THE EFFECTS OF CHANGING ALKYL GROUPS ON THE STRUCTURES AND SELECTIVITIES OF DIALKYLSTANNYLENE ACETALS

by

Xianqi Kong

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

at

Dalhousie University
Halifax, Nova Scotia
February, 1994

ISBN 0-315-93781-5

Canada

Name Xiangi Kong

Dissertation Abstracts International is arranged by broad, general subject categories Please select the one subject which most nearly describes the content of your dissertation Enter the corresponding four-digit code in the spaces provided

Organic Chemistry
SUBJECT TERM

0490
SUBJECT CODE

U·M·I

Subject Categories

THE HUMANITIES AND SOCIAL SCIENCES

COMMUNICATIONS AND THE ARTS
Architecture 0729
Art History 0377
Cinema 0900
Dance 0378
Fine Arts 0357
Information Science 0723
Journalism 0391
Library Science 0399
Mass Communications 0708
Music 0413
Speech Communication 0459
Theater 0465

EDUCATION
General 0515
Administration 0514
Adult and Continuing 0516
Agricultural 0517
Art 0273
Bilingual and Multicultural 0282
Business 0688
Community College 0275
Curriculum and Instruction 0727
Early Childhood 0518
Elementary 0524
Finance 0277
Guidance and Counseling 0519
Health 0680
Higher 0745
History of 0520
Home Economics 0278
Industrial 0521
Language and Literature 0279
Mathematics 0280
Music 0522
Philosophy of 0998
Physical 0523
Psychology 0525
Reading 0535
Religious 0527
Sciences 0714
Secondary 0533
Social Sciences 0534
Sociology of 0340
Special 0529
Teacher Training 0530
Technology 0710
Tests and Measurements 0288
Vocational 0747

LANGUAGE, LITERATURE AND LINGUISTICS
Language
General 0679
Ancient 0289
Linguistics 0290
Modern 0291
Literature
General 0401
Classical 0294
Comparative 0295
Medieval 0297
Modern 0298
African 0316
American 0591
Asian 0305
Canadian (English) 0352
Canadian (French) 0355
English 0593
Germanic 0311
Latin American 0312
Middle Eastern 0315
Romance 0313
Slavic and East European 0314

PHILOSOPHY, RELIGION AND THEOLOGY
Philosophy 0422
Religion
General 0318
Biblical Studies 0321
Clergy 0319
History of 0320
Philosophy of 0322
Theology 0469

SOCIAL SCIENCES
American Studies 0323
Anthropology
Archaeology 0324
Cultural 0326
Physical 0327
Business Administration
General 0310
Accounting 027
Banking 0770
Management 0454
Marketing 0338
Canadian Studies 0385
Economics
General 0501
Agricultural 0503
Commerce Business 0505
Finance 0508
History 0509
Labor 0510
Theory 0511
Folklore 0358
Geography 0366
Gerontology 0351
History
General 0578
Ancient 0579
Medieval 0581
Modern 0582
Black 0328
African 0331
Asia, Australia and Oceania 0332
Canadian 0334
European 0335
Latin American 0336
Middle Eastern 0333
United States 0337
History of Science 0585
Law 0398
Political Science
General 0615
International Law and Relations 0616
Public Administration 0617
Recreation 0814
Social Work 0452
Sociology
General 0626
Criminology and Penology 0627
Demography 0938
Ethnic and Racial Studies 0631
Individual and Family Studies 0628
Industrial and Labor Relations 0629
Public and Social Welfare 0630
Social Structure and Development 0700
Theory and Methods 0344
Transportation 0709
Urban and Regional Planning 0999
Women's Studies 0453

THE SCIENCES AND ENGINEERING

BIOLOGICAL SCIENCES
Agriculture
General 0473
Agronomy 0285
Animal Culture and Nutrition 0475
Animal Pathology 0476
Food Science and Technology 0359
Forestry and Wildlife 0478
Plant Culture 0479
Plant Pathology 0480
Plant Physiology 0817
Range Management 0777
Wood Technology 0746
Biology
General 0306
Anatomy 0287
Biostatistics 0308
Botany 0309
Cell 0379
Ecology 0329
Entomology 0353
Genetics 0369
Limnology 0793
Microbiology 0410
Molecular 0307
Neuroscience 0317
Oceanography 0416
Physiology 0433
Radiation 0821
Veterinary Science 0778
Zoology 0472
Biophysics
General 0786
Medical 0760

EARTH SCIENCES
Biogeochemistry 0425
Geochemistry 0996
Geodesy 0370
Geology 0372
Geophysics 0373
Hydrology 0388
Mineralogy 0411
Paleobotany 0345
Paleoecology 0426
Paleontology 0418
Paleozoology 0985
Palynology 0427
Physical Geography 0368
Physical Oceanography 0415

HEALTH AND ENVIRONMENTAL SCIENCES
Environmental Sciences 0768
Health Sciences
General 0566
Audiology 0300
Chemotherapy 0992
Dentistry 0567
Education 0350
Hospital Management 0769
Human Development 0758
Immunology 0982
Medicine and Surgery 0564
Mental Health 0347
Nursing 0569
Nutrition 0570
Obstetrics and Gynecology 0380
Occupational Health and Therapy 0354
Ophthalmology 0381
Pathology 0571
Pharmacology 0419
Pharmacy 0572
Physical Therapy 0382
Public Health 0573
Radiology 0574
Recreation 0575
Speech Pathology 0460
Toxicology 0383
Home Economics 0386

PHYSICAL SCIENCES
Pure Sciences
Chemistry
General 0485
Agricultural 0749
Analytical 0486
Biochemistry 0487
Inorganic 0488
Nuclear 0738
Organic 0490
Pharmaceutical 0491
Physical 0494
Polymer 0495
Radiation 0754
Mathematics 0405
Physics
General 0605
Acoustics 0986
Astronomy and Astrophysics 0606
Atmospheric Science 0608
Atomic 0748
Electronics and Electricity 0607
Elementary Particles and High Energy 0798
Fluid and Plasma 0759
Molecular 0609
Nuclear 0610
Optics 0752
Radiation 0756
Solid State 0611
Statistics 0463

Applied Sciences
Applied Mechanics 0346
Computer Science 0984
Engineering
General 0537
Aerospace 0538
Agricultural 0539
Automotive 0540
Biomedical 0541
Chemical 0542
Civil 0543
Electronics and Electrical 0544
Heat and Thermodynamics 0348
Hydraulic 0545
Industrial 0546
Marine 0547
Materials Science 0794
Mechanical 0548
Metallurgy 0743
Mining 0551
Nuclear 0552
Packaging 0549
Petroleum 0765
Sanitary and Municipal 0554
System Science 0790
Geotechnology 0428
Operations Research 0796
Plastics Technology 0795
Textile Technology 0994

PSYCHOLOGY
General 0621
Behavioral 0384
Clinical 0622
Developmental 0620
Experimental 0623
Industrial 0624
Personality 0625
Physiological 0989
Psychobiology 0349
Psychometrics 0632
Social 0451

To my parents

Table of Contents

Table of Contents		v
List of Tables		vii
List of Figures		ix
Abstract		xi
List of Abbreviations and Symbols		xii
Acknowledgements		xv
Chapter 1	Background of the Project	1
Chapter 2	An Overview of the Application of Dibutylstannylene Acetals	4
	2.1 Substitution and oxidation reactions of simple diols	5
	2.2 Synthesis of macrocyclic oligolactones	12
	2.3 Applications in carbohydrate chemistry	14
	2.4 Structures of dibutylstannylene acetals	34
Chapter 3	A Convenient Preparation of Hindered Dialkytin(IV) Derivatives	44
	3.1 Introduction	44
	3.2 Results and discussion	45
	3.3 Experimental	61
Chapter 4	An Improved Method for the Regioselective Oxidation of Dibutylstannylene Acetals and Dimerization of the α-Hydroxyketone Products	72
	4.1 Introduction	72
	4.2 Results and discussion	73

	4.3 Experimental	85
Chapter 5	Control of Regioselectivity in Mono-*p*-toluenesulfonation Reactions of Dialkylstannylene Acetals by Altering the Alkyl Groups on Tin	94
	5.1 Introduction	94
	5.2 Results and discussion	96
	5.3 Experimental	143
Chapter 6	Conclusions	172
Appendix	Crystal Structure of 1.1-Stannacycloheptane Bischloroacetate (**95e**)	176
References and Notes		187

List of Tables

Table 2.1	Yields and isomer ratios of monobenzoylation of **4a** and **4b**	10
Table 2.2	Selected results of monobenzoylation of simple diols	11
Table 2.3	Selectivities in monosubstitution reactions of dibutylstannylene acetals derived from carbohydrates with single *cis*-1,2-diol units on six-membered rings	16
Table 2.4	Selectivities in monosubstitution reactions of dibutylstannylene acetals derived from carbohydrates with single *trans*-1,2-diol units on six-membered rings	20
Table 2.5	Selectivities in monosubstitution reactions of dibutylstannylene acetals derived from carbohydrates with more than two hydroxyl groups on pyranose rings	22
Table 2.6	Selectivities in monosubstitution reactions of dibutylstannylene acetals derived from carbohydrates with primary-secondary 1,2-diol units	26
Table 2.7	Major products of benzoylation of L-arabinose derivatives via their dibutylstannylene intermediates	30
Table 2.8	Brominolysis of carbohydrate-derived dibutylstannylene acetals	31
Table 3.1	Tin-119 NMR spectral data of dialkyltin(IV) derivatives	48
Table 3.2	Selected bond distances (Å) for 1,1-stannacycloheptane bischloroacetate (**95e**)	52
Table 3.3	Selected bond angles (deg) for 1,1-stannacycloheptane bischloroacetate (**95e**)	53
Table 4.1	Conformations of dimer **110a**	81
Table 4.2	Proton NMR chemical shifts of **64**, **104**, **105** and **106**	88
Table 4.3	Proton NMR coupling constants of **64**, **104**, **105** and **106**	88
Table 4.4	Carbon-13 NMR chemical shifts of **64**, **104**, **105** and **106**	89

Table 5.1	Selectivities of the dialkylstannylene acetals in *p*-toluenesulfonation	104
Table 5.2	Tin-119 chemical shifts of the dialkylstannylene acetals	115
Table 5.3	Comparison of ^{13}C chemical shifts of the dialkylstannylene acetals with those of their precursors	127
Table 5.4	One bond ^{119}Sn-^{13}C coupling constants and calculated C-Sn-C angles of dialkylstannylene acetals	140
Table A.1	Summary of crystallographic data for 1,1-stannacycloheptane bischloroacetate (**95e**)	178
Table A.2	Fractional atomic positional parameters and equivalent isotropic temperature factors ($Å^2$) for 1,1-stannacycloheptane bischloroacetate (**95e**)	181
Table A.3	Hydrogen atom positional parameters (Å) for 1,1-stannacycloheptane bischloroacetate (**95e**)	182
Table A.4	Anisotropic temperature factors ($Å^2$) for 1,1-stannacycloheptane bischloroacetate (**95e**)	183
Table A.5	Heavy Atom Bond Angles (°) for 1,1-stannacycloheptane bischloroacetate (**95e**)	184
Table A.6	Heavy Atom Torsional Angles (°) for 1,1-stannacycloheptane bischloroacetate (**95e**)	185

List of Figures

Figure 2.1	The structures of diols listed in Table 2.2	10
Figure 2.2	The structures of the carbohydrate derivatives listed in Table 2.3	17
Figure 2.3	The structures of the carbohydrate derivatives listed in Table 2.4	19
Figure 2.4	The structures of the carbohydrate derivatives listed in Table 2.5	21
Figure 2.5	The structures of the carbohydrate derivatives listed in Table 2.6	27
Figure 2.6	The structures of the substrates listed in Table 2.7	29
Figure 2.7	The structures of some substrates listed in Table 2.8	32
Figure 2.8	The structures of dibutylstannylene acetals **82** and **83** in solid state	35
Figure 2.9	The dimeric structure of methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-glucopyranoside (**84**)	36
Figure 2.10	The pentameric structure of methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-mannopyranoside (**85**)	37
Figure 2.11	Monomeric structures of dibutylstannylene acetals of simple diols	39
Figure 2.12	Dimeric structures of the dibutylstannylene acetal of compound **41**	42
Figure 3.1	ORTEP plot of 1,1-stannacycloheptane bischloroacetate (**95e**) with thermal ellipsoids at the 50% probability level	51
Figure 3.2	Representations of the favored geometries of compounds **94a** to **94d**	58
Figure 4.1	The dimeric structure of the dibutylstannylene acetal derived from 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**104**)	76
Figure 4.2	Part of the 400.14 MHz ^{1}H NMR spectra of the crystalline dimer of compound **110** as a function of time after making up the 0.1 M solution in $CDCl_3$	78
Figure 4.3	Two of the minimum energy conformations of the crystalline dimer **110a**	83

Figure 5.1	Diols and triols derived from monosaccharides studied for *p*-toluenesulfonation using their dialkylstannylene acetals	97
Figure 5.2	Dialkylstannylene acetals derived from primary-secondary diols	98
Figure 5.3	134.6 MHz ^{119}Sn NMR spectra of a 0.33 M solution of **137** in chloroform-*d* at different temperatures	123
Figure 5.4	Dimeric structures of dialkylstannylene acetals derived from primary-secondary 1,2-diols	126
Figure 5.5	149.2 MHz ^{119}Sn NMR spectra of a 0.30 M solution of the hexamethylenestannylene acetal of ethane-1,2-diol in chloroform-*d* at different temperatures	138
Figure A.1	The X-ray structure of 1,1-stannacycloheptane bischloroacetate (**95e**): position 1 of disordered atoms	179
Figure A.2	The X-ray structure of 1,1-stannacycloheptane bischloroacetate (**95e**): position 2 of disordered atoms	180

Abstract

The dibutylstannylene acetals of carbohydrate-derived primary-secondary 1,2-diols **64**, **104**, **105** and **106** were found to be oxidized regiospecifically to corresponding α-hydroxyketone derivatives in much better yields (81% to 95%) by *N*-bromosuccinimide in chloroform solution at room temperature than had previously been done with bromine. One of the products, 3-deoxy-1,2-*O*-isopropylidene-α-D-*erythro*-hexofuranos-5-ulose (**110**), exists to about 20% in solution as a mixture of dimers. One of the dimers can be obtained as a solid and its structure was determined tentatively by a combination of NMR experiments and MM3 molecular mechanics calculations.

The regioselectivity of *p*-toluenesulfonation of dialkylstannylene acetals obtained from carbohydrate-derived primary-secondary 1,2-diols (**64**, **66**, **104-106**, **113-117**) was investigated. For a given diol, the regioselectivity depended on solvent, reaction temperature, and the alkyl groups on the tin atom. Selectivity at secondary position increased on changing the solvent from toluene to chloroform, and also increased on lowering reaction temperature (to 5 °C) with prolonged reaction time. Among all factors, the nature of the alkyl groups on tin atom had the greatest influence. When the R groups were changed from butyl to bigger groups such as isopropyl, selectivity for reaction at secondary oxygen atoms was improved. Reversed regioselectivity was achieved through using hexamethylenestannylene acetals.

The causes of regioselectivity for dialkylstannylene acetal reactions were explored by means of ^{119}Sn NMR spectral measurements and kinetic considerations. It was postulated that *p*-toluenesulfonation of dialkylstannylene acetals occurs through equilibrating dimers and the regioselectivity obtained was attributed to competition between dimer populations and rates of reaction at individual oxygen atoms.

A general method for the preparation of pure dialkyltin oxides was developed which involved preparation of dialkyldiphenyltin derivatives and selective cleavage of the two phenyl groups with chloroacetic acid.

List of Abbreviations and Symbols

Å	Angstrom
All	allyl
$[\alpha]_D^t$	specific rotation measured at temperature t °C using the 589 nanometer sodium D line
Anal.	analysis
Bn	benzyl
bp	boiling point
br	broad peak in NMR
Bu	n-butyl
Bz	benzoyl
Calcd	calculated
Compd	compound
COSY	correlated spectroscopy in NMR
CP/MAS	cross polarization/magic angle spinning
d	doublet in NMR, day(s) in reaction time
δ	chemical shift in NMR
dd	doublet of doublet in NMR
deg	degree
diff.	difference
DMF	*N*,*N*-dimethylformamide
eq.	equivalent

Eq.	equation
g.c.	gas chromatography
h	hour(s)
HETCOR	heteronuclear correlated spectroscopy in NMR
Hz	hertz in NMR
IR	infrared
iBu	isobutyl
iPr	isopropyl
J	coupling constant in NMR
lit.	literature
m	multiplet in NMR, minute(s) in reaction time
M	concentration unit: mole per litre
max	maximum
Me	methyl
MHz	megahertz
min	minimum
mL	millilitre
mmol	millimole
mp	melting point
MS	mass spectrometry
m/z	mass-to-charge ratio in MS
NBS	*N*-bromosuccinimide

NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy in NMR
Ph	phenyl
ppm	part(s) per million
q	quartet in NMR
R_F	fractional migration distance of a compound on TLC
s	singlet
t	triplet
t	tertiary
Temp.	temperature
TLC	thin layer chromatography
TMS	tetramethylsilane
Ts	*p*-toluenesulfonyl

Acknowledgements

I would like to express my sincere thanks to Dr. T. Bruce Grindley, my supervisor, for his constant guidance and enthusiastic encouragement that was always willingly given during the course of this research and for his valuable help during the preparation of this thesis. My special thanks are due to the members of the Grindley group, R. Thangarasa, H. Qin, G. Rockwell, H. Namazi and R. Tan, for their friendship and help during my stay at Dalhousie University.

Thanks are extended to G. Wu and Dr. D. L. Hooper for recording some NMR spectra, to P. K. Bakshi and Dr. T. Stanley Cameron for the X-ray structure determination, to ARMRC for the use of their Bruker AC 250F NMR spectrometer, and to IMB (NRC, Halifax) for permission to use their polarimeter.

The author is indebted to Dalhousie University for financial assistance in the forms of a Graduate Fellowship and a Teaching Assistantship, and to the Killam Trust for the award of a Izaak Walton Killam Memorial Scholarship.

Chapter 1

Background of the Project

Selective functionalization and chemical manipulation of diols and polyols have been subjects of much interest to organic chemists. This is particularly the case in the field of carbohydrate chemistry. Carbohydrates and their derivatives are becoming increasingly important because of the widespread recognition that the surfaces of biological materials such as cells, viruses, antibodies, toxins, etc. either contain complex oligosaccharides or polysaccharides, or interact with oligosaccharides on other species. They are also important as sources of chiral building blocks for the synthesis of bioactive compounds or natural products. New protecting groups and methods of manipulation for diol and polyol systems are continuously reported.

Dibutylstannylene acetals were first applied to carbohydrate chemistry, as nucleophilic intermediates, by Moffatt *et al.*[1] and David.[2] During the last two decades, dibutylstannylene acetals derived from different carbohydrates have been observed to react with several types of electrophiles to give predominately monosubstituted products.[3] Moreover, dibutylstannylene acetal formation greatly increases the reactivity of the parent hydroxyl groups towards electrophiles. Regioselectivity of monosubstitution ranges from poor to excellent depending on the structure of the carbohydrate substrate, the reaction conditions, and the nature of electrophile. For particular classes of substrates with common reaction conditions, regioselectivity has become predictable.[3] Thus, the dibutylstannylene acetal reaction has now become one

of the standard methods employed in carbohydrate chemistry and for other organic compounds containing diol and polyol units.

It is well known that primary hydroxyl groups are more reactive than secondary hydroxyl groups in reactions with electrophiles.[4] As a result, it is usually possible to perform regioselective acylation reactions on a primary hydroxyl group in a diol or polyol unit. It has been shown that dibutylstannylene acetals of carbohydrate-derived primary-secondary diols react with acylating reagents to give higher regioselectivity for reaction at the primary oxygen atoms than direct reactions of the parent diols.

Reversal of regioselectivity to direct reaction at secondary hydroxyl oxygen atoms in the presence of primary hydroxyls is often highly desirable. There is no practical method available for this purpose except for the brominolysis of dibutylstannylene acetals and related tributylstannyl ethers. For *trans*-1,2-diols on a pyranose ring, the regioselectivity obtained appears to be related to the dimeric structures assumed by dibutylstannylene acetals. The nature of the dimeric mixtures present in solution is controlled mainly by steric effects.[5] It is reasonable to believe that the population ratio of different dimers in solution can be changed by altering the steric effects of the alkyl groups on tin atoms. Thus, it is conceivable that reversed regioselectivity may be obtained through employing an appropriate dialkylstannylene acetal.

However, almost all dialkylstannylene acetal reactions studied thus far have been performed on dibutylstannylene derivatives. The steric effects of alkyl groups attached to tin atoms on regioselectivity have not been explored. It was highly

desirable to develop an efficient method for acylation and/or alkylation of carbohydrate-derived primary-secondary diols directly at the secondary hydroxyl groups without protecting the more reactive primary hydroxyls. For these reasons, different dialkylstannylene acetals have been studied as intermediates for *p*-toluenesulfonation of a series of carbohydrate-derived primary-secondary 1,2-diols under various conditions in this thesis. The best results were obtained with hexamethylenestannylene acetals derived from primary-secondary 1,2-diols, which reacted with *p*-toluenesulfonyl chloride in chloroform regioselectively at the secondary oxygen atoms.

In order to obtain a variety of dialkyltin oxides (the precursors of stannylene acetals) in high purity for this study, it was necessary to develop a convenient method for preparation of sterically hindered dialkyltin(IV) derivatives.

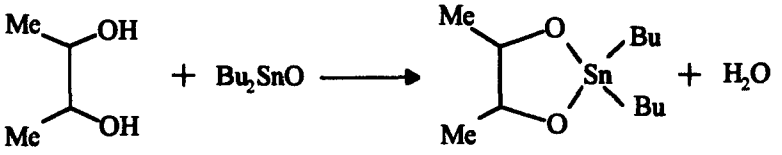
Although oxidation of dibutylstannylene acetals with bromine provides a useful method to transform primary-secondary 1,2-diols directly to α-hydroxyketones, the yields of brominolysis for carbohydrate-derived dibutylstannylene acetals are generally low. Other oxidizing reagents have been examined in this thesis, and *N*-bromosuccinimide proved to be far superior as an oxidizing reagent compared to all of the others studied.

Chapter 2

An Overview of the Applications of Dibutylstannylene Acetals

Dibutylstannylene acetals are easily formed by refluxing a mixture of dibutyltin oxide and one equivalent of a diol or polyol in benzene or toluene in a Dean-Stark apparatus for the continuous removal of water.[3] The formation of the dibutylstannylene acetal of butane-2,3-diol (**1**) illustrates this procedure (Scheme 2.1):

Scheme 2.1



1

These compounds may also be prepared at fairly high dilution (1%) in refluxing methanol, where the soluble methyl ether ($CH_3OSnBu_2OSnBu_2OCH_3$) is probably the reactive species.[1,6]

In most cases, the dibutylstannylene acetal intermediates thus obtained can be used directly in the subsequent reactions without separation or purification, i.e., the manipulation of the parent diols or polyols is a one-pot reaction. These intermediates have proved synthetically useful for accomplishing monosubstitution or monofunctionalization reactions. Acylation, alkylation and oxidation are the most common reactions and the products are often obtained in a regiospecific or highly

regioselective fashion. Sometimes, even enzyme-like selectivity has been observed.[7] Dibutylstannylene acetals also act as templates for the assembly of macrocyclic oligolactones.[8] In addition, dibutylstannylene acetal intermediates have been applied to other chemical manipulations of diols such as the optical enrichment of 1,2-diols[9] and the determination of enantiomeric purity of 1,2-diols in the absence of chiral auxiliaries.[10]

2.1 Substitution and oxidation reactions of simple diols

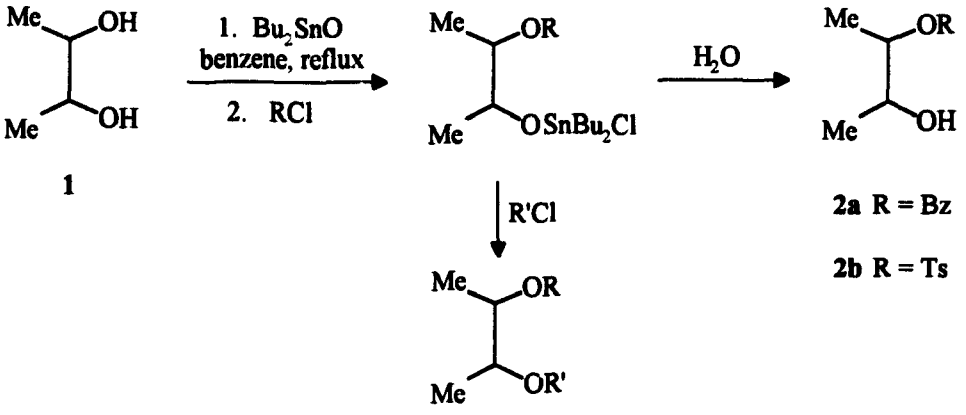
It is highly desirable to develop an efficient method for selective protection of symmetric and unsymmetric diols, because monoprotected diols are often useful as synthetic intermediates of bifunctional compounds in organic synthesis. Various methods have been developed to accomplish this,[4] however, difficulties still arise in practice because of the complexity of diol systems and the different requirements for functionalization. Monosubstitution of diols through dibutylstannylene acetals has been proven to be a solution to this problem.[1-3] This method has also been shown to be valuable in oxidation reactions for symmetric and nonsymmetric diols.

2.1.1 Substitutions of simple 1,2-diols

Dibutylstannylene acetals derived from symmetric 1,2-diols react with one equivalent of electrophiles to give monosubstitution products. For example, Shanzer[11] showed that the dibutylstannylene acetal derived from butane-2,3-diol (**1**) underwent a condensation reaction with one equivalent of benzoyl chloride or *p*-toluenesulfonyl

chloride. Subsequent hydrolysis gave the corresponding hydroxybenzoate **2a** or hydroxy-*p*-toluenesulfonate **2b** in quantitative yields. Nonsymmetric diesters could be prepared if the reaction mixture was treated with a second equivalent of acyl chloride instead of hydrolysis (see Scheme 2.2). Stepwise reaction in double esterification was attributed to the presence of a deactivating electronegative chlorine substituent on tin after the first esterification.

Scheme 2.2



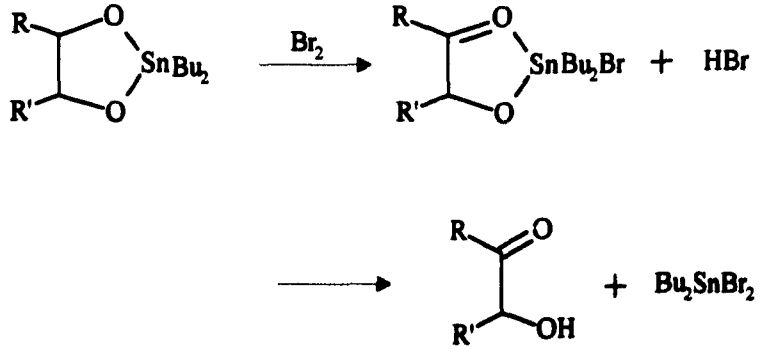
Alkylation of dibutylstannylene acetals generally require fairly strong reaction conditions (*i.e.*, elevated temperature and prolonged reaction time) even with the assistance of a stannophilic catalyst, such as a tetraalkylammonium halide. Nagashima and Ohno[12] found that monoalkylation of dibutylstannylene acetals could be carried out under mild conditions in the presence of cesium fluoride. For example, the dibutylstannylene acetal of dimethyl L-tartrate (**3**) was reacted with benzyl bromide in DMF at room temperature in the presence of cesium fluoride (1.22 mole equivalent)

for 2h, giving 85% of mono-*O*-benzylated product, whereas the same reaction in the absence of cesium fluoride required 3 h at 100 °C and gave only 41% of mono-*O*-benzylated product. When this methodology was applied to nonsymmetric secondary-secondary and secondary-tertiary diols, regioselective monoalkylation was achieved in good to excellent yield. For instance, benzylation of the dibutylstannylene acetal derived from 1-phenylethane-1,2-diol (**4a**) gave mono-*O*-benzylated products quantitatively with the ratio of 90:10 in favour of the primary benzylation.[12a]

2.1.2 Oxidation reactions

Dibutylstannylene acetals are easily oxidized to hydroxyketones by bromine in dichloromethane.[2,3a,13] The reaction proceeds at room temperature at a rate of titration. In many cases, the bromine oxidation becomes sluggish after addition of two-thirds of an equivalent of bromine. It was suggested that HBr generated in the brominolysis step attacked the starting dibutylstannylene acetal and slowed the reaction (see Scheme 2.3). Nevertheless, good to excellent yields may generally be obtained for simple 1,2-

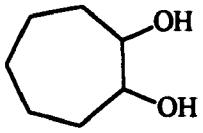
Scheme 2.3



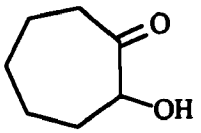
diols in the presence of special bases or HBr scavengers, such as tributyltin methoxide or molecular sieves.

For example, dibutylstannylene acetals formed from *cis* and *trans*-cycloheptane-1,2-diol **5** are oxidized quantitatively to the hydroxyketone **6**. This method also works well for secondary-tertiary diols. Thus, the dibutylstannylene acetals of 1,2-diphenylpropane-1,2-diol (**7**), *trans*-1-methylcyclohexane-1,2-diol (**9**) and *trans*-1-phenylcyclohexane-1,2-diol (**10**) were oxidized to the corresponding α-hydroxyketones **8**, **11** and **12**, respectively (Scheme 2.4). When extended to unsymmetric diols, the reaction proved to be highly regioselective (see Section 2.3.6).

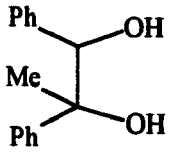
Scheme 2.4



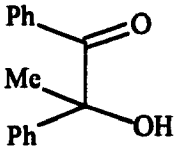
5



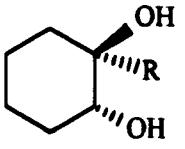
6



7

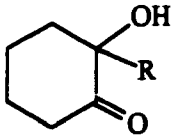


8



9 R = Me

10 R = Ph



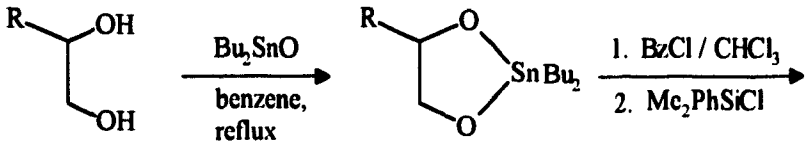
11 R = Me

12 R = Ph

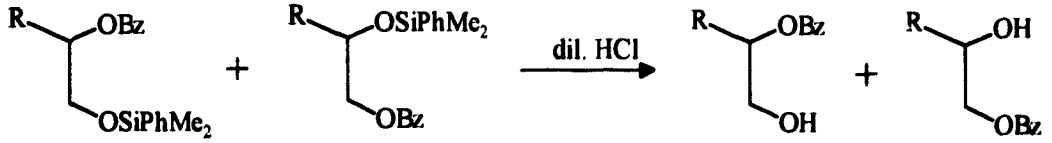
2.1.3 Reversed regioselectivity in acylations of unsymmetric diols

Reversed regioselectivity for esterification has been reported[14] in mono-*O*-acylations of unsymmetrically substituted diols through their dibutylstannylene acetals. 1-Phenylethane-1,2-diol (**4a**) and propane-1,2-diol (**4b**) were quantitatively converted into their corresponding dibutylstannylene acetals (**13a** and **13b**) and treated with benzoyl chloride (1 eq.) and then with phenyldimethylsilyl chloride (1 eq.) at 0 to 5°C in $CHCl_3$. Hydrolysis of the regioisomeric silyl ether esters **14** and **15** was conducted with cold HCl to give the corresponding hydroxyl esters **16** and **17** respectively (Scheme 2.5). In both the reactions, the secondary benzoates were the major products. The yields and regioisomeric ratios of products obtained with this method (Method A) are compared with the results from a conventional method (Method B) in Table 2.1.

Scheme 2.5



4 **13**



14 **15** **16** **17**

a, R = Ph; b, R = Me

Table 2.1 Yields and isomer ratios of monobenzoylation of **4a** and **4b**[a]

1,2-diol	Method A		Method B	
	Yield(%)	Ratio(**14**:**15**)	Yield(%)	Ratio(**14**:**15**)
4a	90	95:5	81	4:96
4b	84	85:15	78	9:91

[a] Values determined by g.c. Method A: as described above; Method B: standard acylation method in benzene, in the presence of stoichiometric amount of pyridine, using (i) PhCOCl and (ii) $Me_2PhSiCl$.

Extensive studies on various unsymmetric 1,2-, 1,3-, and even 1,4-diols indicated that the reversed regioselectivity could be obtained even for some primary-tertiary diols. The results obtained from diols **4a** and **18-26** (see Figure 2.1 for structures) are given in Table 2.2. These results will be discussed further in connection with the results reported in Chapter 5.

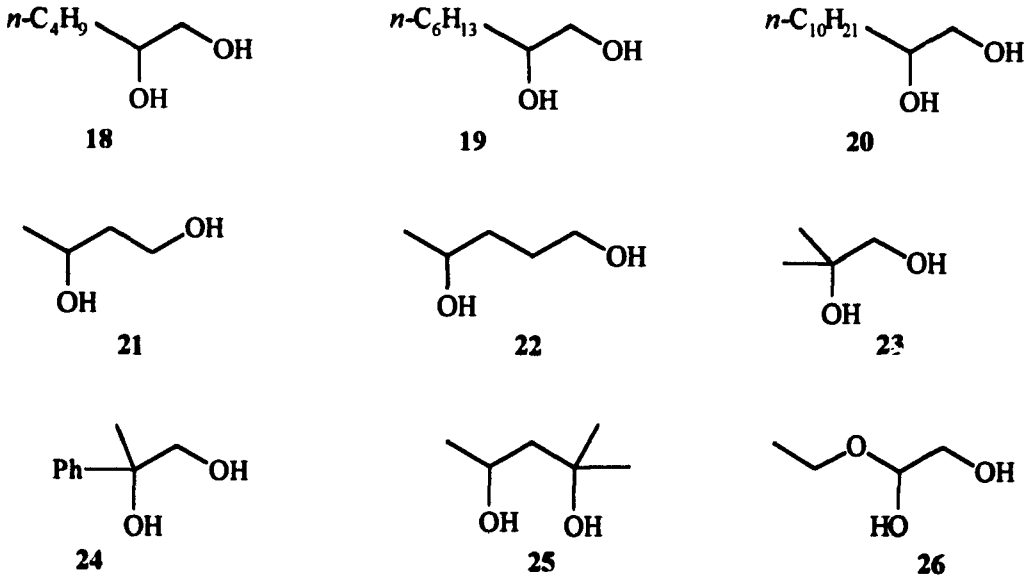


Figure 2.1 The structures of diols listed in Table 2.2

Table 2.2 Selected results of monobenzoylation of simple diols

Diol[a]	Quenching reagent[c]	Monoester yield(%)[b]	Ratio[b] MME[d]	LME[e]
4a	Me_3SiCl	83	98	2
18	$(COOH)_2$	84	72	28
19	$(COOH)_2$	80	72	28
20	$(COOH)_2$	70	66	34
21	$(COOH)_2$	76	78	22
	$PhMe_2SiCl$	80	79	21
22	$PhMe_2SiCl$	61	69	31
23	$PhMe_2SiCl$	61	90	10
24	$PhMe_2SiCl$	50	77	23
25	Me_3SiCl	92	63	37
26	Me_3SiCl	72	76	24

[a] For structures of diols, see Figure 2.1. [b] Yield and selectivity data were obtained by ^1H NMR analysis, not from product separation. [c] the reaction intermediates of stannylene acetals with benzoyl chloride were quenched by quenching reagents indicated and the quenched products were analyzed by ^1H NMR. [d] MME is most substituted monoester. [e] LME is least substituted monoester.

2.2 Synthesis of macrocyclic oligolactones

Esters may be prepared from mixtures of glycols and benzoic acid by heating the mixture in the presence of dibutyltin oxide.[15] This method of esterification proved extremely valuable in the synthesis of macrocyclic lactones and lactams, which were obtained in good to excellent yields by refluxing solutions of an ω-hydroxycarboxylic acid, or an ω-aminocarboxylic acid in mesitylene with 10% (mol-equivalent) dibutyltin oxide, using a Dean-Stark apparatus for continuous removal of water.[16]

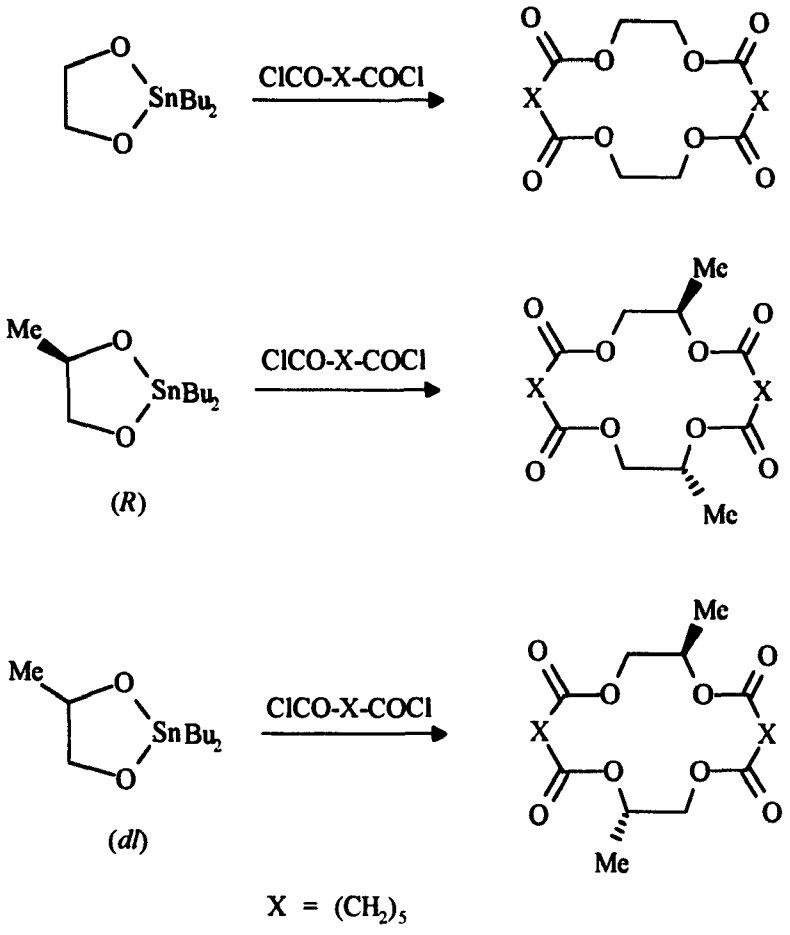
Shanzer *et al.* have developed an important reaction between dibutylstannylene acetals (derived from chiral or achiral 1,2-diols) and diacyl dihalides or dicarboxylic anhydrides (chiral or achiral) in apolar solvents to give macrocyclic tetralactones with remarkable yields and outstanding regio- and stereo-selectivities.[9,17] They also demonstrated that mixed tetralactones could be prepared as the only products by successive addition of two different diacyl dihalides (or dicarboxylic anhydrides). Some examples are given in Scheme 2.6.

Basson and co-workers[17] applied dibutylstannylene acetals to the condensation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside with succinyl chloride, furnishing two macrocyclic tetralactones, a hexalactone and an octalactone. Roelens *et al.*[19] studied the dibutylstannylene-mediated condensations of ethylene glycol with a series of diacyl dichlorides and several types of polylactones were obtained.

Recently, Bredenkamp *et al.*[8] reported the use of dibutylstannylene acetals as templates for the assembly of macrocyclic oligolactones. Dibutylstannylene-mediated macrolactonization of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside with glutaryl and

phthaloyl dichloride yields the respective dilactones, parallel tetra'actones, as well as antiparallel tetralactones.

Scheme 2.6



2.3 Applications in carbohydrate chemistry

Dibutylstannylene acetal reactions have been widely employed in synthetic carbohydrate chemistry during the last twenty years. The major advantages of this method are high regioselectivity and significant enhancement of reactivity of the parent hydroxyl groups. The applications of dibutylstannylene intermediates are mainly focused on acylation, alkylation, and oxidation in diol or polyol systems. By this method, different protecting groups and functional groups can be introduced into the desired positions regioselectively and hydroxyketones are easily obtained from diols through oxidation of dibutylstannylene acetals.

A huge number of publications have appeared in literature. For those published before 1989, several reviews are available.[3,20] The examples given in the following subsections are mainly selected from papers published during the last three years.

2.3.1 Substitution reactions of *cis*-1,2-diols on glycopyranose rings

The reactivity of a hydroxyl group can be predicted to some extent from kinetic and thermodynamic criteria.[4b] For instance, it is well-known that an equatorial hydroxyl group on a pyranose ring can be acylated preferentially in the presence of secondary axial hydroxyls. However, this process may not be sufficient and recourse is made to prior functionalization, followed by generation of the desired hydroxyl group for further transformation. This may involve several steps before the desired transformation can be effected. The dibutylstannylene acetal method makes the

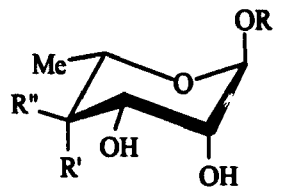
acylation and alkylation reactions occur more efficiently in a one-pot manner and, in most cases, with increased regioselectivity. Some recent literature results are given in Table 2.3.

Monosubstitution (acylation and alkylation) of dibutylstannylene acetals in a polar solvent or in the presence of added nucleophiles occurs regioselectively or regiospecifically at the equatorial hydroxyl groups. Although the direction of selectivity is similar to that obtained with conventional methods (acylation in pyridine, for example),[21] the reactivity and regioselectivity of dibutylstannylene acetals are much higher. In some cases, when the same reaction is carried out in a non-polar solvent in the absence of added nucleophiles, the reaction occurs regioselectively at the axial position. For example, benzoylation of the dibutylstannylene acetal of α-D-mannopyranose derivative **30** in benzene in the presence of *N*-methylimidazole gave 3-*O*-benzoate (reaction at equatorial position) with over 90% yield.[22] However, when the reaction was carried out in the absence of *N*-methylimidazole, the regioselectivity was reversed (85% of 2-*O*-benzoate and 15 % of 3-*O*-benzoate).[23]

Table 2.3 Selectivities in monosubstitution reactions of dibutylstannylene acetals derived from carbohydrates with single *cis*-1,2-diol units on six-membered rings

Diol[a]	Reaction[b]	Solvent	Temp. (°C)	Yield (%)		Ref.
				C-2	C-3	
27	methylation	benzene	80	-	80	[24]
28	PMB	DMF	90	-	83	[25]
29	methylation	benzene[d]	80	-	98	[26]
30	tosylation	dioxane[c]	20	-	97	[22]
	tosylation	dioxane	20	10	40	[22]
31	allylation	DMF	-	-	68	[27]
32	PMB	DMF[e]	20	-	82	[28]
33	PMB	DMF[e]	20	-	85	[29]
				C-3	C-4	
34	DMT	DMF	20	68	-	[30]
35	benzylation	toluene	reflux	47	43	[31]
36	benzylation	DMF[e]	-	70	-	[32]
37	benzylation	DMF[e]	reflux	81	-	[33]
38	benzylation	DMF[e]	reflux	82	-	[34]
39	TBDMS	toluene[d]	reflux	65	-	[35]

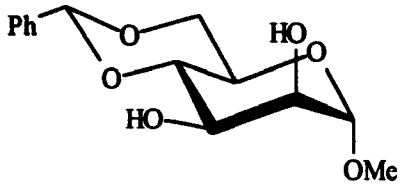
[a] For structures of diols, see Figure 2.2. [b] DMT: dimethoxytritylation; PMB: *p*-methoxybenzylation; TBDMS: *t*-butyldimethylsilation. [c] Added 4-dimethylaminopyridine. [d] Added Bu_4NBr. [e] Added CsF.



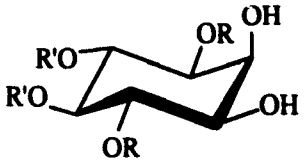
27 R = Me, R' = OBn, R" = H

28 R = All, R' = H, R" = OBn

29 R = Bn, R' = H, R" = OBn



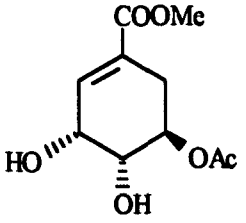
30



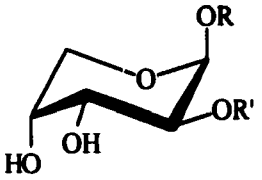
31 R = R' = All

32 R = R' = Bn

33 R = Bn, R' = PrCO

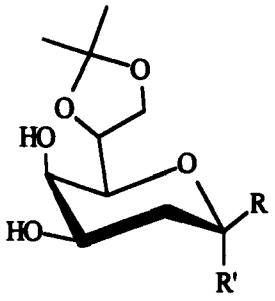


34



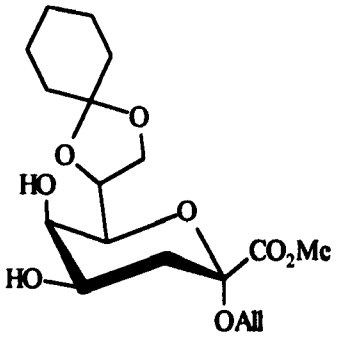
35 R = Me, R' = H

36 R = R' = Bn



37 R = SEt

38 R = $O(CH_2)_3NH_2$



39

Figure 2.2 The structures of the carbohydrate derivatives listed in Table 2.3

2.3.2 Substitution reactions of *trans*-1,2-diols on glycopyranose rings

As for the substitution reactions of *cis*-1,2-diols on glycopyranose rings, regioselective monosubstitution can also be obtained for *trans*-1,2-diols on pyranose rings. In the *trans*-diol systems, the situation becomes more complicated because both of the hydroxyl groups are almost always in equatorial orientations. Several factors may affect regioselectivity as can be seen from the results summarized in Table 2.4.

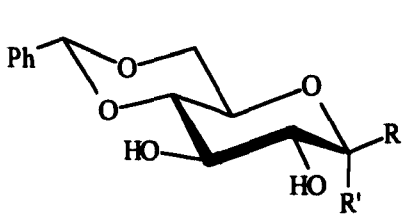
Firstly, axial oxygen-containing substituents adjacent to the diol units have important effects on selectivity. If only one axial oxygen-containing substituent is next to the diol unit, mono-*O*-substitution occurs regioselectively on the hydroxyl group which is adjacent to this axial substituent. For example, acylation reactions of the dibutylstannylene acetal derived from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**40**) in dioxane gave only 2-*O*-acylated products.[22]

Secondly, steric effects of substituents affect regioselectivity. If one side of the diol unit is unsubstituted, *i.e.*, a methylene group which possesses the least steric effect of all substitution situations, the reaction occurs regioselectively at the hydroxyl group adjacent to the methylene group. Compound **47** gives an example in this category.[36] When two axial oxygen-containing substituents are on both side of the diol unit, the reaction is not very selective and the direction of reaction regioselectivity is difficult to predict.

The presence of added nucleophiles and other factors may also change the selectivity of the reaction. Hypotheses have been made to interpret the selectivity of dibutylstannylene acetal reactions by assuming that the reactions occur through the

dimers or oligomers present in solutions (see Section 2.4 for detail).[5,37,38]

Yu and Fraser-Reid[39] reported an example which seemed to be in contrast to the adjacent axial-oxygen-containing group effect. Benzylation of *myo*-inositol derivative **49** (see Figure 2.3 for structure) via its dibutylstannylene acetal in the presence of cesium fluoride gave mono-*O*-benzylated products. The ratio of 6-*O*-benzylation (the oxygen atom next to an equatorial oxygen) to 1-*O*-benzylation was 97 to 3. This is probably due to the distortion of the six-membered ring which is fused to two five-membered rings.

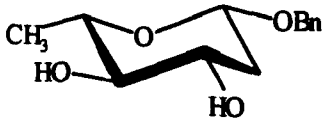


40 R = H, R' = OMe

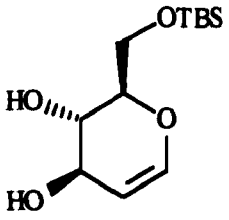
41 R = OBn, R' = H

42 R = OMe, R' = H

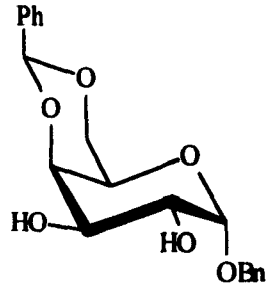
43 R = SPh, R' = H



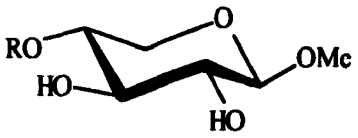
47



48

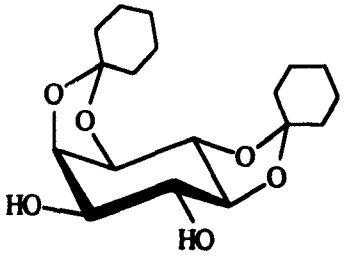


44



45 R = Bz

46 R = Bn



49

Figure 2.3 The structures of the carbohydrate derivatives listed in Table 2.4

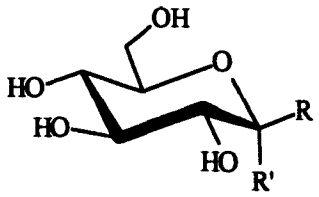
Table 2.4 Selectivities in monosubstitution reactions of dibutylstannylene acetals derived from carbohydrates with single *trans*-1,2-diol units on six-membered rings

Diol[a]	Reaction[b]	Solvent	Temp. (°C)	Yield (%)		Ref.
				C-2	C-3	
40	tosylation	dioxane[c]	reflux	99	-	[22]
	mesylation	dioxane[c]	reflux	93	-	[22]
	Bs	dioxane[c]	reflux	100	-	[22]
	Sf	dioxane[c]	reflux	100	-	[22]
41	benzylation	benzene[d]	80	21	55	[5]
	benzoylation	benzene[e]	25	53	37	[5]
42	tosylation	dioxane[c]	reflux	77	-	[22]
43	benzylation	CH_3CN[e]	reflux	-	48	[40]
44	benzylation	benzene[d]	80	43	49	[5]
	benzoylation	benzene[e]	25	38	46	[5]
	benzoylation	DME[f, g]	25	51	49	[5]
45	benzoylation	benzene	0	-	83	[41]
46	benzoylation	benzene	0	48	34	[41]
				C-3	C-4	
47	tosylation	toluene[h]	26	98	-	[36]
48	benzylation	toluene[d]	-	99	-	[42]

[a] For structures of diols, see Figure 2.3. [b] Bs: benzenesulfonation; Sf: *p*-toluenesulfination. [c] Added 4-dimethylaminopyridine. [d] Added Bu_4NBr. [e] Molecular sieves added. [f] 1,1-Dimethoxyethane. [g] Added triethylamine. [h] Added Bu_4NI.

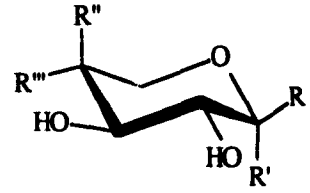
2.3.3 Substitution reactions of carbohydrate derivatives with more than two hydroxyl groups on glycopyranose rings

Considerable work has been done on acylation and alkylation reactions in partially protected or unprotected glycopyranosides. Table 2.6 gives some examples. In most cases, high regioselectivities have been obtained. These results can be understood by combining the regioselectivity arguments discussed in Sections 2.3.1



50 R = H, R' = OMe

51 R = OMe, R' = H



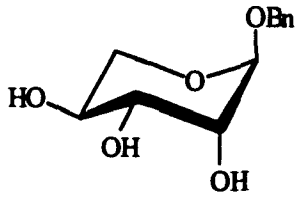
52 R = H, R' = OMe, R" = H, R"' = OH

53 R = OMe, R' = H, R" = H, R"' = OH

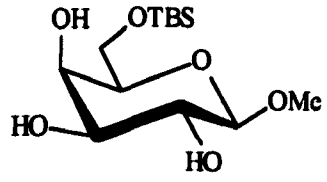
54 R = H, R' = OMe, R" = OH, R"' = H

55 R = All, R' = H, R" = H, R"' = OH

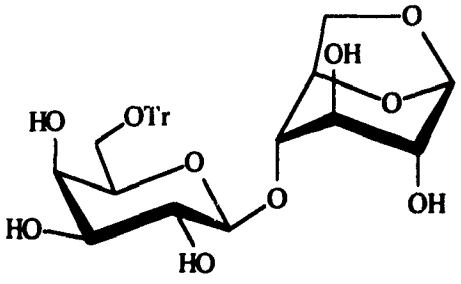
56 R = H, R' = OBn, R" = H, R"' = OH



57



58



59

Figure 2.4 The structures of the carbohydrate derivatives listed in Table 2.5

Table 2.5 Selectivities in monosubstitution reactions of dibutylstannylene acetals derived from carbohydrates with more than two hydroxyl groups on pyranose rings

Diol[a]	Reaction	Solvent	Temp.	Yield (%)				Ref.
			(°C)	C-2	C-3	C-4	C-6	
50	tosylation	dioxane[b]	reflux	28	-	-	22	22
51	tosylation	dioxane[b]	reflux	-		-	92	22
52	tosylation	dioxane[b]	reflux	32	-	52	[c]	22
53	benzoylation	benzene	0	-	-	93	[c]	41
	[d]	benzene	20	-	-	59[e]	[c]	41
	tosylation	dioxane[b]	reflux	-	-	100	[c]	22
54	tosylation	dioxane[b]	reflux	-	41	53	[c]	22
55	benzoylation	benzene	0	-	-	81	[c]	41
56	benzylation	benzene	0	44	-	29[f]	[c]	41
57	methylation	THF[g]	0	-	86	-	[c]	43
58	benzylation	-	-	-	98	-	[c]	44
59	allylation	toluene[h]	95	-	62	-	[c]	45

[a] For structures of diols, see Figure 2.4. [b] Added 4-dimethylaminopyridine. [c] Position not available. [d] 4-*O*-Acetylferuloylation. [e] With 15% of 3,4-di-*O*-substituted product. [f] With 14% of 2,4-dibenzoate. [g] Added CsF and imidazole. [h] Added Bu_4NI.

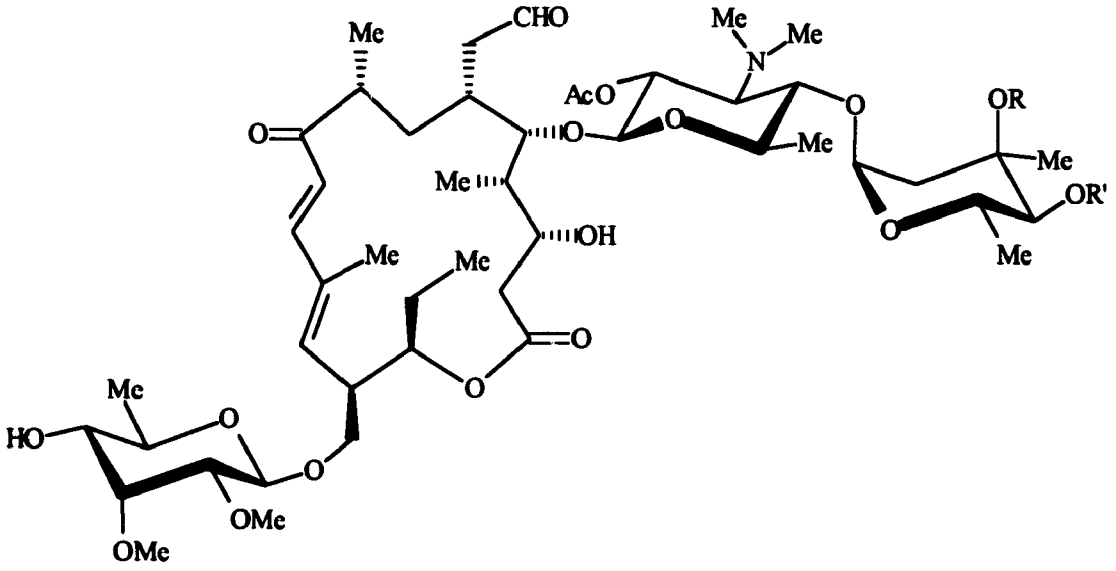
and 2.3.2 and, at the same time, considering the inherent reactivities of different hydroxyl groups, as well as the ease of formation or stability of different dibutylstannylene acetals when more than one such acetal may be formed in the same molecule.

For example, compound **57** is a 2,3,4-trihydroxy derivative that can form two dibutylstannylene acetals, *i.e.*, a 2:3 acetal or a 3:4 acetal. The latter is formed from a *trans*-diol unit and the fused five-membered ring has considerable strain energy.[46] In contrast, incorporating two *cis*-hydroxyls into the five-membered ring to form the 2:3 acetal is much more favourable. Therefore, monosubstitution of **57** should occur dominantly through the 2:3 stannylene acetal which is the one formed from an *axial-equatorial 1,2-diol*. Thus, the reaction is predicted to occur regioselectively at O-3 in spite of the fact that O-4 is the least sterically hindered. Methylation of this compound occurs smoothly in tetrahydrofuran in the presence of cesium fluoride and imidazole, affording the 3-*O*-methylated product in good yield (86%).[43] In disaccharide **59**, five secondary hydroxyl groups exist on the two pyranose rings. Allylation of this compound via its dibutylstannylene acetal in the presence of tetrabutylammonium iodide results in the 3'-*O*-substituted product in 62% yield regioselectively.[45] This also provides a good example for predicting the regioselectivity of this type of reaction.

Kiyoshima *et al.*[47] demonstrated that the dibutylstannylene acetal method could be successfully applied to large molecules such as tylosin (**60**), a macrolide antibiotic which possesses one disaccharide unit and one monosaccharide unit attached to a 16-

membered ring. Compound **60** was first converted to its dibutylstannylene acetal **61** by refluxing with dibutyltin oxide in benzene for 3 h. The stannylated mixture was allowed to react with acyl chlorides or alkyl halides in toluene with or without an added nucleophile, giving 4"-*O*-substituted tylosins **62a-g**, the bio-active derivatives, regioselectively in reasonable yields for all reactions (Scheme 2.7).

Scheme 2.7



60 R = R' = H

61 R, R' = $SnBu_2$

62 R = H:

a, R' = $PhCH_2COO$ **b**, R' = *p*-$MeOPhCH_2COO$

c, R' = $MeOCH_2$ **d**, R' = *p*-$MeOPhCH_2$

e, R' = $PhCH_2$ **f**, R' = *p*-$MeOPhCOCH_2$

g, R' = *p*-$MeCOPhCH_2$

2.3.4 Substitution reactions of carbohydrate-derived primary-secondary 1,2-diols

A few dibutylstannylene acetals derived from carbohydrates with primary-secondary 1,2-hydroxyl groups have been subjected to acylation and alkylation reactions (see Table 2.6). In general, high regioselectivities have been obtained at the primary hydroxyl groups which are inherently more reactive than the secondary hydroxyls.

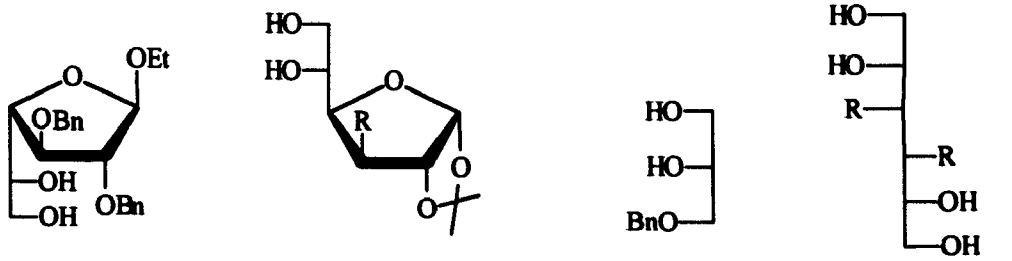
Although electrophilic substitutions selectively occur at primary positions through both the conventional method and dibutylstannylene acetal method, reactions with the latter occur much more efficiently and often give much higher yields. For instance, *p*-toluenesulfonation of 1,2-*O*-isopropylidene-α-D-glucofuranose (**66**) by using its dibutylstannylene acetal afforded the 6-*O*-*p*-toluenesulfonate in 98% yield, while direct *p*-toluenesulfonation of this compound in pyridine gave only 51% yield.[22]

When the reaction was carried out in a non-polar solvent (such as benzene) and in the absence of an added nucleophile, the selectivity at the secondary hydroxyl group increased. In the case of 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose (**64**), when the benzoylation of its dibutylstannylene acetal was carried out in pyridine, a polar nucleophilic solvent, only the primary benzoate was obtained (75% yield). In contrast, the same reaction in benzene gave a mixture of primary benzoate (38%), secondary benzoate (7%), and dibenzoate (24%).[13] As the secondary benzoate was probably the precursor of the dibenzoate, it seemed that the selectivities at both positions were comparable. Nevertheless, this result is very different from the reversed regioselectivity for simple diols that was reported by Reginato *et al* .[14]

Table 2.6 Selectivities in monosubstitution reactions of dibutylstannylene acetals derived from carbohydrates with primary-secondary 1,2-diol units

Diol[a]	Reaction	Solvent	Temp. (°C)	Yield (%) primary	Yield (%) secondary	Ref.
63	Tosylation	MeOH[b]	5	81	-	[48]
64	Benzoylation	benzene[c]	rt	38	7[d]	[13]
	Benzoylation[e]	C_6H_5N	rt	75	-	[13]
65	Benzoylation	C_6H_5N	20	100[f]	-	[49]
66	Tosylation	dioxane[g]	20	98	-	[22]
	Benzoylation	dioxane[g]	20	75	-	[22]
67	Benzoylation	MeOH[b]	0	75	-	[50]
68	Alkylation[h]	DMF	90	65-71	-	[51a]
	Acylation	CH_2Cl_2/THF	0	84	-	[51b]
69a	Benzylation	toluene	70	74[i]	-	[52a]
69b	Benzylation	toluene[j]	70	60[k]	-	[52b]

[a] For structures of carbohydrates see Figure 2.5. [b] Triethylamine added. [c] 4 Å molecular sieves added. [d] With 28% 5,6-di-*O*-benzoate. [e] With 2 eq. of benzoyl chloride. [f] Yield 65% after a second reaction in a one-pot procedure. [g] Added 4-dimethylaminopyridine. [h] Four alkylation reactions, the alkyl groups are $C_{18}H_{37}$, $C_{16}H_{33}$, $C_{14}H_{29}$, and $C_{12}H_{25}$, respectively. [i] Reaction was carried out with 2 equivalents of Bu_2SnO and then with 4 equivalents of BnBr in the presence of Bu_4NI, giving 1,6-di-*O*-benzylated product. [j] Added Bu_4NBr. [k] 1,6-Di-*O*-benzylated product.



63 **64** R = OMe, **65** R = OBz **68** **69a** R = OBn

66 R = OH, **67** R = F **69b** R = H

Figure 2.5 The structures of the carbohydrate derivatives listed in Table 2.6

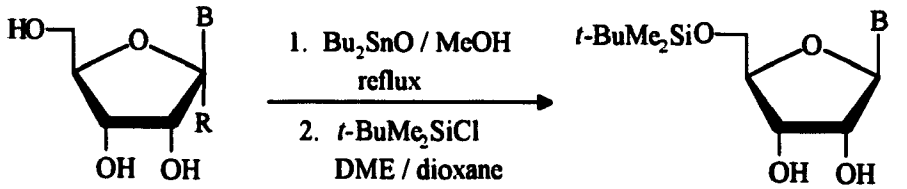
2.3.5 Substitution reactions in other systems

The dibutylstannylene acetal method has also been used in electrophilic substitutions on hydroxyl oxygen atoms in carbohydrates with other structures and related compounds. The earliest application of this method was to the monoacylation and monoalkylation of nucleosides **70a-d**, a system having a *cis*-1,2-diol unit on a furanose ring and a primary hydroxyl group.[1] For this series of nucleosides, reactions conducted in methanol occurred regioselectively at one of the two hydroxyl groups in the 1,2-diol unit on the ring but not at the primary position or on the basic amino groups. In contrast, Gopalakrishnan *et al.*[53] reported a totally different selectivity for silylations on the same nucleosides. For example, silylation of compounds **70a-c** with *t*-butyldimethylsilyl chloride (TBDMS) in DMF/dioxane (dry, 1:4 v/v), in the presence of dibutyltin oxide, gave exclusively 5'-*O*-silyl derivatives **71a-c**, the primary substituted products, in high yields (see Scheme 2.8). No 2'- or 3'-*O*-silylations were observed even with excess silylating reagents. This result was explained as arising

from steric interference of the postulated cyclic stannylene acetal intermediate with the very bulky TBDMS group.[53]

Recently, Grouiller *et al.*[54] reported a steric effect on the regioselectivity of the *p*-toluenesulfonation of unprotected nucleosides **72a-c**. They found that the selectivity was dependent upon the steric bulk at C-1' (see Scheme 2.8 for structures of **72a-c**). Upon treatment overnight at room temperature with 2.2 equivalents of dibutyltin oxide, 1.5 equivalents of *p*-toluenesulfonyl chloride and 1 equivalent of tetrahexylammonium chloride in acetonitrile, compound **72a** gave the 2'-*O*-*p*-toluenesulfonate in 70% yield whereas compounds **72b** and **72c** afforded 70% yield of a mixture of 2'-*O*-*p*-toluenesulfonate and 3'-*O*-*p*-toluenesulfonate.

Scheme 2.8



70 R = H

a, B = uracil; **b**, B = cytosine

c, B = adenine; **d**, B = hypoxanthine

71a (91%)

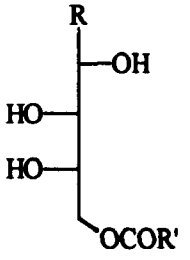
71b (80%)

71c (82%)

72 B = thymine

a, R = H; **b**, R = CN; **c**, R = Me

Bredenkamp *et al.*[55] reported the selective benzoylation of the dibutylstannylene acetals of L-arabinose derivatives (**73a-e**) which are acyclic carbohydrates with three secondary hydroxyl groups. Their results (see Table 2.7) showed that, in all experiments, no 3-*O*-benzoylation occurred. The formation of the dibutylstannylene acetal intermediates selectively activated the 4-positions of both ethyl and benzyl thioacetals (**73a** and **73e**) and of the oxime ether (**73b**). Steric crowding of the ester carbonyl group at position 5 led to loss of selectivity (see the result for compound **73d**), yielding a mixture of 2- and 4-mono-*O*-benzoylated and 2,4-di-*O*-benzoylated products. In fact, the latter was the major product. This suggested that, in this case, the rate for the introduction of the second benzoyl group was of the same order as that of the first. This was quite different from benzoylation of most dibutylstannylene acetals derived from diols or polyols mentioned earlier in this chapter. Replacement of sulphur atoms in the thioacetals with oxygen led to complete reversal of selectivity (see result for **73c**), favouring exclusive benzoylation at position 2.



73a R = CH $(SEt)_2$, R' = Ph

73b R = CHNOBn, R' = Ph

73c R = CH $(OMe)_2$, R' = Ph

73d R = CH $(SEt)_2$, R' = CMe_3

73e R = CH $(SBn)_2$, R' = Ph

Figure 2.6 The structures of the substrates listed in Table 2.7

Table 2.7 Major products of benzoylation of L-arabinose derivatives via their dibutylstannylene intermediates[a]

Substrate[b]	Total yield	Ratio of products			
	(%)[c]	2-*O*-Bz	3-*O*-Bz	4-*O*-Bz	2,4-di-*O*-Bz
73a	88	<1	-	85	14
73b	96	<1	-	95	4
73c	99	98	-	<1	<1
73d	71	26	-	33	41
73e	89	<1	-	90	9

[a] Dibutylstannylene acetals reacted with 1 eq. of benzoyl chloride in benzene at 0°C and then stirred at r.t. for 3 h. [b] For structures see Figure 2.6. [c] As percentage of carbohydrate substrate.

Highly regioselective acylations of free sucrose via the dibutylstannylene acetal method have been patented twice during the last several years.[56] For instance, the dibutylstannylene acetal of sucrose was allowed to react with benzoyl anhydride in DMF at 0-5 °C for 4 h and then at ambient temperature for 48 h to give 96% yield of sucrose 6-benzoate despite the presence of eight hydroxyl groups (three primary and five secondary) in the molecule.

2.3.6 Oxidation reactions of carbohydrate-derived dibutylstannylene acetals

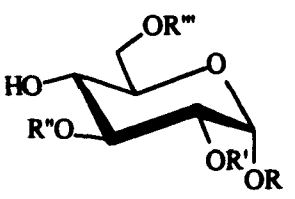
Dibutylstannylene acetals derived from carbohydrates can be easily oxidized by bromine to give hydroxyketones in the same way as those derived from simple diols.

Carbohydrate-based diols are usually unsymmetric, and the brominolysis of dibutylstannylene acetals derived from these diols are highly regioselective. Some examples are illustrated in Table 2.8.

Table 2.8 Brominolysis of carbohydrate-derived dibutylstannylene acetals[a]

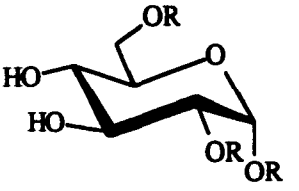
Substrate	Solvent	Yield (%)					Ref.
		C-2	C-3	C-4	C-5	C-6	
56	chloroform[b]	-	-	72	[c]	[c]	57
64	benzene[b]	[c]	[c]	[c]	48	-	13
66	benzene[b]	[c]	-	[c]	50	-	58
74	benzene[b]	[c]	-	72	[c]	[c]	13
75	CH_2Cl_2[d]	[c]	[c]	87	[c]	-	13
76	CH_2Cl_2[d]	[c]	-	75	[c]	[c]	13
77	benzene[b]	-	46	[c]	[c]	[c]	13
	CH_2Cl_2[d]	-	72	[c]	[c]	[c]	13
78	CH_2Cl_2[b,d]	34	17	[c]	[c]	-	59
79	CH_2Cl_2[b,d]	-	50	[c]	[c]	-	58
80	CCl_4	72	-	[c]	[c]	[c]	60

[a] All reactions were carried out at room temperature, for structures of substrate see Figure 2.4, 2.5, and 2.7. [b] Molecular sieves added. [c] Position not available. [d] In the presence of tributyltin methoxide.

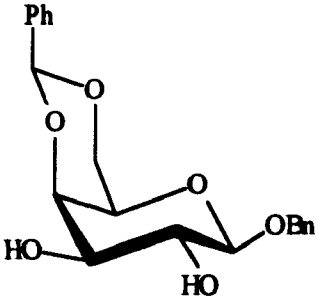


74 R = R' = Me, R" = H, R"' = Tr

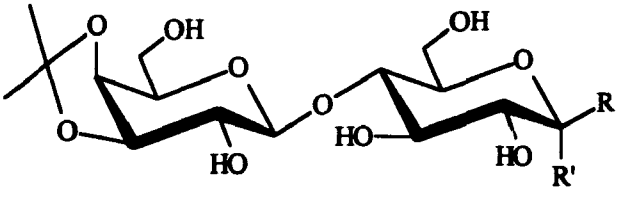
75 R = R' = R" = Bn, R"' = H



76 R = Bn

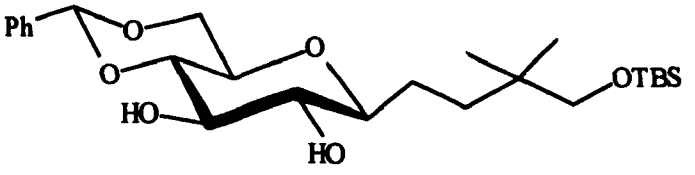


77



78 R = H, R' = OMe

79 R = OMe, R' = H



80

Figure 2.7 The structures of some substrates listed in Table 2.8

Although the reactions are very regioselective, yields are generally low or moderate, often around 50%.[13] In addition, unusual bases such as tributyltin methoxide or molecular sieves are required to scavenge hydrogen bromide generated in the reaction. One obvious advantage of this method is that the primary hydroxyl

group, the inherently more reactive one, is not affected by the oxidizing reagent. For instance, brominolysis of the dibutylstannylene acetals derived from compounds **64** and **65**, the primary-secondary 1,2-diols, gave only 5-oxo derivatives. This is quite dissimilar to the substitution reactions which occur regioselectively at primary positions for both compounds.[13,49] Another noticeable aspect of this oxidation is that in a axial-equatorial 1,2-diol unit, the reaction occurs regiospecifically at the axial hydroxyl groups, while acylation and alkylation reactions give mainly equatorial substituted products.

The related tributylstannyl ethers have also been employed as intermediates for oxidizing diols or polyols with bromine in the very similar manner.[3] Tsuda *et al.*[57,61a-c] claimed that good to excellent yields had been obtained from oxidation of a series of carbohydrate-derived diols and polyols by means of the bis(tributyltin)oxide-bromine oxidation. For instance, 1,2-*O*-isopropylidene-α-D-glucofuranose (**66**) was converted into its 5-oxo derivative in 92% yield with this method. However, Reitz and Baxter[58] could only obtain the same product in 35% yield from compound **66** when they followed the procedure reported by Tsuda's group.[61b] Marco-Contelles *et al.*[62] demonstrated that when treated with this reagent by a similar method, 3-*O*-benzoyl and 3-*O*-*p*-toluenesulfonyl-1,2-*O*-isopropylidene-α-D-glucofuranoses (**65** and **81**) gave corresponding 5-oxo derivatives in yields of about 70%.

2.4 Structures of dibutylstannylene acetals

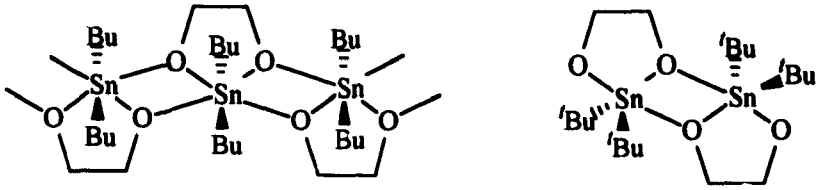
As synthetically useful intermediates, dibutylstannylene acetals both from simple compounds and from carbohydrates have been subjected to structural studies by different methods such as ^{119}Sn and ^{13}C NMR spectroscopy, X-ray crystallography, molecular weight measurement, and mass spectrometry. Each of these methods gives some useful information about the structures.

2.4.1 Structures of dibutylstannylene acetals in solid state

X-ray crystallography often provides direct structural information for compounds forming good single crystals. A study of **82**, the simplest dibutylstannylene acetal derived from ethane-1,2-diol, showed that in the solid state, the individual monomeric units are linked together through planar four-membered Sn-O-Sn-O rings to form an infinite ribbon polymer.[63] The association of the monomeric units places the tin atoms in a severely distorted octahedral environment.

In contrast, an X-ray study of di-*t*-butyl-1,3,2-dioxastannolane (**83**) indicates that this compound exists in the crystal as a dimer containing five-coordinated tin in a distorted trigonal bipyramidal configuration with C_2 symmetry.[64] The bulky *t*-butyl groups prevent further association. The solid state ^{117}Sn NMR spectrum also provides evidence for the symmetric dimer in which the tin atoms show a single resonance at -225 ppm, according to Bates and coworkers.[64] High-resolution ^{119}Sn CP/MAS spectra indicated that the isotropic peaks of compound **83** actually contained four closely spaced peaks at -222, -224, -225, and -226 ppm.[65] This arises from the fact that the

CH_2CH_2 group in the five-membered ring is disordered and that two independent dimeric molecules in the unit cell are slightly different. These chemical shifts correspond to pentacoordinate tin atoms. A schematic illustration for the structures of compounds **82** and **83** is shown in Figure 2.8.



polymeric structure of **82** dimeric structure of **83**

Figure 2.8 The structures of dibutylstannylene acetals **82** and **83** in the solid state

The first X-ray structure determination of a dibutylstannylene acetal derived from a carbohydrate was performed on methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-glucopyranoside (**84**, derived from compound **40**) where a dimeric structure was observed.[66] Each of the tin atoms is in the centre of a trigonal bipyramid with the butyl groups occupying two equatorial positions. The two monomeric units are joined together by a parallelogram involving Sn_2O_2 which has a pseudo C_2 axis of symmetry. In the dimer, one of the oxygen atoms of the diol unit is tricoordinate and the other is dicoordinate. The *R* value obtained in this earlier study was 10.9% and three carbon atoms were not located.[66] Recently, Cameron *et al.*[67] redetermined this structure from data collected at -70 °C and confirmed that this compound exists as a dimer with O-3 being tricoordinate. The deviations from C_2

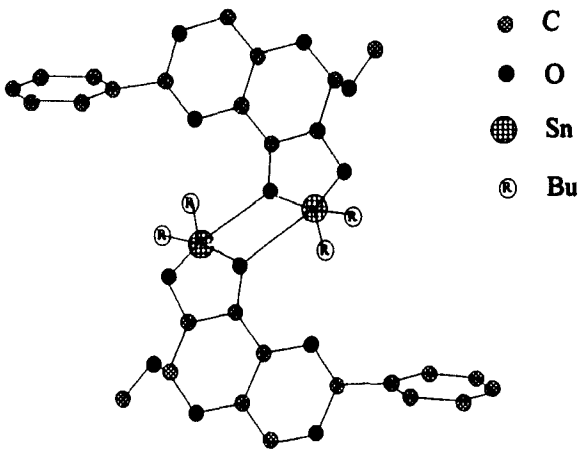


Figure 2.9 The dimeric structure of methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-glucopyranoside (**84**)

symmetry are much smaller than that reported earlier and lie mainly in the orientations of the butyl groups.

Grindley *et al.*[68] reported that compound **84** showed two isotropic peaks with equal intensities on the solid state ^{119}Sn NMR CP/MAS spectrum with chemical shifts at -126 8 and -128.6 ppm. This is in agreement with the configuration obtained by X-ray crystallography with two slightly different pentacoordinate tin atoms in the dimer. The 3,3-dimeric structure of **84** is illustrated in Figure 2.9.

Holzapfel *et al.*[69] determined, by means of X-ray crystallography, the structure of methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-mannopyranoside (**85**). The crystalline **85** obtained from hexane was pentameric (see Figure 2.10, only the rings are shown for simplicity).

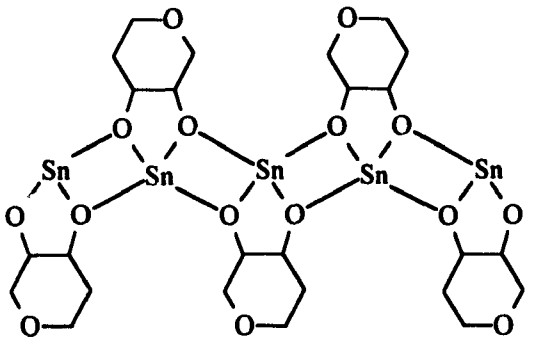


Figure 2.10 The pentameric structure of methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-mannopyranoside (**85**)

Although the solid state ^{119}Sn CP/MAS NMR spectra recorded from crystals of **85**, recrystallized from hexane, showed extensive overlap, it was still possible to confirm the presence of two isotropic peaks in the hexacoordinate tin region (-223 and -224 ppm) and two in the pentacoordinate tin region (-119 and -127 ppm).[65] This is consistent with a pentameric structure in the solid state if one of the peaks in the hexacoordinate region corresponds to two tin sites.

It has been suggested[69] that the difference in association between the two dibutylstannylene acetals (**84** and **85**) is due to the difference in steric interaction between the sugar residues. In the glucose derivative **84**, the pyranose ring units lie in the plane of the dimer and protect the tin atoms from further coordination, whereas the pyranose ring units in the mannose derivative **85** project perpendicularly from this plane and allow the association to proceed as far as a pentamer.

2.4.2 Oligomerization equilibria of dialkylstannylene acetals in solution

It is suggested that the regioselectivity and enhanced reactivity of dibutylstannylene acetals in mono-*O*-substitution reactions are related to the structural and electronic environments of these intermediates in solution.[3,5] Tin-119 NMR spectroscopy has proven to be a very powerful technique for studying the coordination status of tin atoms in dialkylstannylene acetals.[5,38,70]

Grindley and Thangarasa[38] systematically studied the oligomerization equilibria and dynamics of dibutylstannylene acetals **82**, **86**, **87** and **88** and found that these stannylenes exist in solution in non-polar solvents as mixtures of oligomers, including dimers, trimers, tetramers, and pentamers. The amount of monomer present in solution is below the level of detection by ^{119}Sn NMR at room temperature. The constitution of the mixture present in solution is influenced by temperature, concentration, and the nature of the substituents on the ring of the 1,3,2-dioxastannolane. For the parent compound **82** (dibutylstannylene acetal of ethane-1,2-diol, or 2,2-dibutyl-1,3,2-dioxastannolane), the trimer and tetramer constitute the majority of the species present below -20°C, but the dimer dominates increasingly as the temperature is raised. Two small *trans*-substituents on the parent diol do not influence the equilibria much, however, with four methyl substituents in the diol unit, compound **86** exists almost entirely as dimer. It has been concluded that 1,3,2-dioxastannolanes undergo particularly complex exchange processes through a series of related association-dissociation equilibria involving dimers, trimers, tetramers, and pentamers and possibly monomers and hexamers (Scheme 2.9). The lowest energy barriers for compounds **82**,

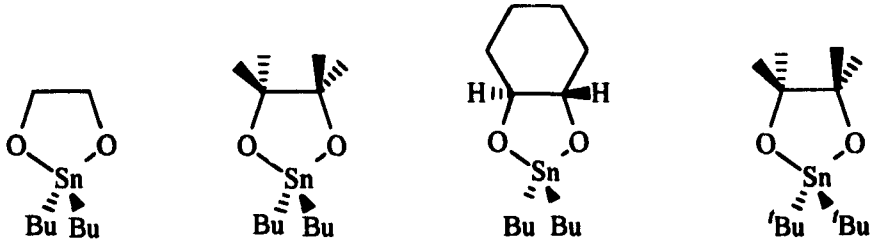
86, (1*S*,6*S*)-8,8-dibutyl-7,9,8-dioxastannabicyclo[4.3.0]nonane (**87**) and its racemate (**88**) were observed for association of two dimer molecules to a tetramer and a dimer and a trimer to a pentamer (For monomeric structures, see Figure 2.11).[38]

Scheme 2.9

monomer + monomer ⇌ dimer dimer + monomer ⇌ trimer

dimer + dimer ⇌ tetramer dimer + trimer ⇌ pentamer

dimer + tetramer ⇌ hexamer trimer + trimer ⇌ hexamer



82 **86** **87** (1*S*, 2 *S*) **89**

88 (1*R*, 2*R*)

Figure 2.11 Monomeric structures of dibutylstannylene acetals of simple diols

The only 1,3,2-dioxastannolane, 2,2-di-*t*-butyl-4,4,5,5-tetramethyl-1,3,2-dioxastannolane (**89**) which exists in solution as a monomer, was prepared recently.[71] This compound contains large substituents on both the tin and the carbon atoms in the ring and the steric interaction of these substituents prevents the molecule from self-associating. The concentration of monomer falls off steeply as the size of substituents

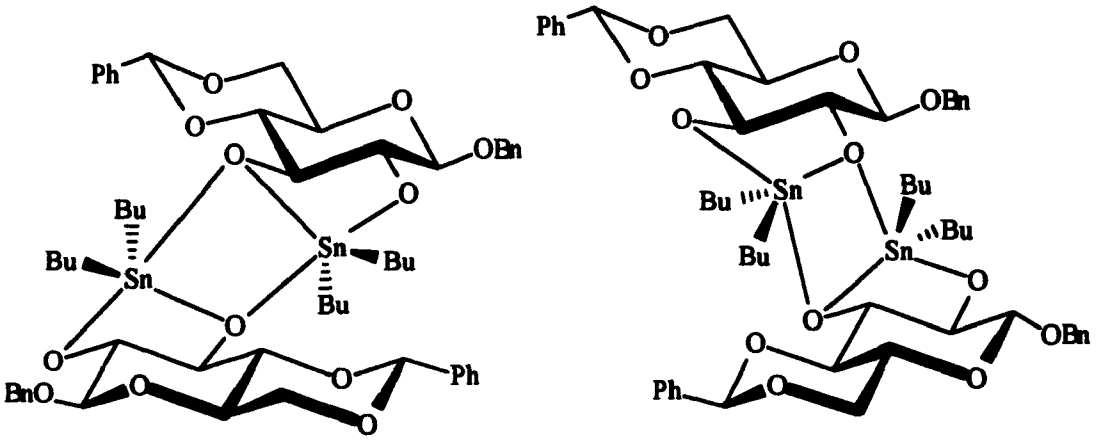
decreases. For example, compound **86**, for which the substituents on tin atom are *n*-butyl groups instead of *t*-butyl groups as in **89**, exists in solution chiefly as a dimer although a small proportion of monomer is present above room temperature.

2,2-Dibutyl-1,3,2-dioxastannane, a six-membered ring analog of **82**, exists in the crystal as a infinitive polymer. In liquid phases, this compound is present as mixtures of oligomers ranging from the dimer to higher oligomers. The compositions of the oligomers vary widely depending on temperature and concentration.[72] The tendency to form oligomers containing hexacoordinate tin for this compound is slightly less than that for 2,2-dibutyl-1,3,2-dioxastannolane (**82**).

David *et al.*, after investigation of stannylene derivatives of carbohydrates by X-ray,[66] ^{119}Sn NMR spectroscopy,[37] field desorption,[37] and analysis of reaction products,[13,73] suggested that the dibutylstannylene acetals derived from **40**, **64**, benzyl 2,3-di-*O*-benzyl-β-D-glucopyranoside (**90**) and benzyl 2,6-di-*O*-benzyl-β-D-galactopyranoside (**91**) exist as dimers with C_2 symmetry in all three physical states. They attributed the driving forces for dimerization to the presence of two electronegative substituents at tin atom and an acute angle at the tetrahedral tin which can only be achieved with *d*-orbital participation. Specification of the favored dimer of the two possible dimers with C_2 symmetry was not given.

Grindley *et al.*[5] studied the dibutylstannylene acetals derived from **40**, **41**, **44**, benzyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**92**) and benzyl 4,6-*O*-benzylidene-α-D-galactopyranoside (**93**) in solution by means of ^{1}H, ^{13}C, and ^{119}Sn NMR spectroscopy. The species present in solution have been identified from ^{119}Sn NMR spectral data, by

comparison of the ^{13}C NMR chemical shifts of the stannylene acetals and their parent carbohydrates and also by analysis of the products of reactions performed without added nucleophiles. The results showed that the dibutylstannylene acetals derived from compounds **40** and **93** in chloroform-*d* and the dibutylstannylene acetal of **40** in toluene-d_8 gave spectra containing a single line in the region of the spectrum where pentacoordinate tin is expected to absorb, consistent with a single dimeric structure. For the dibutylstannylene acetal of **40**, the structure of the dimer was confirmed as a 3,3-dimer which is consistent with its structure in the solid state as determined by X-ray crystallography[66,67] and solid state ^{119}Sn NMR spectroscopy.[68] Similarly, the dibutylstannylene acetal of **92**, the benzyl analog of **40**, exists in chloroform as a 3,3-dimer. The situation for the stannylene acetal derived from compound **41** is more complex although it exists only as dimers in chloroform, in benzene and in toluene. Two dimers have been identified by means of ^{119}Sn NMR spectroscopy. The major isomer is a symmetric one (2,2 or 3,3-dimer) while the minor one is asymmetric (the 2,3-dimer). The 3,3-dimeric structure was suggested as the structure of the symmetric dimer of this dibutylstannylene derivative and that of its methyl analog derived from compound **44** based on analysis of benzylation and benzoylation products of these acetals. In addition, an X-ray structure of crystals obtained for this stannylene acetal showed that it was present as a 3,3-dimer.[74] The structures of the two dimers present for the dibutylstannylene acetal of **41** are given in Figure 2.12. In chloroform, the dibutylstannylene acetal of **93** is present as a single dimer, but a different one, the 2,2-dimer.



3,3-dimer 2,3-dimer

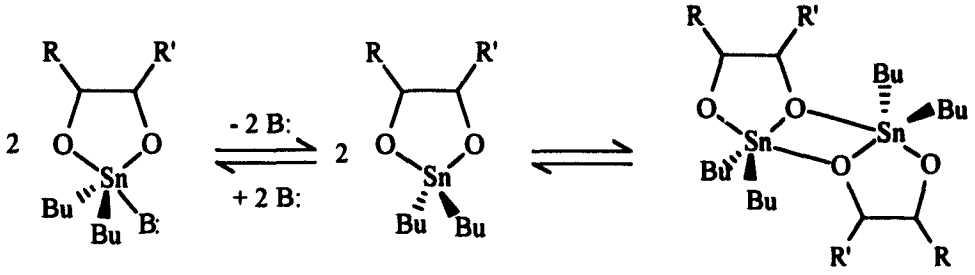
Figure 2.12 The dimeric structures of the dibutylstannylene acetal of compound **41**

The identification of the dimeric structure assumed by a stannylene acetal in solution is very helpful for explanation of the regioselectivity associated with stannylene acetal reactions. In a dimer, one of the two oxygen atoms in the diol unit is dicoordinate and the other tricoordinate. The former should be much more reactive towards electrophiles than the latter. Thus, when a dibutylstannylene acetal exists predominately as a single dimer (such as the acetals from **40**, **92**, and **93**), reactions normally occur at the dicoordinate oxygen, although the products of attack at the other oxygen atom are sometimes observed. These other products are mainly found when the reaction is conducted in the presence of added nucleophiles or polar solvents at higher than room temperature.[5]

When the reaction is carried out in polar solvents (methanol, DMF, dioxane etc.) or in the presence of added nucleophiles, the situation becomes more

complicated. Competitive equilibria between the intermolecular coordination of a tin-bounded oxygen atom in one monomeric molecule to the tin atom in the other and the coordination of the tin by solvent molecules or other Lewis bases[23] may occur as shown in Scheme 2.10. In monomeric species, the relative reactivities of the two oxygen atoms result only from steric and electronic properties of the parent compounds.

Scheme 2.10



Chapter 3

A Convenient Preparation of Hindered Dialkyltin(IV) Derivatives

3.1 Introduction

Dibutylstannylene acetals are widely used intermediates for the regioselective monosubstitution of diol or polyol hydrogens by electrophiles.[3,5] The regioselectivity obtained ranges from poor to excellent depending on the structure of the diol and the reaction conditions. It was postulated that good regioselectivity in the absence of added nucleophiles was obtained only when one of the three possible stannylene acetal dimers was dominant in solution.[5] Steric effects appear to be the major factor in determining which dimers are populated.[5] On this basis, it was thought that changing the sizes and shapes of the substituents on tin would alter the relative populations of the three dimers and hence modify the regioselectivity obtained in reactions with electrophiles. Thus, a general synthetic procedure was required for dialkyltin oxides, the precursors of dialkylstannylene acetals.

Because electronegative substituents on dialkyltin(IV) derivatives can be converted easily into other substituents,[75] preparation of any such derivative provides a pathway for all derivatives. Most available methods have proceeded via the halides. Three techniques are commonly used: cleavage reactions of tetraalkyltin(IV) compounds, redistribution reactions of equimolar amounts of tetraalkyltin(IV) compounds and tin tetrahalides, and direct synthesis from alkyl halides and metallic tin. All of these methods yield equilibrium mixtures from which the major product,

the dialkyltin(IV) dihalide, is separated by distillation.[75] The major products are pure enough to be adequate for most purposes if the alkyl group is primary and not hindered but even then it is difficult to obtain absolutely pure products. Difficulties arise when the alkyl groups become more complex. If the alkyl groups are hindered, as for neopentyl groups, the tetraalkyltin derivatives are very difficult to prepare. Pure dialkyltin dihalides containing secondary alkyl groups are difficult to obtain by distillation because significant disproportionation occurs at the temperature required for distillation. A number of solutions to this problem have appeared for specific compounds (see later). This chapter outlines a general procedure for the preparation of dialkyltin(IV) derivatives that works efficiently for all compounds, including those containing bulky alkyl groups, and yields pure products.

3.2 Results and Discussion

3.2.1 Synthesis

The method reported here first involved formation of a dialkyldiphenyltin(IV), then cleavage of the two phenyl groups by chloroacetic acid, followed by conversion to the diorganotin(IV) oxide by reaction with sodium hydroxide.

In the first step, dialkyldiphenyltin(IV) derivatives (**94**) are formed by reaction of diphenyltin dichloride with two equivalents of an alkyl Grignard reagent, usually in tetrahydrofuran. Diphenyltin dichloride is a stable crystalline compound easily obtained from inexpensive tetraphenyltin by disproportionation with tin tetrachloride. In most cases, the Grignard reaction proceeds in high yield. No difficulty was

encountered in the preparation of compounds in which the R groups were large, such as the neopentyl derivatives, where the tetraalkyltin derivative is very difficult to prepare.[75,76] For larger groups like *t*-butyl or $CH_2C(Me)_2Ph$ groups, tetraalkyltin derivatives can only be prepared in very low yields.[77,78] Molloy and coworkers have recently used this strategy to prepare several diphenyltin(IV) derivatives bearing two hindered alkyl groups different from the ones studied here.[79] The reaction and the yields obtained in this study are shown in Scheme 3.1.

Scheme 3.1

$Ph_2SnCl_2 + 2\ RMgX \longrightarrow R_2Ph_2Sn + 2\ MgXCl$

X = Br or Cl		**94**
a	R = $(CH_3)_3CCH_2$-	98%
b	R = $(CH_3)_3SiCH_2$-	97%
c	R = $(CH_3)_3CCH_2CH_2$-	98%
d	R = cyclo-C_6H_{11}-	88%
e	2 R = -$(CH_2)_6$-	30%

The yield of 1,1-diphenylstannacycloheptane **94e** obtained from the di-Grignard reagent derived from 1,6-dibromohexane was lower than the others, but this reaction had been performed previously with a yield of 26%.[80] Similar yields were obtained in other studies where preparations of monomeric stannacycloalkanes were attempted.[81] Dimeric and oligomeric species are also obtained in these reactions but purification of the monomer can be performed easily by distillation or silica gel chromatography.

The products were fully characterized by ^{1}H, ^{13}C, and ^{119}Sn NMR spectroscopy and analysis where the compounds were new. Some of the data are listed in Table 3.1, the remainder in the experimental (Section 3.3).

Table 3.1 Tin-119 NMR spectral data of dialkyltin(IV) derivatives

Compd	δ	Coupling constant to alkyl carbons and protons (Hz)						θ value (°)
	(ppm)	$^1J_{Sn\text{-}119,C}$	$^1J_{Sn\text{-}117,C}$	$^2J_{Sn,C}$	$^3J_{Sn,C}$ [a]	$^3J_{Sn\text{-}119,C}$ [b]	$^2J_{Sn,H}$	from Eq. 3.1
94a	-90.1	362.4	346.2	19.1	35.3	36.1	54.1	111
94b	-48.6	265.7	253.7	c	15.3	15.6	73.7	101
94c	-64.2	367.2	351.0	21.9	66.8	68.3	d	111
94d	-106.3	384.6	367.6	17.3	62.0, 59.2	62.0	d	113
94d[e]	d	386.9	369.6	16.7	64.9	66.4	d	113
94e	-58.5	360.0	343.8	11.4	21.5	22.0	d	111
95a	-113.3	507.4	484.5	31.5	63.4, 60.6	63.4	65.3	125
95b	-76.7	470.0	439.7	c	52.5	53.7	103.2, 98.9	122
95c	-120.1	553.2	528.4	39.1	109.7	112.2	d	130
95d	-186.3	488.8	467.3	21.4	104, 100	104.2	d	124
95e	-58.0	488.0	466.0	10.0	21.9	22.4	d	124

[a] Measured values. [b] Either measured value or where only an average value was measured, calculated by multiplying the measured value by 2 $\gamma_{Sn\text{-}119}/(\gamma_{Sn\text{-}119} + \gamma_{Sn\text{-}117})$. [c] Not applicable. [d] Not measured. [e] Values measured for a solution in dichloromethane-d_2 at 203 K.

Many of the major peaks in the mass spectrum of **94e** were the same peaks as those from 1,1-diphenylstannacyclopentane,[81] $Sn^{+\cdot}$, $PhSn^{+}$, $Ph_2Sn^{+\cdot}$, and $M^{+\cdot}$. A large peak was observed at $M^{+\cdot}$- PhH for **94e**, whereas that of 1,1-diphenylstannacyclopentane contained peaks for both $M^{+\cdot}$- PhH and $M^{+\cdot}$- Ph$^{\cdot}$ in equal amounts at low intensities.

The key step in the procedure is the cleavage of the phenyl groups in the dialkyldiphenyltin derivatives (**94**). It is well-known that electrophiles such as halogens or acids cleave phenyl groups from tetraorganotin compounds more readily than alkyl groups.[82] Neither halogens or hydrogen halides were used here for three reasons: firstly, the products are liquids and the potential mono- and di-cleavage products are sometimes difficult to separate; secondly, the products are somewhat reactive, being subject to hydrolysis and other reactions, and thus are less convenient to store; finally, chloroacetic acid is much more convenient to handle than the halogens or hydrogen halides.

Some time ago, Sasin *et al.* observed that gentle reflux of tetrapropyltin or tetraisopropyltin with one or two equivalents of chloroacetic acid for 0.5 h yielded the crystalline mono- and bis-chloroacetates in moderate yields, 35 and 47%, respectively.[83] Similar results were obtained with dichloroacetic acid.[83] On the other hand, trifluoroacetic acid cleaves vinyl or phenyl groups from tin derivatives, however, only three vinyl groups were replaced when tetravinyltin was heated with trifluoroacetic acid at 100 °C for several hours[84] while all vinyl groups were replaced by reaction with alkanoic acids.[85] It has been suggested that increasing the number of

bonds to acidic carboxylate groups strengthens the remaining tin-carbon bonds and that the more acidic carboxylate groups are more effective.[85,86]

It has been found in the present work that diphenyldialkyltin compounds react with two equivalents of chloroacetic acid to give the dialkyltin(IV) bischloroacetate products in high yield. The reaction proceeds at 120 °C, but 20 min at 160 °C ensures completion. Isolation is particularly simple. All of the bischloroacetates were crystalline and could be obtained conveniently in high purity by recrystallization, as shown in Scheme 3.2.

Scheme 3.2

$$R_2Ph_2Sn + 2\ ClCH_2COOH \longrightarrow R_2Sn(OCOCH_2Cl)_2 + 2\ PhH$$

94	**95**
a R = $(CH_3)_3CCH_2$-	90%
b R = $(CH_3)_3SiCH_2$-	98%
c R = $(CH_3)_3CCH_2CH_2$-	96%
d R = cyclo-C_6H_{11}-	97%
e 2 R = -$(CH_2)_6$-	96%

The crystal structure of **95e** was determined to confirm the assigned structure and to determine the geometry about tin. Selected bond lengths and bond angles are given in Tables 3.2 and 3.3. Compound **95e** is present as a monomer with no intermolecular Sn-O contacts less than 4.0 Å (see Figure 3.1).

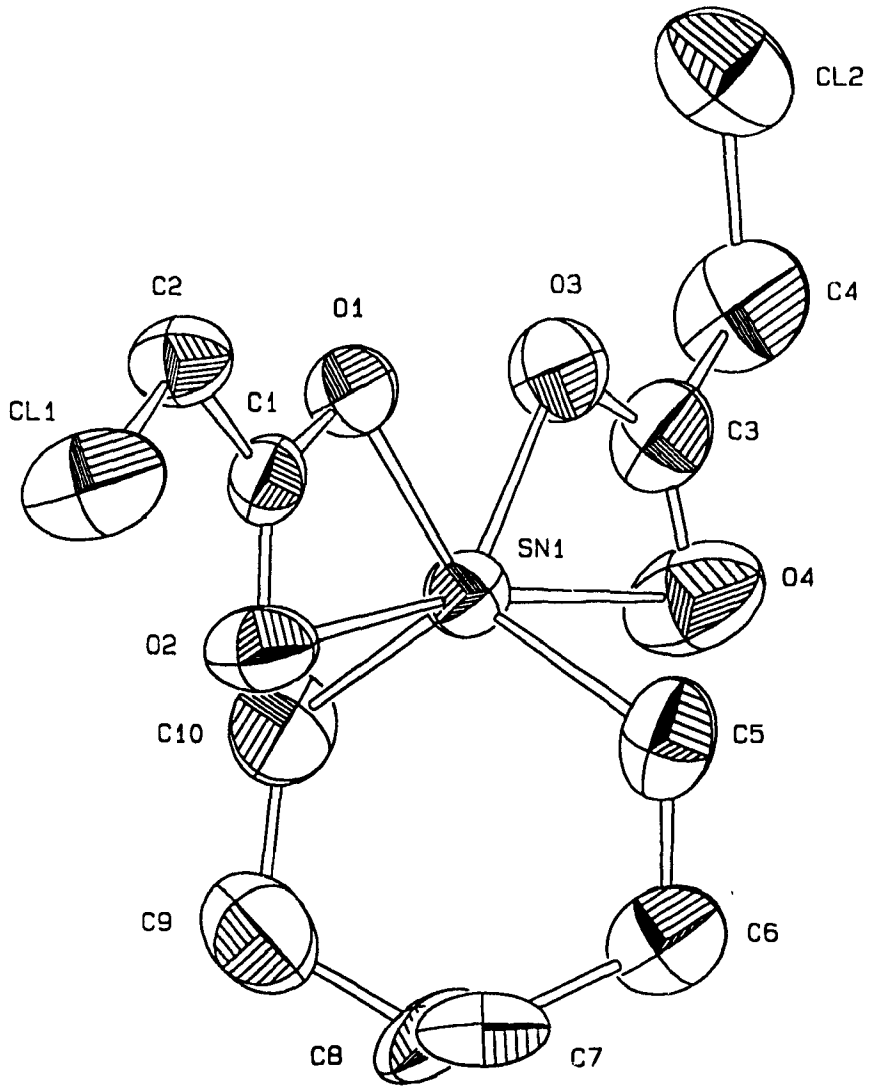


Figure 3.1 ORTEP plot of 1,1-stannacycloheptane bischloroacetate **(95e)** with thermal ellipsoids at the 50% probability level.

(Only one position of the disordered atoms is shown.)

Table 3.2 Selected bond distances (Å) for 1,1-stannacycloheptane bischloroacetate (**95e**)[a]

Sn(1)-O(1)	2.089(5)	Sn(1)-O(2)	2.635(5)
Sn(1)-O(3)	2.079(5)	Sn(1)-O(4)	2.696(7)
Sn(1)-C(5)	2.115(8)	Sn(1)-C(10)	2.104(8)
Cl(1)-C(2)	1.756(8)	Cl(2)-C(4)	1.768(10)
O(1)-C(1)	1.284(8)	O(2)-C(1)	1.235(9)
O(3)-C(3)	1.310(10)	O(4)-C(3)	1.216(11)
C(1)-C(2)	1.490(10)	C(3)-C(4)	1.502(13)
C(5)-C(6)	1.551(15)	C(6)-C(7)	1.53 (2)
C(7)-C(8)	1.54 (2)	C(8)-C(9)	1.52 (2)
C(9)-C(10)	1.52 (2)	C(5)-C(6*)	1.52 (2)
C(6*)-C(7*)	1.50 (2)	C(7*)-C(8*)	1.53 (2)
C(8*) -C(9*)	1.52 (2)	C(9*)-C(10)	1.53 (2)

[a] * indicates the second position of a disordered atom.

Table 3.3 Selected bond angles (deg) for 1,1-stannacycloheptane bischloroacetate (**95e**)[a]

O(1)-Sn(1)-O(2)	53.9 (2)	O(1)-Sn(1)-O(3)	82.4 (2)
O(1)-Sn(1)-O(4)	135.2 (2)	O(1)-Sn(1)-C(3)	109.7 (2)
O(1)-Sn(1)-C(5)	111.9 (2)	O(1)-Sn(1)-C(10)	112.6 (3)
O(2)-Sn(1)-O(3)	136.3 (2)	O(2)-Sn(1)-O(4)	170.3 (2)
O(2)-Sn(1)-C(5)	87.6 (2)	O(2)-Sn(1)-C(10)	90.1 (3)
O(3)-Sn(1)-O(4)	53.1 (2)	O(3)-Sn(1)-C(5)	113.9 (3)
O(3)-Sn(1)-C(10)	106.7 (3)	O(4)-Sn(1)-C(5)	85.3 (2)
O(4)-Sn(1)-C(10)	88.1 (3)	C(5)-Sn(1)-C(10)	122.2 (3)
Sn(1)-C(5)-C(6)	108.3 (6)	C(5)-C(6)-C(7)	114.7 (10)
C(6)-C(7)-C(8)	104.0 (10)	C(7)-C(8)-C(9)	110.3 (11)
C(8)-C(9)-C(10)	113.8 (11)	Sn(1)-C(10)-C(9)	120.4 (7)
Sn(1)-C(5)-C(6*)	114.9 (7)	C(5)-C(6*)-C(7*)	117.4 (12)
C(6*)-C(7*)-C(8*)	116.1 (14)	C(7*)-C(8*)-C(9*)	113.0 (13)
C(8*)-C(9*)-C(10)	112.6 (12)	Sn(1)-C(10)-C(9*)	110.0 (7)

[a] * indicates the second position of a disordered atom.

The hexacoordinate tin atom forms two bonds to each of the two anisobidentate carboxylate groups. The Sn-O bond lengths to each group are very different: 2.089(5) and 2.635(5) Å for one, 2.079(5) and 2.696(7) Å for the other. The four carbon atoms in the stannacycloheptane ring that are not attached to tin are 50% disordered. The ring adopts the lowest energy cycloheptane conformation, an approximately C_2-symmetric twist chair with the tin atom on the axis. In comparison to cycloheptane,[87] the conformation is flattened about the tin atom and more puckered at the other end. The disorder arises because the ring is twisted but has no preference for the direction of twist.

There has been considerable interest in the structures of dialkyltin dicarboxylates [$R_2Sn(O_2CR')_2$] because of their importance in industrial applications, e.g., as PVC stabilizers[75] and as catalysts for a variety of reactions.[88,89] The crystal structures of a number of derivatives of this type have appeared in the last few years. The crystal structures can be classified into three types: polymers with bridging ester groups, loosely associated dimers, and monomers. Only one polymer is known, dimethyltin(IV) diformate.[90] Crystals of dibutyltin(IV) di-*o*-bromobenzoate (**96**) contain monomeric units loosely associated in pairs through two additional weak interactions between tin and oxygen atoms at somewhat less than the sum of the van der Waals radii, 3.70 Å, to give dimers containing four-membered rings.[91] Narula *et al.* have reported two new structures and reanalysed several of the earlier structures[92] and noted that most of these were also loosely bound dimers similar to that of **96**.[93] Three of those analyzed were monomers without further close intermolecular

associations.[94] Five further structures have heen examined in current study; four were monomers with no intermolecular Sn-O associations shorter than 3.70 Å;[95] one was a dimer,[96] an *ortho*-substituted dibenzoate similar to many of the compounds that were found to be dimeric.[93] Narula *et al.* noted that in dimers, the C-Sn-C bond angle increases from about 140 to 159° as the intermolecular Sn-O distance between monomers decreases, consistent with conversion of the bonding arrangement at tin from capped tetrahedral to distorted pentagonal bipyramidal.[93] In monomers, the bond angle is smaller, ranging from 130.6 to 140.7°.[94,95]

The structure of **95e** is very similar to the monomeric structures described earlier,[94,95] having hexacoordinate tin atoms coordinated to anisobidentate carboxylate groups. The most marked difference is in the C-Sn-C angle, being 122.2(3)° here as a result of ring formation. This bond angle is considerably smaller than any previously reported for diorganotin(IV) dicarboxylates. Vedejs *et al.* have recently reported a C-Sn-C bond angle of 121.4° in a 1,1-dichloro-2,3:6,7-dibenzostannacycloheptane derivative.[97] Compounds like this and **95e** are expected to have unusual properties because of their small bond angles. Perhaps as a result of the small bond angle, the carboxylate groups in **95e** are slightly more anisobidentate than any previously examined,[90-95] having both among the shortest Sn-O bonds and the longest Sn-O bond, 2.696(7) Å.

For compound **95e**, the ^{119}Sn NMR chemical shift measured in chloroform-*d*, -58.0 ppm, was very similar to that obtained from the CP/MAS spectrum of **95e** in the solid state, -61.8 ppm. If compound **95e** had a different structure in solution than

in the solid state, quite different chemical shifts would be expected.

The dialkyltin bischloroacetates (**95**) were transformed into dialkyltin oxides (**97**) by treatment of solutions in organic solvents with aqueous sodium hydroxide solutions for times ranging up to one hour (Scheme 3.3).

Scheme 3.3

$$R_2Sn(OCOCH_2Cl)_2 + 2\ NaOH \longrightarrow R_2SnO + 2\ ClCH_2CO_2Na + H_2O$$

95	**97**
a R = $(CH_3)_3CCH_2$-	92%
b R = $(CH_3)_3SiCH_2$-	98%
c R = $(CH_3)_3CCH_2CH_2$-	93%
d R = cyclo-C_6H_{11}-	98%
e 2 R = -$(CH_2)_6$-	100%

3.2.2 Other Preparations

Zimmer *et al.* reported that dibutyldineopentyltin reacted with two equivalents of bromine at reflux in carbon tetrachloride to yield only dineopentyltin dibromide (**98**), the product of selective cleavage of the less hindered butyl group.[76] Repetition of this work revealed that the cleavage process was not as selective as had been reported; the product obtained was a 3:2 mixture of **98** and butylneopentyltin dibromide (**99**), as determined by ^{119}Sn and ^{13}C NMR spectroscopy (see experimental). The original characterization of the product mixture had only been performed by

elemental analysis and a 3:2 mixture of **98** and **99** fits the analytical data better than pure **98**.

Attempt was made to prepare dibenzyltin oxide following literature methods.[98] The preparation was unsuccessful because the dibenzyltin oxide is unstable on standing at room temperatu

3.2.3 Geometry and ^{119}Sn NMR Parameters

The $^{1}J_{Sn\text{-}119,C\text{-}13}$ values yield interesting geometrical information. These have been related to C-Sn-C bond angles by the relationships

$$^{1}J_{Sn\text{-}119,C\text{-}13} = 9.99\ \theta - 746\ Hz \qquad (3.1)$$

for dibutyltin(IV) compounds,[99] and

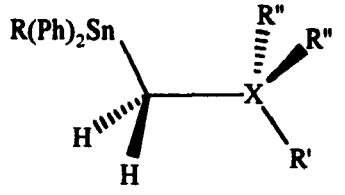
$$^{1}J_{Sn\text{-}119,C\text{-}13} = 10.7\ \theta - 778\ Hz \qquad (3.2)$$

for dimethyltin(IV) groups.[100] The two equations give fairly similar θ values for compounds **94a** to **94e**. Those from Eq. 3.2 are 3-6° less than those from Eq. 3.1. The values from Eq. 3.1 are listed in Table 3.1 and seem reasonable except for those of **94b**. The geometry of compound **94b** should not be markedly different than that of **94a**. The silicon atoms geminal to tin presumably alter the electronic characteristics of the molecule sufficiently to change the $^{1}J_{Sn,C}$ value.

Geometrical information can also be obtained from $^{3}J_{Sn\text{-}119,C\text{-}13}$ values.[101,102] The following Karplus-type relationship has been developed for trimethylorganotin(IV) compounds:[101]

$$^{3}J_{Sn\text{-}119,\,C\text{-}13} = 30.4 - 7.6 \cos\theta + 25.2 \cos 2\theta \qquad (3.3)$$

Many of the compounds used to develop the relationship were strained compounds, e.g. norbornyl derivatives. The geometries of most of the compounds studied here are reasonably well defined (see following); thus these compounds provide an interesting test to determine whether this Karplus-type relationship applies to all tin compounds. The three methyl groups on tin are replaced by varying organic groups, and all compounds are relatively unstrained. Often only average $^{3}J_{Sn\text{-}119,C\text{-}13}$ and $^{3}J_{Sn\text{-}117,C\text{-}13}$ values could be obtained when the values were small and, particularly when the S/N ratio was not large enough to perform resolution enhancement. The average values were converted to $^{3}J_{Sn\text{-}119,C\text{-}13}$ values by assuming that the center to the average peak is half-way between the satellites due to coupling to ^{117}Sn and ^{119}Sn atoms.



94a R = Me_3CCH_2, R' = R" = Me, X = C

94b R = Me_3SiCH_2, R' = R" = Me, X = Si

94c R = $Me_3CCH_2CH_2$, R' = CMe_3, R" = H, X = C

94d

Figure 3.2 Representations of the favored geometries of compound **94a** to **94d**

In compounds **94a** and **94b**, the tin atom is *gauche* to two methyl groups and *anti* to the other and the observed coupling constant will be an weighted average of the values for the two *gauche* relationships and the one *anti* relationship. For compound

94c, the vicinal coupling constants, $^3J_{H,H}$, in the CH_2CH_2 unit were obtained by simulation and values of 14.4 and 4.1 Hz were obtained. The very different magnitudes of these values and the very large size of the value for the protons having *anti* relationships indicate that **94c** is close to being in a conformation where the Sn-C-C-C torsional angle is close to 180°. In compound **94d**, the Sn atom is *anti* to C-3 and C-5 in the cyclohexane ring, if the Sn-bearing substituent is equatorial. A solution of **94d** in CD_2Cl_2 was examined by ^{13}C NMR spectroscopy as a function of temperature. Coalescence was observed for the signals of several cyclohexane carbons at about -30 °C. The $^3J_{Sn\text{-}119,\ C\text{-}13}$ values obtained were 62.1 Hz at 25 °C and 66.4 Hz for the major species at -70 °C indicating that the 25 °C spectra arise from a conformational mixture. The signals of the minor species were too small for coupling constants to be obtained. The actual Sn-C-C-C torsional angle in the equatorial conformation of **94d** is probably about 175° because cyclohexane rings are normally flattened by about 5°.[103] In compound **94e**, the Sn-C-C-C torsional angle will be approximately *gauche*.

The values calculated by means of Eq. 3.3 are in the right order but are slightly small. For instance, for the compounds best defined geometrically, **94a**, **94c**, and **94d**, values of 30.4, 63.2 and 62.8 Hz were calculated, whereas 36.1, 68.3, and 66.4 Hz were observed. Adjusting Eq. 3.3 to Eq. 3.4 fits these values (± 1.5 Hz):

$$^3J_{Sn\text{-}119,\ C\text{-}13} = 36.1 - 7.3 \cos\theta + 24.9 \cos 2\theta \qquad (3.4)$$

Equation 3.3 gives an Sn-C-C-C value for **94e** of 49° , whereas Eq. 3.4 gives 57°. Both values are within the range of torsional angles expected for **94e**.

The series of bischloroacetates can be considered in the same way. The C-Sn-

C bond angles calculated for compounds **95a**, **95c**, and **95d** by means of Eq. 3.1 (see Table 3 1) are slightly smaller than those previously determined from X-ray structures of compounds found to be monomers, 130.6 to 140.7°.[94,95] However, that calculated for **95e**, 123.5° is almost the same as the value obtained in the X-ray structure determination (1.3° larger). Thus, the calculated bond angles probably are quite close to actual values.

In contrast, the $^3J_{Sn\text{-}119,\,C\text{-}13}$ values for compounds **95a** to **95e** are much larger than the values calculated by equations 3.3 or 3.4. Attempts were made to fit the values for this series of compounds both to equations having the same form as equations 3.3 and 3.4 and to A $(\cos\theta)^2$ + B under the following constraints: **95b** was not included; the crystal structure torsional angle, -49.5°, was used for **95e**, and it was assumed that all coupling constants had the same sign. These attempts were unsuccessful, even though it was apparent that torsional angles were the most significant factor in determining the magnitudes of these values. An equation

$$^3J_{Sn\text{-}119,\,C\text{-}13} = 50 - 30\cos\theta + 40\cos 2\theta \qquad (3.5)$$

calculates J values to within 15 Hz of the observed values but is still unsatisfactory. Other effects must be important enough for these compounds that simple Karplus equations do not fit the data with a reasonable degree of precision.

3.3 Experimental

General Methods. Melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected. Dry column chromatography was done using TLC grade silica gel (60 PF-254, Merck). NMR spectra were recorded on Bruker AC 250F or AMX 400 spectrometers at 20 °C for solutions in $CDCl_3$ unless otherwise specified; ^1H and ^{13}C NMR spectra were referenced to internal TMS or for ^{13}C to chloroform-*d* as 77.0 ppm, ^{119}Sn NMR spectra to external tetramethyltin. The ^{119}Sn CP/MAS spectrum was recorded on a Bruker AMX 400 spectrometer, in a 4 mm rotor spun at rates of 7 to 9 kHz. Shifts were referenced to tetracyclohexyltin, which has a chemical shift of -97.35 ppm relative to tetramethyltin.[104] AA'BB' ^1H NMR patterns were analyzed using the iterative fitting program, LAME8.[105] Mass spectra were measured on a Dupont-CEC 21-104 Mass Spectrometer at 70 eV ionization and a source temperature of 105 °C, using a glass, direct-insertion probe. Microanalyses were performed by Canadian Microanalytical Service Ltd., Vancouver, B. C.

General method for preparation of dialkyldiphenyltin compounds. The corresponding Grignard reagent was prepared by adding an alkyl chloride or bromide (0.16 mol) dropwise to magnesium turnings (0.15 mol) in dry THF (100 mL), then refluxing the mixture overnight under a nitrogen atmosphere. The heat source was removed and a solution of diphenyltin dichloride (20.6 g, 0.06 mol) in THF (35 mL) was added in dropwise fashion at a rate that maintained reflux (about 30 min). The mixture was refluxed overnight under nitrogen, then allowed to cool to room temperature. Excess

Grignard reagent was hydrolysed with saturated ammonium chloride solution (30 mL). The organic layer was filtered and the residue was washed with ether (3 x 30 mL). The filtrate and washings were combined and the solvents were removed on a rotary evaporator. The residue was taken up in ether (100 mL) and the resulting solution was washed with 10% KF solution (30 mL) and then with water (2 x 25 mL). The ether solution was dried over sodium sulfate. Removal of solvent afforded the desired compound.

Dineopentyldiphenyltin (94a). Preparation using the general method gave compound **94a**, yield 24.4 g, 98%. Recrystallization was performed from hexane: mp 43-4 °C; ^{1}H NMR δ 7.65-7.20 (m, 10 H, Ar-H), 1.51 (s, 4H, CH_2), 0.96 (s, 18H, CH_3); ^{13}C NMR δ 142.4 (s, C_{arom}, J_{Sn-C} = 430.1 Hz and 412.0 Hz), 137.1 (d, $C_{arom-ortho}$, J_{Sn-C} = 33.4 Hz), 128.3 (d, $C_{arom-meta}$, J_{Sn-C} = 43.9 Hz), 128.2 (d, $C_{Arom-para}$), 33.6 (q, CH_3), 32.11 (s, C_q), 32.08 (t, CH_2); ^{119}Sn NMR (pentane) δ -90.1. Anal. Calcd: C 63.64, H 7.77; Found: C 63.67, H 7.61.

Bis(trimethylsilylmethyl)diphenyltin (94b). Preparation using the general method gave compound **94b**, yield 26.2 g, 97%: bp 131-134 °C/0.18 torr, lit. 130-132 °C/0.2 torr[106]; ^{1}H NMR δ 7.7 - 7.2 (m, 10H, Ar-H), 0.26, (s, 4H, CH_2), -0.04 (s, 18H, CH_3); ^{13}C NMR δ 141.6 (s, C_{arom}, J_{Sn-C} = 475.9 Hz and 454.9 Hz), 136.6 (d, $C_{arom-ortho}$, J_{Sn-C} = 37.2 Hz), 128.4 (d, $C_{arom-meta}$, J_{Sn-C} = 47.7 Hz), 128.2 (d, $C_{arom-para}$), 1.6 (q, CH_3), -3.6 (t, CH_2); ^{119}Sn NMR (neat) δ -48.6.

Dineohexyldiphenyltin (94c). Preparation using the general method gave compound **94c**, yield 26.0 g, 98%; bp 150 °C/0.18 torr; ^{1}H NMR δ 7.6-7.3 (m, 10H,

Ar-H), 1.304, 1.567 (2 AA'BB' patterns, 8H, $J_{AA'}$ = -13.63 Hz, $J_{BB'}$= -12.62 Hz, J_{AB} = 14.37 Hz, $J_{AB'}$ = 4.07 Hz, from simulation, rms standard deviation 0.053 Hz, 2 CH_2-CH_2), 0.97 (s, 18H, CH_3); ^{13}C NMR δ 140.2 (s, C_{arom}, J_{Sn-C} = 434.9 Hz and 415.8 Hz), 136.9 (d, $C_{arom-ortho}$, J_{Sn-C} = 32.4 Hz), 128.3 (d, $C_{arom-meta}$, J_{Sn-C} = 23.9 Hz), 128.6 (d, $C_{Arom-para}$), 40.6 (t, CH_2), 32.2 (s, C_q), 28.7 (q, CH_3), 4.2 (t, CH_2-Sn); ^{119}Sn NMR (neat) δ -64.2. Anal. Calcd: C 65.03, H 8.19; Found: C 64.81, H 8.08.

Dicyclohexyldiphenyltin (94d). Preparation using the general method gave compound **94d**, yield 23.2 g, 88%; mp 122-3 °C, lit.[107] 119-20 °C; ^1H NMR δ 7.6-7.2 (m, 10H, Ar-H), 2.1-1.8 (m, 3H, H-1, H-2e, H-6e), 1.8-1.6 (m, 5H, H-2a,H-3e,H-4e, H-5e, H-6a), 1.35-1.30 (m, 3H, H-3a, H-4a, H-5a); ^{13}C NMR δ 139.9 (s, C_{arom}, $J_{Sn,C}$ = 389.9 Hz and 371.9 Hz), 137.5 (d, $C_{arom-ortho}$, J_{Sn-C} = 29.3 Hz), 128.2 (d, $C_{arom-meta}$, J_{Sn-C} = 41.5 Hz and 39.6 Hz), 128.3 (d, $C_{Arom-para}$), 32.0 (t, CH_2-2,6), 29.1 (t, CH_2-3,5), 27.8 (d, CH), 27.0 (t, CH_2-4); ^{119}Sn NMR δ -106.3, lit.[108] -106.5 ($CHCl_3$).

1,1-Diphenylstannacycloheptane (94e). Compound **94e** was prepared by a modification of Zimmer's method.[80] The Grignard reagent was prepared by stirring a mixture of 1,6-dibromohexane (29 g, 0.118 mol) and magnesium turnings (5.75 g, 0.236 mol) in anhydrous ether (1.0 L) at reflux for 12 h. A solution of diphenyltin dichloride (33.4 g, 0.100 mol) in anhydrous THF (500 mL) was quickly added to the cloudy Grignard reagent mixture. The reaction mixture was refluxed 12 h then allowed to cool to room temperature. Water (50 mL) was added slowly. The precipitate was removed by filtration, then washed with pentane (2 x 100 mL). The combined filtrate and washings were concentrated on a rotary evaporator. The residue

was taken up in hexane (300 mL). The solution was dried (Na_2SO_4) and concentrated. Column separation of the residue (hexane as eluent) afforded the title compound (yield, 10.7 g, 30%); bp 146 ° C / 0.08 torr, lit.[80] 140 °C / 0.07 torr; ^1H NMR δ 7.6-7.2 (m, 10H, Ar-H), 1.95 (m, 4H, H_β), 1.64 (m, 4H, H_γ), 1.41 (m, 4H, H_α); ^{13}C NMR δ 141.1 (s, C_{arom}, $J_{Sn,C}$ = 434.9 Hz and 414.9 Hz), 136.7 (d, $C_{arom\text{-}ortho}$, $J_{Sn\text{-}C}$ = 33.4 Hz), 128.4 (d, $C_{arom\text{-}meta}$, $J_{Sn\text{-}C}$ = 43.8 Hz), 128.5 (d, $C_{Arom\text{-}para}$, $J_{Sn\text{-}C}$ = 10.5 Hz), 31.4 (d, C_β), 25.4 (d, C_γ) , 11.2 (d, C_α); ^{119}Sn NMR δ -58.5; ms 358 (7.8%, $M^{+\cdot}$), 281 (25%, $PhSn(CH_2)_6^+$), 280 (51%, $M^{+\cdot}$ - PhH), 274 (20%, $Ph_2Sn^{+\cdot}$), 197 (84%, $PhSn^+$), 120 (100%, $Sn^{+\cdot}$), m* 215-224 [$(280)^2$ / 358 = 219.0, $(281)^2$/ 358 = 220.6], 135-143 [$(197)^2$ / 280 =138.6].

General method for preparation of dialkyltin bischloroacetates. The corresponding dialkyldiphenyltin (0.02 mol) and chloroacetic acid (0.04 mol) were gradually heated in a oil bath to 160 °C. The temperature was maintained at 160 °C for 20 min. After the reaction mixture had cooled to room temperature, hexane (50 mL) was added and the mixture was refluxed until the crystalline material dissolved. Cooling the filtered solution to room temperature gave colourless crystals that were washed with hexane (3 x 3 mL). The analytical samples were recrystallized again from hexane.

Dineopentyltin bischloroacetate (95a). Preparation using the general method gave compound **95a**, yield 8.0 g, 90%; mp 75-6 °C; ^1H NMR δ 4.10 (s, 4H, CH_2Cl), 1.91 (s, 4H, CH_2Sn), 1.08 (s, 18H, CH_3); ^{13}C NMR δ 176.0 (s, C=O), 45.3 (t, CH_2Sn), 41.2 (t, CH_2Cl), 32.3 (q, CH_3), 32.7 (s, C_q); ^{119}Sn NMR (neat) δ -113.3.

Anal. Calcd: C 37.54, H 5.85, Cl 15.83; Found. C 37.54, H 5.84, Cl 15.90.

Bis(trimethylsilylmethyl)tin bischloroacetate (95b). Preparation using the general method gave compound **95b**, yield 9.4 g, 98%; mp 104-6 °C; ^{1}H NMR δ 4.10 (s, 4H, CH_2Cl), 0.76 (s, 4H, CH_2Sn), 0.11 (s, 18H, CH_3); ^{13}C NMR δ 176.3 (s, C=O), 41.1 (t, CH_2Cl), 10.2 (t, CH_2Sn), 0.8 (q, CH_3); ^{119}Sn NMR (neat) δ -76.7. Anal. Calcd: C 30.02, H 5.46. Found: C 29.95, H 5.45.

Dineohexyltin bischloroacetate (95c). Preparation using the general method gave compound **95c**, yield 9.14 g, 96%; mp 94-6 °C; ^{1}H NMR δ 4.15 (s, 4H, CH_2Cl), 1.698, 1.529 (2 AA'BB' patterns, 8H, $J_{AA'}$ = -12.40 Hz, $J_{BB'}$= -13.61 Hz, J_{AB}= 13.49 Hz, $J_{AB'}$= 4.56 Hz, analyzed by simulation, rms standard deviation, 0.039 Hz, 2 CH_2CH_2), 0.88 (s, 18H, CH_3); ^{13}C NMR δ 176.7 (s, C=O), 40.91 (t, CH_2Cl), 37.3 (t, CH_2), 32.0 (s, C_q), 28.5 (q, CH_3), 20.6 (t, CH_2Sn); ^{119}Sn NMR (neat) δ -120.1. Anal. Calcd: C 40.37, H 6.35, Cl 14.90 ; Found: C 39.88, H 6.20, Cl 15.26.

Dicyclohexyltin bischloroacetate (95d). Preparation using the general method gave compound **95d**, yield 9.16 g, 97%; mp 102-3 °C; ^{1}H NMR δ 4.13 (s, 4 H, CH_2Cl), 2.34 (m, 1H, H-1), 1.94 (m, 2H, H-2e, 6e), 1.77-1.57 (m, 5H, H-2a, 6a, 3e, 4e, 5e), 1.31 (m, 3H, H-3a, 4a, 5a); ^{13}C NMR δ 176.4 (s, C=O), 44.4 (d, C-1), 40.9 (t, CH_2Cl), 29.5 (t, C-2,6), 28.3 (t, C-3,5), 26.1 (t, C-4, J_{Sn-C} = 12 Hz); ^{119}Sn NMR δ -186.3. Anal. Calcd: C 40.72, H 5.55, Cl 15.02; Found: C 40.78, H 5.51, Cl 14.86.

1,1-Stannacycloheptane bischloroacetate (95e). Preparation using the general method gave compound **95e**, yield 7.30 g, 96%; mp 96-8 °C; ^{1}H NMR δ 4.13 (s, 4H, CH_2Cl), 1.94 (m, 4H, H_β), 1.75-1.68 (m, 8H, H_α + H_γ); ^{13}C NMR δ 175.8 (s, C=O),

40.9 (t, CH_2Cl), 30.3 (t, C_γ), 25.3 (t, C_α), 23.2 (t, C_β); ^{119}Sn NMR δ -58.0.

Preparation of dialkyltin oxide.

Dineopentyltin oxide (97a). Dineopentyltin bischloroacetate (11.2 g, 0 025 mol) in ether (80 mL) was shaken with an aqueous sodium hydroxide solution (2.5 g, 0.062 mol in 25 mL) in a separatory funnel. Hexane (50 mL) was added and the organic layer was separated and dried over anhydrous sodium sulfate. Removal of solvents gave a colourless powder (6.6 g, 92%). The analytical sample was recrystallized from hexane: mp 202-204 °C; ^1H NMR δ 1.40 (s, 4H, $J_{Sn,H}$ = 62.6 Hz, CH_2), 1.10 (s, 18H, $J_{Sn,H}$ = 31.7 Hz, CH_3); ^{13}C NMR δ 43.0 (t, $^1J_{Sn,C}$ = 501.5 and 460.6 Hz, CH_2), 33.6 (q, $^3J_{Sn,C}$ = 49.6 Hz, CH_3), 31.8 (s, $^2J_{Sn,C}$ = 23.4 Hz, C_q); ^{119}Sn NMR δ 15.3. Anal. Calcd: C 43.36, H 8.01; Found: C 42.96, H 7.85.

Bis(trimethylsilylmethyl)tin oxide (97b). A solution of bis(trimethylsilylmethyl)tin bischloroacetate (9.60 g, 0.020 mol) in ether (100 mL) was shaken with an aqueous sodium hydroxide solution (2.0 g, 0.050 mol in 20 mL) in a separatory funnel. Hexane (50 mL) was added and the organic layer was separated and dried over anhydrous sodium sulfate. Removal of solvents gave a colourless powder (6.1 g, 98%). The analytical sample was recrystallized from ethyl acetate; mp 152 °C, lit.[106] softens and melts over the range 145-160 °C; ^1H NMR δ 0.24 (s, 4 H, CH_2), 0.11 (s, 18 H, CH_3); ^{13}C NMR δ 8.9 (t, $^1J_{Sn,C}$ = 348 Hz, CH_2), 1.7 (q, $^3J_{Sn,C}$ = 21.9 Hz, CH_3); ^{119}Sn NMR δ 50.0.

Dineohexyltin oxide (97c). A solution of dineohexyltin bischloroacetate (9.52

g, 0.020 mol) in ether (75 mL) was stirred with an aqueous solution of sodium hydroxide (2.0 g, 0.050 mol in 25 mL) for 1/2 h. The resulting precipitate was collected and washed with water (10 mL x 3). The colourless powder was refluxed in 100 mL of toluene overnight with azeotropic removal of water. Filtration gave a white amorphous solid (5.7 g, 93%), which is polymeric **97c**: mp > 300 °C. Anal. Calcd: C 47.25, H 8.59; Found: C 46.99, H 8.49.

Dicyclohexyltin oxide (97d). A solution of dicyclohexyltin bischloroacetate (9.44 g, 0.020 mol) in ether (140 mL) was stirred with an aqueous sodium hydroxide solution (2.0 g, 0.050 mol in 25 mL) for 1 h. The resulting precipitate was collected and washed with water (10 mL x 5) and acetone (20 x 3). The colourless powder was dried under vacuum at 100 °C overnight. A white amorphous solid was obtained, 5.93 g, 98%, which is polymeric **97d**: mp dec. over the range 283-290 °C, lit.[109] dec. ca. 285 °C.

Hexamethylenetin oxide (97e). To a solution of 1,1-stannacycloheptane bischloroacetate (3.8 g, 0.010 mol) in dichloromethane (20 mL) was added an aqueous sodium hydroxide solution (0.9 g in 20 mL). The mixture was stirred for 0.5 h and the resulting solid was filtered, washed with H_2O (6 x 10 mL), acetone (3 x 10 mL), and ether (3 x 10 mL) in sequence, then dried under reduced pressure at 100 °C. The title oxide was obtained quantitatively as a colourless powder, polymeric **97e**: mp dec. over the range 200-220 °C. Anal. Calcd: C 32.93, H 5.53; Found: C 32.92, H 5.47.

Other preparations.

Diisobutyltin oxide (100). Tetraisobutyltin was prepared by the conventional Grignard method with isobutyl bromide.[110] Organotin chloride or bromide impurities were removed as insoluble organotin fluorides by treatment with potassium fluoride. Distillation under reduced pressure afforded tetraisobutyltin, b.p. 87°C/0.04 mm, ^{119}Sn NMR δ -30.5. Tetraisobutyltin was converted to diisobutyltin dichloride, ^{119}Sn NMR δ 121, by heating for 22 h with one equivalent of tin tetrachloride at 200°C according to the literature method.[111]

The diisobutyltin dichloride thus obtained (12 g) was dissolved in ether (150 mL) and shaken with 5M NaOH (100 mL).[112] The white solid that formed at the interface was collected and washed with water, methanol and ether. The very fine powder of (**100**) was dried under vacuum at 100°C for 24 h (8.2 g, 82%). Anal. Calcd: C 38.68, H 7.29; Found: C 38.38, H 7.03.

Diisopropyltin oxide (101). A solution of tin tetrachloride (86 g, 0.33 mole) in hexane (150 mL) was slowly added to a Grignard reagent solution [from magnesium (1.5 m) and 2-bromopropane (1.6 m) in THF (1000 mL)] under a nitrogen atmosphere. The work-up procedure was the same as in the preparation of tetraisobutyltin. Vacuum distillation afforded tetraisopropyltin (77 g, 81% from $SnCl_4$); b.p. 88°C/0.55 mm; ^{119}Sn NMR δ -42.

To tetraisopropyltin (17.5 g, 0.06 mol) was added monochloroacetic acid (11.3 g, 0.12 mol) in approximately three equal portions over a period of 15 m, with intermittent refluxing.[83] The reaction mixture was boiled under gentle reflux for an

additional 20 m. The solid which resulted on cooling was recrystallized twice from pet-ether. Colourless diisopropyltin bischloroacetate (15 g, 64%) was obtained; m.p. 54-56 °C, lit.[83] 54-55 °C; ^{119}Sn NMR δ -172.4.

Diisopropyltin bischloroacetate (12 g, 0.03 mol) was dissolved in hot hexane (150 mL) and stirred with 5N NaOH (45 mL) at room temperature for 4 h. The colourless solid thus formed was filtered and washed with water, acetone and ether. Diisopropyltin oxide (**101**, 4.6 g, 70%) was obtained which is insoluble in water and in organic solvents but dissolved on refluxing in toluene containing a small amount of water. Anal. Calcd: C 32.63, H 6.39; Found: C 32.76, H 6.01.

Dimethyltin oxide (102).[113] Dimethyltin dichloride (5 g) was dissolved in water (100 mL). To this solution was gradually added 0.05 M NaOH (100 mL). The final pH was 8. The white powder formed was collected and washed with water, then with ether. The solid was poured into toluene (80 mL) and refluxed overnight with azeotropic removal of water. Filtration afforded a very fine white powder of **102** (3.3 g, 88%).

Di-*t*-butyltin oxide (103).[114] Di-*t*-butyltin dichloride (5 g) was dissolved in toluene (100 mL). The solution was poured carefully into boiling 5N NaOH (50 mL). After cooling, the colourless crystals were separated and washed with water (15 mL x 3). Recrystallization from toluene afforded colourless crystalline **103** (2.7 g, 68%); mp dec. at 250-270°C; lit.[114] mp ca. 250°C.

Diphenyltin oxide. This compound was prepared using a literature method.[115]

Attempted preparation of dineopentyltin dibromide (98). Dibutyldineopentyltin

(^{119}Sn NMR δ -31.4 ppm; 25.7 g, 0.068 mol) was dissolved in dry carbon tetrachloride (25 mL). A solution of bromine (22.0 g) in dry carbon tetrachloride (25 mL) was added dropwise to this solution at the boiling point. After completion of the addition, the mixture was refluxed for an additional two hours. The solvent was removed under reduced pressure and the residue was fractionally distilled using a concentric tube column at a pressure of 0.25 torr. Three fractions were collected of 2 g, 5 g, and 20 g. The ^{119}Sn NMR spectra of all fractions were very similar each containing two peaks at 114.3 and 103.4 ppm, having ratios of the integrals of 2:3, respectively. The former peak was assigned to butylneopentyltin dibromide (**99**) and the latter to **98**. The ^{13}C NMR spectrum contained two sets of peaks; one set at 47.2, 32.9, and 32.6 ppm (CH_2, CH_3, and C_q of neopentyl, respectively) assigned to **98**; another set having approximately 1/3 the intensity of those assigned to **98** at 46.7, 33.0, 32.7 ppm (CH_2, CH_3, and C_q of neopentyl, respectively), 27.7, 26.8, and 26.1, and 13.4 ppm (3 CH_2 and CH_3 of Bu, respectively), that were assigned to **99**. The ^{13}C NMR spectrum of dibutyltin dibromide contained peaks at 27.0 ($J_{Sn\text{-}119,C\text{-}13}$ = 389.1 Hz, C-α), 27.6 ($J_{Sn,C\text{-}13}$ = 33.4 Hz, C-β), 26.0 ($J_{Sn,C\text{-}13}$ = 83.9 Hz, C-γ), 13.5 (C-δ) ppm, consistent with the above spectrum of **99**.

Attempted preparation of dibenzyltin oxide. Dibenzyltin dichloride was prepared according to a literature method:[98a] mp 162-163 °C, lit.[98a] mp 163-164 °C. A solution of dibenzyltin dichloride (7 g) in ethanol (10 mL) was poured into 10% NaOH solution (30 mL). The mixture was stirred at room temperature for 1 h. The resulting white fine powder was collected by filtration and washed with water, ethanol

and then with ether. The solid material turned to slightly yellowish during washing and some greyish powder appeared on the surface of the sintered glass in the collecting funnel. The crude dibenzyltin oxide could not be purified further.

Crystal Structure of 1,1-stannacycloheptane bischloroacetate (95e). The X-ray crystal structure of compound **95e** was determined by P. K. Bakshi and T. S. Cameron, Department of Chemistry, Dalhousie University. For details, see Appendix.

Chapter 4

An Improved Method for the Regioselective Oxidation of Dibutylstannylene Acetals and Dimerization of the α-Hydroxyketone Products

4.1 Introduction

Dibutylstannylene acetals are readily prepared from diols or polyols by refluxing with dibutyltin oxide with azeotropic removal of water.[3a] David showed in 1974 that dibutylstannylene acetals are oxidized by bromine at the speed of a titration.[2] The products of the reaction are α-hydroxyketones and normally only a single regioisomer is obtained.[13,57,59,116,117] The products are obtained in excellent yields for dibutylstannylene acetals derived from simple diols[2] but the yields from carbohydrate-derived diols are usually lower,[13,59,116,117] and those from terminal carbohydrate diols are often below 50%.[13] In addition, if a base is not added to the reaction mixture the released hydrogen bromide causes the reaction to slow.[13,59] Rather unusual bases, such as tributyltin methoxide, have been found to be most effective.[13,59] Although the reaction has been considered to be a very promising method to convert diols regioselectively to α-hydroxyketones,[3a,b] it has been employed in only a few syntheses.[58,59,61b,118] Tributylstannyl ethers react similarly with bromine and it has been suggested that the yields are higher than with stannylene acetals.[57] However, more recent studies have found that for terminal diols the tributyltin ether method gives lower yields.[58]

Understanding the causes of the regioselectivity in reactions of

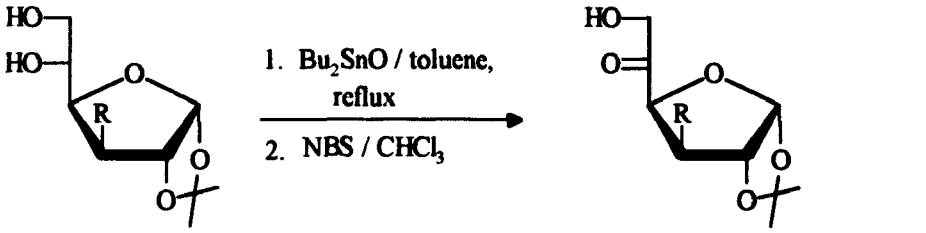
dibutylstannylene acetals is important for improving the regioselectivity.[5,38] Because of the unexploited promise of this oxidation and because bromine oxidation did not work well with terminal carbohydrate-derived diols, it was decided to examine oxidizing reagents other than bromine. *N*-Bromosuccinimide (NBS) was found to be the best of those studied. In this chapter, the results of the oxidation of dibutylstannylene acetals with NBS will be described. The dimerization of the α-hydroxyketone products will also be considered.

4.2 Results and Discussion

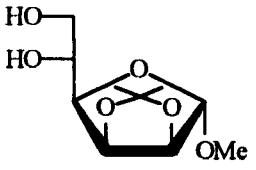
4.2.1 Reactions

The diols used in this study were 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose (**64**), 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**104**), 3-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose (**105**), methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside (**106**), and benzyl 4,6-*O*-benzylidene-α-D-galactopyranoside (**107**). All the diols were converted to their corresponding dibutylstannylene acetals by refluxing with one equivalent of dibutyltin oxide in toluene. The acetals were directly oxidized with NBS in chloroform at room temperature. In all cases single products were obtained. For the terminal or primary-secondary 1,2-diols, yields were excellent (compounds **104** and **64**, 90% and 95%, respectively) or good (compounds **105** and **106**, 84% and 81%, respectively). The secondary-secondary diol **107** was regioselectively oxidized to one product in 44% yield but 55% of the starting material **107** was recovered giving a yield of 97% based

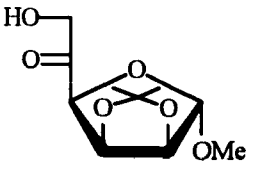
Scheme 4.1



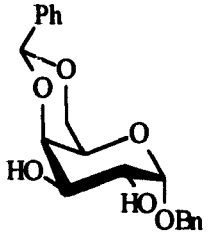
64	R = OMe		**108**	R = OMe, 95%
104	R = OBn		**109**	R = OBn, 90%
105	R = H		**110**	R = H, 84%



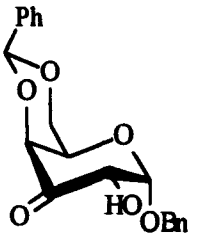
106



111



107



112

on consumed **107**. Conditions could not be found to get the reaction to go to completion. The general procedure of the oxidation and the structures of the related compounds are given in Scheme 4.1.

Structures of the oxidation products were established primarily from their ^{1}H and ^{13}C NMR spectra, using COSY and HETCOR experiments to confirm the assignments. The oxidation was highly regioselective in a consistent fashion. All of the terminal diols (**64**, and **104-106**) gave α-hydroxyketones (**108-111**). Compound **107**, a 2,3-diol on a pyranose ring, gave the 2-hydroxy-3-ketone **112**.

The products obtained are consistent with the idea that the reaction is initiated by the most nucleophilic oxygen in the stannylene acetal attacking the electrophilic oxidizing agent. Tin-119 NMR spectra of chloroform-*d* solutions of dibutylstannylene acetals of compounds **64** and **104-107** indicate that the dibutylstannylene acetals are present either as a single dimer (those derived from **64**, **104**, **106**, **107**) (to the level of detection) or as a mixture in which the major dimer constitutes > 90% (that derived from **105**).[5,119] For the stannylene acetals of **64** and **104-106**, the major dimer has O-5 dicoordinate,[119] and for the stannylene acetal of **107**, O-3 is dicoordinate.[5,119] See Figure 4.1 for the structure of the dimer of the dibutylstannylene acetal derived from **104**. Dicoordinate oxygens were found to be more nucleophilic in acylation and alkylation reactions.[5]

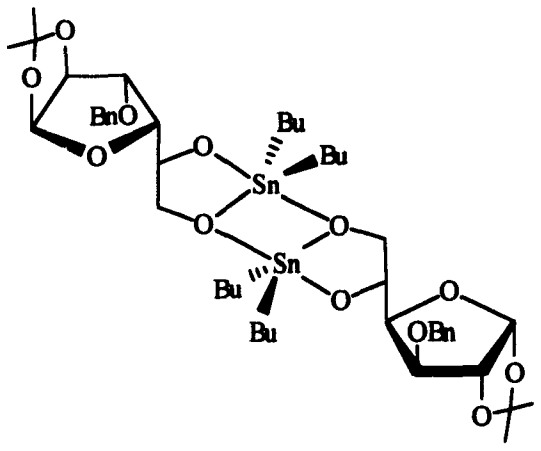


Figure 4.1 The dimeric structure of the dibutylstannylene acetal derived from 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**104**)

4.2.2 Dimer Formation

Oxidation of the dibutylstannylene acetal derived from diol **105** was complete almost instantaneously. TLC indicated that the reaction mixture contained one major product, the monomeric α-hydroxyketone **110**, plus a minor component with a much smaller R_F value that was later considered to be a mixture of dimeric structures based on the following information.

The major product was isolated by directly placing the reaction mixture on a flash column for purification. Despite the large difference in R_F values, the syrup that was isolated still contained the apparent impurity. The ^1H NMR spectrum indicated that the syrup was a mixture of **110** (major) and minor amounts of other complex components. Compound **110** was a monomeric α-hydroxyketone based upon a carbonyl absorption in its IR spectrum and a signal at 207 ppm due to a ketone carbon

in its ^{13}C NMR spectrum.

On being kept under pentane for 12 h, the syrup deposited a colorless solid in high yield. Recrystallization from ethyl acetate and hexane afforded fine crystals (**110a**) that gave a very different ^{1}H NMR spectrum than that of **110** when the spectrum was recorded as soon as possible after the chloroform-*d* solution was prepared. However, the peaks assigned to **110** grew into the new spectrum with time (see Figure 4.2) and after 24 h the spectrum was similar to that of the syrup obtained from the column. The presence of an equilibrium was confirmed by variable temperature measurements; in the ^{1}H and ^{13}C NMR spectra of samples that had been kept 2 h at 60 °C before recording, the signals assigned to compounds other than **110** had been reduced so that they were only just perceptible. Allowing the heated sample to sit for 24 h resulted in spectra identical to the original spectra. The behaviour of the specific rotation of this compound provides further evidence for an equilibrium between monomer and dimer. The -30° $[\alpha]_D$ value measured in chloroform at 21 °C just after solution preparation from crystalline material gradually increased to a final value of -70°.

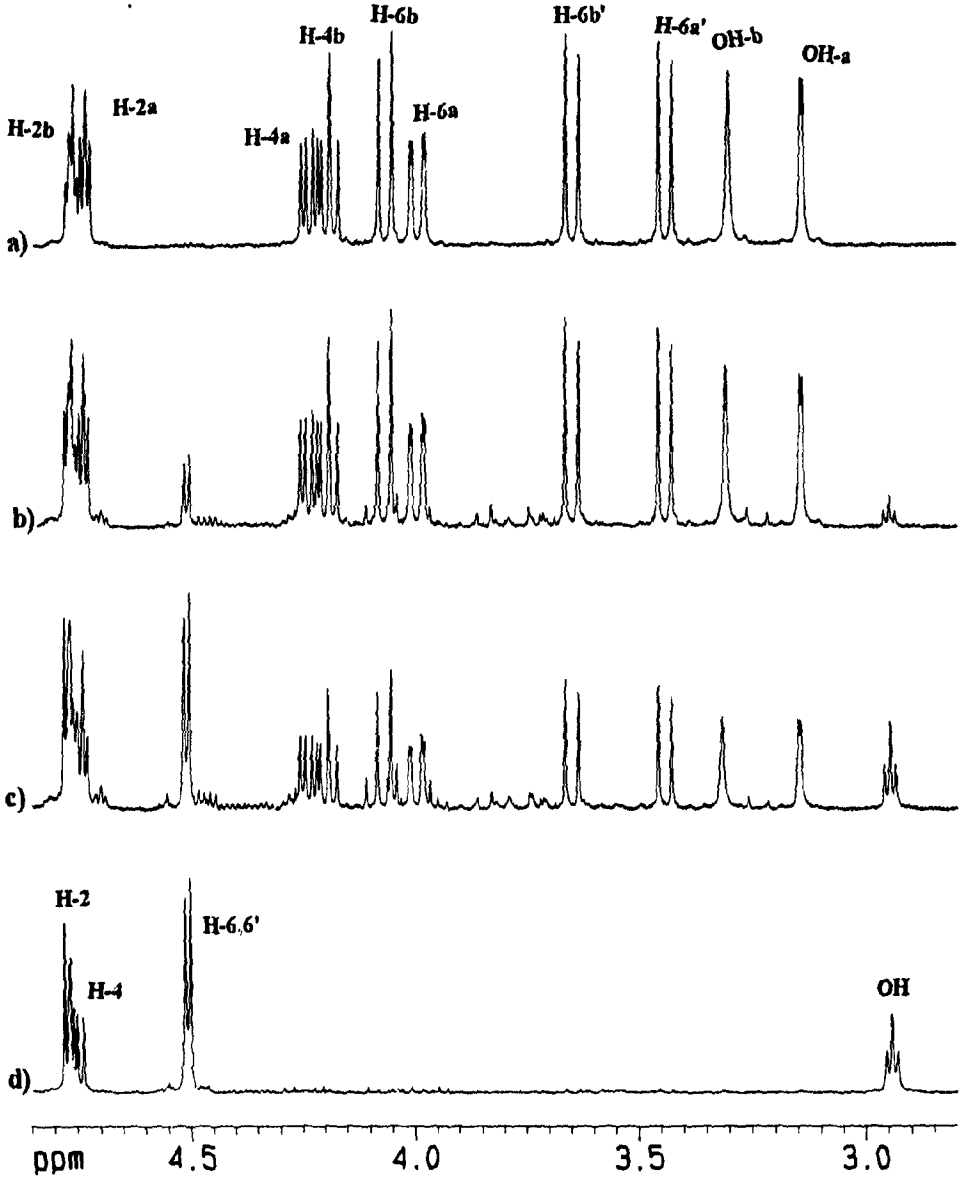


Figure 4.2 Part of the 400.14 MHz ^{1}H NMR spectra of the crystalline dimer of compound **110** as a function of time after making up the 0.1 M solution in $CDCl_3$ (a, after 5 m; b, after 90 m; c, after 4 h; d, after 22.5 h)

The NMR spectra recorded shortly after the crystalline material (**110a**) dissolved were consistent with it being a nonsymmetrical dimer of **110**. Both the ^{1}H and ^{13}C NMR spectra contained two sets of peaks having equal intensities. The only signal which occurred at the same chemical shift for both halves was that of C-1. A particularly noticeable difference from the spectra of the monomer occurred for the H-6 and H-6' signals; in the monomer, they were observed as either a singlet at 4.50 ppm or, if the sample was carefully dried, as a doublet due to coupling to the OH proton. In the dimer, an AX pattern and an AMX were observed for the two sets of H-6 and H-6' signals with doublets at 3.64 and 4.07 ppm coupled by -11.8 Hz and a doublet of doublets at 3.99 ppm and a doublet at 3.44 ppm coupled by -11.6 Hz. The chemical shift differences and coupling constants observed are typical of axial and equatorial protons in conformationally fixed 1,4-dioxane rings as expected in the dimer. The additional coupling of 2.1 Hz of the signal at 3.99 ppm was to an OH proton. The asymmetry in the dimer arises because the two new stereogenic hemiacetal centres must have opposite chirality if the two furanosyl groups are to be equatorial and the two new anomeric hydroxyl groups axial in the 1,4-dioxane ring; thus one new stereogenic center is *R*, the other *S*.

Assignment of which half of the dimer contains which stereogenic center can be made tentatively by means of a combination of molecular mechanics calculations and NMR experiments. In a COSY spectrum, the signals for H-3b and H-3b' at almost identical chemical shifts showed weak cross peaks with H-6b and H-6b' while the a-pairs did not show cross-peaks. In a NOESY spectrum, the signal for H-4b

showed a cross-peak with both H-6b and H-6b' but no cross-peaks to H-6 signals were observed for H-4a. Both observations [illegible] the assignment of the pairs of H-6 signals to particular monomer units in the dimer. The NOESY observation indicates that conformations in which H-4 is close to the H-6 hydrogens are more populated at the "b" end of the molecule.

MM3 Molecular mechanics calculations were performed to try to evaluate the conformational properties of dimer **110a**. The program used was MM3(89),[120] modified to run on a 486 microcomputer. The parameters present in the program and an improved set of OCCO torsional parameters[121] were both tried; the results differed by < 0.2 kcal-mol^{-1}. Similarly, using the dielectric constant of chloroform (4.7) rather than the default value (1.5) had very little effect on the results. Numerical values reported are with the standard parameters and the default dielectric constant. The conformational space accessible was evaluated by first driving the two inter-ring torsional angles in 45° steps. Two rotamers were found to be > 2 kcal-mol^{-1} more stable than the rest. For each of these conformations, the effects of torsions about the two hemiacetal OHs were evaluated by driving the appropriate torsional angles in 120° steps. Of the 18 possible conformers, six were within 2 kcal-mol^{-1} of the overall minimum. These conformations were then fully minimized. Table 4.1 lists their torsional angles and strain energies with respect to the overall minimum. The conformations of the furanose rings were checked by arbitrarily starting with alternative geometries. Only one conformation of the furanose rings gave minimum energies for the overall conformations; a $^3T_4$ conformation which has the 1,4-dioxane

ring at an equatorial position and the torsional angle at the position of the fused *O*-isopropylidene ring small (-13 to -13.6°).

Table 4.1 Conformations of dimer **110a**

Conformer	Torsional Angles[a]				Energy[b]
	O-4a C-4a C-5a O-5a	O-4b C-4b C-5b O-5b	C-6a C-5a O-5a' H-OHa	C-6b C-5b O-5b' H-OHb	(kcal-mol^{-1})
1a	174.2	-61.6	33.0	-37.5	0.0
1b	173.7	-63.0	37.9	-153.6	0.22
1c	-172.8	-65.1	-74.0	-154.1	0.56
1d	-173.0	-63.7	-72.1	-35.2	0.17
2a	73.6	-61.6	41.5	-37.0	0.42
2b	72.3	-63.6	156.0	-39.1	0.48

[a] Torsional angles (°); O-5 is in the 1,4-dioxane ring, O-5' is the OH O. [b] The energies reported are strain energies relative to the global minimum.

The calculations indicate that only the rotamer with H-4 *gauche* to C-6 is significantly populated at the (*S*)-end of the central 1,4-dioxane ring. At the (*R*)-end of the central 1,4-dioxane ring, rotamers with H-4 *gauche* to C-6 and H-4 *anti* to C-6 are both significantly populated. A *gauche* relationship between H-4 and C-6 is necessary for H-4 to be within 3 Å of an H-6. On this basis, H-4 in the monomer unit containing the *S*-center will spend more time close to the H-6s. Hence, the NMR signals labelled b in the experimental section and elsewhere were assigned to the monomer unit having the new *S*-stereogenic center. Figure 4.3 shows two of the low energy conformations that have different rotameric orientations at the (*R*)-end of the 1,4-dioxane ring.

The spectra of the original syrup indicated that more than one dimer was present. In the region of the ^{1}H NMR spectrum where anomeric protons absorb, a single doublet and a set of two equal intensity doublets appeared in addition to signals assigned to **110** and **110a**. The single doublet could be due either to a symmetrical dimer or to the hydrated monomer. The pair of doublets must be assigned to a non-symmetrical dimer that could be another 1,4-dioxane derivative, a 1,3-dioxolane derivative or a mixed dimer with only one center as a hemiacetal. An integral of the spectrum of the syrup indicated that the monomer constituted 70 ± 5 % of the mixture; in the more dilute (0.1 M) sample obtained by allowing the dimer to equilibrate, the monomer made up 83 ± 5 % of the mixture.

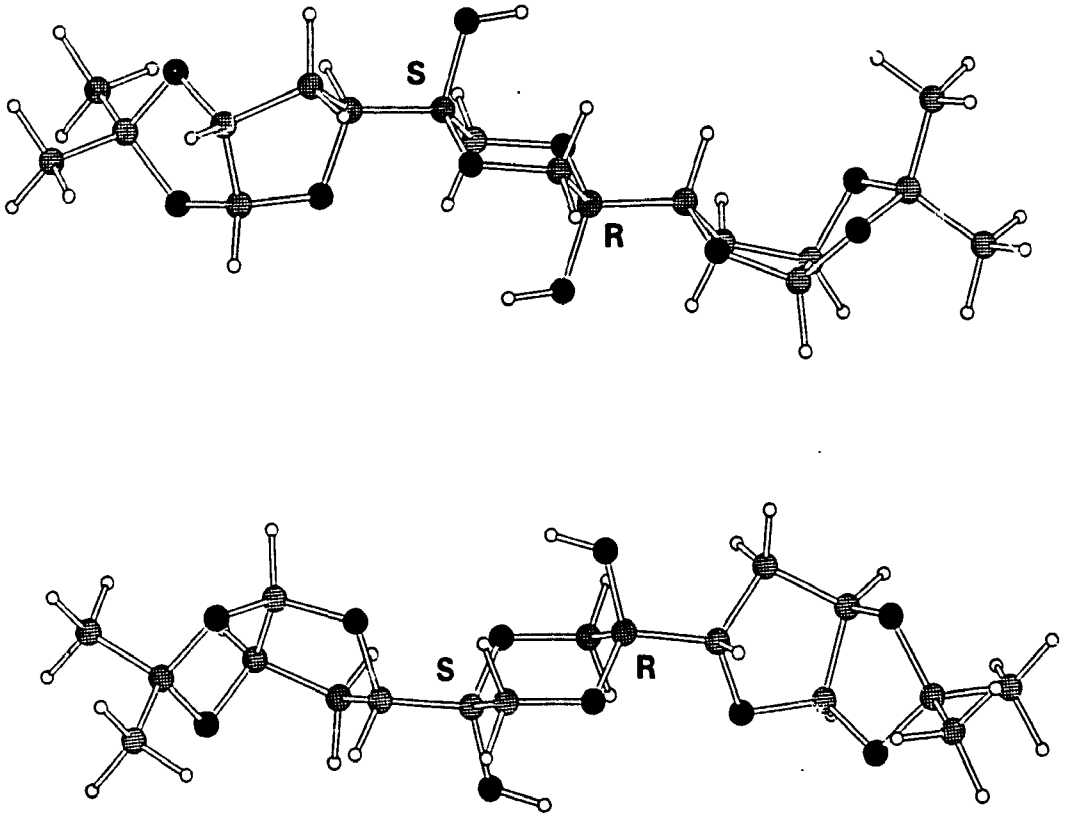


Figure 4.3 Two of the minimum energy conformations of the crystalline dimer **110a**: top, conformer 1a; bottom, conformer 2a. Oxygen atoms are represented by solid black circles, carbon atoms by checked circles, and hydrogen atoms by open circles. The positions of the new stereogenic centers are shown by the labels *S* and *R*. The "b" end of the dimer is on the left for both conformers.

There was no evidence for dimerization of any of the other α-hydroxyketones obtained here. Steric effects must play a major role in the stability of dimers relative to monomers. The absence of a substituent at C-3 in **110** allows it to dimerize to some extent.

Other α-hydroxycarbonyl compounds dimerize; both glycolaldehyde[122] and 1,3-dihydroxyacetone[123] exist as dimers having 1,3-dioxane rings in the solid. Glycolaldehyde and also glyceraldehyde equilibrate to complex mixtures containing monomer, 1,3-dioxane-ring-containing dimers, 1,3-dioxolane-ring-containing dimers and hydrated monomers in solvents containing water.[117, 122] The equilibrium mixture present for 1,3-dihydroxyacetone in water and in dimethylsulfoxide contained no dimer to the limit of observation on a 60 MHz NMR spectrometer.[123] Several carbohydrates containing α-hydroxyketones on pyranose rings have been observed to dimerize. Solutions of 2,3-*O*-isopropylidene-β-D-*threo*-hexo-2,4-diulopyranose are reported to contain 40% of a symmetric dimer which is pictured as having C_i symmetry.[117, 122] The structure shown is clearly wrong since the two halves of the dimer cannot be related by an S_2 axis if both halves are derived from D-fructose. Similarly, the C_i-symmetric structure shown for the dimer of 1,2-*O*-isopropylidene-β-D-*threo*-hexo-2,5-diulopyranose must also be incorrect.[117] Methyl β-L-*threo*-pentopyranosid-4-ulose is also reported to contain dimers of an unspecified structure.[116] Dimers have also been obtained from carbohydrate-derived β-hydroxy carbonyl compounds.[124]

The unrecognized formation of dimers from carbohydrate-derived α-hydroxyketones appears to have had an impact on their synthetic utility. During the

synthesis of isopropylidenedioxytetrahydrofuran derivatives, Marco[125] tried to prepare compound **110** with two different sequences which had as their last steps removal of *t*-butyldimethylsilyl and pivaloyl groups from O-6. The last deprotection steps were reported to fail but it is suspected that a complex mixture of dimers and monomer was obtained which could not be separated or identified. The same group reported the synthesis of compound **110** through brominolysis of tributyltin ether but claimed that it was extremely unstable.[62] It was found here that compound **110** is quite stable.

4.3 Experimental

General Procedures. Assignments of ^{1}H NMR spectra were made by first-order analysis using COSY experiments to confirm assignments where necessary; ^{13}C NMR spectra were assigned by HETCOR experiments. Specific rotations were determined with a Perkin-Elmer 141 polarimeter at 21 °C, and IR spectra were recorded on a Nicolet 205 FTIR spectrophotometer. Molecular mechanics calculations were performed with the MM3(89) program modified to run on 386 and 486 microcomputers using an NDP Fortran compiler (version 4.0.2). Structures were drawn with the program ATOMS. For all other general methods see Chapter 3.

Starting Materials.

3-O-Methyl-1,2-O-isopropylidene-α-D-glucofuranose (64). 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose was prepared from D-glucose in acetone in the presence of zinc chloride and phosphoric acid.[126] Recrystallization from hexane-

chloroform (2:1 v/v) afforded colourless crystals; m.p. 110-111 °C; lit.[126] 105-109 °C. A suspension of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (15.6 g, 0.06 mol) in ether (60 mL) was added to the suspension of sodium hydride (14.4 g, 0.6 mole) in ether (60 mL). The mixture was stirred at 25 °C for 20 m. Dimethyl sulphate (22.6 g, 0.09 mol) was added to the mixture in portions over 20 m. TLC indicated that methylation was complete as soon as all dimethyl sulphate had been added. The mixture was filtered and the filtrate was shaken with concentrated ammonium hydroxide (100 mL). The ether layer was separated, washed with water, and dried over potassium carbonate. A syrup was obtained after removal of solvent. To this syrup was added 40% acetic acid (200 mL) and the mixture was stirred at room temperature for 5 h. After water and acetic acid were removed under reduced pressure at 50 °C, column separation afforded a syrup of the title compound **4** (12.5 g, 89% for two steps): $[\alpha]_D^{21}$ -52.5° (*c* 1.4, chloroform), lit.[127] $[\alpha]_D$ -54°. Data for ^{1}H NMR are listed in Tables 4.2 and 4.3. Carbon-13 NMR chemical shifts are given in Table 4.4.

3-O-Benzyl-1,2-O-isopropylidene-α-D-glucofuranose (104). The crystalline 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (20 g) were dissolved in redistilled benzyl chloride (120 mL). To this solution was added powdered potassium hydroxide (80 g). The mixture was stirred at 135 °C for 3 h.[128] After the mixture was cooled to room temperature, water (400 mL) was added and the mixture was extracted with chloroform (2 x 150 mL). The extract was dried over potassium carbonate and the solvent was removed under reduced pressure. A yellow syrup was obtained, which

was directly hydrolysed overnight with 30% acetic acid (400 mL) at 40-45 °C.[129] After removal of solvents under reduced pressure, column separation afforded **78** (12 g, a syrup) $[\alpha]_D^{21}$ -47.3° (*c* 1 0, chloroform), lit [130] -48 4° Proton NMR spectral data are listed in Tables 4 2 and 4 3 Assignments were made by selective decoupling experiments. Carbon-13 NMR chemical shifts are given in Table 4 4.

3-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose (105). Compound **105** was prepared by a literature method as colourless crystals[131] mp 83-84 °C, lit.[131] mp 82-83 °C Proton NMR spectral data are listed in Tables 4.2 and 4 3. Carbon-13 NMR chemical shifts are given in Table 4 4

Methyl 2,3-O-isopropylidene-α-D-mannofuranoside (106). Compound **106** was prepared by a literature method[132] as a syrup For ^{1}H NMR spectral data see Tables 4 2 and 4 3 Carbon-13 NMR chemical shifts are given in Table 4.4.

Benzyl 4,6-*O*-benzylidene-α-D-galactopyranoside (107). Compound **107** was prepared by a literature method[5] as colourless needles with identical melting point, specific rotation, ^{1}H and ^{13}C NMR spectra as those reported in the literature.[5]

Table 4.2 Proton NMR chemical shifts for **64**, **104**, **105** and **106**[a]

Compd	H-1	H-2	H-3	H-3'	H-4	H-5	H-6	H-6'	CH_3O/PhCH_2
64	5.91	4.60	3.89	[b]	4.12	3.99	3.83	3.71	3.46
104	5.39	4.62	4.10	[b]	4.11	4.03	3.80	3.68	4.72, 4.56
105	5.78	4.72	2.03	1.81	4.17	3.86	3.67	3.55	[b]
106	4.92	4.58	4.84	[b]	3.94	4.02	3.86	3.72	3.30

[a] Chemical shifts are in ppm. [b] Not applicable.

Table 4.3 Proton NMR coupling constants for **64**, **104**, **105** and **106**[a]

Compd	$J_{1,2}$	$J_{2,3}$	$J_{3,3'}$	$J_{3,4}$	$J_{3',4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
64	3.8	0	[b]	3.2	[b]	7.8	3.3	5.6	11.5
104	3.7	0	[b]	3.7	[b]	7.3	3.1	5.5	11.5
105	3.7	0	13.4	4.6	10.6	4.5	[c]	[c]	[c]
106	0	5.9	[b]	3.8	[b]	7.9	3.5	5.9	11.4

[a] Coupling constants are in Hz. [b] Not applicable. [c] Unresolved.

Table 4.4 Carbon-13 NMR chemical shifts for **64**, **104**, **105** and **106**[a]

Compd	C1	C2	C3	C4	C5	C6	C_q[b]	CH_3O/PhCH_2
64	105.0	81.4	84.5	79.8	69.4	64.4	111.7	57.8
104	105.1	82.1	82.0	80.0	69.2	64.4	111.8	72.1
105	105.1	80.5	33.7	78.5	72.2	63.5	111.3	[c]
106	107.2	84.8	79.8	80.1	70.4	64.5	112.7	54.5

[a] Chemical shifts are in ppm. [b] Acetal carbon. [c] Not applicable.

Dibutyltin oxide. This compound (purity, 98%) was a product of Aldrich Chemical Company, Inc. and was used directly without purification.

***N*-Bromosuccinimide.** This compound was a product of Fisher Scientific Company and was purified by recrystallization from water[133] before use.

General methods for oxidation of dibutylstannylene acetals with N-bromosuccinimide. The diol (1 mmol) was refluxed with dibutyltin oxide (1 eq.) for 12 h in toluene (20 mL) in an apparatus for the continuous removal of water. The toluene was removed on a vacuum line at 20 °C and the residue was dried for 30 m under reduced pressure (0.1 torr). The residue was taken up in dry chloroform (10 mL) and *N*-bromosuccinimide (NBS, 1 eq.) was added. The stirred reaction mixture was monitored by TLC and the reaction was complete at times ranging from 2 to 30 m. The mixture was poured directly onto a silica gel column for separation using the

eluent listed for each compound.

1,2-*O*-Isopropylidene-3-*O*-methyl-α-D-*xylo*-hexofuranos-5-ulose (108). Oxidation of the dibutylstannylene acetal derived from 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose (**64**) with NBS was finished within 5 m. Column chromatography (hexane:ethyl acetate from 4:1 to 2:1) afforded compound **108** (yield 95%) as a syrup: $[\alpha]_D^{21}$ -129.3° (*c* 1.30, chloroform), lit.[134] -92.5° (*c* 1, acetone); ^{1}H NMR (250.13 MHz) δ 6.01 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.77 (d, 1H, $J_{3,4}$ = 3.7 Hz, H-4), 4.58 (d, 1H, H-2), 4.50 (d, 1H, $J_{6,6'}$ = -20.5 Hz, H-6), 4.41 (d, 1H, H-6'), 4.06 (d, 1H, H-3), 3.32 (s, 3H, OCH_3), 1.47 (s, 3H, CH_3-*endo*), 1.33 (s, 3H, CH_3-*exo*), lit.[13] chemical shifts agreed within 0.05 ppm, $J_{1,2}$ = 3.5 Hz, $J_{3,4}$ = 4 Hz; ^{13}C NMR (62.90 MHz) δ 208.0 (C-5), 112.6 (C_{acetal}), 105.9 (C-1), 85.7 (C-3), 84.4 (C-4), 81.0 (C-2), 68.1 (C-6), 58.3 (OCH_3), 26.9 ($CH_{3\ endo}$), 26.2 ($CH_{3\ exo}$).

3-*O*-benzyl-1,2-*O*-Isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (109). Oxidation of the dibutylstannylene acetal derived from 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**104**) with NBS was finished within 5 m. The eluent for column separation was the mixture of hexane and ethyl acetate (from 4:1 to 2:1). Evaporation of solvent from the corresponding fractions afforded **109** (280 mg, 90%). Colorless crystals were obtained from ethyl acetate-hexane: mp 117-8 °C, lit.[135] 115-6 °C (hemihydrate); $[\alpha]_D^{21}$ -114.5° (*c* 1.00, chloroform), lit.[135] $[\alpha]_D^{20}$ -110.5° (*c* 1.13, chloroform, hemihydrate); IR (nujol) 3491 cm^{-1} (OH), 1725 cm^{-1} (C=O); ^{1}H NMR (250.13 MHz) δ 7.18-7.34 (m, 4H, Ar-H), 6.05 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.82 (d, 1H, $J_{3,4}$ = 3.6 Hz, H-4), 4.60 (d, 1H, H-2), 4.57 (d, 1H, $J_{ArC\text{-}Ha,ArC\text{-}Hb}$ = -11.7 Hz,

ArC-Ha), 4.52 (d, 1H, H-6), 4.48 (d, 1H, $J_{6,6'}$ = -20.4 Hz, H-6'), 4.47 (d, 1H, ArC-Hb), 4.31 (d, 1H, H-3), 2.87 (br, 1H, OH), 1.47 (s, 3H, CH_3- *endo*), 1.32 (s, 3H, CH_3- *exo*); ^{13}C NMR (62.90 MHz) δ 208.2 (C-5), 136.6 (C_{arom}), 128.6, 128.2, 127.7 (CH_{arom}), 112.7 (C_{acetal}), 106.0 (C-1), 84.5 (C-4), 83.4 (C-3), 81.7 (C-2), 72.6 (C_{Benzyl}), 68.3 (C-6), 26.9 ($CH_{3\ endo}$), 26.3 ($CH_{3\ exo}$).

Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. Found: C, 62.04; H, 6.37.

3-Deoxy-1,2-*O*-isopropylidene-α-D-*erythro*-hexofuranos-5-ulose (110). Oxidation of the dibutylstannylene acetal derived from 3-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose (**105**) with NBS was finished in 1 m. Column separation (hexane:ethyl acetate from 4:1 to 2:1) afforded **110** (yield 84%) as a syrup: $[\alpha]_D^{21}$ 70.0° (*c* 1.30, chloroform);[136] IR ($CHCl_3$) 1724 cm^{-1}, s (C=O), 3515 cm^{-1} m (OH); ^1H NMR (400.14 MHz) δ 5.91 (d, 1H, $J_{1,2}$ = 4.5 Hz, H-1), 4.77 (dd, 1H, $J_{2,3'}$ = 4.4 Hz, H-2), 4.75 (dd, 1H, $J_{3,4}$ = 5.3 Hz, $J_{3',4}$ = 11.0 Hz, H-4), 4.50 (d, 2H, $J_{6,OH}$ = 4.6 Hz, 2H-6), 2.94 (t, 1H, OH), 2.46 (dd, 1H, $J_{3,3'}$ = -13.7 Hz, H-3), 1.81 (ddd, 1H, H-3'), 1.51 (s, 3H, CH_3-*endo*), 1.36 (s, 6H, CH_3-*exo*), ^{13}C NMR (100.6 MHz) δ 209.1 (C-5), 112.1 (C_{acetal}), 106.1 (C-1), 80.6 (C-4), 79.6 (C-2), 65.8 (C-6), 36.4 (C-3), 26.7 ($CH_{3\ exo}$), 26.1 (2 $CH_{3\ endo}$). The syrup deposited a colorless solid on being kept under vacuum or under pentane. Recrystallization of the solid (**110a**) from ethyl acetate-hexane provided a very fine powder, a dimer of compound **110**: mp 119-22 °C; IR (Nujol) 3442 cm^{-1} (OH), no C=O absorption; ^1H NMR (400.14 MHz) δ[137] 5.86 (d, 1H, $J_{1a,2a}$ = 3.5 Hz, H-1a), 5.83 (d, 1H, $J_{1b,2b}$ = 3.5 Hz, H-1b), 4.77 (m, 1H, H-2b), 4.74 (m, 1H, H-2a), 4.24 (dd, 1H, $J_{3a,4a}$ = 4.4 Hz, $J_{3a',4a}$ = 11.0 Hz, H-4a), 4.19 (t, 1H, $J_{3b,4b}$ + $J_{3b',4b}$ =

15.2 Hz, H-4b), 4.07 (d, 1H, $J_{6b,6b'}$ = -11.8 Hz, H-6b), 3.99 (dd, 1H, $J_{6a,6a'}$ = -11.6 Hz, $J_{6a,OH-a}$ = 2.1 Hz, H-6a), 3.64 (d, 1H, H-6b'), 3.44 (d, 1H, H-6a'), 3.28 (s, 1H, OH-b), 3.13 (d, 1H, OH-a), 2.13-2.18 (m, 2H, H-3b and H-3b'), 1.98 (dd, 1H, $J_{3a,3a'}$ = -13.1 Hz, H-3a), 1.76 (ddd, 1H, $J_{2a,3a'}$ = 4.6 Hz, H-3a'), 1.50 (br, 6H, $CH_{3\ a+b}$-*endo*) 1.32 (br, 6H ,$CH_{3\ a+b}$-*exo*); ^{13}C NMR (100.6 MHz) δ 112.0, 111.8 (C_{acetal} a,b), 105.7 (C-1a,b), 92.6, 92.0 (C-5a,b), 80.6 (C-2b), 80.2 (C-2a), 79.9 (C-4b), 79.7 (C-4a), 64.1 (C-6a), 62.2 (C-6b), 32.7 (C-3a), 32.3 (C-3b), 26.9, 26.8, 26.3, 26.2 (4 CH_3).

Anal. Calcd for $C_{18}H_{28}O_{10}$: C, 53.46; H, 6.98. Found: C, 53.42; H, 6.84.

Methyl 2,3-*O*-isopropylidene-α-D-*xylo*-hexofuranosid-5-ulose (111). Oxidation of the dibutylstannylene acetal derived from methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside (**106**) with NBS was complete in 15 m. The eluents used for column separation were mixtures of hexane and ethyl acetate (from 19:1 to 2:1). Hydroxyketone **111** was obtained (yield, 81%) as a solid, which was recrystallized from ethyl acetate-hexane, giving colorless needles: mp 110-1 °C; $[\alpha]_D^{21}$ -20.3° (*c* 1.00, chloroform); IR (Nujol) 3500-3400 cm^{-1} (OH), 1727 cm^{-1} (C=O); ^{1}H NMR (250.13 MHz) δ 5.04 (s, 1H, H-1), 5.03 (dd, 1H, $J_{3,4}$ = 4.1 Hz, $J_{2,3}$ = 5.8 Hz, H-3), 4.60 (d, 1H, H-4), 4.58 (d, 1H, H-2), 4.55 (dd, 1H, $J_{6,6'}$ = -20.1 Hz, $J_{6,OH}$ = 4.8 Hz, H-6), 4.45 (d, 1H, $J_{6',OH}$ = 4.0 Hz, H-6'), 3.35 (s, 3H, OCH_3), 3.03 (dd, 1H, OH), 1.43 (s, 3H, CH_3-*endo*), 1.28 (s, 3H, CH_3-*exo*); ^{13}C NMR (62.90 MHz) δ 206.8 (C-5), 113.2 (C_{acetal}), 107.7 (C-1), 84.1 (C-2), 83.6 (C-4), 81.0 (C-3), 67.9 (C-6), 55.1 (OCH_3), 25.8 ($CH_{3\ endo}$), 24.3 ($CH_{3\ exo}$).

Anal. Calcd for $C_{10}H_{16}O_6$: C, 51.72; H, 6.95. Found: C, 51.76; H, 6.90.

Benzyl 4,6-*O*-benzylidene-α-D-*xylo*-hexopyranosid-3-ulose (112). Oxidation of the dibutylstannylene acetal derived from benzyl 4,6-*O*-benzylidene-α-D-galactopyranoside (**107**) with NBS was carried out for 20 m in chloroform. Column separation (hexane:ethyl acetate from 9:1 to 2:1) gave a white solid, compound **112**, (yield 44%) and starting material (55%). Compound **107** had mp 146-9 °C; $[\alpha]_D^{21}$ +141.0°; IR (Nujol) 3400-3260 cm^{-1} (OH), 1744 cm^{-1} (C=O); ^1H NMR (250.13 MHz) δ 7.24-7.50 (m, 10H, aromatic H), 5.58 (s, 1H, acetal H), 5.40 (d, 1H, $J_{1,2}$ = 4.3 Hz, H-1), 4.97 (d, 1H, H-2), 4.72 (d, 1H, $J_{ArC\text{-}Ha,ArC\text{-}Hb}$ = -12.1 Hz, ArC-Ha), 4.63 (d, 1H, ArC-Hb), 4.54 (d, 1H, $J_{4,5}$ = 1.2 Hz, H-4), 4.32 (dd, 1H, $J_{5,6}$ = 2.30 Hz, $J_{6,6'}$ = -12.8 Hz, H-6), 4.11 (dd, 1H, $J_{5,6'}$ = 1.8 Hz, H-6'), 3.83 (m, 1H, H-5), 3.08 (br, 1H, OH); ^{13}C NMR (62.90 MHz) δ 200.8 (C-3), 136.9, 136.5 (C_{arom}), 129.4, 128.6, 128.4, 128.2, 127.9, 126.1 (CH_{arom}), 101.7 (C-1), 100.6 (C_{acetal}), 81.1 (C-4), 73.9 (C-2), 70.5 (C_{Benzyl}), 68.7 (C-6), 65.2 (C-5).

Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.41; H, 5.66. Found: C, 67.25; H, 5.64.

Chapter 5

Control of Regioselectivity in Mono-*p*-toluenesulfonation Reactions of Dialkylstannylene Acetals by Altering the Alkyl Groups on Tin

5.1 Introduction

Dibutylstannylene acetals have been widely used for accomplishing mono-*O*-substitution reactions for diols and polyols.[3] The success of this method lies mainly in its high regioselectivity, enhanced reactivity and convenient one-pot procedure. For secondary-secondary 1,2-diols on pyranose rings, the regioselectivity obtained appears to be related to the dimeric structures assumed by dibutylstannylene acetals. The nature of the dimeric mixtures present in solution is controlled mainly by steric effects in the parent diols.[5] As a result, the regioselectivity can often be predicted, especially for isolated *trans*- or *cis*- 1,2-diols on pyranose rings.[3]

When the dibutylstannylene acetal method was applied to carbohydrate-derived primary-secondary 1,2-diols, mono-*O*-substitution reactions usually occurred preferentially at the primary oxygen atoms (see Table 2.6 for examples). Although this regioselectivity can be obtained with conventional method such as acylation in pyridine, formation of dibutylstannylene acetal increases the reactivity of the parent diol or polyol towards electrophiles. In some cases, reaction at the secondary position increases if the reaction is carried out in a non-polar solvent in the absence of added nucleophiles.[13]

As mentioned in Chapter 1, it is desirable to develop a method for mono-*O*-

substitution of primary-secondary 1,2-diols with reversed regiochemistry. Based on earlier results and a consideration of probable reaction mechanism, it was thought this aim could be accomplished by reaction via stannylene acetals. Oxidation of dibutylstannylene acetals derived from primary-secondary 1,2-diols results in α-hydroxyketones in a highly regioselective manner (see Chapter 4 in this thesis). However, reversed regiochemistry had not been reported for mono-*O*-substitution reactions of carbohydrate-derived primary-secondary 1,2-diols.

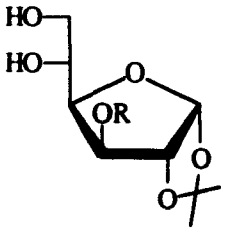
It was thought that altering the steric effects of the alkyl groups on the tin atoms in stannylene acetals would change the population ratio of different dimers in solution and hopefully change the regioselectivity for mono-*O*-substitution reactions of dialkylstannylene acetals towards electrophiles. In secondary-secondary 1,2-diols, the steric effects on both hydroxyls may be changed by substituents in molecules and by orientation of hydroxyl groups and other substituents. In primary-secondary 1,2-diols, the primary hydroxyl groups are always much less sterically hindered than the secondary hydroxyl groups. Thus, dimers of dialkylstannylene acetals formed through primary oxygen atoms should be highly favoured. On this basis, dialkylstannylene acetals with different steric environments have been studied as a means to obtain regioselective *p*-toluenesulfonation of a series of carbohydrate-derived primary-secondary diols.

5.2 Results and Discussion

5.2.1 Reactions

The diols used in this study are all primary-secondary 1,2-diols derived from monosaccharides, including glucose derivatives **64**, **104** and **66**, a mannose derivative **106**, allose derivatives **113**, **114** and **115**, a 3-deoxy-*xylo*-hexose derivative **105**, and mannitol derivatives **116** and **117** (see Figure 5.1 for structures). All the compounds possess furanose ring units, except mannitol derivatives **116** and **117**. Compounds **66** and **115** are triols with their third hydroxyl groups well separated from the diol units. Dialkyltin oxides prepared for use in this study include dibutyltin oxide, diisobutyltin oxide (**100**), diisopropyltin oxide (**101**), dineopentyltin oxide (**97a**), dineohexyltin oxide (**97c**), dicyclohexyltin oxide (**97d**), hexamethylenetin oxide (**97e**), and dihexyltin oxide. As noted in Chapter 3, it was necessary to develop a new synthetic approach in order to obtain these dialkyltin oxides pure.

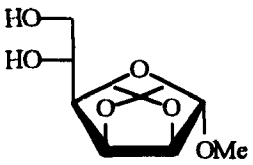
For all *p*-toluenesulfonation reactions, dialkylstannylene acetals were prepared from diols and dialkyltin oxides (1 mol-equivalent) in benzene or in toluene by the standard method. The dialkylstannylene acetals thus obtained were used directly, without separation or purification, for the subsequent *p*-toluenesulfonation. Monomeric structures of the dialkylstannylene acetals **118** to **150** are given in Figure 5.2. In addition, diphenyl-, di-*t*-butyl- and dimethylstannylene acetals were tried on some 1,2-diols and the results will be discussed in Section 5.2.2.



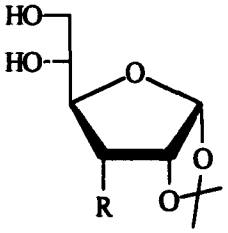
64 R = Me

66 R = H

104 R = Bn



106

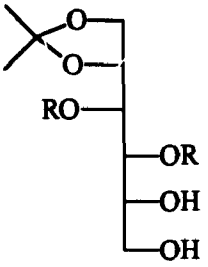


113 R = OMe

114 R = OTs

115 R = OH

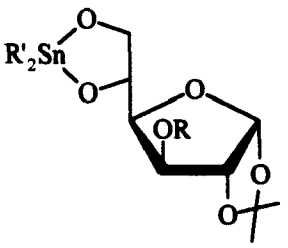
105 R = H



116 2 R = CMe_2

117 R = Bn

Figure 5.1 Diols and triols derived from monosaccharides studied for *p*-toluenesulfonation using their dialkylstannylene acetals



118 R = Bn, R' = Bu

119 R = Bn, R' = iBu

120 R = Bn, R' = iPr

121 R = Bn, R' = hexamethylene

122 R = Bn, R' = neohexyl

123 R = Bn, R' = cyclohexyl

124 R = Bn, R' = hexyl

125 R = H, R' = Bu

126 R = Me, R' = Bu

127 R = Me, R' = iBu

128 R = Me, R' = iPr

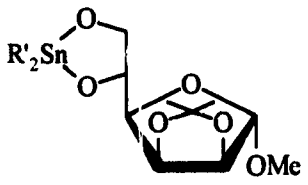
129 R = Me, R' = hexamethylene

130 R = Me, R' = neohexyl

131 R = Me, R' = cyclohexyl

132 R = Me, R' = hexyl

133 R = Me, R' = neopentyl



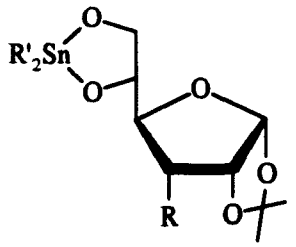
134 R' = Bu

135 R' = iPr

136 R' = hexamethylene

Figure 5.2 Dialkylstannylene acetals derived from primary-secondary diols

(continued on next page)



137 R = OMe, R' = Bu

138 R = OMe, R' = *i*Pr

139 R = OTs, R' = Bu

140 R = OTs, R' = iPr

141 R = OH, R' = Bu

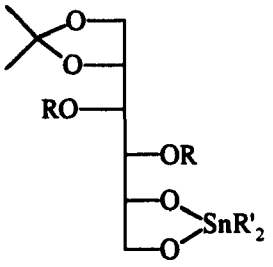
142 R = OH, R' = hexamethylene

143 R = *H*, R' = Bu

144 R = H, R' = iBu

145 R = H, R' = iPr

146 R = H, R' = hexamethylene



147 2 R = CMe_2, R' = Bu

148 2 R = CMe_2, R' = hexamethylene

149 R = Bn, R' = Bu

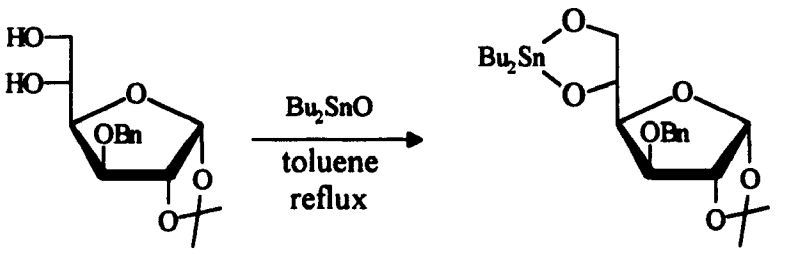
150 R = Bn, R' = hexamethylene

***Figure 5.2** continued*

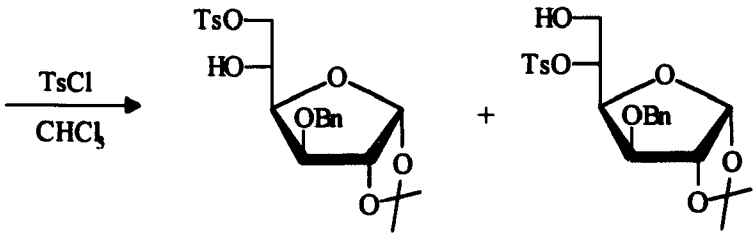
A typical example for the reaction sequence is outlined in Scheme 5.1. 3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**104**, a carbohydrate-derived primary-secondary 1,2-diol) was first refluxed with one equivalent of dibutyltin oxide in toluene to form the corresponding dibutylstannylene acetal **118**. Dry chloroform was added after toluene was removed on a vacuum line. To this chloroform solution of stannylene acetal **118** was added one equivalent of *p*-toluenesulfonyl chloride. The reaction mixture was kept at room temperature for 20 h and then poured directly onto a column for separation of the mono-*O*-substituted products, 3-*O*-benzyl-1,2-*O*-isopropylidene-6-*O*-*p*-toluenesulfonyl-α-D-glucofuranose (**104P**) and 3-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-α-D-glucofuranose (**104S**). Throughout the text in this chapter, mono-*O*-*p*-toluenesulfonation products of diols are numbered in the same way as used above for **104P** and **104S**: the number of the parent compound with a capital letter **P** or **S**. **P** stands for the primary or the 6-*O*-*p*-toluenesulfonate, and **S** for the secondary or the 5-*O*-*p*-toluenesulfonate.

Structural assignments for compounds **104P** and **104S** were made from their ^{1}H and ^{13}C NMR spectra. Both were obviously mono-*O*-toluenesulfonyl derivatives from integrations of the signals of the aromatic protons and aryl methyl protons versus those of the anomeric proton and the isopropylidene methyl groups. The most obvious indication of structure was appearance of the signal for the OH proton of **104P**; it was a sharp doublet which could only arise from ^{3}J coupling to one proton, H-5 of **104P**. The OH signal for **104S** was a broadened signal without obvious coupling. In addition, expected downfield shifts were observed for the protons on the carbons

Scheme 5.1



104 **118**



104P **104S**

bearing the OTs group. The signals of H-6 and H-6' moved from 3.68 and 3.80 ppm in the spectrum of **104** to between 4.05 and 5.15 ppm in the spectrum of **104P**. The signal of H-5 moved from 4.03 ppm in the spectrum of **104** to 5.04 ppm in the spectrum of **104S**. Similar effects were noted for the corresponding signals in the ^{13}C NMR spectra.

5.2.2 Regioselectivities

Solvent effect on regioselectivity. Several carbohydrate-derived primary-secondary 1,2-diols had been subjected to mono-*O*-substitution reactions via their dibutylstannylene acetals.[13,22,48-52] In most cases, polar-nucleophilic solvents such as methanol[48,50] and pyridine[13,49] or a non-polar solvent containing an added nucleophile[52] were used for reactions. Under these conditions, all reactions occurred exclusively at primary positions. In present work, *p*-toluenesulfonations of dialkylstannylene acetals were performed in different non-nucleophilic solvents in the absence of added nucleophiles and it was found that chloroform was the best for increasing regioselectivity for reaction at secondary positions.

Dibutylstannylene acetal **118** (from diol **104**) was allowed to react with one equivalent of *p*-toluenesulfonyl chloride at 20 °C to give mono-*O*-*p*-toluenesulfonates **104P** and **104S** in high yield. The ratios of **104S**:**104P** were 31:69 in toluene, 55:45 in chloroform, and 43:57 in dichloromethane (Table 5.1, entries 1 to 3). Thus, reaction selectivity at the secondary position was higher in both chloroform and dichloromethane than that in toluene. *p*-Toluenesulfonation of diisopropylstannylene

acetal **120** showed similar solvent effect but differences in selectivity were not as large (Table 5.1, entries 7, 8 and 10). When *p*-toluenesulfonation of stannylene acetals **118** and **120** were carried out in acetonitrile, selectivity at the secondary position was lower than that in toluene (Table 5.1, entries 4 and 12). The lower selectivity at the secondary position for reaction in acetonitrile was believed to be due to the nucleophilicity of CH_3CN. Acetonitrile is a weaker nucleophile in comparison with DMF, pyridine and methanol which were used as solvents in similar reactions in literature, thus the reaction still occurs at the secondary position to some extent.

Results from stannylene acetals **126**, **134** and **135** (Table 5.1, entries 18, 19, 29 to 32) also indicated that chloroform was more effective than toluene for increasing regioselectivity for reaction at secondary positions, although the differences were not very large.

Tsuda and coworkers reported that *p*-toluenesulfonation of dibutylstannylene acetal **125** (from glucose derivative **66**, a triol) in dioxane in the presence of 4-dimethylaminopyridine gave only the 6-*O*-toluenesulfonate (**66P**) in high yield.[22] In current study, the same reaction was carried out in toluene in the absence of added nucleophile. The reaction occurred slowly at 20 °C for 4 days in a lower yield (51%), however, the selectivity at the secondary position increased substantially (24% of the products being **66S**).

Temperature effect on regioselectivity. It was found that temperature affected both regioselectivity and reaction speed. *p*-Toluenesulfonation of stannylene acetal **120** in chloroform, for example, gave an 88% yield of mono-*O*-substitution products in

Table 5.1 Selectivities of the dialkylstannylene acetals in *p*-toluenesulfonation

Entry	Acetal[a]	Reaction conditions			Selectivity (%)		Yield[b]
		Solvent	Temp.(°C)	Time[c]	P[d]	S[e]	(%)
Glucose derivatives							
1	**118**	toluene	20	48 h	69	31	99
2	**118**	$CHCl_3$	20	20 h	45	55	95
3	**118**	CH_2Cl_2	20	12 h	57	43	95
4	**118**	CH_3CN	20	20 h	71	29	93
5	**119**	toluene	20	48 h	42	58	67
6	**119**	$CHCl_3$	20	48 h	31	69	97
7	**120**	toluene	20	48 h	37	63	98
8	**120**	$CHCl_3$	20	48 h	31	69	88
9	**120**	$CHCl_3$	5	14 d	20	80	94
10	**120**	CH_2Cl_2	20	12 h	32	68	95
11	**120**	CH_2Cl_2	5	48 h	28	72	87
12	**120**	CH_3CN	20	20 h	71	29	93
13	**121**	$CHCl_3$	20	20 h	4	96	99
14	**122**	$CHCl_3$	20	10 h	57	43	98
15	**123**	$CHCl_3$	20	36 h	48	52	96
16	**124**	$CHCl_3$	20	12 h	45	55	96
17	**125**	toluene	20	4 d	76	24	51
18	**126**	toluene	20	48 h	80	20	97
19	**126**	$CHCl_3$	20	12 h	60	40	98

(continued on next page)

(*Table 5.1 continued*)

20	**127**	toluene	20	48 h	40	60	77
21	**128**	toluene	20	24 h	40	60	80
22	**128**	$CHCl_3$	5	14 d	25	75	96
23	**128**	CH_2Cl_2	5	48 h	35	65	80
24	**129**	$CHCl_3$	20	12 h	5	95	94
25	**130**	$CHCl_3$	20	12 h	70	30	98
26	**131**	$CHCl_3$	20	36 h	44	56	85
27	**132**	$CHCl_3$	20	12 h	58	42	98
28	**133**	$CHCl_3$	20	14 d	30	70	65
Mannose derivatives							
29	**134**	toluene	20	12 h	100	0	98
30	**134**	$CHCl_3$	20	5 h	>95	<5	98
31	**135**	toluene	20	60 h	67	33	98
31a[f]	**135**	toluene	20	2 h	68	32	99
32	**135**	$CHCl_3$	20	12 h	62	38	91
33	**136**	$CHCl_3$	20	12 h	30	70	92
Allose derivatives							
34	**137**	$CHCl_3$	20	12 h	100	0	98
35	**138**	$CHCl_3$	20	12 h	67	33	67
36	**139**	$CHCl_3$	20	12 h	92	8	97
37	**140**	$CHCl_3$	20	12 h	64	36	88
38	**141**	$CHCl_3$	20	8 h	100	0	90
39	**142**	$CHCl_3$	20	12 h	92	8	99

(continued on next page)

(*Table 5.1 continued*)

3-Deoxy-erythro-hexose derivatives							
40	**143**	$CHCl_3$	20	12 h	95	5	99
41	**144**	$CHCl_3$	20	20 h	79	21	90
42	**145**	$CHCl_3$	20	20 h	78	22	90
43	**146**	$CHCl_3$	20	20 h	48	52	99
Mannitol derivatives							
44	**147**	$CHCl_3$	20	24 h	98	2	98
45	**148**	$CHCl_3$	20	24 h	40	60	96
46	**149**	$CHCl_3$	20	24 h	87	13	92
47	**150**	$CHCl_3$	20	24 h	22	78	77

[a] Dialkylstannylene acetal, for structure see Figure 5.2. [b] Separated yield of mono-*p*-toluenesulfonates in total. [c] For reaction time: h stands for hour and d for day. [d] Primary *p*-toluenesulfonate. [e] Secondary *p*-toluenesulfonate; in the cases for triols (Entries 14, 33 and 34), S stands for the 5-*O*-*p*-toluenesulfonate. [f] This reaction was carried out with 12 eq. of TsCl.

48 h with the ratio of **104S**:**104P** being 7:3 at 20°C. The same reaction conducted at 5 °C resulted in mono-*O*-substitution products with a yield of 94%. The ratio of **104S**:**104P** increased to 8:2. This was the best selectivity obtained at the secondary position for *p*-toluenesulfonation of compound **104** through acyclic dialkylstannylene acetals (for a result with the cyclic hexamethylenestannylene acetal, see later). Similarly, good selectivity at the secondary position for compound **64** was also obtained when the reaction was performed with diisopropylstannylene acetal at 5 °C (**64S**:**64P**, 3:1). However, reactions at the lower temperature were very slow, taking 14 d to be complete.

Steric effect of substrates on regioselectivity. Very different regioselectivities were observed from different diols. Diisopropylstannylene acetal **120** reacted with one equivalent of *p*-toluenesulfonyl chloride in chloroform at 20 °C giving the secondary *p*-toluenesulfonate as the major product (**104S**:**104P**, 69:31, Entry 8 in Table 5.1), but under the exact same conditions, diisopropylstannylene acetals **135**, **138** and **140** resulted in the primary *p*-toluenesulfonates as the major products (primary:secondary, 62:38, 67:33 and 64:36 respectively, see entries 32, 35 and 37 in Table 5.1). Similarly, dibutylstannylene acetal **118** gave the highest regioselectivity at the secondary position among all the dibutylstannylene acetals studied here. When the reaction was carried out in chloroform at 20 °C, **118** slightly favoured substitution at the secondary position whereas other dibutylstannylene acetals (**137**, **139**, **143**, **147** and **149**) gave preferentially primary *p*-toluenesulfonates in yields ranging from 87% to 100%. In general, 3-*O*-substituted glucofuranose derivatives are the most selective at

the secondary oxygen atoms. All the other carbohydrate-derived diols have very strong preference for reaction at the primary positions. The differences in selectivity are probably related to the relative reactivity of the primary and secondary hydroxyl groups of the parent diols and will be further discussed in Section 5.2.5 together with the kinetics of the dialkylstannylene acetal reaction.

Effect of the alkyl groups (on tin atom) on regioselectivity. In order to examine the steric effect of the alkyl groups (on tin atom) on regioselectivity, *p*-toluenesulfonation reactions have been performed on different dialkylstannylene acetals in this study.

Reginato *et al.* reported that benzoylation of simple primary-secondary 1,2-diols (such as propane-1,2-diol, **4b**) via their dibutylstannylene acetals in chloroform gave highly reversed regioselectivity (see Chapter 2, Section 2.1.3).[14] They claimed that this method had also been successful when applied to 1,3- and 1,4-diols of primary-secondary and even primary-tertiary types. In this study, a very similar method was employed for a carbohydrate-derived primary-secondary 1,2-diol **104** (a glucofuranose derivative) but reversed regioselectivity could not be achieved with this substrate. In a typical experiment, benzoylation of **104** through its dibutylstannylene acetal (**118**) with benzoyl chloride (1 eq.) in benzene gave 77% of the primary benzoate and 15% of the secondary benzoate. This result was very similar to that obtained from benzoylation of **64**, the methyl analog of **104**, via its dibutylstannylene acetal, by David and Thieffry, where they reported a lower overall yield with 38% of the primary benzoate and 7.5% of the secondary benzoate.[13] An effort that was made to repeat Reginato's

work on propane-1,2-diol (**4b**) failed to achieve the reversed regiochemistry that had been reported.

One problem associated with benzoylation of stannylene acetals is that migration of benzoyl groups in the originally formed products was observed to occur while the reaction was in progress. Benzoylation of **118** in benzene was traced by TLC. It was clearly shown that migration of benzoyl group occurred at a rate comparable to benzoylation. Thus, *p*-toluenesulfonation was selected as the reaction to study instead of benzoylation because the *p*-toluenesulfonyl group does not rearrange under the conditions used for reaction.

The most common dialkylstannylene acetals are dibutylstannylene acetals. They have been widely used as intermediates for regioselective mono-*O*-substitution reactions (alkylation and acylation, in most cases) of carbohydrate-related diols or polyols on six-membered rings or similar systems. As mentioned earlier in this chapter, only in several occasions have dibutylstannylene acetals found applications in mono-*O*-substitutions of carbohydrate-derived primary-secondary diols.[13,22,48-52] No reversed regiochemistry has been achieved with substitution reactions of this type of stannylene acetal. Changing reaction conditions (to conduct reactions in non-polar solvents and in the absence of added nucleophiles) did increase the relative amounts of products at secondary positions. However, the primary substitution products were still the major constituents in *p*-toluenesulfonation reactions of all dibutylstannylene acetals studied here except for that of compound **104**, where secondary substitution was slightly favoured over primary substitution (**104S**:**104P**, 55:45) when the reaction was

carried out in chloroform (Table 5.1, entry 2).

It was clearly shown from the data in Table 5.1 that the sizes and shapes of alkyl groups on tin atoms in dialkylstannylene acetals had a substantial effect on regioselectivity. Changing the alkyl groups (R' groups on tin) from two butyl groups to two isopropyl groups increased the selectivity at the secondary positions in all cases. For example, both stannylene acetals **118** and **120** are derived form diol **104**. The alkyl groups (R' on tin) are butyl in **118** and isopropyl in **120**. *p*-Toluenesulfonation of **118** in toluene at 20 °C yielded 69% **104P** and 31% **104S** whereas the same reaction carried out using **120** as the intermediate under exactly the same conditions resulted in a reversed regioselectivity, the ratio of **104P**:**104S** being 37:63. The diisobutylstannylene acetal of **104** also gave the reversed regiochemistry. *p*-Toluenesulfonation of diol **64** in toluene gave similar results: the ratios of **64S** to **64P** increased from 20:80 with dibutylstannylene acetal (Table 5.1, entry 18) to 60:40 with diisopropylstannylene acetal (Table 5.1, entry 21). For other substrates like **106**, **114** and **105**, significant increases of selectivity at the secondary position were also achieved by changing the R' groups from butyl to isopropyl, but the major products were still the primary *p*-toluenesulfonates in these cases. In the case of diol **113**, *p*-toluenesulfonation through its dibutylstannylene acetal **137** yielded the primary *p*-toluenesulfonate **113P** as the only product. In contrast, 33% of the mono-*O*-substituted products was the secondary *p*-toluenesulfonate **113S** when the reaction was carried out through the diisopropylstannylene acetal **138** (Table 5.1, entries 34 and 35).

Diisobutylstannylene acetals afforded very similar regioselectivity in

comparison with diisopropylstannylene acetals. Dineohexyl-, dicyclohexyl- and dihexyl-stannylene acetals resulted in the regioselectivities comparable to those obtained from dibutylstannylene acetals with slight variations depending on the alkyl groups and substrates. For example, dineohexylstannylene acetal **122** (from diol **104**) was slightly less selective at the secondary position than the dibutyl analog **118** although the neohexyl group is much larger and more sterically hindered. The same trend was found for *p*-toluenesulfonation of diol **64**. The dicyclohexylstannylene acetal provided roughly the same selectivity as the dibutylstannylene acetal in the case of diol **104**, whereas a better selectivity for reaction at the secondary position was obtained using dicyclohexylstannylene acetal rather than using the dibutyl analog for *p*-toluenesulfonation of diol **64**. For the reaction on diol **64**, good selectivity at the secondary position was observed by using dineopentylstannylene acetal **133**, a very sterically hindered stannylene acetal. However, the reaction became very slow and an overall yield of only 65% was obtained after the reaction mixture was kept at 20 °C in chloroform for 14 days.

In general, diisopropylstannylene acetals were best suited for selective *p*-toluenesulfonation of carbohydrate-derived primary-secondary 1,2-diols at the secondary positions among all acyclic dialkylstannylene acetals studied here.

A breakthrough on inversion of regioselectivity in *p*-toluenesulfonation of diols via stannylene acetal intermediates was achieved through the use of hexamethylenestannylene acetals. In all cases, the hexamethylenestannylene acetals of carbohydrate-derived primary-secondary 1,2-diols yielded the secondary

p-toluenesulfonates as major products of the *p*-toluenesulfonation reactions. For example, *p*-toluenesulfonation of glucofuranose derivatives **64** and **104** using their hexamethylenestannylene acetals (**129** and **121**) occurred at secondary hydroxyl oxygen atoms (OH-5) selectively in excellent yields. The ratios of the mono-*O*-substituted products at secondary oxygen atoms to those at primary oxygen atoms were 95:5 (for **64**) and 96:4 (for **104**), respectively (Table 5.1, entries 13 and 24). Even for diol **116**, where *p*-toluenesulfonation of its dibutylstannylene acetal (**147**) gave almost entirely the primary substitution product (**116S**:**116P**, 2:98; Table 5.1, entry 44), the ratio of selectivity at the secondary position to that at the primary position was increased to 60:40 by using hexamethylenestannylene acetal **148** (Table 5.1, entry 45). One exception was observed in the case of allofuranose derivative **115**, a triol with the third hydroxyl group on the C-3 position. Stannylene acetals of this compound had great preference for reaction at the primary position. The dibutylstannylene acetal of **115**, on reaction with *p*-toluenesulfonyl chloride in chloroform for 8 h, gave the primary *p*-toluenesulfonate as the only product in a yield of 90%. *p*-Toluenesulfonation of the hexamethylenestannylene acetal of **115** also occurred quickly in very high yield (99%), but only 8% of the mono-*O*-substituted products was the secondary *p*-toluenesulfonate. This will be discussed in Section 5.2.3.

When compound **64** or **104** was refluxed with 1 eq. of diphenyltin oxide in toluene in a standard method, the anticipated diphenylstannylene acetal did not form and no reaction occurred after reacting the mixture with *p*-toluenesulfonyl chloride in the standard way at room temperature for one week.

p-Toluenesulfonation of the dimethylstannylene acetal derived from compound **64** in chloroform gave a mixture of mono-*O*-*p*-toluenesulfonates. The ratio of **64S** to **64P** was 1:15 as shown by ^{1}H NMR spectrum.

Di-*t*-butylstannylene acetals derived from compounds **104, 105** and **113** were also subjected to *p*-toluenesulfonation using the standard method in chloroform at room temperature. In all the cases, reaction occurred very slowly giving primary *O*-*p*-toluenesulfonates as major products. For example, *p*-toluenesulfonation of **113** was carried out via its di-*t*-butylstannylene acetal in chloroform at room temperature for two weeks, giving mono-*O*-substituted products in a yield of 36% with the ratio of **113S** to **113P** being 10:90.

5.2.3 Dimerization of dialkylstannylene acetals in solution

It is well known that oligomerization of dibutylstannylene acetals occurs both in solution and in the solid state.[3,5,38] For carbohydrate-derived dibutylstannylene acetals, the major species present in solution are dimers. When the parent diol is nonsymmetric, there are three possible dimeric structures. The major factor determining which dimer of the three is more populated than the others has been shown to be steric effects in the dimer molecule.[5] A well established method to study oligomerization of dibutylstannylene acetals is ^{119}Sn NMR spectroscopy. In general, the region of the NMR spectrum where absorption occurs for tin atoms depends on the coordination status of the tin atom. This methodology was employed in this thesis to study dimerization (oligomerization, in general) of different dialkylstannylene acetals

and thus to understand the sources of regioselectivity of dialkylstannylene acetals in mono-*O*-substitution reactions.

All NMR samples of dialkylstannylene acetals were prepared carefully on a vacuum line to avoid atmospheric moisture which can cause hydrolysis of stannylene acetals. Tin-119 NMR spectra were recorded in 10 mm tubes on a Bruker AMX 400 spectrometer at 149.20 MHz or on a Nicolet NT-360 NB spectrometer at 134.62 MHz and referenced to external tetramethyltin at 20 °C. Tin-119 NMR chemical shifts for dialkylstannylene acetals are listed in Table 5.2.

The ^{119}Sn NMR spectra of dialkylstannylene acetals derived from most diols contained a single sharp peak at room temperature with a chemical shift typical of pentacoordinate tin atoms.[5] The ^{119}Sn NMR line widths varied considerably due to the decoupling efficiency and the presence of exchange processes (see later). When the lines were narrow, additional ^{117}Sn satellite signals were observed due to coupling to ^{117}Sn atoms in the 7.5% of molecules containing ^{119}Sn that also contained ^{117}Sn atoms. Observation of such coupling confirms that these compounds were indeed present as dimers or higher oligomers, i.e. that more than one tin atom was present in the structure.

The dialkylstannylene acetals can be classified into three different types, according to the position of absorption in their ^{119}Sn NMR spectra: (i) those with chemical shifts typical of pentacoordinate tin atoms in dimeric 2,2-dibutyl-1,3,2-dioxastannolane structures (-115 to -124 ppm), (ii) the stannylene acetals with chemical shifts at lower frequencies (-169 to -186 ppm), and (iii) the compounds with

Table 5.2 Tin-119 NMR spectral data of the dialkylstannylene acetals[a]

Compd	Solvent	Temp. (°C)	Conc.(M)	Chemical Shift (δ)	$J_{Sn\text{-}119,Sn\text{-}117}$[b]
118	C_7D_8	19	0.2	-119.6	
	$CDCl_3$	26	0.2	-118.3	146.3
	$CDCl_3$	-60	0.2	-118.9	152.6
119	$CDCl_3$	19	0.33	-120.1	
	$CDCl_3$	-60	0.33	-120.8	
120	$CDCl_3$	19	0.33	-170.1	
	$CDCl_3$	-60	0.33	-167.8	
121	$CDCl_3$	20	0.3	-99.2	
126	$CDCl_3$	26	0.5	-118.9	143.2
	$CDCl_3$	26	0.2	-118.8	148.5
	$CDCl_3$	-60	0.2	-119.7	
127	$CDCl_3$	19	0.33	-120.1	
	$CDCl_3$	-60	0.33	-123.8	
128	$CDCl_3$	19	0.33	-171.3	
	$CDCl_3$	-60	0.33	-169.8	
129	$CDCl_3$	20	0.3	-98.9	142
130	$CDCl_3$	20	0.3	-114.5	137

(continued on next page)

(*Table 5.2 continued*)

131	$CDCl_3$	20	0.3	-186.4	
133	$CDCl_3$	20	0.3	-120.2	134
134	$CDCl_3$	19	0.33	-118.9	
135	$CDCl_3$	19	0.33	-168.9	
136	$CDCl_3$	20	0.3	-92.8	152.4
137	$CDCl_3$	19	0.33	-119.3	
138	$CDCl_3$	19	0.33	-169.0	
141	$CDCl_3$	19	0.33	-121.8 (-130.8)[c]	
147	$CDCl_3$	20	0.3	-116.7	
148	$CDCl_3$	20	0.3	-93.5	149 2
149	$CDCl_3$	20	0.3	-118.9	131.0
150	$CDCl_3$	20	0.3	-97.2	140.2

[a] Spectra were recorded in $CDCl_3$ solution in sealed tubes at 20 °C with concentrations from 0.2 to 0.3 M, chemical shifts are in ppm from external tetramethyltin at 20 °C. [b] Coupling constants are in Hz; no entry indicates that the coupling constant could not be measured (see text). [c] The minor peak.

slightly higher frequency chemical shifts (-93 to -99 ppm). The first type of dialkylstannylene acetal includes all the stannylene acetals which have two primary alkyl groups attached to tin atoms regardless of the structures of these groups. For instance, stannylene acetals **126** and **133** have very similar chemical shifts (-118.8 ppm for **126** and -120.2 ppm for **133**), even though the former possesses two n-butyl groups and the latter has two sterically hindered neopentyl groups. A single sharp peak in each ^{119}Sn NMR spectrum at room temperature suggests that only one of the three possible dimers is being observed. This dimer must be symmetric because the asymmetric dimer should give two peaks with the same intensity corresponding to the different environments of the two tin atoms. Carbon-13 NMR spectroscopy also support symmetric dimeric structures because only one set of peaks was observed.

Diisopropylstannylene acetals **120**, **128**, **135** and **138** and dicyclohexyl-stannylene acetal **131** belong to the second type. The difference between this type of stannylene acetal and the first type lies in that the alkyl groups form carbon-tin bonds through secondary carbon atoms. Although chemical shifts have been observed at much lower frequencies for these stannylene acetals, the chemical shifts still fall in the range of pentacoordinate tin absorption. Thus, this type of stannylene acetal also exists in solution as single symmetric dimers.

Comparison of the increment in ^{119}Sn NMR chemical shift from dibutylstannylene acetal and diisopropylstannylene acetal derived from same diol gives some interesting results. For instance, dibutylstannylene acetal **118**, derived from diol **104**, gives a chemical shift of -118.3 ppm and diisopropylstannylene acetal **120**, also

derived from diol **104**, has a single sharp peak at -170.1 ppm. The chemical shift increment from **118** to **120** is -51.8 ppm. Each of the other three dibutyl-diisopropyl pairs of stannylene acetals (**126-128**, **134-135** and **137-138**) gives a very similar chemical shift increment (-50 ± 2 ppm). This increment argument can be extended to simple 2,2-dialkyl-1,3,2-dioxastannolanes. For example, the dimer of 2,2-dibutyl-1,3,2-dioxastannolanes **82** has a ^{119}Sn NMR chemical shift of -126.8 in chloroform-*d* solution whereas the dimer of 2,2-di-*t*-butyl-1,3,2-dioxastannolane **83**, the analog of **82** with two tertiary alkyl groups on tin atom, gives a ^{119}Sn NMR chemical shift of -225 ppm.[71] The chemical shift increment from n-butyl (primary) to *t*-butyl (tertiary) is -98.2 ppm. 2,2-Diisopropyl-1,3,2-dioxastannolane, which has secondary alkyl groups, should have a chemical shift of -176 ppm (half way between those of **82** and **83**). The dicyclohexylstannylene acetal **131**, another stannylene acetal with secondary alkyl groups, has a chemical shift of -186.4 ppm (68 ppm low frequency compared to that of **126**). This is perhaps due to the special conformation of the cyclohexyl groups in this compound.

The third type of stannylene acetal consists of five hexamethylenestannylene acetals. They are also present as single symmetric dimers in solution because there is only one single sharp peak in the region where pentacoordinate tin absorptions appear at room and at low temperature. In hexamethylenestannylene acetals, the hexamethylene groups are bonded to tin atoms through two primary carbon atoms on both ends. In contrast to the chemical shifts ranging from -115 to -124 ppm for all the dialkylstannylene acetals of the first type, these stannylene acetals have chemical shifts

from -93 to -99 ppm. The decreased shielding of ^{119}Sn absorption in this type of stannylene acetal is probably caused by the presence of a seven-membered ring. The substantial differences in shifts of signals from Sn atoms in five and six-membered rings[138] has been attributed to bond-angle changes. The C-Sn-C bond angles in hexamethylenestannylene acetals are slightly smaller than those in most acyclic dialkylstannylene acetals(see Table 5.4 and related discussion).

Low temperature ^{119}Sn NMR spectra of a number of dialkylstannylene acetals were recorded in chloroform-*d* and a few were also recorded in toluene-d_8.

The glucofuranose derivatives will be considered first. In chloroform-*d*, all derivatives showed single lines at all temperatures. These results are summarized in Table 5.2.

The ^{119}Sn NMR spectra of one compound, 5,6-*O*-dibutylstannylene-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose (**126**) were recorded for a 0.2 M solution in toluene-d_8. It had previously been noted[38] that stannylene acetals are more aggregated in toluene than in chloroform, and this was observed here. At room temperature, one peak was present at -119.0 ppm with a line width of 115 Hz at 134.6 MHz. As the temperature was lowered, the main signal broadened and then split. By -20 °C, three sharp equal intensity signals at -112.9, -115.7 and -287.6 ppm had emerged from the main peak which had broadened and moved to a lower frequency. The three sharp equal intensity signals can only be assigned to a trimer, since one signal (at -287.6 ppm) is in the hexacoordinate tin region. By -40 °C, the major peak was ca. 35 ppm wide and centered at -127.0 ppm. As the temperature was lowered

further, the main peak sharpened and moved to larger frequencies, being 25 ppm wide at -123.0 ppm at -50 °C, 12 ppm wide at -122.0 ppm at -60 °C, 7 ppm wide at -120.0 ppm at -70 °C, 7 ppm wide at -119.5 ppm at -80 °C and 7 ppm wide at -119.3 ppm at -90 °C. The trimer peaks gradually decreased in relative intensity becoming negligible at -90 °C.

The outcome of this process was the observation of two peaks at the lowest temperature studied (-90 °C), one at -269.2 ppm and another, two to three times bigger, at -119.3 ppm. The latter peak is at about the same chemical shift as the original peak at -119.0 ppm. It seems likely that the coalescence process is for a dimer-tetramer equilibrium. The tetramer has to have C_2 symmetry to give only one peak in each of the pentacoordinate and hexacoordinate regions of the spectrum. It was found earlier that hexacoordinate peaks in tetramers are less shielded than those in trimers.[5,38] The dimer peak and the pentacoordinate tin tetramer peak occur at the same chemical shift.

Rates of interconversion and activation barriers can be obtained from coalescence processes. The equations normally used:[139]

$$k = \pi \, \Delta\nu / 2^{1/2} \qquad (5.1)$$

and $$\Delta G^{\neq} = 1.986 \times 10^{-3} \, T \, [23.76 + \ln (T / k) + \ln \kappa] \qquad (5.2)$$

apply to situations where two equally populated singlets coalesce. In the current situation, a signal at -119.0 ppm (dimer) is exchanging with two signals at -119.3 ppm (pentacoordinate tin in tetramer) and -269.6 ppm (hexacoordinate tin in tetramer). The populations of the species present are changing rapidly as a function of temperature, and

also the chemical shifts are changing as a function of temperature, particularly that at -269.6 ppm. From equation 5.2, it can be seen that the main factor influencing the size of $\Delta G^{\neq}$ is the temperature of coalescence, not the rate constant at coalescence. Therefore, a rough estimate of $\Delta G^{\neq}$ for coalescence can be obtained from the coalescence temperature, -45 °C and the chemical shift difference between the fartherest apart exchanging signals, 2.0×10^4 Hz. This yields $k = 4.5 \times 10^4$ s^{-1}, $\Delta G^{\neq} = 8.4$ kcal-mol^{-1}. Assuming the exchange is between the dimer peak and halfway between the tetramer peaks and gives a $\Delta G^{\neq}$ value of 8.7 kcal-mol^{-1}, thus a reasonable estimate is 8.5 ± 1 kcal-mol^{-1}. The dimer-trimer barrier is even more difficult to estimate but a T_c of -50 °C and a $\Delta\nu$ of 10,000 Hz gives $\Delta G^{\neq}$ of 10.3 kcal-mol^{-1}.

The spectra of benzyl 5,6-*O*-dibutylstannylene-2,3-*O*-isopropylidene-α-D-mannofuranoside were slightly more complex. At room temperature in chloroform-*d*, a single peak was observed at -114.8 ppm for a 0.4 M sample and at -114.3 ppm for a 0.15 M sample, with a $J_{Sn\text{-}119,Sn\text{-}117}$ value of 140.5 Hz. The ^{119}Sn NMR spectrum of the 0.15 M sample contained no additional signals at low temperature but the spectrum of the 0.4 M sample contained small amounts of trimer peaks at -111.6, -117.1 and -274.9 ppm. From peak heights the ratio [trimer] / [dimer] was 0.072 at -60 °C. A 0.15 M sample of the same compound in toluene-d_8 precipitated at low temperature but at 25 °C contained a broad peak (half-height line width, 3 ppm) at -120.1 ppm plus a much smaller broad peak at about -112 ppm. The small broad peak probably contained the pentacoordinate trimer signals that were starting to coalesce. The analogous methyl glycoside showed similar behaviour.

The spectra of the allofuranose compounds are still more complicated. Figure 5.3 shows variable temperature spectra of 0.3 M solution of 5,6-*O*-dibutylstannylene-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-allofuranose (**137**) in chloroform-*d*. At room temperature, a slightly broadened peak at -119.5 ppm is accompanied by a small broad peak on its deshielded side. By -20 °C, in addition to the main peak at -117.9 ppm, small peaks are clearly visible at -112.8, -119.6, -123.9 and -277.4 ppm. The peak at -277.4 ppm increases in intensity as the temperature is lowered as does that at -119.6 ppm and these two peaks are about the same size at -60 °C. The signal at -277.4 ppm must be assigned to the hexacoordinate tin atom in a trimer; a signal at -119.6 ppm is due to the same trimer; a third signal is still needed. The only possibility is that the third signal overlaps with the major peak. The two other small signals present at -20 °C in the pentacoordinate region could be due to either dimers or trimers. The very small signal that appears at about -295 ppm in the -60 °C spectrum must be assigned to a second trimer, because a tetramer would be expected to give a hexacoordinate tin atom which would be expected to be less shielded than the signal at -277 ppm.[5,38]

The stannylene acetals with the most complicated behaviour in solution were the derivatives of 1,2-*O*-isopropylidene-α-D-allofuranose (**115**). The ^{119}Sn spectra of compound **141**, the dibutylstannylene acetal of **115**, will be discussed as the following.

The spectrum of a 0.3 M solution of **141** in chloroform-*d* at 20 °C contained one large peak at -121.8 ppm plus a much smaller one at -130.8 ppm. When the

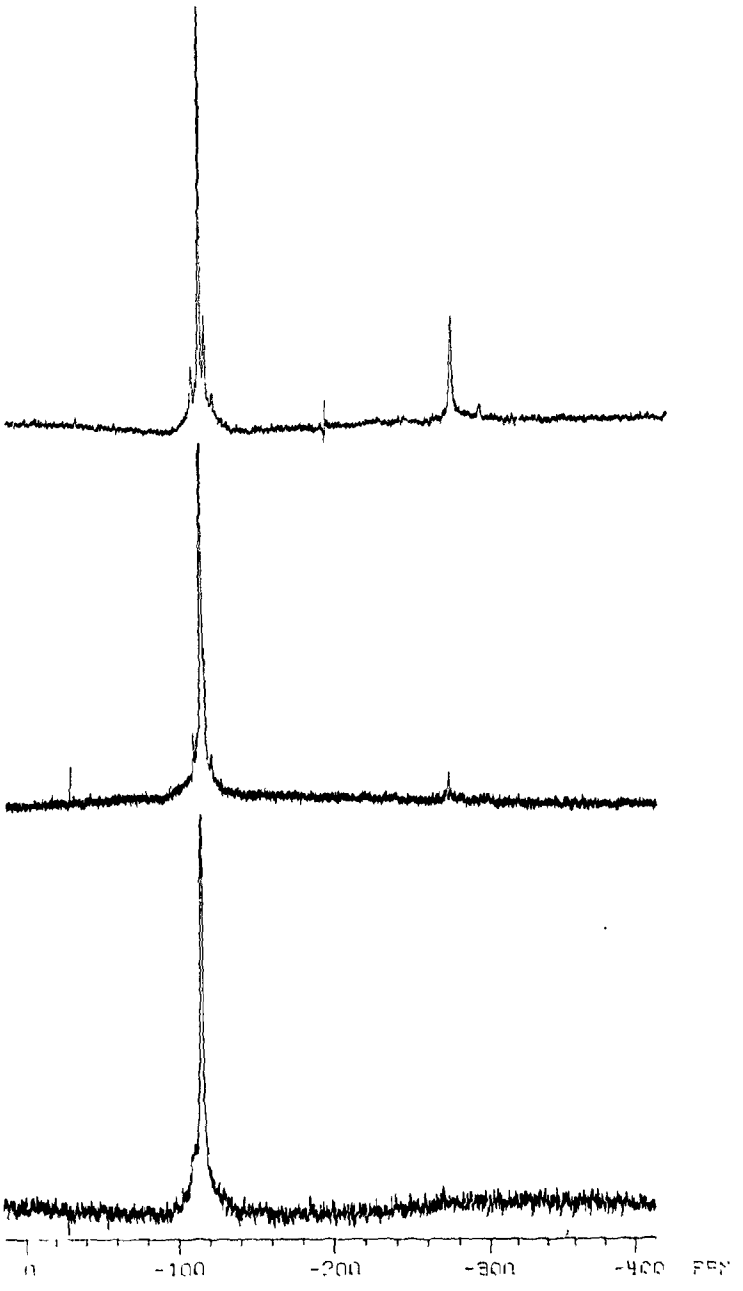


Figure 5.3 134.6 MHz ^{119}Sn NMR spectra of a 0.33 M solution of **137** in chloroform-*d* at different temperatures (top to bottom: -60 °C, -20 °C, 20°C)

temperature was raised the minor signal broadened and coalesced with the major signal at about 60 °C then reappeared when the temperature was lowered, proving that it was not an impurity. The minor signal is probably due to a second 5,6-*O*-dibutylstannylene dimer. It cannot be due to a 3,5-dimer because tin atoms in six-membered stannylene acetals absorb at very different ^{119}Sn NMR chemical shifts approximately 60 ppm more shielded.[72] Cooling the sample to 0 °C produced a new signal at -332.4 ppm, plus another signal at -138.1 ppm. These latter signals continued to grow as the temperature was lowered until by -60 °C, the ratio of intensities was 6:3:1:1 for the peaks at -137.4, -331.9, -129.2 and -120.9 ppm, respectively. The very shielded position for the hexacoordinate tin signal make it unclear what the structure of the major species at low temperature is, although the 2:1 ratio of signal intensities at -137.4 and -332.4 ppm suggests a trimer. Participation by the oxygen atom of third OH group in the molecule to give a six-membered ring would be consistent with the greater shielding.

In summary, oligomerization of dialkylstannylene acetals depends on the structure of their precursors. For the dialkylstannylene acetals of glucofuranose derivatives, only single symmetric dimers were observed in chloroform-*d* at all temperatures. The stannylene acetals of allofuranose derivatives were present as dimers at room temperature, and at lower temperature higher oligomers were also observed. For one compound, the dibutylstannylene acetal of 1,2-isopropylidene-α-D-allofuranose, a second dimer was present as a minor species even at room temperature.

There are known to be large temperature effects on dimer-oligomer equilibria.[38]

Even for compounds in which oligomers are dominant at -100 °C, dimers constitute the majority of the species present at room temperature.

5.2.4 Regioselectivity and dimeric structure of dialkylstannylene acetals

The three possible dimeric structures of dialkylstannylene acetals derived from primary-secondary 1,2-diols (a primary-primary dimer, a primary-secondary dimer and a secondary-secondary dimer) are illustrated in Figure 5.3 (R stands for the remaining part of the parent diol in general). From the point of view of steric effects, the stability of the three dimers is decreased in the order: primary-primary dimer (p-p dimer) to primary-secondary dimer (p-s dimer) to secondary-secondary dimer (s-s dimer). In the secondary-secondary dimeric structure, the steric interaction between the R groups in the diol molecules and the two R' groups on the tin atoms is very strong. This steric interaction makes the secondary-secondary dimer less stable. Only in primary-primary dimers can the steric interaction be fully avoided (see Figure 5.4). Therefore, whenever a single symmetric dimer of a dialkylstannylene acetal is observed, it must be the primary-primary dimer.

It has been reported that ^{13}C NMR chemical shifts provided useful information about the dimeric structures of dibutylstannylene acetals.[5] Grindley and Thangarasa found that formation of dibutylstannylene acetals caused deshielded chemical shift changes for all carbon atoms (C-1 to C-6) in the diol molecule. The largest downfield shifts (from 3.5 to 4.4 ppm) were observed on the carbon atoms bearing the dicoordinate oxygens.[5]

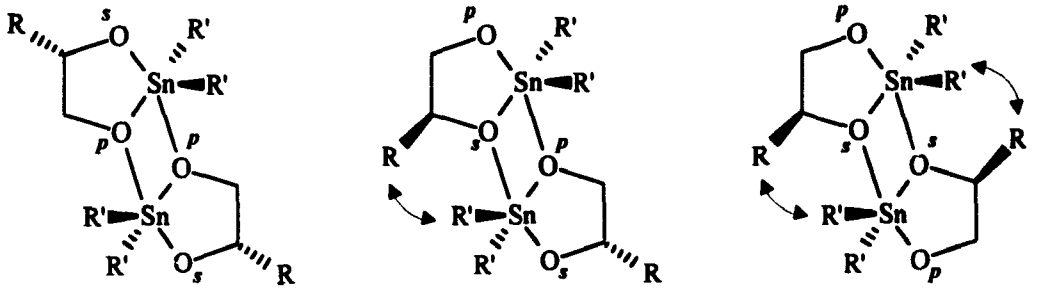


Figure 5.4 Dimeric structures of dialkylstannylene acetals derived from primary-secondary 1,2-diols

Sixteen dialkylstannylene acetals derived from five primary-secondary diols were subjected to ^{13}C NMR spectroscopic study in this thesis. The data obtained from stannylene acetals are compared with their precursors in Table 5.3.

In contrast to the literature results[5], both upfield and downfield shifts in ^{13}C NMR spectra were observed for the dialkylstannylene acetals derived from the primary-secondary 1,2-diols studied here. The biggest changes were often observed on the signals of carbon atoms next to the five-membered stannylene acetal ring, i.e., the C-4, which were shifted downfield in most of the cases. The chemical shift changes on C-5 and C-6 were generally quite small.

Changes in ^{13}C NMR chemical shifts are dependent on the nature of diol structures. For example, downfield shifts of the C-4 signals are quite large for the stannylene acetals of diols **104**, **64** and **117** but are small for the stannylene acetals of diols **106** and **116**. However, the results from compounds with very similar structure give some interesting trends. Both diols **64** and **104** are glucofuranose derivatives.

Table 5.3 Comparison of ^{13}C NMR chemical shifts of the dialkylstannylene acetals with those of their precursors[a]

Compd	Chemical shifts[b]					
	C-1	C-2	C-3	C-4	C-5	C-6
Glucofuranose derivatives						
*104	105.1	82.1	82.0	80.0	69.2	64.4
118	105.1 (0.0)	82.9 (+0.8)	81.6 (-0.4)	84.2 (+4.2)	68.6 (-0.6)	65.0 (+0.6)
120	105.1 (0.0)	82.9 (+0.8)	81.6 (-0.4)	84.1 (+4.1)	68.7 (-0.5)	67.0 (+2.6)
121	105.1 (0.0)	83.0 (+0.9)	81.4 (-0.6)	83.2 (+3.2)	68.6 (-0.6)	65.3 (+0.9)
* 64	105.0	81.4	84.5	79.8	69.4	64.4
126	105.1 (+0.1)	81.9 (+0.5)	83.6 (-0.9)	83.4 (+3.6)	68.5 (-0.9)	64.7 (+0.3)
128	105.0 (0.0)	82.0 (+0.6)	83.7 (-0.8)	83.4 (+3.6)	68.6 (-0.8)	69.9 (+5.5)
129	105.1 (+0.1)	82.1 (+0.7)	83.7 (-0.8)	82.3 (+1.5)	68.6 (-0.8)	64.8 (+0.4)
130	105.1 (+0.1)	81.9 (+0.5)	83.6 (-0.9)	83.4 (+3.6)	68.7 (-0.7)	65.3 (+0.9)
131	105.2 (+0.2)	82.0 (+0.6)	83.9 (-0.6)	83.7 (+3.9)	68.8 (-0.6)	67.0 (+2.6)
133	105.3 (+0.3)	81.9 (+0.5)	84.5 (0.0)	83.8 (+4.0)	68.1 (-1.3)	64.9 (+0.5)
Mannofuranoside derivatives						
*106	107.2	84.8	79.8	80.1	70.4	64.5
134	107.3 (+0.1)	84.7 (-0.1)	79.9 (+0.1)	81.8 (+1.7)	69.4 (-1.0)	64.2 (-0.3)
135	107.4 (+0.2)	84.7 (-0.1)	80.0 (+0.2)	82.2 (+2.1)	69.3 (-1.1)	66.0 (+1.5)
136	107.4 (+0.2)	84.9)+0.1)	80.0 (+0.2)	80.4 (+0.3)	68.9 (-1.5)	63.8 (-0.7)
Mannitol derivatives						
*116	67.9	76.4	80.6	80.6	72.3	63.8
147	65.4 (-2.5)	76.4 (0.0)	79.8 (-0.8)	81.6 (+1.0)	73.8 (+1.6)	64.0 (+0.2)
148	65.9 (-2.0)	76.5 (+0.1)	79.9 (-0.7)	81.6 (+1.0)	72.7 (+0.4)	63.3 (-0.5)
*117	66.5	76.0	79.2	78.6	71.1	63.6
149	67.3 (+0.8)	75.4 (-0.6)	79.4 (+0.2)	83.4 (+4.8)	71.8 (+0.7)	65.5 (+1.9)
150	67.7 (+1.2)	75.2 (-0.8)	79.8 (+0.6)	82.3 (+3.7)	70.9 (-0.2)	64.6 (+1.0)

[a] Compound number with * is for parent compound. [b] Number in () is the chemical shift increment, $\Delta\delta = \delta_{\text{stannylene acetal}} - \delta_{\text{diol}}$.

Comparison of their ^{13}C NMR chemical shifts with those of the nine corresponding dialkylstannylene acetals gave the following results: formation of stannylene acetals caused deshielded shifts on C-2, C-4 and C-6, and shielded shifts on C-3 and C-5 in all cases. The largest changes in chemical shifts were observed for signals of C-4, the carbon atoms next to the stannylene rings.

The difference between the results in Table 5.3 and those in reference 5 are apparently caused by the structural dissimilarity of the parent diols. All the diols studied in reference 5 were *trans*-1,2-diols on pyranose rings. Steric interaction between the butyl groups on tin atoms and substituents in diol molecules exist in any of the three possible dimers of a dibutylstannylene acetal, although the magnitudes of the interaction may be very different. In the dialkylstannylene acetal derived from a primary-secondary diol with a furanose ring structure, there is no significant interaction between the alkyl groups on tin and the remaining part of the diol if the p-p dimers are formed. The observed chemical shifts changes for C-5 and C-6 are consistent with what would be expected if electronic effects were most important in determining chemical shifts. In the dimer, the tricoordinate oxygen atom bears a positive charge according to Lewis structure. Withdrawal of electrons from the carbon atom bonded to tricoordinate oxygen atom should result in deshielding in the ^{13}C NMR spectrum. Similarly, the signal of the carbon atom with the electron-rich, dicoordinate oxygen atom is shielded. Other factors, such as β- and γ- effects introduced by formation of dimer, also influence the chemical shifts of carbon atoms.

Two factors need to be considered when evaluating how dimer formation

influences the reactivity and selectivity of dialkylstannylene acetals. One is steric effects and the other, electronic effects. In the primary-primary dimer of a stannylene acetal, each of the monomeric units uses the primary oxygen atom to form a coordination bond to the tin atom in the other monomeric unit. Thus, the primary oxygen atom becomes tricoordinate and the secondary oxygen atom remains dicoordinate. Formation of the third bond makes it difficult for an electrophile to access the primary oxygen atom. The four R' groups on both tin atoms also shield the primary oxygen atoms in space. These effects dramatically decrease the reactivity of the primary oxygen atom. On the other hand, electron density will be redistributed on formation of dimer. If the Lewis structure picture of bonding in these molecules is considered to have some validity, the tricoordinate oxygen atoms in the dimer bear positive charges because of donation of electron pairs to the tin atoms. In contrast, the dicoordinate oxygen atoms become more electron-rich in the dimer than in the monomer due to the higher electron density on the tin atoms. On this basis, the electronic effects of dimer formation are to increase the reactivity of the secondary oxygen atoms and to decrease the reactivity of the primary oxygen atoms.

On this basis, all dialkylstannylene acetals would be anticipated to react regioselectively at the secondary oxygen atoms of primary-secondary diols. In fact, this is not the case. Other factors must be taken into account.

Although only one single sharp line corresponding to the primary-primary dimer was observed in the ^{119}Sn NMR spectra of most dialkylstannylene acetals, other dimers or higher oligomers may exist in concentrations below the level of detection by

NMR spectroscopy. For dibutylstannylene acetals formed from secondary-secondary 1,2-diol units on pyranose rings, different dimeric species were observed with ^{119}Sn NMR experiments.[5] In some cases, trimers were also present in solutions in significant amounts. It has been demonstrated that dimers and higher oligomeric species are in equilibrium in solutions.[5]

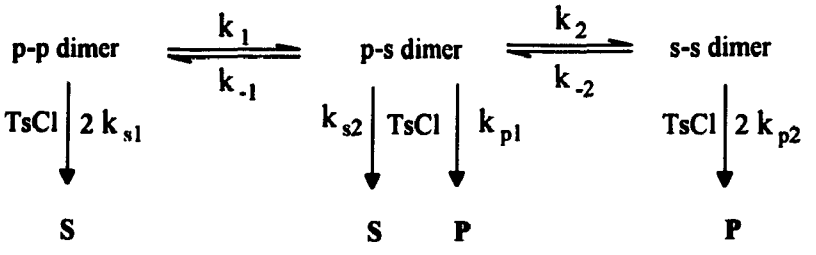
For the dialkylstannylene acetals studied here, dimers other than the primary-primary one have at least one primary oxygen atom dicoordinate. The primary oxygen atoms are inherently much more reactive than the secondary oxygen atoms. In dimers, reactivity of the dicoordinate primary oxygen atoms is very high. Reaction through dicoordinate oxygen atoms occurs very quickly. If all the products are formed through the dimers of a dialkylstannylene acetal, the primary *p*-toluenesulfonate (**P**) is obtained from the primary-secondary dimer (p-s dimer) and secondary-secondary dimer (s-s dimer), and the secondary *p*-toluenesulfonate (**S**) is formed from the primary-primary dimer (p-p dimer) and p-s dimer.

5.2.5 Kinetics

As demonstrated by Grindley and Thangarasa, oligomerization equilibria of dibutylstannylene acetals in solution are quite complicated.[38] Although conversion of one dimer to another may be achieved through higher oligomers or perhaps through a monomer, the overall reaction mechanism of dialkylstannylene acetals will follow Scheme 5.2 for the following reasons. Oligomers will not be reactive intermediates because their terminal units should have about the same reactivity as the much more

populated dimers. On electronic grounds, monomers should be less reactive than dimers and they are much less populated than dimers. In support of this statement, tributylstannyl ethers, which normally exist as monomers with tetracoordinate tin, are much activated for reaction when an adjacent oxygen atom has the correct orientation to form a intermediate with a five-coordinate tin atom.[3]

Scheme 5.2



p-p: primary-primary; p-s: primary-secondary; s-s: secondary-secondary
P - primary *p*-toluenesulfonate; **S** - secondary *p*-toluenesulfonate

The following basic equations can be derived from the mechanism in Scheme 5.2,

$$d[S]/dt = 2\ k_{s1}\ [p\text{-}p]\ [TsCl] + k_{s2}\ [p\text{-}s]\ [TsCl] \qquad (5.3)$$

$$d[P]/dt = k_{p1}\ [p\text{-}s]\ [TsCl] + 2\ k_{p2}\ [s\text{-}s]\ [TsCl] \qquad (5.4)$$

$$K_1 = k_1/k_{-1} \qquad (5.5)$$

and $$K_2 = k_2/k_{-2} \qquad (5.6)$$

where [p-p] is the concentration of the primary-primary dimer, [p-s] is the concentration of the primary-secondary dimer and [s-s], the concentration of the secondary-secondary dimer.

Since precise kinetic measurements have not been made, it will be assumed

that the environments of the dicoordinate secondary oxygen atoms in the primary-primary dimer and in the primary-secondary dimer are very similar. The environments of the dicoordinate primary oxygen atoms in the primary-secondary dimer and in the secondary-secondary dimer are almost the same. Therefore

$$k_{s1} = k_{s2} = k_s$$

and $$k_{p1} = k_{p2} = k_p,$$

Similarly, it may be assumed that

$$K_1 = K_2 = K$$

According to ^{119}Sn NMR spectroscopy where only the signal of p-p dimer was observed, it is always the case that

$$[p\text{-}p] >> [p\text{-}s]$$

and it can be assumed similarly that

$$[p\text{-}s] >> [s\text{-}s]$$

Therefore, the following conclusions can be arrived:

$$k_{s1}\,[p\text{-}p] >> k_{s2}\,[p\text{-}s]$$

$$k_{p1}\,[p\text{-}s] >> k_{p2}\,[s\text{-}s]$$

Thus, the equations 5.3, 5.4 and 5.5 become

$$d[S]/dt = 2\,k_s\,[p\text{-}p]\,[TsCl] \qquad (5.7)$$

$$d[P]/dt = k_p\,[p\text{-}s]\,[TsCl] \qquad (5.8)$$

$$K = k_1/k_{-1} \qquad (5.9)$$

The ratio of the increment of the product at the secondary oxygen atom to that at the primary oxygen atom can be expressed in Eq. 5.10.

$$d[S]/d[P] = (2\ k_s/k_p)\ ([p\text{-}p]/[p\text{-}s]) \quad (5.10)$$

There are two possible kinetic situations corresponding to the concentration of the p-s dimer present in solution, true equilibrium and steady-state.

When $k_p << k_{-1}$, the p-p dimer and the p-s dimer are in equilibrium and the concentration of p-s dimer can be expressed as:

$$[p\text{-}p]/[p\text{-}s] = 1/K$$

Thus, the regioselectivity of the *p*-toluenesulfonation reaction, or the ratio of the increment of the product at the secondary oxygen atom to that at the primary oxygen atom, depends only on the relative reactivity of the dicoordinate secondary and primary oxygen atoms and the relative populations of the p-p dimer and the p-s dimer:

$$d[S]/d[P] = (2\ k_s/k_p)\ (1/K) \quad (5.11)$$

When k_p is comparable to or larger than k_{-1}, the concentration of the p-s dimer can be assumed to be in a steady-state. Under this condition, the concentrations of p-p dimer and p-s dimer can be related in the following:

$$k_1\ [p\text{-}p] = k_{-1}\ [p\text{-}s] + k_p\ [p\text{-}s]\ [TsCl]$$

$$[p\text{-}p]/[p\text{-}s] = (k_{-1} + k_p\ [TsCl])/k_1 = 1/K + [TsCl]\ (k_p/k_1)$$

Thus, Eq. 5.10 becomes

$$d[S]/d[P] = (2\ k_s/k_p)\ \{1/K + [TsCl]\ (k_p/k_1)\} \quad (5.12)$$

Therefore, the ratio of the reaction at the secondary hydroxyl oxygen atom to that at the primary hydroxyl oxygen atom increases with the increase of the concentration of TsCl used for the reaction.

In order to examine the magnitude of the effect of the concentration of TsCl on

regioselectivity under steady-state condition, a special case can be considered as follows.

If $k_p = k_{-1}$, Eq. 5.12 can be rewritten as Eq. 5.13.

$$d[S]/d[P] = (2\ k_s/k_p)\ (1/K)\ (1+ [TsCl]) \qquad (5.13)$$

i.e., $d[S]/d[P] \propto (1+ [TsCl])$

Suppose that the concentration of TsCl is changed from 0.1 M to 1.2 M and all other conditions are unchanged, the ratio of selectivity at the secondary position to that at the primary position will be doubled.

$$(d[S]/d[P])_{[TsCl] = 1.2\ M} = 2\ (d[S]/d[P])_{[TsCl] = 0.1\ M} \qquad (5.14)$$

When $k_p > k_{-1}$, equation 5.14 becomes equation 5.15.

$$(d[S]/d[P])_{[TsCl] = 1.2\ M} > 2\ (d[S]/d[P])_{[TsCl] = 0.1\ M} \qquad (5.15)$$

The steady-state reaction can be easily ruled out by the following observation. Reaction of stannylene acetal **135** (1 mmol) with TsCl (1 mmol, $[TsCl]_0$ = 0.1 M) in toluene (10 mL) gave a mixture of mono-*p*-toluenesulfonates in 60 h with a overall yield of 98%. The ratio of **106S** to **106P** was 33:67. When the above reaction was carried out with 12 eq. of TsCl, i.e., $[TsCl]_0$ = 1.2 M, the reaction was speeded up dramatically and finished in 2 h with a yield of 99%. Nevertheless, the regioselectivity remained the same as that obtained from the reaction with 0.1 M TsCl, the ratio of **106S** to **106P** being 32:68. The very small difference in selectivity (33:67 and 32:68) was within experimental error. If the steady-state mechanism operated, a large difference in selectivity (**106S**:**106P**, 33:67 at $[TsCl]_0$ = 0.1 M and > 50:50 at $[TsCl]_0$ = 1.2 M) would be expected.

On the other hand, regioselectivity under true equilibrium conditions is independent of the concentration of TsCl. Increasing the concentration of TsCl can only shorten the reaction time. Therefore, *p*-toluenesulfonation of dialkylstannylene acetals occurs under dimer equilibrium conditions.

Under these conditions, selectivity is determined by two factors, the equilibrium constant, K, and the relative reactivity of dicoordinate secondary oxygen atom and the dicoordinate primary oxygen atom, k_s/k_p. For a given starting diol, altering alkyl groups on the tin atom in its dialkylstannylene acetals changes k_s/k_p, but probably not by much. For example, when the alkyl groups become more sterically hindered, it will decrease the reactivity of the dicoordinate oxygen atoms on both primary and secondary positions. If the effects on both kinds of oxygen atoms were different, it would slow down the reactivity of the secondary oxygen atom more than that of the primary oxygen atom because the former is already very sterically hindered. This is in conflict with the observation that introduction of sterically hindered alkyl groups on tin increases the selectivity for reaction at the secondary position.

A reasonable explanation is that altering alkyl groups on the tin atom changes selectivity of dialkylstannylene acetals through the effect of the alkyl groups on K, the equilibrium constant between the p-p dimer and the p-s dimer. In other words, the populations of the p-p dimer and the p-s dimer are controlled by the steric effects of the alkyl groups (R') on the tin atom. When the alkyl groups on tin are small or not sterically hindered (such as butyl group), the p-s dimer in solution is populated to a certain extent. When the alkyl groups on the tin atom become larger or more

sterically hindered, the population of the p-s dimer decreases. Therefore, sterically hindered alkyl groups on the tin atom increase the regioselectivity for reaction at secondary oxygen atoms in the dialkylstannylene acetal reactions. In fact, the selectivity at secondary oxygen atoms was increased by changing the R' groups from butyl to isobutyl or isopropyl, both being more hindered than butyl.

The cyclic hexamethylene group on tin atom exhibits the largest steric effect of all stannylene acetals because the ring system is unable to adopt very different orientations to escape steric interactions. Therefore, the best selectivity can be obtained through using hexamethylenestannylene acetal as an intermediate for reaction. On the other hand, sterically hindered alkyl groups on tin slow reactions down due to their shielding effect of adjacent oxygen atoms. The cyclic hexamethylene group does not move around as freely as do acyclic groups and is mainly restricted to certain orientations with respect to the adjacent oxygen atoms. Therefore, it does not affect the accessibility of the dicoordinate oxygen atoms and the reaction is not slowed down.

Another factor that may influence the regioselectivity of reactions of hexamethylenestannylene acetals is the geometry about tin in these compounds. If it is changed in hexamethylenestannylene acetals, it could affect both conformational flexibility as discussed above and also the geometry necessary for reaction to occur.

Evidence about changes in geometry of hexamethylenestannylene acetal with respect to that of dibutylstannylene acetals comes from two sources. The first is a preliminary study of the equilibria present for hexamethylenestannylene acetal of

ethane-1,2-diol. Figure 5.5 shows ^{119}Sn NMR spectra of a 0.3 M solution of hexamethylenestannylene acetal of ethane-1,2-diol in chloroform-*d* at 0 °C, -40 °C and -60 °C. The mole fraction of dimer was calculated from integrals of the areas of the large pentacoordinate tin peak and the hexacoordinate tin peak with the following assumptions. The hexacoordinate tin peak is due to trimer but the trimer pentacoordinate tin peak is coincident with the pentacoordinate tin peak of the dimer. With these assumptions, the mole fraction of dimer of the hexamethylenestannylene acetal of ethylene glycol is 0.90 at -60 °C. In comparison with the dimer mole fraction of 0.14 for a much more dilute solution of the dibutylstannylene acetal of ethylene glycol at -73 °C,[38] it is obvious that hexamethylenestannylene acetals favours dimers over higher oligomers much more than do acyclic dialkylstannylene acetals bearing alkyl groups of comparable bulk.

The source of the difference between the two types of stannylene acetals is probably due to steric restriction of C-Sn-C angles by ring formation. In pentacoordinate tin sites of dibutylstannylene acetals, C-Sn-C bong angles average 127.8 $\pm$ 5.1° whereas in structures where the tin atom is hexacoordinate the bond angles are larger, averaging 138.1$\pm$3.0°.[65] Stannacycloheptane rings are unable to accommodate the larger bond angles required in higher oligomers as easily and thus disfavour formation of higher oligomers.

Additional evidence for this point comes from that the C-Sn-C bond angle of 122.3° in hexamethylenetin bischloroacetate (**95e**) is much smaller than those of 136 $\pm$ 5° in acylic dialkyltin dicarboxylates (for detail, see Chapter 3).

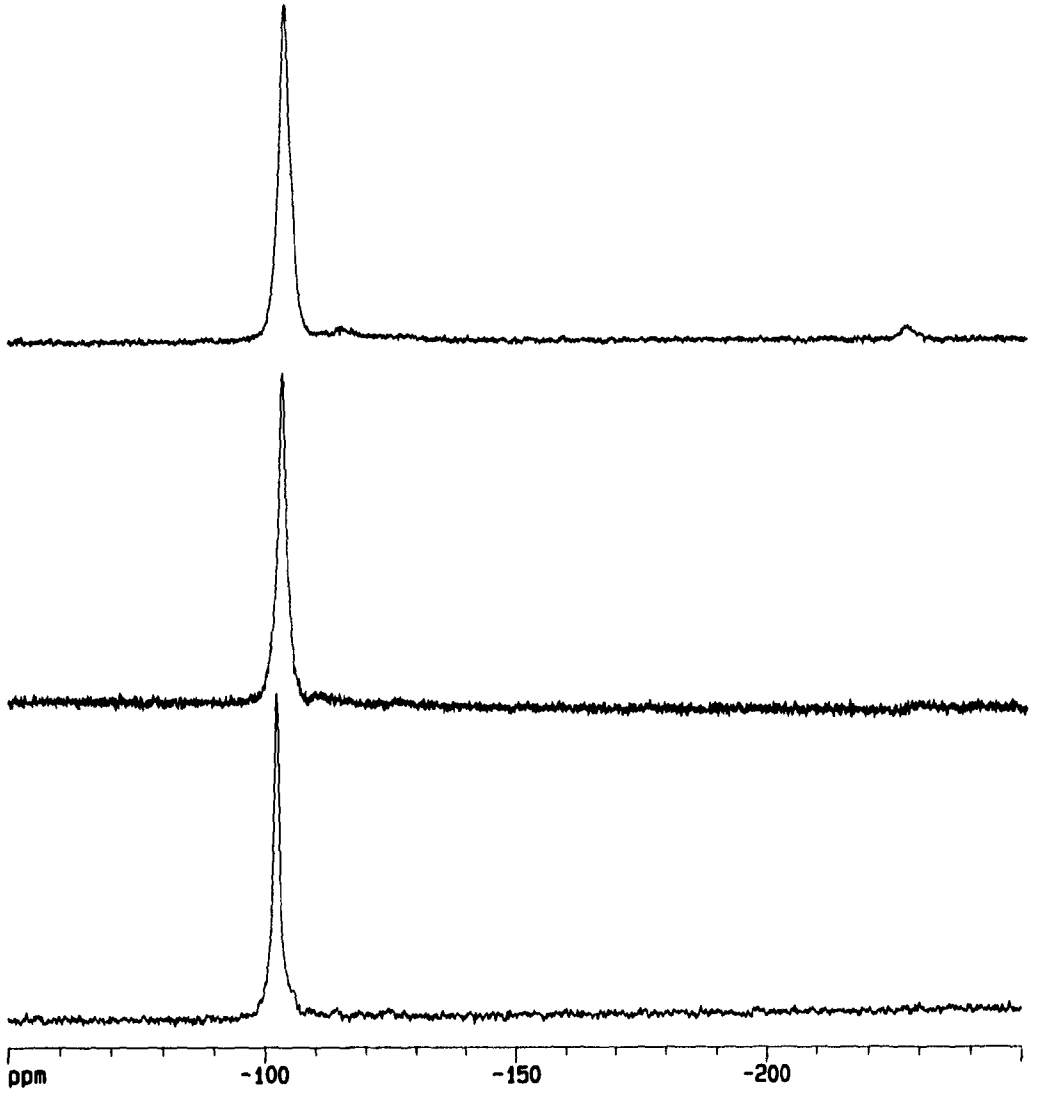


Figure 5.5 149.2 MHz ^{119}Sn NMR spectra of a 0.30 M solution of hexamethylenestannylene acetal of ethane-1,2-diol in chloroform-*d* at different temperatures (top to bottom: -60 °C, -20 °C, 0°C)

The actual bond angles in dialkylstannylene acetals can be calculated approximately from $^{1}J_{Sn\text{-}119,\,C\text{-}13}$ values using Eq. 3.1. Table 5.4 lists the $^{1}J_{Sn\text{-}119,\,C\text{-}13}$ values for a variety of stannylene acetals and the calculated bond angles. The C-Sn-C bond angles for the hexamethylenestannylene acetals appear to be slightly smaller than those of acyclic dialkylstannylene acetals.

In comparison to the regioselective *p*-toluenesulfonation reaction, oxidation of dibutylstannylene acetals derived from primary-secondary 1,2-diols gave α-hydroxyketones with very high regioselectivity. The selectivity difference between these two types of reactions can be explained by means of Scheme 5.2 and equation 5.10. *p*-Toluenesulfonation of dialkylstannylene acetals is much slower taking between 12 h and 2 d to go to completion with one equivalent of *p*-toluenesulfonyl chloride at room temperature if the alkyl group is not large. Oxidation of dibutylstannylene acetals with bromine is complete almost instantaneously at room temperature and with *N*-bromosuccinimide is complete between 1 m and 20 m (see Chapter 4). The products obtained in oxidation reactions are consistent with control by the relative populations of dibutylstannylene acetal dimers present in solution. As discussed above, the only detectable species of a dibutylstannylene acetal of a carbohydrate-derived primary-secondary 1,2-diol by ^{119}Sn NMR spectroscopy in solution is the primary-primary dimer. Oxidation of this dimer can only occur at the secondary position, resulting in the corresponding α-hydroxyketone. Thus, the second kinetic situation, steady-state of the minor dimer applies.

Table 5.4 One bond ^{119}Sn-^{13}C coupling constants and calculated C-Sn-C angles of dialkylstannylene acetals

Compd	Coupling constant (Hz)[a] $^1J_{Sn\text{-}119,C\text{-}13}$		$^1J_{Sn\text{-}119,C\text{-}13}$ used for calculation[b]	Calcd C-Sn-C Bond Angle (°)[c]
118	585.8	584.2	585.0	133.2
119	575.0		575.0	132.2
121	557.4	561.9	559.7	130.7
127	574.1	574.7	574.4	132.2
128	584.1		584.1	133.2
129	556.2	560.7	558.5	130.6
130	588.2	582.0	585.1	133.2
131	562.6		562.6	131.0
133	575.8	554.4	565.1	131.2
136	559.1	552.6	555.9	130.3
147	603.5		603.5	133.1
148	566.5	546.8	556.7	130.4
149	588.0	577.9	583.0	133.0
150	561.9	551.7	556.8	130.4

[a] The two numbers are from the two carbon atoms which are not equivalent in the dimer. [b] When two different coupling constants observed, the number used for calculation is the average number. [c] Calculated using Eq. 3.1.

Under these conditions the product ratio can be predicted from equation 5.10, converted into a more usable form for these purposes as equation 5.16.

$$d[S]/d[P] = 2\ (k_s/k_p)(1/k_1)(k_{-1} + k_p\ [O]) \qquad (5.16)$$

where [O] is the concentration of oxidizing reagent.

Because the reaction is very fast, return of the minor dimer to major dimer is much slower than conversion to product. Therefore, as long as oxidizing reagent concentration is reasonable, equation 5.16 simplifies to

$$d[S]/d[P] = 2\ (k_s/k_1)\ [O] \qquad (5.17)$$

that is, the product ratio is determined by the relative rates at which the major dimer goes to product or to minor dimer. Product formation is undoubtedly considerably faster for bromine oxidation and, most probably, is also faster for NBS oxidation. Simply, the oxidizing reagent reacts with the major dimer faster than the dimers equilibrate. In other words, oxidation of dibutylstannylene acetals is so fast that all species present in solution are converted to their corresponding products and there is no time for the interchange of the different species to occur.

This conclusion explains many results in the literature where the regioselectivity of bromine oxidation reactions had seemed at odds in comparison to the regioselectivity obtained from other reactions. For example, bromine oxidation of the dibutylstannylene acetal of benzyl 2,6-di-*O*-benzyl-α-D-galactopyranoside in benzene gave only the 4-keto product in a yield of 69% at room temperature, whereas benzoylation of this dibutylstannylene acetal under the same conditions as used for oxidation resulted in a 74% yield of 3-*O*-benzoyl derivative after 24 h of reaction.[13]

There is no evidence as yet available about the structures of the dimers present for this type of *cis*-1,2-diol. However, if the 3,3-dimer is strongly favored in solution, the results can be explained. Oxidation traps the 3,3-dimer by reaction at axial dicoordinate 4-oxygen. Other reactions are much slower allowing equilibration to take place so that the much more reactive equatorial 3-oxygen in 3,4-dimers reacts preferentially. However, it is also possible that the 3-*O*-benzoyl derivative was obtained by rearrangement of the initially formed 4-*O*-benzoate since benzoates are known to rearrange under these conditions.

5.3 Experimental

General methods. For general methods, see experimental sections in Chapters 3 and 4.

Starting materials.

For the preparation of dialkyltin oxides see Chapter 3. For the preparation of carbohydrate-derived diols other than described in the follows, see experimental section in Chapter 4.

1,2-*O*-Isopropylidene-α-D-glucofuranose (66). This compound was prepared using a literature method:[126] mp 162-163°C, lit.[126] 161-162°C; $[\alpha]_D^{23}$ -12.7° (*c* 1.0, water), lit.[126] $[\alpha]_D^{20}$ -11.4°; ^{1}H NMR (D_2O) δ 6.00 (d,1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.69 (d, 1H, H-2), 4.31 (d, 1H, $J_{3,4}$ = 2.1 Hz, H-3), 4.08 (dd, 1H, $J_{4,5}$ = 8.9 Hz, H-4), 3.90 (m, 1H, H-5), 3.79 (dd, 1H, $J_{5,6}$ = 2.5 Hz, $J_{6,6'}$ = 12.0 Hz, H-6), 3.63 (dd, 1H, $J_{5,6'}$ = 6.0 Hz, H-6'), 1.51 (s, 3H, CH_3), 1.35 (s, 3H, CH_3).

1,2-*O*-Isopropylidene-3-*O*-methyl-α-D-allofuranose (113). This compound was prepared according to a literature method:[140] mp 116-118 °C, lit.[140] 120-121 °C; $[\alpha]_D^{23}$ +105° (*c* 1.0, water); lit.[140] $[\alpha]_D^{20}$ +108.8° ; ^{1}H NMR δ 5.80 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.72 (dd, 1H, $J_{2,3}$ = 4.2 Hz, H-2), 4.04-4.01(m, 2H, H-4, H-5), 3.82 (m, 1H, H-3), 3.75-3.65 (m, 2H, H-6, H-6'), 3.50 (s, 3H, OCH_3), 3.14 (br, 1H, OH), 2.98 (br, H, OH), 1.59, 1.37 (2s, 6H, $2CH_3$); ^{13}C NMR δ 113.2 (s, C_{acetal}), 104.1 (d, C-1), 79.1 (d, C-3), 78.8 (d, C-4), 77.0 (d, C-2), 70.9 (d, C-5), 63.0 (t, C-6), 57.8 (q, CH_3O), 26.7, 26.5 (2q, $2CH_3$).

1,2-*O*-Isopropylidene-3-*O*-tosyl-α-D-allofuranose (114). This compound was prepared as described by Heap *et al*:[141] mp 151-153 °C (from ethyl acetate), lit.[141] 130 °C (from ethanol); $[\alpha]_D^{23}$ 48.3° (*c* 1.0, acetone), lit.[141] $[\alpha]_D^{24}$ +50°; ^{1}H NMR δ (DMSO-d_6) 7.82 (d, 2H, J = 8.0 Hz, 2Ar-H), 7.48 (d, 2H, 2Ar-H), 5.69 (br, 1H, H-1), 4.99 (m, 1H, H-2), 4.78 (m, 1H, H-3), 4.60, 4.51 (2m, 2H, H-6, H-6'), 4.07 (m, 1H, H-4), 3.57 (m, 1H, H-5), 1.41, 1.20 (2s, 6H, $2CH_3$); ^{13}C NMR δ (DMSO-d_6) 145.1 (s, C_{arom}), 132.5 (s, $C_{arom\text{-}para}$), 129.9 (d, $2C_{arom\text{-}ortho}$), 127.9 (d, $2C_{arom\text{-}meta}$), 112.2 (s, C_{acetal}), 103.5 (d, C-1), 77.8 (d, C-2), 75.8 (d, C-3), 77.5 (d, C-4), 70.0 (d, C-5), 61.6 (t, C-6), 26.6, 26.4 (2q, $2CH_3$), 21.2 (q, $ArCH_3$).

1,2-*O*-Isopropylidene-α-D-allofuranose (115). This compound was prepared using a literature method:[142] mp 131-133 °C, lit.[140] mp 129-130 °C; $[\alpha]_D^{23}$ +44.4° (*c* 1.0, water), lit.[140] $[\alpha]_D^{20}$ +47.8°; ^{1}H NMR δ (D_2O) 5.70 (d, 1H, $J_{1,2}$ = 3.3 Hz, H-1), 4.56 (m, 1H, H-2), 4.04 (m, 1H, H-3), 3.84-3.80 (m, 2H, H-4, H-5), 3.60-3.43 (m, 2H, H-6, H-6'), 1.41, 1.23 (2s, 6H, $2CH_3$); ^{13}C NMR δ 116.2 (s, C_{acetal}), 106.4 (d, C-1), 82.3 (d, C-2), 82.2 (d, C-4), 73.6 (d, C-5), 72.6 (d, C-3), 64.8 (t, C-6), 28.4, 28.2 (2q, $2CH_3$).

1,2:3,4-Di-*O*-isopropylidene-D-mannitol (116). This compound was prepared from 1,2:3,4:5,6-tri-*O*-isopropylidene-D-mannitol according to Wiggins' method:[143] $[\alpha]_D^{23}$ +5.6° (*c* 1.0, chloroform); mp 36-37 °C, lit.[143] mp 37 °C; ^{1}H NMR δ (D_2O) 4.21 (m, 1H, H-2), 4.1-4.0 (m, 2H, H-1, H-1'), 3.91 (m, 1H, H-3), 3.8-3.6 (m, 4H, H-4, H-5, H-6, H-6'), 1.39 (s, 3H, CH_3), 1.38 (s, 9H, $3CH_3$); ^{13}C NMR δ 110.3, 109.6 (2s, $2C_{acetal}$), 80.6 (d, C-3, C-4), 76.4 (d, C-2), 72.3 (d, C-5), 67.9 (t, C-1), 63.8 (t, C-6), 26.8 (q, $2CH_3$), 26.3, 25.0 (2q, $2CH_3$).

3,4-Di-*O*-benzyl-1,2-*O*-isopropylidene-D-mannitol (117).

(A) 1,2:5,6-Di-*O*-isopropylidene-D-mannitol (**A**) was prepared from D-mannitol using a literature method:[144] mp 118-119 °C, lit.[144] mp 119-121 °C; $[\alpha]_D^{23}$ +8.5° (*c* 1.0, chloroform), lit.[144] $[\alpha]_D$ +7.5-8.3° ; ^{1}H NMR δ 4.18 (m, 2H, H-2, H-5), 4.12 (dd, 2H, J_{gem} = 8.4 Hz, J_{vic} = 6.4 Hz, H-1, H-6), 3.99 (dd, 2H, J_{vic} = 5.4 Hz, H-1', H-6'), 3.74 (dd, $J_{2,3 \text{ or } 4,5}$ = 6.1 Hz, $J_{OH,\ 3 \text{ or } 4}$ = 6.7 Hz, 2H, H-3, H-4), 2.77 (d, 2H, 2OH), 1.42 (s, 6H, $2CH_3$), 1.36 (s, 6H, $2CH_3$); ^{13}C NMR δ 109.3 (s, $2C_{acetal}$), 76.1 (d, C-2, C-5), 71.1 (d, C-3, C-4), 66.7 (t, C-1, C-6), 26.7 (q, $2CH_3$), 25.2 (q, $2CH_3$).

(B) 3,4-Di-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-D-mannitol (**B**), a syrup, was prepared from compound **A** according to Gurjar's method:[145] $[\alpha]_D^{23}$ +37.2° (*c* 1.0, chloroform), lit. $[\alpha]_D$ +29.6°[145] and $[\alpha]_D^{25}$ +36°;[146] ^{1}H NMR δ 7.31 (s, 10H, 10Ar-H), 4.70 (s, 4H, $2ArCH_2$), 4.24 (m, 2H, H-2, H-5), 3.99 (dd, 2H, J_{gem} = 8.3 Hz, J_{vic} = 6.4 Hz, H-1, H-6), 3.88 (dd, J_{vic} = 6.5 Hz, H-1', H-6'), 3.82 (m, 2H, H-3, H-4), 1.41 (s, 6H, $2CH_3$), 1.33 (s, 6H, $2CH_3$); ^{13}C NMR δ 138.3 (s, C_{arom}), 128.4 (d, $C_{arom\text{-}ortho}$), 128.1 (d, $C_{arom\text{-}meta}$), 127.8 (d, $C_{arom\text{-}para}$), 108.6 (s, $2C_{acetal}$), 80.0 (d, C-3, C-4), 75.9 (d, C-2, C-5), 74.7 (t, $2C_{benzyl}$), 66.8 (t, C-1, C-6), 26.8 (q, $2CH_3$), 25.3 (2q, $2CH_3$).

(C) Compound **B** (20 g) was dissolved in 70% ethanol-water (40 mL). To this solution was added conc. hydrochloric acid (1.5 mL). The mixture was kept at 40 °C for 2.5 h and then cooled to room temperature. The reaction mixture was neutralized with barium carbonate until slightly basic. The solid materials were removed by filtration and the filtrate was concentrated to dryness. The residue was extracted with acetone (200 mL). The combined extracts were dried (K_2CO_3) and the solvent was

removed on a rotary evaporator after dried with anhydrous potassium carbonate. This residue was stirred with hexane (300 mL) for 1 h at room temperature. The hexane layer was decanted and concentrated to dryness to give starting material (7.04 g). The residue after extraction was separated by flash column chromatography with hexane-ethyl acetate as eluent. The first fraction was 3,4-di-*O*-benzyl-1,2-*O*-isopropylidene-D-mannitol (**117**), 5.5 g (47% based on the consumed starting material), as a syrup: $[\alpha]_D^{23}$ +25.8° (*c* 1.0, chloroform); ^{1}H NMR δ 7.31 (m, 10H, 10Ar-H), 4.76 (d, 1H, $J_{(ArCH,ArCH')a}$ = 11.3 Hz, ArCH-a), 4.71 (d, 1H, ArCH'-a), 4.66 (d, 1H, $J_{(ArCH,ArCH')b}$ = 11.3 Hz, ArCH-b), 4.61 (d, 1H, ArCH'-b), 4.31 (m, 1H, H-2), 4.07 (dd, 1H, $J_{1,1'}$ = 8.24 Hz, $J_{1,2}$ = 6.4 Hz, H-1), 3.97 (dd, 1H, $J_{2,3 \text{ or } 3,4}$ = 3.4 Hz, $J_{3,4 \text{ or } 2,3}$ = 5.5 Hz, H-3), 3.95 (dd, 1H, $J_{1',2}$ = 4.9 Hz, H-1'), 3.79 (m, 1H, H-5), 3.75-3.60 (m, 3H, H-6, H-4, H-6'), 2.91 (d, 1H, $J_{OH,5}$ = 5.5 Hz, OH), 2.05 (m, 1H, OH), 1.45 (s, H, CH_3), 1.36 (s, H, CH_3); ^{13}C NMR δ 137.9, 137.8 (2s, $2C_{arom}$), 128.7, 128.6, 128.5, 128.2, 128.1, 158.0 (6d, $8C_{arom}$), 108.6 (s, C_{acetal}), 79.2 (d, C-3), 78.6 (d, C-4), 76.0 (d, C-2), 74.5, 73.9 (2t, $2C_{benzyl}$), 71.1 (d, C-5), 66.5 (t, C-1), 63.6 (t, C-6), 26.6 (q, CH_3), 25.2 (q, CH_3). Anal. Calcd: C 68.64, H 7.51; Found: C 68.17, H 7.47.

The second fraction, which crystallized after being kept under toluene, was 3,4-di-*O*-benzyl-D-mannitol, weighing 5.1 g (48% based on the consumed starting material): mp 73-75 °C; ^{1}H NMR δ 7.3 (m, 10H, 10Ar-H), 4.65 (m, 4H, 4ArCH), 4.15 (br, 2H, 2OH), 3.90 (br, 2H, H-2, H-5), 3.8-3.6 (m, 6H, H-1, H-1', H-3, H-4, H-6, H-6'), 3.32 (br, 2H, 2OH); ^{13}C NMR δ 137.5 (s, $2C_{arom}$), 128.6, 128.3, 128.1 (3d, $8C_{arom}$), 77.8 (d, C-3, C-4), 73.8 (t, $2C_{benzyl}$), 71.5 (d, C-2, C-5), 63.4 (t, C-1, C-6).

Other analyses were not performed because this compound proved to be highly hygroscopic.[146]

General methods for preparation of dialkylstannylene acetals.

A 1,2-diol or triol (1 mmol) derived from a monosaccharide was refluxed with one equivalent of dialkyltin oxide overnight in benzene (20 mL) or toluene with continuous removal of water in a Dean-Stark apparatus. The solvent was removed on a vacuum line and the stannylene acetal residue was kept under vacuum for an additional half hour. To this residue was added a dry solvent (usually 10 mL) which was used for *p*-toluenesulfonation reaction. The solvent used will be specified for each reaction.

General method for work-up after p-toluenesulfonation reactions.

In all cases, unless specified elsewhere, the reaction of the stannylene acetal intermediate with the electrophile was stopped by adding water and diluting with methylene chloride as follows. To the reaction mixture [1 mmol stannylene acetal and 1 mmol electrophile in benzene (20 mL) or toluene (20 mL), or in chloroform (5 mL), methylene chloride (5 mL), or acetonitrile (5 mL)] was added water (5 mL) and the mixture was stirred for 2 h at room temperature. The mixture was filtered and the filtrate was diluted with methylene chloride (25 mL) and washed with water (15 mL x 2). The organic layer was separated and dried over potassium carbonate. The solvent was removed on a rotary evaporator. The residue thus obtained was separated or

purified by means of dry column flash chromatography with hexane-ethyl acetate as the eluent (usually in gradient manner).

p-Toluenesulfonation of 3-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose (104).

Using dibutylstannylene acetal (118) in toluene. The stannylene acetal **118** was prepared using the general method from **104** (0.310 g, 1.0 mmol) and dibutyltin oxide (0.249 g, 1 mmol), then reacted with *p*-toluenesulfonyl chloride (0.191 g, 1 mmol) in toluene (20 mL) at room temperature for 48 h. Column separation of the reaction mixture resulted in two monosubstituted products. The first fraction gave 3-*O*-benzyl-1,2-*O*-isopropylidene-6-*O*-*p*-toluenesulfonyl-α-D-glucofuranose (**104P**, 0.310 g, 67%) as a syrup: $[\alpha]_D^{23}$ -8.0° (*c* 1.0, CH_3OH), -23.7° (*c* 1.1, $CHCl_3$); lit. $[\alpha]_D^{20}$ -7.24° (CH_3OH),[147] -39.2° ($CHCl_3$);[148] ^1H NMR δ 7.27-7.81 (m, 9H, Ar-H), 5.90 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 4.71 (d, 1H, $J_{ArCH,ArCH'}$ = 11.7 Hz, $ArCH_2$-H), 4.62 (d, 1H, H-2), 4.58 (d, 1H, $ArCH_2$-H'), 4.28 (dd, 1H, $J_{5,6}$ = 2.7 Hz, $J_{6,6'}$ = 10.0 Hz, H-6), 4.23 (m, 1H, H-5), 4.19-4.22 (m, 3H, H-3, H-4, H-6'), 2.68 (d, 1H, $J_{OH,5}$ = 5.8 Hz, OH), 2.46 (s, 3H, CH_3-Ar), 1.48 (s, 3H, CH_3), 1.35 (s, 3H, CH3); ^{13}C NMR δ 127-145 (12C, Ar-C), 112.0 (s, q-C), 105.2 (d, C-1), 82.18 (d, C-2), 81.93 (d, C-3), 78.3 (d, C-4), 72.3 (t, 2C, $ArCH_2$-C and C-6), 67.4 (d, C-5), 26.8 (q, CH_3), 26.3 (q, CH_3), 21.61 (q, CH_3-Ar).

The second fraction afforded 3-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-α-D-glucofuranose (**104S**, 0.150 g, 32%), which was also a syrup: $[\alpha]_D^{23}$ -16.3° (*c* 1.2, chloroform); ^1H NMR δ 7.20-7.76 (m, 9H, Ar-H), 5.85 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 5.04 (m, 1H, H-5), 4.57 (d, 1H, $J_{ArC\text{-}H,ArC\text{-}H'}$ = 11.0 Hz, $ArCH_2$-H), 4.56 (d,

1H, H-2), 4.54 (d, 1H, $ArCH_2$-H'), 4.36 (dd, 1H, $J_{3,4}$ = 2.8 Hz, $J_{4,5}$ = 7.7 Hz, H-4), 4.00 (d, 1H, H-3), 3.92 (m, 1H, H-6), 3.80 (m, 1H, H-6'), 2.40 (s, 3H, CH_3-Ar), 2.26 (br, 1H, OH), 1.46 (s, 3H, CH_3), 1.29 (s, 3H, CH_3). ^{13}C NMR δ 127-145 (12C, Ar-C), 112.2 (s, q-C), 105.1 (d, C-1), 81.5, 81.3 (2d, C-2 and C-3), 78.8, 78.5 (2d, C-4 and C-5), 72.1 (t, $ArCH_2$-C), 62.3 (t, C-6), 26.8 (q, CH_3), 26.3 (q, CH_3), 21.6 (q, CH_3-Ar).

Compound **104S** (0.300 g, 0.65 mmol, obtained from the previous reaction) was dissolved in pyridine (1 mL). To this solution was added a solution of benzoyl chloride (0.5 mL) in methylene chloride (3 mL) in 3 portions over 20 min with intermittent shaking. The mixture was allowed to stand at room temperature for 1 h and then diluted with methylene chloride (20 mL). The mixture was washed with water (10 mL x 2) and the organic layer was dried over potassium carbonate. After solvent was removed, column purification of the residue afforded 6-*O*-benzoyl-3-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-α-D-glucofuranose (**104D**, 0.310 g, 86%): $[\alpha]_D^{23}$ -0.7° (*c* 1.35, chloroform), lit.[149] $[\alpha]_D$ -2.2 ° (*c* 3.12, chloroform); mp 68-69 °C, lit[149] mp 64-67 °C; ^1H NMR δ 7.10-7.91 (m, 14H, Ar-H), 5.88 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1), 5.32 (m, 1H, H-5), 4.43-4.68 (m, 4H, H-2, H-4, $H\text{-}6_a$, $H\text{-}6_b$), 4.11 (d, 1H, $J_{3,4}$ = 2.6 Hz, H-3), 2.27 (s, 3H, CH_3-Ar), 1.45 (s, 3H, CH_3), 1.30 (s, 3H, CH_3).

Using dibutylstannylene acetal in chloroform. The stannylene acetal **118** (1 mmol) was prepared with the general method. The *p*-toluenesulfonation reaction was carried out in chloroform (10 mL) at room temperature for 20 h. Column separation gave the 6-*O*-*p*-toluenesulfonate **104P**, 0.200 g, 43%, and the 5-*O*-*p*-toluenesulfonate **104S**, 0.240 g, 52%, respectively.

Using dibutylstannylene acetal in dichloromethane. The stannylene acetal **119** (1 mmol, prepared with the general method) was reacted with TsCl (1 eq.) in toluene (20 mL) for 48 h. Column separation gave the 6-*O*-*p*-toluenesulfonate **104P** (0.251 g, 54%) and the 5-*O*-*p*-toluenesulfonate **104S** (0.189 g, 41%).

Using dibutylstannylene acetal in acetonitrile. The stannylene acetal **118** (1 mmol) was prepared with the general method. The *p*-toluenesulfonation reaction was carried out in chloroform (10 mL) at room temperature for 20 h. Column separation gave the 6-*O*-*p*-toluenesulfonate **104P**, 0.305 g, 66%, and the 5-*O*-*p*-toluenesulfonate **104S**, 0.125 g, 27%, respectively.

Using diisobutylstannylene acetal in toluene. The stannylene acetal **119** (1 mmol, prepared with the general method) was reacted with TsCl (1 eq.) in toluene (20 mL) for 48 h. Column separation gave the 6-*O*-*p*-toluenesulfonate **104P** (0.132 g, 28%) and the 5-*O*-*p*-toluenesulfonate **104S** (0.183 g, 39%).

Using diisobutylstannylene acetal in chloroform. The stannylene acetal **119** (1 mmol, prepared with the general method) was reacted with TsCl (1 eq.) in toluene (20 mL) for 48 h. Column separation gave the 6-*O*-*p*-toluenesulfonate **104P** (0.141 g, 30%) and the 5-*O*-*p*-toluenesulfonate **104S** (0.311 g, 67%).

Using diisopropylstannylene acetal in toluene. The stannylene acetal **120** (1 mmol, prepared with the general method) was allowed to react with TsCl (1 eq.) in toluene (20 mL) for 48 h. Column separation gave the 6-*O*-*p*-toluenesulfonate **104P** (0.139 g, 30%) and the 5-*O*-*p*-toluenesulfonate **104S** (0.237 g, 51%).

Using diisopropylstannylene acetal in chloroform. The stannylene acetal **120** (1

mmol, prepared with the general method) was allowed to react with TsCl (1 eq.) in chloroform (10 mL) for 48 h. Column separation gave the 6-*O*-*p*-toluenesulfonate **104P** (0.141 g, 30%) and the 5-*O*-*p*-toluenesulfonate **104S** (0.316 g, 68%).

Using diisopropylstannylene acetal in chloroform at 5 °C. The stannylene acetal **120** (1 mmol) was prepared with the general method. The residue was dissolved in chloroform (8 mL) and the solution thus obtained was cooled to 0 °C in a desiccator. A cold solution of TsCl (0.191 g, 1 mmol) in chloroform (2 mL) was added quickly, with a syringe, to the stannylene acetal solution. The reaction mixture was kept at 5 °C for two weeks. Hydrolysis of the reaction mixture was done by adding to the mixture a pre-cooled solution of 0.5 M HCl (5 mL). The organic layer was separated and dried over anhydrous potassium carbonate. Column separation afforded the 6-*O*-*p*-toluenesulfonate **104P** (0.087 g, 19%) and the 5-*O*-*p*-toluenesulfonate **104S** (0.359 g, 75%).

Using diisopropylstannylene acetal in methylene chloride. The stannylene acetal **120** (1 mmol, prepared with the general method) was reacted with TsCl (1 eq.) in methylene chloride (10 mL) at room temperature for 12 h. Column separation gave the 6-*O*-*p*-toluenesulfonate **104P** (0.137 g, 30%) and the 5-*O*-*p*-toluenesulfonate **104S** (0.300 g, 65%).

Using diisopropylstannylene acetal in methylene chloride at 5 °C. The stannylene acetal **120** (1 mmol, prepared with the general method) was reacted with TsCl (1 eq.) in methylene chloride (10 mL) at 5 °C for 48 h. Column separation gave the 6-*O*-*p*-toluenesulfonate **104P** (0.112 g, 24%) and the 5-*O*-*p*-toluenesulfonate **104S**

(0.290 g, 63%).

Using diisopropylstannylene acetal in acetonitrile. The stannylene acetal **120** (1 mmol, prepared with the general method) was reacted with TsCl (1 eq.) in acetonitrile (10 mL) at room temperature for 20 h. Column separation gave the 6-*O*-*p*-toluenesulfonate **104P** (0.304 g, 66%) and the 5-*O*-*p*-toluenesulfonate **104S** (0.127 g, 27%).

Using hexamethylenestannylene acetal in chloroform. The stannylene acetal **121** (1 mmol, prepared with the general method) was reacted with TsCl (1 eq.) in chloroform (10 mL) at room temperature for 20 h. Column separation gave the 6-*O*-*p*-toluenesulfonate **104P** (0.020 g, 4%) and the 5-*O*-*p*-toluenesulfonate **104S** (0.440 g, 95%).

Using dineohexylstannylene acetal in chloroform. The stannylene acetal **122** (1 mmol, prepared with the general method) was reacted with TsCl (1 eq.) in chloroform (10 mL) at room temperature for 10 h. Column separation gave the 6-*O*-*p*-toluenesulfonate **104P** (0.260 g, 56%) and the 5-*O*-*p*-toluenesulfonate **104S** (0.195 g, 42%).

Using dicyclohexylstannylene acetal in chloroform. The stannylene acetal **123** (1 mmol, prepared with the general method C) was reacted with TsCl (1 eq.) in chloroform (10 mL) at room temperature for 36 h. Column separation gave the 6-*O*-*p*-toluenesulfonate **104P** (0.212 g, 46%) and the 5-*O*-*p*-toluenesulfonate **104S** (0.230 g, 50%).

Using dihexylstannylene acetal in chloroform. The stannylene acetal **124** (1

mmol, prepared with the general method) was reacted with TsCl (1 eq.) in chloroform (10 mL) at room temperature for 12 h. Column separation gave the 6-*O*-*p*-toluenesulfonate **104P** (0.200 g, 43%) and the 5-*O*-*p*-toluenesulfonate **104S** (0.246 g, 53%).

Using di-*t*-butylstannylene acetal in chloroform. The di-*t*-butylstannylene acetal of **104** (1 mmol, prepared with the general method) was reacted with TsCl (1 eq.) in chloroform (10 mL) at room temperature for 5 d. Column separation gave the 6-*O*-*p*-toluenesulfonate **104P** (0.097 g, 25%) and the 5-*O*-*p*-toluenesulfonate **104S** (0.015 g, 4%).

***p*-Toluenesulfonation of 1,2-O-isopropylidene-α-D-glucofuranose (66).**

Using dibutylstannylene acetal. The stannylene acetal **125** (1 mmol, prepared using the general method from **66** and dibutyltin oxide) was allowed to react with *p*-toluenesulfonyl chloride (0.191 g, 1 mmol) in toluene (20 mL). The mixture was kept at room temperature for 4 days. The first fraction from column separation was a di-*O*-*p*-toluenesulfonate of compound **66** (0.030 g, 6%) which was not characterized. The following fraction contained 1,2-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-α-D-glucofuranose (**66S**, 0.045 g, 12%): mp 121-122°C, lit.[150] 122-124°C; $[\alpha]_D^{23}$ +6.5° (*c* 1.0, chloroform), lit.[150] $[\alpha]_D^{22}$ +6°; ^{1}H NMR δ 7.27-7.84 (m, 4H, Ar-H), 5.90 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.83 (m, 1H, H-5), 4.58 (d, 1H, H-2), 4.36 (br, 1H, H-3), 4.27 (dd, 1H, $J_{3,4}$ = 2.4 Hz, $J_{4,5}$ = 9.3 Hz, H-4), 3.72-3.76 (m, 2H, H-6, H-6'), 3.31 (d, 1H, $J_{OH,3}$ = 4.4 Hz, C_3-OH), 2.47 (s, 3H, $ArCH_3$), 2.05 (br, 1H, C_6-OH), 1.47 (s, 3H, CH_3), 1.31

(s, 3H, CH_3). The third fraction gave 1,2-*O*-isopropylidene-6-*O*-*p*-toluenesulfonyl-α-D-glucofuranose (**66P**, 0.145 g, 39%): mp 99-100 °C, lit.[151] 100-101°C; $[\alpha]_D^{23}$ -5.7° (*c* 1.1, chloroform), lit.[151] $[\alpha]_D^{23}$ -6°; ^{1}H NMR δ 7.34-7.80 (m, 4H, Ar-H), 5.90 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.51 (d, 1H, H-2), 4.35 (br, 1H, H-3), 4.28 (dd, 1H, $J_{5,6}$ = 2.5 Hz, $J_{6,6'}$ = 10.2 Hz, H-6), 4.18 (br, 1H, H-5), 4.10 (dd, 1H, $J_{5,6'}$ = 6.8 Hz, H-6'), 4.01 (dd, 1H, $J_{3,4}$ = 2.7 Hz, $J_{4,5}$ = 7.8 Hz, H-4), 3.73 (br, 1H, OH), 3.50 (br, 1H, OH), 2.45 (s, 3H, $ArCH_3$), 1.45 (s, 3H, CH_3), 1.29 (s, 3H, CH_3).

***p*-Toluenesulfonation of 3-O-methyl-1,2-O-isopropylidene-α-D-glucofuranose (64).**

Using dibutylstannylene acetal in toluene. The stannylene acetal **126** was prepared using the general method from **64** (0.234 g, 1.0 mmol) and dibutyltin oxide (0.249 g, 1 mmol), then reacted with *p*-toluenesulfonyl chloride (0.191 g, 1 mmol) in toluene (20 mL) at room temperature for 48 h. Column purification gave a syrupy mixture of two monosubstitution products (0.376 g, 97%) which could not be separated by chromatography. The mixture contained 3-O-methyl-1,2-O-isopropylidene-6-*O*-*p*-toluenesulfonyl-α-D-glucofuranose (**64P**) as the major product (80%) and 3-O-methyl-1,2-O-isopropylidene-5-*O*-*p*-toluenesulfonyl-α-D-glucofuranose (**64S**) as the minor (20%). These percentages were obtained by integration of several well-separated signals in the ^{1}H nmr spectrum, and averaging the results. NMR data for the 6-*O*-*p*-toluenesulfonate **64P** (δ): ^{1}H 7.27-7.84 (m, 4H, Ar-H), 5.85 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1), 4.56 (d, 1H, H-2), 4.26 (dd, 1H, $J_{3,4}$ = 2.8 Hz, $J_{4,5}$ = 8.0 Hz, H-4), 3.79-4.20 (m, 3H, H-5, H-6, H-6'), 3.88 (d, 1H, H-3), 3.43 (s, 3H, OCH_3), 2.94 (d, 1H,

$J_{OH,5}$ = 6.0 Hz, OH), 2.45 (s, 3H, CH_3-Ar), 1.46 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); ^{13}C 145.0 (s, C_{arom}), 132.4 (s, $C_{arom\text{-}para}$), 129.9 (d, $2C_{arom\text{-}ortho}$), 128.0 (d, $2C_{arom\text{-}meta}$), 111.86 (s, C_{acetal}), 104.98 (d, C-1), 84.17 (d, C-3), 81.31 (d, C-2), 78.95 (d, C-4), 72.23 (t, C-6), 67.39 (d, C-5), 57.94 (q, OCH_3), 26.76 (q, CH_3), 26.19 (q, CH_3), 21.68 (q, CH_3-Ar). NMR data for **64S** (δ, only data significantly different from those of the 6-*O*-*p*-toluenesulfonate **64P** are given): ^1H 4.92 (m, 1H, H-5), 3.75-3.95 (m, 2H, H-6_a, H-6_b), 3.27 (s, 3H, OCH_3), 2.45 (s, 3H, CH_3-Ar), 2.38 (br, 1H, OH); ^{13}C, 78.34 (d, C-5), 62.34 (t, C-6).

Using dibutylstannylene acetal in chloroform. The stannylene acetal **126** (1 mmol, prepared using the general method) was reacted with *p*-toluenesulfonyl chloride (0.191 g, 1 mmol) in chloroform (10 mL) at room temperature for 12 h, giving a mixture of monotosylates (0.380 g, 98%). The major product was the 6-*O*-*p*-toluenesulfonate **64P** and the minor the 5-*O*-*p*-toluenesulfonate **64S** in a ratio of 60:40.

Using diisobutylstannylene acetal in toluene. The stannylene acetal **127** (1 mmol, prepared using the general method) was allowed to react with TsCl (1 eq.) in toluene (20 mL) at room temperature for 48 h, giving a mixture of monotosylates (0.299 g, 77%). The major product was the 5-*O*-*p*-toluenesulfonate **64S** and the minor, the 6-*O*-*p*-toluenesulfonate **64P**, in a ratio of 60:40.

Using diisobutylstannylene acetal in chloroform. The stannylene acetal **127** (1 mmol, prepared using the general method) was allowed to react with TsCl (1 eq.) in toluene (20 mL) at room temperature for 48 h, giving a mixture of monotosylates (0.370 g, 97%). The major product was the 6-*O*-*p*-toluenesulfonate **64P** and the

minor, the 5-*O*-tosylate **64S**, in a ratio of 68:32.

Using diisopropylstannylene acetal in toluene. The stannylene acetal **128** (1 mmol, prepared using the general method) was allowed to react with TsCl (1 eq.) in toluene (20 mL) at room temperature for 24 h, giving a mixture of monotosylates (0.310 g, 80%). The major product was the 6-*O*-*p*-toluenesulfonate **64P** and the minor, the 5-*O*-tosylate **64S**, in a ratio of 60:40.

Using diisopropylstannylene acetal in chloroform at 5 °C. The stannylene acetal (**128**, 1 mmol) was prepared using the general method. The residue was dissolved in chloroform (8 mL) and the solution thus obtained was cooled to 0 °C in a desiccator. A cold solution of TsCl (0.191 g, 1 mmol) in chloroform (2 mL) was added quickly, with a syringe, to the stannylene acetal solution. The reaction mixture was kept at 5 °C for two weeks. Hydrolysis of the reaction mixture was done by adding to the mixture a pre-cooled solution of 0.5 M HCl (5 mL). The organic layer was separated and dried over anhydrous potassium carbonate. Column purification afforded a mixture of monosubstitution products (0.372 g, 96%). The ratio of the 6-*O*-*p*-toluenesulfonate **64P** to the 5-*O*-*p*-toluenesulfonate **64S** was 25:75.

Using diisopropylstannylene acetal in methylene chloride at 5 °C. The stannylene acetal **128** (1 mmol, prepared using the general method) was allowed to react with TsCl (1 eq.)) in methylene chloride (10 mL) at 5 °C for 48 h, giving a mixture of mono-*O*-*p*-toluenesulfonates (0,345 g, 89%). The major product was the 5-*O*-*p*-toluenesulfonate **64S** and the minor, the 6-*O*-*p*-toluenesulfonate **64P**, in a ratio of 65:35.

Using hexamethylenestannylene acetal in chloroform. The stannylene acetal **129** was prepared using the general method from **64** (0.234 g, 1.0 mmol) and hexamethylenetin oxide (0.219 g, 1 mmol), was then reacted with *p*-toluenesulfonyl chloride (0.191 g, 1 mmol) in chloroform (10 mL) at room temperature for 12 h, giving a mixture of mono-*O*-*p*-toluenesulfonates (0.365 g, 94%). The major product was the 5-*O*-*p*-toluenesulfonate **64S** and the minor, the 6-*O*-*p*-toluenesulfonate **64P**, in a ratio of 95:5.

Using dineohexylstannylene acetal in chloroform. The stannylene acetal **130** (1 mmol, prepared using the general method) was reacted with TsCl (1.1 eq.) in chloroform (10 mL) at room temperature for 12 h, giving a mixture of mono-*O*-*p*-toluenesulfonates (0.380 g, 98%). The major product was the 6-*O*-*p*-toluenesulfonate **64P** and the minor, the 5-*O*-*p*-toluenesulfonate **64S**, in a ratio of 70:30.

Using dicyclohexylstannylene acetal in chloroform. The stannylene acetal **131** was prepared using the general method from **64** (0.234 g, 1.0 mmol) and dicyclohexyltin oxide (0.249 g, 1 mmol), then was reacted with *p*-toluenesulfonyl chloride (0.191 g, 1 mmol) in chloroform (10 mL) at room temperature for 36 h, giving a mixture of mono-*O*-*p*-toluenesulfonates (0.330 g, 85%). The ratio of the 6-*O*-*p*-toluenesulfonate **64P** to the 5-*O*-*p*-toluenesulfonate **64S** was 44: 56.

Using dihexylstannylene acetal in chloroform. The stannylene acetal **132** (1 mmol, prepared using the general method) was allowed to react with TsCl (1 eq.) in chloroform (10 mL) at room temperature for 12 h, giving a mixture of mono-*O*-*p*-toluenesulfonates (0.381 g, 98%). The ratio of the 6-*O*-*p*-toluenesulfonate **64P** to the

5-*O*-*p*-toluenesulfonate **64S** was 58:42.

Using dineopentylstannylene acetal in chloroform. The stannylene acetal **133** (1 mmol, prepared using the general method) was reacted with TsCl (1.1 eq.) in chloroform (10 mL) at room temperature for two weeks, giving a mixture of mono-*O*-*p*-toluenesulfonates (0.252 g, 65%). The major product was the 5-*O*-*p*-toluenesulfonate **64S** and the minor, the 6-*O*-*p*-toluenesulfonate **64P**, in a ratio of 70:30.

***p*-Toluenesulfonation of methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside (106).**

Using dibutylstannylene acetal in chloroform. The stannylene acetal **134** (1 mmol, prepared from **106** and dibutyltin oxide using the general method) was allowed to react with *p*-toluenesulfonyl chloride (0.191 g, 1 mmol) in chloroform (10 mL) at room temperature. The reaction was complete after 12 h according to TLC. A syrup was obtained after standard work-up, which contained a mixture of monosubstitution products (0.373 g, 98%). ^{1}H NMR spectroscopy showed that over 95% of the product was the 6-*O*-tosylate **106P** (form integration of the well-separated signals of methoxy protons). Treatment of the syrup with diethyl ether-hexane afforded colourless crystals of methyl 1,2-*O*-isopropylidene-6-*O*-*p*-toluenesulfonyl-α-D-mannofuranoside (**106P**): mp 95-96°C, lit.[152] mp 94-95°C; $[\alpha]_D^{23}$ 4.1° (*c* 1.0, chloroform), lit.[152] $[\alpha]_D^{26}$ 4.5°; ^{1}H NMR δ 7.2-7.8 (m, 5H, Ar-H), 4.86 (s, 1H, H-1), 4.79 (dd, 1H, $J_{2,3}$ = 5.8 Hz, $J_{3,4}$ = 3.3 Hz, H-3), 4.55 (d, 1H, H-2), 4.30 (dd, 1H, $J_{6,6'}$ = 10.1 Hz, $J_{5,6}$ = 3.0 Hz, H-6), 4.18 (dd,1H, $J_{5,6'}$ = 5.9 Hz, H-6'), 4.13 (m, 1H, H-5), 3.90 (dd, 1H, $J_{4,5}$ = 7.8 Hz, H-4), 3.26 (s, 3H, OCH_3), 2.75 (br, 1H, OH), 2.45 (s, 3H, Ar-CH_3), 1.43 (s, 3H, CH_3), 1.31 (s,

3H, CH_3); ^{13}C NMR δ 144.9 (s, $C_{arom\text{-}para}$), 129.8 (s, C_{arom}), 129.5 (d, $C_{arom\text{-}ortho}$), 127.9 (d, $C_{arom\text{-}meta}$), 112.7 (s, C_{acetal}), 107.0 (d, C-1), 84.6 (d, C-2), 79.6 (d, C-3), 78.0 (d, C-4), 71.5 (t, C-6), 68.0 (d, C-5), 54.6 (q, CH_3O), 25.8 (q, CH_3), 24.5 (q, CH_3), 21.6 (q, CH_3-Ar).

Using diisopropylstannylene acetal in toluene. The stannylene acetal **135** (1 mmol, prepared from **106** and diisopropyltin oxide using the general method) reacted with *p*-toluenesulfonyl chloride in toluene at room temperature for 60 h, giving a mixture of monosubstitution products (0.380 g, 98%) which were consisted of the 5-*O*-*p*-toluenesulfonate **106S** (33%) and the 6-*O*-*p*-toluenesulfonate **106P** (67%), as measured by integration of the signals of the methoxy group (3.28 ppm for **106S** and 3.26 ppm for **106P**) and the signals of the methyl groups in CMe_2 (1.27 and 1.12 ppm for **106S**, 1.43 and 1.31 ppm for **106P**). In the ^1H NMR spectrum of the mixture, the following signals could be assigned to the 5-*O*-tosylate **106S**, δ 4.82 (s H-1), 2.40 (t, OH), 3.28 (s, OCH_3), 1.27 and 1.12 (2s, CMe_2).

The above reaction, carried out with 12 equivalent of TsCl (**135**, 1 mmol; TsCl, 12 mmol; toluene, 10 mL), was complete in 2 h at room temperature. Column purification afforded a mixture of monosubstitution products (0.385 g, 99%) which were consisted of the 5-*O*-*p*-toluenesulfonate **106S** (32%) and 6-*O*-*p*-toluenesulfonate **106P** (68%).

Using diisopropylstannylene acetal in chloroform. The same reaction was carried out with stannylene acetal **135** in chloroform (10 mL) at room temperature for 12 h. A mixture of two monosubstitution products was obtained in 91% yield (0.353

g) with the ratio of the 6-*O*-*p*-toluenesulfonate **106P** to the 5-*O*-*p*-toluenesulfonate **106S** being 62 to 38.

Using hexamethylenestannylene acetal in chloroform. The stannylene acetal **136** (1 mmol, prepared using the general method) was reacted with TsCl (1 eq.) in chloroform (10 mL) at room temperature for 12 h, giving a mixture of mono-*O*-*p*-toluenesulfonates in 92% yield (0.357 g). The major product was the 5-*O*-*p*-toluenesulfonate **106S** and the minor, the 6-*O*-*p*-toluenesulfonate **106P**, in a ratio of 70:30.

***p*-Toluenesulfonation of 1,2-O-isopropylidene-3-O-methyl-α-D-allofuranose (113).**

Using dibutylstannylene acetal. The stannylene acetal **137** (1 mmol, prepared from **113** and dibutyltin oxide using the general method) reacted with one equivalent of TsCl in chloroform at room temperature for 12 h. Column separation afforded 1,2-*O*-isopropylidene-3-*O*-methyl-6-*O*-*p*-toluenesulfonyl-α-D-allofuranose (**113P**, 0.380 g, 98%) as the only product: ^{1}H NMR δ 7.79 (d, 2H, J = 8.2 Hz, 2Ar-H_{ortho}), 7.34 (d, 2H, 2Ar-H_{meta}), 5.74 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.68 (dd, $J_{2,3}$ = 4.1 Hz, H-2), 4.18-4.09 (m, 2H, H-5, H-6), 4.03 (dd, $J_{5,6'}$ = 8.0 Hz, $J_{6,6'}$ = 10.4 Hz, H-6'), 3.92 (dd, 1H, $J_{3,4}$ = 8.7 Hz, $J_{4,5}$ = 3.5 Hz, H-4), 3.76 (dd, 1H, H-3), 3.42 (s, 3H, OCH_3), 2.79 (d, 1H, $J_{OH,5}$ = 1.7 Hz, OH), 2.45 (s, 3H, $ArCH_3$), 1.55, 1.35 (2s, 2 x 3H, $2CH_3$); ^{13}C NMR δ 145.0 (s, C_{arom}), 132.6 (s, $C_{arom\text{-}para}$), 129.9 (d, $2C_{arom\text{-}ortho}$), 128.0 (d, $2C_{arom\text{-}meta}$), 113.3 (s, C_{acetal}), 104.2 (d, C-1), 79.6 (d, C-4), 77.4 (d, C-3), 76.9 (d, C-2), 70.5 (t, C-6), 69.1 (d, C-5), 57.9 (q, OCH_3), 26.8, 26.4 (2q, $2CH_3$), 21.6 (q, $ArCH_3$).

Using diisopropylstannylene acetal. The same reaction carried out with the stannylene acetal **138** gave an overall yield of 86% (0.334 g) as a mixture of primary and secondary *p*-toluenesulfonates which contained 67% of the 6-*O*-*p*-toluenesulfonate **113P** and 33% of 1,2-*O*-isopropylidene-3-*O*-methyl-5-*O*-*p*-toluenesulfonyl-α-D-allofuranose (**113S**) by the integration of signals of H-1s, methoxyl and isopropylidene methyl groups on the ^{1}H NMR spectrum. For **113S**: ^{1}H NMR δ 7.79 (m, 2H, 2Ar-H), 7.34 (m, 2H, 2Ar-H), 5.38 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 4.84 (m, 1H, H-5), 4.58 (dd, $J_{2,3}$ = 4.2 Hz, H-2), 3.44 (s, 3H, OCH_3), 2.76 (m, 1H, OH), 2.44 (s, 3H, $ArCH_3$), 1.51, 1.32 (2s, 2 x 3H, $2CH_3$); ^{13}C NMR δ 144.8 (s, C_{arom}), 133.8 (s, $C_{arom\text{-}para}$), 129.6 (d, $2C_{arom\text{-}ortho}$), 128.0 (d, $2C_{arom\text{-}meta}$), 113.4 (s, C_{acetal}), 103.9 (d, C-1), 81.1 (d, C-5), 79.2 (d, C-4), 77.5 (d, C-3), 76.7 (d, C-2), 61.6 (t, C-6), 57.9 (q, OCH_3), 26.8, 26.5 (2q, $2CH_3$), 21.6 (q, $ArCH_3$).

Using di-*t*-butylstannylene acetal. The di-*t*-butylstannylene acetal of **113** (1 mmol, prepared using standard method) was allowed to react with 1 eq. of TsCl in chloroform at room temperature for 14 days, giving an overall yield of 36% (0.140 g) as a mixture of primary and secondary *p*-toluenesulfonates which contained 90% of the 6-*O*-*p*-toluenesulfonate **113P** and 10% of 1,2-*O*-isopropylidene-3-*O*-methyl-5-*O*-*p*-toluenesulfonyl-α-D-allofuranose (**113S**).

***p*-Toluenesulfonation of 1,2-O-isopropylidene-3-O-tosyl-α-D-allofuranose (114).**

Using dibutylstannylene acetal. The stannylene acetal **139** (1 mmol, prepared using the general method) was allowed to react with one equivalent of TsCl in

chloroform at room temperature for 12 h. The first fraction from column separation afforded 1,2-*O*-isopropylidene-3,6-di-*O*-*p*-toluenesulfonyl-α-D-allofuranose (**114P**, 0.470 g, 89%): mp 118-119 °C, lit.[141] mp 117-118 °C; ^{1}H NMR δ 7.85-7.76 (m, 4H, 4Ar-H_{ortho}), 7.35 (m, 4H, 4Ar-H_{meta}), 5.69 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.69 (dd, $J_{2,3}$ = 4.6 Hz, $J_{3,4}$ = 8.0 Hz, H-3), 4.55 (dd, 1H, H-2), 4.11-4.01 (m, 2H, H-4, H-5), 3.99 (dd, $J_{5,6}$ = 2.5 Hz, H-6), 3.87 (dd, 1H, $J_{5,6'}$ = 7.9 Hz, $J_{6,6'}$ = 10.2 Hz, H-6'), 2.57 (d, 1H, $J_{OH,5}$ = 3.7 Hz, OH), 2.46 (s, 6H, 2ArCH_3), 1.49, 1.28 (2s, 2 x 3H, 2CH_3). The second fraction from column separation contained 1,2-*O*-isopropylidene-3,5-di-*O*-*p*-toluenesulfonyl-α-D-allofuranose (**114S**, 0.042 g, 8%) which decomposed quickly: ^{1}H NMR δ 7.85-7.76 (m, 4H, 4Ar-H_{ortho}), 7.38-7.32 (m, 4H, 4Ar-H_{meta}), 5.42 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1), 4.77 (m, 1H, H-5), 4.67 (dd, $J_{2,3}$ = 4.6 Hz, $J_{3,4}$ = 8.6 Hz, H-3), 4.47 (dd, 1H, H-2), 4.17 (dd, 1H, $J_{4,5}$ = 1.6 Hz, H-4), 3.59 (m, 2H, H-6, H-6'), 2.47, 2.45 (2s, 2 x 3H, 2ArCH_3), 2.10 (t, 1H, $J_{OH,6}$ = 6.6 Hz, OH), 1.43, 1.24 (2s, 2 x 3H, 2CH_3).

Using diisopropylstannylene acetal. The same reaction using stannylene acetal **140** gave 0.296 g (56%) of the 3,6-di-*O*-toluenesulfonate **114P** and the 0.169 g (32%) of the 3,5-di-*O*-toluenesulfonate **114S**.

***p*-Toluenesulfonation of 1,2-O-isopropylidene-α-D-allofuranose (115).**

Using dibutylstannylene acetal. The *p*-toluenesulfonation of **115** using 1:1 equivalent of the stannylene acetal **141** and TsCl in chloroform at room temperature finished in 8 h. The first fraction from column separation contained 1,2-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-α-D-allofuranose (**115P**, 0.336 g, 90%) as the

only product: mp 115-117 °C, lit.[153] 117-119 °C; $[\alpha]_D^{23}$ +30.2° (*c* 1.0, chloroform); lit.[153] $[\alpha]_D^{23}$ +31.2° (*c* 0.81, chloroform); ^{1}H NMR δ 7.77 (m, 2H, Ar-H_{ortho}), 7.35 (m, 2H, 2Ar-H_{meta}), 5.74 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 4.56 (dd, 1H, $J_{2,3}$ = 5.0 Hz, H-2), 4.24-4.02 (m, 4H, H-3, H-5, H-6, H-6'), 3.73 (dd, 1H, $J_{3,4}$ = 8.5 Hz, $J_{4,5}$ = 4.8 Hz, H-4), 2.99 (d, $J_{OH,3\ or\ 5}$ = 7.5 Hz, OH), 2.72 (d, 1H, $J_{OH,5\ or\ 3}$ = 9.1 Hz, OH), 2.57 (d, 1H, $J_{OH,5}$ = 3.7 Hz, OH), 2.43 (s, 3H, $ArCH_3$), 1.53, 1.34 (2s, 2 x 3H, $2CH_3$), ^{13}CNMR δ 145, 132 (2s, $2C_{arom}$), 129.9, 127.9 (2d, 2 x $2C_{arom}$), 113.0 (s, C_{acetal}), 103.9 (d, C-1), 78.8 (d, C-2), 78.7 (d, C-4), 72.0 (d, C-3), 70.6 (t, C-6), 69.7 (d, C-5), 26.5 (q, $2CH_3$), 21.6 (q, $ArCH_3$).

Using hexamethylenestannylene acetal. The stannylene acetal **142** (1 mmol, prepared using the general method) was allowed to react with one equivalent of *p*-toluenesulfonyl chloride in chloroform at room temperature for 12 h, giving the 6-*O*-*p*-toluenesulfonate **115P** (0.340 g, 91%) , and 1,2-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-α-D-allofuranose (**115S**, 0.030 g, 8%): mp 175-177 °C, lit.[153] 178-179 °C; $[\alpha]_D^{23}$ +83.8° (*c* 1.0, chloroform), lit.[153] $[\alpha]_D^{23}$ +85.8° (*c* 0.88, acetone);

p-Toluenesulfonation of 3-deoxy-1,2-O-isopropylidene-α-D-erythro-hexofuranose (105).

Using dibutylstannylene acetal. The stannylene acetal **143** (prepared from dibutyltin oxide and compound **105** using the general method) was reacted with TsCl (1 eq.) in chloroform at room temperature for 12 h. Column purification yielded a syrupy mixture of two monosubstituted products which could not be separated by TLC. The overall yield was 99% (0.370 g), consisting of 3-deoxy-1,2-*O*-

isopropylidene-6-*O*-*p*-toluenesulfonyl-α-D-*erythro*-hexofuranose (**105P**, 94%) and 3-deoxy-1,2-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-α-D-*erythro*-hexofuranose (**105S**, 5%). This ratio was obtained from integration of well-separated signals in ^{1}H NMR spectrum: for the 6-*O*-*p*-toluenesulfonate **105P**, 5.73 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1); for the 5-*O*-*p*-toluenesulfonate **105S**, 5.49 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.27 (m, 1H, H-5).

Using diisobutylstannylene acetal. The *p*-toluenesulfonation of **105** using 1:1 mole ratio of the stannylene acetal **144** (1 mmol, prepared using the general method) and TsCl in chloroform at room temperature finished in 20 h, giving 71% (0.264 g) of the 6-*O*-*p*-toluenesulfonate **105P** and 19% (0.072 g) of 5-*O*-*p*-toluenesulfonate **105S**.

Using diisopropylstannylene acetal. The same reaction using stannylene acetal **145** (1 mmol, prepared from the general method) in chloroform at room temperature finished in 20 h, yielding 70% (0.260 g) of 6-*O*-*p*-toluenesulfonate **105P** and 20% (0.075 g) of 5-*O*-*p*-toluenesulfonate **105S**.

Using hexamethylenestannylene acetal. The stannylene acetal **146** (1 mmol, prepared using the general method) was reacted with one equivalent of TsCl in chloroform (7 mL) at room temperature for 20 h. Column separation resulted in 51% (0.191 g) of 6-*O*-*p*-toluenesulfonate **105P** and 48% (0.178 g) of 5-*O*-*p*-toluenesulfonate **105S**.

Using di-*t*-butylstannylene acetal. The di-*t*-butylstannylene acetal of **105** (1 mmol, prepared using the general method) was reacted with one equivalent of TsCl in chloroform (7 mL) at room temperature for 14 d. Column separation resulted in 50% (0.182 g) of 6-*O*-*p*-toluenesulfonate **105P** and 45% (0.096 g) of starting material was

recovered.

p-Toluenesulfonation of 1,2:3,4-di-O-isopropylidene-D-mannitol (116).

Using dibutylstannylene acetal. The stannylene acetal (**147**, 1 mmol, prepared using the general method) was allowed to react with TsCl (1 eq.) in chloroform for 24 h. The first fraction from column separation afforded 1,2:3,4-di-O-isopropylidene-6-*O*-*p*-toluenesulfonyl-D-mannitol (**116P**, 0.400 g, 96%), the major product, as a syrup: $[\alpha]_D^{23}$ 19.8° (*c* 1.3, chloroform); ^{1}H NMR δ 7.80 (m, 2H, Ar-H), 7.32 (m, 2H, Ar-H), 4.29 (dd, 1H, $J_{5,6}$ = 1.6 Hz, $J_{6,6'}$ = 10.3 Hz, H-6), 4.17 (dd, 1H, $J_{1,1'}$ = 8.0 Hz, $J_{1,2}$ = 2.3 Hz, H-1), 4.17 (dd, 1H, $J_{5,6'}$ = 5.3 Hz, H-6'), 4.07-3.9 (m, 2H, H-2, H-1'), 4.3.82-3.65 (m, 4H, H-5, H-3, H-4, OH), 2.40 (s, 3H, CH_3-Ar), 1.40 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.30 (s, 6H, $2CH_3$); ^{13}C NMR δ144.7 (s, $C_{arom\text{-}para}$), 133.0 (s, C_{arom}), 129.8 (d, $2C_{arom\text{-}ortho}$), 128.0 (d, $2C_{arom\text{-}meta}$), 110.3 (s, C_{acetal}), 109.9 (s, C_{acetal}), 80.9 (d, C-4), 79.2 (d, C-3), 76.1 (d, C-2), 71.3 (t, C-6), 70.7 (d, C-5), 67.7 (t, C-1), 26.8 (q, $2CH_3$), 26.3 (q, CH_3), 25.0 (q, CH_3), 21.6 (q, CH_3-Ar). Anal. Calcd for $C_{19}H_{28}O_8S$: C 54.79, H 6.78; Found: C 54.48, H 6.77. The second fraction gave the minor product, also a syrup, which was assigned to be 1,2:3,4-di-O-isopropylidene-5-*O*-*p*-toluenesulfonyl-D-mannitol (**116S**, 0.010 g, 2%): $[\alpha]_D^{23}$ 10.8° (*c* 0.86, chloroform); ^{1}H NMR δ 7.82 (m, 2H, Ar-H), 7.33 (m, 2H, Ar-H), 4.78 (m, 1H, H-5), 4.19 (dd, 1H, $J_{3,4 \text{ or } 4,5}$ = 3.6 Hz, $J_{4,5 \text{ or } 3,4}$ = 6.4 Hz, H-4), 4.10 (dd, 1H, $J_{1,1'}$ = 8.2 Hz, $J_{1,2}$ = 5.8 Hz, H-1), 4.0-3.7 (m, 5H, H-2, H-1', H-3, H-6, H-6'), 2.73 (t, $J_{OH,6}$ = 7.0 Hz, OH), 2.43 (s, 3H, CH_3-Ar), 1.37 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.27 (s, 3H, CH_3); ^{13}C NMR δ145.1

(s, $C_{arom\text{-}para}$), 133.5 (s, C_{arom}), 130.1 (d, $2C_{arom\text{-}ortho}$), 128.1 (d, $2C_{arom\text{-}meta}$), 110.5 (s, C_{acetal}), 110.1 (s, C_{acetal}), 80.8 (d, C-5), 79.1 (d, C-4), 77.6 (d, C-3), 77.0 (d, C-2), 67.6 (t, C-1), 61.3 (t, C-6), 27.2 (q, CH_3), 27.0 (q, CH_3), 26.3 (q, CH_3), 25.2 (q, CH_3), 21.7 (q, CH_3). Anal. Calcd for $C_{19}H_{28}O_8S$: C 54.79, H 6.78; Found: C 54.48, H 6.74.

Using hexamethylenestannylene acetal. The stannylene acetal (**148**, 1 mmol, prepared using the general method) was reacted with TsCl (1 eq.) in chloroform for 24 h. Column separation afforded the 6-*O*-*p*-toluenesulfonate **116P** (0.160 g, 38%) as the minor product and the 5-*O*-*p*-toluenesulfonate **116S** (0.240 g, 58%) as the major.

***p*-Toluenesulfonation of 3,4-di-*O*-benzyl-1,2-O-isopropylidene-D-mannitol (117).**

Using dibutylstannylene acetal. The stannylene acetal (**149**, 1 mmol, prepared using the general method) was allowed to react with TsCl (1 eq.) in chloroform for 24 h. The first fraction from column separation afforded 3,4-di-O-benzyl-1,2-*O*-isopropylidene-6-*O*-*p*-toluenesulfonyl-D-mannitol (**117P**, 0.445 g, 80%) as a syrup: $[\alpha]_D^{24}$ 27.2° (*c* 0.90, chloroform); ^{1}H NMR δ 7.76 (m, 2H, Ar-H), 7.4-7.2 (m, 12H, Ar-H), 4.69 (d, 1H, $J_{(ArCH,ArCH')a}$ = 11.6 Hz, $ArCH_a$), 4.65 (d, 1H, $ArCH_a'$), 4.60 (d, 1H, $J_{(ArCH,ArCH')b}$ = 11.3 Hz, $ArCH_b$), 4.49 (d, 1H, $ArCH_b'$), 4.24 (m, 1H, H-5), 4.17 (dd, $J_{5,6}$ = 6.4 Hz, $J_{6,6'}$ = 10.2 Hz, H-6), 4.08 (dd, 1H, $J_{5,6'}$ = 5.2 Hz, H-6'), 4.03 (dd, 1H, $J_{1,1'}$ = 8.7 Hz, $J_{1,2}$ = 6.4 Hz, H-1), 3.99 (m, 1H, H-5), 3.89 (dd, $J_{2,3}$ = 6.1 Hz, $J_{3,4}$ = 2.8 Hz, H-3), 3.85 (dd, $J_{1',2}$ = 6.4 Hz, H-1'), 3.66 (dd, 1H, $J_{4,5}$ = 7.6 Hz, H-4),2.48 (br, 1H, OH), 2.42 (s, 3H, CH_3-Ar), 1.42 (s, 3H, CH_3), 1.33 (s, 3H, CH_3); ^{13}C NMR δ145.0, 137.7, 137.4, 132.4, (4s, $4C_{arom}$), 130.0, 128.5, 128.4, 128.22, 128.20, 128.0, 127.97

(7d, 14C_{arom}), 108.7 (s, C_{acetal}), 78.9 (d, C-3), 78.1 (d, C-4), 76.0 (d, C-2), 74.5 (t, CH_2Ar), 74.0 (t, CH_2Ar), 71.6 (t, C-6), 69.2 (d, C-5), 67.7 (t, C-1), 26.6 (q, CH_3), 25.1 (q, CH_3), 21.7 (q, CH_3-Ar). Anal. Calcd for $C_{30}H_{36}O_8S$: C 64.73, H 6.52; Found: C 64.38, H 6.58. The second fraction gave the minor product (0.067 g, 12%) also as a syrup which decomposed on storage at room temperature. It was assigned to 3,4-di-O-1,2-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-D-mannitol (**117S**): $[\alpha]_D^{24}$ 19.3° (*c* 0.90, chloroform); ^{1}H NMR δ 7.78 (m, 2H, Ar-H), 7.4-7.2 (m, 12H, Ar-H), 4.84 (m, 1H, H-5), 4.74 (d, 1H, $J_{(ArCH,ArCH')a}$ = 11.3 Hz, ArCH-a), 4.65 (s, 2H, $ArCH_2$-b), 4.63 (d, 1H, ArCH'-a), 4.08 (m, 1H, H-2), 3.99 (dd, $J_{1,1'}$ = 8.3 Hz, $J_{1,2}$ = 6.1 Hz, H-1), 3.96-3.91 (m, 2H, H-6, H-4), 3.87 (dd, 1H, $J_{1,2}$ = 6.1 Hz, H-1'), 3.83 (m, 1H, H-6'), 3.68 (dd, 1H, $J_{3,4}$ = 4.3 Hz, $J_{2,3}$ = 6.1 Hz, H-3), 2.24 (t, $J_{OH,6}$ = 6.4 Hz, OH), 2.43 (s, 3H, CH_3-Ar), 1.38 (s, 3H, CH_3), 1.30 (s, 3H, CH_3); ^{13}C NMR δ145.2. 137.8, 137.5, (4s, 4C_{arom}), 130.0, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9 (7d, 14C_{arom}), 108.9 (s, C_{acetal}), 83.2 (d, C-5), 80.4 (d, C-4), 79.3 (d, C-3), 76.2 (d, C-2), 75.0 (t, CH_2Ar), 74.7 (t, CH_2Ar), 66.7 (t, C-1), 61.3 (t, C-6), 26.5 (q, CH_3), 25.2 (q, CH_3), 21.7 (q, CH_3). Anal. Calcd for $C_{30}H_{36}O_8S$: C 64.73, H 6.52; Found: C 63.72, H 6.49.

Using hexamethylenestannylene acetal. The stannylene acetal (**150**, 1 mmol, prepared using the general method) reacted with TsCl (1 eq.) in chloroform for 24 h. Column separation afforded the 6-*O*-*p*-toluenesulfonate (**117P**, 0.094 g, 17%) as the minor product and the 5-*O*-*p*-toluenesulfonate (**117S**, 0.333 g, 60%) as the major.

Benzoylation of 3-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose (104).

The dibutylstannylene acetal **118** (1 mmol) was prepared from **104** and dibutyltin oxide in benzene (20 mL). To this acetal solution was added powdered 4Å molecular sieves (1 g). At room temperature, a solution of freshly distilled benzoyl chloride (0.15 g, 1 mmol) in benzene (12 mL) was added dropwise over 20 min and the mixture was stirred for 4 h. The molecular sieves were removed by filtration and the resulting solution was worked up in the standard fashion. Chromatographic separation afforded 6-*O*-benzoyl-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (0.320 g, 77%) as a syrup: ^{1}H NMR δ 7.30-8.10 (m, 10H, Ar-H), 5.97 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 4.73 (d, 1H, $J_{ArCH,ArCH'}$ = 11.7 Hz, ArCH), 4.65 (d, 1H, H-2), 4.63 (dd, 1H, $J_{5,6}$ = 2.8 Hz, $J_{6,6'}$ = 11.7 Hz, H-6), 4.58 (d, 1H, ArCH'), 4.42 (dd, 1H, $J_{5,6'}$ = 6.0 Hz, H-6'), 4.33 (m, 1H, H-5), 4.24 (dd, 1H, $J_{3,4}$ = 3.1 Hz, $J_{4,5}$ = 5.0 Hz, H-4), 4.15 (d, 1H, H-3), 3.2 (br, 1H, OH), 1.48 (s, 3H, CH_3), 1.32 (s, 3H, CH_3); and 5-*O*-benzoyl-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (0.062 g, 15%), also a syrup, ^{1}H NMR δ 7.1-8.0 (m, 10H, Ar-H), 5.95 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 5.45 (m, 1H, H-5), 4.63 (d, 1H, H-2), 4.56 (d, 1H, $J_{ArCH,ArCH'}$ = 11.3 Hz, ArCH), 4.54 (dd, 1H, $J_{3,4}$ = 3.2 Hz, $J_{4,5}$ = 6.0 Hz, H-4), 4.37 (d, 1H, ArCH'), 4.08 (dd, 1H, $J_{5,6}$ = 3.0 Hz, $J_{6,6'}$ = 12.5 Hz, H-6), 4.02 (d, 1H, H-3), 3.96 (dd, 1H, $J_{5,6'}$ = 4.2 Hz, H-6'), 2.5 (br, 1H, OH), 1.53 (s, 3H, CH_3), 1.33 (s, 3H, CH_3).

Benzylation of 3-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose (104).

The stannylene acetal **118** (1 mmol) was prepared from **104** and dibutyltin

oxide in benzene (20 mL). To this benzene solution were added powdered 4 Å molecular sieves (1.5 g), tetrabutylammonium iodide (0.406 g, 1.1 mmol) and benzyl chloride (0.140 g, 1.1 mmol). The mixture was refluxed for three days. The molecular sieves and other insoluble materials were removed by filtration. Standard work-up followed by flash chromatography yielded 3,6-di-*O*-benzyl-1,2-isopropylidene-α-D-glucofuranose (0.24 g, 60%), a syrup: $[\alpha]_D^{23}$ -20.6° (*c* 1.1, chloroform), lit. $[\alpha]_D^{25}$ -25.9°[154] and $[\alpha]_D^{23}$ -14.5°;[155] ^{1}H NMR δ 7.30-7.35 (m, 10H, Ar-H), 5.92 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 4.66 (d,1H, $J_{ArCH, ArCH'}$ = 12.6 Hz, ArCH), 4.59 (d, 1H, H-2), 4.5-4.6 (m, 3H, 3 ArCH), 4.1-4.2 (m, 3H, H-3, H-4, H-5), 3.73 (dd, 1H, $J_{5,6}$ = 2.8 Hz, $J_{6,6'}$ = 9.7 Hz, H-6_a), 3.60 (dd, 1H, $J_{5,6'}$ = 5.6 Hz, H-6'), 2.72 (br, 1H, d, OH), 1.48 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), and 3,5-*O*-dibenzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (0.041 g, 10%), a syrup: ^{1}H NMR δ 7.25-7.31 (m, 10H, Ar-H), 5.91 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 4.67 (d, 1H, J = 11.6 Hz, ArCH), 4.63 (d, 1H, J = 12.0 Hz, $ArCH_2'$-H_a), 4.62 (d, 1H, H-2), 4.48 (d, 1H, $ArCH_2$ or $ArCH_2'$-H_b), 4.47 (d, 1H, $ArCH_2$ or $ArCH_2'$-H_b), 4.30 (dd, 1H, $J_{3,4}$ = 3.1 Hz, $J_{4,5}$ = 8.6 Hz, H-4), 4.11 (d, 1H, H-3), 3.77-3.95 (m, 3H, H-5, H-6, H-6'), 1.80 (br, 1H, OH), 1.49 (s, 3H, CH_3), 1.31 (s, 3H, CH_3).

Benzoylation of benzyl 2,3-O-isopropylidene-α-D-mannofuranoside.

Benzyl 2,3-*O*-isopropylidene-α-D-mannofuranoside (0.31 g, 1 mmol) and dibutyltin oxide (0.274 g, 1.1 mmol) were refluxed overnight in benzene (20 mL) with azeotropic removal of water. To this solution, at room temperature, was added a solution of benzoyl chloride (0.191 g, 1 mmol) in benzene (6 mL) and the mixture was

stirred at room temperature for half an hour. Standard work-up afforded a colourless solid which was recrystallized from ethyl acetate and hexane. Colourless crystalline benzyl 6-*O*-benzoyl-2,3-*O*-isopropylidene-α-D-mannofuranoside was obtained (0.290 g, 70%): mp 116-118 °C, ^{1}H NMR δ 7.25-8.08 (m, 10H, Ar-H), 5.14 (s, 1H, H-1), 4.91 (dd, 1H, $J_{2,3}$ = 5.9 Hz, $J_{3,4}$ = 3.6 Hz, H-3), 4.68 (d, 1H, H-2), 4.63 (dd, 1H, $J_{5,6}$ = 2.9 Hz, $J_{6,6'}$ = 11.7 Hz, H-6_a), 4.62 (d, 1H, $J_{ArCH,ArCH'}$ = 11.7 Hz, ArCH), 4.90 (dd, 1H, $J_{5,6'}$ = 6.6 Hz, H-6'), 4.46 (d, 1H, ArCH'), 4.32 (m, 1H, H-5), 4.06 (dd, 1H, H-4), 3.01 (d, 1H, $J_{OH,H-5}$ = 5.7 Hz, OH), 1.50 (s, 3H, CH_3), 1.34 (s, 3H, CH_3).

Benzoylation of 1,2-O-isopropylidene-α-D-glucofuranose (66).

To the solution of dibutylstannylene acetal **125** (1 mmol, prepared from compound **66** and dibutyltin oxide using the general method) in toluene (20 mL) was added benzoyl chloride (0.15 g, 1.05 mmol) in chloroform (7 mL) at -5°C with vigorous stirring. The cold bath was removed after 30 min and the mixture was kept at room temperature for 3 h. After work-up, recrystallization of obtained residue from ethyl acetate afforded 6-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose (0.250 g, 75%): mp 194-195 °C, lit.[156] mp 196 °C; ^{1}H NMR δ (DMSO-6_d) 7.51-8.03 (m, 5H, Ar-H), 5.82 (d, 1H, $J_{1,2}$ = 3.6, H-1), 5.32 (d, 1H, J = 5.0, OH), 5.23 (d, 1H, J = 5.7, OH), 4.47 (dd, 1H, $J_{5,6}$ = 1.9 Hz, $J_{6,6'}$ = 11.3 Hz, H-6), 4.42 (d, 1H, H-2), 4.20 (dd, 1H, $J_{5,6'}$ = 5.4 Hz, H-6'), 4 09 (dd, 1H, $J_{3,4}$ = 2.3 Hz, $J_{4,5}$ = 4.9 Hz, H-4), 4.04 (m, 1H, H-5), 4.02 (d, 1H, H-3), 1.37 (s, 3H, CH_3), 1.27 (s, 3H, CH_3).

Preparation of dialkylstannylene acetal samples for NMR spectroscopy

The mixture of a carbohydrate-derived diol (1 mmol) and dialkyltin oxide (1 mmol) was refluxed overnight in toluene (20 mL) with azeotropic removal of water. The solvent was removed under reduced pressure and the residue was dried under vacuum for one hour. Dry chloroform-*d* or toluene-d_8 (3 mL) was distilled through a vacuum line onto the stannylene acetal thus obtained. The chloroform-*d* solution was first filtered, under vacuum, into a pre-connected NMR tube through a bridge equipped with a sintered glass, and then the tube was sealed. ^{119}Sn and ^{13}C NMR data for dialkylstannylene acetals are listed in Tables 5.2, 5.3 and 5.4.

Chapter 6

Conclusions

Regioselectivity of p-toluenesulfonation of dialkylstannylene acetals.

For *p*-toluenesulfonation of carbohydrate-derived primary-secondary 1,2-diols through their dialkylstannylene acetals, the regioselectivity depended on the nature of the alkyl groups on tin atom, the solvent and temperature used for the reaction, as well as the inherent steric environment in the parent diols. Among all factors, the nature of the alkyl groups on tin had the greatest influence on regioselectivity for each diol.

Larger alkyl groups on tin increased the selectivity for reaction at secondary hydroxyl oxygen atoms. Diisopropyl- and diisobutylstannylene acetals gave higher selectivity for reaction at secondary oxygen atoms than did dibutylstannylene acetals. Dineopentylstannylene acetal also resulted in higher selectivity for reaction at secondary positions, however, the bulk of these groups caused the reaction to become extremely slow.

Hexamethylenestannylene acetals of carbohydrate-derived primary-secondary 1,2-diols gave good to excellent regioselectivity for *p*-toluenesulfonation at secondary oxygen atoms. In all cases, the hexamethylenestannylene acetals of primary-secondary 1,2-diols yielded secondary *p*-toluenesulfonates as major products, especially those derived from glucofuranose derivatives, **64** and **104**, where about 95% of the products were secondary *p*-toluenesulfonates. In contrast to the reactions with bulky dialkylstannylene derivatives, the reaction with these intermediates occurred at about

the same speed as with dibutylstannylene acetals. Therefore, hexamethylenestannylene acetals show great promise as intermediates to obtain reversed regioselectivity in electrophilic substitutions of carbohydrate-derived primary-secondary 1,2-diols.

At room temperature, dialkylstannylene acetals exist in chloroform-*d* solutions as single symmetric dimers to the detection limits of ^{119}Sn NMR spectroscopy. It was assumed that the symmetric dimers were primary-primary dimers based on consideration of steric effects. At low temperature, the dialkylstannylene acetals of glucofuranose derivatives were also present as single dimers, whereas the stannylene acetals of allofuranose derivatives showed a substantial amount of other oligomers.

The regioselectivity of *p*-toluenesulfonation of dialkylstannylene acetals was independent of the concentration of *p*-toluenesulfonyl chloride, but a higher concentration of *p*-toluenesulfonyl chloride increased the reaction rate. Based on kinetic considerations, it was concluded that *p*-toluenesulfonation of dialkylstannylene acetals occurred through a mechanism in which dimer-dimer equilibration occurred faster than reaction with *p*-toluenesulfonyl chloride.

Oxidation of dibutylstannylene acetals with N-bromosuccinimide.

N-Bromosuccinimide was a much better choice for the oxidation of dibutylstannylene acetals of primary-secondary 1,2-diols than bromine which had been often used for this purpose in the literature. Oxidation of dibutylstannylene acetals of carbohydrate-derived primary-secondary 1,2-diols (**64**, **104-106**) with NBS gave the corresponding α-hydroxyketone products in good yield (81-95%). No aldehyde

products were found in NBS oxidation of all the primary-secondary 1,2-diols studied in this thesis.

In comparison with the *p*-toluenesulfonation reaction, it was postulated that the oxidation reaction occurred through a steady-state mechanism in which the minor dimer led to product. This hypothesis explains the difference in regioselectivities between oxidation and substitution reactions of dialkylstannylene acetals for most literature results and for the results obtained here.

Dimerization of the α-hydroxyketone products occurred only where the steric effects in the monomeric molecules were not very large, such as for 3-*O*-deoxy derivative **110**. Other α-hydroxyketone products did not form dimers in observable amounts.

Preparation of hindered dialkytin(IV) derivatives.

Dialkyldiphenyltin derivatives (R_2Ph_2Sn) were easily prepared by reacting diphenyltin dichloride with excess Grignard reagent. The reaction gave excellent yield when R was acyclic (compounds **94a** to **94d**). However, a lower yield was obtained when use this method to prepare a cyclic compound, 1,1-diphenylstannacycloheptane (**94e**).

Cleavage of the two phenyl groups occurred in excellent yield on heating of the dialkyldiphenyltin derivatives (**94**) with two equivalent of chloroacetic acid, and the resulting dialkyltin(IV) bischloroacetates (**95**) were easily purified by a single recrystallization from hexane or dichloromethane-hexane. This method provide a

solution to the contamination of the dialkyltin(IV) derivatives by mono- and trialkyltin(IV) derivatives which was a recurring problem with other preparative methods. With this procedure, no difficulty was encountered in the preparation of sterically hindered compounds, such as dineopentyltin(IV) derivatives. Dialkyltin(IV) bischloroacetates were readily converted to the corresponding dialkyltin oxides by reaction with sodium oxide.

Stannacycloheptane bischloroacetate (**95e**) exists as monomer both in the crystal and in solution as determined by X-ray structural determination, ^{119}Sn NMR spectral experiments in solution and in the solid state.

Appendix

Crystal Structure of 1.1-Stannacycloheptane Bischloroacetate (95e)

A colourless hexagonal prismatic crystal of **95e** was mounted in a glass capillary on a Rigaku AFC5R diffractometer as summarized in Table A.1. Cell constants and an orientation matrix for data collection were obtained from a least-squares refinement using the setting angles of 19 carefully centered reflections in the range $40.33 < 2\theta < 44.38°$. Based on the systematic absences of: h00: $h \neq 2n$; 0k0: $k \neq 2n$; and 00l: $l \neq 2n$, and the successful solution and refinement of the structure, the space group was determined to be: $P2_12_12_1$. Of the 1517 reflections that were collected, 1516 were unique ($R_{int} = 0.056$). Lorentz, polarization, empirical absorption[157] and linear decay (27.0%) were applied to the data. The structure was solved by direct methods.[158] The non-hydrogen atoms were refined anisotropically. Four carbon atoms of the seven-membered ring are disordered; two positions of each (C6 and C6*, C7 and C7*, C8 and C8* and C9 and C9*) were located and refined with occupation factors of 0.5. The hydrogen atoms were placed in their geometrically calculated positions with a distance of C-H 1.08 Å; their positions and their temperature factors were refined isotropically. Neutral atom scattering factors were taken from Cromer and Waber.[159] Anomalous dispersion effects were included in Fcalc;[160] the values for $\Delta f'$ and $\Delta f''$ were those of Cromer.[161] All calculations were performed using SHELX 76.[162]

Representations of the full X-ray structure with positions of disordered atoms

of compound **95e** are given in Figures A.1 and A.2. For supplemental X-ray data of compound **95e**, see Tables A.2 to A.6.

Table A.1 Summary of crystallographic data for 1,1-stannacycloheptane bischloroacetate (**95e**)

molecular formula	$C_{10}H_{16}O_4Cl_2Sn$
formula weight	389.83
crystal colour, habit	colourless, hexagonal prism
crystal dimensions (mm)	0.45 x 0.40 x 0.35
crystal system	orthorhombic
space group	$P2_12_12_1$
a, Å	10.405 (2)
b, Å	17.990 (2)
c, Å	7.752 (2)
V, Å^3	1451.2 (5)
Z	4
D(calcd), g/cm^3	1.784
F(000)	768
diffractometer	Rigaku AFC5R
monochromator	graphite
temperature	18 °C
radiation	MoKα (λ = 0.71069 Å)
μ, cm^{-1}	21.37
scan type	ω-2θ
scan rate	8.0°/m (in omega)
2θ limit, deg	50
scan width	(1.78 + 0.35 tan θ)°
unique reflections measured	1516
observed data (I >3.00σ(I))	1134
no. of variables	218
$R = \Sigma\|Fo\| - \|Fc\| / \Sigma\|Fo\|$	0.0241
$R_w = [(\Sigma w (\|Fo\| - \|Fc\|)^2 / \Sigma wFo^2]^{1/2}$	0.0241
goodness of fit	1.132
max and min peaks in final diff. map	0.305 e-/Å^3, -0.323 e-/Å^3

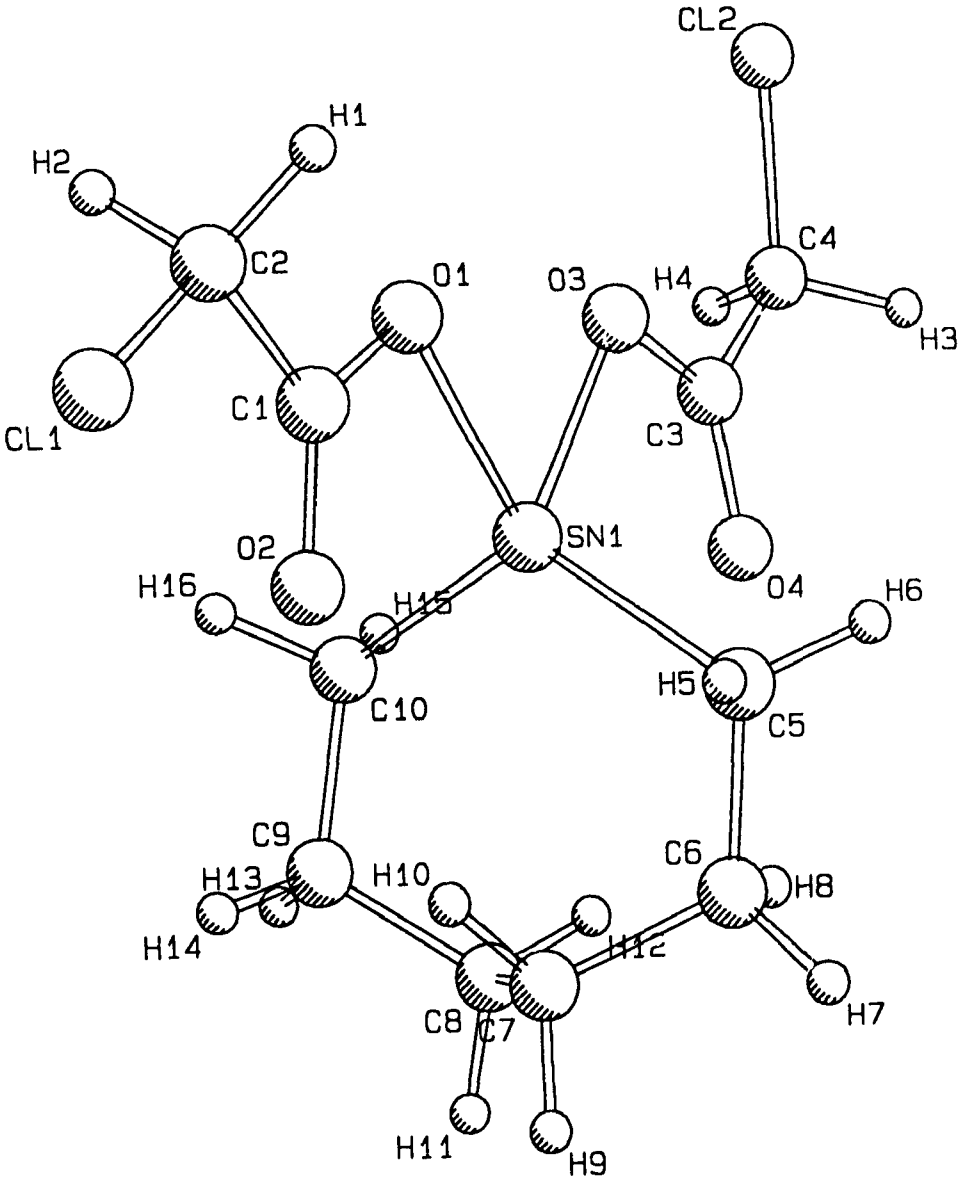


Figure A.1 The X-ray structure of 1,1-stannacycloheptane bischloroacetate **(95e)**: position 1 of disordered atoms

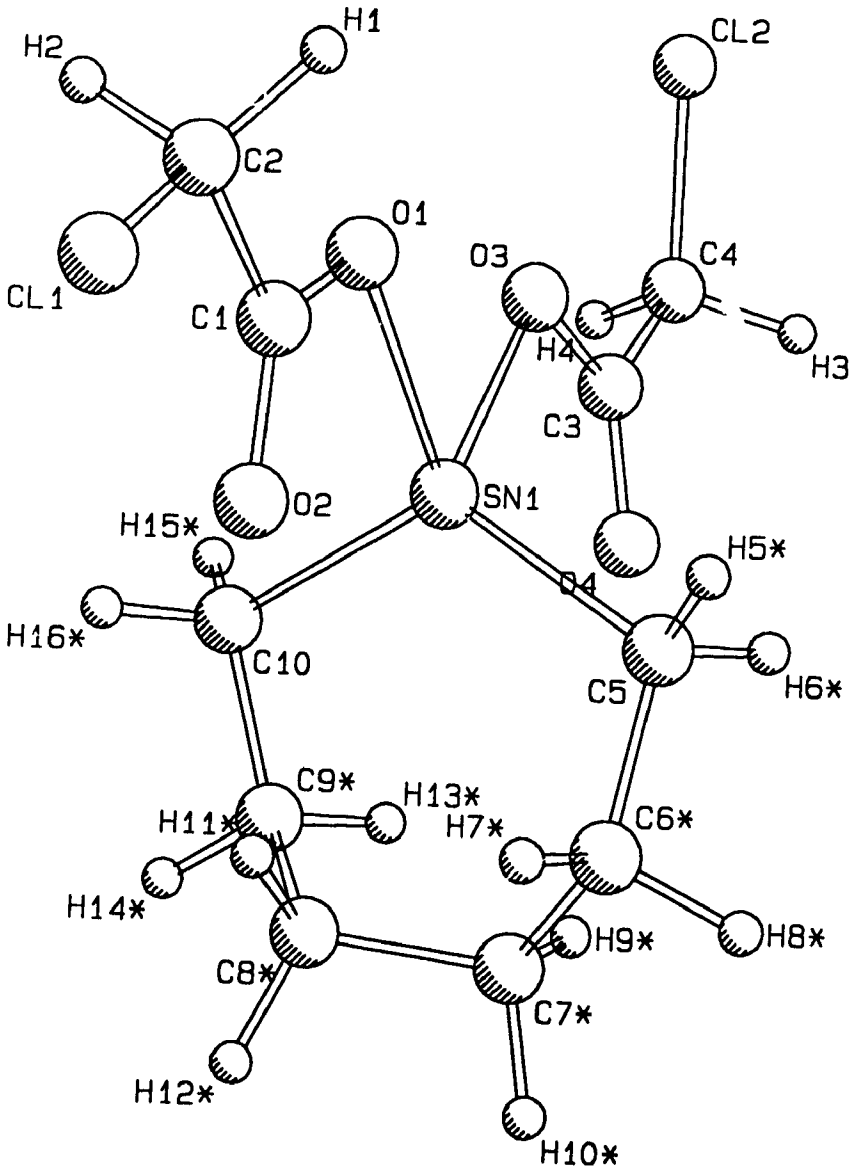


Figure A.2 The *X*-ray structure of 1,1-stannacycloheptane bischloroacetate (**95e**): position 2 of disordered atoms

Table A.2 Fractional atomic positional parameters and equivalent isotropic temperature factors ($Å^2$) for 1,1-stannacycloheptane bischloroacetate (**95e**)

	x/a	y/b	z/c	Ueq
Sn1	0.00581(4)	0.67456(2)	0.09638(6)	0.0450
Cl1	0.3946 (2)	0.4870 (1)	-0.0232 (3)	0.0867
Cl2	0.0439 (2)	0.8801 (1)	0.5277 (3)	0.0905
O1	0.1877 (4)	0.6431 (2)	0.1837 (5)	0.0482
O2	0.1411 (4)	0.5605 (2)	-0.0153 (7)	0.0614
O3	0.0259 (5)	0.7553 (2)	0.2864 (6)	0.0600
O4	-0.1554 (6)	0.7885 (3)	0.1611 (8)	0.0932
C1	0.2169 (6)	0.5861 (3)	0.0919 (9)	0.0438
C2	0.3475 (6)	0.5555 (4)	0.1252 (10)	0.0537
C3	-0.0757 (8)	0.7979 (4)	0.2737 (10)	0.0646
C4	-0.0932 (8)	0.8598 (5)	0.4016 (12)	0.0894
C5	0.0117 (8)	0.7169 (3)	-0.1580 (8)	0.0689
C6	-0.1145 (11)	0.6945 (7)	-0.2506 (17)	0.0668
C6*	-0.0604 (13)	0.6708 (9)	-0.2913 (15)	0.0933
C7	-0.1498 (12)	0.6121 (7)	-0.2350 (16)	0.0626
C7*	-0.1958 (13)	0.6482 (10)	-0.2487 (22)	0.1108
C8	-0.2610 (11)	0.6112 (9)	-0.1035 (16)	0.0709
C8*	-0.2104 (19)	0.5813 (9)	-0.1292 (17)	0.1096
C9	-0.2262 (15)	0.5633 (7)	0.0506 (16)	0.0879
C9*	-0.2515 (12)	0.6027 (11)	0.0526 (16)	0.0939
C10	-0.1397 (7)	0.6019 (5)	0.1804 (10)	0.0707

Table A.3 Hydrogen atom positional parameters (Å) for 1,1-stannacycloheptane bischloroacetate (**95e**)

Atom	x/a	y/b	z/c	U(iso)
H1	0.417 (1)	0.600 (0)	0.122 (1)	0.067 (4)
H2	0.346 (1)	0.531 (0)	0.252 (1)	0.061 (4)
H3	-0.117 (1)	0.910 (1)	0.331 (1)	0.083 (4)
H4	-0.172 (1)	0.845 (1)	0.486 (1)	0.076 (4)
H5	0.092 (1)	0.694 (0)	-0.228 (1)	0.062 (4)
H6	0.019 (1)	0.777 (0)	-0.154 (1)	0.063 (4)
H5*	0.111 (1)	0.720 (0)	-0.199 (1)	0.058 (4)
H6*	-0.028 (1)	0.772 (0)	-0.153 (1)	0.062 (4)
H7	-0.108 (1)	0.708 (1)	-0.386 (2)	0.054 (4)
H8	-0.192 (1)	0.726 (1)	-0.193 (2)	0.046 (4)
H7*	-0.004 (1)	0.622 (1)	-0.324 (2)	0.062 (4)
H8*	-0.069 (1)	0.706 (1)	-0.403 (2)	0.058 (4)
H9	-0.180 (1)	0.590 (1)	-0.358 (2)	0.060 (4)
H10	-0.068 (1)	0.581 (1)	-0.188 (2)	0.059 (4)
H9*	-0.246 (1)	0.694 (1)	-0.188 (2)	0.061 (4)
H10*	-0.244 (1)	0.634 (1)	-0.368 (2)	0.058 (4)
H11	-0.344 (1)	0.588 (1)	-0.166 (2)	0.050 (4)
H12	-0.282 (1)	0.667 (1)	-0.064 (2)	0.059 (4)
H11*	-0.118 (2)	0.555 (1)	-0.122 (2)	0.068 (4)
H12*	-0.280 (2)	0.543 (1)	-0.181 (2)	0.069 (4)
H13	-0.316 (2)	0.553 (1)	0.117 (2)	0.066 (4)
H14	-0.184 (2)	0.511 (1)	0.010 (2)	0.061 (4)
H13*	-0.290 (1)	0.658 (1)	0.048 (2)	0.061 (4)
H14*	-0.326 (1)	0.565 (1)	0.094 (2)	0.065 (4)
H15	-0.198 (1)	0.634 (1)	0.269 (1)	0.050 (4)
H16	-0.092 (1)	0.558 (1)	0.250 (1)	0.067 (4)
H15*	-0.175 (1)	0.620 (1)	0.304 (1)	0.053 (4)
H16*	-0.102 (1)	0.546 (1)	0.192 (1)	0.063 (4)

Table A.4 Anisotropic temperature factors ($Å^2$) for 1,1-stannacycloheptane bischloroacetate (**95e**)

Atom	U11	U22	U33	U23	U13	U12
Sn1	0.0452(2)	0.0446(2)	0.0454(2)	-0.0001(2)	-0.0031(3)	0.0014(3)
Cl1	0.0775(14)	0.1067(17)	0.0760(13)	-0.0366(13)	-0.0126(12)	0.0394(13)
Cl2	0.1046(18)	0.0884(15)	0.0785(13)	-0.0315(12)	0.0225(13)	-0.0055(13)
O1	0.050 (2)	0.049 (2)	0.046 (2)	-0.005 (2)	-0.002 (2)	0.007 (2)
O2	0.051 (3)	0.069 (3)	0.064 (3)	-0.017 (3)	-0.017 (2)	0.010 (2)
O3	0.064 (3)	0.054 (2)	0.062 (3)	-0.006 (2)	-0.003 (3)	0.008 (3)
O4	0.081 (3)	0.111 (3)	0.087 (3)	-0.021 (3)	-0.024 (3)	0.037 (3)
C1	0.051 (3)	0.041 (3)	0.039 (3)	0.004 (3)	-0.001 (3)	0.003 (3)
C2	0.043 (3)	0.063 (3)	0.056 (3)	-0.009 (3)	-0.006 (3)	0.008 (3)
C3	0.076 (4)	0.064 (4)	0.054 (3)	-0.003 (3)	0.001 (3)	0.018 (3)
C4	0.096 (4)	0.094 (4)	0.078 (4)	-0.024 (4)	0.003 (4)	0.044 (4)
C5	0.084 (4)	0.065 (3)	0.058 (3)	0.009 (3)	0.007 (4)	0.012 (4)
C6	0.072 (4)	0.077 (4)	0.051 (4)	-0.021 (4)	0.005 (4)	0.027 (4)
C6*	0.147 (5)	0.086 (4)	0.047 (4)	-0.014 (4)	0.018 (4)	0.027 (5)
C7	0.046 (4)	0.094 (4)	0.048 (4)	-0.025 (4)	-0.009 (4)	-0.005 (4)
C7*	0.091 (5)	0.117 (5)	0.124 (5)	-0.016 (5)	-0.043 (5)	0.024 (5)
C8	0.048 (4)	0.098 (4)	0.066 (4)	0.021 (4)	-0.027 (4)	0.003 (4)
C8*	0.115 (5)	0.087 (5)	0.126 (5)	-0.022 (5)	-0.051 (5)	0.010 (5)
C9	0.082 (4)	0.068 (4)	0.113 (5)	-0.008 (4)	-0.006 (5)	-0.006 (4)
C9*	0.078 (4)	0.093 (5)	0.111 (5)	-0.005 (5)	-0.004 (4)	-0.041 (4)
C10	0.052 (3)	0.082 (4)	0.078 (4)	0.015 (4)	0.004 (3)	-0.006 (3)

Table A.5 Heavy Atom Bond Angles (°) for 1,1-stannacycloheptane bischloroacetate (**95e**).

Atoms	Bond Angle	Atoms	Bond Angle
O(1)-Sn(1)-O(2)	53.9 (2)	O(1)-Sn(1)-O(3)	82.4 (2)
O(1)-Sn(1)-O(4)	135.2 (2)	O(1)-Sn(1)-C(3)	109.7 (2)
O(1)-Sn(1)-C(5)	111.9 (2)	O(1)-Sn(1)-C(10)	112.6 (3)
O(2)-Sn(1)-O(3)	136.3 (2)	O(2)-Sn(1)-O(4)	170.3 (2)
O(2)-Sn(1)-C(3)	163.6 (2)	O(2)-Sn(1)-C(5)	87.6 (2)
O(2)-Sn(1)-C(10)	90.1 (3)	O(3)-Sn(1)-O(4)	53.1 (2)
O(3)-Sn(1)-C(1)	109.7 (2)	O(3)-Sn(1)-C(5)	113.9 (3)
O(3)-Sn(1)-C(10)	106.7 (3)	O(4)-Sn(1)-C(1)	162.2 (2)
O(4)-Sn(1)-C(5)	85.3 (2)	O(4)-Sn(1)-C(10)	88.1 (3)
C(1)-Sn(1)-C(3)	137.0 (2)	C(1)-Sn(1)-C(5)	100.1 (3)
C(1)-Sn(1)-C(10)	102.9 (3)	C(3)-Sn(1)-C(5)	100.6 (3)
C(3)-Sn(1)-C(10)	97.2 (3)	C(5)-Sn(1)-C(10)	122.2 (3)
Sn(1)-O(1)-C(1)	104.5 (4)	Sn(1)-O(2)-C(1)	80.2 (4)
Sn(1)-O(3)-C(3)	105.9 (5)	Sn(1)-O(4)-C(3)	79.3 (5)
Sn(1)-C(1)-O(1)	48.2 (3)	Sn(1)-C(1)-O(2)	73.2 (4)
Sn(1)-C(1)-C(2)	162.5 (5)	O(1)-C(1)-O(2)	121.4 (6)
O(1)-C(1)-C(2)	114.5 (6)	O(2)-C(1)-C(2)	124.1 (6)
Cl(1)-C(2)-C(1)	113.6 (5)	Sn(1)-C(3)-O(3)	46.8 (4)
Sn(1)-C(3)-O(4)	74.9 (5)	Sn(1)-C(3)-C(4)	165.3 (6)
O(3)-C(3)-O(4)	121.6 (8)	O(3)-C(3)-C(4)	118.8 (7)
O(4)-C(3)-C(4)	119.6 (8)	Cl(2)-C(4)-C(3)	114.8 (7)
Sn(1)-C(5)-C(6)	108.3 (6)	C(5)-C(6)-C(7)	114.7 (10)
C(6)-C(7)-C(8)	104.0 (10)	C(7)-C(8)-C(9)	110.3 (11)
C(8)-C(9)-C(10)	113.8 (11)	Sn(1)-C(10)-C(9)	120.4 (7)
Sn(1)-C(5)-C(6*)	114.9 (7)	C(5)-C(6*)-C(7*)	117.4 (12)
C(6*)-C(7*)-C(8*)	116.1 (14)	C(7*)-C(8*)-C(9*)	113.0 (13)
C(8*)-C(9*)-C(10)	112.6 (12)	Sn(1)-C(10)-C(9*)	110.0 (7)

Table A.6 Heavy Atom Torsional Angles (°) for 1,1-stannacycloheptane bischloroacetate (**95e**)

Atoms	Torsional Angle	Atoms	Torsional Angle
O(1)-Sn(1)-O(2)-C(1)	-1.2 (4)	O(2)-Sn(1)-O(1)-C(1)	1.2 (4)
O(1)-Sn(1)-O(3)-C(3)	175.9 (5)	O(3)-Sn(1)-O(1)-C(1)	178.7 (4)
O(1)-Sn(1)-O(4)-C(3)	-10.0 (6)	O(4)-Sn(1)-O(1)-C(1)	-174.7 (4)
O(1)-Sn(1)-C(3)-O(3)	-4.3 (5)	O(1)-Sn(1)-C(3)-O(4)	172.6 (5)
O(1)-Sn(1)-C(3)-C(4)	-16.1 (25)	C(3)-Sn(1)-O(1)-C(1)	-179.3 (4)
O(1)-Sn(1)-C(5)-C(6)	146.0 (6)	C(5)-Sn(1)-O(1)-C(1)	-68.4 (5)
O(1)-Sn(1)-C(10)-C(9)	-123.0 (8)	C(10)-Sn(1)-O(1)-C(1)	73.8 (5)
O(2)-Sn(1)-O(3)-C(3)	178.7 (4)	O(3)-Sn(1)-O(2)-C(1)	-4.7 (5)
O(2)-Sn(1)-O(4)-C(3)	-169.5 (10)	O(4)-Sn(1)-O(2)-C(1)	161.1 (10)
O(2)-Sn(1)-C(3)-O(3)	-3.1 (11)	O(2)-Sn(1)-C(3)-O(4)	173.8 (6)
O(2)-Sn(1)-C(3)-C(4)	-14.9 (30)	C(3)-Sn(1)-O(2)-C(1)	-2.6 (9)
O(2)-Sn(1)-C(5)-C(6)	96.7 (6)	C(5)-Sn(1)-O(2)-C(1)	118.3 (4)
O(2)-Sn(1)-C(10)-C(9)	-72.5 (8)	C(10)-Sn(1)-O(2)-C(1)	-119.4 (5)
O(3)-Sn(1)-O(4)-C(3)	-1.8 (5)	O(4)-Sn(1)-O(3)-C(3)	1.7 (5)
O(3)-Sn(1)-C(1)-O(1)	-1.3 (5)	O(3)-Sn(1)-C(1)-O(2)	176.6 (4)
O(3)-Sn(1)-C(1)-C(2)	-10.1 (17)	C(1)-Sn(1)-O(3)-C(3)	176.5 (5)
O(3)-Sn(1)-C(5)-C(6)	-122.6 (6)	C(5)-Sn(1)-O(3)-C(3)	65.2 (5)
O(3)-Sn(1)-C(10)-C(9)	148.4 (8)	C(10)-Sn(1)-O(3)-C(3)	-72.7 (5)
O(4)-Sn(1)-C(1)-O(1)	12.4 (9)	O(4)-Sn(1)-C(1)-O(2)	-169.7 (5)
O(4)-Sn(1)-C(1)-C(2)	3.6 (21)	C(1)-Sn(1)-O(4)-C(3)	-18.0 (9)
O(4)-Sn(1)-C(5)-C(6)	-76.7 (6)	C(5)-Sn(1)-O(4)-C(3)	-126.6 (5)
O(4)-Sn(1)-C(10)-C(9)	98.0 (8)	C(10)-Sn(1)-O(4)-C(3)	110.8 (6)
C(1)-Sn(1)-C(3)-O(3)	-4.8 (7)	C(1)-Sn(1)-C(3)-O(4)	172.1 (4)
C(1)-Sn(1)-C(3)-C(4)	-16.6 (26)	C(3)-Sn(1)-C(1)-O(1)	1.0 (6)
C(3)-Sn(1)-C(1)-O(2)	178.9 (4)	C(3)-Sn(1)-C(1)-C(2)	-7.7 (18)
C(1)-Sn(1)-C(5)-C(6)	120.3 (6)	C(5)-Sn(1)-C(1)-O(1)	118.8 (4)
C(5)-Sn(1)-C(1)-O(2)	-63.3 (4)	C(5)-Sn(1)-C(1)-C(2)	110.0 (16)
C(1)-Sn(1)-C(10)-C(9)	-96.2 (8)	C(10)-Sn(1)-C(1)-O(1)	-114.6 (4)
C(10)-Sn(1)-C(1)-O(2)	63.3 (5)	C(10)-Sn(1)-C(1)-C(2)	-123.3 (16)
C(3)-Sn(1)-C(5)-C(6)	-97.6 (6)	C(5)-Sn(1)-C(3)-O(3)	-122.4 (5)
C(5)-Sn(1)-C(3)-O(4)	54.5 (5)	C(5)-Sn(1)-C(3)-C(4)	-134.2 (24)
C(3)-Sn(1)-C(10)-C(9)	122.2 (8)	C(10)-Sn(1)-C(3)-O(3)	112.8 (5)
C(10)-Sn(1)-C(3)-O(4)	-70.3 (5)	C(10)-Sn(1)-C(3)-C(4)	101.0 (25)
C(5)-Sn(1)-C(10)-C(9)	14.8 (9)	C(10)-Sn(1)-C(5)-C(6)	8.0 (7)

(continued on next page)

(*Table A.6 continued*)

Sn(1)-O(1)-C(1)-O(2)	-2.4 (7)	Sn(1)-O(1)-C(1)-C(2)	177.1 (5)
Sn(1)-O(2)-C(1)-O(1)	1.8 (6)	Sn(1)-O(2)-C(1)-C(2)	-177.6 (7)
Sn(1)-O(3)-C(3)-O(4)	-3.5 (9)	Sn(1)-O(3)-C(3)-C(4)	176.6 (6)
Sn(1)-O(4)-C(3)-O(3)	2.7 (8)	Sn(1)-O(4)-C(3)-C(4)	-177.5 (8)
Sn(1)-C(1)-C(2)-Cl(1)	-163.7 (7)	O(1)-C(1)-C(2)-Cl(1)	-170.9 (4)
O(2)-C(1)-C(2)-Cl(1)	8.6 (7)	Sn(1)-C(3)-C(4)-Cl(2)	22.6 (19)
O(3)-C(3)-C(4)-Cl(2)	12.9 (9)	O(4)-C(3)-C(4)-Cl(2)	-167.0 (5)
Sn(1)-C(5)-C(6)-C(7)	-49.5 (10)	C(5)-C(6)-C(7)-C(8)	105.2 (9)
C(6)-C(7)-C(8)-C(9)	-121.2 (11)	C(7)-C(8)-C(9)-C(10)	79.9 (12)
C(8)-C(9)-C(10)-Sn(1)	-37.2 (10)	O(1)-Sn(1)-C(5)-C(6*)	115.4 (7)
O(1)-Sn(1)-C(10)-C(9*)	-152.7 (7)	O(2)-Sn(1)-C(5)-C(6*)	66.1 (7)
O(2)-Sn(1)-C(10)-C(9*)	-102.3 (7)	O(3)-Sn(1)-C(5)-C(6*)	-153.2 (7)
O(3)-Sn(1)-C(10)-C(9*)	118.7 (7)	O(4)-Sn(1)-C(5)-C(6*)	-107.3 (8)
O(4)-Sn(1)-C(10)-C(9*)	68.2 (7)	C(1)-Sn(1)-C(5)-C(6*)	89.8 (8)
C(1)-Sn(1)-C(10)-C(9*)	-125.9 (7)	C(3)-Sn(1)-C(5)-C(6*)	-128.1 (7)
C(3)-Sn(1)-C(10)-C(9*)	92.4 (8)	C(5)-Sn(1)-C(10)-C(9*)	-15.0 (8)
C(10)-Sn(1)-C(5)-C(6*)	-22.6 (9)	Sn(1)-C(5)-C(6*)-C(7*)	49.4 (13)
C(5)-C(6*)-C(7*)-C(8*)	-80.3 (14)	C(6*)-C(7*)-C(8*)-C(9*)	105.9 (13)
C(7*)-C(8*)-C(9*)-C(10	-101.9 (12)	C(8*)-C(9*)-C(10)-Sn(1)	57.7 (10)

References and Notes:

1. D. Wagner, J. Verheyden, and J. G. Moffatt, *J. Org. Chem.*, **39**, 24 (1974).

2. S. David, *C. R. Acad. Sci. Ser., C*, **278**, 1051 (1974).

3. (a) S. David and S. Hanessian, *Tetrahedron*, **41**, 643 (1985); (b) M. Pereyre, J. P. Quintard, and A. Rahm, *Tin in organic synthesis*, Butterworths, London, 1987. Chap. 11; (c) S. J. Blunden, P. A. Cusack, and P. J. Smith, *J. Organomet. Chem.*, **325**, 141 (1987).

4. (a) T. W. Greene, *Protective Groups in Organic Synthesis*; Wiley-Interscience: New York, 1981; p 50; (b) A. H. Haines, *Adv. Carbohydr. Chem. Biochem.*, **33**, 11 (1976).

5. T. B. Grindley and R. Thangarasa, *Can. J. Chem.*, **68**, 1007 (1990).

6. A. G. Davies, *Organotin Compounds* (Edited by A. K. Sawyer), Vol. I, Chap. 4, Marcel Dekker, New York (1971).

7. J. Alais, A. Maranduba, and A. Veyrieres, *Tetrahedron Lett.*, **24**, 2383 (1983).

8. M. W. Bredenkamp, H. M. Flowers, and C. W. Holzapfel, *Chem. Ber.*, **125**, 1159 (1992).

9. A. Shanzer, J. Libman, and H. E. Gottlieb, *J. Org. Chem.*, **48**, 4612 (1983).

10. C. Luchinat and S. Roelens, *J. Am. Chem. Soc.*, **108**, 4873 (1986).

11. A. Shanzer, *Tetrahedron Lett.*, **21**, 221 (1980).

12. (a) N. Nagashima and M. Ohno, *Chem. Pharm. Bull.*, **39**, 1972 (1991); (b) N. Nagashima and M. Ohno, *Chem. lett.*, 141 (1987).

13. S. David and A. Thieffry, *J. Chem. Soc., Perkin 1*, 1568 (1979).

14. (a) G. Reginato, A. Ricci, S. Roelens, and S. Scapecchi, *J. Org. Chem.*, **55**, 5132 (1990); (b) A. Ricci, S. Roelens, and A. Vannucchi, *J. Chem. Soc., Chem. Commun.*, 1457 (1985).

15. (a) O. M. O. Habib and J. Malek, *Coll. Czech. Chem. Commun.*, **41**, 2724 (1976); (b) L. Nondek and J. Malek, *Makromol. Chem.*, **178**, 2211 (1977); (c) L. Nondek and J. Malek, *Coll. Czech. Chem. Commun.*, **43**, 424 (1978).

16. K. Stelio:, A. Szcygielska-Nowosielska, A. Favre, M. A. Poupart, and S. Hanessian, *J. Am. Chem. Soc.*, **192**, 7578 (1980).

17. (a) A. Shanzer, J. Libman, H. E. Gottlieb, and F. Frolow, *J. Am. Chem. Soc.*, **104**, 4220 (1982); (b) A. Shanzer, N. Mayer-Shochet, F. Frolow, and D. Rabinoich, *J. Org. Chem.*, **46**, 4662 (1981).

18. M. M. Basson, M. W. Bredenkamp, and C. W. Holzapfel, *Tetrahedron Lett.*, **30**, 591 (1989).

19. (a) S. Roelens, *J. Chem, Soc., Perkin 2.*, 1617 (1988); (b) A. Mordini and S. Roelens, *J. Org. Chem.*, **54**, 2643 (1989); (c) L. Mandolini, G. Montaudo, E. Scamporrino, S. Roelens. and D. Vitalini, *Macromolecules*, **22**, 3275 (1989).

20. R. Thangarasa, Ph.D Thesis, Dalhousie Univ., 1990.

21. A. H. Haines, *Adv. Carbohydr. Chem. Biochem.*, **33**, 11 (1976).

22. Y. Tsuda, M. Nishimura, T. Kobayashi, Y. Sato, and K. Kanemitsu, *Chem. Pharm. Bull.*, **39**, 2883 (1991).

23. C. W. Holzapfel, J. M. Koekemoer, and C. F. Marais, *S. Afr. J. Chem.*, **37**, 19 (1984).

24. M. K. Gurjar and U. K. Saha, *Tetrahedron Lett.*, **33**, 4979 (1992).

25. M. K. Gurjar and A. S. Mainkar, *Tetrahedron*, **48**, 6729 (1992).

26. R. L. Halcomb, S. H. Boyer, and S. J. Danishefsky, *Angew. Chem., Int. Ed. Engl.*, **31**, 338 (1992).

27. J. F. Marecek and G. D. Prestwich, *Tetrahedron Lett.*, **32**, 1863 (1991).

28. D. A. Sawyer and B. V. L. Potter, *J. Chem. Soc., Perkin 1*, 923 (1991).

29. D. Lampe, S. J. Molls, and B. V. L. Potter, *J. Chem. Soc., Perkin 1*, 2899 (1991).

30. L. Chahoua, M. Baltas, L. Gorrichon, P. Tisnes, and C. Zedde, *J. Org. Chem.*, **57**, 5798 (1992).

31. E. A. Mash and S. K. Nimkar, *Tetrahedron Lett.*, **34**, 385 (1993).

32. S.-H. Chen and S. J. Danishefsky, *Tetrahedron Lett.*, **31**, 2229 (1990).

33. C. G. P. H. Boons, F. L. van Delft, P. A. M. van der Klein, G. A. van der Marel, and J. H. van Boom, *Tetrahedron*, **48**, 885 (1992).

34. P. A. M. van der Klein, W. Filemon, C. G. P. H. Boons, G. H. Veeneman. G. A. van der Marel, and J. H. van Boom, *Tetrahedron*, **48**, 4649 (1992).

35. F.-I. Auzanneau, D. Charon, L. Szilagyi, and L. Szabo, *J. Chem. Soc., Perkin 1*, 803 (1991).

36. R. S. Coleman and J. R. Fraser, *J. Org. Chem.*, **58**, 385 (1993).

37. S. David, A. Thieffry, and A. Forchioni, *Tetrahedron Lett.*, **22**, 2647 (1981).

38. T. B. Grindley and R. Thangarasa, *J. Am. Chem. Soc.*, **112**, 1364 (1990).

39. K. L. Yu and B. Fraser-Reid, *Tetrahedron Lett.*, **29**, 979 (1988).

40. V. Pedreti, A. Veyrires, and P. Sinay, *Tetrahedron*, **46**, 77 (1990).

41. R. F. Helm, J. Ralpha, and L. Anderson, *J. Org. Chem.*, **56**, 7015 (1991).

42. S.-H. Chen, R. F. Horvath, J. Joglar, M. J. Fisher, and S. J. Danishefsky, *J. Org. Chem.*, **56**, 5834 (1991).

43. M. W. Bredenkamp, C. W. Holzapfel, and F. Toerien, *Synth. Commun.*, **22**, 2459 (1992).

44. A. Villalobos and S. Danishefsky, *J. Org. Chem.*, **55**. 2776 (1990).

45. S.-I. Nishimura, S. Murayama, K. Kurita, and H. Kuzuhara, *Chem. Lett.*, 1413 (1992).

46. H. Qin and T. B. Grindley, *J. Carbohydr. Chem.*, accepted.

47. K. Kiyoshima, M. Sacamoto, T. Ishikura, Y. Fukagawa, T. Yoshioka, H. Naganawa, T. Sawa, and T. Takeuchi, *Chem. Pharm. Bull.*, **37**, 861 (1989).

48. J. Thiem and H.-P. Wessel, *Liebigs Ann. Chem.*, 2173 (1983).

49. S. David and G. De Sennyey, *Carbohydr. Res.*, 77, 79 (1979).

50. M. H. Kim, J. W. Yang, B. J. Lee, H. O. Kim and M. W. Chun, *Soul Taehakkyo Yakhak Nonmunjip.*, **11**, 71 (1986), *CA* **109**, 55069d.

51. (a) F. Bauer, K.-P. Rueβ, and M. Liefländer, *Liebigs Ann. Chem.*, 756 (1991); (b) F. Aragozzini, E. Maconi, D. Potenza and C. Scolastico, *Synthesis*, 225 (1989).

52. (a) A. Duréault, M. Portal, and J. C. Depeazy, *Synlett.*, 225 (1991); (b) M. Marzi and D. Misti, *Tetrahedron Lett.*, **30**, 6075 (1989).

53. V. Gopalakrishnan, H. Mereyala, A. G. Samuel, and K. N. Ganesh, *Tetrahedron Lett.*, **31**, 1613 (1990).

54. A. Grouiller, V. Buet, V. Uteza, and G. Descotes, *Synlett.*, 221 (1993).

55. M. W. Bredenkamp, C. W. Holzapfel, and A. D. Swanepoel, *Tetrahedron Lett.*, **31**, 2759 (1990).

56. (a) J. L. Navia. **Eur. Pat. Appl. EP 352,084** (Cl. C07H13/04), 24 Jan 1990, *CA.* **113**, 78895s; (b) R. E. Walkup, N. M. Vernon, and R. E. Wingard Jr. **Eur. Pat. Appl. EP 448,431** (Cl. C07H13/04), 25 Sep 1991, *CA.* **115**, 280470w.

57. Y. Tsuda, M. Hanajima, N. Matsuhira, Y. Okuno, and K. Kanemitsu, *Chem. Pharm. Bull.*, **37**, 2344 (1989).

58. A. B. Reitz and E. W. Baxter, *Tetrahedron Lett.*, **31**, 6777 (1990).

59. A. Fernandez-Mayoralas, M. Bernabe, and M. Martin-Lomas, *Tetrahedron*, **44**, 4877 (1988).

60. R. Tsang and B. Fraser-Reid, *J. Org. Chem.*, **57**, 1065 (1992).

61. (a) Y. Tsuda, Y. Okuno, M. Iwaki, and K. Kanemitsu, *Heterocycles*, **27**, 63 (1988); (b) Y. Tsuda, Y. Okuno, M. Iwaki, and K. Kanemitsu, *Chem. Pharm. Bull.*, **37**, 2673 (1989); (c) Y. Tsuda and H.-M. Liu, *Chem. Pharm. Bull.*, **40**, 1975 (1992).

62. J. L. Marco-Contelles, C. Fernandez, N. Martin-Leon, and B. Fraser-Reid, *Synlett.*, 167 (1990).

63. A. G. Davies, A. J. Price, H. M. Dawes, and M. B. Hursthouse, *J. Chem. Soc., Dalton Trans*, 297 (1986).

64. P. A. Bates, M. B. Hursthouse, A. G. Davies, and S. D. Slater, *J. Organomet. Chem.*, **363**, 45 (1989).

65. T. B. Grindley, R. E. Wasylishen, R. Thangarasa, W. P. Power, and R. D. Curtis, *Can. J. Chem.*, **70**, 205 (1992).

66. S. David, C. Pascard, and M. Cesario, *Nov. J. Chim.* **3**, 63 (1979).

67. T. S. Cameron, P. K. Bakshi, R. Thangarasa, and T. B. Grindley, *Can. J. Chem.*, **70**, 1623 (1992).

68. T. B. Grindley, R. D. Curtis, R. Thangarasa, and R. E. Wasylishen, *Can. J. Chem.*, **68**, 2102 (1990).

69. C. W. Holzapfel, J. M. Koekemoer, C. F. Marais, G. J. Kruger, and J. A. Pretorius, *S. Afr. J. Chem.*, **35**, 80 (1982).

70. B. Wrackmeyer, *Ann. Rep. NMR Spectrosc.*, **16**, 73 (1985).

71. R. Thangarasa and T. B. Grindley, *Organometallics*, in preparation.

72. T. B. Grindley, R. Thangarasa, P. K. Bakshi, and T. S. Cameron, *Can. J. Chem.*, **70**, 197 (1992).

73. S. David, A. Thieffry, and A. Veyrieres, *J. Chem. Soc., Perkin 1*, 1796 (1981).

74. P. K. Bakshi, T. S. Cameron, R. Thangarasa, and T. B. Grindley, unpublished results.

75. (a) R. C. Poller, *Chemistry of Organotin Compounds*, Logos Press: London, 1970; (b) *Chemistry of Tin*, P. G. Harrison Ed. Blackie: Glasgow and London, 1989; (c) A. G. Davies and P. J. Smith, In *Comprehensive Organometallic Chemistry*, G. Wilkinson Ed, Pergamon Press: Oxford, 1982; Vol. 2, Ch. 11.

76. H. Zimmer, I. Hechenbleikner, O. A. Homberg, and M. Danzik, *J. Org. Chem.*, **29**, 2632 (1964).

77. R. H. Prince, *J. Chem. Soc.*, 1783 (1959).

78. W. T. Reichle, *Inorg. Chem.*, **5**, 87 (1966).

79. P. Brown, M. F. Mahon, and K. C. Molloy, *J. Chem. Soc., Dalton Trans.*, 2643 (1990).

80. H. Zimmer, C. W. Blewett, and A. Brakas, *Tetrahedron Lett.*, 1615 (1968).

81. A. G. Davies, M.-W. Tse, J. D. Kennedy, W. McFarlane, G. S. Pyne, M. F. C. Ladd, and D. C. Povey, *J. Chem. Soc., Perkin Trans. II*, 369 (1981).

82. R. K. Ingraham, S. D. Rosenburg, and H. Gilman, *Chem. Rev.*, **60**, 459 (1960).

83. G. S. Sasin, A. L. Borror, and R. Sasin, *J. Org. Chem.*, **23**, 1366 (1958).

84. H. D. Kaesz and F. G. A. Stone, In *Organometallic Chemistry*, H. Zeiss Ed.; Rheinhold: New York, 1960; p 123.

85. A. Henderson and A. K. Holliday, *J. Organomet. Chem.*, **4**, 377 (1965).

86. C. D. Garner and B. Hughes, *J. Chem. Soc., Dalton Trans.*, 1306 (1974).

87. *Conformational Analysis of Medium-Sized Heterocycles*, R. S. Glass Ed.; VCH Publishers: New York, 1988, and references therein.

88. D. C. Gross, *Inorg. Chem.*, **28**, 2355 (1985).

89. D. C. Evans and S. Karpel, *J. Organomet. Chem. Libr.*, **16**, 1 (1985).

90. F. Mistry, S. J. Rettig, J. Trotter, and F. Aubke, *Acta Crystallogr.*, **46C**, 2091 (1990).

91. S. W. Ng, V. G. Kumar Das, W.-H. Yip, R.-J. Wang, and T. C. W. Mak, *J. Organomet. Chem.*, **393**, 201 (1990).

92. S. P. Narula, S. K. Bharadwaj, Y. Sharada, R. O. Day, L. Howe, and R. R. Holmes, *Organometallics*, **11**, 2206 (1992).

93. (a) J. H. Wengrovius and M. F. Garbauskas, *Organometallics*, **11**, 1334 (1992); (b) M. F. Garbauskas and J. H. Wengrovius, *Acta Crystallogr.*, **C47**, 1969 (1991); (c) E. R. T. Tiekink, *J. Organomet. Chem.*, **408**, 323 (1991); (d) C. Vatsa, V. K. Jain, T. Kesavadas, and E. R. T. Tiekink, *J. Organomet. Chem.*, **410**, 135 (1991).

94. (a) S. W. Ng, V. G. Kumar Das, B. W. Skelton, and A. H. White, *J. Organomet. Chem.*, **377**, 221 (1989); (b) V. Chandresekhar, R. O. Day, J. M. Holmes, and R. R. Holmes, *Inorg. Chem.*, **27**, 958 (1988); (c) G. K. Sandhu, N. Sharma, and E. R. T. Tiekink, *J. Organomet. Chem.*, **371**, C1 (1989).

95. (a) T. P. Lockhart, J. C. Calabrese, and F. Davidson, *Organometallics*, **6**, 2479 (1987); (b) G. K. Sandhu, N. Sharma, and E. R. T. Tiekink, *J. Organomet. Chem.*, **403**, 119 (1991); (c) G. K. Sandhu, R. Hundal, and E. R. T. Tiekink, *J. Organomet. Chem.*, **412**, 31 (1991); (d) P. Harston, R. A. Howie, J. L. Wardell, S. M. S. V. Doidge-Harrison, and P. J. Cox, *Acta Crystallogr.*, **C48**, 279 (1992).

96. S. P. Narula, S. K. Bharadwaj, H. K. Sharma, Y. Sharda, and G. Mairesse, *J. Organomet. Chem.*, **415**, 203 (1991).

97. E. Vedejs, D. E. Erdman, and D. R. Powell, *J. Org. Chem.*, **58**, 2840 (1993).

98. (a) K. Sisido, Y. Takeda, and Z. Kinugawa, *J. Am. Chem. Soc.*, **83**, 538 (1961); (b) T. A. Smith and F. S. Kipping, *J. Chem. Soc.*, **103**, 2034 (1913).

99. (a) J. Holeček, and A. Lyčka, *Inorg. Chim. Acta*, **118**, L15 (1986); (b) J. Holeček, M. Nádvorník, K. Handlíř, and A. Lyčka, *J. Organomet. Chem.*, **315**, 299 (1986).

100. T. P. Lockhart and W. F. Manders, *J. Am. Chem. Soc.*, **109**, 7015 (1987).

101. D. Doddrell, I. Burfitt, W. Kitching, M. Bullpitt, C.-H. Lee, R. J. Mynott, J. L. Considine, H. G. Kuvila, and R. H. Sarma, *J. Am. Chem. Soc.*, **96**, 1640 (1974).

102. B. Wrackmeyer, *Ann. Rep. NMR Spectrosc.*, **16**, 73 (1985).

103. O. Bastiansen, L. Fernholt, H. M. Seip, H. Kambara, and K. Kuchitsu, *J. Mol. Struct.*, **18**, 163 (1973).

104. R. K. Harris and A. Sebald, *Magn. Reson. Chem.*, **27**, 1058 (1987).

105. C. W. Haigh, *Ann. Rep. NMR Spectrosc.*, **4**, 311 (1974).

106. D. Seyferth, *J. Am. Chem. Soc.*, **79**, 5881 (1957).

107. Ch. S. Bobashinskaya, and K. A. Kocheshkov, *J. Gen. Chem., U.S.S.R.*, **8**, 1850 (1938).

108. B. K. Hunter and L. W. Reeves, *Can. J. Chem.*, **46**, 1399 (1968).

109. W. F. Howard, Jr. and W. H. Nelson, *J. Mol. Struct.*, **53**, 165 (1979).

110. (a) C. K. Chu and J. D. Murry, *J. Chem. Soc. (A)*, 360 (1970); (b) E. Krause, *Ber.*, **51**, 1447 (1918).

111. W. P. Neumann and G. Burkhardt, *Liebigs Ann. Chem.*, **663**, 11 (1963).

112. S. A. Kandil and A. L. Allred, *J. Chem. Soc. (A)*, 2987 (1970).

113. E. G. Rochow and D. Seyferth, *J. Am. Chem. Soc.*, **75**, 2877 (1953).

114. H. Puff, W. Schuh, R. Sievers, W. Wald, and R. Zimmer, *J. Organomet. Chem.*, 260, 271 (1984).

115. O. A. Ptitsyna, O. A. Reutov, and M. F. Turchinskii, *Doklady Akad. Nauk. S. S. S. R.*, **114**, 110 (1957): *CA*. 52, 1090b.

116. Y. Tsuda, M. Hanajima, and K. Yoshimoto, *Chem. Pharm. Bull.*, **31**, 3778 (1983).

117. L. Den Driver, C. W. Holzapfel, J. M. Koekemoer, G. J. Kruger, and M. S. Van Dyk, *Carbohydr. Res.*, **155**, 141 (1986).

118. S. Hanessian and R. Roy, *J. Am. Chem. Soc.*, **101**, 5839 (1979).

119. See Chapter 5 in this thesis for detail.

120. (a) N. L. Allinger, Y. H. Yuh, and J.-H. Lii, *J. Am. Chem. Soc.*, **111**, 8552 (1989); (b) N. L. Allinger, M. Rahman, and J.-H. Lii, *J. Am. Chem. Soc.*, **112**, 8293 (1990).

121. T. B. Grindley and A. Cude, Abs. Carb. 86, 204th ACS National Meeting, 1992.

122. (a) G. K. Glushonok, E. P. Petryaev, and O. I. Shadyro, *Zh. Fiz. Khim.*, **58**, 107 (1984); (b) *ibid*, **58**, 111 (1984); (c) G. C. S. Collins and W. O. George, *J. Chem. Soc. (B)*, 1352 (1971); (d) S. J. Angyal and R. G. Wheen, *Austral. J. Chem.*, **33**, 1001 (1980).

123. L. Davis, *Biorganic Chem.*, **2**, 197 (1973).

124. A. Maradufu and A. S. Perlin, *Carbohydr. Res.*, **32**, 127 (1974), and references therein.

125. J. L. Marco, *Tetrahedron*, **45**, 1475 (1989).

126. O. Th. Schmidt. *Methods Carbohydr. Chem.* **2**, 318 (1963).

127. R. B. Duff and E. G. V. Percival. *J. Chem. Soc.* 1675 (1947).

128. H. G. Fletcher, Jr. *Methods Carbohydr. Chem.* **2**, 166 (1963).

129. R. L. Whistler and W. C. Lake. *Methods Carbohydr. Chem.* **8**, 286 (1972).

130. R. E. Gramera, R. M. Bruce, S. Hirase, and R. L. Whistler. *J. Org. Chem.* **28**, 1401 (1963).

131. D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin I*, 1574 (1975).

132. M. E. Evans and F.W. Parrish. *Methods Carbohydr. Chem.* **8**, 173 (1980).

133. *Reagents for Organic Synthesis.* L. F. Fieser and M. Fieser Eds., John Wiley and Sons, Inc.: New York-London-Sydney, 1967, p78.

134. G. Descotes, D. Sinou, and J.-P. Praly, *Carbohydr. Res.*, **78**, 25 (1980).

135. D. E. Kiely and H. G. Fletcher, Jr., *J. Org. Chem.*, **33**, 3723 (1968).

136. The specific rotation given was measured 24 h after the crystalline material was dissolved in chloroform (see discussion).

137. The two different halves of the dimer are designated as a and b. Assignments to each half were made unambiguously by a combination of first-order analyses, COSY, NOESY, and HETCOR experiments.

138. J. D. Kennedy and W. MacFarlane, In *Multinuclear NMR*, Ed. J. Mason, Pergamon Press, London, 1988, pp 311-312.

139. M. L. Martin, G. J. Martin and J. J. Delpuech, *Practical NMR Spectroscopy*, Heyden, London, 1980, p300, p340.

140. M. Haga, M. Takano, and S. Tejima. *Carbohydr. Res.* **21**, 440 (1972).

141. J. M. Heap and L. N. Owen. *J. Chem. Soc. (C).* 707 (1970).

142. R. R. Schmidt and A. Gohl. *Chem. Ber.* **112**, 1689 (1979).

143. L. F. Wiggins. *J. Chem. Soc.* 13 (1946).

144. C. Morpain, B. Laude, and N. Latruffe. *Org. Prep. Proced. Int.* **22**, 540 (1990).

145. M. K. Gurjar and S. M. Pawar. *Indian J, Chem.* **26B**, 55 (1987).

146. J. Jurczak, T. Bauer, and M. Chemielewski. *Carbohydr. Res.* **164**, 493 (1987).

147. H. Redlich, J. B. Lenfers, and W. Bruns, *Liebigs Ann. Chem.*, 1570 (1985).

148. H. Weidmann and H. Schwarz. *Monatsh. Chem.* **103**, 218 (1972).

149. A. S. Mayer and T. Reichstein. *Helv. Chim. Acta.* **29**, 152 (1946).

150. M. Blanc-Muesser and J. Defaye. *Synthesis.* 568 (1977).

151. S. Valaerde, A. Fernandez, B. Herradon, R. M. Rabanal, and M. Martin-Lomas. *Tetrahedron.* **43**, 3499 (1987).

152. A. Dmytraczenko, W. A. Szarek, and J. K. N. Jones. *Carbohydr. Res.* **26**, 297 (1973).

153. J. Jary, Z. Kefurtova, and J. Kovar. *Coll. Czech. Chem. Commun.* **34**, 1452 (1969).

154. H. Yamamoto, C. Hosoyamada, H. Kawamoto, and S. Inokawa. *Carbohydr. Res.* **102**, 159 (1982).

155. H. Hori, Y. Nishida, H. Ohrui, and H. Meguro. *J. Org. Chem.* **54**, 1346 (1989).

156. L. Vargha. *Ber.* **66**, 704 (1933).

157. N. Walker and D. Stuart, *Acta Crystallogr.*, **A39**, 158 (1983).

158. The programs used were SHELXS 86, G. M. Sheldrick. In *Crystallographic Computing*; G. M. Sheldrick, C. Kruger and R. Goddard Eds; Oxford University Press: Oxford, U.K., 1985; pp 175-189 and DIRDIF, P. T. Beurskens. *DIRDIF: Direct Methods for Difference Structures - an automatic procedure for phase extension and refinement of difference structure factors.* Technical Report 1984/1 Crystallography Laboratory, Toernooiveld, 6525 Ed Nijmegen, Netherlands.

159. D. T. Cromer and J. T. Waber, *International Tables for X-ray Crystallography*, The Kynoch Press: Birmingham, England, 1974; Vol. IV, Table 2.2 A.

160. J. A. Ibers and W. C. Hamilton, *Acta Crystallogr.*, **17**, 781 (1974).

161. D. T. Cromer and J. T. Waber, *International Tables for X-ray Crystallography*, The Kynoch Press: Birmingham, England, 1974; Vol. IV, Table 2.3.1.

162. G. M. Sheldrick, *SHELX 76. Program for Crystal Structure Determination*, University of Cambridge: Cambridge, U.K., 1976.