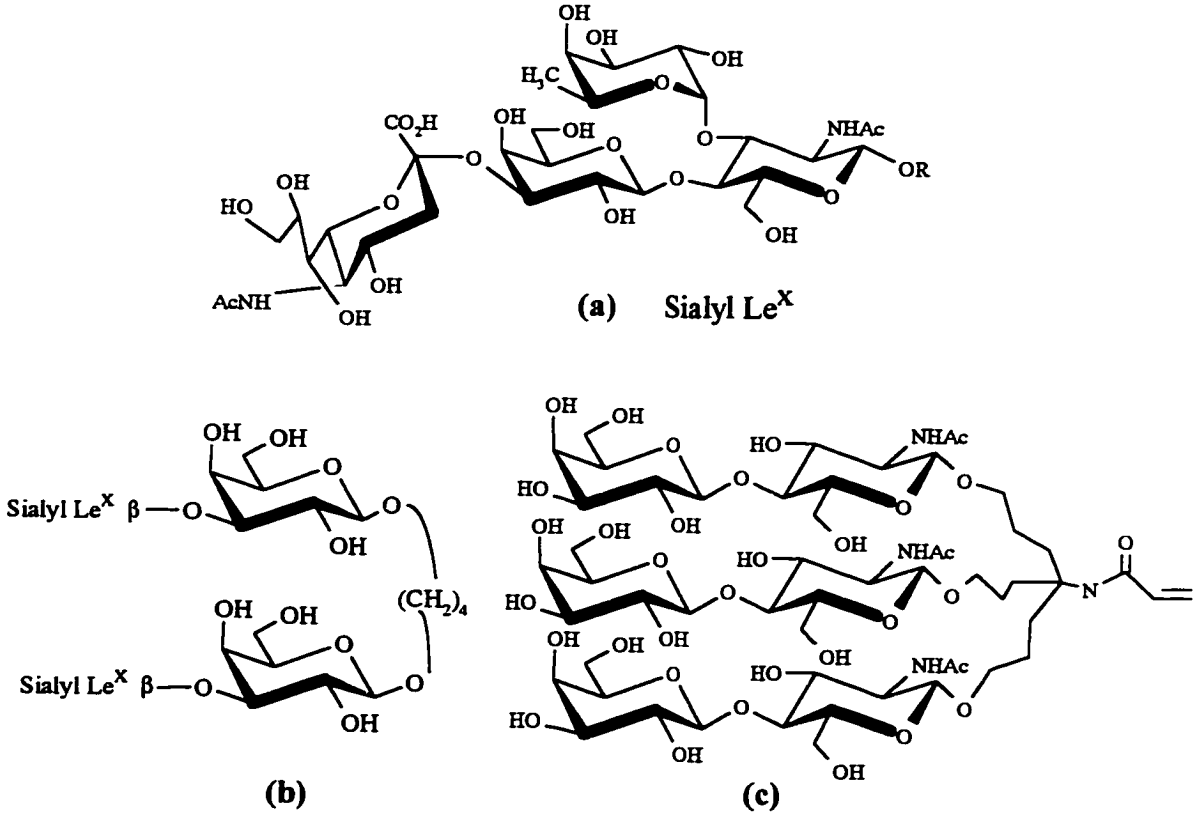


Figure 2.1 The structures of univalent SLe^x (a), bivalent SLe^x (b) and triantennary glycoside (c)

outlined. All of above mentioned methods require the formation of glycosidic bonds during cluster preparation. Syntheses of glycosidically-linked oligosaccharides can be difficult, particularly when more than one hydroxyl group is involved. Here, it will be shown that a new class of carbohydrate clusters, non-glycosidically linked carbohydrates,

can be prepared efficiently. This method avoids the problems associated with glycoside formation. Spacer groups can be chosen so as to allow one to control the distances between the biologically active units to match that required for efficient binding with certain proteins. It will be demonstrated that disaccharides and oligosaccharides can be prepared easily in a highly regioselective fashion in high yields by reaction of dibutylstannylene acetal intermediates with di- or tri- functional electrophiles.

2.2 Results and discussion

2.2.1 Synthesis of non-glycosidically linked disaccharides and oligosaccharides with *trans*-1,2-diols

As outlined in Chapter 1, dialkylstannylene acetals can serve as useful intermediates on the way to obtaining highly regioselective mono-substitution of diols and polyols.[2,3,6] This convenient methodology is now applied to synthesize non-glycosidically linked disaccharides and trisaccharides for the first time using difunctional and trifunctional electrophiles as linker reagents. A variety of diacyl linkers, and different monosaccharides containing *cis*- and *trans*-1,2-diols, and in one case, a polyol were examined. In most of the reactions, one major symmetric disaccharide was isolated in high yield and in a highly regioselective manner. For instance, reaction of methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-glucopyranoside (**11a**) with aliphatic diacyl chlorides such as succinyl chloride at 20 °C in toluene resulted in a non-glycosidically linked disaccharide regioselectively at C-2 in 91% yield as shown in Figure 2.2.

Performing similar reactions diacyl chlorides having different sized alkyl connectors led to the formation of symmetric non-glycosidically linked disaccharides as the major products from compound **32**. The length of the chain in the linkage group affects the yields of the symmetric products; increasing the size of the alkyl chain causes the yield of the symmetric disaccharide to be slightly decreased

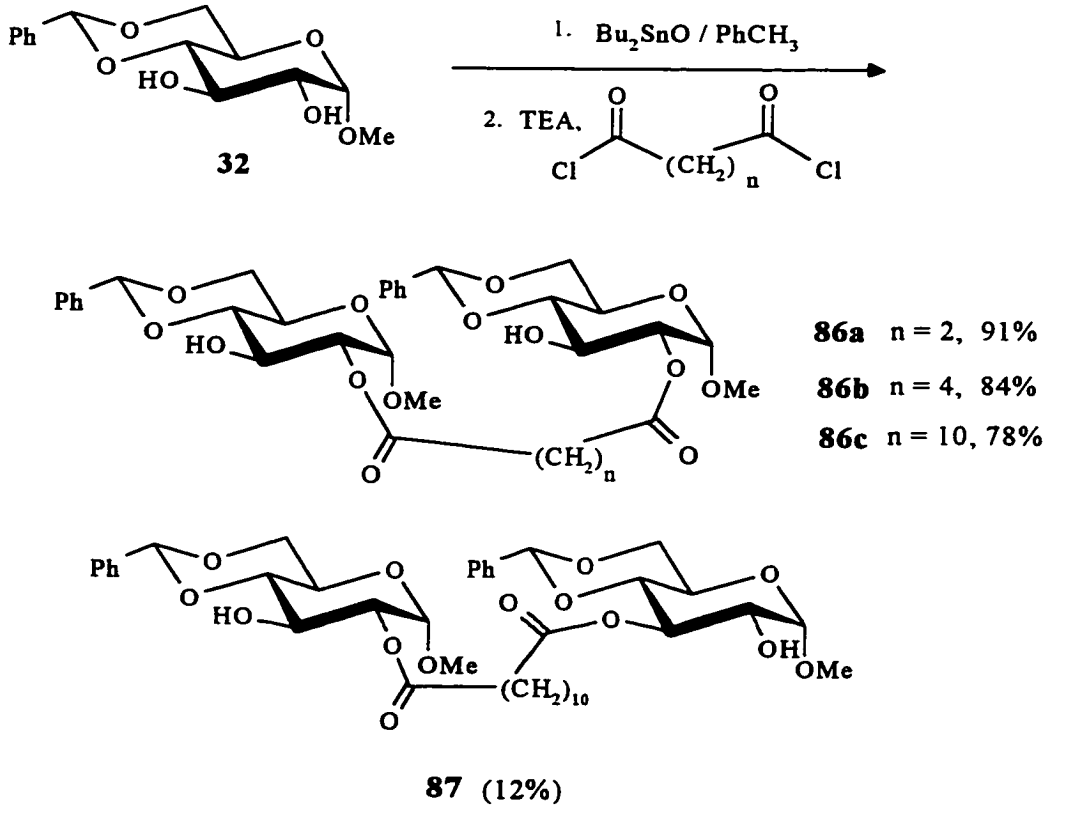


Figure 2.2 The reactions of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**32**) with diacyl chlorides

With the largest diacyl chloride, dodecanedioyl chloride, a second product, the non-symmetric disaccharide **87**, was also obtained in 12% yield. In theory, three types of

disaccharide products containing two monosaccharides with one linker unit can be formed in the reaction. These possible products are the 2,2'-, 2,3'- and 3,3'- diesters. Symmetric products can be readily distinguished from their non-symmetric isomers from their NMR spectra as shown in Figures 2.3 and 2.4. One set of signals is observed for the carbohydrate nuclei in the ^{1}H and ^{13}C NMR spectra of symmetric products, but in non-symmetric products, two sets of signals appear in the spectra. Monocyclic and cyclic oligomer compounds have also been isolated from some of the reactions, depending on the nature of carbohydrate and the type of linker. The details of these reactions will be discussed later.

The nomenclature used for these compounds in this thesis is based on rule 10 of the IUPAC nomenclature rules for carbohydrates.[95] Using this rule, the name of compound **86a** is bis-(methyl 4,6-*O*-benzylidene-α-D-glucopyranoside) 2,2'-butandioate.

Addition of nucleophiles to the reaction mixtures of dibutylstannylene acetals with electrophiles remarkably increases the rate of reaction.[96] The dibutylstannylene acetal of **32** has reacted with one equivalent of various acyl chlorides under similar reactions to produce 2-*O*-acylated products with very good regiochemistry.[2,3,6] Therefore, high yield and high regioselectivity are expected for the reaction of the dibutylstannylene acetal of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside with diacyl chlorides. This expectation was confirmed in reactions with a variety of diacyl chlorides in the presence of triethylamine. Reactions in the presence of triethylamine are fast and are complete in 5-30 min at 20 °C. In these reactions, the symmetric 2,2'-disaccharide was isolated as single product or, in some of the reactions, as the major product.

In each reaction, the structures of the isolated products were assigned by ^{1}H and ^{13}C NMR, COSY and HETCOR experiments. The structures of symmetric disaccharides can be easily established from the ^{1}H and ^{13}C NMR spectra. However, the non-symmetric disaccharides give somewhat complex spectra and their structures were assigned by using 2D NMR experiments. Integration of the ^{1}H NMR spectra of symmetric disaccharides indicated that the signals of carbohydrates and linkage group were in the ratio of two to one. The position of the acyl linker in the monosaccharides was determined unambiguously from the identity of the most deshielded secondary proton (s) in the ^{1}H NMR spectra. These assignments were supported by assigning the signals of the free hydroxyl group (s) in the disaccharides. In the ^{1}H NMR spectra of very carefully dried samples of disaccharides in dry chloroform-*d*, sharp doublet signal (s) are usually observed for free hydroxyls at more shielded chemical shifts than most carbohydrate protons. From the size of coupling constants and by correlation of the hydroxyl signal to the proton on the attached carbon in COSY experiments, it was possible to assign the positions of free hydroxyls in the molecules. Assigning the location of the hydroxyl groups in the monosaccharide units confirms the assignments of the acylation positions in the structures of the non-glycosidically linked dimers.

Reactions of dialkylstannylene acetals with electrophiles in the absence of added nucleophiles sometimes occur with different regioselectivity than in the presence of added nucleophiles.[27,35] Good regioselectivity and high yields of monosubstituted products have been obtained with dibutylstannylene acetals derived from *trans*-1,2-diols when base was

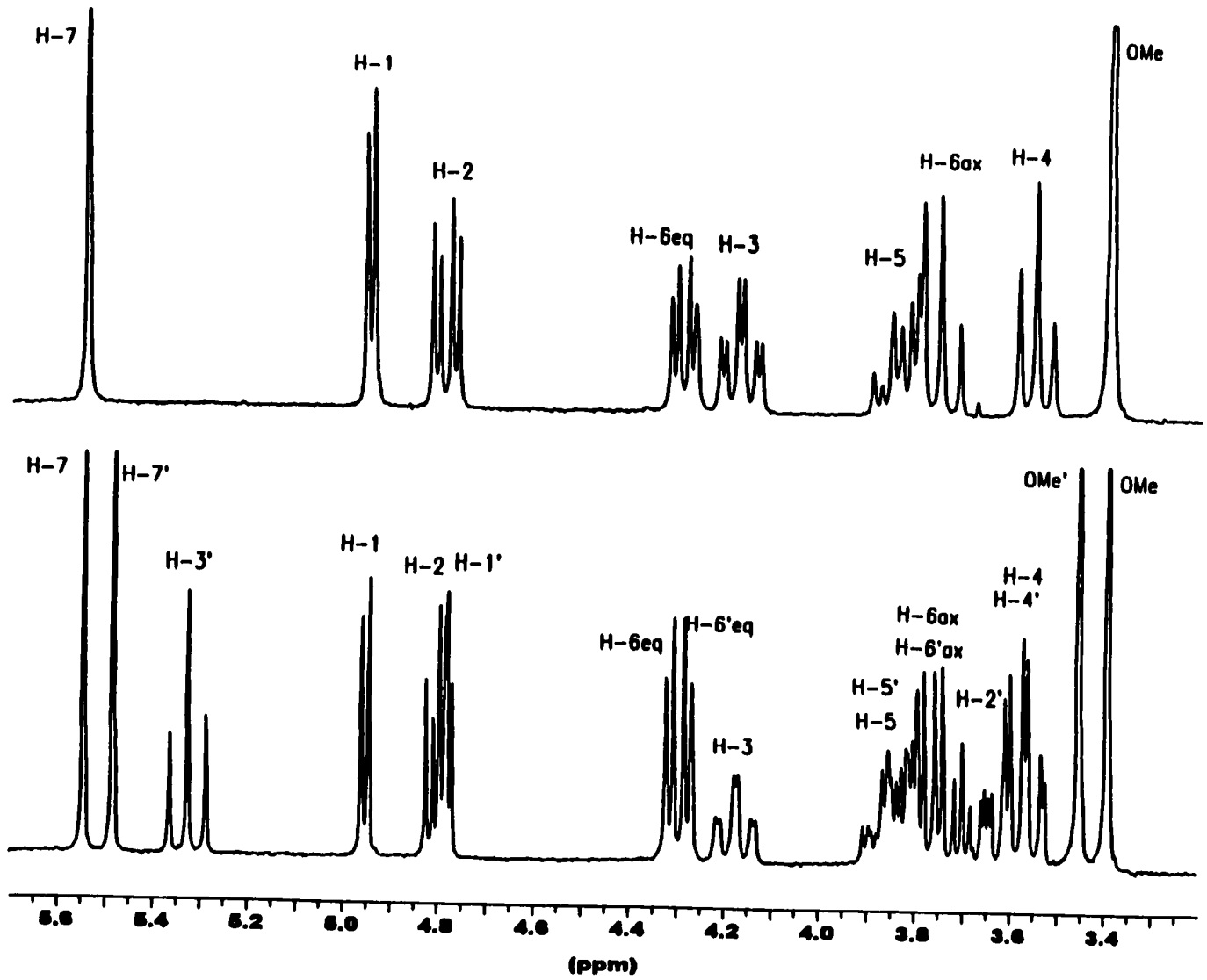


Figure 2.3 Expansion of parts of the ^{1}H NMR spectra at 250.13 MHz of the symmetric 2,2'-disaccharide **86c** (top) and non-symmetric 2,3'-disaccharide **87** (bottom) in chloroform-*d*

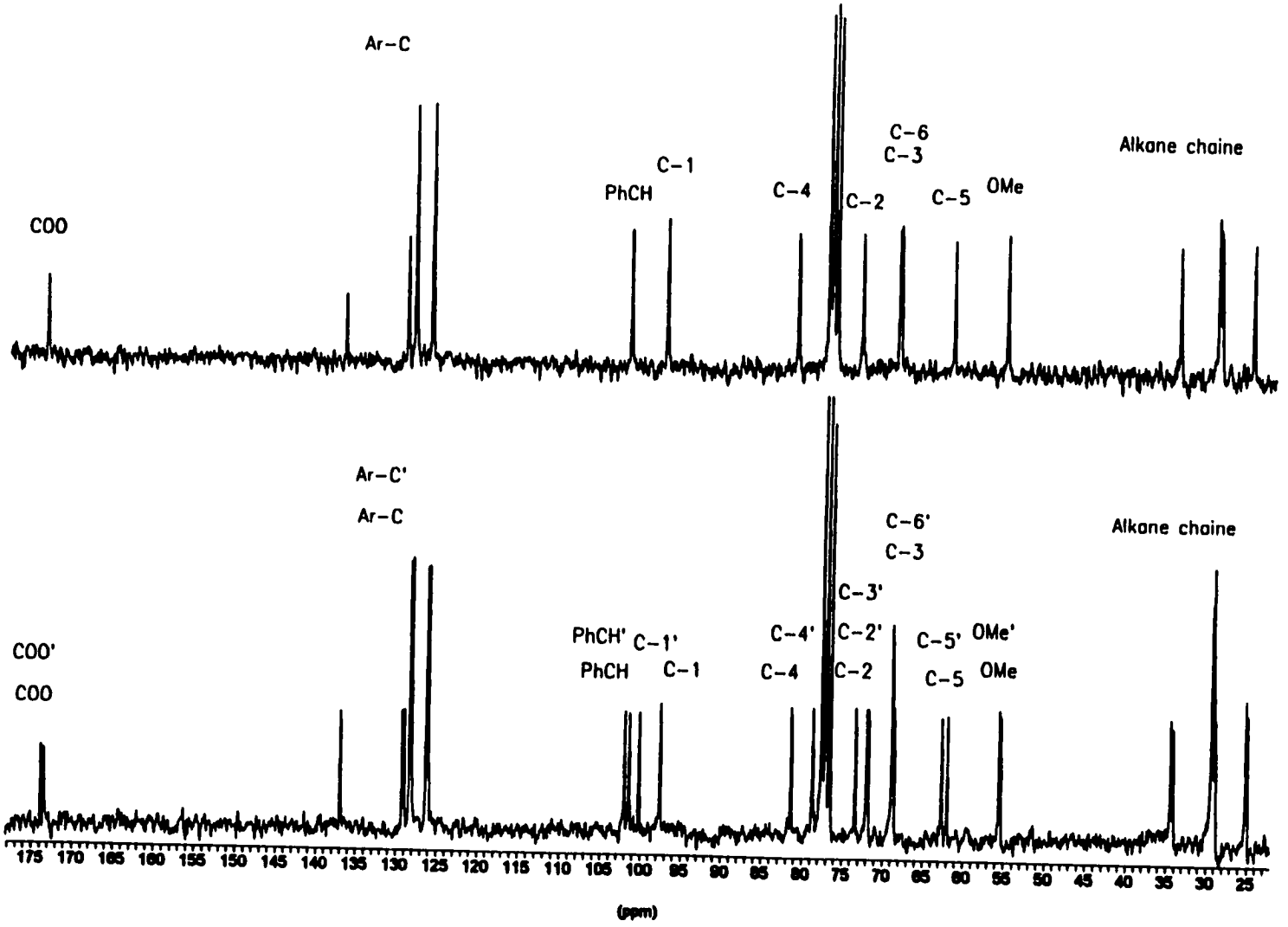


Figure 2.4 62.9 MHz ^{13}C NMR spectra of the symmetric 2,2'-disaccharide **86c** (top) and non-symmetric 2,3'-disaccharide **87** (bottom) in chloroform-*d*.

added to the reaction.[97] Reaction of compound **32** with succinyl chloride in the absence of base took longer to be complete (2 h) than the same reaction conducted in the presence of triethylamine. Also a cyclic oligomer **88** was obtained as a second product in the absence of base in yields between 5-20%.

The reaction conditions were altered to increase the yield of compound **88** by changing the stoichiometry to 1:1 and conducting the reaction at a higher temperature under more dilute conditions in toluene. These changes increased the yield of **88** to 50%. The structure of **88** was established from its NMR spectra and its molecular weight. In

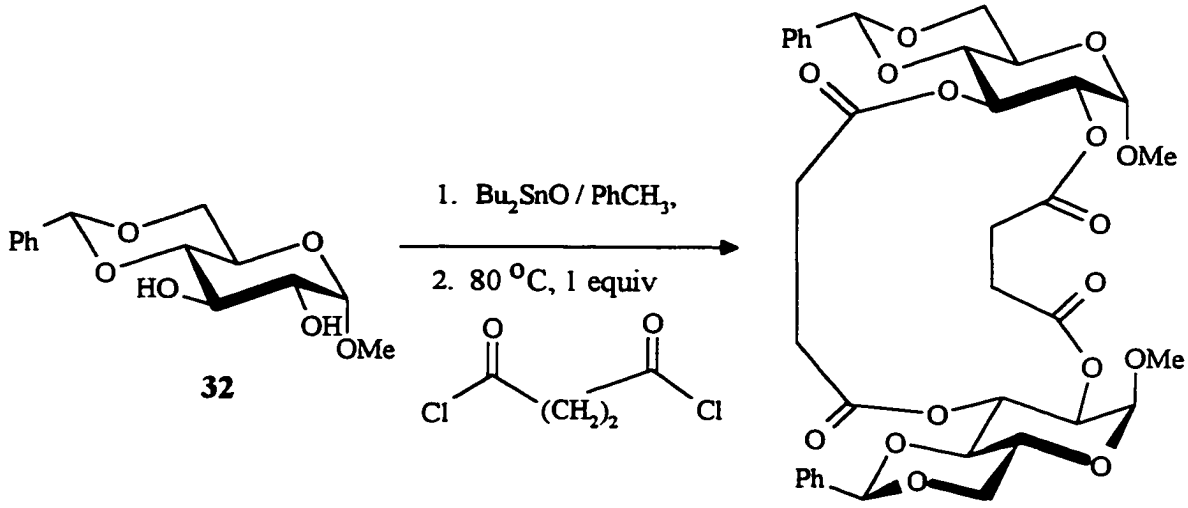
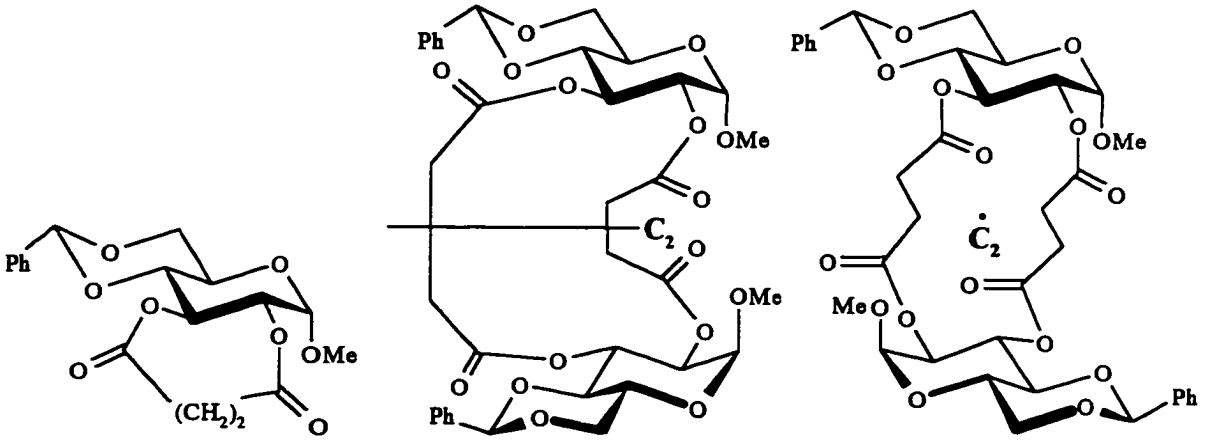


Figure 2.5 The reaction of **32** with one equivalent of succinyl chloride

the ^{1}H NMR spectrum of **88**, two signals appear for H-2 and H-3 at 4.80 and 5.50 ppm, respectively. These signals are deshielded by about 1 ppm from their position in the starting material **32**, indicating that both O-2 and O-3 have been esterified. Integration of

the ^{1}H NMR signals indicated the ratio of carbohydrate and linker was one to one. Monomeric, dimeric or higher oligomeric structures were possible for this cyclic compound. The mass spectrum of **88** measured under a variety of ionization conditions (EI, electrospray, APCI) did not contain any peak at M^+ of m/z = 364, indicating that the product was not monomeric. However, a peak appeared for M^+ for a dimer at m/z = 728, that had the correct exact mass. Because no peak was observed at m/z values greater than 730 daltons, it was concluded that the compound was not a higher oligomer than a dimer. Two structures, **88b** and **88c**, are possible for a dimeric compound (see Figure 2.6). In one structure (**88b**), the two monosaccharides are linked through the same oxygen atoms (O-2 to O-2' and O-3 to O-3') and in other structure (**88c**) through two different oxygen atoms (O-2 to O-3' and O-3 to O-2'). The two potential dimeric compounds both have



88a 2,3-Cyclic monomer **88b** 2,2':3,3'-Cyclic dimer **88c** 2,3':3,2'-Cyclic dimer

Figure 2.6 The structures of possible monomeric and dimeric products containing **38** and succinate in 1:1 stoichiometry

C_2 symmetry as shown in Figure 2.6. To determine which structure corresponds to the isolated product, the possible CH_2 patterns in the ^1H NMR spectra of these two structures had to be analysed. In dimeric structure **88c**, the CH_2 units in each succinyl chain are not equivalent. The two succinyl chains are related to each other by a C_2 symmetry axis and therefore, the CH_2 units in the each succinyl unit are chemically and magnetically equivalent to the symmetry axis-related CH_2 unit in the other succinyl chain. None of the protons in each chain are related by symmetry to any other in that chain; as a result, one ABCD pattern is expected to appear in the ^1H NMR spectrum for **88c**. However, in structure **88b**, the two CH_2's in each succinyl chain are related to each other by a C_2 axis but are not related to the CH_2's in the second succinyl chain. Consequently, two AA'BB' patterns must appear in its ^1H NMR spectrum. The complex region of the 400.14 ^1H NMR spectrum of oligomeric **88** showed two overlapping AA'BB' patterns. NMR simulation using the program LAME8[98] showed that these patterns corresponded to the CH_2 signals of structure **88b** (see Figure 2.7).

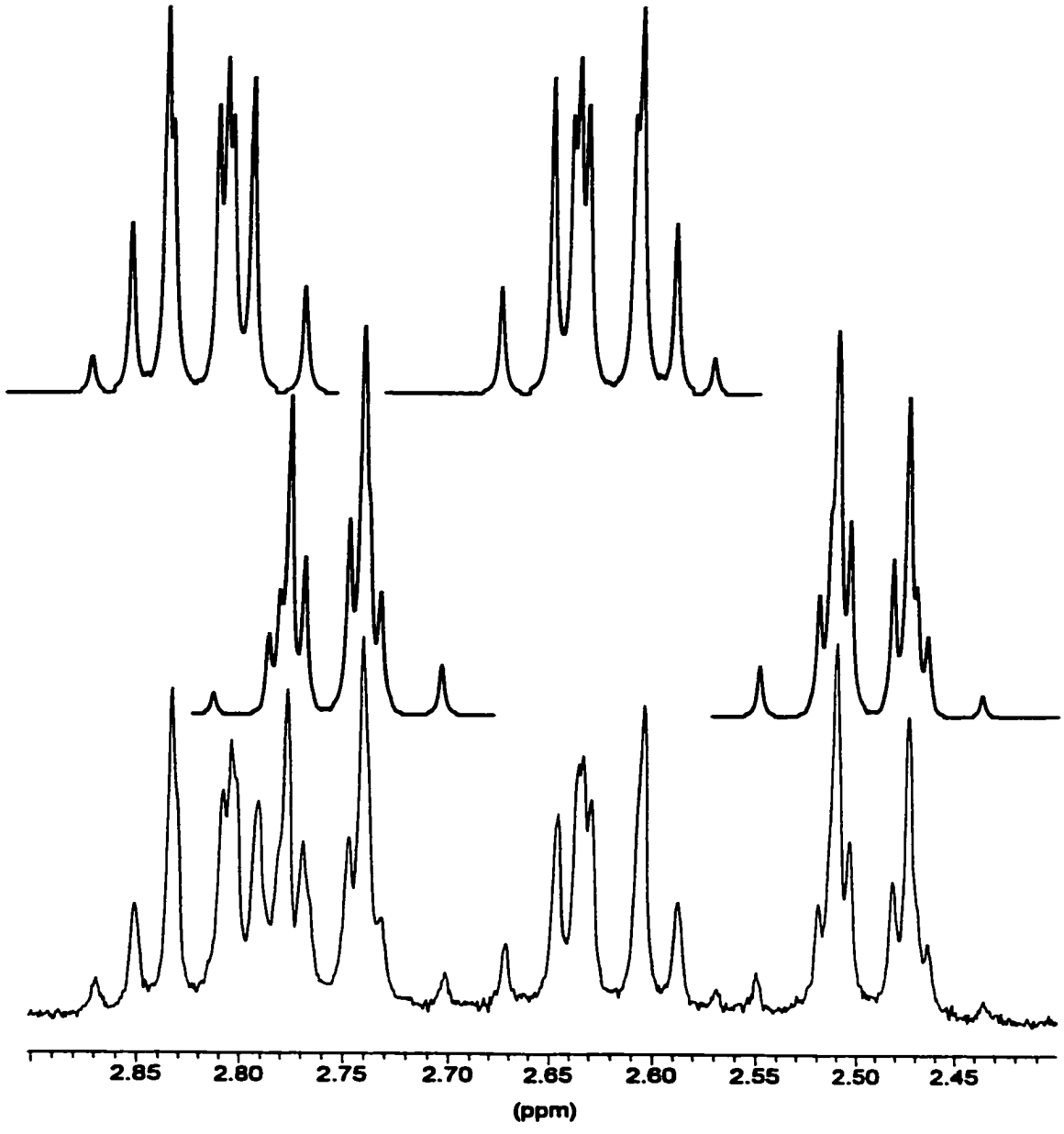
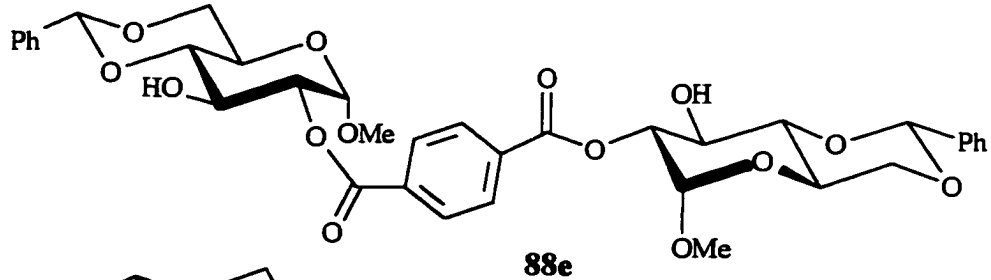
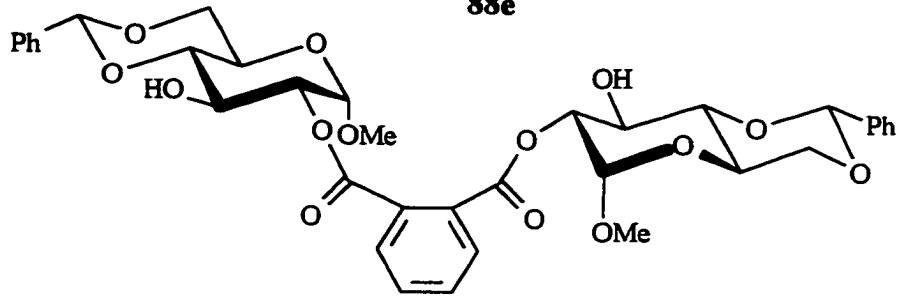


Figure 2.7 The region of the 400.14 MHz NMR spectrum of **88** containing the signals of the two CH_2CH_2 groups: bottom, experimental spectrum; middle, LAME8 simulation of one AA'BB' pattern, top, LAME8 simulation of the other AA'BB' pattern. The iterative simulation were performed using the transitions from resolution-enhanced spectra.

The reaction of the dibutylstannylene acetal derived from **32** with aromatic dicarbonyl dichlorides linkers also resulted in the formation of single non-glycosidically linked disaccharides. For instance, in the reaction of **32** with terephthaloyl chloride at 20 °C, the 2,2'-diester linked disaccharide **88e** was obtained in excellent yield (95%). The



88e



88f

reaction with orthophthaloyl chloride under the same reaction conditions again led to the formation of a symmetric 2,2'-linked disaccharide (**88f**), isolated in 85% yield after chromatography.

The ^{1}H NMR spectrum of **88e** showed unusual concentration and temperature dependent features in chloroform-*d* (see Figure 2.8). All carbohydrate signals in the 400.14 MHz ^{1}H NMR spectrum of a 0.016 M solution at 20 °C were broadened. When the concentration of the sample was lowered to 0.008 M, all of the broad signals turned into sharp signals.

This unusual phenomenon, which was not observed for analogous compounds, is

probably caused by self association of two or more disaccharides units. Association of two symmetric disaccharides through hydrogen bonding presumably forms a symmetric cyclic macromolecule containing four monosaccharides (see Figure 2.9). The ^{1}H NMR spectrum of **88e** showed that the chemical shift of the hydroxyl signal is changed on altering the concentrations of the samples. X-ray crystallography could provide useful information by determining the structure of the possible macrocyclic compound. So far, attempts to crystallize compound **88e** from different solvent systems failed to give suitable sized crystals. The nature of the association and the structure of possible compounds are a topic for future investigation.

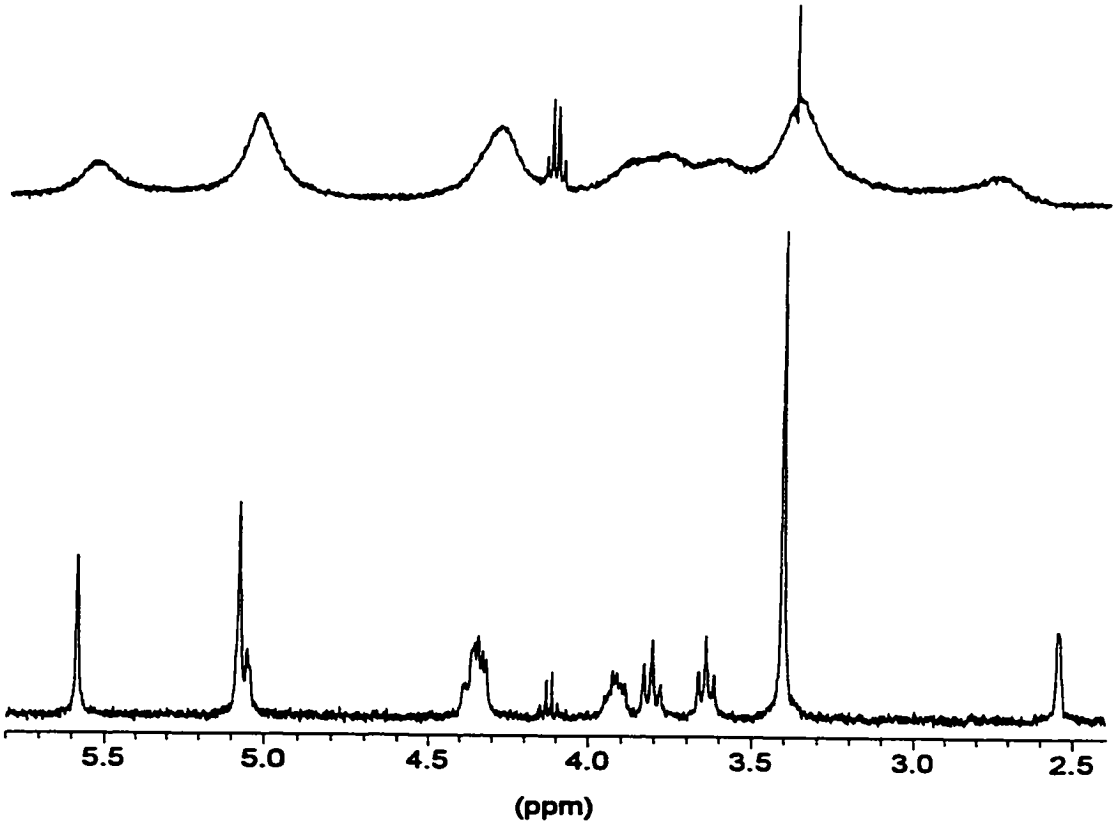


Figure 2.8 The 400.14 MHz ^{1}H NMR spectra of compound **88e** in chloroform-*d* at two concentrations: top, 0.016 M, bottom, 0.008 M. For assignments, see the experimental section.

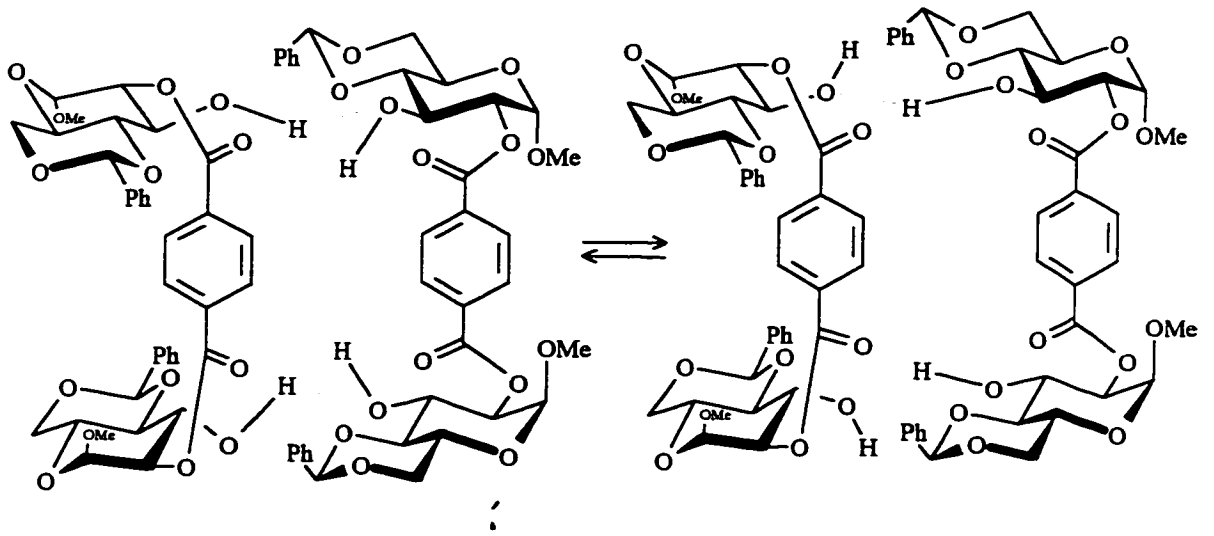


Figure 2.9 A possible structure of the product of self association of **88e** in concentrated solution in chloroform-*d*

When the reaction of the dibutylstannylene acetal of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**32**) was conducted with polyfunctional electrophiles, the formation of regioselective non-glycosidically linked oligosaccharides resulted. The reaction with 1,3,5-benzenetricarbonyl trichloride in toluene at 20 °C gave the corresponding symmetric non-glycosidically linked trisaccharide **88g** in excellent yield as shown in Figure 2.10. Structure assignment of the symmetric trisaccharide was made from its ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR signals assigned to the carbohydrate and spacer integrated in a ratio of three to one.

The synthesis of non-glycosidically linked disaccharides was successfully carried out with an unprotected sugar. Reaction conditions for this unprotected sugar had to be different than those for the protected sugars because of the lower solubility of the former in organic solvents. The dibutylstannylene acetal of methyl α-D-glucopyranoside (**89**) was

prepared in methanol. The very carefully dried residue of the activated sugar was treated with succinyl chloride in dioxane to give the symmetric 2,2'-diester linked disaccharide **90a** in 72% yield plus a small amount (5%) of a syrupy product that was tentatively identified as a methyl (methyl α-D-glucopyranoside) 2-butanedioate (**90b**), presumably arising from residual methanol from the previous step. Regioselective reaction at the secondary hydroxyls (O-2) in the presence of more reactive primary hydroxyls have been previously observed with dibutylstannylene acetals.[99,100] The secondary oxygen atom reacts in preference to the normally more reactive primary oxygen atom because the five-membered ring dibutylstannylene acetal formed from O-2 and O-3 is more favored than the six-membered ring that contains the primary oxygen atom.[39, 40] This regioselectivity is well established by isolation of mono-2-*O*-substitution products in good yields from the reactions of the dibutylstannylene acetal of **89** with electrophiles such as benzoyl chloride and *p*-toluenesulfonyl chloride in polar solvents.[52]

The reaction of other *trans*-diols, such as benzyl 4,6-*O*-benzylidene-α-D-galactopyranoside (**38**), were also investigated. The dibutylstannylene acetal of **38** reacted with terephthaloyl chloride to give the symmetric non-glycosidically 3,3'-*O*-linked disaccharide **91** in good yield (78%). The position of the linkage ester in **91** was assigned from its ^{1}H and ^{13}C NMR spectra. In the ^{1}H NMR spectrum, a deshielded doublet of doublets which appeared at 5.13 ppm with coupling constants of 3.7 and 10.4 Hz, was assigned to H-3. This assignment was supported by assigning the sharp doublet signal related to the free hydroxyl group to OH-2. The cause of the different regioselectivity

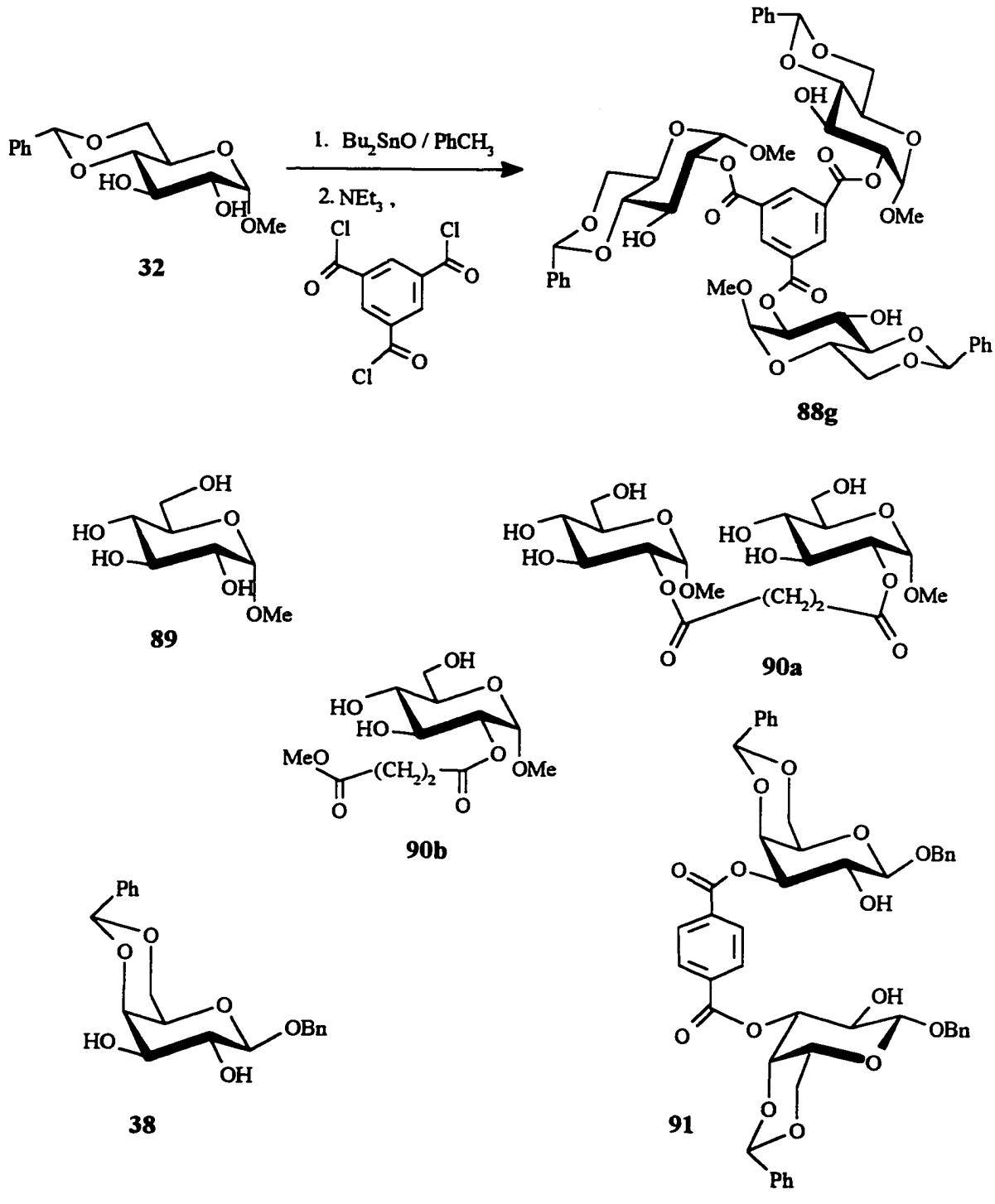
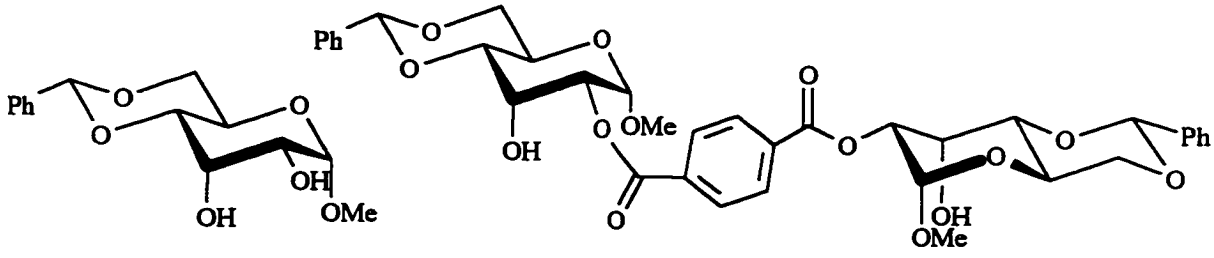


Figure 2.10 The synthesis of trisaccharide (88g) and structures of disaccharides from 38 and 89.

obtained with this molecule than for the stannylene acetal of **32**, specifically for reaction at O-3 rather than O-2 originates from the different structures of their populated symmetric dimers in solution. It was found that each of these molecules is present as a single symmetric dimer in solution as well as in the solid state.[20] The dicoordinate oxygen atoms responsible for the regioselectivity in their symmetric dimers in solution, O-3 for **15** and O-2 for **11a**, were found to be adjacent to the axial oxygen atoms.[17]

2.2.2 Synthesis of non-glycosidically linked disaccharides from *cis*-1,2-diols

Similar reactions were carried out with *cis*-1,2-diols. Regioselectivity with dibutylstannylene acetals derived from *cis*-diols depends on the nature of the carbohydrate and the reaction conditions. As shown in the previous chapter, reaction usually occurs on the equatorial oxygen atoms in preference to the axial oxygen atoms,[3,6,42] although some exceptions have been observed.[27] Reaction of the dibutylstannylene acetal derived from methyl 4,6-*O*-benzylidene-α-D-allopyranoside (**54**) with terephthaloyl chloride at room temperature in the presence of one equivalent of triethylamine gave the symmetric 2,2'-



54 **92**

diester disaccharide **92** as a single product in excellent yield (97%). The structure of the

disaccharide was assigned from its ^{1}H and ^{13}C NMR spectra in comparison with those of the starting compound. The ^{1}H NMR spectrum of this compound did not show any of the concentration and temperature dependence observed in those of disaccharide **88**.

Reactions of the dibutylstannylene acetal derived from methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (**28**) with adipoyl chloride gave different results in the presence and in the absence of added base. Acylation reactions of this *cis*-diol with one equivalent of electrophile also gave different regioselectivity under these varying conditions as outlined in Chapter one. A variety of nucleophiles, such as tetraalkylammonium halides, cesium fluoride, and tertiary amines are known to increase the reaction rate.[101,102] The investigation of the regioselective synthesis of non-glycosidically linked disaccharides through the dibutylstannylene acetal of compound **28** under different conditions is discussed below.

The reaction of the 2,3-*O*-dibutylstannylene acetal of **28** with adipoyl chloride in the absence of any added nucleophile gave a mixture of compounds **93a, 93b** and **93c**, as the 2,2'-, 2,3'- and 3,3'-linked disaccharides (see Figure 2.11). Examination by TLC as the reaction progressed suggested that the spot related to the initially formed symmetric 3,3'-linked disaccharide with the smallest R_f value gradually decreased in intensity and spots related to the nonsymmetric 2,3'- and symmetric 2,2'- disaccharides with larger R_f values became more intense, indicating that the acyl group migrated during the reaction. Similar rearrangements have been observed in the benzoylation reactions of dibutylstannylene acetals derived from primary-secondary 1,2-diols.[58] The substitution reaction in the absence of added base is slow and non-glycosidically linked disaccharides were obtained in

a close to statistical distribution under these conditions. In this reaction, a monocyclic diester product **94** also was isolated in 10% yield. EI mass spectrometry gave a molecular ion peak with an exact mass corresponding to that expected for the monomeric structure **94**. Integration of the carbohydrate and adipoyl signals indicated a ratio of 1:1 in the ^{1}H NMR spectrum. The signals of both H-2 and H-3 were deshielded in comparison to their positions in the spectrum of the starting compound. The reason for formation of the internal cyclic diester with this sugar molecule in contrast to the dimer formed from **32** can be rationalized. Firstly, the succinyl group is too short to allow the formation of an internal cyclic diester with *trans*-diol **32**. In the *cis*-diol, the geometry of the diol is suitable for internal cyclization, and the adipoyl linker is long enough and flexible enough to allow the formation of a cyclic internal derivative.

In order to optimize the reaction conditions for the regioselective synthesis of non-glycosidically linked disaccharides with **74**, several bases were examined as added nucleophiles. Good regioselectivity has been obtained at O-3 when the 2,3-*O*-dibutylstannylene acetal **74** has been reacted with benzoyl chloride in polar solvents or in the presence of added nucleophiles in non-polar solvents.[27] Reaction in the presence of one equivalent of triethylamine gave the best yield of the 2,2'-non-glycosidically linked disaccharide **93a** from mannopyranoside **74** (see Figure 2.11) but conditions were never found that yielded a single product from this starting material, possibly because the initially formed product rearranged during isolation. Reaction in the presence of one equivalent of diisopropylethylamine (DIPEA) gave a mixture of the three possible disaccharides. Integration of the ^{1}H NMR spectrum of the mixture showed the

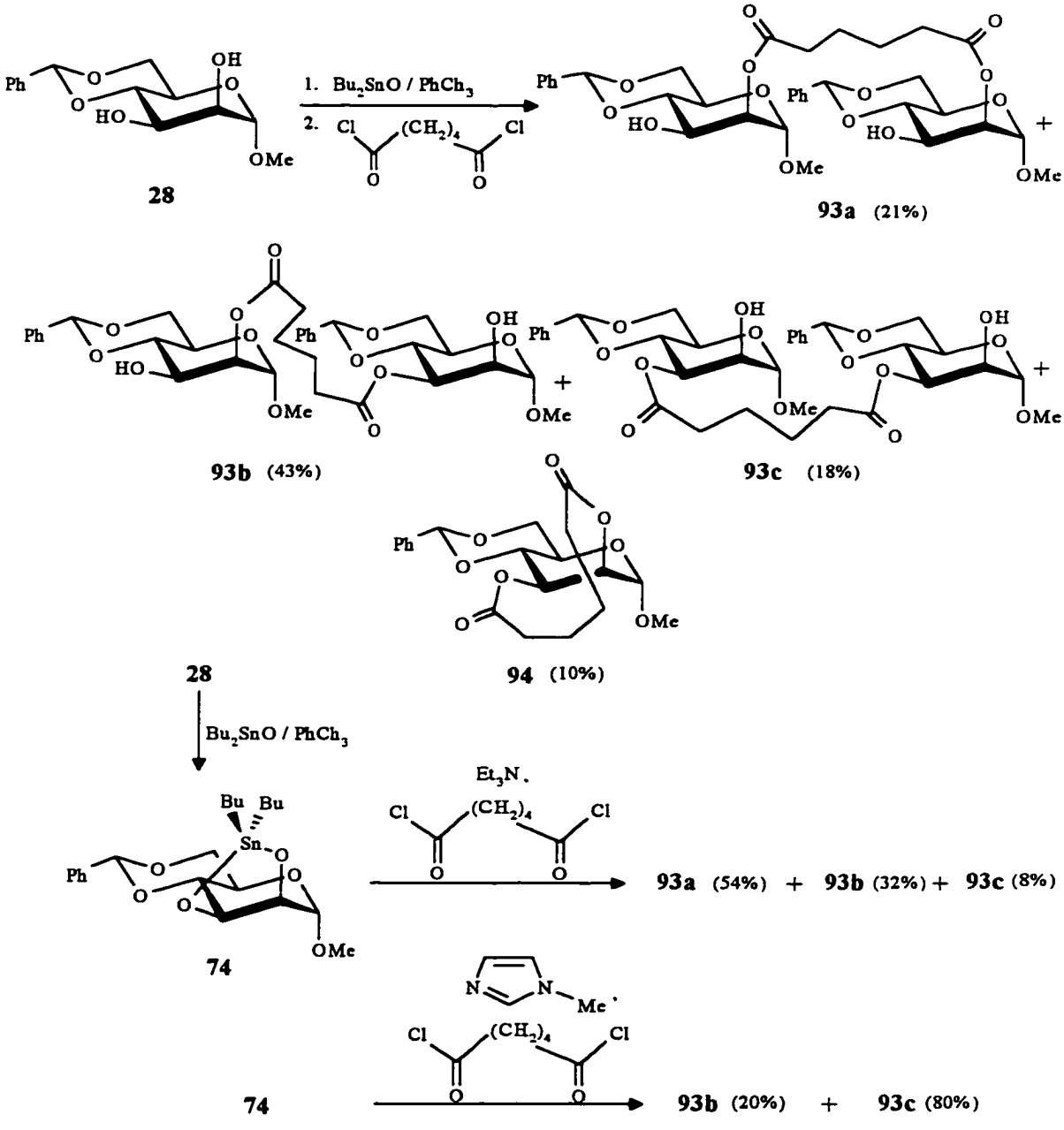


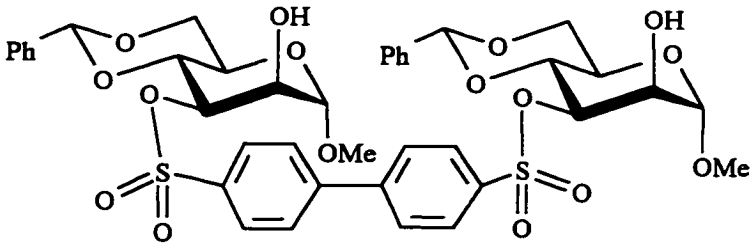
Figure 2.11 The reaction of **28** with adipoyl chloride under different conditions.

product ratio to be 1:2:2 for the 2,2'-, 2,3'- and 3,3'-linked disaccharides, respectively.

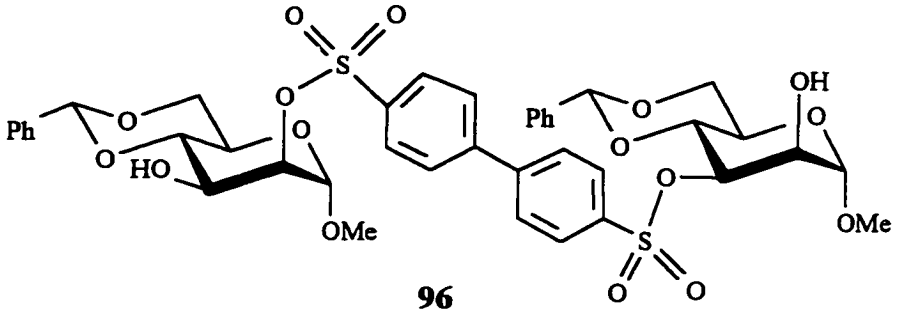
The best yield of symmetric non-glycosidically linked disaccharide, the 3,3'-linked compound **93c**, was obtained by reaction of the 2,3-*O*-dibutylstannylene acetal **74** in the presence of 10 equivalents of *N*-methylimidazole (NMI) as added nucleophile. This result was consistent with the observation of Holzapfel *et al.*[27] on the benzoylation of the same compound.

Reaction of the 2,3-*O*-dibutylstannylene acetal **74** was also carried out with 4,4'-diphenyldisulfonyl dichloride. It has been shown that the *p*-toluenesulfonyl groups do not rearrange under the dialkylstannylene acetal reaction conditions and during isolation.[58] In the presence of one equivalent of *N*-methylimidazole, the reaction led to the formation of the 3,3'-disulfonyl disaccharide **95** and the 2,3'-linked non-symmetric disaccharide **96** in 93% and 5% yields, respectively, after chromatography.

The structure of these compounds were established by their ^{1}H and ^{13}C NMR spectra and a COSY experiment. In the spectrum of the symmetric dimer **94**, the signal of H-3 appeared as a doublet of doublets at 4.84 ppm. This signal was the most deshielded secondary proton with coupling constants of 3.1 and 10.1 Hz. In addition, a hydroxyl signal was observed at 3.48 ppm and was correlated with H-2 in the COSY spectrum. The chemical shift and coupling constants of H-3 and the presence of a free hydroxyl on C-2 were all consistent with the presence of the sulfonyl group at C-3. In the structure of the non-symmetric disaccharide **96**, two set of signals appeared in the ^{1}H and ^{13}C NMR spectra because of the lack of symmetry in the molecule.



95



96

Two deshielded signals are observed at 4.82 and 4.84 ppm both as doublet of doublets, with coupling constants 3.5 and 10.1 Hz, and 1.5 and 3.7 Hz, respectively, consistent with the axial and equatorial orientations of H-3' and H-2, respectively. Each of these deshielded signals belong to one of the monosaccharides in the non-symmetric dimer in which their attached carbons have been functionalized with a sulfonyl group. Two hydroxyl signals appeared as doublets at 2.42 and 3.04 ppm with J values of 4.6 and 4.0 Hz, respectively in the ^{1}H NMR spectrum. From the correlation of these hydroxyl signals to their corresponding protons, the structure of compound **96** was confirmed as being the non-symmetric 2,3'-disulfonyl disaccharide.

The prepared oligosaccharide can be used for the further extension of molecules to synthesize larger carbohydrate clusters. This could be done by the activation of free

secondary hydroxyl groups and regioselective opening of the 4,6-*O*-benzylidene group, to allow expansion of the molecule. Recently, the conversion of a free hydroxyl in carbohydrates to the corresponding acid chloride in reaction with anhydrides has been reported by Valverde *et al.*[103] The combination of these methods allows one to synthesize a variety of larger carbohydrate clusters. Dibutylstannylene acetals derived from other sugars could be reacted with acid chloride carbohydrates prepared using the above method.

2.3 Conclusions

Non-glycosidically linked oligosaccharides were synthesized in high yields and with high regioselectivity from dibutylstannylene acetal intermediates. The regioselectivity obtained here was the same as previously observed from the reaction of dibutylstannylene acetals of the same carbohydrates in reaction with monofunctional electrophiles. This methodology avoided the problems associated with glycosidation reactions in synthesis of disaccharides and oligosaccharides. Potentially, it also allows one to control the distance between carbohydrate molecules by introducing variable-sized spacers between attached sugar molecules. Repetition of this strategy could be used with a wide variety of possible linkers and carbohydrates to prepare biologically active carbohydrates to match those required for efficient binding with certain proteins. Also, the synthesized non-glycosidically linked carbohydrate clusters could be resistant to glycoside degradation and may have interesting biological activities.

Formation of diesters in these reactions as the minor competing reactions can be

minimized by making the initial esterification as fast as possible. Formation of cyclic diester can be maximized by adding base to the reactions and by conducting the reactions at higher temperatures using a 1:1 stoichiometry. The nature of carbohydrates and the size of diacyl chlorides influence whether monomeric and oligomeric cyclic compounds are formed.

2.4 Experimental

2.4.1 General methods

General method were the same as in section 1.4.1 with the following exceptions. One ^{1}H NMR spectrum was recorded with a Bruker AMX-400 NMR spectrometer at 400.14 MHz. Some chemical shifts were referenced to the central lines of different solvents in this section: dimethyl sulfoxide-d_6 (δ_H = 2.49 and δ_C = 39.7), benzene-d_6 (δ_H =7.15 and δ_C = 128.0). ^{13}C NMR spectral assignments were confirmed by JMD and HETCOR experiments. APCI or electrospray mass spectra were recorded on a Fisons VG Quattro mass spectrometer. Methyl α-D-glucopyranoside, methyl α-D-mannopyranoside and linker reagents were purchased from Aldrich.

2.4.2 General method for preparation of dibutylstannylene acetals

Unless otherwise stated, the specified monosaccharide 1,2-diol (1 mmol) and dibutyltin oxide (1.1 mmol) were refluxed for 12 h in toluene (20 mL) with continuous azeotropic removal of water. The reaction solution was concentrated to 12 mL and the

residue was used directly without further purification for the synthesis of the oligosaccharide with the specified spacer reagent.

2.4.3 Standard workup

Water (2 mL) was added to the reaction mixture in toluene and the mixture was stirred for 1 hour at room temperature, then diluted with chloroform (15 mL). The organic layer was washed sequentially with a dilute solution of hydrochloric acid (0.1 M, 5 mL), with water (2 x 15 mL), and with a saturated solution of sodium bicarbonate (15 mL), unless otherwise specified, then dried over magnesium sulfate, and concentrated.

2.4.4 Bis-(methyl 4,6-*O*-benzylidene-α-D-glucopyranoside) 2,2'-butanedioate (86a)

Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**32**, 0.423 g, 1.5 mmol) was treated with dibutyltin oxide (0.441 g, 1.65 mmol) as in the general method to give the dibutylstannylene acetal. The stirred solution was cooled to room temperature and triethylamine (230 μL, 1.65 mmol) was added. After 0.5 h, a solution of freshly distilled succinyl chloride (72 μL, 0.652 mmol) in toluene (1 mL) was added slowly. The colour of the solution gradually changed to dark brown. Standard work up after 30 min was followed by purification of the residue by dry column flash chromatography using a solvent gradient from cyclohexane to cyclohexane/ethyl acetate 1:5 as eluant. The product, a solid, was recrystallized from ethyl acetate and cyclohexane to give fine colourless needles of the title compound **86a**; mp 117-118 °C, R_F = 0.25 (ethyl acetate: hexane, 1:1), yield 0.383 g (91%); $[\alpha]_D^{24}$ +76.7° (*c* 1.25, chloroform); ^{1}H NMR δ : 2.72 (s, 4H, 2 x

CH_2), 3.38 (s, 6H, 2 x OMe), 3.52 (t, 2H, $J_{4,5} = J_{3,4} = 8.9$ Hz, 2 x H-4), 3.72 (t, 2H, $J_{5,6a} = J_{6a,6e} = 10.1$ Hz, 2 x H-6_{ax}), 3.82 (td, 2H, $J_{5,6a} = J_{4,5} = 9.6$ Hz, $J_{5,6e} = 4.2$ Hz, 2 x H-5), 4.15 (t, 2H, $J_{2,3} = J_{3,4} = 9.2$ Hz, 2 x H-3), 4.26 (X of ABX pattern, 2H, 2 x H-6_{eq}), 4.79 (dd, 2H, $J_{2,3} = 9.5$ Hz, $J_{1,2} = 4.0$ Hz, 2 x H-2), 4.90 (d, 2H, $J_{1,2} = 3.7$ Hz, 2 x H-1), 5.51 (s, 2H, 2 x PhCH), 7.26-7.58 (m, 10H, 2 x ArH); ^{13}C NMR δ: 29.2 (2C, 2 xCH_2), 55.3 (2C, 2 x OMe), 62.0 (2C, 2 x C-5), 68.4 (2C, 2 x C-3), 68.7 (2C, 2 x C-6), 73.9 (2C, 2 x C-2), 81.1 (2C, 2 x C-4), 97.4 (2C, 2 x C-1), 101.9 (2C, 2 x PhCH), 126.2, 128.1, 129.2 (6C, 2 x Ar-C), 136.9 (2C, 2 x Ar-C_{ipso}), 172.0 (2C, 2 x COO).

Anal. calcd. for $C_{32}H_{38}O_{14}$: C 59.44, H 5.92; found: C 59.12, H 5.95.

2.4.5 Bis-(methyl 4,6-*O*-benzylidene-α-D-glucopyranoside) 2,2'-hexanedioate (86b)

Compound **32** (0.564 g, 2 mmol) was treated with dibutyltin oxide (0.523 g, 2.1 mmol) as in the standard method. The solution was concentrated to 15 mL and triethylamine (297 μL, 2.1 mmol) was added to the stirred room temperature solution. After 30 min, the solution was cooled to 0 °C and freshly distilled adipoyl chloride (98 μL, 0.67 mmol) was added dropwise. The cooling bath was removed 30 min later, then the reaction was stopped after a further 20 min and worked up in the standard fashion. Dry column flash chromatography (gradient from cyclohexane to ethyl acetate) gave the title compound **86b**, as a solid: R_F = 0.23 (ethyl acetate/ hexanes, 1:1); yield 0.380 g (84%); mp 165-166 °C; $[\alpha]_D^{22}$ +102 ° (*c* 1.08, chloroform); ^{1}H NMR δ: 1.71 (b m, 4H, 2 x $CH_2C\mathit{H}_2CH_2$), 2.43 (b m, 2 x CH_2CO), 2.94 (d, 2H, $J_{3,OH-3} = 3.1$ Hz, 2 x OH-3), 3.37 (s, 6H, 2 x OMe), 3.53 (t, 2H, $J_{4,5} = J_{3,4} = 9.2$ Hz, 2 x H-4), 3.74 (t, 2H, $J_{5,6ax} = J_{6eq,6ax} = 9.8$

Hz, 2 x H-6_{ax}), 3.82 (td, 2H, $J_{5,6eq}$ = 4.3 Hz, $J_{4,5}$ = $J_{5,6ax}$ = 9.8 Hz, 2 x H-5), 4.15 (dt, 2H, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, 2 x H-3), 4.27 (X of ABX pattern, 2H, 2 x H_{6eq}), 4.81 (dd, 2H, $J_{1,2}$ = 3.7 Hz, $J_{2,3}$ = 9.8 Hz, 2 x H-2), 4.93 (d, 2H, 2 x H-1), 5.53 (s, 2H, 2 x PhCH), 7.32-7.52 (m, 10H, 2 x Ar-H); ^{13}C NMR δ: 24.0 (2 x $CH_2CH_2CH_2$), 33.6 (2 x CH_2CO), 55.3 (2 x OMe), 62.0 (2 x C-5), 68.5 (2 x C-3), 68.8 (2 x C-6), 73.5 (2 x C-2), 81.3 (2 x C-4), 97.5 (2 x C-1), 101.9 (2 x PhCH), 126.3, 128.3, 129.2 (Ar-C), 136.9 (2 x Ar-C_{ipso}), 173.1 (2 x COO).

Anal. calcd. for $C_{34}H_{42}O_{14}$: C 60.53, H 6.27; found: C 60.76, H 6.34.

2.4.6 Bis-(methyl 4,6-*O*-benzylidene-α-D-glucopyranoside) 2,2'-dodecanedioate (86c)

Treatment of compound **32** (0.564 g, 2 mmol) with dibutyltin oxide (0.523 g, 2.1 mmol) as in the standard method gave the dibutylstannylene acetal. The reaction mixture was concentrated to 15 mL and triethylamine (297 μL, 2.1 mmol) was added. After 0.5 h, the solution was cooled to 0 °C and freshly distilled dodecanedioyl chloride (175 μL, 0.7 mmol) was added dropwise to the magnetically stirred solution. The cooling bath was removed after 30 min and 1 h later the reaction was quenched by adding water. Standard workup yielded a syrupy residue that was fractionated by means of dry column flash chromatography using ethyl acetate/cyclohexane 2:1 as eluant. The first fraction was the title compound **86c**, a solid, R_F = 0.76 (ethyl acetate/cyclohexane, 2 :1); yield 0.415 g (78%); mp 123-124 °C; $[\alpha]_D^{23}$ +256° (*c* 0.29, chloroform); ^{1}H NMR δ: 1.28 (b, 12H, 6 x CH_2), 1.65 (b p, J = 7 Hz, 4H, 2 x CH_2CH_2CO), 2.40 (t, 4H, J = 7.3 Hz, 2 x CH_2CO), 2.50 (d, 2H, $J_{3,OH-3}$ = 3.1 Hz, 2 x OH-3), 3.39 (s, 6H, 2 x OMe), 3.55 (t, 2H, $J_{3,4}$ = $J_{4,5}$ = 9

Hz, 2 x H-4), 3.75 (t, 2H, $J_{5,6ax}$ = $J_{6ax,6eq}$ = 9.8 Hz, 2 x H-6_{ax}), 3.84 (td, 2H, $J_{5,6e}$ = 4.2 Hz, $J_{4,5}$ = $J_{5,6a}$ = 9.7 Hz, 2 x H-5), 4.17 (td, 2H, $J_{2,3}$ = $J_{3,4}$ = 9.3 Hz, $J_{3,OH}$ = 2.8 Hz, 2 x H-3), 4.29 (dd, 2H, 2 x H-6_{eq}), 4.80 (dd, 2H, H-2), 4.97 (d, 2H, $J_{1,2}$ = 4.0 Hz, 2 x H-1), 5.54 (s, 2H, 2 x PhCH), 7.36-7.42 (m, 6H, Ar-H), 7.46-7.51 (m, 4H, Ar-H); ^{13}C NMR δ: 24.8(2 x CH_2CH_2CO, 28.9, 29.1, 29.3 (6 x CH_2), 34.4 (2 x CH_2CO), 55.4 (2 x OMe), 61.9 (2 x C-5), 68.6 (2 x C-3), 68.8 (2 x C-6), 73.4 (2 x C-2), 81.3 (2 x C-4), 97.5 (2 x C-1), 102.0 (2 x PhCH), 126.3, 128.3, 129.3 (Ar-C), 136.9 (2 x Ar-C_{ipso}), 173.5 (2 x COO).

Anal. calcd. for $C_{40}H_{54}O_{14}$: C 63.31, H 7.17; found: C 62.94, H 6.81.

Further elution gave *bis*-(methyl 4,6-*O*-benzylidene-α-D-glucopyranoside) 2,3'-dodecanedioate (**87**), a solid, recrystallized from ethyl acetate / cyclohexane, mp 134-135 °C; R_F = 0.57 (ethyl acetate : cyclohexane, 2 :1); yield 0.065 g (12%); $[\alpha]_D^{23}$ +171 ° (*c* 0.39, chloroform); ^{1}H NMR δ: 1.17-1.33 (m, 12H, 6 x CH_2), 1.56-1.70 (m, 5H, 2 x CH_2CH_2CO), 2.32(d, 1H, $J_{2',OH-2'}$ = 11.6 Hz, OH-2'), 2.36, 2.40 (2 t, 4H, J = 7.5 Hz, 2 x CH_2CO), 2.60 (br d, 1H, $J_{3,OH-3}$ = 2.2 Hz, OH-3), 3.39 (s, 3H, OMe), 3.45 (s, 3H, OMe'), 3.56 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.3 Hz, H-4), 3.71 (t, 1H, $J_{3',4'}$ = $J_{4',5'}$ = 9.5 Hz, H-4'), 3.65 (ddd, 1H, $J_{1',2'}$ = 3.8 Hz, $J_{2',3'}$ = 9.8 Hz, $J_{2',OH-2'}$ = 11.6 Hz, H-2'), 3.74 (t, 1H, $J_{5',6'ax}$ = $J_{6'eq,6'ax}$ = 10.1 Hz, H-$6'_{ax}$), 3.76 (t, 1H, $J_{5,6ax}$ = $J_{6eq,6ax}$ = 9.8 Hz, H-6_{ax}), 3.84, 3.86 (2 td, 2H, $J_{5,6e}$ = 3.4 Hz, $J_{4,5}$ = $J_{5,6a}$ = 10.0 Hz, H-5 and H-5'), 4.17 (td, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, $J_{3,OH-3}$ = 2.2 Hz, H-3), 4.30 (dd, 2H, $J_{6eq,6ax}$ = $J_{6'eq,6'ax}$ = 9.5 Hz, $J_{5,6eq}$ = $J_{5',6'eq}$ = 4.0 Hz, H-6_{eq} and H-$6'_{eq}$), 4.78 (d, 1H, $J_{1',2'}$ = 3.8 Hz, H-1'), 4.81 (dd, 1H, $J_{1,2}$ = 3.7 Hz, $J_{2,3}$ = 9.8 Hz, H-2), 4.95 (d, 1H, $J_{1,2}$ = 4.0 Hz, H-1), 5.33 (t, 1H, $J_{2',3'}$ = $J_{3',4'}$ = 9.6 Hz, H-3'), 5.49 (s, 1H, PhCH'), 5.55 (s, 1H, PhCH), 7.33-7.52 (m, 10H, Ar-H and Ar'-H), ^{13}C NMR δ: 24.8, 25.0 (2 x

CH_2CH_2CO), 28.8, 28.9, 29.1, 29.2, 29.3 (5 x CH_2), 34.0, 34.3 (2 x CH_2CO), 55.4, 55.5 (2 x OMe), 61.9 (C-5), 62.6 (C-5'), 68.6 (C-3), 68.8 (C-6 and C-6'), 71.8 (C-2'), 72.0 (C-3'), 73.3 (C-2), 78.6 (C-4'), 81.3 (C-4), 97.5 (C-1), 100.1 (C-1'), 101.4, 101.9 (2 x CHPh), 126.1, 126.3, 128.1, 128.3, 129.0, 129.2 (Ar-C), 136.91, 136.94 ($Ar\text{-}C_{ipso}$), 173.5, 173.9 (COO).

Anal. calcd. for $C_{10}H_{54}O_{14}$: C 63.31, H 7.17; found: C 63.05, H 7.12.

2.4.7 Bis-(methyl 4,6-*O*-benzylidene-α-D-glucopyranoside 2,2':3,3'-butanedioate) (88)

Compound **32** (0.423 g, 1.5 mmol) was treated with dibutyltin oxide (0.373 g, 1.5 mmol) in toluene (20 mL) as in the general method. Toluene (350 mL) was added and the resulting solution was heated to 80 °C. Succinyl chloride (1.5 mmol, 164 μL) in toluene (5 mL) was added dropwise to the solution stirred at that temperature. The reaction was stopped after 10 h and worked up as in the standard method. The solid residue was separated by means of dry column flash chromatography using a gradient from cyclohexane to ethyl acetate as eluant. The first fraction was present in very small amounts and was not identified. The second fraction was the title compound **88**, a solid, that was recrystallized from ethyl acetate and cyclohexane; mp 209-210 °C; yield 0.275 g (50%); R_F = 0.5 (ethyl acetate: hexane, 1:1); $[\alpha]_D^{23}$ +52.2° (*c* 0.465, chloroform); ^1H NMR (400.14 MHz) δ: 2.493, 2.757 (AA'XX' pattern, 4H, $J_{AX} = J_{A'X'} =$ -17.3 Hz, $J_{AX'} = J_{A'X} = 2.4$ Hz, $J_{AA'} = 10.6$ Hz, $J_{XX'} = 8.1$ Hz, one CH_2CH_2 unit, RMS error for LAME8 simulation 0.18 Hz), 2.620, 2.817 (AA'BB' pattern, 4H, $J_{AB} = J_{A'B'} = -17.0$ Hz, $J_{AB'} = J_{A'B}$

= 6.4 Hz, $J_{AA'}$ = $J_{BB'}$ = 7.3 Hz, the 2nd CH_2CH_2 unit, RMS error for LAME8 simulation 0.14 Hz), 3.40 (s, 3H, OMe), 3.71 (t, 1H, $J_{3,4} = J_{4,5}$ = 9.6 Hz, H-4), 3.75 (t, 1H, $J_{5,6ax}$ = $J_{6ax,6eq}$ = 10.1 Hz, H-6_{ax}), 3.91 (td, 1H, H-5), 4.30 (dd, 1H, $J_{6eq,6ax}$ = 9.8 Hz, $J_{5,6eq}$ = 4.3 Hz, H-6_{eq}), 4.80 (dd, 1H, $J_{2,3}$ = 9.8 Hz, $J_{1,2}$ = 3.7 Hz, H-2), 5.00 (d, 1H, H-1), 5.50 (t, 1H, $J_{2,3} = J_{3,4}$ = 9.6 Hz, H-3), 5.51 (s, 1H, PhCH), 7.24-7.55 (m, 5H, Ar-H); ^{13}C NMR δ: 28.9, 29.3 (2 CH_2), 55.4 (OMe), 62.2 (C-5), 68.8 (C-6), 69.9 (C-3), 72.8 (C-2), 78.6 (C-4), 97.5 (C-1), 101.7 (PhCH), 126.2, 128.2, 129.2 (Ar-C), 136.9 (Ar-C_{ipso}), 170.7, 171.5 (CO); mass spectrum (EI) (scan from m/z 800 to m/z 150) m/z: M^+ (11%), M^+-1 (2.7%), 579 (1.7%), 465 (2.9%), 410 (1.7%), 386 (4.2), 368 (2.5%), 247 (100%).

HRMS (EI) calcd. for $C_{36}H_{40}O_{16}$: 728.2316; found: 728.2310.

Anal. calcd. for $C_{36}H_{40}O_{16} \cdot H_2O$: C 58.56, H 5.58; found: C 58.68, H 5.60.

The third fraction was compound **86a**, yield 0.443 g (46%).

2.4.8 Bis-(methyl 4,6-*O*-benzylidene-α-D-glucopyranoside) 2,2'-terephthaloate (88e)

Compound **38** (0.282 g, 1 mmol) was treated with dibutyltin oxide (0.2738 g, 1.1 mmol) as in the general method. To the dibutylstannylene acetal solution was added triethylamine (156 μL, 1.1 mmol) and the resulting solution was stirred for 0.5 h. Terephthaloyl chloride (79 mg, 0.43 mmol) was added slowly to the mixture and stirring was continued for 1 h, then standard workup was performed. The residue was purified by dry column flash chromatography (cyclohexane: ethyl acetate, gradient elution) which gave the title compound (**88e**) as a solid, R_F = 0.54 (ethyl acetate/cyclohexane, 1: 1); yield 0.283 g (95%), that was recrystallized from ethyl acetate and cyclohexane to give needle-

like crystals: mp 139-140 °C; $[\alpha]_D^{25}$ +129 ° (*c* 0.73, chloroform); ^{1}H NMR δ: 2.26 (d, 2H, $J_{3,3\text{-OH}}$ = 2.8 Hz, 2 x OH-3), 3.41 (s, 6H, 2 x OMe), 3.64 (t , 2H, $J_{3,4} = J_{4,5}$ = 9.2 Hz, 2 x H-4), 3.81 (t, 2H, $J_{5,6ax} = J_{6ax,6eq}$ = 10.1 Hz, 2 x H-6_{ax}), 3.92 (td, 2H, $J_{5,6eq}$ = 4.3 Hz, $J_{4,5} = J_{5,6ax}$ = 9.7 Hz, 2 x H-5), 4.34 (dd, 2H, $J_{5,6eq}$ = 4.3 Hz, $J_{6eq,6ax}$ = 9.8 Hz, H-6_{eq}), 4.37 (b dt, 2 x H-3), 5.04-5.09 (m, 4H, 2 x H-1 and 2 H-2), 5.59 (s, 2H, 2 x PhCH), 7.36-7.42 (m, 6H, 2 x Ar-H), 7.48-7.54 (m, 4H, 2 x Ar-H), 8.17 (s, 4H, Ar'-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz), δ: 55.5 (2C, 2 x OMe), 62.0 (2C, 2 x C-5), 68.8 (2C, 2 x C-3), 68.9 (2C, 2 x C-6), 74.4 (2C, 2 x C-2), 81.5 (2C, 2 x C-4), 97.6 (2C, 2 x C-1), 102.1 (2C, 2 x PhCH), 126.3, 128.4, 129.0 (2 x Ar-C), 129.4 (2 x Ar'-C), 133.7 (2 x Ar'-C_{ipso}), 136.9 (2 x Ar-C_{ipso}), 165.3 (2C, 2 x COO).

2.4.9 Bis-(methyl 4,6-*O*-benzylidene-α-D-glucopyranoside) 2,2'-phthaloate (88f)

Compound **32** (0.564 g, 2 mmol) was treated with dibutyltin oxide (0.523 g, 2.1 mmol) under standard conditions to give a solution of the dibutylstannylene acetal. The solution was concentrated to 15 mL and cooled to room temperature, triethylamine (297 μL, 2.1 mmol) was added and the solution was stirred for 30 min. The solution was cooled to 0 °C and freshly distilled phthaloyl dichloride (97 μL, 0.67 mmol) was added dropwise. The reaction mixture was stirred 30 min at 0 °C, then another 30 min at room temperature. Workup using the standard method gave a solid residue that was separated by dry column flash chromatography (hexane, ethyl acetate as gradient). The first fraction, yield (0.014 g, 4.4%) was not identified.

The second fraction was the title compound (**88f**), a solid: R_F = 0.51 (ethyl acetate/

cyclohexane, 1 :1); yield 0.378 g (81%). It was recrystallized from chloroform and hexane; mp 124-125 °C, $[\alpha]_D^{22}$ +82.4 °(*c* 0.418, chloroform); ^{1}H NMR δ: 3.32 (bd, 2H, $J_{3,OH-3}$ = 2.4 Hz, 2 x OH-3), 3.38 (s, 6H, 2 x OMe), 3.58 (t, 2H, $J_{4,5} = J_{3,4}$ = 9.2 Hz, 2 x H-4), 3.74 (t, 2H, $J_{5,6ax} = J_{6eq,6ax}$ = 9.8 Hz, 2 x H-6_{ax}), 3.84 (td, 2H, $J_{4,5} = J_{5,6ax}$ = 9.6 Hz, $J_{5,6eq}$ = 4.3 Hz, 2 x H-5), 4.23 (td, 2H, $J_{3,OH-3}$ = 1.8 Hz, $J_{2,3} = J_{3,4}$ = 9.2 Hz, 2 x H-3), 4.28 (dd, 2H, $J_{5,6eq}$ = 3.7 Hz, $J_{6eq,6ax}$ = 9.2 Hz, 2 x H-6_{eq}), 5.01 (m, 4H, 2 x H-2 and 2 x H-1), 5.52 (s, 2H, 2 x PhCH), 7.33-7.42 (m, 6H, Ar-H), 7.47-7.59 (m, 6H, ArH +2 Phth ArH), 7.78-7.82 (m, 2H, σ-Phth Ar-H); ^{13}C NMR δ: 55.4 (2C, 2 x OMe), 62.0 (2C, 2 x C-5), 68.5 (2C, 2 x C-3), 68.7 (2C, 2 x C-6), 74.9 (2C, 2 x C-2), 81.1 (2C, 2 x C-4), 97.4 (2C, 2 x C-1), 101.9 (2C, 2 x PhCH), 126.3, 128.2, 129.1, 129.6 (Ar-C), 130.9 (Ar'-C_{ipso}), 131.6 (Ar-C), 136.9 (2 x Ar-C_{ipso}), 167.1 (2C, 2 x COO).

HRMS (FAB) for M + H^+, calcd for $C_{36}H_{39}O_{14}$: 695.2340; found: 695.2336; for M+ H^+ - CH_3OH, calcd for $C_{35}H_{35}O_{13}$: 663.2078; found: 663.2090.

2.4.10 Tris-(methyl 4,6-*O*-benzylidene-α-D-glucopyranoside) 2,2',2''-(1,3,5-benzenetricarboxylate) (88g)

Compound **32** (0.564 g, 2 mmol) was treated with dibutyltin oxide (0.523 g, 2.1 mmol) in toluene (30 mL) as in the standard method. The resulting solution was concentrated to 15 mL, cooled to the room temperature and triethylamine (296 μL, 2.1 mmol) was added. The reaction mixture was stirred for 0.5 h, then cooled to 0 °C. 1,3,5-Benzenetricarbonyl trichloride (0.159 g, 0.6 mmol) was added slowly to the cooled mixture. The cooling bath was removed after 30 min and the solution was stirred a further

1 h. Standard workup gave a solid that was purified by means of flash column dry chromatography (cyclohexane, ethyl acetate) to give the title compound **88g**, R_F = 0.8 (ethyl acetate: hexane, 3: 2); a colourless solid; mp 172-173 °C; yield 0.531 g (88%); $[\alpha]_D^{24}$ + 123° (*c* 1.63, chloroform), ^{1}H NMR δ: 3.28 (s, 9H, 3 x OMe), 3.64 (t, 3H, $J_{3,4}$ = $J_{4,5}$ = 9.2 Hz, 3 x H-4), 3.75 (t, 3H, $J_{5,6ax}$ = $J_{6ax,6eq}$ = 9.6 Hz, 3 x H-6_{ax}), 3.86 (td, 3H, $J_{4,5}$ = $J_{5,6ax}$ = 9.6 Hz, $J_{5,6eq}$ = 4.2 Hz, 3 x H-5), 4.02 (b s, 3H, 3 x OH-3), 4.27 (X of ABX pattern, 3H, 3 x H-6_{eq}), 4.35 (t, 3H, $J_{2,3}$ = $J_{4,5}$ = 9.3 Hz, 3 x H-3), 4.99 (dd, 3H, $J_{1,2}$ = 3.7 Hz, $J_{2,3}$ = 9.2 Hz, 3 x H-2), 5.04 (d, 3H, $J_{1,2}$ = 4.0 Hz, 3 x H-1), 5.54 (s, 3H, 3 x PhCH), 7.28-7.35 (m, 9H, Ar-H), 7.46-7.52 (m, 6H, Ar-H), 8.74 (s, 3H, Ar'-H); ^{13}C NMR δ: 55.2 (3C, 3 x OMe), 62.0 (3C, 3 x C-5), 68.4 (3C, 3 x C-3), 68.7 (3C, 3 x C-6), 75.0 (3C, 3 x C-2), 81.2 (3C, 3 x C-4), 97.3 (3C, 3 x C-1), 102.0 (3C, 3 x PhCH), 126.3, 128.3, 129.2 (2 x Ar-C), 130.3 (3 x Ar'-C_{ipso}), 135.4 (2 x Ar-C_{ipso}), 137.0 (3 x Ar'-C), 164.4 (3C, 3 x COO).

HRMS (ES) for M+H$^+$, calcd for $C_{51}H_{55}O_{21}$: 1003.3236; found: 1003.3227.

2.4.11 Bis-(methyl α-D-glucopyranoside) 2,2'-butanedioate (90a)

The milky solution resulting from refluxing methyl α-D-glucopyranoside (**89**) (0.583 g, 3 mmol) and dibutyltin oxide (0.747 g, 3 mmol) in freshly dried methanol (30 mL) became a clear homogenous solution after about 1 h and was refluxed for an additional 1.5 h. The solution was concentrated and then kept under vacuum (0.1 torr) for an additional 1 h. This residue was dissolved in dry dioxane (15 mL), cooled to 0 °C and a solution of freshly distilled succinyl chloride (144 μL, 1.304 mmol) in dioxane (2 mL) was

added dropwise. After 30 min, the cooling bath was removed, and the solution was stirred a further 8 h. The solution was concentrated and the syrupy residue was separated by dry column flash chromatography using a solvent gradient from ethyl acetate to ethanol. The first fraction was methyl (methyl α-D-glucopyranoside) 2-butanedioate (**90b**) as a syrup, R_F = 0.66 (ethyl acetate/ methanol 1:2), yield 0.022 g, (5.4%), $[\alpha]_D^{24}$ +131° (*c* 0.61, chloroform); ^{1}H NMR δ: 2.7 (m, 4H, 2 x CH_2), 3.38 (s, 3H, OMe), 3.55-3.75 (b m, 2H, H-4 and H-5), 3.70 (s, 3H, COO*Me*), 3.86 (b s, 2H, H-6 and H-6'), 3.96 (t, 1H, $J_{2,3} = J_{3,4}$ = 8.9 Hz, H-3), 4.77 (dd, 1H, $J_{1,2}$ = 3.7 Hz, $J_{2,3}$ = 9.8 Hz, H-2), 4.86 (d, 1H, H-1); ^{13}C NMR δ: 29.0, 29.2 (2 CH_2), 52.1 (COO*Me*), 55.2 (glycoside OMe), 61.7 (C-6), 70.2 (C-5), 70.9 (C-4), 71.6 (C-3), 73.5 (C-2), 97.1 (C-1), 172.3, 173.3 (COO).

The second fraction was the title compound **90a**, R_F = 0.52 (ethyl acetate/ethanol, 2:7), a solid, mp 38- 40 °C; yield 0.441 g (72%); $[\alpha]_D^{23}$ + 105° (*c* 2.97, chloroform); ^{1}H NMR (D_2O) δ : 2.52 (s, 4H, 2 x CH_2), 3.13 (s, 6H, 2 x OMe), 3.24 (t, 2H, $J_{3,4} = J_{4,5}$ = 9.5 Hz, 2 x H-4), 3.36-3.44 (m, 2H, 2 x H-5), 3.34-3.64 (m, 6H, 2 x H-3, 2 x H-6 and 2 x H-6'), 4.50 (dd, 2H, $J_{2,3}$ = 10.1 Hz, 2 x H-2), 4.68 (d, 2H, $J_{1,2}$ = 3.5 Hz, 2 x H-1); ^{13}C NMR (D_2O) δ: 31.3 (4C, 4 x CH_2), 57.5 (2C, 2 x OMe), 63.1 (2C, 2 x C-6), 72.1 (2C, 2 x C-4), 73.4 (2C, 2 x C-3), 74.2 (2C, 2 x C-5), 75.9 (2C, 2 x C-2), 99.1 (2C, 2 x C-1), 176.5 (2C, 2 x COO).

Anal. calcd. for $C_{18}H_{30}O_{14}.H_2O$: C 44.26, H 6.60; found: C 43.83, H 6.43.

2.4.12 Bis-(benzyl 4,6-*O*-benzylidene-β-D-galactopyranoside) 3,3'-terephthaloate (91)

The solution from the reaction of benzyl 4,6-*O*-benzylidene-β-D-galactopyranoside (**38**)[104] (0.197 g, 0.55 mmol) with dibutyltin oxide (0.192 g, 0.77 mmol) as in the standard method was concentrated to 10 mL, triethylamine (109 μL, 0.77 mmol) was added and the resulting solution was stirred at room temperature for 0.5 h. Terephthaloyl chloride (65 mg, 0.32 mmol) was added and the mixture was stirred until TLC (ethyl acetate : cyclohexane, 1 : 1) indicated that starting material was consumed (2 h). Standard workup gave a syrupy residue that was purified using dry column flash chromatography with a solvent gradient from cyclohexane to ethyl acetate. The title compound **91**, R_F = 0.41, a solid, was recrystallized from ethyl acetate, cyclohexane to give fine crystals: mp 223-224 °C; yield 0.210 g (78%); $[\alpha]_D^{25}$ +69.9 ° (*c* 0.925, chloroform); ^{1}H NMR δ: 1.61 (s, 2H, H_2O), 2.52 (d, 2H, $J_{2,OH-2}$ = 1.8 Hz, 2 x OH-2), 3.56 (b s, 2H, H-5), 4.10 (dd, 2H, $J_{5,6ax}$ = 1.4 Hz, $J_{6ax,6eq}$ = 12.5 Hz, 2 x H-6_{ax}), 4.23 (ddd, 2H, $J_{1,2}$ = 7.9 Hz, $J_{2,3}$ = 10.4 Hz, 2 x H-2), 4.39 (b d, 2H, 2 x H-6_{eq}), 4.48 (b d, 2H, $J_{3,4}$ = 4.3 Hz, 2 x H-4), 4.51 (d, 2H, 2 x H-1), 4.65 (d, 2H, J = 11.6 Hz, ½ $PhCH_2$), 5.01 (d, 2H, ½ $PhCH_2$), 5.13 (dd, 2H, $J_{2,3}$ = 10.4 Hz, $J_{3,4}$ = 3.7 Hz, 2 x H-3), 5.51 (s, 2H, 2 x PhCH), 7.31-7.36 (m, 20H, Ar-H), 8.09 (s, 4H, tereph Ar-H); ^{13}C NMR δ: 66.6 (2 x C-5), 68.7 (2 x C-2), 69.0 (2 x C-6), 71.0 (2 x $PhCH_2$), 73.5 (2 x C-4), 74.4 (2 x C-3), 100.7 (2 x PhCH), 101.8 (2 x C-1), 126.1, 128.08, 128.11, 128.2, 128.5, 128.9, 129.9 (Ar-C), 133.7, 136.9, 137.5 (Ar-C_{ipso}), 165.5 (2 x COO).

Anal. calcd. for $C_{48}H_{46}O_{14}.H_2O$: C 66.66, H 5.59; found: C 66.22, H 5.22.

2.4.13 Bis-(methyl 4,6-*O*-benzylidene-α-D-allopyranoside) 2,2'-terephthalate (92)

Methyl 4,6-*O*-benzylidene-α-D-allopyranoside (**54**) (0.113 g, 0.4 mmol) was treated with dibutyltin oxide (0.110 g, 0.44 mmol) as in the standard method to give a solution that was concentrated to 6 mL and cooled to room temperature. Triethylamine (63 μL, 0.44 mmol) was added and the resulting solution was stirred at ambient temperature for 0.5 h. Then terephthaloyl chloride (41 mg, 0.2 mmol) was added and stirring was continued a further 20 min. Standard workup gave a solid residue that was purified by means of dry column flash chromatography using cyclohexane-ethyl acetate gradient elution. The title compound **92** was obtained as a solid, then recrystallized from ethyl acetate and cyclohexane to give fine crystals; mp 151-152 °C, yield 0.135 g (97%), $[\alpha]_D^{29}$ + 81.5 ° (*c* 5.97, chloroform); ^{1}H NMR δ: 3.23 (d, 2H, $J_{3,3\text{-OH}}$ = 7.6 Hz, 2 x OH-3), 3.48 (s, 6H, 2 x OMe), 3.68 (dd, 2H, $J_{3,4}$ = 2.4 Hz, $J_{4,5}$ = 9.8 Hz, 2 x H-4), 3.83 (t, 2H, $J_{5,6ax}$ = $J_{6ax,6eq}$ = 10.2 Hz, 2 x H-6_{ax}), 4.25 (td, 2H, 2 x H-5), 4.41(dd, 2H, $J_{5,6eq}$ = 5.2 Hz, $J_{6ax,6eq}$ = 10.1 Hz, 2 x H-6_{eq}), 4.52 (b m, 2H, 2 x H-3), 5.05 (d, 2H, $J_{1,2}$ = 3.7 Hz, 2 x H-1), 5.10 (t, 2H, $J_{2,3}$ = 3.5 Hz, 2 x H-2), 5.63 (s, 2H, 2 x PhCH), 7.35-7.40 (m, 6H, ArH), 7.50-7.55 (m, 4H, ArH), 8.21 (s, 4H, tereph ArH); ^{13}C NMR δ: 56.2 (2 x OMe), 57.9 (2 x C-5), 68.1 (2 x C-3), 69.0 (2 x C-6), 70.2 (2 x C-2), 78.5 (2 x C-4), 98.5 (2 x C-1), 102.0 (2 x PhCH), 126.3, 128.3, 129.2, 130.1 (Ar-C), 133.5, 136.9 (Ar-C_{ipso}), 164.8 (2 x COO).

Anal. calcd. for $C_{36}H_{38}O_{14}$: C 62.24, H 5.51; found: C 62.42, H 5.60.

2.4.14 Reaction of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside with adipoyl chloride

2.4.14.1 Without added base

The stirred solution resulting from the reaction of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (**28**)[105] (0.282 g, 1 mmol) and dibutyltin oxide (0.274 g, 1.1 mmol) as in the general method was cooled to room temperature. A solution of freshly distilled adipoyl chloride (61 μL, 0.415 mmol) in toluene (2 mL) was added dropwise and stirring was continued for 45 min. Standard workup gave a syrupy residue that was separated by means of dry column flash chromatography (eluant gradient: hexane to ethyl acetate). The first fraction from the column was methyl 4,6-*O*-benzylidene-2,3-deoxy-α-D-mannopyranoside 2,3-hexanedioate (**94**), a solid; R_F = 0.8 (ethyl acetate: hexane, 2 : 1); yield 0.016 g (9.8%). It was recrystallized from ethyl acetate and hexane to give fine needles: mp 194-196 °C; $[\alpha]_D^{23}$ -19.6 ° (*c* 0.32, chloroform); ^{1}H NMR δ: 1.90-1.98 (m, 2H, CH_2), 2.18-2.36 (m, 2H, CH_2), 2.37-2.52 (m, 4H, 2 x CH_2CO), 3.42 (s, 3H, OMe), 3.86 (t, 1H, $J_{5,6ax} = J_{6ax,6eq} = 9.8$ Hz, H-6_{ax}), 3.98 (td, 2H, $J_{4,5} = J_{5,6ax} = 9.5$ Hz, $J_{5,6eq} = 4.3$ Hz, H-5), 4.08 (t, 2H, $J_{3,4} = J_{4,5} = 9.3$ Hz, H-4), 4.33 (dd, 1H, $J_{5,6eq} = 4.6$ Hz, $J_{6eq,6ax} = 9.6$ Hz, H_{6eq}), 4.77 (d, 1H, $J_{1,2} = 1.2$ Hz, H-1), 5.08 (dd, 1H, $J_{2,3} = 4.4$ Hz, $J_{3,4} = 9.2$ Hz, H-3), 5.56 (dd, 1H, $J_{1,2} = 1.2$ Hz, $J_{2,3} = 4.3$ Hz, H-2), 5.62 (s, 1H, PhCH), 7.35-7.46 (m, 5H, Ar-H), ^{13}C NMR δ: 26.5, 26.9 (CH_2), 35.1, 35.9 (CH_2CO), 55.1 (OMe), 62.1 (C-5), 68.9 (C-6), 69.8 (C-2), 70.1 (C-3), 76.5 (C-4), 99.7 (C-1), 102.2 (PhCH), 126.2, 128.3, 129.3 (Ar-C), 137.0 (Ar-C_{ipso}), 172.2, 173.8 (COO).

EI MS for $C_{20}H_{24}O_8$: M^+ (16%), M-30 (5%), 243 (34%), 55 (100%), no peaks at

masses greater than 393; HRMS (EI), calcd: 392.1471; found: 392.1460.

The second fraction was a solid, bis-(methyl 4,6-*O*-benzylidene-α-D-mannopyranoside) 2,2'-hexanedioate (**93a**), mp 87-88 °C; R_F = 0.65 (ethyl acetate: hexane, 2 : 1); yield 0.058 g (21%), $[\alpha]_D^{24}$ +11.2 ° (*c* 2.02, chloroform); ^{1}H NMR δ: 1.73-1.83 (m, 4H, 2 x CH_2), 2.45-2.51 (m, 4H, 2 x CH_2CO), 2.72 (b s, 2H, OH-3), 3.39 (s, 6H, 2 x OMe), 3.80-3.92 (m, 6H, 2 H-4, 2 x H-5 and 2 x H-6_{ax}), 4.15 (dd, 2H, $J_{2,3}$ = 3.7 Hz, $J_{3,4}$ = 9.5 Hz, 2 x H-3), 4.25-4.28 (m, 2H, 2 x H-6_{eq}), 4.67 (d, $J_{1,2}$ = 1.5 Hz, 2 x H-1), 5.21 (dd, 2H, $J_{1,2}$ = 1.5 Hz, $J_{2,3}$ = 3.7 Hz, 2 x H-2), 5.59 (s, 2H, 2 x PhCH), 7.33-7.51 (m, 10H, 2 x Ar-H); ^{13}C NMR δ: 24.1 (2 x CH_2), 33.8 (2 x CH_2CO), 55.2 (2 x OMe), 63.2 (2 x C-5), 67.1 (2 x C-3), 68.7 (2 x C-6), 71.8 (2 x C-2), 79.0 (2 x C-4), 99.6 (2 x C-1), 102.2 (2 x PhCH), 129.2, 128.3, 129.2 (Ar-C), 137.1 (2 x Ar-C_{ipso}), 172.9 (2 x COO).

Anal. calcd. for $C_{34}H_{42}O_{14}$: C 60.53, H 6.27; found : C 59.94, H 5.94.

The third fraction, also a solid, was *bis*-(methyl 4,6-*O*-benzylidene-α-D-mannopyranoside) 2,3'-hexanedioate (**93b**), R_F = 0.38 (ethyl acetate/hexane 2:1); mp 87-88 °C; yield 0.120 g (43%); $[\alpha]_D^{24}$ +19.7 ° (*c* 1.11, chloroform); ^{1}H NMR δ: 1.71-1.78 (m, 4H, 2 x CH_2), 2.40-2.48 (m, 4H, 2 x CH_2CO), 2.63 (d, 1H, $J_{3',OH-2'}$ = 4.3 Hz, OH-2'), 3.01 (d, 1H, $J_{2,OH-3}$ = 4.3 Hz, OH-3), 3.37, 3.38 (s, 2 x 3H, 2 OMe), 3.79-3.90 (m, 4H, H-5, H-5', H-6_{ax} and H-$6'_{ax}$), 4.05-4.15 (m, 4H, H-2', H-3, H-4 and H-4'), 4.24-4.29 (m, 2H, H-6_{eq} and H-$6'_{eq}$), 4.66 (d, 1H, $J_{1,2}$ = 1.8 Hz, H-1), 4.71 (d, 1H, $J_{1',2'}$ = 1.2 Hz, H-1'), 5.22 (dd, 1H, $J_{1,2}$ = 1.8 Hz, $J_{2,3}$ = 3.7 Hz, H-2), 5.31 (dd, 1H, $J_{2',3'}$ = 3.7 Hz, $J_{3',4'}$ = 9.8 Hz, H-3'), 5.52, 5.60 (2s, 2H, 2 PhCH), 7.31-7.53 (m, 10H, PhCH and PhCH'); ^{13}C NMR δ: 23.7, 24.2 (2 CH_2), 33.5, 33.7 (2 CH_2CO), 55.0, 55.2 (OMe), 63.2, 63.8 (C-5 and C-5'), 67.1

(C-3), 68.7, 68.8 (C-6 and C-6'), 69.5 (C-2), 70.6 (C-3'), 71.9 (C-2), 76.0 (C-4'), 78.9 (C-4), 99.5 (C-1), 101.6 (C-1'), 101.8, 102.1 (PhCH), 126.16, 126.23, 128.2, 128.3, 129.0, 129.2 (Ar-C), 137.1, 137.2 (Ar-C_{ipso}), 172.2, 173.2 (COO).

Anal. calcd. for $C_{34}H_{42}O_{14}$: C 60.53, H 6.27; found C 60.16, H 6.36.

The fourth fraction was bis-(methyl 4,6-*O*-benzylidene-α-D-mannopyranoside)3,3'-hexanedioate (**93c**) a solid, mp 90-91 °C; R_F = 0.16 (ethyl acetate/hexane, 2 : 1); yield 0.051 g (18%); $[\alpha]_D^{24}$ +32.0 °(*c* 2.07, chloroform); ^{1}H NMR δ: 1.61-1.70 (b m, 4H, 2 x CH_2), 2.33-2.42 (b m, 4H, 2 x CH_2CO), 2.95 (d, $J_{2,OH-2}$ = 4.3 Hz, 2 x OH-2), 3.41 (s, 6H, 2 x OMe), 3.85 (t, 2H, $J_{5,6ax} = J_{6eq,6ax}$ = 10.4 Hz, 2 x H-6_{ax}), 3.93 (td, 2H, 4.11 (t, 2H, $J_{3,4} = J_{4,5}$ = 9.8 Hz, 2 x H-4), 4.14 (b m, 2H, 2 x H-2), 4.28 (dd, 2H, $J_{5,6ea}$ = 3.66 Hz, $J_{6eq,6ax}$ = 9.16 Hz, 2 x H-6_{eq}), 4.75 (d, 2H, $J_{1,2}$ = 1.8 Hz, 2 x H-1), 5.35 (dd, 2H, $J_{2,3}$ = 3.1 Hz, $J_{3,4}$ = 10.4 Hz, 2 x H-3), 5.52 (s, 2H, 2 x PhCH), 7.29-7.50 (m, 10H, 2 x Ar-H); ^{13}C NMR δ: 23.7 (2C, 2 x CH_2), 33.6 (2C, 2 x CH_2'), 55.0 (2C, 2 x OMe), 63.7 (2C, 2 x C-5), 68.8 (2C, 2 x C-6), 69.6 (2C, 2 x C-2), 70.8 (2C, 2 x C-3), 76.1 (2C, 2 x C-4), 101.6 (2C, 2 x C-1), 101.9 (2C, 2 x PhCH), 126.2, 128.2, 129.1 (Ar-C), 137.2 (2 x Ar-C_{ipso}), 172.7 (2C, 2 x COO). Despite repeated chromatography, this compound was always obtained contaminated by a small amount of a dibutyltin-containing impurity, as apparent from small signals ascribed to a butyl group in its ^{1}H NMR spectra (not listed).

2.4.14.2 In the presence of triethylamine

To the solution resulting from treatment of compound **28** (0.564 g, 2 mmol) with dibuthyltin oxide (0.795 g, 2.2 mmol) in toluene (20 mL) as in the general method was

added triethylamine (0.307 mL, 2.2 mmol) and the reaction mixture was stirred for 20 min at 25 °C, then cooled to 0 °C. A solution of adipoyl chloride (0121 mL, 0.83 mmol) in toluene (3 mL) was added dropwise. After 30 min, cooling was removed and the reaction mixture was stirred for 2 h. Standard workup yielded a solid residue that was separated as previously to give compound **93a** yield 0.305 g (54%), compound **93b**) yield 0.182 g (32%), and compound **93c**, yield 0.043 g (8%).

2.4.14.3 In the presence of diisopropylethylamine (DIPEA)

To the room temperature solution arising from the reaction of compound **28** (0.141 g, 0.5 mmol) and dibuthyltin oxide in toluene (15 mL) as in the general method was added freshly distilled diisopropylethylamine (0.96 mL, 0.55 mmol) and stirring was continued for 20 min. The reaction mixture was cooled to 0 °C and a solution of adipoyl chloride (0.034 mL, 0.23 mmol) in toluene (2 mL) was added dropwise. The resulting solution was stirred at room temperature until TLC (ethyl acetate\hexane, 2:1) showed no further change in reaction (1.5 h) . Standard workup yielded a colourless solid residue that was analysed by ^{1}H NMR spectroscopy. Integration indicated that the products formed were compounds **93a** (20%), **93b** (42%), and **93c** (38%).

2.4.14.4 In the presence of *N*-methylimidazole (NMI)

To the solution arising from treatment of compound **28** (1 mmol, 0.282 g) with dibutyltin oxide (0.274 g, 1.1 mmol) as in the general method was added *N*-

methylimidazole (0.876 mL, 10 mmol) and stirring was continued for 20 min before the solution was cooled to 0 °C. A solution of adipoyl chloride (61 μL, 0.415 mmol) in toluene (2 mL) was added dropwise to the cooled mixture that was then stirred at room temperature for 1.5 h. Standard workup gave a syrupy residue shown by TLC (ethyl acetate\hexane, 2:1) to contain only two products **93b** and **93c**. ^{1}H NMR integration indicated that the ratio of compounds **93b** to **93c** was 20 to 80%.

2.4.15 Bis-(methyl 4,6-*O*-benzylidene- -D-mannopyranoside) 3,3'-(4,4'-biphenyldisulfonate) (95)

The solution resulting from treatment of compound **28** (0.564 g, 2 mmol) with dibutyltin oxide (0.523 g, 2.1 mmol) as in the general method was concentrated to 15 mL and cooled to the room temperature. *N*-Methylimidazole (796 μL, 10 mmol) was added and the solution was stirred for 20 min at room temperature, then cooled to 0 °C. When a solution of 4,4'-biphenyldisulfonyl chloride (0.2985 g, 0.85 mmol) in toluene (2 mL) was added dropwise, the colour of the mixture turned yellowish immediately. The mixture was stirred at room temperature until TLC showed the starting material was consumed (14 h). Standard work up yielded a solid residue which was separated by dry column flash chromatography using a gradient of hexane to ethyl acetate as eluant. The first fraction was bis-(methyl 4,6-*O*-benzylidene- -D-mannopyranoside) 2,3'-(4,4'-biphenyldisulfonate) **96**, R_F = 0.72 (benzene / ethyl acetate, 1 : 1), a solid; mp 97-99 °C; yield 0.034 g (5 %); $[\ ]_D^{23}$ +6.8 ° (*c* 2.26, chloroform); ^{1}H NMR : 2.42 (d, 1H, $J_{3,OH-3}$ = 4.6 Hz, OH-3), 3.04 (d, 1H, $J_{2',OH-2'}$ = 4.0 Hz, OH-2'), 3.38, 3.41 (2 s, 6H, 2 x OMe), 3.76-3.91 (m, 5H, H-5,

H-5', H-6_{ax}, H-$6'_{ax}$ and H-4), 4.08 (t,1H, $J_{3',4'} = J_{4',5'} = 9.3$ Hz, H-4'), 4.15-4.32 (m, 3H, H-3, H-6_{eq}, H-$6'_{eq}$), 4.35 (m, 1H, H-2'), 4.76 (d, 1H, $J_{1',2'} = 1.5$ Hz, H-1'), 4.82 (dd, 1H, $J_{2',3'} = 3.5$, $J_{3',4'} = 10.1$ Hz, H-3'), 4.84 (dd, 1H, $J_{1,2} = 1.5$ Hz, $J_{2,3} = 3.7$ Hz, H-2), 4.93 (d, 1H, $J_{1,2} = 1.5$ Hz, H-1), 5.37 (s, 1H, PhCH'), 5.55 (s, 1H, PhCH), 7.13-7.19 (m, 5H, Ar-H), 7.33-7.37 (m, 5H, Ar-H), 7.43- 7.47 (m, 2H, Ar), 7.59 (XX' part of AA'XX' pattern, 2H, ArH' meta to SO_2), 7.89 (AA' part of AA'XX' pattern, 2H, $J_o = 6.7$ Hz, ArH ortho to SO_2), 8.08 (AA' part of AA'XX' pattern, 2H, $J_o = 6.7$ Hz, ArH' ortho to SO_2); ^{13}C NMR δ: 55.1, 55.4 (OMe), 63.3, 63.7 (C-5, C-5'), 66.8 (C-3), 68.6, 69.3 (C-6, C-6'), 70.6 (C-2'), 75.5 (C-4'), 78.4 (C-4), 78.9 (C-2), 79.3 (C-3'), 99.6 (C-1), 101.4 (C-1'), 101.9 (PhCH'), 102.2 (PhCH), 126.1, 126.2, 127.6, 128.0, 128.3, 128.9, 129.0, 129.3 (Ar-C, Ar'-C and Ar''-C), 135.8, 135.9, 136.8 (Ar-C_{ipso}), 140.0, 144.5 (Ar'-C_{ipso}).

The second fraction was the title compound **95**, $R_F = 0.55$ (benzene/ethyl acetate, 1: 1); a colourless solid; mp 141-143 °C; yield 0.667 g (93%); $[\alpha]_D^{23}$ +23.3° (*c* 1.83, chloroform); ^1H NMR δ: 3.40 (s, 6H, 2 OMe), 3.48 (b s, 2H, 2 OH-2), 3.70-3.86 (m, 4H, H-5 and H-6_{ax}), 4.08-4.25 (m, 4H, H-4 and H-6_{eq}), 4.39 (bs, 2H, 2 x H-2), 4.81 (d, 2H, $J_{1,2} = 1.8$ Hz, H-1), 4.84 (dd, $J_{2,3} = 3.1$ Hz, $J_{3,4} = 10.1$ Hz, H-3), 5.42 (s, 2H, PhCH), 7.08-7.27 (m, 14H, Ar-H and Ar-H'), 7.92 (d, 4H, $J_{ortho\text{-}Ar'\text{-}H} = 8.6$ Hz, ArH ortho to SO_2), ^{13}C NMR δ: 55.1 (2 x OMe), 63.7 (2 x C-5), 68.5 (2 x C-6), 70.4 (2 x C-2), 75.4 (2 x C-3), 79.2 (2 x C-4), 101.5 (2 x C-1), 101.8 (2 x CHPh), 126.1, 127.2, 127.9, 128.7, 129.0 (Ar-C), 135.6 (2 x Ar'-C_{ipso}), 136.8 (2 x Ar-C_{ipso}), 143.8 (2 x Ar'-C_{ipso}).

HRMS (ES) calcd. for $M+H^+$, $C_{40}H_{42}O_{16}S_2$: 843.1992; found: 843.2009.

Chapter 3

Regioselective mono-*O*-*p*-toluenesulfonylation and poly-*O*-*p*-toluenesulfonylation of OH-2 of β-cyclodextrin

3.1 Introduction

Cyclodextrins (CDs) are a group of naturally occurring cyclic oligosaccharides which are constructed from α (1→4)-linked glucopyranose units. The most common cyclodextrins contain 6, 7, or 8 of these units and are termed α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin, respectively (see Figure 3.1). Minor amounts of higher oligomers containing 9-13 glucose residue units have been isolated by chromatographic methods.[106] Difficulties in purification have limited investigation of their properties.[107]

CDs are of great interest for chemists because they have well defined hydrophobic cavities of various sizes and are water soluble. Enzymatic degradation of starch using cyclodextrin glycosyl transferases gives linear and cyclic maltooligosaccharides. The enzyme used in this process is an amylase from the bacterium *Bacillus macerans*.[108] This enzyme is not specific for ring size and isolation of a particular cyclodextrin is carried out by the addition of a specific precipitating reagent. These compounds were isolated for the first time by Villiers in 1891.[109] Because of their similarity to cellulose they were called "cellulosine" and sometimes these compounds are called cycloamyloses.

The most characteristic property of CDs is their ability to form inclusion compounds with a variety of compounds. In this process, various molecules of suitable sizes are trapped inside the hydrophobic cavity of CDs as guest molecules. Modification of the basic cyclodextrin structure to provide derivatives with ideal cavities either in size

or in chemical properties has also been of great interest. The including capability of CDs makes them ideal molecules to which catalytic functional groups can be attached in order to form enzyme mimic models.[110] As a result, CDs have been the subject of many detailed investigations in the last 2-3 decades in order to provide basic understanding of specific binding and catalysis of enzyme action.

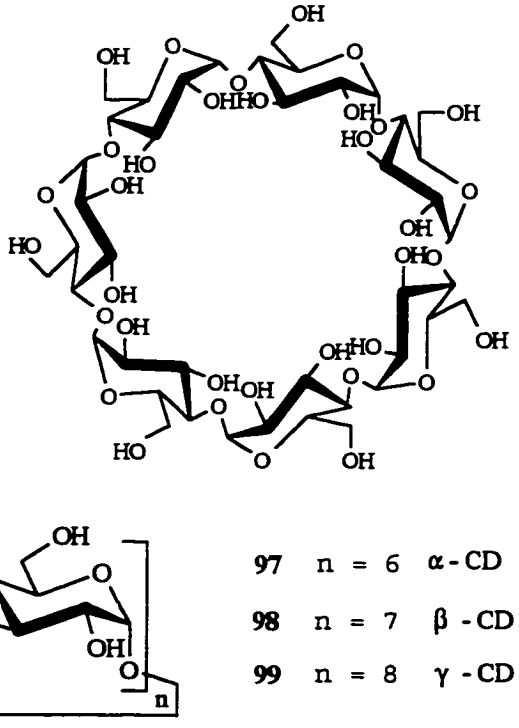


Figure 3.1. The structures of α-, β-, and γ- cyclodextrins

Regioselective substitution of hydroxyl groups is an important research area in cyclodextrin chemistry. Many researchers have attempted to change the structure and properties of these compounds by chemical modification of hydroxyl groups.[111] However,

due to their symmetry and high functionality, and problems associated with their chemo- and regioselective functionalization, mixtures of compounds are usually obtained, and the subsequent purification of the derivatives is still a highly challenging task. For this reason, designing methods for the regioselective substitution of CDs with new inclusion and catalytic properties is an important field for future work.

3.1.1. Structure of cyclodextrins

Structural studies of CDs in the solid state and solution have shown that the overall molecular shapes of CDs are truncated cones as shown in Figure 3.2. They have approximate C_n symmetry where n is the number of glucose units in the structure of CDs.[112,113] In these structures, the pyranose rings adopt the normal $^4C_1$ chair conformation of glucopyranose derivatives. In this conformation, the secondary hydroxyl groups at C-2 and C-3 of two adjacent glucose units form hydrogen bonds from OH-3 to OH-2' and vice versa. Consequently, circular belts of hydrogen bonding form through the secondary hydroxyls, giving CDs more rigid structures. This factor stabilizes the shape of CDs and influences their solubility. The hydrogen-bonding phenomena in CDs will be discussed in more detail later.

In cyclodextrins, with glucose units adopting the $^4C_1$ chair conformation, the primary and secondary hydroxyls lie on the exterior of the cavity and make the outside of cavity hydrophilic and water-soluble.[114] The hydrogens attached to C-2 and C-3 lie in the interior of the cone and make the inside of the cavity relatively hydrophobic.

In the cyclodextrin truncated cone shape, the primary hydroxyls lie at the narrow end and this end is called the primary face. The wider side, occupied by the secondary hydroxyls as shown in Figure 3.2, is called the secondary face. The number of

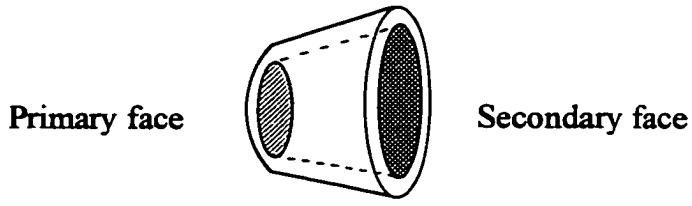


Figure 3.2 Functional schematic of cyclodextrins

glucopyranose residues determines the size of the cavity in CDs; the cavity diameters of α-, β-, and γ- CDs are 4.7, 6.0, and 7.5 Å, respectively, while the height of all CDs remain constant at 7.9 Å. Because of the large cavity in γ-CD, its inclusion properties are different. It can include two guest molecules whereas other CDs can only contain one.[106]

The vast majority of chemically modified CDs, like their parent CDs, have C_n molecular symmetry and adopt the $^4C_1$ chair conformations for their relatively rigid glucose residues. However, in some chemically modified CDs such as 3,6-anhydro-β-CDs **101**, the conformations all of the glucopyranose residues have been inverted to the $^1C_4$ chair conformation (Figure 3.3). The parent monosaccharide, 3,6-anhydro-D-glucopyranose, is known to adopt to a $^1C_4$ conformation.

3.1.2 Properties of cyclodextrins

CDs are water soluble compounds although not to the extent expected for glucose polymers. Their solubilities greatly increase at higher temperatures. The solubilities of α-, β-, and γ-CDs in water at 25 °C are 14.5, 1.85, and 23.2 g/100 mL, respectively. This relatively low water solubility of CDs, particularly for β-CD, is attributed to the aggregation of CDs in solution, in which they are bound together by a hydrogen bonding network.[115,116] Thermodynamic parameters have been measured which show that CDs have lower solubilities in comparison with normal saccharides because their enthalpies of solution are unfavorable, partially offset by more favorable entropies of solution. Among the CDs, α- and γ-CDs have very similar thermodynamic properties, while β-CD is less soluble than the others; both its enthalpy and entropy of solvation are less favorable.[117]

Cyclodextrins are stable under alkaline conditions. The hydroxyl groups at the secondary positions are weakly acidic (pK_a = 12.2) and in strongly alkaline solutions, CDs are present as the corresponding oxanions.[118] The anionic species have been used for the direct substitution of CDs with electrophiles. Under acidic conditions with pH higher than 3.5, and at temperatures lower than 60 °C, CDs are fairly stable. However, under more acidic conditions, they are susceptible to hydrolysis.[113]

Crystallographic studies of CDs and their derivatives indicated that the cavity of CDs crystallized from water is filled with water molecules.[119,120] Some of the water molecules are included in the cavity, others are integral parts of the crystal structure (crystal water). The number of water molecules in hydrated crystals of CDs increase with the size of the cavity. Depending on the conditions of crystallization, the same

cyclodextrin can give different crystalline forms, having different numbers of water molecules included in the cavity and outside. For instance, α-CD has been obtained in three crystalline forms. In one form, crystals contain six water molecules of which two are inside the cavity and four water molecules are outside. The two water molecules with van der Vaals radii of 3.8 Å occupy the cavity in the absence of a guest molecule. In contrast to the guest molecule (s), these water molecules are fixed in the cavity by means of hydrogen bonds to the primary hydroxyls and cause a distortion of one of the glucopyranose residue units. β-Cyclodextrin has been crystallized in two types of hydrated crystals containing 11 and 12 water molecules. The distribution of water molecules in β-CD is different from that in α-CD. In β-CD·$11H_2O$, some water molecules have been located in the cavity and were distributed in disorderd form. Removal of water molecules is difficult and elimination of water at high temperatures results in an amorphous structure.

When a compound less polar than water, but having a size and shape compatible with the CD's cavity, is added to an aqueous solution of these compounds, the water molecules in the cavity are displaced by that new guest molecule.[118] This kind of interaction (molecular encapsulation) occurs with a variety of molecules, even volatile and sensitive compounds. Guest molecules in the cavity can be protected from oxidation or stabilized as crystalline complexes. X-ray crystallography[121] and NMR spectroscopic studies have determined that the incorporated guest molecules occupy the centre of the cavity.[122]

The driving force ($-\Delta G$) which brings a hydrophobic guest molecule into the cavity of CD and drives water molecules out is a complex composite of different "elemental" forces such as conformational energy, solvation energy, hydrogen bonding, etc.[123,124,125] In particular, entropy plays an important role. The incorporation of a guest molecule causes a decrease in the number of degrees of freedom of the guest which results in a decrease in entropy. The loss of entropy in the system has to be compensated for by favorable interactions between host and guest molecules.[126] The stabilizing effect of complex formation results from the increase in entropy during the inclusion process when water molecules are expelled from the cavity. In addition, on entering the cavity from an aqueous solution, the guest molecule loses its hydration envelope, further increasing entropy. A change in conformation of the cyclodextrin during the replacement also plays a role.

3.1.3 Applications of cyclodextrins and their derivatives

Cyclodextrins and their chemically modified derivatives have found much use in different research and industrial areas.[127,128,129] These applications are widely spread from basic and applied science to enzymatic modeling. Applications of cyclodextrins in other fields such as catalysis of chemical reactions,[130] microencapsulation, chiral complexing agents,[131,132] molecular recognition,[133,134,135,136] rate acceleration,[137] and photochemical reactions,[138,139] and applications to the pharmaceutical[140] and food industry[141] have been explored. In addition, cyclodextrins have established their abilities as chromatographic separation media for HPLC,[142] GC,[143] electrophoresis,[144] and thin-layer chromatography.

Cyclodextrins have also been used as shift reagents in NMR spectroscopy.[145] Because of their highly selective complexation with molecules, in comparison with a single solvent or a traditional stationary phase, cyclodextrins have found a considerable number of important applications in the separation of enantiomers, diastereomers, structural isomers, geometric isomers, and in all current types of chromatography.[128]

Cyclodextrins can be compared in a number of ways to other well-known hosts like crown ethers. They have the ability to incorporate other molecules in their cavity both in solution as well as in the solid state. Secondly, their hydrophobic cavities exhibit size selectivity. Finally, they show satisfactory solubility in water and some aprotic solvents such as dimethylsulfoxide and *N,N*-dimethylformamide.

3.1.4 β-Cyclodextrin and their analogues containing sugar units other than glucose

Although considerable attention has been focussed on the applications of CDs, there were no methods available for the chemical synthesis of natural and unnatural analogues of these versatile compounds until a few years ago. The first total synthesis of naturally occurring α- and γ-cyclodextrins in very low yields after 21 steps, starting from maltose, was reported by Ogawa *et al.*[146,147] The synthesis of an unnatural cyclodextrin from mannose derivative **107** resulted in new tower-shaped (see Figure 3.3) molecules.[148,149]

Also, the synthesis of cyclooligosaccharides which contain unnatural β-(1→3)-linked glucopyranose units was reported by Collins and Ali.[150] Since only the D-series of cyclooligosaccharides had been synthesized, a method of synthesis of L-series compounds,

namely cyclo-L-rhamnohexaose (100), by the α-selective thermal glycosylation from an acyclic hexamer has been developed by Nishizawa *et al.*[151]

Beyond the inherent difficulties of glycosylation, chemical synthesis of these kinds of cyclodextrins which have flexibility and topological shape different from the naturally occurring cyclodextrins opened a new dimension for looking at their catalytic and inclusion properties.

It has been found that when one of the glucose units was replaced with any other sugar (see Figure 3.3), the shape of a cavity is changed. For instance, in manno-epoxy β-cyclodextrin **103**, the oxygen of the oxirane ring is directed to the outside of cavity center, and, in allo-epoxy β-cyclodextrin **104**, the oxygen is directed to the center of cavity. In $3^A,6^A$-anhydro-β-CD[152] **105**, the conformation of one sugar has been changed to $^1C_4$. The binding abilities of all of these deformed CDs, except that of **108** for methyl orange, are decreased in comparison to that of the parent β-CD.[153] The cyclic sugar **108** contains an interglucosyl 2,3'-anhydride bridge.

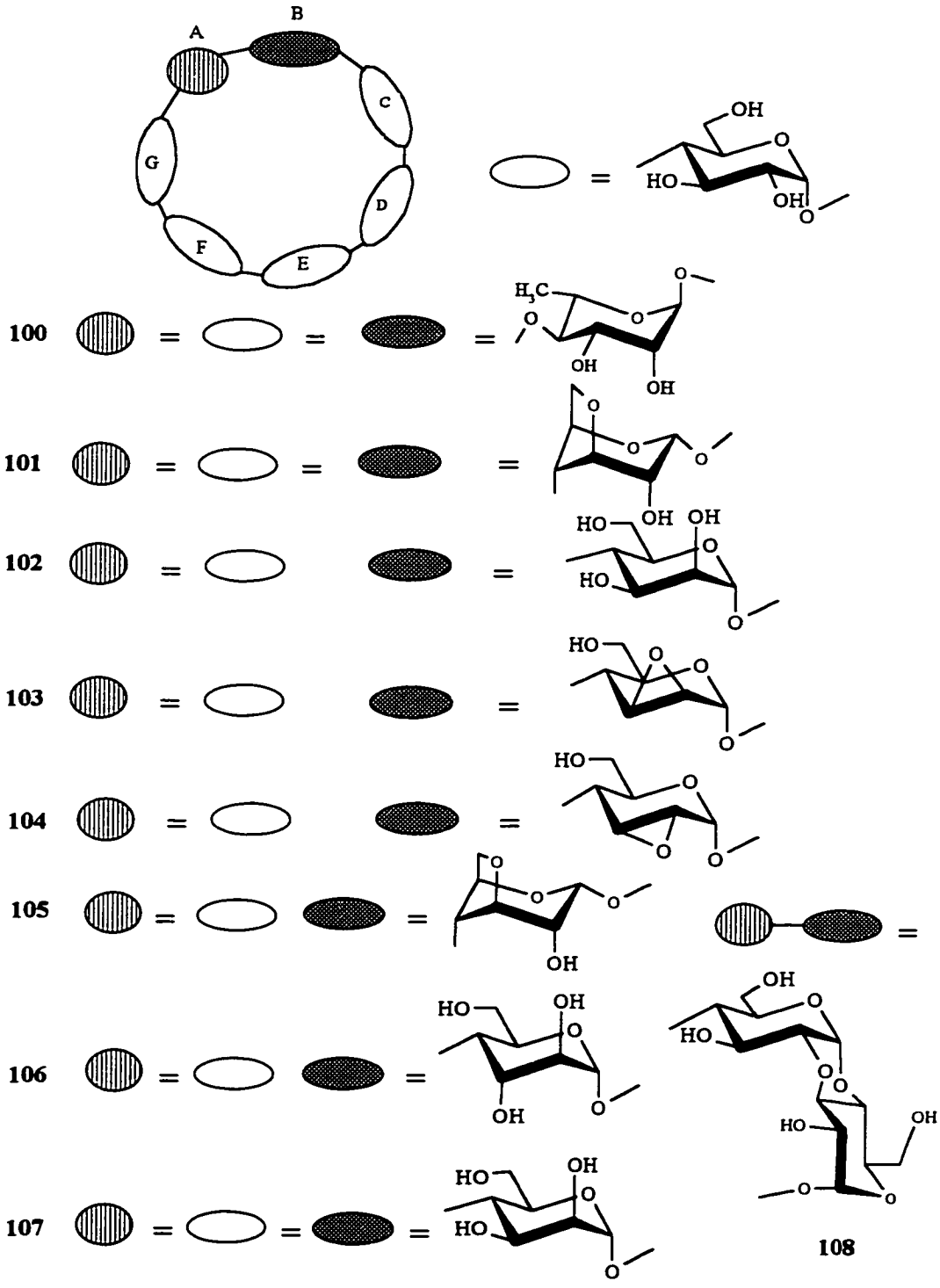


Figure 3.3 Structures of cyclodextrins in which one or more of the glucose units of β-cyclodextrin have been replaced or modified

3.1.5 Hydrogen bonding in cyclodextrins

X-ray and neutron diffraction studies on CDs by Betzel *et al.*[154] showed that a circular hydrogen bonding network containing several O–H···O–H units from cyclodextrin hydroxyls as well as waters of hydration exists for the crystalline structure of α-CD·6H_2O. In this molecule, all of the water molecules are well ordered. However in β-CD·11H_2O, the hydrogen bonding is very complex. The water molecules located in the cavity are distributed over eight positions and are not ordered.

In β-CD·11H_2O, 35 of the 53 hydrogen bonds are in the form of H···O-H and in the remaining 18 hydrogen bonds, the hydrogen atoms have been arranged in a form similar to the O–HH–O, with the sum of the occupancy factors for the two hydrogen positions being equal to one H. In this arrangement, the hydrogens are located between two oxygen atoms. The oxygen atoms are in the normal range of distance (2.7-3.0 Å) for O–H···O bonds. The two hydrogen positions are separated from each other by ~1 Å. To better explain, an equilibrium system such as

$$H\text{–}O(2)\cdots H\text{–}O(3) \rightleftharpoons O(2)\text{–}H\cdots O(3)\text{–}H$$

for this hydrogen bonding network has been suggested. The "flip flop" concept has been used to describe this kind of hydrogen bonding.[155,156] In the above hydrogen bonding system, only one of the two hydrogen positions between the two oxygen atoms is occupied at any time. When one hydrogen in the hydrogen bonding position flips, all other hydrogens in the hydrogen bonding chain in above arrangement automatically reverse to the other direction in a concerted manner.[154]

3.1.6 Nomenclature of cyclodextrin derivatives

Chemical Abstracts specifies the glucopyranose residues with capital letters in their name but this nomenclature system is not widely used. For instance, the name of per-*O*-toluenesulfonyl β-cyclodextrin in this nomenclature system is 2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},2^{G},3^{A},3^{B},3^{C}, 3^{D},3^{E},3^{F},3^{G},6^{A},6^{B},6^{C},6^{D},6^{E},6^{F},6^{G}-heneicosa-*O*-toluenesulfonyl-β-cyclodextrin.

A different but standard form of trivial nomenclature is used in most of the primary literature. In this method, the substituents are named in alphabetical order using the IUPAC prefixes. Substituents and the position of substitution on the glucose residue are specified in parentheses or brackets. A multiplying prefix indicates the number of the glucose residues. The substituent names precede the portion of the name in parentheses, with the name of the parent cyclodextrin following the closing parentheses. For instance, in this nomenclature system, a β-CD derivative in which all of the primary and secondary hydroxyls have been toluenesulfonylated is heptakis-(2,3,6-tri-*O*-*p*-toluenesulfonyl)-β-cyclodextrin. An example of a case where only one hydroxyl group in a cyclodextrin has been substituted but the position of substitution is not certain is mono [2(3)(6)-*O*-*p*-toluenesulfonyl]-β-cyclodextrin. An example of a cyclodextrin that is substituted on every primary oxygen using this trivial nomenclature is heptakis-(6-*O*-*p*-toluenesulfonyl)-β-cyclodextrin. If a cyclodextrin has been substituted more than once, the substituted positions and the substituted rings are shown in the nomenclature with capital letters. For instance, the name of a di-2-*O*-*p*-toluenesulfonylated-β-cyclodextrin with substitution in rings A and C will be 2^{A},2^{C}-di-*O*-*p*-toluenesulfonyl-β-cyclodextrin. If the substituted rings were not assigned, it will be called as 2^{A},2^{X}-di-*O*-*p*-toluenesulfonyl-β-cyclodextrin. The

name of a tri- or n-substituted β-CD will be similar to the di-substituted. For instance, $3^{A},3^{C},3^{D}$-tri-*O*-*p*-toluenesulfonyl-β-cyclodextrin means that the oxygen atoms at O-3 of rings A, C and D of β-cyclodextrin have been *p*-toluenesulfonylated.

3.1.7 Regioselective functionalization of cyclodextrins

In order to change the chemical properties, solubility and binding ability of CDs to achieve the more efficient and selective binding, chemical modification of CDs is essential. Despite the difficulties originating from high symmetry and high functionality of CDs, regioselective substitution of hydroxyls is possible. Of the three types of hydroxyl groups per glucose unit, the primary hydroxyls at C-6 are the most reactive, followed by the 2-OH's which are inherently more reactive than 3-OH's. So far a large number of modified CDs bearing specific functional groups have been synthesized. Most of these modifications have been done by persubstitution at the primary hydroxyls because of their greater reactivity. However, there are still many challenges in developing new methods for selective modification of CDs.

p-Toluenesulfonyl derivatives or other sulfonyl derivatives are important intermediates for further modification of CDs. Mono-*O*-*p*-toluenesulfonylation of primary or secondary hydroxyls breaks the symmetry of the cyclodextrin which makes the characterization of the product difficult. However, mono-*O*-*p*-toluenesulfonylation allows one to prepare the mono manno-epoxy or allo-epoxy cyclodextrins that are precursors for the introduction of nucleophilic substitutents. Functionalization of the secondary hydroxyls compared to the primary hydroxyls results in more complexity and in lower

yields. This is due to statistical and steric problems imposed by the large number of hydroxyl groups and the truncated cone structure.[157,158,159] Controlling the degree of functionalization of both primary and secondary hydroxyls is the most difficult task. However, despite all of these problems and the resulting low yields of isolated products, there are a few methods that allow regioselective substitution of either primary or secondary hydroxyl groups.

3.1.7.1 Regioselective functionalization of primary hydroxyls

It has been found that the most specific inclusion properties of CDs is on the secondary face. Consequently, the protection of the more reactive primary hydroxyls in order to do further modification on the secondary face is necessary. Two effective methods for the per-*O*-substitution of the primary CDs have been described in literature.[158] In the first method, all of primary and secondary hydroxyl groups are protected by acylation reactions. Then the primary positions are selectively deprotected. In the second stage, after substitution of primary alcohols, the acyl groups are selectively deprotected and the result is a 6-*O*-perfunctionalized cyclodextrin.

In the second approach, primary hydroxyls are directly functionalized in an appropriate solvent. *p*-Toluenesulfonyl chloride reacts mainly with primary hydroxyls in pyridine and per-6-*O*-*p*-toluenesulfonyl derivatives are stable to many reaction conditions and isolation processes.[160] Preparation of hexakis-(6-*O*-*p*-toluenesulfonyl)-α-cyclodextrin and hexakis-[(6-*O*-(2-naphthalenesulfonyl)]-α-cyclodextrin through tributylstannyl ether intermediates have been reported in 32% and 78% yield respectively.[161] Regioselective

silylation of the primary hydroxyls of α- and β-cyclodextrins with the *tert*-butyldimethylsilyl group has also been reported.[162,163] The protection of primary hydroxyls of β-CD with a *tert*-butyldimethylsilyl group allows for the purification and preparation of cyclodextrin derivatives on a large scale and improves the solubility. Heptakis-(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (**113**), which is easily prepared by the reaction of *tert*-butyldimethyl silyl chloride in pyridine, is less polar than the parent β-CD and, consequently, is soluble in a wide range of organic solvents and can be purified by chromatography on silica gel. The *tert*-butyldimethylsilyl group is stable under normal conditions. This approach to the protection of primary hydroxyls has found many applications in mono-*O*- and per-*O*-substitution of secondary hydroxyls.[164,165] Although polysulfonylated CDs are key intermediates in the preparation of selective cavities for α- and β-CDs, there is only one publication[166] on the poly-*p*-toluenesulfonylation of γ-CD. Difficulties due to the presence of more hydroxyl groups in γ-CD give rise to more complicated reaction mixtures containing under- and over-sulfonylated derivatives. In addition, the high price of γ-CD possibly has limited the investigation of this compound.

Perhalogenated CDs have been selectively synthesized by the displacement of 6-sulfonated CDs by halides[157,167] or direct halogenation of CDs with methanesulfonyl halide in DMF.[157,168] To increase the solubility of β-CD in water, which is limited to 1.85 g/100 mL at 25 °C, preparation of 6^-amino-6^-deoxy-β-cyclodextrin *via* the azido group has been reported.[169] A similar approach has been used to obtain the corresponding α-cyclodextrin derivative by Brown *et al.*[170]

In general, per-*O*-substitution at primary positions is easier than at secondary

positions and gives products in high yields. In contrast to per-*O*-substitution of primary hydroxyls, regioselective monofunctionalization is difficult and usually the resulting product is obtained in lower yield.

3.1.7.2. Regioselective functionalization of secondary hydroxyls

3.1.7.2.1. Regioselective per-2-*O*-substitution of secondary hydroxyls

The secondary face of modified CDs shows dramatically different reactivity from the primary face. In contrast to the chemical modification of primary hydroxyls which has been studied extensively, the modification of the secondary hydroxyls of CDs has been investigated less. Selective modification of secondary hydroxyls in the presence of the more active primary 6-OH's, has proven difficult to accomplish.[160,168] Also, the yield of regioselective functionalization reactions of secondary hydroxyls in CDs with literature procedures are low and the resulting products are difficult to characterize.

So far a few strategies have been developed for the per-*O*-substitution of secondary OH's in CDs but none are particularly high yielding. Rong and D' Souza[171] developed a method to selectively functionalize all of the hydroxyls groups at the C-2-positions of CDs. Their strategy was based on the deprotonation of 2-OH's with sodium hydride in DMF followed by reaction with *N*-methyl-4-chloromethyl-2-nitroaniline. The reaction gave one product, heptakis-[2-*O*-(4-methylamino-3-nitro)benzyl]-β-cyclodextrin isolated in 30% yield. The degree of functionalization was controlled by the amount of sodium hydride present in the reaction mixture.

In another approach, all of the primary hydroxyls were protected with *tert*-

butyldimethylsilyl groups initially. Treating this intermediate with *p*-toluenesulfonyl chloride in pyridine and catalyzing the reaction with 4-*N,N*-dimethylaminopyridine resulted in the per-*O*-substitution of all 2-OH groups to give **118** in 50% yield, the best yield reported[172] to the current time.

Stoddart and coworkers[173] reported the synthesis of heptakis-(2,6-di-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin in high yield from reaction of β-CD with *tert*-butyldimethylsilyl chloride in a mixture of DMF and pyridine in the presence of DMAP.

3.1.7.2.2 Regioselective mono-2-*O*-substitution of secondary hydroxyls

Regiospecific monofunctionalization of secondary hydroxyls (C-2-OH' s or C-3-OH' s) of CDs is a challenging task because controlling the degree of substitution is difficult. Different methods have been developed for the monosubstitution of secondary hydroxyls but the yields of isolated products have not been high. Reported yields for mono-2-*O*-substituted products by different approaches are in the range of 5-34%. For instance, the synthesis of mono 2-*O*-*p*-toluenesulfonyl-β-CD in 10% yield has been reported by Ueno and Breslow by reaction of β-CD with 3-nitrophenyltoluenesulfonate (*m*-NPTs) in a carbonate buffer solution of DMF.[174]

Fujita *et al.*[175] were able to isolate the 2-*O*-*p*-toluenesulfonyl-α-CD and 2-*O*-*p*-toluenesulfonyl γ-CD in 17 and 2% yields respectively by using an alkaline aqueous solution method.

As was explained in Chapter 1 of this thesis, dibutylstannylene acetal intermediates are widely used as a standard method to achieve regioselective monosubstitution of

carbohydrates in high yield.[3,6] Only one application has appeared[176] in the literature on using this method for the monosubstitution of CDs. In this approach, the CDs were treated by dibutyltin oxide in DMF at 100 °C to obtain the dibutylstannylene acetal. Then the activated CDs were treated with *p*-toluenesulfonyl chloride in the presence of triethylamine. The reactions resulted in the mono-2-*O*-*p*-toluenesulfonyl derivatives of α-, β- and γ-CDs in 30, 32, and 28% yields, respectively, and a mixture of di-2-*O*-*p*-toluenesulfonylated-β-derivatives in 5% yield.

Pregel and Buncel[164] also reported the mono-2-*O*-*p*-toluenesulfonyl derivatives of β-CD *via* heptakis-(6-O-*tert*-butyldimethylsilyl)-β-cyclodextrin. *p*-Toluenesulfonylation of heptakis-(6-O-*tert*-butyldimethylsilyl)-β-cyclodextrin with *N*-tosylimidazole and NaOMe in chloroform gave heptakis-(6-*O*-*tert*-butyldimethylsilyl)-2-*O*-*p*-toluenesulfonyl-β-cyclodextrin in 22% yield. This compound has also been reported by Venema *et al.*[177] in 34% yield by the deprotonation technique with heptakis-(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin and sodium hydride in refluxing THF. Also, a similar approach using sodium hydride in DMF has been reported.[178]

Toda and coworkers[179] synthesized mono-3-amino-3-deoxy-α-CD and its analogous histamine derivative. This monosubstituted compound was prepared from mono $2^A,3^A$-anhydro-α-CD. The precursor of the anhydro compound was the 2-*O*-*p*-toluenesulfonyl derivative, obtained by reaction of α-CD with *p*-toluenesulfonyl chloride in alkaline aqueous solution. The configuration of the substituted unit changed to $^1C_4$ as the configuration changed from gluco to altro during substitution with the amino group.

In another procedure, the C-3 hydroxyl of β-CD was selectively sulfonylated with

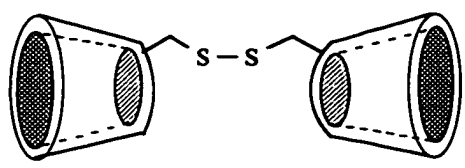
β-naphthalenesulfonyl chloride in aqueous CH_3CN in 18% yield.[180] In this reaction, a mixture of positional isomers of disulfonated products consisting mainly of $3^A,3^C$ and $3^A,3^D$ isomers were isolated in lower yield and characterized. The $3^A,3^C,3^E$-tri-*O*-(2-naphthalenesulfonylate) derivative has been prepared using the same procedure in aqueous acetonitrile at pH 12.[181]

In summary, examination of all of these methods for the functionalization of CDs showed the lack of a general and effective procedure. Therefore, designing new methods to give regioselectively substituted CDs in satisfactorily yields, particularly for β-CD, is necessary.

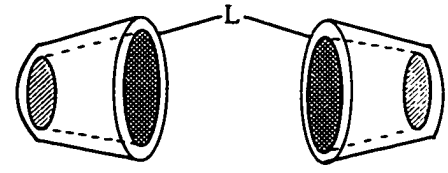
3.1.8 Dimeric cyclodextrins and their binding ability

To increase the selectivity and binding properties of CDs, numerous modified CDs have been synthesized and investigated as mimics of antibodies (binding) or enzymes (binding and catalysis).[182] It has been found that the binding constants of individual parent CDs ($K = 10^4\ M^{-1}$) with substrates are not as large as binding constants of antibodies ($K = 10^8$-$10^9\ M^{-1}$) and complexation is not as strong as enzymes.[183] Modification of CDs by attachment of complementary functional groups can increase their binding ability, but the modified CDs are not as strong as the natural receptors. Some workers have found that supplying another hydrophobic cavity centre in the structure of CDs has dramatically increased their binding constant with guest molecules.[184] Therefore, considerable attention has been paid to the synthesis of cyclodextrin dimers.[185,186] In dimeric cyclodextrins (see Figure 3.4), two CD unit are linked covalently to each other through one or two spacer

arms. According to the substitution position of the spacer, three type of CDs, "head to head", "head to tail", and "tail to tail" can be prepared.[187,188,189,190] The terms head and tail refer to the primary and secondary face (see Figure 3.3) of CDs, respectively. Dimeric CDs, which contain two hydrophobic cavity sites, can recognize and bind ditopic substrates very strongly.[191]



109



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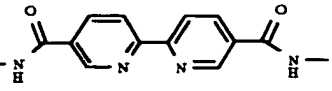

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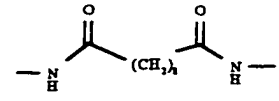
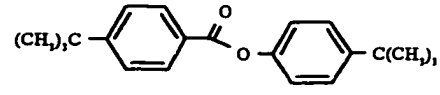


Figure 3. 4 The structures of "head to head" and "tail to tail' dimeric cyclodextrins



112

Binding constants of some of the dimeric CDs with appropriate substrates are comparable to binding constants of enzymes and antibodies. For instance, dimeric CD **109** with guest molecule **112** containing two *tert*-butyl groups showed a binding constant of 1 x 10^8 M^{-1}.[182] This strong binding constant was caused by involving both of the cavities in the binding of the guest molecule. To better understand the binding phenomena, syntheses of various dimeric CDs with spacers containing functional groups have been reported.[177,192,193]

In some of the dimeric CDs, such as **110** and **111**, a smaller binding constant has been observed because of cavity deformation. In fact, synthesis of a dimer through nucleophilic attack of the potential spacer on the epoxy ring of a mono-epoxy-CD results in inversion of the conformation of the sugar unit bearing the epoxide.[153]

Therefore, the development of new high yielding methods for the synthesis of dimeric CDs that have strong binding constants without inducing conformational change in Cds' shape is still necessary.

3.2 Results and discussion

As part of our interest in regioselective mono-*O*-substitution of carbohydrates with dibutylstannylene acetal intermediates, this methodology was used for the regioselective substitution of β-cyclodextrin. Based on the high regioselectivity in carbohydrates through dibutylstannylene acetals as explained in Chapter 1, it was expected that 2-*O*-substitution products would be obtained from dialkylstannylene acetals of cyclodextrins with good regioselectivity. Murakami *et al.*[176] used this method to obtain 2-*O*-*p*-toluenesulfonyl-β-cyclodextrin in 32% yield by the reaction of the dibutylstannylene acetal with *p*-toluenesulfonyl chloride in DMF at 100 °C. However, this publication attracted little attention. Despite several careful attempts to reproduce these results here, no *p*-toluenesulfonyl derivative of β-cyclodextrin was isolated under the reported conditions. Removal of water from the reaction environment is necessary to drive formation of the dibutylstannylene acetal to completion. One approach that has been used with starting

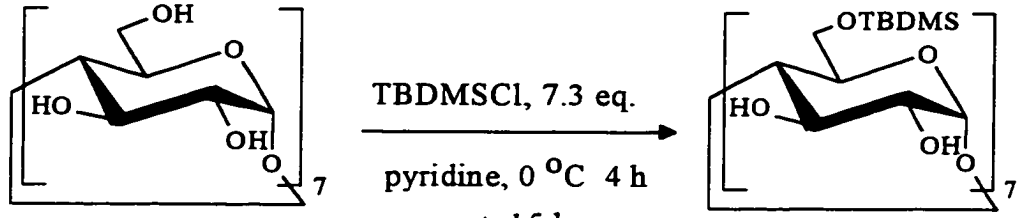
materials that have very little solubility in organic solvents is to azeotropically remove water from a DMF solution during dibutylstannylene acetal formation by codistillation[194] with cyclohexane. Even under these condition, the reactions failed to give the desired product.

It has now been found that heptakis-(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin forms dibutylstannylene acetals with a wide range of stoichiometries of dibutyltin oxide, all of which are soluble in organic solvents. These soluble dibutylstannylene derivatives have been found to react in much the same way that comparable monosaccharide derivatives react.

3.2.1 Synthesis of heptakis-(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (113)

Heptakis-(6-*O*-tert-butyldimethylsilyl)-β-cyclodextrin was prepared in improved yield by a slight modification of the Fugedi method.[163] After several repetitions of the procedure, the mole ratio of β-cyclodextrin to *tert*-butyldimethylsilyl chloride and also the workup procedure were slightly changed. In the conditions developed here, dry β-cyclodextrin was treated with 7.3 equivalents of *tert*-butyldimethylsilyl chloride at 0 °C in pyridine for 4 h, then at room temperature for 15 h. The resulting solution was vigorously stirred in water then the precipitate was washed with water to give desired compound **113** in 89% yield after column chromatography on silica gel. Reducing the amount of *tert*-butyldimethylsilyl chloride from 7.7 equivalents in the original method[163] to the 7.3 equivalents used here reduced the over-silylated products to a negligible amount. NMR spectra of the product were mostly in accord with previous reports[163,164] but some new

features will be discussed below. Because of the symmetric structure of heptakis-(6-*O*-



97 **113** 89%

Figure 3.5 Synthesis of heptakis-(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin

tert-butyldimethylsilyl)-β-cyclodextrin (**113**), its ^{1}H NMR spectrum showed one set of carbohydrate signals that could be assigned easily. In this spectrum, two singlets due to hydroxyl protons are observed at 6.73 and 5.25 ppm in chloroform-*d*. The COSY spectrum did not show any correlation between hydroxyl signals and H-2 and H-3. Therefore, assigning these signals to OH-2 or OH-3 was not possible using normal NMR experiments. An expansion of part of the ^{1}H NMR spectrum of **113** is shown in Figure 3.7(a). The acidity of the secondary hydroxyls (pK_a = 12.2)[195] may cause the marked unusual deshielding of these hydroxyl signals. Presumably, the hydrogen bonding belt across the seven member glucopyranose rings between C-2-OH of one ring and C-3-OH of neighbouring ring is maintained after silylation of the primary hydroxyls.[154] These two sharp singlets do not show any significant broadening over temperature ranges from +50 ° C to -60 °C in chloroform-*d* and at -90 °C in dichloromethane-d_2. They also remained as two singlets in toluene-d_8 from 20 ° to 110 °C.

3.2.2 Regioselective mono-2-*O*-*p*-toluenesulfonylation of heptakis-(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin

Heptakis-(6-*O*-*tert*-butyldimethylsilyl)-mono-2-*O*-toluenesulfonyl-β-cyclodextrin was prepared through its dibutylstannylene acetal intermediate. Carefully dried heptakis-(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin was refluxed with 1.85 equivalents of dibutyltin oxide to give a homogeneous 2,3-*O*-dibutylstannylene acetal solution. On reaction of the dibuthylstannylene acetal with 1.85 equivalents of triethylamine and *p*-toluenesulfonyl chloride, the 2-*O*-*p*-toluenesulfonyl derivative **114** was obtained as a single product in 59% yield (70% yield based on **113** consumed). After column chromatography on silica gel, some starting material was also recovered (16% yield). The complex ^{1}H and ^{13}C NMR spectra of this compound have been discussed by Pregel and Buncel[164] but some new features were observed here.

Introduction of one substituent destroys the rotational symmetry of the β-cyclodextrin molecule (see Figure 3.6). Despite the considerable complexity of the NMR spectra of compound **114** (see Figure 3.7-c), its structure was established by analyzing the ^{1}H and ^{13}C NMR spectra plus results from TOCSY, HMQC and other 2D NMR experiments (see Figures 3.8 and 3.9). The ^{1}H NMR spectrum contained patterns from

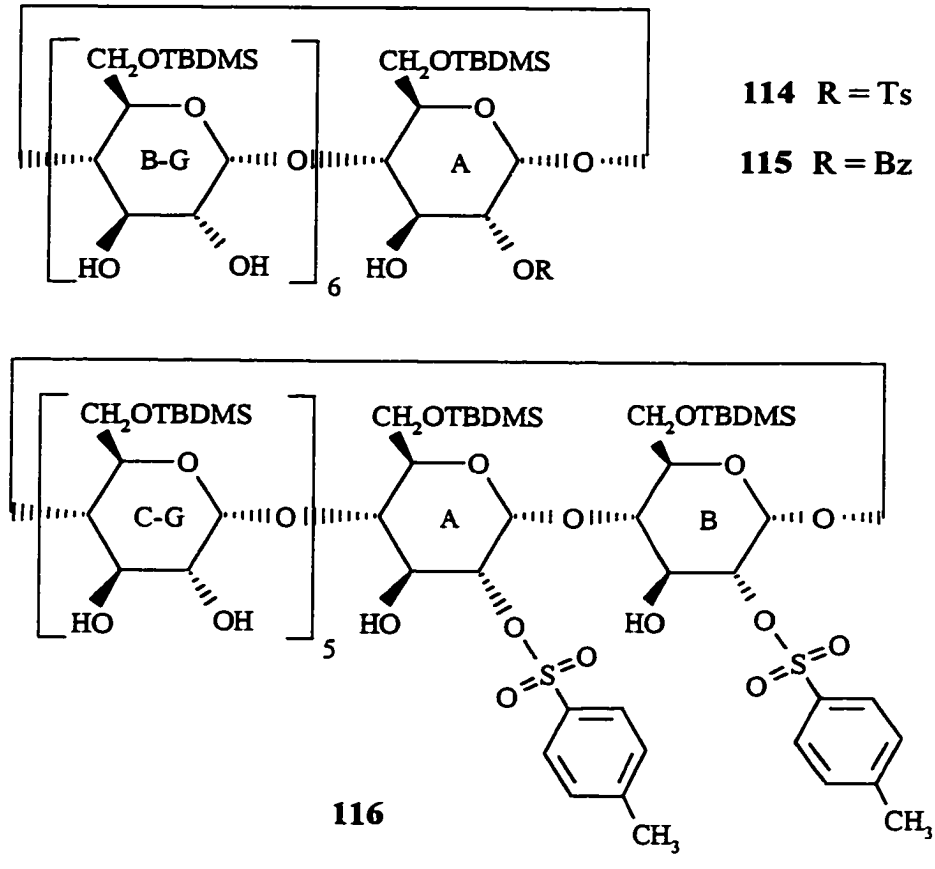


Figure 3. 6 Structures of heptakis-(6-*O*-*tert*-butyldimethylsilyl)- mono- and di-2-*O*-*p*-toluenesulfonyl- β-cyclodextrins

two glucopyranose rings that were distinguishable from those of the other rings. The glucopyranose ring on which the substituent is located will be termed ring A. The most deshielded doublet, at 5.29 ppm, was that of H-1A. The most shielded doublet of those assigned to H-1s, at 4.48 ppm, comes from H-1 in a second ring termed ring X (H-1X). The position of the second ring (X) relative to the ring A is still unclear. The remaining H-

1's appear as a broad singlet at 4.87 ppm. Using COSY and TOCSY experiments, by correlation from the defined signal at 5.29 ppm for H-1A, other peaks for the H-2A, H-3A and H-4A were assigned (see Figure 3.8). In the same way, signals related to H-1, H-2 and H-3 in ring X were assigned. These signals in the second ring (X) are shielded by about 0.4, 0.3 and 0.3 ppm, respectively, in comparison with the positions of the signals of the comparable protons from the five rings that have not been affected by substitution. The number of *p*-toluenesulfonyl groups introduced can be easily determined from the integration of the aromatic and methyl protons of the *p*-toluenesulfonyl group against that of the other signals in the molecule. In mono-2-*O*-*p*-toluenesulfonyl-β-CD, only one *p*-toluenesulfonyl ring gives resonances in the aromatic region at 7.29 and 7.85 ppm as an AA'XX' pattern. The *p*-toluenesulfonyl methyl appears at a normal shift of 2.39 ppm.

In a dry sample of heptakis(6-*O*-*tert*-butyldimethylsilyl)-2-*O*-p-toluenesulfonyl-β-CD, an interesting feature was observed in the ^{1}H NMR spectrum. Thirteen individual hydroxyl signals appear as singlets, six of them between 5.88 and 6.29 ppm, close to the chemical shift of the most deshielded hydroxyl signal of heptakis-(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (**113**). The other seven hydroxyls exhibit resonances between 4.61 and 5.22 ppm. Due to exchange with atmospheric moisture on standing,

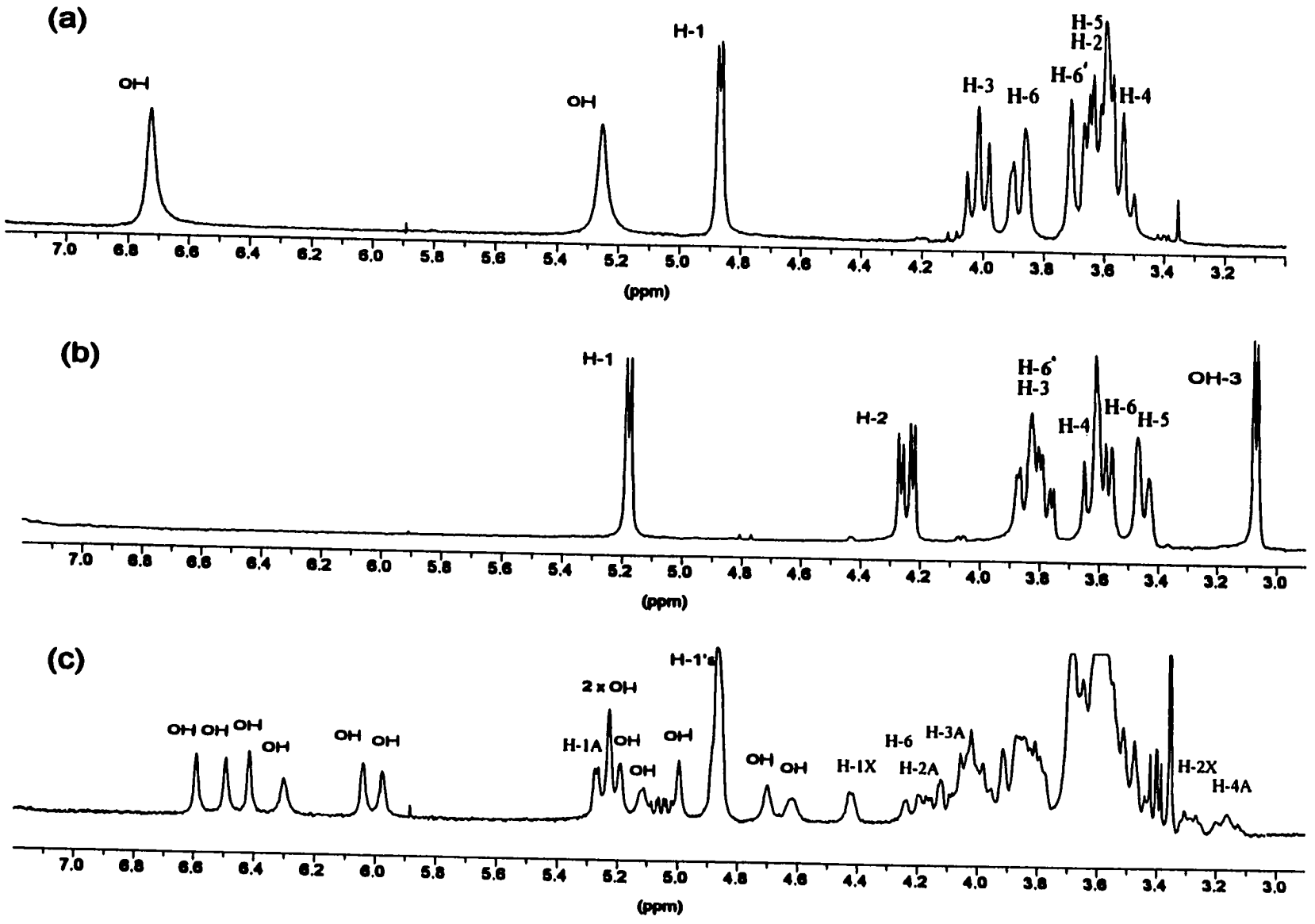


Figure 3.7 Expansion of part of the ^{1}H NMR spectra of compounds **113** (a), **118** (b) and **114** (c) in chloroform-*d*.

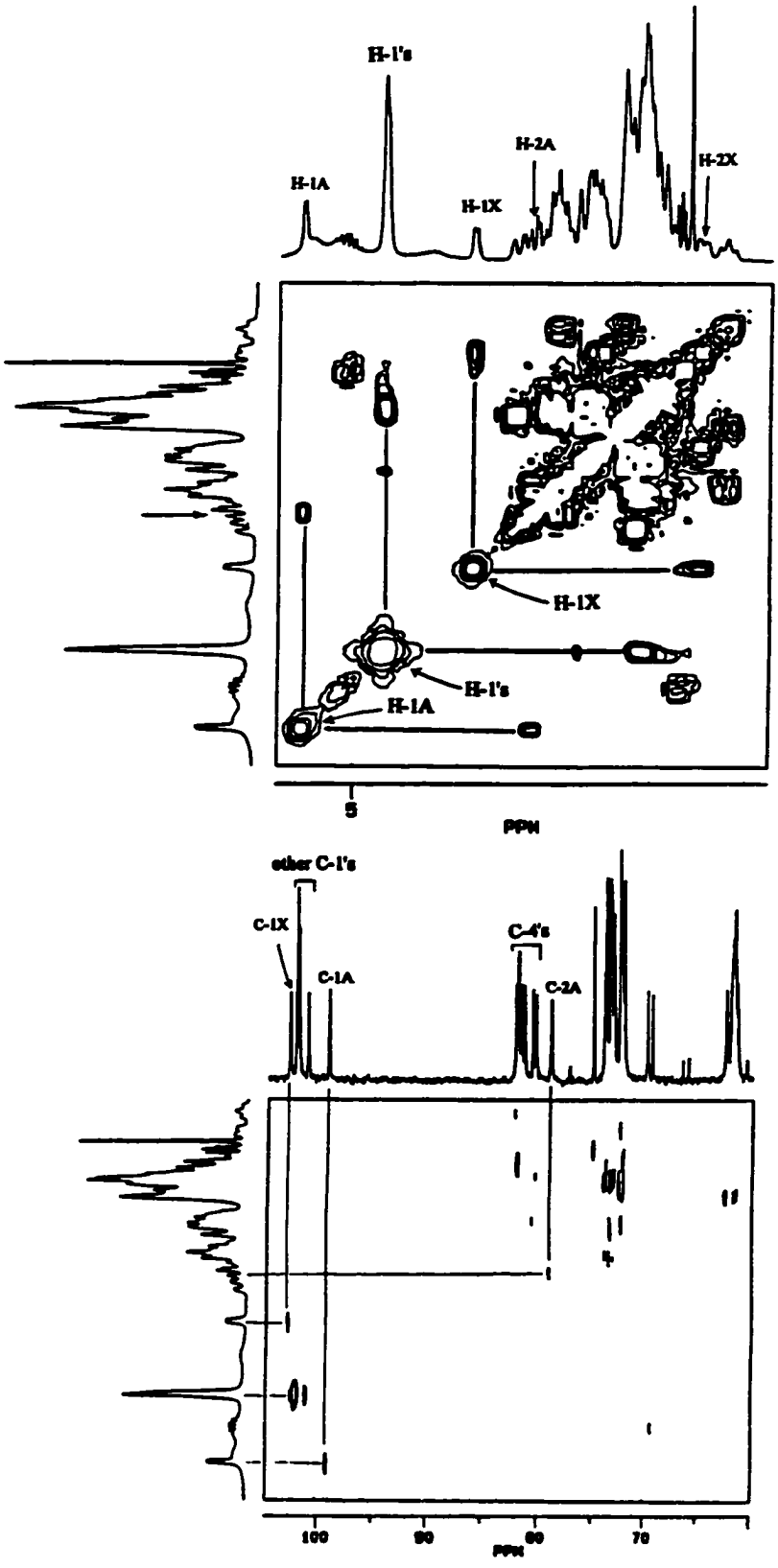


Figure 3.8 Parts of COSY and HETCOR spectra of compound 114 in chloroform-*d*.

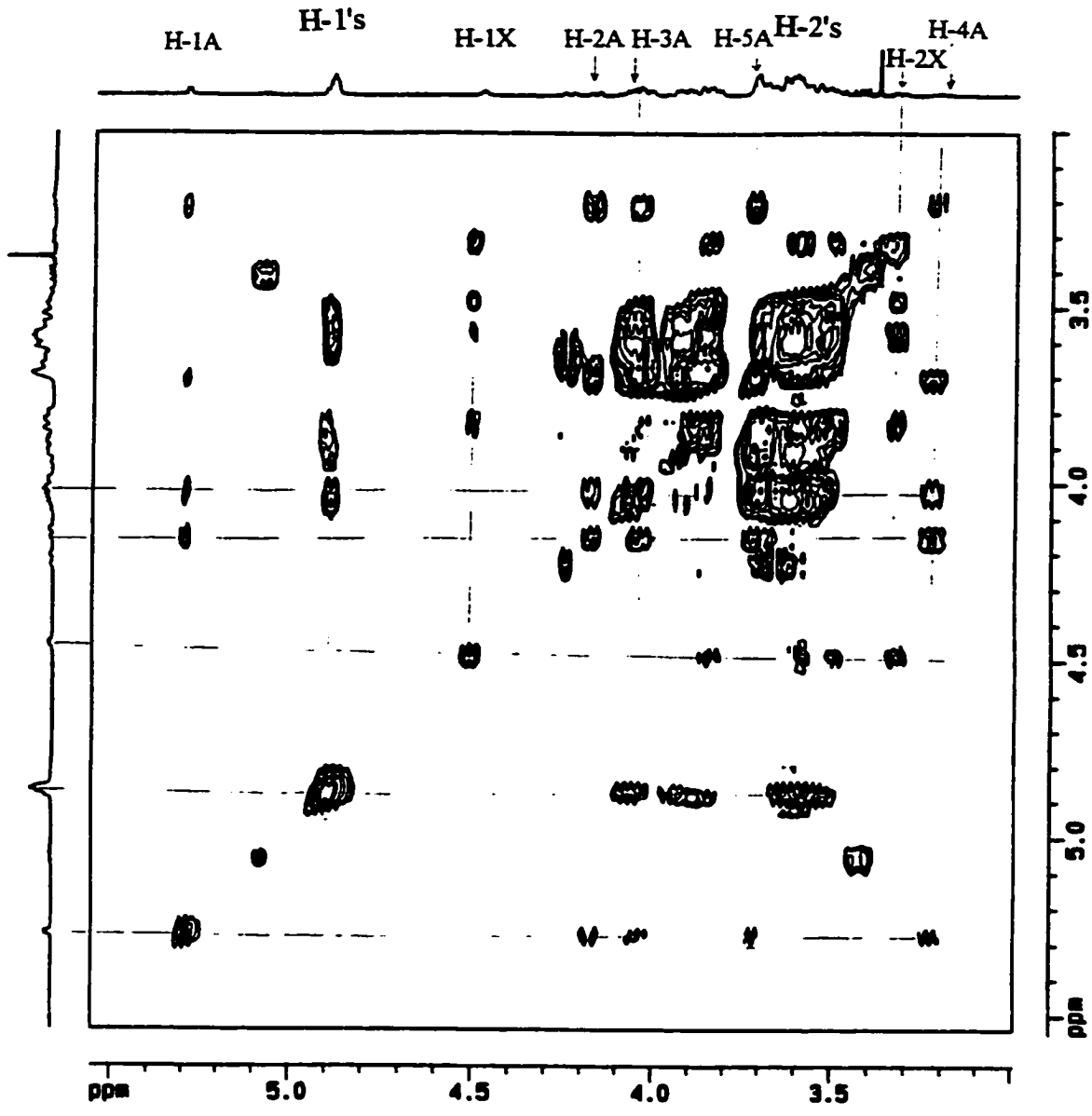


Figure 3.9 Expansion of part of the 400.14 MHz TOCSY spectrum of **114** in chloroform-*d*.

the hydroxyl signals gradually broadened and finally disappeared to give a spectrum identical to that reported earlier.[164]

Another *p*-toluenesulfonylation experiment was performed as previously except that 2.8 equivalents of dibutyltin oxide, triethylamine and *p*-toluenesulfonyl chloride and a

longer reaction time were used. This yielded heptakis-(6-*O*-*tert*-butyldimethylsilyl)-di-2-*O*-*p*-toluenesulfonyl-β-cyclodextrin (**116**) as a mixture of the three possible isomers in 32% yield and the mono-2-*O*-*p*-toluenesulfonyl derivative **114** in 40% yield. Di-2-*O*-*p*-toluenesulfonyl derivatives move faster than mono-*O*-substituted derivatives on TLC. From integration of *p*-toluenesulfonyl aromatic hydrogens and *p*-toluenesulfonyl methyl hydrogens against silyl groups, it was determined that this compound is a di-2-*O*-*p*-toluenesulfonyl derivative. If the capital letters of A, B, C, D, E, F and G are used to name the seven glucopyranose rings in β-cyclodextrin, three positional isomers namely, AB, AC, and AD, are possible. From comparison of the ^{13}C NMR spectra of mono-2-*O*-*p*-toluenesulfonylated and di-2-*O*-*p*-toluenesulfonylated compounds, it is clear that the fraction containing the di-2-*O*-*p*-toluenesulfonylated compounds has three sets of signals in regions in which C-1, C-2 and C-3 absorb; in particular, six signals are observed in the region of C-1 at about 99 ppm, where C-1 signals in 2-*O*-*p*-toluenesulfonyl substituted rings appear, consistent with a mixture of three possible isomers. For instance, in the ^{13}C NMR spectrum of the mono-2-*O*-*p*-toluenesulfonyl derivative (**114**), C-1A has a resonance at 99.2 ppm, whereas the other C-1 signals all appear at chemical shifts >101 ppm. All three di-2-*O*-*p*-toluenesulfonylated isomers have identical R_f values and separation of these regioisomers using normal chromatographic methods was not possible.

To try to obtain different degrees of substitution, a series of reaction conditions have been investigated using triethylamine and 4-*N*,*N*-dimethylaminopyridine (DMAP) as added nucleophiles. Treatment of the above-mentioned dibutylstannylene acetal solution with 6.4 equivalents of *p*-toluenesulfonyl chloride in the presence of 6.4 equivalents of

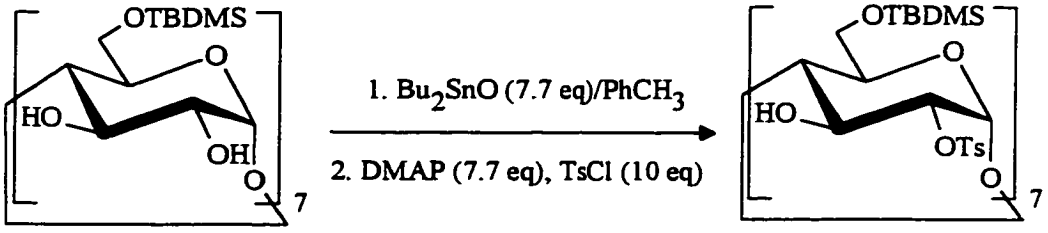
triethylamine resulted in a mixture of compounds. Chromatography on silica gel yielded heptakis-(*6-O-tert*-butyldimethylsilyl)-tri-2-*O*-*p*-toluenesulfonyl-β-cyclodextrin (**117**), and di-*p*-toluenesulfonylated and mono-*p*-toluenesulfonylated derivatives in 19%, 22% and 17% yields, respectively.

The reaction was repeated as previously except DMAP was used instead of triethylamine. TLC of the reaction mixture and after workup suggested that at least two additional products had been formed than in the previous reaction. The two new products moved faster on TLC than all of the previously isolated products. Presumably, the compound that has a larger R_f value than the tri-*O*-substituted product is the tetra-*O*-*p*-toluenesulfonyl derivative. Several attempts to isolate this compound using column chromatography with different solvent systems failed to give pure tetra-*O*-substituted product. From these results, it can be concluded that under the reaction conditions where the reaction is catalyzed by triethylamine, the dibutylstannylene acetal derived from **114** with *p*-toluenesulfonyl chloride did not proceed beyond the tri-substituted stage. However, reactions catalyzed with DMAP produced at least two compounds other than the tri-*O*-substituted derivative which moved faster on TLC and presumably had higher degrees of substitution.

3.2.3 Regioselective per-2-*O*-*p*-toluensulfonylation of heptakis-(6-*O*-*tert*-butyldimethylsilyl-β-cyclodextrin

To prepare the per-*2-O-p*-toluenesulfonylated derivative **118**, the reaction of compound **113** with 7.7 equivalents of dibutyltin oxide was performed. The

dibutylstannylene acetal solution was directly treated with 7.7 equivalents of DMAP and an excess of *p*-toluenesulfonyl chloride (10 eq) to give heptakis-(6-*O*-*tert*-



113 **118** 62%

Figure 3. 10 Synthesis of heptakis-(6-*O*-*tert*-butyldimethylsilyl-2-*O*-*p*-toluenesulfonyl)-β-cyclodextrin (**118**)

butyldimethylsilyl-2-*O*- *p*-toluenesulfonyl)-β-cyclodextrin (**118**) as the major product in 62% yield after column chromatography on silica gel. The per-2-*O*-*p*-toluenesulfonylated derivative **118** is a symmetric product with seven-fold rotational symmetry and is easily characterized using ^{1}H and ^{13}C NMR spectroscopy. The position of *O*-*p*-toluenesulfonylation was expected to be at O-2. This expectation was confirmed by the ^{1}H NMR spectrum (see Figure 3.7 (b)) in which H-2 was a doublet of doublets at 3.61 ppm, deshielded by 0.56 ppm from its position in the spectrum of the starting material **113**. The aromatic *p*-toluenesulfonyl protons appear as an AA'XX' pattern at 7.24 and 7.72 ppm. The remaining OH-3 hydroxyl protons appear as a sharp doublet at 3.07 ppm with a coupling constant of 3.4 Hz, noticed previously.[165] Since the hydroxyl signals in the

starting compound **113** appeared at 5.25 and 6.73 ppm, this chemical shift is the result of a very marked shielding effect. In the ^{13}C NMR spectrum, the signals of C-2 appeared at 79.9 ppm, deshielded by 6.3 ppm from its original position in the spectrum of compound **113**. These facts all demonstrate that compound **113** has been per-*O*-*p*-toluenesulfonylated at O-2.

3.2.4 Regioselective mono-2-*O*-benzoylation of heptakis-(6-*O*-*t*ert-butyldimethylsilyl)-β-cyclodextrin

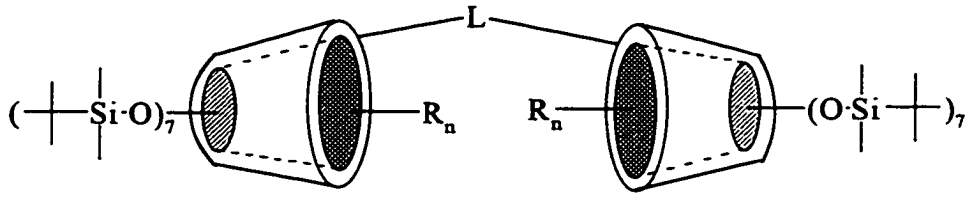
2-*O*-Benzoyl-heptakis-(6-*O*-*t*ert-butyldimethylsilyl)-β-cyclodextrin was prepared by refluxing compound **113** with 1.25 equivalents of dibutyltin oxide under azeotropic conditions to give an uncharacterized mixture of 2,3-*O*-dibutylstannylene acetals which was treated with equimolar triethylamine and distilled benzoyl chloride. TLC of the reaction mixture suggested the formation of various degrees of benzoylated products with different R_f's, of which only the most polar product was isolated by column chromatography on silica gel in 25% yield. From the ^1H and ^{13}C NMR spectra and COSY, J-MOD and HETCOR experiments, the structure of the isolated product was assigned as 2-*O*-*p*-benzoyl-heptakis-(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (**115**). It has been shown that acyl groups can rearrange under stannylene acetal conditions.[58] The lower yield of the mono-2-*O*-benzoyl derivative in comparison with mono-2-*O*-*p*-toluenesulfonyl product could be caused by migration of the benzoyl group during reaction and /or during isolation. A freshly isolated sample of mono-2-*O*-benzoylated compound from the column showed a ^1H NMR spectral pattern similar to that of the mono-2-*O*-*p*-toluenesulfonyl

derivative, particularly for the hydroxyl signals. Two sets of broad singlets appeared due to hydroxyl protons. The first set of hydroxyl signals was present between 6.2 to 6.6 ppm and the second set of hydroxyl signals was spread between 4.45 to 5.5 ppm. After 10 h of exchange with atmospheric moisture, all of the hydroxyl signals had disappeared. In the ^{1}H NMR spectrum of **115**, three types of H-1 signals and two distinct rings, A and X, which contained approximately isolated signals are observed. The signals of H-1A and H-1X appear as doublets at 5.37 and 4.94 ppm with J values of 2.8 Hz and 3.8 Hz, respectively. The remaining H-1's are present as a broad doublet at 4.87 ppm. The signal of H-1X for this compound, in contrast to that from mono-2-*O*-*p*-toluenesulfonyl derivative, has been deshielded more than the signals of the remaining H-1's. In the ^{13}C NMR spectrum, C-2A which bears the benzoate group, had a resonance at 74.3 ppm, deshielded by 0.7 ppm in comparison with the remaining C-2 signals. The signal of C-1A was shielded by 4.3 ppm, and appears at 97.7 ppm, which is consistent with benzoylation at O-2.

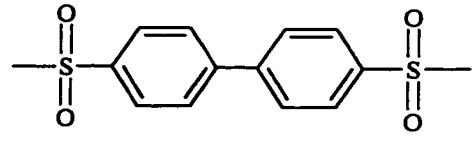
3.2.5 Synthesis of dimeric β-cyclodextrins

As explained in Section 3.1.8, dimeric cyclodextrins have shown very strong binding properties with substrates.[191] The direct attachment of cyclodextrins through electrophilic spacers results in low yields of dimeric CDs.[196,197] On the other hand, nucleophilic attack by spacers in S_N2 reactions on electrophilic cyclodextrin derivatives changes the configuration and conformation of the attached sugar unit and causes deformation of the cavity.[187,177] As a result of this deformation, the binding ability of

dimeric CDs is decreased.[153] We decided to try to synthesize the dimeric CDs using dibutylstannylene acetal intermediates. The resulting dimeric CD from this procedure would not have an altered conformation. With this in mind, synthesis of dimeric cyclodextrins were attempted. Heptakis-(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin was treated with dibutyltin oxide in order to make the dibutylstannylene acetal intermediate. One equivalent of triethylamine and the difunctional linker 4,4'-biphenyldisulfonyl chloride were added. The resulting product was isolated in 19% yield by column chromatography on silica gel and it was tentatively assigned as the dimeric cyclodextrin **119**. The compound was only partially characterized because the NMR spectra of this compound



119 n = 13 R = OH L =



120 n = 13 R = AcO L = 4,4'-diphenyldisulfonyl

121 n = 13 R = OH L =

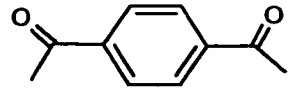


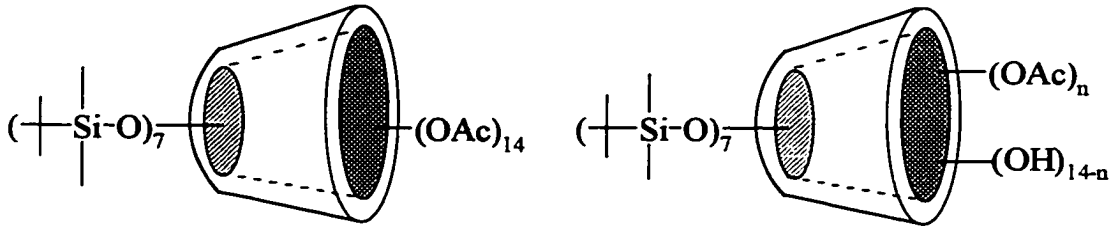
Figure 3.11 The structures of dimeric cyclodextrins

were too broadened to make complete assignments of its signals. The solubility behavior of the compound in organic solvents was completely different from that of all of the heptakis-(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin derivatives which have been isolated

previously in this laboratory. In contrast to the other *O-p*-toluenesulfonylated compounds, the dimeric CD was only soluble in chloroform with difficulty. Attempts at recording the ^{1}H NMR spectrum of compound **119** in other solvents, such as DMSO-d_6, and also at various temperatures, did not improve the spectral resolution.

In order to break possible intermolecular hydrogen-bonding networks of this molecule and with the aim of improving the poor resolution of the ^{1}H NMR spectral signals, compound **119** was acetylated. The acetylation reaction was performed in pyridine and an excess of acetic anhydride. However, the resulting acetylated compound **120** gave a ^{1}H NMR spectrum even more complicated than the nonacetylated compound **119**. Broadening of NMR spectra of this type of dimeric cyclodextrins have been reported in the literature.[177,187] In order to avoid this problem, other types of dimeric cyclodextrins, using different spacer reagent such as terephthaloyl chloride and adipoyl chloride, were synthesized, but the isolated product(s) exhibited the same broadening as before.

In order to understand the cause of complexity and broadening in the acetylated dimeric CD derivative, it was decided to synthesize the per-*O*-acetyl-heptakis-(*6-O-tert*-butyldimethylsilyl)-β-cyclodextrin (**122**). Reaction of a solution of compound **113** with equimolar 4-*N,N*-dimethylaminopyridine and an excess of acetic anhydride in pyridine gave one product. The crude product was purified by means of column chromatography on silica gel to give the peracetylated derivative **122** in 84% yield. This compound is symmetric and was characterized with ^{1}H and ^{13}C NMR and COSY, J-MOD and HETCOR experiments. In the ^{1}H NMR spectrum, the most downfield signal at 5.32 ppm is a triplet, deshielded by 1.31



122 84% **123** n = 12 78%

Figure 3.12 Schematic structures of different *O*-acetyl derivatives of heptakis-(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin

ppm from the position in the parent cyclodextrin **113**. This signal was assigned to the H-3's. A doublet of doublets at 4.67 ppm that had been shifted 1.1 ppm, was assigned to the H-2's. From correlation of these assigned signals in the COSY spectrum, other peaks were assigned for **122**. Integration of the acetyl methyl signals and the most deshielded signals is in agreement with complete acetylation O-2 and O-3 of compound **122**. A comparison of peracetylated cyclodextrin derivative with acetylated dimeric cyclodextrin suggested that the broadening problem in the NMR spectra of dimeric CDs is possibly related to the conformations of the compound. An understanding of the conformation and its effect on broadening in dimeric CDs requires further work.

Acetylation of compound **113** in pyridine without adding catalyst (DMAP) did not give the per-*O*-acetyl product **122** even with a large excess of acetic anhydride. This reaction gave one major plus two minor products that were not isolated. The faster moving major product, $R_f = 0.63$ (ethyl acetate), was isolated (74% yield) and its ^1H NMR spectrum indicated that it was a partially acetylated derivative **123**. This was confirmed

when treatment of compound **123** in pyridine with acetic anhydride in the presence of DMAP gave **122**. Preparation of the partially acetylated compound was reproducible; in another experiment, a very similar yield was obtained. The ^{1}H NMR spectrum of **123** did not display the C_7 symmetry of **122**. In order to determine the number of free hydroxyls in the partially acetylated compound it was treated with trichloromethyl isocyanate. The ^{1}H NMR spectrum of the resulting carbamate showed two broad signals at 6.81 and 7.03 ppm possibly indicating the possibility of existence of two free hydroxyl groups in the structure of compound **123**. However, if two free hydroxyls are present, three isomers are possible, assuming that only one of OH-2 or OH-3 is not acetylated. The appearance of the H-1 region in the 400.14 MHz ^{1}H NMR spectrum suggests that a mixture was present but its composition was not established further.

3.2.6 Hydrogen bonding in heptakis-(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin and its derivatives

The ^{1}H NMR spectrum of compound **113** in chloroform-*d* solution at 20 °C showed two sharp singlets at 5.25 and 6.73 ppm attributable to OH-2 and OH-3. The deshielded positions of these signals may be due to the relative acidity of secondary hydroxyls (pK_a = 12.2).[195] In order to consider the hydrogen bonding and to distinguish which signal is related to OH-2 and which to OH-3, variable temperature ^{1}H NMR spectra of compound **113** were investigated from +50 °C to -60 °C in chloroform-*d*, from 20 °C to -90 °C in dichloromethane-d_2, and from 20 °C to 110 °C in toluene-d_8. The chemical shift changes of H-1, and those of OH-2 and OH-3 as functions of temperature in these three

solvent systems are shown in Figure 3.13.

The signals of H-1 in chloroform-*d* and dichloromethane-d_2 at temperatures between +50 °C and -20 °C appear as narrow doublets (J = 3.2 Hz) but at lower temperatures appeared as a broad singlet because of general broadening of the spectra. The chemical shift of H-1 in all experiments remained constant at 4.85 ppm. The signals of both OH's were gradually shielded on lowering the temperature (see Figure 3.13). At temperatures between +50 to -20 °C in chloroform-*d* and from 20 °C to -40 °C in dichloromethane-d_2, the signals remained as sharp singlets. On lowering the temperatures to -40 °C in chloroform-*d* and -60 °C in dichloromethane-d_2 the signals gradually broadened. In particular, at -90 °C in dichloromethane-d_2 all of the signals are significantly broadened without splitting. In toluene-d_8, on increasing the temperature both of the hydroxyl peaks are deshielded and gradually broaden. Although the broadening of signals at 110 °C is significant, the chemical shift difference did not decrease significantly. Therefore, coalescence must occur at a significantly higher temperature.

Two effects could have been observed in the spectra on lowering the temperature from ambient. As the temperature is lowered, the OH signals in the spectra of most alcohols start to exhibit coupling to the attached CH protons with coalescence temperatures for this process ranging from above room temperature to about 0 °C or slightly lower. Coupling constants range in size from close to 0 Hz to as large as 12 Hz[64,65] but are normally 6-7 Hz, much larger than the splitting of H-1. No hint of such coupling was observed here for the OH signals and, given the general spectral broadening, it should have been observable in the chloroform-*d* spectrum at -40 °C or possibly in the

dichloromethane-d_2 spectrum at -60 °C. The absence of such coupling for these carefully dried samples in carefully dried solvents indicates that the OH protons must be exchanging rapidly even at these low temperatures. The most likely explanation is that the signals for each OH group are exchanging rapidly between its two "flip-flop" hydrogen bonding sites. Alternatively, exchange with water that is still retained by the cyclodextrin derivative cannot be ruled out at this time.

The second possible effect that could have been observed was that exchange between the two "flip-flop" sites for each OH proton could have been slowed enough as the temperature was lowered for coalescence to be observed to give four signals, in two possibly unequally populated sets. Depending on the chemical shift differences between sites, the coalescence could have been observed at different temperatures. However, no coalescences were observed so either the rates of exchange for both hydroxyls are still large at -90 °C or the chemical shift differences between the "flip-flop" sites are very small.

The spectra were also studied at elevated temperatures, up to +60 °C in chloroform-*d* and up to 110 °C in toluene-d_8. Here, the aim was to see if the two OH signals coalescenced by exchange between the two hydroxyl sites. No such effects were observed except for a slight signal broadening at the highest temperatures studied. If the two OH protons exchanged sites with each other through water or through hydrogen-bonded dimers, coalescence would have been observed. An estimate of the smallest size possible for the barrier to exchange can be obtained from the two-site coalescence formula, $k = \pi \Delta\nu / \sqrt{2}$.[198] Using a $\Delta\nu$ value of 354 Hz, k is 786 s^{-1}. From this value of k assuming coalescence at 110 °C, $\Delta G^{\ddagger}$ would be 17.6 kcal / mol^{-1} (73.6 KJ / mol^{-1}).[198]

Since there was only the slightest indication that coalescence was approaching when the temperature was raised to 110 °C, a more realistic estimate of the lowest possible coalescence temperature would be 20 °C higher or 130 °C. Coalescence at this temperature gives a minimum $\Delta G^{\ddagger}$ value of 18.5 kcal / mol^{-1} (77.4 kJ / mol^{-1}). These activation barriers are much higher than commonly observed for hydroxyl protons in chloroform-*d* or toluene-d_8 where all hydroxyl signals normally are observed as one line due to intermolecular exchange. Further investigation of this problem would be interesting.

The relaxation times for protons of **113**, that is, T_1 values, were determined for a chloroform-*d* solution at room temperature in order to find the best parameters to perform NOE experiments. Values of 311 and 309 ms were obtained for the hydroxyl signals at 6.72 and 5.25 ppm, respectively. T_1 values of 322, 457, 179 and 162 ms were obtained for the signals of H-1, H-3, H-6, and H-6', respectively.

An NOE difference experiment was performed at room temperature. In the NOE experiment, when one of the hydroxyl groups was irradiated, the signal of the second hydroxyl showed a large negative enhancement. Much smaller negative enhancements were observed for some of the other signals when either one of the hydroxyl signals or the H-1 signal were saturated (see Figure 3.15).

The 2D NOESY experiment showed very strong correlation between the two hydroxyl signals (see Figure 3.16). A second less marked correlation was observed between the hydroxyl signal at 5.25 ppm and that of H-1 at 4.89 ppm suggesting that these two protons are close to each other in space. There was no clear cut correlation between

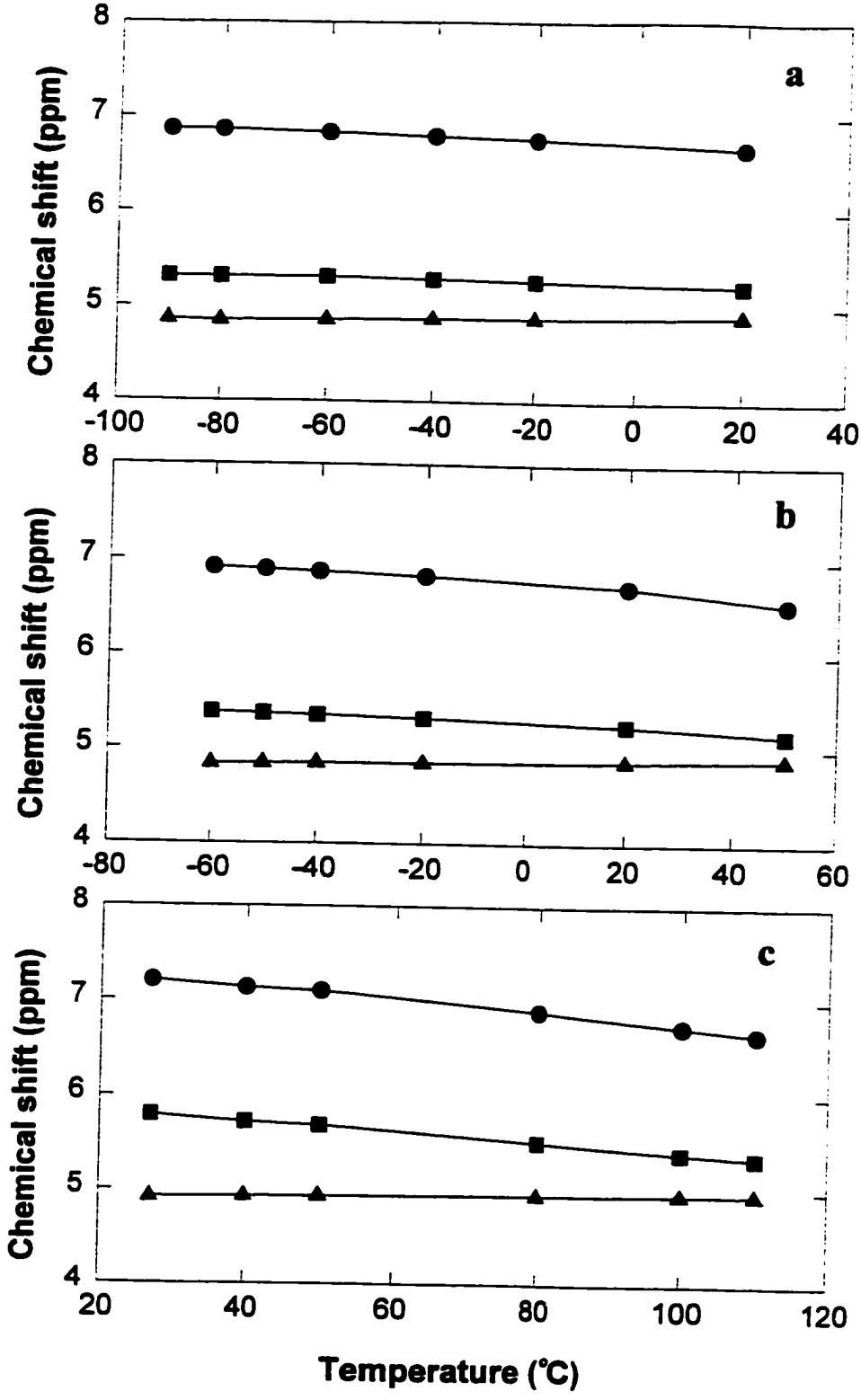


Figure 3.13 The plot of chemical shift changes of H-1 (▲), OH-X (■) and OH-X' (●) signals of **113**: from the top in dichloromethane-d_2, in chloroform-d, and in toluene-d_8.

the OH signal at 6.72 ppm and the signals of H-1, H-2, H-3 or any of the other CH protons. These experiments were aimed at assigning the hydroxyl signals. Two types of assignments are possible. A normal assignment would label one OH signal as being due to OH-2 and the other to OH-3. In this molecule, with its belt of clockwise or counterclockwise hydrogen-bonded hydroxyls potentially involved in "flip-flop" hydrogen bonding, a second type of assignment is possible in which one OH signal is assigned to the intra-ring OH, hydrogen bonded between OH-2 and OH-3, while the other OH signal is assigned to the inter-ring OH, hydrogen bonded between OH-2 and OH-3'. The variable temperature experiments indicate that the "flip-flop" hydrogen bonding model is appropriate here. If so, the NOESY correlation between H-1 and the OH signal at 5.25 ppm suggests that this signal is the inter-ring OH.

All of these data are consistent with fast equilibration between two directions of intramolecular hydrogen bonding as illustrated in Figure 3.14. In this equilibrium, the two hydrogens from OH-2 of one glucopyranose ring and OH-3 of the neighboring ring each can adopt two positions *via* "flip flop" hydrogen bonding.[154] Two positions arise for each hydrogen atom between two oxygen atoms because the hydrogen atom is formally bonded to one oxygen atom (shorter distance) and hydrogen bonded to the other oxygen atom (longer distance). When one of the hydrogen atoms flips from being bonded to one oxygen atom to being bonded to the other, all of the other hydrogen atoms in the hydrogen-bonding network reverse to being bonded in the other direction.

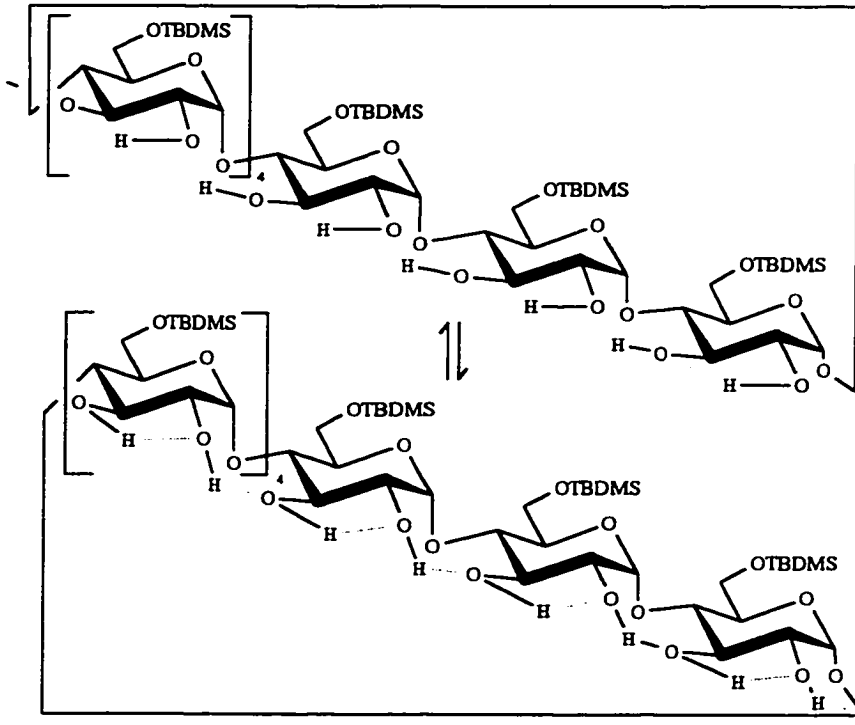


Figure 3.14 Possible hydrogen bonding structures in silylated β-cyclodextrin derivatives

The ^{1}H NMR spectrum of heptakis-(6-*O*-*tert*-butyldimethylsilyl-2-*O*-*p*-toluenesulfonyl)-β-CD (**118**) showed a sharp doublet at 3.07 ppm (J = 3.4 Hz) for the remaining hydroxyl proton (OH-3), significantly shielded in comparison with the hydroxyl signals in compound **113**, but at a position that is more normal for carbohydrate hydroxyl protons in chloroform-*d*. Observation of a sharp doublet indicates that exchange of this OH proton is slow and suggests that hydrogen bonding occurs between OH-3 and the sulfonyl group at O-2 and OH-3 as shown in Figure 3.17. However, it remains uncertain as to which hydrogen-bonding system, A or B, as shown in Figure 3.17 causes this

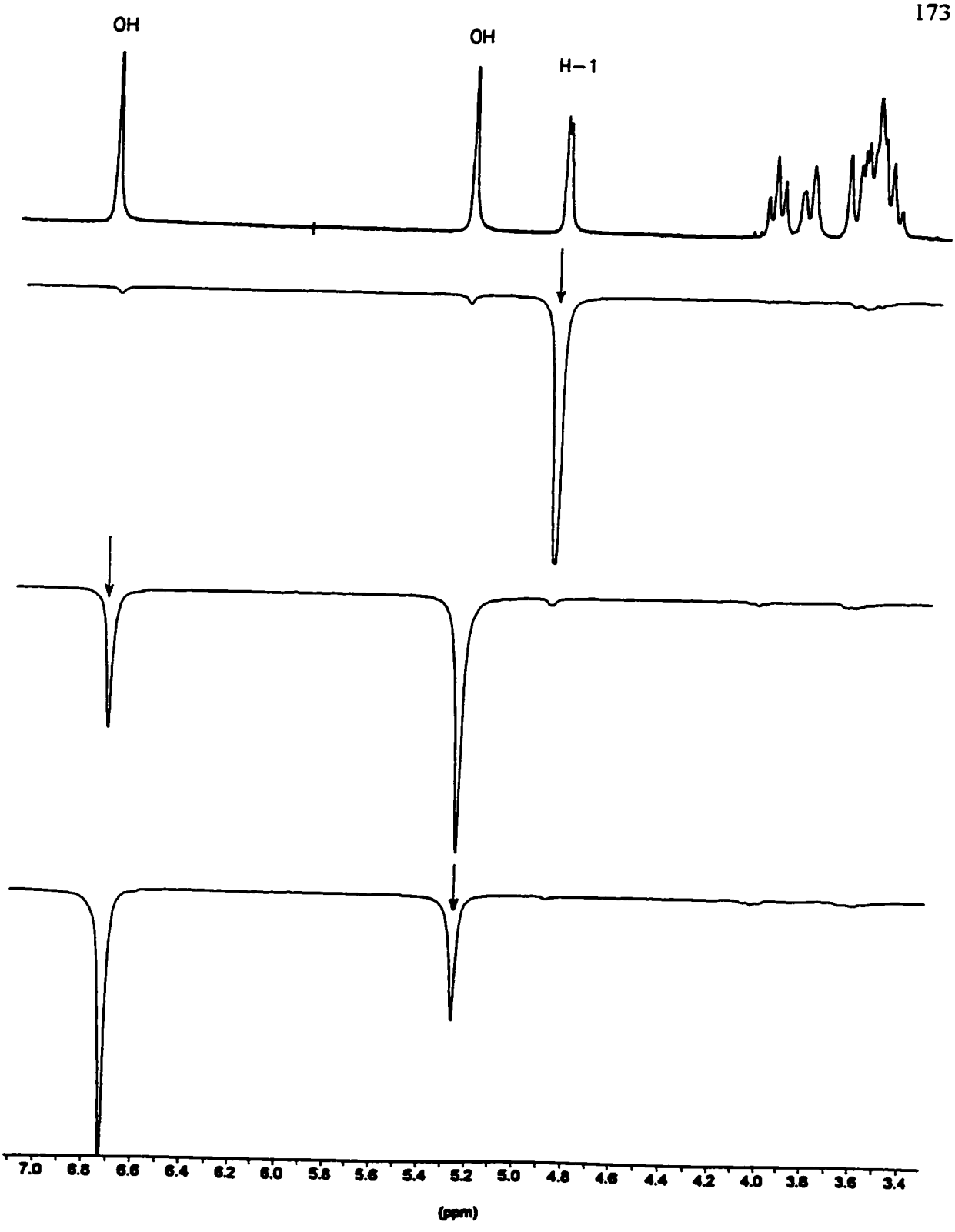


Figure 3.15 NOE difference spectra of **113** in chloroform-*d*; arrows indicate the positions of irradiation

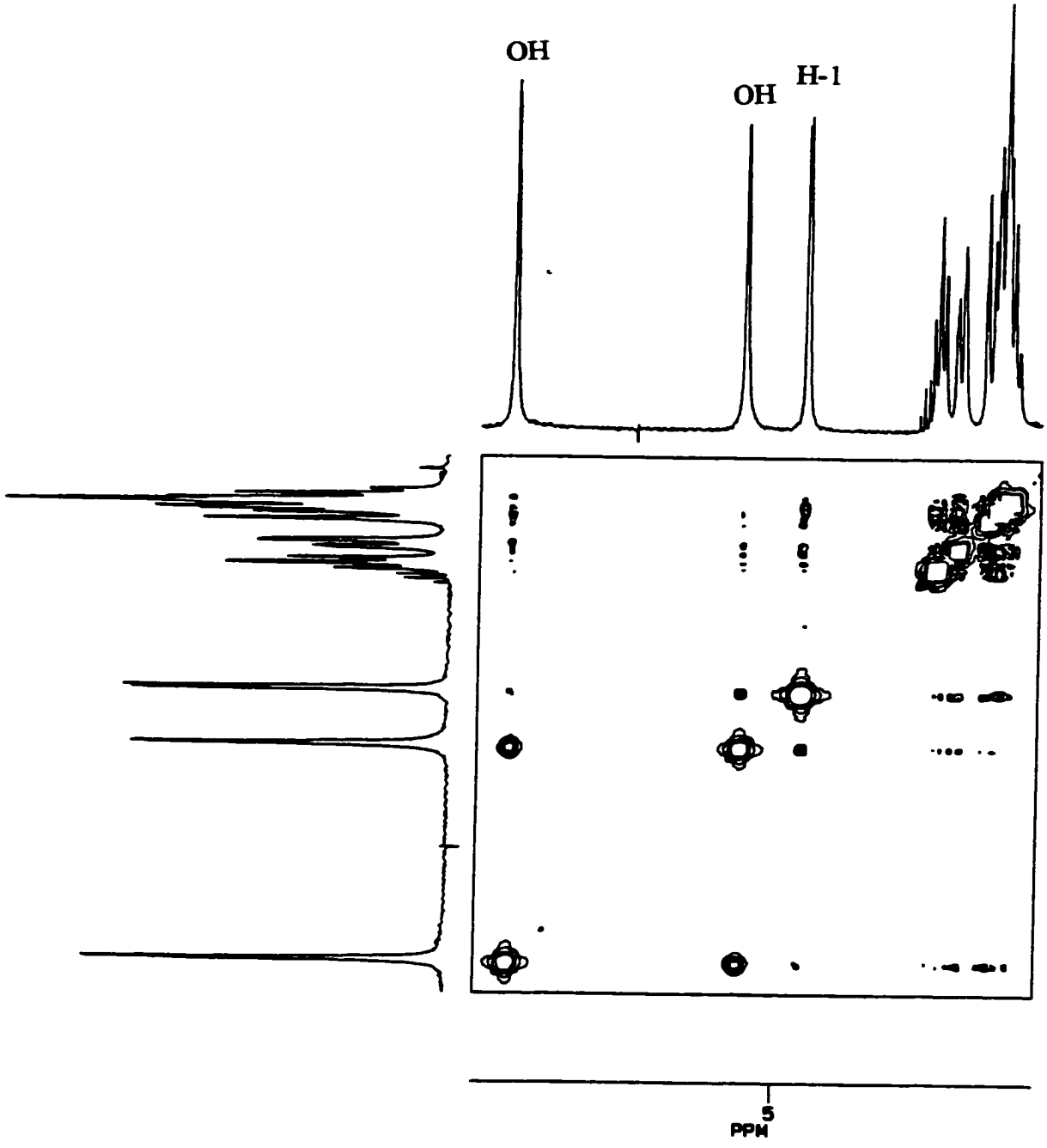


Figure 3.16 Expansion part of the NOESY spectrum of 113 in chloroform-*d*.

situation. The size of the coupling constant gives information about the populations of C-O rotamers because H-C-O-H Karplus equations have been established.[64,65] Based on these equations, a J_{HCOH} value of 3.4 Hz indicates that HCOH conformations in which the two hydrogens are *gauche* are populated much more than *anti* conformations. However, two *gauche* conformers are possible; if the torsional angle is about +60°, the OH proton is inclined towards C-2 and intra-ring hydrogen bonding has occurred; if it is about -60°, the OH proton is inclined towards C-4 and inter-ring hydrogen bonding has occurred. A NOESY spectrum of **118** (see Figure 3.18) showed correlations between the hydroxyl signal at 3.07 and H-1, H-2, H-3 and H-5. However, the correlation of the hydroxyl with H-2 is much stronger than that to H-1, which suggests that the hydroxyl proton is close to H-2 in space. If this is true, then the *gauche* conformation with a + sign is populated and the intra-ring hydrogen bonding (state B) is the correct model.

In heptakis-(6-*O*-*tert*-butyldimethylsilyl)-2-O-*p*-toluenesulfonyl-β-CD (**114**) the C_7 symmetry of the parent molecule is destroyed. Thirteen hydroxyl signals were observed in the ^{1}H NMR spectrum of **114**, some of them broadened consistent with this loss of symmetry. Six separate singlets appeared between 5.88 and 6.59 ppm, roughly corresponding to the more deshielded hydroxyl signal of compound heptakis-(6-*O*-*t*ert-butyldimethylsilyl)-β-cyclodextrin. A further seven singlets, two quite broadened, appeared between 4.61 and 5.22 ppm. On standing, all thirteen signals broaden and eventually disappear, due to exchange with atmospheric moisture. If the assignment made

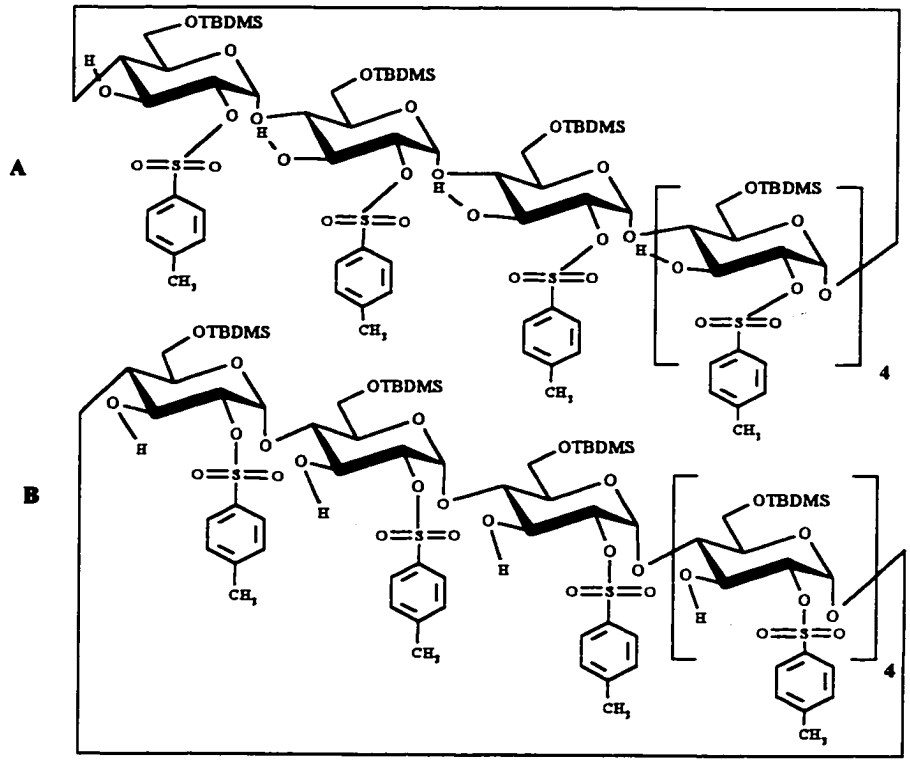


Figure 3.17 Possible hydrogen bonding structures in per-2-*O*-*p*-toluensulfonylated-β-cyclodextrin **118**

for **113** is correct, the six deshielded hydroxyl protons are intra-ring OH's which the seven others are inter-ring OHs. Two models can be proposed, each of which would have six normal intra-ring OHs and six normal inter-ring OHs plus one OH that is hydrogen bonded to the *p*-toluenesulfonyl group either in an inter-ring or intra-ring fashion. These two models would correspond to the last hydrogen bond being as in structure A in Figure 3.17 (inter-ring hydrogen bond) or as in structure B in Figure 3.17 (intra-ring hydrogen bond). If the assignment for **118** was correct, the intra-ring hydrogen bond to the *p*-toluenesulfonyl group is more stable.

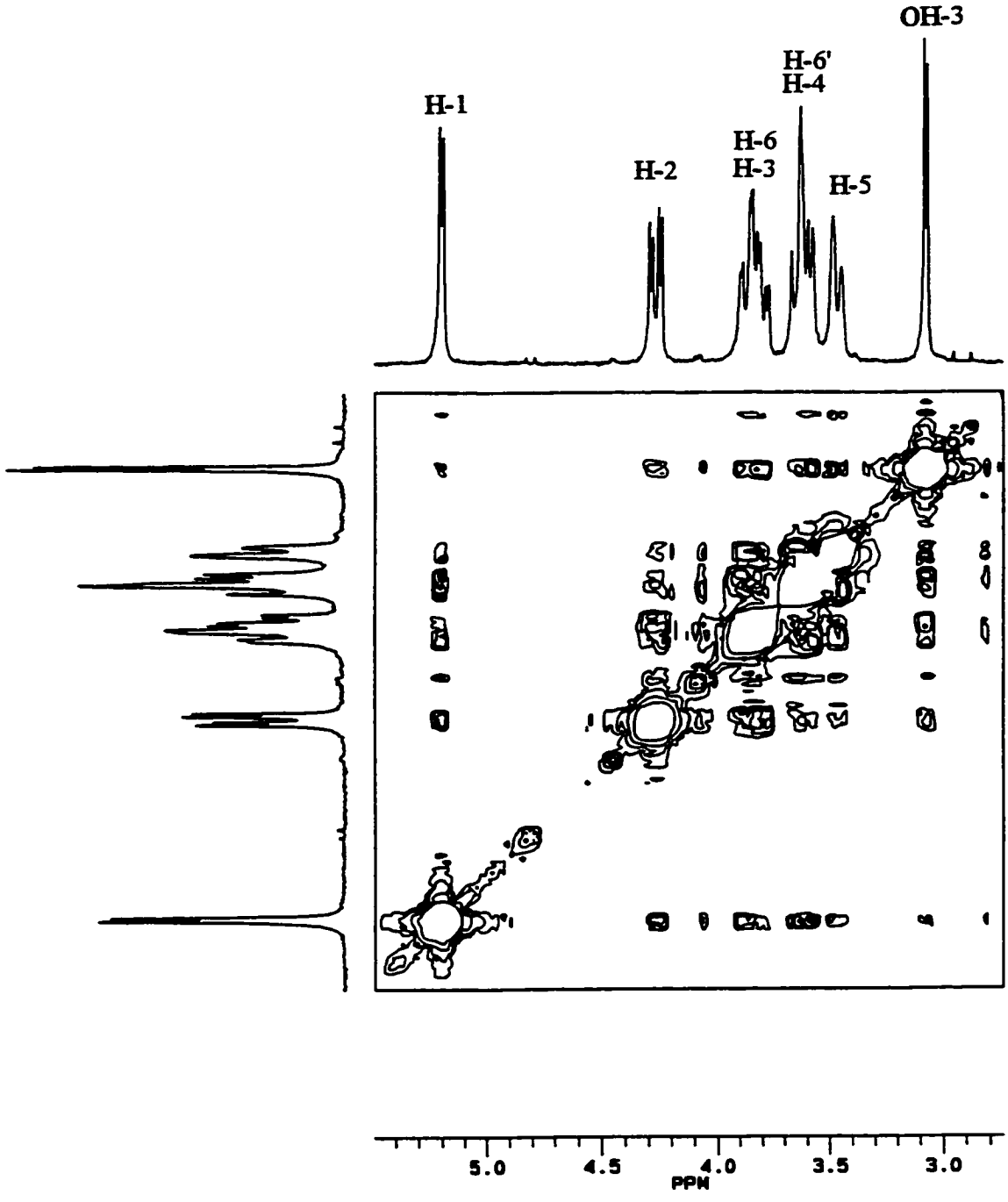


Figure 3.18 The expansion part of NOESY spectrum of **118** in chloroform-*d*.

3.3 Conclusions

The conversion of the primary hydroxyls of β-cyclodextrin to *tert*-butyldimethylsilyl ethers were shown to be an essential step for preparing dibutylstannylene acetal intermediates that are useful. It was found that the heptakis-(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (**113**) forms dibutylstannylene acetals, in a wide range of stoichiometries, that are soluble in organic solvents. Heptakis-(6-*O*-*tert*-butyldimethylsilyl)-2-*O*-*p*-toluenesulfonyl-β-cyclodextrin (**114**) and heptakis-(6-*O*-*tert*-butyldimethylsilyl-2-*O*-*p*-toluenesulfonyl)-β-cyclodextrin (**118**) were synthesized *via* their dibutylstannylene acetal intermediates in good yields (59% and 62%, respectively).

More complete assignments of the ^{1}H NMR spectra of **114** were made here for chloroform-*d* solutions based on TOCSY, HMQC and other 2D experiments than were made previously.[164] An interesting feature of these spectra is that two glucopyranoside rings give distinct spectral patterns.

The dibutylstannylene acetal strategy was used in the synthesis of dimeric silylated β-cyclodextrins, but the broadening caused by extensive overlapping of signals in the NMR spectra limited precise assignment of the structure of the product.

It was found that the dibutylstannylene acetal procedure can be used in preparing *O*-*p*-toluenesulfonyl-substituted cyclodextrins with various degrees of substitution by adjusting the stoichiometry and the type of added nucleophile in the reaction.

An interesting and unusual hydrogen-bonding situation was observed for silylated β-cyclodextrin derivatives here and the possible hydrogen bonding in the structure of mono-2-*O*-*p*-toluenesulfonyl and per-2-*O*-*p*-toluenesulfonyl derivatives was discussed.

3.4 Experimental

3.4.1 General methods

General methods were the same as in section 1.4.1 with the following exceptions. Commercially available β-cyclodextrin was dried before use at 100 °C under reduced pressure for 24 h. Solvents were purified prior to use according to the literature procedures.[199] Purification of compounds was performed with column chromatography on silica gel (200-425 mesh, type 60 A special, Mallinckrodt). Organic solutions were dried over magnesium sulfate. Some NMR samples were prepared as solutions in DMSO-d_6 and chemical shifts in this solvent are given in ppm relative to the central line of the solvent: dimethyl sulfoxide-d_6 (δ_H = 2.49 and δ_c = 39.7). ^{1}H NMR spectra were assigned by first order analysis and by using COSY, HETCOR, and TOCSY experiments. Compounds used for variable temperature NMR experiments were carefully dried at 100 °C under reduced pressure for 48 h. NMR samples were prepared by dissolving 10 to 15 mg compound in $CDCl_3$ or CD_2Cl_2 that had been dried (molecular sieves 4 Å) in a glove bag in an atmosphere of Ar. Infrared spectra were recorded on a 510P FT-IR Nicolet spectrometer.

3.4.2 Heptakis-(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (113)

A solution of dry β-cyclodextrin (3.42g, 3 mmol) in anhydrous pyridine (50 mL) was cooled to 0 °C and a solution of *tert*-butyldimethylsilyl chloride (3.32g, 2.2 mmol) in dry pyridine (30 mL) was added dropwise. The resulting solution was stirred for 4 h at 0

°C, then 15 h at room temperature. Water (100 mL) was added and the reaction mixture was stirred vigorously for 1 h, during which time a precipitate formed. The precipitate was isolated by filtration, washed with water (2 x 100 mL) and dried at 100 °C under reduced pressure to give crude solid product. Silica gel column chromatography using ethyl acetate-ethanol-water (25 : 2 : 1 v/v) as eluant gave the title compound **113**, subsequently recrystallized from ethyl acetate and ethanol to give large colorless cubes: mp 311-313 °C, lit.[163] 314-318 °C and lit.[164] 299-300 °C, yield 5.18 g (89%); R_F = 0.47; $[\alpha]^{26}$ +107 ° (*c* 0.96, chloroform) (lit.[164] $[\alpha]_D$ +111°); δ_H ($CDCl_3$, 250.13 MHz): 0.02 (s, 42H, $SiMe_2$), 0.85 (s, 63H, *t*-Bu), 3.54 (t, 7H, $J_{3,4} = J_{4,5}$ = 8.9 Hz, H-4), 3.57-3.65 (m, 14 H, H-2 and H-5), 3.69 (br d, 7H, $J_{6,6'}$ = 11.1 Hz, H-6), 3.88 (br dd, 7H, H-6'), 4.01 (t, 7H, $J_{2,3}$ = 8.9 Hz, H-3), 4.87 (d, 7H, $J_{1,2}$ = 3.35 Hz, H-1), 5.26 (br s, 7H, OH), 6.73 (br s, 7H, OH); δ_C ($CDCl_3$, 62.9 MHz): -5.1 ($SiMe_2$), 18.3 (*t*-Bu qC), 25.9 (*t*-Bu Me), 61.6 (C-6), 72.5 (C-5), 73.4 (C-3), 73.6 (C-2), 81.731 (C-4), 102.0 (C-1).

3.4.3 Heptakis-(6-*O*-*tert*-butyldimethylsilyl)-2-*O*-*p*-toluenesulfonyl-β-cyclodextrin (114)

Heptakis (6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin (**113**) (0.191 g, 0.1 mmol) and dibutyltin oxide (0.046 g, 0.185 mmol) were refluxed in toluene (12 mL) with azeotropic removal of water for 6 h. The reaction mixture became homogeneous after about ½ h. The reaction mixture was concentrated to about 7 mL then cooled to the 0 °C in a ice-bath. Triethylamine (27 μL, 0.185 mmol) was added and the solution was stirred for 20

min. A solution of *p*-toluenesulfonyl chloride (0.035 g, 0.185 mmol) in toluene (2 mL) was added dropwise to the stirred solution at 0 °C, which was kept at 0 °C for 1h, then allowed to warm to the room temperature and stirred for 40 h. Water was added (3 mL), and the reaction mixture was stirred for 0.5 h, then diluted with chloroform (12 mL). The organic layer was washed with water (2 x 100 mL), dried, concentrated, and the solid residue was separated by column chromatography on silica gel using as eluant, ethyl acetate-ethanol-water (50 : 2 : 1). The first fraction was the title compound (**114**), a solid, mp 214-215 °C (lit.[164] 199-200 °C); yield 0.123 g, (59%); $[\alpha]_D^{31}$ +100 ° (*c* 2.17, chloroform) (lit.[164] $[\alpha]_D$ +102 °); δ_H ($CDCl_3$, 400.14 MHz for the D_2O- exchanged sample, 250.13 MHz for the non-exchanged sample, signal appearance except for OH signals from the exchanged sample): 0.005-0.04 (br s, 42H, $SiMe_2$), 0.84 - 0.87 (br s, 63H, *t*-Bu Me), 2.39 (s, 3H, tosyl Me), 3.21 (br t, 1H, $J_{3A,4A} = J_{4A,5A} = 9.4$ Hz, H-4A), 3.32 (dd, 1H, $J_{1X,2X} = 3.8$ Hz, $J_{2X,3X} = 9.8$ Hz, H-2X), 3.45 - 3.75 (complex pattern, H5A, most H-4s, most H-2s, most H-6s), 3.80 - 3.97 (H_{3X}, most H-5s), 4.00-4.12 (H-3A and H-3's), 4.17 (dd, $J_{1A,2A} = 3.3$ Hz, $J_{2A,3A} = 9.7$ Hz, H-2A), 4.24 (dd, 1H, $J_{6,6'} = 10.2$ Hz, $J_{5,6} = 1.7$ Hz, a H-6), 4.48 (br d, 1H, $J_{1X,2X} = 2.9$ Hz, H-1X), 4.61, 4.70 (2 br s, 2x1H, 2OH), 4.87 (br m, 5H, H-1's), 4.99, 5.11, 5.19 (3 br s, 3x1H, 3OH), 5.23 (br 2H, 2 x OH), 5.29 (d, 1H, $J_{1A,2A} = 3.0$ Hz, H-1A), 5.97, 6.04, 6.30, 6.41, 6.49, 6.59 (6 br s, 6x1H, 6OH), 7.29 (br d, 2H, J = 8.2 Hz, tosyl H), 7.85 (br d, 2H, J = 8.2 Hz, tosyl H); δ_C ($CDCl_3$, 100.61 MHz): -5.2, -5.1, -5.0, -4.9 (SiMe2), 18.2, 18.3, 18.4 (q-t-Bu C), 21.7 (tosyl Me), 25.9, 26.0 (t-Bu-Me), 61.3, 61.5, 61.6 (C-6s), 61.8 (C-6 attached to H at 4.24), 62.3 (C-6), 69.8 (C-3A), 72.2, 72.3, 72.5, 73.0, 73.1, 73.3, 73.4, 73.8, 73.9, 75.0 (most C-2s and C-3s and all C-5s), 79.1 (C-

2A), 80.5,80.6, 81.5, 81.7, 81.9 (C-4's), 82.2 (C-4A), 99.2 (C-1A), 101.3, 102.0, 102.2, 102.8 (C-1's), 129.3, 129.4, 132.4, 145.2 (tosyl C).

The second fraction was starting material **113** (0.031g, 16% yield).

3.4.4 Heptakis-(6-*O*-*tert*-butyldimethylsilyl-2-*O*-*p*-toluenesulfonyl)-β-cyclodextrin (118)

Compound **113** (0.194 g, 0.1 mmol) and dibutyltin oxide (0.192g, 0.77 mmol) were refluxed in toluene (12 mL) with azeotropic removal of water for 6 h. The solution was concentrated to about 7 mL, cooled to room temperature and 4-*N,N*-dimethylaminopyridine (DMAP) (0.094 g, 0.77 mmol) was added. A solution of *p*-toluenesulfonyl chloride (0.191 g, 1 mmol) in toluene (2 mL) was added dropwise over 5 min and then the solution was stirred for 15 h. Water (3 mL) was added and the mixture was stirred for 0.5 h. The mixture was diluted with chloroform (15 mL) and the organic layer washed with water (2 x 15 mL), dried, and concentrated. The residue was separated by silica gel column chromatography (eluant, chloroform-butanone, 97 : 3 v/v) to give the title compound (**118**) as a colourless solid, yield 0.187 g (62%); mp 150-152 °C; R_f = 0.53 (ethyl acetate-hexane, 1 : 2 v/v); $[\alpha]_D^{25}$ + 57.6 ° (*c* 2.27, $CHCl_3$); δ_H ($CDCl_3$, 250.13 MHz): -0.02 (s, 6H, $SiMe_2$), 0.84 (s, 9H, *t*-Bu), 2.43 (s, 3H, tosyl Me), 3.07(d, 1H, $J_{3,OH}$ = 3.4 Hz, OH-3), 3.45 (br d, $J_{4,5}$ = 9.2 Hz, H-5), 3.58 (br d, 1H, $J_{6,6'}$ = 9.9 Hz, H-6), 3.61 (t, 1H, $J_{3,4} + J_{4,5}$ = 18.2 Hz, H-4), 3.80 (dt, 1H, $J_{3,4} = J_{2,3}$ = 9.6 Hz, H-3), 3.85 (br d, 1H, H-6'), 4.25 (dd, 1H, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 9.8 Hz, H-2), 5.18 (d, $J_{1,2}$ = 3.67 Hz, H-1), 7.24 (br d, 2H, J = 8.2 Hz, aryl H), 7.72 (br d, 2H, aryl H); δ_C ($CDCl_3$, 62.9 MHz): -5.4, -5.2

($SiMe_2$), 18.3 (*t*-Bu qC), 21.8 (aryl Me), 25.8 (t-Bu Me), 61.6 (C-6), 69.9 (C-3), 71.6 (C-5), 79.9 (C-2), 80.0 (C-4), 98.9 (C-1), 128.3, 129.6, 133.0, 145.1 (aryl C); IR (CH_2Cl_2, cm^{-1}) 3577, 2930, 2857, 1600, 1472, 1379, 1252, 1191.

3.4.5 Heptakis-(6-*O*-*tert*-butyldimethylsilyl)-di-2-*O*-*p*-toluenesulfonyl-β-cyclodextrin (116).

Compound **113** (0.191 g, 0.1 mmol) and dibutyltin oxide (0.070g, 0.28 mmol) were refluxed in toluene (12 mL) with azeotropic removal of water for 5 h. The solution was concentrated to 7 mL and then cooled to 0 °C. Triethylamine (60 μL, 0.42 mmol) was added and mixture solution was stirred for 20 min. A solution of *p*-toluenesulfonyl chloride (0.053 g, 0.28 mmol) in toluene (2 mL) was added dropwise at 0 °C to the stirred solution and stirring was continued at room temperature for 48 h. Water (4 mL) was added and the reaction was worked up as above. The residue was separated by column chromatography using ethyl acetate/ethanol/water: 50/2/1 as eluant into three fractions. The first fraction (R_f 0.63 in ethyl acetate/ethanol/water: 50/2/1), the title compound (**116**), was a solid, yield 0.071g (32%); mp 199-200 °C; $[\alpha]_D^{31}$ 81.8 ° (*c* 3.22, chloroform); δ_H [$CDCl_3$, 250.13 MHz, relative numbers of H at each site evaluated by the size of the integral with respect to those of the *t*-butyl signal (0.86 ppm) as 63 H and the $SiMe_2$ signal as 42 H (0.02 ppm)]: 0.02 ppm (brs, 42H, $SiMe_2$), 0.86 (s, 63H, *t*-Bu), 2.47(s, 6H, $ArCH_3$), 3.2-4.3 (glucose H), 4.5 -5.5 (complex ms, H-1s), 7.20-7.42 (complex m, aryl H ortho to Me +$CHCl_3$), 7.77-7.96 (4H, complex m, aryl H ortho to S); δ_C ($CDCl_3$, 62.9 MHz) 0.02 ppm (brs, 42H, $SiMe_2$), 0.86 (s, 63H, *t*-Bu), 2.47(s, 6H,

$ArCH_3$), 3.2-4.3 (glucose H), 4.5-5.5 (complex ms, H-1s), 7.20-7.42 (complex m, aryl H ortho to Me +$CHCl_3$), 7.77-7.96 (4H, complex m, aryl H ortho to S); ^{13}C NMR ($CDCl_3$, 100.62 MHz), δ: -5.18 (b, $SiMe_2$, 18.2 and 18.3 (q-t-Bu), 21.7 (b, tosyl CH_3), 25.9 (b, t-Bu-Me), 61.2,61.5, 61.7, 61.8, 62.0, 62.2 (C-6's), 71.8, 72.0, 72.2, 72.4, 72.6, 72.7, 73.0, 73.4, 73.6, 73.7 (C-2's, C-3's), 78.8, 79.8, 80.8, 80.9, 81.6, 81.8, 81.9 and 82.3 (C-2's and C-4), 98.1, 98.4, 99.0, 99.1, 99.8, 99.14 (C-1'), 101.3, 101.4, 101.5, 102.0, 102.2, 102.4, 102.9 and103.1 (C-1's), 127.1, 129.4, 145,2 and 145.3 (Ar-C).

The second fraction was compound **114**, yield 0.083 g (40%), and the third was starting material, yield 0.023 g (12%).

3.4.6 Heptakis-(6-*O*-*tert*-butyldimethylsilyl)-tri-2-*O*-*p*-toluenesulfonyl-β-cyclodextrin (117)

3.4.6.1 Using triethylamine

Compound **113** (0.191g, 0.1 mmol) and dibutyltin oxide (0.159 g, 0.64 mmol) were refluxed in toluene (22 mL) with removal of water first using a Dean-Stark apparatus for azeotropic removal for 5 h, then using a soxhlet apparatus containing activated 4Å molecular sieves for 2 h. The solution was concentrated to 12 mL and then cooled to 0 °C. Triethylamine (93 μL, 0.64 mmol) was added and the reaction mixture stirred for 20 min. A solution of *p*-toluenesulfonyl chloride (0.121 g, 0.64 mmol) in toluene (3 mL) was added dropwise and the solution was stirred at 0 °C for 3 h, then allowed to warm up to room temperature. After 48 h, water (3 mL) and then chloroform (12 mL) were added. The organic layer was washed with water (2 x 100 mL), dried, and concentrated, and the

residue was separated by column chromatography using ethyl acetate/ethanol/water: 50/2/1 as eluant. The first fraction was the title compound (**117**), yield 0.046 g, (19%), mp 204-205 °C; $[\alpha]_D^{23}$ +90.8° (*c* 1.99, chloroform); δ_H [$CDCl_3$, 250.13 MHz, relative numbers of H at each site evaluated by the size of the integral with respect to those of the *t*-butyl signal (0.86 ppm) as 63 H and the $SiMe_2$ signal as 42 H (0.02 ppm)]: -0.01- 0.1 (br s, $SiMe_2$), 0.80-0.90 (overlapping s, 63H, *t*-Bu), 2.36-2.40 (overlapping s, 9H, tosyl Me), 7.20-7.40 (complex m, aryl H ortho to Me +$CHCl_3$), 7.85-7.95 (complex m, 6H, aryl H ortho to S).

The second fraction was compound **116**, yield 0.048g (22%), and the third fraction was compound **114**, yield 0.035g, 17%.

3.4.6.2 Using 4-*N*,*N*-dimethylaminopyridine

Compound **113** (0.191g, 0.1 mmol) was treated with dibutyltin oxide (0.163 g, 0.66 mmol) as above. The toluene solution was concentrated to 12 mL, cooled to 0 °C, and DMAP (0.080 g, 0.64 mmol) was added and the solution stirred for 20 min. A solution of *p*-toluenesulfonyl chloride (0.121 g, 0.64 mmol) in toluene (3 mL) was added dropwise to the stirred solution at 0 °C. A colorless precipitate formed immediately. The cooling bath was removed and the reaction mixture was stirred for 35 h, until TLC (ethyl acetate-ethanol-water, 50 : 2 : 1 v/v) indicated the presence of products with larger R_F's (0.64 and 0.76) than that of **117** (35 h). When water (3 mL) was added, the precipitate dissolved and the solution turned slightly yellow. Workup as above gave a syrup and several attempts to isolate these two compounds in pure form failed. By referencing the

TLC of the reaction mixture with the disubstituted derivative **116**, the trisubstituted derivative **117**, and the heptakis derivative **118**, the fastest moving component was identified as compound **118** and the second fast moving component was tentatively considered to be heptakis-(6-*O*-*tert*-butyldimethylsilyl)-tetra-2-*O*-*p*-toluenesulfonyl-β-cyclodextrin.

3.4.7 2-*O*-Benzoyl-heptakis-(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (115)

Compound **113** (0.194 g, 0.1 mmol) and dibutyltin oxide (0.31 g, 0.125 mmol) were refluxed in toluene (15 mL) with azeotropic removal of water for 5 h. The solution was cooled to 0 °C, then triethylamine (18 μL, 0.125 mmol) was added, followed by freshly distilled benzoyl chloride (15 μL, 0.125 mmol). The reaction was stirred at 0 °C for 4 h, then 24 h at 25 °C. Water (3 mL) was added and then chloroform (12 mL). The organic layer was washed sequentially with dilute HCl (10 mL), water (3 x 15 mL), saturated $NaHCO_3$ (15 mL), then dried ($MgSO_4$), and concentrated to a syrup. Chromatography on silica gel using ethyl acetate/ethanol/water: 50/2/1 as eluant, gave the title compound **115**, a colourless solid, yield 0.052 g (25%); mp 255-256 °C; R_f = 0.35 (ethyl acetate/ethanol/water: 50/2/1); $[\alpha]_D^{31}$ +95 ° (*c* 2.02, chloroform); δ_H ($CDCl_3$, 250.13 MHz): -0.0132, -0.001, 0.008, 0.014, 0.026, 0.033, 0.041, 0.047, 0.073 (6H, $SiMe_2$), 0.835, 0.847, 0.856, 0.861, 0.885 (9H, *t*-Bu), 3.38-3.767 (strongly overlapped, H-2's, H-2B, H-4's, H-5's and H-6_a's), 3.860-3.989 (m, H-3's and H-6_b's), 4.044-4.153 (m, H-3B and H-6), 4.295-4.418 (m, H-3A), 4.823-4.867 (m, 6H, H-2A and H-1's), 4.94 (br d, 1H, $J_{1,2}$ = 3.8 Hz, H-1), 5.37 (br d, 1H, J = 2.8 Hz, H-1A), 8.03 (d, 2H, J = 8.2 Hz, Ar-

H), 7.44 (d, 2H, Ar-H), 7.34 (t, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz, ref. $CDCl_3$ = 77.0 ppm), δ : -5.2 ($SiMe_2$), 18.3 (q-*t*-Bu), 25.9 (*t*-Bu Me), 59.2, 61.2, 61.7 (C-6's), 62.9 (C-6A), 69.3, 69.9 (C-5), 71.7, 72.0, 72.2, 72.5, 72.8, 72.9, 73.3, 73.5 (C-2's and C-3's), 74.3 (C-2A), 75.0, 77.2, 79.1, 80.6, 81.7, 82.4 (C-4's), 97.7 (C-1A), 101.3, 101.9 (C-1's), 128.3, 130.0, 133.1 (Ar-C), 166.7 (COO).

3.4.8 Synthesis of dimeric heptakis-(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (119)

Heptakis-(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (**113**) (0.191 g, 0.1 mmol) and dibutyltin oxide (0.046 g, 0.185 mmol) were refluxed overnight in toluene (12 mL) with azeotropic removal of water to give the dibutylstannylene acetal. The solution was cooled to 0 °C, triethylamine (27 μL, 0.185 mmol) was added and the reaction mixture was stirred for 0.5 h. A solution of 4,4'-biphenyldisulfonyl chloride (0.040 g, 0.1 mmol) in toluene (2 mL) was added dropwise. The reaction mixture was stirred for 2 h at 0 °C and then warmed to room temperature. The reaction was continued until TLC showed no change (48 h). When the reaction was quenched by adding water (3 mL), some precipitate was formed. The reaction mixture was diluted with chloroform (12 mL) and the organic layer was washed sequently with dilute HCl (10 mL), water (2 x 15 mL) and saturated $NaHCO_3$ (15 mL), then dried ($MgSO_4$), and concentrated. Column chromatography of the residue on silica gel using ethyl acetate/ethanol/water: 50/2/1 as eluant gave the title compound (**119**) as an amorphous solid: yield 0.081 g, (19%); R_f= 0.66; ^{1}H NMR ($CDCl_3$, 250.13 MHz, ref. $CHCl_3$ as 7.24 ppm) gave very broad signals, δ : 0.02 (br s, 42H, SiMe2), 0.85 (br s, 78H, t-Bu Me), 3.45-5.3 (very br, H-1 to H-6), 7.80

(br, Ar-H), 8.12 (br, Ar-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz, ref. $CHCl_3$ = 77.0 ppm), δ: -5.1 ($SiMe_2$), 18.3 (t-Bu qC), 25.9 (t-BuMe), 60.4, 60.715, 61.0, 61.4, 61.5, 61.6, 61.9 (C-6), 71,1, 71.3, 71.8, 72.1, 72.2, 72.3, 72.6, 73.2, 73.4, 73.6, 74.0 (C-5 and C-2), 75.6, 75.7, 75.8, 76.0, 76.5 (C-3), 78.4, 78.6, 78.9, 79.1, 81. 0 (C-4), 97.6, 57.8, 99.0, 98.6, 99.7, 99.8, 100.4, 101.0, 101.9, 102.1 (C-1), 127.1, 127.3, 127.7, 128.2, 128.4, 128.7 (Ar-C), 144.0, 144.6 (Ar-C).

The ^{1}H NMR of this compound in various temperature and also in other solvents such as DMSO-d_6 gave broadened signals.

3.4.9 Synthesis of heptakis-(2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (122)

A solution of heptakis- (6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (**113**) (0.194 g, 0.1 mmol) in anhydrous pyridine (3.5 mL) was cooled to 0 °C and 4-*N*,*N*-dimethylaminopyridine (0.122 g, 0.1 mmol) and then acetic anhydride (5 mL) were added. After the reaction mixture had been stirred for 1 h at 0 °C, it was warmed to room temperature when the colour of the solution changed to brown. After 2 h, TLC (ethyl acetate) showed that all of the starting material had been consumed with the production of a single product. The reaction was stopped by adding cold water (5 mL) to the cooled solution (0 °C) and then chloroform (15 mL) was added. The organic layer was washed with cold water (3 x 100 mL), then dried ($MgSO_4$) and concentrated to give a syrupy residue. The product was purified by column chromatography on silica gel to give the title compound (**122**) as a syrup, yield 0.212 g, (84%); R_f= 0.61 (ethyl acetate); $[\alpha]_D^{23}$ +61.5 °

(*c* 5.16, chloroform); ^{1}H NMR ($CDCl_3$, 250.13 MHz, ref. $CHCl_3$ as 7.24 ppm) δ : 0.02 (s, 6H, $SiMe_2$), 0.85 (s, 9H, *t*-BuMe), 1.98 (s, 3H, C_2OCOMe), 2.01 (s, 3H, COMe), 3.69 (br d, 1H, $J_{6,6'}$ = 11.9 Hz, H-6), 3.84-3.90 (m, 2H, H-4 and H-5), 4.01 (br d, 1H, $J_{6,6'}$ = 11.90 Hz, H-6'), 4.67 (dd, $J_{1,2}$ = 3.7 Hz, $J_{2,3}$ = 10.1 Hz, H-2), 5.13 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 5.32 (t, 1H, $J_{2,3}$ = 10.1 Hz, $J_{3,4}$ = 9.8 Hz, H-3); ^{13}C NMR ($CDCl_3$, 62.9 MHz, ref. $CHCl_3$ = 77.0 ppm), δ : -5.4, -5.1 ($SiMe_2$), 18.2 (*t*-Bu qC), 20.7 (COMe), 20.9 (C_3OCOMe), 25.8 (*t*-Bu Me), 61.8 (C-6), 71,2 (C-2), 71.5 (C-3), 71.7 (C-5), 76.2 (C-4), 96.4 (C-1), 169.4 (COO), 170.7 (COO).

3.4.10 Synthesis of partially acetylated heptakis-(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin (123)

Compound **113** (0.194 g, 0.1 mmol) was dissolved in distilled pyridine (5 mL), cooled to 0 °C, and then acetic anhydride (3.5 mL) was added with stirring. The reaction mixture was allowed to warm to room temperature. TLC showed the consumption of all of the starting material in 16 h and formation of one major compound and two other minor products. The reaction was continued for 48 h at room temperature but no change was observed by TLC. The reaction was halted by adding water (2 mL) and then chloroform (10 mL) was added. The organic layer was washed sequentially with dilute HCl (2 mL), saturated sodium bicarbonate (15 mL), and with water (5 x 15 mL), then dried ($MgSO_4$), and concentrated to a solid residue. Column chromatography on silica gel gave the title compound (**123**) as an amorphous solid, yield 0.189 g (78%); mp 138-139 °C; R_f= 0.63 (ethyl acetate); $[\alpha]_D^{32}$ +85 ° (*c* 3.25, chloroform); ^{1}H NMR ($CDCl_3$, 400.13 MHz, ref.

$CHCl_3$ as 7.24 ppm) δ: -0.1 (br s, 6H, $SiMe_2$), 0.82-0.84 (br, *t*-BuMe), 2.00 (br s, COMe), 3.64-3.81 (m, H-6's), 3.86-4.01 (m, H-4's and H-5's), 4.02 (br d, J = 10,6 Hz, H-6s), 4.61-4.74 (m, H-2's), 4.83 (dd, 1H, $J_{1,2}$ = 3.4 Hz and $J_{2,3}$ = 10.2 Hz, H-2'), 5.02 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 5.10 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1), 5.15 (br d, 3H, J = 3.6 Hz, H-1), 5.19 (d, $J_{1,2}$ = 3.4 Hz, H-1), 5.22 (d 1H, $J_{1,2}$ = 3.6 Hz, H-1), 5.31-5.36 (m, 5H, H-3's), 5.31-5.38 (m, 5H, H-3), 5.41 (t, 1H, $J_{2,3}$ = 9.6 Hz, H-3'), 5.51 (t, 1H, $J_{2,3}$ = 10.0 Hz, H-3'); ^{13}C NMR ($CDCl_3$, 62.9 MHz, ref. $CHCl_3$ = 77.0 ppm), δ: -5.0 (SiMe), 20.8, 20.9, 21.1, 21.2 (C-2-OAc and C-3-OAc), 21.3 (*t*-Bu), 25.8, 25.9 (q-*t*-Bu Me), 59.1, 61.8 (C-6), 69.3, 69.5, 71.2, 71.5, 71.8, 72.0, 72.3, 72.5, 73.1, 74.0, 75.8, 76.0, 82.0 (C-5's and C-4'), 95.5, 95.7, 96.4, 96.8, 97.2, 99.3 (C-1's), 169.5, 169.6, 169.8, 170.3, 170.6, 170.8, 171.1 (COO's).

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