Synthesis of Novel Types of Polyester Glycodendrimers and the Development and Applications of an Efficient Alternative to Multistep Regioselective Esterification in Diols and Polyols

by

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

at

Dalhousie University
Halifax, Nova Scotia
June 2013

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Dated: June 7, 2013

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DATE: June 7, 2013

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TITLE: Synthesis of Novel Types of Polyester Glycodendrimers and the Development and Applications of an Efficient Alternative to Multistep Regioselective Esterification in Diols and Polyols

DEPARTMENT OR SCHOOL: Department of Chemistry

DEGREE: PhD CONVOCATION: October YEAR: 2013

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To my father who always advised me to make education my top priority no matter what else maybe going on in my life and to Manuela Gania Twibanire, who I love very much.
# TABLE OF CONTENTS

LIST OF FIGURES ................................................................................................................................. ix
LIST OF SCHEMES ........................................................................................................................................ x
LIST OF TABLES .......................................................................................................................................... xiii
ABSTRACT ...................................................................................................................................................... xiv
LIST OF ABBREVIATIONS AND SYMBOLS USED .................................................................................... xv
ACKNOWLEDGEMENTS .................................................................................................................................. xviii

Chapter 1. Introduction .......................................................................................................................... 1

1.1. Origin of Dendrimers ......................................................................................................................... 2

1.2. Chemistry, Structure, and Synthetic Methods .................................................................................... 3

1.3. Functionalization and Properties of Dendrimers ............................................................................. 8

1.4. Applications of Dendrimers .............................................................................................................. 9

1.4.1. Introductory Remarks .................................................................................................................. 9

1.4.2. Dendrimers for Biological Applications ...................................................................................... 9

1.4.3. Concluding Remarks ................................................................................................................... 12

1.5. Polyester Dendrimers ..................................................................................................................... 13

1.5.1. Introductory Remarks .................................................................................................................. 13

1.5.2. Summary of Other Polyester Dendrimers .................................................................................. 13

1.5.3. Concluding Remarks ................................................................................................................... 34

Chapter 2. Design and Synthesis of Core Molecules and Dendrons ......................................................... 35

2.1. Core Molecules .............................................................................................................................. 35

2.1.1. Introductory Remarks ................................................................................................................ 35

2.1.2. Design and Synthesis .................................................................................................................. 35

2.1.3. Concluding Remarks ................................................................................................................... 40

2.2. Dendrons ........................................................................................................................................... 40
2.2.1. Introductory Remarks ................................................................................................... 40
2.2.2. Design and Synthesis ................................................................................................... 41
2.2.3. Configuration of Synthetic 5-Methyl-2-phenyl-1,3-dioxane-5-carboxylic acid (43) ......... 47
2.2.4. Concluding Remarks ..................................................................................................... 49

2.3. Experimental Section ..................................................................................................... 50
  2.3.1. General ................................................................................................................ 50
  2.3.2. Synthesis of Core Molecules .................................................................................... 51
  2.3.3. Synthesis of Dendrons ............................................................................................ 57

Chapter 3. Efficient and Controllably Selective Preparation of Esters ............................................. 69
  3.1. Introductory Remarks ................................................................................................... 69
  3.2. The Use of Uronium-based Coupling Agents .................................................................. 69
  3.3. Esterification Using COMU ............................................................................................ 70
  3.4. Esterification Using TBTU ............................................................................................ 74
  3.5. Esterification Using TATU ............................................................................................ 76
  3.6. Mechanistic Considerations .......................................................................................... 77
  3.7. Convergent Synthesis .................................................................................................. 80
  3.8. Regioselective Esterification of Diols and Polyols .......................................................... 82
  3.9. Concluding Remarks ................................................................................................... 83
  3.10. Experimental Section .................................................................................................. 84
    3.10.1. General ............................................................................................................. 84
    3.10.2. Synthesis ............................................................................................................. 85

Chapter 4: Synthesis of Lyme Disease Glycolipid Antigens ......................................................... 104
  4.1. Introductory Remarks ................................................................................................... 104
  4.2. Antigens Against Lyme Disease .................................................................................... 104
  4.3. Concluding Remarks ................................................................................................... 109
LIST OF FIGURES

Figure 1 A depiction of the features of dendritic architecture ................................................................. 4
Figure 2 Benzylidene-protected 4th generation polyester dendrimer .......................................................... 20
Figure 3 Hydroxyl-terminated 4th generation polyester dendrimer............................................................. 21
Figure 4 Second-generation dendrimer with a bifunctionalized periphery .................................................. 25
Figure 5 Azide-functionalized polyester dendrons ..................................................................................... 26
Figure 6 Selected cores ............................................................................................................................... 35
Figure 7 500.13 MHz 1H NMR spectrum of a 5:1 mixture of 85 and 86 in chloroform-d ......................... 37
Figure 8 Cis and trans isomers of 5-methyl-2-phenyl-1,3-dioxane-5-carboxylic acid, 43 ......................... 48
Figure 9 Coupling agents investigated ....................................................................................................... 70
Figure 10 Structures of alcohols and carboxylic acids used .................................................................... 70
Figure 11 125.7 MHz 13C NMR spectrum of the reactive intermediate IV in CDCl3 ............................... 79
Figure 12 Borrelia burgdorferi glycolipid antigens ..................................................................................... 105
Figure 13 Trehalose 6,6'-diesters ............................................................................................................. 118
Figure 14 Structure of triester products (175) .......................................................................................... 122
Figure 15 Newman projection from C5 to C6 illustrating the three rotamers and atom labeling .......... 125
Figure 16 A conformation illustrating how adopting the gt conformation for C5-C6 bond in the monosubstituted glucose ring allows van der Waals between the long chains of the 6'-ester and the 2-ester .......................................................................................................................... 127
Figure 17 Benzylidene and acetonide-protected dendrons of bis-HMPA ................................................ 141
Figure 18 Binding constants of two monomeric mannoses with FimH ..................................................... 149
Figure 19 A hexameric compound with a Kd per mannose residue of 18 nM ........................................ 149
Figure 20 Azide-functionalized acid dendron .......................................................................................... 182
Figure 21 A potential mannose-tipped dendronized polymer based on PVA ........................................ 182
LIST OF SCHEMES

Scheme 1 Vögtle's early synthesis of dendritic species ................................................................. 2

Scheme 2 Tomalia's synthesis of the class of dendrimers known as PAMAM .............................. 3

Scheme 3 The first example of the divergent growth approach to polyester dendrimers .......... 5

Scheme 4 The first convergent synthesis of a deprotected polyester dendrimer ......................... 6

Scheme 5 Double exponential dendron growth ............................................................................ 7

Scheme 6 Functionalization of bow-tie dendrimers for therapeutic studies .............................. 11

Scheme 7 Synthetic route to 1st, 2nd, 3rd, and 4th generation dendrons .................................... 14

Scheme 8 Synthetic route to 1st, 2nd, 3rd, and 4th generation acetate-terminated dendrimers .... 15

Scheme 9 Synthesis and deprotection of the acetonide-protected 4th generation dendrimer ........ 16

Scheme 10 Surface functionalization of the 4th generation polyester dendrimer ....................... 17

Scheme 11 Synthesis of the first ferroelectric dendritic liquid crystalline polymer .................... 18

Scheme 12 Preparation of 1st generation using benzylidene-protected bis-HMPA .................... 19

Scheme 13 Acetonide-protected building block ....................................................................... 22

Scheme 14 Divergently-grown acetonide-protected 4th generation dendrimer ............................ 22

Scheme 15 Spacer addition to the porphyrin core ..................................................................... 23

Scheme 16 Divergent construction of the 4th generation free base porphyrin-cored dendrimer .... 24

Scheme 17 Synthesis of a 2nd generation dendrimer with a cyclic carbonate periphery .......... 25

Scheme 18 Synthesis of tetravalent cyclen core ..................................................................... 27

Scheme 19 Synthesis of 4th generation dendrimer using a click reaction ................................. 27

Scheme 20 Synthesis of acetonide-protected 1st generation ................................................... 29

Scheme 21 Synthesis of 2nd generation unsymmetrical polyester dendrimers ........................... 30

Scheme 22 Enzymatic preparation of enantiopure building blocks ............................................ 31

Scheme 23 Modification of azide-terminated dendrimers with different ratios of enantiomers ... 31

Scheme 24 Synthesis of core molecule 74 .............................................................................. 32
Scheme 25 Synthesis of dendron 77 ........................................................................................................... 32
Scheme 26 A novel second generation dendrimer 78 ................................................................................. 33
Scheme 27 Initial synthesis of 1,4-benzenediethanol .................................................................................. 36
Scheme 28 Improved synthesis of 1,4-benzenediethanol ........................................................................... 37
Scheme 29 The synthesis of 1,3,5-triallylb enzene and 1,3,5-benzenetriethanol .............................................. 38
Scheme 30 The synthesis of 2-hydroxyethoxy derivatives ............................................................................ 39
Scheme 31 Mono-O-benzyla tion ................................................................................................................ 42
Scheme 32 Mono-O-benzyla tion ................................................................................................................ 42
Scheme 33 Acid-catalyzed equilibrium of 98/99 ....................................................................................... 43
Scheme 34 Merck oxidation .................................................................................................................... 44
Scheme 35 Dendron activation ................................................................................................................ 45
Scheme 36 Preparation of anhydride 108 .................................................................................................... 45
Scheme 37 Preparation of anhydride 112 .................................................................................................... 46
Scheme 38 Potential preparation of orthogonally protected 116 .................................................................... 46
Scheme 39 Preparation of allyl-protected anhydride 119 ............................................................................... 47
Scheme 40 Preparation of anhydride 44 ..................................................................................................... 49
Scheme 41 Proposed reaction mechanisms: top level on each line, TBTU mechanism; bottom level, COMU mechanism ......................................................................................................................... 78
Scheme 42 Reactive intermediate IV forms quickly even in the presence of DIEA ............................................. 79
Scheme 43 Divergent growth of second generation acid dendron .................................................................... 80
Scheme 44 TBTU-promoted convergent synthesis of a 2\textsuperscript{nd} generation dendrimer ....................... 81
Scheme 45 TBTU-promoted ester formation ................................................................................................. 81
Scheme 46 Selective esterifications. Note that 144 was accompanied by 5% of the ester of the secondary alcohol ................................................................................................................................................. 83
Scheme 47 Formation of secondary product is via migration ......................................................................... 83
Scheme 48 Synthesis of cholesteryl β-D-galactopyranoside (168) ........................................................... 106
Scheme 49 Possible pathways for the last step of TBTU-promoted esterification. B = base .................. 109
Scheme 50 Synthesis of trehalose 6-monoesters and 6,6'-diesters ......................................................... 121
Scheme 51 Synthesis of nonsymmetric trehalose 6,6'-diesters .............................................................. 123
Scheme 52 Preparation of a first-generation dendrimer with a hydroquinone core, a tetraol .......... 141
Scheme 53 Preparation of a second-generation dendrimer with a hydroquinone core, an octaol .... 142
Scheme 54 An alternative route to second-generation dendrimer 182 ..................................................... 142
Scheme 55 Elaboration of octaol 182 into G-3(OH)16 186 ...................................................................... 143
Scheme 56 Synthesis of 1st generation dendrimer (188), a hexaol, using a tribranched dendron .... 143
Scheme 57 Preparation of diol 190 ........................................................................................................ 144
Scheme 58 Preparation of 2nd generation hydroquinone-cored dendrimer 191, a dodecaol .......... 144
Scheme 59 Potential preparation of protected third generation dendrimer ........................................ 145
Scheme 60 Potential preparation of allyl-terminated third generation dendrimer .............................. 145
Scheme 61 Preparation of second generation mixed polyester dendron 193 ........................................... 146
Scheme 62 Preparation of anhydride 194 .................................................................................................. 146
Scheme 63 Synthesis of benzyl-terminated dendrimer 195 ................................................................. 147
Scheme 64 Synthesis of benzyl-terminated dendrimer 196 ................................................................. 147
Scheme 65 Synthesis of mannose residues 198 and 201 ................................................................. 149
Scheme 66 Preparation of 6-azidohexanoic acid .............................................................................. 150
Scheme 67 Preparation of divalent azide compounds 204 and 207 ................................................... 151
Scheme 68 Preparation of an azide-terminated third generation polyester dendrimer ...................... 151
Scheme 69 Synthesis of divalent mannose clusters 209 and 210 ...................................................... 152
Scheme 70 Synthesis of a highly mannosylated system 211 .............................................................. 153
Scheme 71 Synthesis of divalent mannoside cluster 213 ................................................................. 154

xii
LIST OF TABLES

Table 1 Merck oxidation results on compound 98 ................................................................. 44
Table 2 Esterification results using COMU (equimolar conditions) ........................................... 71
Table 3 Solvent flexibility with COMU ................................................................................. 72
Table 4 Base flexibility with COMU .................................................................................... 73
Table 5 Optimization for secondary alcohols with COMU ...................................................... 73
Table 6 Base flexibility with TBTU ...................................................................................... 74
Table 7 Solvent flexibility with TBTU .................................................................................... 75
Table 8 Optimization for secondary alcohols with TBTU ...................................................... 75
Table 9 Esterification results using TATU ............................................................................. 76
Table 10 Esterification results with MTBD .............................................................................. 77
Table 11 TBTU-promoted esterification (Scheme 45) using second-generation acid dendron 136 .... 82
Table 12 Effect of variation of conditions on glycosylation .................................................... 107
Table 13 Regioselective esterification results ...................................................................... 108
Table 14 Conditions and outcomes for the reactions of trehalose (172) with fatty acids .......... 121
Table 15 Conditions and outcomes for the reactions of 6-O-oleoyltrehalose with fatty acids ...... 123
Table 16 Three-bond coupling constants observed for C6 protons (CD3OD, 22 °C) .................. 125
Table 17 Percentage population of rotamers (CD3OD, 22 °C) .................................................. 126
ABSTRACT

Polyester dendrimers are attractive for biological applications because they are biodegradable and non-toxic. The preparation of a variety of core molecules that are compatible with deprotection using hydrogenolysis is presented. Previous syntheses of polyester dendrimers have mainly focused on the use of dibranched building blocks or dendrons. Chemistry was developed for the synthesis of novel tribranched dendrons and lower generation dendrimers have been prepared. It was found that formation of successive generations using tribranched dendrons was not possible, presumably because of steric hindrance, but dendrimers containing alternating generations of dibranched and tribranched dendrons could be formed.

In the search for a mild esterification method which would allow convergent synthesis of dendrimers, it was demonstrated that coupling agents namely, TBTU, TATU, and COMU are efficient promoters of ester bond formation between carboxylic acids and all types of alcohols in the presence of organic bases. It was shown that regioselective esterification of diols and polyols is possible based on whether the alcohols are primary, secondary, or tertiary, with choice of base and coupling agent. The base sensitivity of the TBTU-promoted esterification was used in the preparation of a library of the Lyme disease antigens termed *Borrelia burgdorferi* glycolipid 1 that contain esters of different fatty acids connected to O-6 of cholesteryl β-D-galactopyranoside. In addition, the direct synthesis of maradolipids from the dauer form of the nematode *Caenorhabditis elegans*, and other trehalose 6-monoesters and 6,6’-diesters was demonstrated.

Finally, novel types of polyester glycodendrimers have been synthesized using click chemistry to attach α-D-mannopyranosyl glycosides bearing alkyne groups at the termini of their aglycones to polyester dendrimers with terminal azide groups, and these will be evaluated as anti-adhesion drugs against urinary tract infections.
LIST OF ABBREVIATIONS AND SYMBOLS USED

Ac acetyl
ADH alcohol dehydrogenase
ADH-LB alcohol dehydrogenase from *Lactobacillus brevis*
ADH-T alcohol dehydrogenase from *Thermoanaerobacter sp.*
ax axial
bis-HMPA 2,2-bis(hydroxymethyl)propanoic acid
Bn benzyl
br broad
Bz benzoyl
ºC degree Celcius
CAN ceric ammonium nitrate
COMU 1-[(1-(cyano-2-ethoxy-2-oxoethylideneaminoxy)
dimethylaminomorpholinomethylene)] methanaminium
hexafluorophosphate
d doublet
DBU 1,8-diazabicyclo[5.4.0]undec-7-ene
DCC *N,N*-dicyclohexylcarbodiimide
DCM dichloromethane
DDQ 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H diisobutylaluminium hydride
DIEA diisopropylethylamine
DMAP 4-(*N,N*-dimethylamino)pyridine
DMF $N,N$-dimethylformamide
DOX doxorubicin
DPTS 4-(dimethylamino)pyridinium $p$-toluenesulfonate
DTPA diethylenetriaminepentaacetic acid
EDC 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ESI electrospray ionization
Et ethyl
eq equatorial
equiv equivalent(s)
EtOAc ethyl acetate
FLCPs ferroelectric liquid crystalline polymers
$J$ coupling constant
LCPs linear crystalline polymers
LD Lyme disease
M unit of concentration: moles per litre
Me methyl
MeOH methanol
MRI magnetic resonance imaging
MS mass spectrum
MTBD 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
Mw molecular weight
$m/z$ mass to charge ratio
NaAsc sodium ascorbate
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>NADH</td>
<td>nicotinamide adenine dinucleotide (reduced form)</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>NSERC</td>
<td>Natural Science and Engineering Research Council of Canada</td>
</tr>
<tr>
<td>PAMAM</td>
<td>polyamidoamine</td>
</tr>
<tr>
<td>PBS</td>
<td>phosphate buffered saline</td>
</tr>
<tr>
<td>PEG</td>
<td>polyethylene glycol</td>
</tr>
<tr>
<td>PVA</td>
<td>polyvinyl alcohol</td>
</tr>
<tr>
<td>Py</td>
<td>pyridine</td>
</tr>
<tr>
<td>quat</td>
<td>quaternary</td>
</tr>
<tr>
<td>$R_f$</td>
<td>retention factor for relative migration of a compound on a TLC plate</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>TATU</td>
<td>2-($H$-7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate</td>
</tr>
<tr>
<td>TBTU</td>
<td>2-($H$-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate</td>
</tr>
<tr>
<td>TEMPO</td>
<td>(2,2,6,6-tetramethylpiperidin-1-yl)oxyl</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>tetramethylsilane</td>
</tr>
<tr>
<td>TOF</td>
<td>time of flight</td>
</tr>
<tr>
<td>TsOH</td>
<td>$p$-toluenesulfonic acid</td>
</tr>
<tr>
<td>TTF</td>
<td>tetrathiafulvalene</td>
</tr>
<tr>
<td>UPEC</td>
<td>uropathogenic <em>Escherichia coli</em></td>
</tr>
<tr>
<td>UTIs</td>
<td>urinary tract infections</td>
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ACKNOWLEDGEMENTS

I would like to sincerely thank my supervisor, Professor T. Bruce Grindley for his advice, encouragement, support, and patience. Dr. Grindley was always there to listen and always provided the best advice on both research and personal life. Dr. Grindley was flexible and willing to accommodate new changes and new reactions I suggested about the research. This freedom has helped in providing me with the autonomy and qualities necessary to become an independent and efficient scientist. Sincere appreciation also goes to Professor Jean Burnell who became my co-supervisor towards the end of my studies. A lot of amazing things can be said about Dr. Burnell including the fact that he is the “best teacher I have ever met.” Listening to you teach, has been a pleasure. Thank you sir!

I would like to thank members of the Grindley group, both past and present: Malcolm Huestis, Alfred Rolle, Raha Omran, and Dr. Nusrat Jahan. Matthew Wu, Elizabeth Maclsaac, and Nicole Crosier prepared starting materials for dendron synthesis and I acknowledge their contribution. Dr. Hussein Al-Mughaid for his contribution on core synthesis and Dr. Nawal Paul for a fantastic partnership on maradolipids synthesis and for various positive discussions we have had about my project and other aspects of life.

I thank Mr. Xiao Feng of the Department of Chemistry, Dalhousie University, for recording both low resolution and high resolution mass spectra of various compounds. Sincere appreciation also goes to Dr. Mike Lumsden and Dr. Kathy Robertson of NMR-3 for training me in the use of Bruker AC-250 MHz, AV-300, and AV-500 MHz NMR spectrometers. I would like to extend thanks to the members of my supervisory committee, Dr. Alison Thompson, Dr. Jean Burnell, and Dr. Norman Schepp, for their availability to advice and support over the course of my graduate studies.
Thank you Dr. Burnell for providing the ozone generator and thank you Dr. Thompson for providing the hydrogenolysis apparatus. Special thanks go to Stephanie Forget of the Jakeman group for technical assistance with the purification of water soluble compounds using Sephadex LH-20 and Sandra Chukwu for helpful discussions on the separation of $\alpha$ and $\beta$ anomers for the Lyme disease project. Griselda, thank you for taking care of Manuela. I am thankful to Natural Science and Engineering Research Council of Canada for financial support and the Department of Chemistry of Dalhousie University for the Gerry Dauphinee Scholarship.
Chapter 1. Introduction

Dendrimers are complex macromolecules with well-defined chemical structures. These molecules have attracted the interest of chemists owing to their potential applications in many areas. Dendrimers are nearly perfect monodisperse macromolecules with regular and highly branched three-dimensional architectures, extending outwards from a central core bearing more than one identical reactive center using branched monomers. These architectures are in contrast to those of traditional polymers, which are linear macromolecules with limited branching. The rapidly expanding area of hyperbranched polymers lies between dendrimers and linear polymers. The spectrum of the fields of potential applications of dendrimers is very diverse, ranging from the engineering sector to the medical sector. Activity in the dendrimer field has continued to accelerate since its inception in the 1980s. For instance, there were 132 citations to the terms “dendrimer or dendrimers” in 1995, 677 citations in 2000, 1196 citations in 2005, 16372 citations in 2008, 28429 in 2011, and 37189 in 2012. Although many types of structures have been synthesized, the enormous structural diversity of both organic and inorganic chemistry guarantees that there are a huge number of potential novel types of dendrimers yet to be synthesized. Consequently, properties and new potential applications are still essentially unexplored.

The synthesis of new types of dendrimers with new properties and new potential applications was targeted here. By using known methods, the focus was on the synthesis of polyester dendrimers because they are non-toxic and they offer the possibility of releasing entrapped or covalently attached biologically active molecules in vivo.

This thesis contains an introduction to dendrimers that discusses a wide range of key issues including their origin, chemistry and structure, functionalization and properties, synthetic
methods, and applications. Following this is a summary of other polyester dendrimers that have appeared in the literature. The next five chapters discuss results, which include the design and synthesis of core molecules and dendrons, esterification using uronium-based coupling agents, the preparation of Lyme disease antigens, the direct synthesis of maradolipids, and the preparation of early generation dendritic polyols. Also discussed herein is the synthesis of novel polyester glycodendrimers as potential inhibitors of urinary tract infections.

1.1. Origin of Dendrimers

Dendrimers are the most recently recognized members of the polymer family, with the first dendrimer report published in 1978. In this report, Vögtle and coworkers described highly branched molecules prepared by exhaustively performing Michael-type reactions of acrylonitrile with an amine followed by the reduction of nitrile groups to primary amines. When this first generation polyamine was treated with acrylonitrile followed by reduction in the same way, a second-generation dendrimer was produced. Further repetition produced higher generation highly branched amines with defined structures as shown in Scheme 1.

![Scheme 1](image)

Scheme 1 Vögtle's early synthesis of dendritic species

In 1981, Denkewalter (then at Allied Corporation) and coworkers described dendritic polylysine. A few years later in 1985, Tomalia reported the synthesis and characterization of a
new dendritic family. In this synthesis, ammonia was reacted with methyl acrylate, followed by amidation of the resulting esters with excess ethylenediamine, which produced the next layer of reactive amine groups. Scheme 2 illustrates the synthesis of Tomalia’s dendrimers, now commercialized as poly(amido amine) (PAMAM) dendrimers. Shortly after, in the same year, Newkome reported initial results about the synthesis of tribranched dendritic amides. Further developments occurred in the late 1980s but the review by Tomalia sparked an explosion of research that has continued to the present, including the first syntheses of polyester dendrimers.

Scheme 2 Tomalia's synthesis of the class of dendrimers known as PAMAM

1.2. Chemistry, Structure, and Synthetic Methods

Dendrimers are regularly branched macromolecules composed of multiple perfectly branched monomers that elongate radially from a central core, similar to the branches of some trees. A dendrimer can be divided into three different regions: the core, the interior (or branches) and the periphery. Figure 1 depicts the features of a dendritic architecture. The number of branching points encountered upon moving outward from the core to its periphery defines its generation. These macromolecules are prepared in a stepwise fashion and therefore, the products are theoretically monodisperse in size. A monodisperse product is extremely desirable not only for synthetic reproducibility, but also for reducing experimental and therapeutic
variability. A dendrimer may be based on practically any type of chemistry, the nature of which can determine its solubility, degradability and biological activity. Dendrimers are associated with various interesting properties, but perhaps the most exploited of them all is their multivalency. Unlike in linear polymers, as dendrimer molecular weight and generation increase, the terminal units become more closely packed. This feature has been exploited by many researchers as a way of achieving concentrated payloads of drugs or spectroscopic labels for therapeutic and imaging applications. The resulting interaction between a dendritic array of ligands and a cell or other target bearing multiple receptors leads to a greatly increased binding affinity between the dendrimer and the cell compared with the binding of the monovalent ligand to the cell.

![Figure 1](image.png)

**Figure 1** A depiction of the features of dendritic architecture

Two strategies have been formulated for dendrimer synthesis. The divergent approach is more obvious and was used by most of the early workers in the area. In this method,
dendrimers grow outwards from a multifunctional core molecule. The core molecule reacts with monomeric molecules containing one reactive and various dormant groups giving the first generation dendrimer. Then the new periphery of the molecule is activated for reactions with more monomers. The process is repeated several times and a dendrimer is built generation after generation. See Scheme 3 for the first example of polyester dendrimer synthesis using this approach.47

Scheme 3 The first example of the divergent growth approach to polyester dendrimers
Scheme 4 The first convergent synthesis of a deprotected polyester dendrimer

The second, convergent route was developed by Hawker and Fréchet\textsuperscript{39} as a response to the weaknesses of the divergent approach. In this approach, the units that will be attached to the core, the dendrons, are constructed first. When the growing dendrons have reached the desired size, they are attached to the multifunctional core molecule. This method has several advantages.
It is relatively easy to purify the final product and the occurrence of defects in the final structure is minimised. The convergent route provides better structural control since intermediates are purified better at successive stages of the synthesis. However, this method may not allow the formation of high generations because steric problems may occur in the reactions of the dendrons with the core molecule. Scheme 4 illustrates this approach.\(^{34}\)

Scheme 5 Double exponential dendron growth

Reduction in the number of both synthetic and purification steps in convergent dendrimer synthesis can be achieved if a convergent approach is taken to dendron synthesis rather than the strictly divergent synthesis of the dendron illustrated in Scheme 4. This approach, termed double exponential growth,\(^{15,48,49}\) is illustrated for polyester dendrimers in Scheme 5.\(^{50}\) In this
methodology, monomers of both convergent and divergent growth are prepared using a single starting material. When the two resulting monomers are reacted, an orthogonally protected trimer that is usually ready to repeat the growth is obtained.

1.3. Functionalization and Properties of Dendrimers

Polymer chemistry and technology have traditionally focused on linear polymers, which are widely in use. Linear macromolecules only occasionally contain some smaller or longer branches. In the recent past it has been found that the properties of highly branched macromolecules can be very different from conventional polymers. The structure of these materials has also a great impact on their applications.

Following their synthesis, dendrimers are typically functionalized in accordance to the features the researcher wants them to display and the application they are intended for. The functionalization methods most commonly used are filling the dendrimer cavities, modification of the dendrimer core, and modification of the dendrimer surface. A literature review revealed that modification of the dendrimer’s surface is the method mostly used, after which dendrimers may display a range of properties such as polyvalency, flexible charge, solubility properties, and flexible binding properties.

Because of their molecular architecture, dendrimers show some significantly different physical and chemical properties when compared to traditional linear polymers. In solution, linear chains exist as flexible coils; in contrast, dendrimers form tightly packed balls. The presence of many chain-ends is responsible for high solubility and miscibility and for high reactivity. Because of their globular shape and the presence of internal cavities, dendrimers have some interesting properties; one of the most important ones is the possibility to encapsulate guest molecules in the macromolecule’s interior. Meijer and co-workers trapped small
molecules like $p$-nitrobenzoic acid inside the ‘dendritic box’ of a poly(propylene imine) dendrimer with 64 branches on the periphery and guest molecules were stably encapsulated inside the dendritic box. Hydrolysing the outer shell could liberate the guest molecules.

1.4. Applications of Dendrimers

1.4.1. Introductory Remarks

There are now many families of dendrimers, each with interesting properties, since the surface, interior and core can be tailored to different sorts of applications. Many potential applications of dendrimers are based on their unparalleled molecular uniformity, multifunctional surface and presence of internal cavities.25,64,65 These specific properties make dendrimers suitable for a variety of high technology uses including biomedical and industrial applications. Properties like polyvalency, defined architecture, size and shape control, loading capacity, and biocompatibility could be exploited singularly or in combination, making it possible to use dendrimers in a large variety of fields.

1.4.2. Dendrimers for Biological Applications

The early use of dendrimers in biology and medicine has been reviewed.17,21,41 However, new applications and new dendrimer architectures have appeared in the past few years.

1.4.2.1. Drug Delivery

By attaching a drug to a suitable carrier it is possible to enhance its aqueous solubility, increase its circulation half-life, target the drug to certain tissues, improve drug transit across biological barriers, and slow drug metabolism. Optimization of these features to maximize drug bioavailability to diseased tissues while minimizing drug exposure to healthy tissues, results in improved therapeutic efficacy.
A variety of carriers, including small molecule substrates for cellular receptors and transporters, proteins, and soluble polymers, have been used for this purpose. Numerous reports on the in vitro efficacy of purely dendrimer-based drug carriers have been published, but only a few in vivo therapeutic studies exist. One of the earliest examples of anti-tumor drug delivery with dendrimers was achieved by complexing cisplatin (20–25% by weight) to the surface groups of a G-4 carboxylate-terminated PAMAM dendrimer. A PAMAM dendrimer with a sodium carboxylate surface was conjugated to cisplatin giving a dendrimer-platinate which was highly water soluble and released platinum slowly in vitro. The dendrimer-Pt was also less toxic than cisplatin and thus had potential for further investigation as a novel antitumor approach.

Polyester dendrimers also look very promising as drug delivery systems. A classic example is that of Lee, Gillies, Fréchet, and coworkers. The antitumor effect of doxorubicin (DOX) conjugated to a polyester dendrimer was evaluated in mice bearing cancerous tumors. An asymmetric biodegradable polyester dendrimer containing doxorubicin was prepared as shown in Scheme 6. The design of the dendrimer carrier optimized blood circulation time through size and molecular architecture, drug loading through multiple attachment sites, solubility through PEGylation, and drug release through the use of pH-sensitive hydrazone linkages. In culture, dendrimer–DOX was greater than 10 times less toxic than free DOX after exposure for 72 h. Upon in vivo administration to mice with tumors, dendrimer–DOX was eliminated from the serum with a half-life of 16 hours, and its tumor uptake was ninefold higher than in vivo administered free DOX at 48 h.
1.4.2.2. Dendrimers with Drug-like Properties

Whereas the majority of dendrimers have been used as carriers for drugs and nucleic acids, some dendrimers act as drugs themselves. Supattapone and coworkers\textsuperscript{70} discovered that branched polyamines, including PAMAM dendrimers and hyperbranched polymers, stimulate the removal of prion proteins present in infected cells. The branched architecture appears essential to this application because linear polyamines and small molecule amines were ineffective.

Multivalent display of ligands on the surface of a dendrimer has also proven to be a viable method of inhibiting multivalent binding between cells, viruses, bacteria, and proteins.\textsuperscript{45,46,71} For example, a G-4 poly(lysine) dendrimer bearing sulfate groups at its periphery is being utilized as an anti-viral topical ointment.\textsuperscript{72,73} By binding in a multivalent fashion to viral
envelope proteins, the dendrimer is able to block adsorption and subsequent entrance of the virus into cells. Although similar results have been achieved previously with linear polyanions, dendrimer polysulfates should be easier to move from the laboratory to the clinic because of their monodispersity, which translates into a consistent product with less therapeutic variability.

1.4.2.3. Imaging

Magnetic resonance imaging (MRI) is a diagnostic method which produces anatomical images of organs and blood vessels. Addition of contrast agents improves the sensitivity and specificity of the method. The gadolinium salt of diethylenetriaminepentaacetic acid (DTPA) is used clinically, but it diffuses into the extravenous area due to its low molecular mass.\(^\text{74}\) Dendrimers are now being utilized as contrast agents for magnetic resonance.\(^\text{75,76}\) Due to their properties dendrimers are highly suited for use as image contrast agents. Several groups have designed and prepared dendritic species for this purpose.\(^\text{77,78}\) Independent findings by these research groups were that dendrimers are stronger contrast agents than conventional ones.

1.4.3. Concluding Remarks

Dendrimers have shown to be associated with various novel applications and are particularly very promising as drug carriers. However, an understanding of the pharmacokinetics of dendrimers is essential for their applications in medicine because the bioavailability, toxicity and ultimately the efficiency of dendrimer-based drugs or imaging agents will depend on their pharmacokinetic profiles.\(^\text{79}\)
1.5. Polyester Dendrimers

1.5.1. Introductory Remarks

Polyester dendrimers are of considerable interest for biological applications because they are biodegradable and biocompatible. A major incentive for the use of polyester dendrimers as frameworks for biological applications is that whenever they have been tested, they have been found to have low toxicity, unlike many other dendrimers. The first report for macromolecules of this type was published in 1991. In this report, Hawker and Fréchet described a one-step synthesis of a hyperbranched polyester possessing a dendritic structure achieved by thermal self-condensation of 3,5-bis(trimethylsiloxy)benzoyl chloride. Interest in polyester dendrimers has increased considerably since the late 1990s, and today many types of polyester dendrimers have been prepared.

1.5.2. Summary of Other Polyester Dendrimers

Since the pioneering work of Vögtle, Tomalia, and Newkome, regarding the synthesis of well-defined three-dimensional macromolecules, interest in dendrimers has continued to increase. Early reports about the synthesis of polyester dendrimers include the work of Ihre, Hult, and Söderlind. First to fourth generation dendrons were synthesized from by protecting the carboxylic acid as a benzyl ester group and the hydroxyls as acetate esters (Scheme 7). Esterifications were performed by conversion of the acid into the corresponding acid chloride with oxalyl chloride followed by reaction of the acid chloride with the hydroxyl groups in the presence of triethylamine (TEA) and 4-(dimethylamino)pyridine (DMAP). Deprotection using hydrogenolysis allowed repetition. Acetate-terminated polyester dendrimers with 1,1,1-tris(p-hydroxyphenyl)ethane as a core were synthesized from generation one to four.
(Mₙ: 906, 1,856, 3,754, and 7,549 g/mol) by adding the above dendrons in a convergent growth approach.²⁸ The simplicity of the ¹H NMR and ¹³C NMR spectra and elemental analyses suggest that pure and monodisperse dendrimers were obtained. However, attempts to selectively remove the acetate groups in order to obtain the corresponding hydroxyl terminated dendrimers for further chemical surface modification were not successful due to the lack of selectivity in the hydrolysis of the acetate and other ester groups. In addition, lower yields were obtained in the final coupling step of the fourth generation dendrons to the core molecule when compared to the coupling steps used to prepare lower generation dendrimers.

Scheme 7 Synthetic route to 1ˢᵗ, 2ⁿᵈ, 3ʳᵈ, and 4ᵗʰ generation dendrons
Two years later, Ihre and Hult in collaboration with Fréchet and Gitsov\textsuperscript{50} published their new work as a response to weaknesses of the strict convergent approach described above. Here, a double-stage convergent growth approach, which allowed the synthesis of the fourth generation acetate-terminated dendrimers.

**Scheme 8** Synthetic route to 1\textsuperscript{st}, 2\textsuperscript{nd}, 3\textsuperscript{rd}, and 4\textsuperscript{th} generation acetate-terminated dendrimers
hydroxyl-terminated polyester dendrimer to be synthesized in nine steps involving only three purification steps by column chromatography, was employed. The reduced number of steps in the new synthetic route also afforded a significantly improved yield of the product when compared to a strict convergent growth approach. In addition, the modified synthetic route allowed the selection of different protective groups, allowing the selective and high yield deprotection of the fourth generation protected polyester dendrimer. Hydroxyl groups of bis-HMPA were protected to afford acetonide groups by reacting bis-HMPA with 2,2-dimethoxypropane and a catalytic amount of $\rho$-toluenesulfonic acid (TsOH) in acetone. Scheme 5 illustrates the preparation of a fourth generation dendron using the double-stage convergent growth approach. Reacting this dendron with 1,1,1-tris(hydroxyphenyl)ethane as in Scheme 9 gave a fourth generation polyester dendrimer in good yield.

Scheme 9 Synthesis and deprotection of the acetonide-protected 4th generation dendrimer
The periphery of the hydroxyl-terminated polyester dendrimer was then functionalized using reactions of its hydroxyl groups with various acid chlorides (benzoyl, octanoyl, and palmitoyl chloride) in the presence of TEA and DMAP to give high yields of monodisperse dendrimers, according to $^1$H NMR spectra, $^{13}$C NMR spectra, size exclusion chromatography, and elemental analyses of the products (Scheme 10).

![Scheme 10 Surface functionalization of the 4th generation polyester dendrimer](image)

When conventional mesogenic groups in linear crystalline polymers (LCPs) are replaced by chiral mesogens, ferroelectric liquid crystalline polymers (FLCPs) are obtained. FLCPs are regarded as important species for optical switching and electrooptical applications. Because of chain entanglements however, their viscosity is often high which leads to slow switching thereby narrowing the field of their potential practical applications. Knowing that using dendritic structures may result in monodisperse FLCPs and therefore low viscosity and less chain
entanglements, Busson, Ihre, and Hult synthesized the first ferroelectric dendritic liquid crystalline polymer. In this work,\textsuperscript{89} a third generation aliphatic polyester dendrimer, bearing 24 hydroxyl groups on its surface, was functionalized using a ferroelectric mesogen.

\textbf{Scheme 11} Synthesis of the first ferroelectric dendritic liquid crystalline polymer
The mesogenic group, 4''-((R)-1-methylheptyloxy)phenyl 4-(4'-{(hydroxycarbonyl)decyloxy)-phenyl)benzoate, responsible for realization of the liquid crystalline state, was coupled to the dendritic matrix via acid chloride reaction as shown in Scheme 11. The purity and hence the monodispersity of the final compound was established using $^1$H NMR spectroscopy and size exclusion chromatography (SEC) measurements. For instance, the SEC trace of the final product consisted of a single peak after purification.

![Scheme 12 Preparation of 1st generation using benzylidene-protected bis-HMPA](image)

While exploring various routes to dendrimers, Annby, Malmberg, Pettersson, and Rehnberg demonstrated that the benzylidene-protected bis-HMPA was a versatile reagent for the formation of esters. Here, polyester dendrimers were prepared up to the fourth generation using even sterically congested cores like pentaerythritol in good yields. Since then, a number of research groups have continued to synthesize and utilize the benzylidene-protected bis-HMPA as a convenient building block. Using 1,1,1-tris(hydroxyphenyl)ethane as the core molecule, the benzylidene-protected anhydride of bis-HMPA as the dendron, and a catalytic amount of DMAP, a novel divergent approach was developed for the synthesis of dendritic aliphatic polyester.
structures. As mentioned in section 1.2, structural uniformity is usually difficult to maintain in the divergent approach, because the number of reactions that must be completed at each step of growth increases exponentially, thus requiring large excesses of reagents. However, this divergent approach, unlike all others, required only a small excess of reagent to achieve quantitative growth, and it required no means of purification other than a simple solvent extraction or precipitation to obtain monodisperse dendritic structures up to the sixth generation.

The preparation of the activated building block 44 is shown in Scheme 12. Compound 44 was then coupled to the core using only 1.25 equivalents per hydroxyl group to give a trivalent benzylidene-protected first generation 45. Catalytic hydrogenolysis selectively removed the benzylidene protecting groups of 45 and other higher generation dendrimers without affecting the ester bonds of the dendritic backbone. Figures 2 and 3 illustrate protected and hydroxyl-terminated fourth generations of this type.

Figure 2 Benzylidene-protected 4th generation polyester dendrimer
In efforts to establish a large dendritic library comprising of dendritic compounds based on bis-HMPA, Malkoch, Malmström, and Hult became inspired by the efficiency of the above anhydride chemistry. However, the synthesis of dumbbell-shaped dendrimers often requires the use of orthogonally protected dendrons. The benzylidene-protected anhydride does not allow selective deprotection in the presence of other groups susceptible toward hydrogenolysis, such as a benzyl ester which is commonly employed in the synthesis of bis-HMPA dendrons. To complement the benzylidene-protected anhydride esterification strategy reported by Fréchet and coworkers in the synthesis of aliphatic polyester dendrons and dendrimers,⁹⁴ the acetonide-protected bis-HMPA anhydride⁹⁶ was introduced to combine the anhydride chemistry with the possibility of using the benzyl ester-protected focal point.⁹⁶ About the same time, a paper by Fréchet and coworkers appeared describing the use of the acetonide-protected bis-HMPA anhydride but no synthetic details were reported.⁹⁷
Three different fourth generation dendrons based on a 2,2,2-tris(chloroethyl) ester, a benzyl ester, and a decanoyl benzyl ether as focal points were divergently synthesized in high yields. In order to demonstrate the versatility of the anhydride chemistry, a fourth generation polyester dendrimer 50 was also divergently constructed as in Scheme 14.96

Two years later, Malmström, Hult and coworkers reported the synthesis and characterization of dendron-coated porphyrins up to the fifth generation.98 Here, both free-base
and zinc-cored tetraphenylporphyrin (TPPH₂ and TPPZn) were used, from which the dendrons were divergently grown using the acetonide-protected bis-HMPA anhydride 49. Porphyrins were selected as core molecules because of their potential applications in many areas.⁹⁹-¹⁰³ Reports dealing with porphyrin-decorated dendrimers had previously appeared.¹⁰⁴-¹¹³

After investigating three different synthetic strategies for this study, it was concluded that a spacer was required to be attached to the porphyrin to increase the hydrolytic stability and allow synthesis of higher generations. Normally acidic DOWEX resin is used for the deprotection of the acetonide groups, but here the porphyrin core attached irreversibly to the resin. A number of various dilute acids were explored for this deprotection, but the results from these acidic deprotections showed that the porphyrin phenolic ester linkage also hydrolyzes, hence the need for a spacer. The spacer was added through the reaction of the the porphyrin with 3-bromopropanol to afford 51. The dendrimers were then grown by subsequent addition of an acetonide-protected building block followed by deprotection with 2M H₂SO₄ in tetrahydrofuran. The preparation of a fourth generation free base porphyrin-cored polyester dendrimer of this type is shown in Scheme 16.⁹⁸

Scheme 15 Spacer addition to the porphyrin core
Scheme 16 Divergent construction of the 4th generation free base porphyrin-cored dendrimer

The synthesis of bis-HMPA acid-based polyester dendrimers continued to accelerate around this time as various researchers continued to publish reports of new dendritic architectures with new potential applications. For example, novel carborane-containing dendritic species based on bis-HMPA were reported by both Adronov114 and Zharov115 and one year later, Fréchet and coworkers116 presented polyester dendrimers bearing two types of peripheral groups
prepared by employing a cyclic carbonate as a symmetrical substrate that can yield a bifunctional product. The reaction of a cyclic carbonate and an amine has been used previously and has even shown to be efficient and selective enough to be run in water with quantitative yields. In the reaction, the amine opens the ring, forming a carbamate linkage with liberation of an alcohol that may then be used for a subsequent functionalization step. Two different moieties may be added in immediate succession without any deprotection steps or functional group conversions.

**Scheme 17** Synthesis of a 2nd generation dendrimer with a cyclic carbonate periphery

**Figure 4** Second-generation dendrimer with a bifunctionalized periphery
To provide a model platform for testing the reaction, dendrimer **54** with eight hydroxyl groups was prepared from pentaerythritol. DCC coupling of **53** and **54** furnished carbonate-bearing dendrimer **55** (Scheme 17). Finally, reacting **55** with (MeO)$_2$CHCH$_2$NH$_2$ and then propargyl bromide afforded dendrimer **56** (Figure 4). This is an example of how dendrimers can be precisely designed and functionalized to impart certain desired properties.$^{116}$

![Figure 5 Azide-functionalized polyester dendrons](image)

The work of Malkoch and Hult presenting novel architectures of bis-HMPA-based polyester dendrimers has also received attention.$^{119}$ Polyester dendrimers up to the fourth generation were successfully synthesized using a click reaction. Here, acetonide-protected dendrons wedges were divergently grown and after being functionalized at the focal point using 6-azidohexanol, they were subsequently attached to a tetravalent alkyne functional cyclen core to give new dendrimer architectures. Figure 5 illustrates four generations of azide-functionalized
dendrons. The preparation of tetravalent alkyne functional cyclen core is shown in Scheme 18. Architectures of first to fourth generation polyester dendrimers of this type were obtained

Scheme 18 Synthesis of tetravalent cyclen core

Scheme 19 Synthesis of 4th generation dendrimer using a click reaction
when the cyclen core 62 was reacted with 57, 58, 59, and 60 respectively. Scheme 19 illustrates the preparation of a fourth generation of this type of dendrimers.119

The synthesis and exploration of dendrimers containing functionalities associated with well-known interesting applications have continued to be of particular interest for many researchers. For example, since the publication of the first azobenzene dendrimers,120 various reports of azobenzene-containing dendrimers121-124 have continued to appear mostly because azobenzenes, which are synthetic dyes, are associated with several applications due to their interesting properties.125-129 With this in mind, Rissanen’s group has shown interest in the synthesis of Janus-type dendrimers having possible non-linear optical properties arising from the non-centrosymmetric structure of the chiral azobenzene conjugates. One report describes the synthesis of bisfunctionalized Janus-type polyester dendrimers, which consist of a polar hydroxyl functionalized end, and a photoactive end constructed from donor–acceptor azobenzenes and chiral naproxen units.130 Using pentaerythritol core and anhydride of bis-HMPA, the aliphatic polyester skeleton was constructed. Incorporated azobenzene moieties, previously reported by the same research group131 were chosen as electron donor–acceptor chromophores, since they possess non-linear optical properties.132 Shown in Schemes 20 and 21 are the syntheses of first and second generations for this type of unsymmetrical dendrimers.130

Heise and coworkers reported the synthesis of encoded dendrimers with defined chiral composition via ‘click’ reaction of enantiopure building blocks.133 Heise had previously reported the synthesis of copolymers from the enantiomerically pure monomers of (R) and (S)-p-vinylphenylethanol,134 but copolymers have a disadvantage in that there is uncertainty about the distribution of chiral units along the polymer skeleton. A viable approach was then to use
dendrimers of defined architectures in which orthogonal functionalization encodes a defined optical rotation into the dendrimer by the use of enantiomerically pure building blocks.

Scheme 20 Synthesis of acetonide-protected 1st generation
Here, an azide-terminated dendrimer\textsuperscript{133} based on bis-HMPA was divergently constructed as previously described\textsuperscript{135} and functionalized using the 1,3-dipolar cycloaddition reaction and different ratios of the matching alkyne functional enantiopure building blocks (Scheme 23).\textsuperscript{133} Scheme 22 shows the selective alcohol dehydrogenase (ADH) reduction of 1-(4-ethynylphenyl)ethanone to give the desired chiral building blocks.\textsuperscript{133} When measurements of the optical rotation were taken, it was found that the specific optical rotation of the dendrimers increased linearly with increasing percentage of (R) end-groups in the dendrimer, indicating that both (R) and (S) building blocks had been incorporated into the dendrimer in agreement with the enantiomeric feed ratio.
Scheme 22 Enzymatic preparation of enantiopure building blocks

Scheme 23 Modification of azide-terminated dendrimers with different ratios of enantiomers

The discovery and development of new and potent drugs is a time-consuming and costly process. It may take up to 15 years to develop mostly because of lengthy clinical trials. A
more economical and viable strategy is to devise effective delivery systems for drugs that have failed to provide optimum therapeutic benefit. It is postulated that controlled release of a drug at a specific target can significantly improve the effectiveness of a drug and thereby increase the therapeutic benefit.\textsuperscript{137}

\textbf{Scheme 24 Synthesis of core molecule 74}

Hildgen and coworkers\textsuperscript{5} at the Université de Montréal synthesized novel polyester-\textit{co}-polyether dendrimers consisting of a hydrophilic core. The core was synthesized using biocompatible moieties, butanetetracarboxylic acid and aspartic acid, and the dendrons from
PEG (poly(ethylene glycol)), dihydroxybenzoic acid or gallic acid, and PEG monomethacrylate. The dendrimers were then obtained by coupling the dendrons to the core. Syntheses of core molecule 74, dendron 77, and a second generation 78 are shown in Schemes 24, 25, and 26.\(^5\)

![Scheme 26](image)

**Scheme 26** A novel second generation dendrimer 78

This type of dendrimer demonstrated good ability to encapsulate the guest molecule, with loadings of 15.80 and 6.47% w/w for rhodamine and \(\beta\)-carotene, respectively. The release of the encapsulated compounds was found to be slow and sustained, suggesting that these dendrimers can serve as potential drug delivery systems.
1.5.3. Concluding Remarks

There has been a substantial interest in the area of dendrimers because of their interesting properties and wide potential applications and activity in this area has intensified over the last few years. However, there is still a wide range of dendrimer families with new properties and new potential applications that have not yet been synthesized. The following chapters discuss obtained results. Chapter 2 of this thesis discusses new dendrons and core molecules that have been prepared. This discussion will lead to esterification using uronium-based coupling agents, the direct synthesis of maradolipids, and the synthesis of Lyme disease glycolipid antigens.
Chapter 2. Design and Synthesis of Core Molecules and Dendrons

2.1. Core Molecules

2.1.1. Introductory Remarks

Stable and non-sterically congested core molecules are essential for the successful preparation of higher generation dendrimers. From the early days of dendrimers to the present day, dendrimer synthesis has largely focused on the use of easily accessible cores from commercial sources. Examples of these include pentaerythritol, 1,1,1-tris(hydroxyphenyl)ethane, and 2-ethyl-2-(hydroxymethyl)-1,3-propanediol, just to name a few. It is therefore interesting to synthesize cores that have never been used before in the preparation of dendrimers and to see the impact these would have on the architectures, properties, and applications of the resulting dendrimers.

2.1.2. Design and Synthesis

![Selected cores](image)

Figure 6 Selected cores

We wanted aromatic cores with non-benzylic and non-phenolic hydroxyl groups for ester stability that would not be cleaved under mild acidic (for selective removal of isopropylidene acetics) or hydrogenolysis conditions (for reductive removal of benzylidene acetics and benzyl
ethers). Molecules in Figure 6 were selected as synthetic targets. None of these compounds has been used previously for the preparation of dendrimers. These compounds all have terminal CH₂CH₂OH groups and so one synthetic route that could be used for all was employed: reduction of the products of reductive ozonolysis of allyl groups. This approach had not been used previously to prepare any of these compounds and it proved to be convenient and high yielding. 1,4-Benzenediethanol 79 has been prepared previously by Clark and O’Reilly using the reaction of the Grignard reagent obtained from 1,4-dibromobenzene with ethylene oxide.\(^{138}\) However, the yield reported was 52\% and ethylene oxide, a toxic gas, is both expensive and inconvenient to handle on a laboratory scale. Our initial approach via the diallyl derivative 85 is shown in Scheme 27. Steiger and coworkers reported the synthesis of 85 in 32\% yield via coupling of the bis Grignard reagent of 1,4-dibromobenzene with allyl bromide.\(^{139}\) In our hands, 85 was always accompanied by the monoadduct 86, even after chromatography. Figure 7 shows a 500 MHz \(^{1}\)H NMR spectrum of chromatographically purified 85, which contains about 15\% of the mono-allylated product 86 as part of the mixture. Performing the reaction in two separate steps did not improve the yield. Reaction of the mono Grignard reagent with allyl bromide gives 86\(^{140}\) in 63\% yield in our hands and the yield in the second step was similar (59\%).

![Scheme 27 Initial synthesis of 1,4-benzenediethanol](image)
Figure 7 500.13 MHz $^1$H NMR spectrum of a 5:1 mixture of 85 and 86 in chloroform-$d$

Scheme 28 Improved synthesis of 1,4-benzenediethanol

An alternative route to 1,4-diallylbenzene 85 proved to be cost effective and high yielding. The copper-catalysed coupling of vinyl magnesium bromide with the known diiodide 88$^{141}$ gave a good yield of the diallyl derivative in one hour. Compound 85 has also been made in excellent yield by performing Stille coupling of the bistriflate of hydroquinone with tributylallylstannane in the presence of PdCl$_2$(PPh$_3$)$_2$ (20 mol%) and LiCl.$^{142}$ Conversion to 79 via ozonolysis followed by the same-pot reduction proceeded in good yield (Scheme 28).
Two groups had reported the synthesis of 1,3,5-benzenetriethanol 80 by quite different methods. Cochrane et al.\textsuperscript{143} prepared it by reduction of triethyl 1,3,5-benzenetriacetate.\textsuperscript{144} The precursor 1,3,5-benzenetriacetic acid was made from 1,3,5-triacetylbenzene using the Kindler modification of the Willgerodt reaction\textsuperscript{144} and 1,3,5-triacetylbenzene can be prepared by an acid-catalyzed trimerization of formyl acetone,\textsuperscript{145} overall a four-step process. Bradshaw and Krakowiak used the same method but chose to reduce the precursor triacid in 45\% yield.\textsuperscript{146} An alternative one-pot synthesis of compound 80 gave a non-separated mixture of tris-(2-hydroxyethyl)benzenes using a cobalt-catalyzed trimerization of 3-butyn-1-ol but the starting material is expensive and the separation is impractical.\textsuperscript{147}

A reaction scheme analogous to Scheme 28 could not be followed because the required precursor, 1,3,5-tris(chloromethyl)benzene, is not commercially available. An attempt was made to prepare 1,3,5-triallylbenzene 89 from 1,3,5-tribromobenzene via the Grignard method but it gave inseparable mixtures of partially allylated derivatives along with the desired product.

Allylation of aromatic halides with allyltributyltin\textsuperscript{148} in the presence of tetrakis(triphenylphosphine)palladium(0) has been known for more than 30 years.\textsuperscript{149} The triplicate version of this reaction worked well with 1,3,5-tribromobenzene on scales of < 10 g as shown in Scheme 29. The product 89 was converted to the desired triol 80 as described above in the synthesis of 79.

![Scheme 29](image)

**Scheme 29** The synthesis of 1,3,5-triallylbenzene and 1,3,5-benzenetriethanol
2-Hydroxyethoxy derivatives of aromatic compounds, such as \( \text{81} - \text{84} \), have been made in a variety of ways. Compounds \( \text{81} \) and \( \text{84} \) were originally prepared by reaction of the sodium salts of the phenols with 2-chloroethanol\(^{150}\) and 2-bromoethanol has also been used.\(^{151}\) The patent literature contains numerous reports of the formation of \( \text{81} \) by reaction of the dianion with ethylene oxide. Compound \( \text{83} \) has been made by iodination of 2-hydroxyethoxybenzene.\(^{152-154}\) Surprisingly, compound \( \text{84} \) has commonly been made from phloroglucinol by reaction with ethylene carbonate in DMF at 150 °C in the presence of tetrabutylammonium bromide.\(^{155}\) Although this reaction is a one-step reaction, it suffers from low yields. Values of between 20

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**Scheme 30** The synthesis of 2-hydroxyethoxy derivatives
and 37% have been reported.\textsuperscript{146,156-158} An alternative two-step approach involving displacement of methyl bromoacetate by phenoxide,\textsuperscript{159} followed by reduction has also been used for \textit{84}.\textsuperscript{160}

The reduction of the products of reductive ozonolysis of allyl ethers yielded the remaining core molecules, compounds \textit{81},\textsuperscript{161} \textit{82},\textsuperscript{150,162} \textit{83},\textsuperscript{163} and \textit{84},\textsuperscript{146} in excellent yields (see Scheme 30). The required allyl ethers were obtained in 10 to 15 min at -10 to -15 \degree C by reaction of the phenoxide anions with allyl bromide in DMF.

\subsection*{2.1.3. Concluding Remarks}

One-pot reductive ozonolysis of allyl derivatives followed by reduction with sodium borohydride is an efficient general procedure for the production of terminal CH\textsubscript{2}CH\textsubscript{2}OH groups. The allyl groups can be either C-allyl or O-allyl groups. The latter are readily accessible and a variety of strategies have been employed for the introduction of one to three C-allyl groups onto aromatic rings.

\subsection*{2.2. Dendrons}

\subsubsection*{2.2.1. Introductory Remarks}

The synthesis of polyester dendrimers has largely relied on the use of bis-HMPA acid dendron. Since the 1990s, this aliphatic building block has continued to be the dendron of choice. Bis-HMPA is commercially available. It has allowed easy preparation of higher generation polyester dendrimers because it is not sterically hindered, and most importantly, the resulting polyester dendrimers are non-toxic and biodegradable, which makes them attractive for biological and drug delivery applications. The following section describes our approaches to the preparation of new dendrons.
2.2.2. Design and Synthesis

The preparation of polyester dendrimers with new properties and new potential applications depends largely on the ability of researchers to synthesize new dendrimers with increasing structural diversity. The use of new building blocks that have never been used previously is one way of achieving this goal. We decided to design and prepare dendrons derived from pentaerythritol that have three branching points. Dendrons with three branching points can potentially allow the synthesis of polyester dendrimers that are more highly branched than any polyester dendrimer in the literature today. Such dendrimers should have the advantage that they are likely to be less easily hydrolyzed in vivo than previously synthesized polyester dendrimers, but share the advantages of synthesis under mild conditions of other polyester dendrimers and potential biological release of bioactive molecules either trapped or conjugated. We desired a flexible high-yielding route to trivalent dendrons. Issidorides and Gulen\textsuperscript{164} described an efficient procedure for the synthesis of 5,5-bis(hydroxymethyl)-2-phenyl-1,3-dioxane, also known as mono-\textit{O}-benzylidene-pentaerythritol \textbf{94}. As shown in Scheme 31, slow addition of benzaldehyde to a solution of pentaerythritol in water, in the presence of an acid catalyst yields the acetal in good yield. We prepared compound \textbf{94} on a large scale.

Dibutyltin acetals have shown to be useful for selective chemical manipulations of diols and polyols.\textsuperscript{165-167} They are formed readily from diols\textsuperscript{168,169} and have served as convenient intermediates for the formation of monobenzyl ethers from diols or polyols by reacting with benzyl bromide in benzene or toluene in the presence of tetrabutylammonium bromide.\textsuperscript{168,170} Following the procedure developed earlier in this laboratory,\textsuperscript{171} \textbf{94} was refluxed with one equivalent of dibutyltin oxide in toluene followed by the subsequent benzylation in situ, to give
isomers 95 and 96 as thick colorless syrups. When p-methoxybenzaldehyde is employed as in Scheme 32, the resulting isomers 98 and 99 are colorless crystalline solids.

Scheme 31 Mono-\(\text{O}\)-benzylation

Scheme 32 Mono-\(\text{O}\)-benzylation
These isomers were characterized using \(^1\)H NMR and \(^{13}\)C NMR spectroscopy and their structures were assigned. While clean NMR spectra for \(95\), \(96\), and \(98\) could be obtained in chloroform-\(d\), a pure sample of \(99\) equilibrated when it was dissolved in chloroform-\(d\) to give a 3:2 mixture of \(98\) and \(99\) respectively. This ratio was consistent each time NMR experiments were performed on \(99\) regardless of the length of time the sample was left in the chloroform-\(d\) solution (right away, two hours, or 36 hours after dissolving the sample in chloroform-\(d\)). It is known that chloroform-\(d\) decomposes slightly on standing to release dichlorocarbene and HCl. When acetone-\(d_6\) was used for NMR experiments on \(99\), no equilibration was observed. Scheme 33 shows the observed equilibrium in chloroform-\(d\).

Scheme 33 Acid-catalyzed equilibrium of \(98/99\)

Oxidation is a fundamental transformation in organic synthesis and numerous methods have been reported for the desired transformation.\(^\text{172-175}\) When the starting alcohols have labile functional groups that can cleave under acidic conditions as it is the case here for \(95\), \(96\), \(98\), and \(99\), fewer methods exist for the transformation to carboxylic acids. After trying a few other methods, we found that Zhao’s method, the so-called “Merck oxidation”,\(^\text{176}\) worked efficiently
either on the individual isomers 95/96 or the mixture of isomers. The reaction between each of the primary alcohols and a stoichiometric amount of sodium chlorite in the presence of catalytic TEMPO and bleach at 38 °C for 12 h in a buffered solution, gave the corresponding acid in good yield as shown in Scheme 34. When isomer 98 was subjected to the same conditions, a low yield of the corresponding acid was obtained. Consequently, this reaction was investigated in more detail by varying temperature and reaction times. Results are summarized in Table 1. Oxidation of compound 99 always gave a mixture of the two corresponding isomeric acids.

Scheme 34 Merck oxidation

Table 1 Merck oxidation results on compound 98

<table>
<thead>
<tr>
<th>Temp. (° C)</th>
<th>rxn time (h)</th>
<th>% yield</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - RT</td>
<td>12</td>
<td>0</td>
<td>Most of the alcohol</td>
</tr>
<tr>
<td>RT</td>
<td>12</td>
<td>15</td>
<td>recovered</td>
</tr>
<tr>
<td>RT</td>
<td>20</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>12</td>
<td>22</td>
<td>Some alcohol</td>
</tr>
<tr>
<td>30</td>
<td>16</td>
<td>21</td>
<td>recovered</td>
</tr>
<tr>
<td>35</td>
<td>6 - 8</td>
<td>25</td>
<td>No alcohol was</td>
</tr>
<tr>
<td>35</td>
<td>11 - 12</td>
<td>40</td>
<td>recovered</td>
</tr>
<tr>
<td>35</td>
<td>16</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>18</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>4</td>
<td>15</td>
<td>No alcohol was</td>
</tr>
<tr>
<td>45</td>
<td>8</td>
<td>0</td>
<td>recovered</td>
</tr>
</tbody>
</table>
The activated anhydride dendrons were synthesized from the respective carboxylic acids using DCC as in Scheme 35. Anhydrides 103 and 104 are crystalline products, and they remained stable over a period of several months at room temperature.

Scheme 35 Dendron activation

In other reactions, a symmetrical dendron 107 that is an AB₃ dendron, was prepared by selective reduction of known di-O-benzyl-O-benzylidenepentaerythritol 105 to tri-O-benzylpentaerythritol 106 as shown in Scheme 36. This approach avoids the use of excess benzyl bromide required for the direct synthesis of 106 from pentaerythritol. Jones oxidation of 106 gave carboxylic acid 107, that was converted to crystalline anhydride 108 using DCC.

Scheme 36 Preparation of anhydride 108

When benzyl bromide was replaced by methyl iodide in step one of Scheme 36, a new dendron 111 was produced in good yield. Using hydrogenolysis, dendrons such as 111 can be
activated at a single position for the next round of reaction. This could be important for alleviating steric hindrance at higher generations and for dendrimer surface functionalization.

#### Scheme 37 Preparation of anhydride 112

Orthogonal protection plays an essential part in organic synthesis manipulations. By choosing the right protecting groups, it is possible to remove one set of protecting groups in any order, using reagents and conditions that do not affect other sets of protecting groups present in the molecule. Dendrons such as 116 that have both benzyl and \( p \)-methoxybenzyl groups would
be of considerable utility as the $p$-methoxybenzyl group can be selectively removed in high yield using DDQ or CAN.\textsuperscript{180,181} This would allow subsequent manipulation of the resulting single hydroxyl group without affecting the rest of the molecule. Attempts to prepare 116 are illustrated in Scheme 38. When selective cleavage of $p$-methoxybenzylidene acetal was tried on compound 113 using cobalt (II) chloride and borane-tetrahydrofuran complex, equimolar amounts of dibenzylpentaerythritol and $p$-methoxybenzaldehyde were obtained in 30 minutes. Successful cleavage of the acetal to the corresponding alcohol 115 was achieved in 87\% yield when DIBAL-H was used at -78 °C (for 6 h) or in 92\% yield at -10 °C (for 3 h) in dichloromethane. Unfortunately, all attempts to oxidize the alcohol to the corresponding acid dendron 116 gave $p$-methoxybenzoic acid as the major product as shown in Scheme 38.

Technical tri-$O$-allylpenterythritol, the commercially available tri-$O$-allylpenterythritol, is stated to have 70\% purity, and contains small amounts of both monoallylpentaerythritol and diallylpentaerythritol, which are easily removed using column chromatography. Jones oxidation of the purified triallyl derivative gave acid dendron 118, which was transformed into the corresponding acid anhydride with DCC (Scheme 39).

![Scheme 39 Preparation of allyl-protected anhydride 119](image)

2.2.3. Configuration of Synthetic 5-Methyl-2-phenyl-1,3-dioxane-5-carboxylic acid (43)

A number of research groups have synthesized and utilized compound 43,\textsuperscript{90,92,93,95,182} apparently as a single isomer, but its configuration had not been established as far as we are
Two stereoisomers of compound 43 are possible as shown in Figure 8. \(^1\)H NMR and \(^{13}\)C NMR spectra of this compound showed that a single isomer had also been isolated here (Scheme 40), not the mixture of cis- and trans- isomers expected based on the free energy difference for the isomers of 5-carboxymethyl-2-isopropyl-5-methyl-1,3-dioxane.\(^{183}\)

![Figure 8 Cis and trans isomers of 5-methyl-2-phenyl-1,3-dioxane-5-carboxylic acid, 43](image)

Piasecki and coworkers\(^{184-186}\) synthesized a series of 1,3-dioxanes bearing various long chain alkyl substituents at C-2 and a methyl group and a carboxyl group at C-5. The protons of the methyl group at C-5 in these compounds resonated as singlets at 1.02 ppm. Eliel and Enanoza had noted that an axially-oriented –CH\(_3\) group at C-5 (chemical shifts ~1.5 – 1.6 ppm in 5-methyl-2-substituted-1,3-dioxanes) is deshielded by 0.5 - 0.6 ppm with respect to an equatorially-oriented CH\(_3\) group (chemical shifts ~ 1 ppm).\(^{183}\) In addition, in isomers with the CH\(_3\) group and the C-2 group cis, the chemical shift difference between the two protons at C-4,6 is negligible or small,\(^{183}\) whereas in the trans-isomer it is large, about 1 ppm for those prepared by Piasecki.\(^{186}\) For 43, the methyl group resonated at 1.11 ppm when the sample was run in chloroform-\(d\) or at 1.05 ppm when the sample was run in acetone-\(d_6\). The chemical shift difference between the two protons on C-4,6 was 0.91 ppm in chloroform-\(d\) and 0.83 ppm in acetone-\(d_6\). Based on these grounds, compound 43 is the cis-isomer (Figure 8).

Kaloustian et al. attributed the axial preference at C-5 of 1,3-dioxanes for positively charged groups such as trimethylammonium groups on the electrostatic attraction of the resultant C-O dipole and the C-N\(^+\) dipole in this geometric arrangement and suggested that the small
conformational effect of a carbonyl group at C-5 had a contribution from the same effect.\textsuperscript{187} However, a similar favoring of the axial orientation for 5-fluoro derivatives must arise from the gauche effect,\textsuperscript{188} where bonding interactions favor gauche arrangements and dipole-dipole repulsion disfavors them. Piasecki found that formation of the acetal in non-polar solvents such as hexane gave mixtures whereas formation in polar solvents such as acetonitrile gave only the cis-isomer,\textsuperscript{185} consistent with the measured effects of solvent polarity on conformational equilibria and with decrease of through space dipole-dipole repulsion in polar solvents.\textsuperscript{187} Compound $43$ was prepared here in a polar solvent, water, and only the cis-isomer was observed. This acid was converted into the anhydride $44$ as earlier\textsuperscript{90,182} using DCC for dendrimer formation (Scheme 40).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {OH};
\node (b) at (1,0) {OH};
\node (c) at (2,0) {OH};
\node (d) at (3,0) {OH};
\node (e) at (4,0) {Ph};
\node (f) at (5,0) {Ph};
\node (g) at (2,1) {OH};
\node (h) at (2,2) {HO-};
\node (i) at (1,1) {HO-};
\node (j) at (0,1) {HO-};
\node (k) at (0,2) {HO-};
\node (l) at (3,1) {OH};
\node (m) at (3,2) {OH};
\node (n) at (4,1) {OH};
\node (o) at (4,2) {OH};
\node (p) at (5,1) {Ph};
\node (q) at (5,2) {Ph};
\node (r) at (6,1) {Ph};
\node (s) at (6,2) {Ph};
\draw (a) -- (b) -- (c) -- (d) -- (e) -- (f);
\draw (h) -- (i) -- (j) -- (k) -- (l) -- (m) -- (n) -- (o) -- (p) -- (q) -- (r) -- (s);
\draw (a) -- (g) -- (i) -- (b) -- (c) -- (h) -- (e) -- (d) -- (l);
\node at (2,4) {cis $43$};
\node at (5,4) {91\%};
\node at (0,4) {54\%};
\draw[->, thick] (2,4) -- (5,4);
\end{tikzpicture}
\end{center}

\textbf{Scheme 40} Preparation of anhydride $44$

### 2.2.4. Concluding Remarks

Pentaerythritol is an easily accessible versatile starting material. The manipulation of its hydroxyl groups using various chemical transformations and various protection/ deprotection strategies allowed the preparation of new types of tribranched dendrons such as $100$, $101$, $102$, $107$, $111$, and $118$. The successful synthesis of these dendrons leaves the desire to investigating how versatile they are in the preparation of polyester dendrimers. This will be discussed in Chapter 6, in which an efficient esterification method between carboxylic acids and alcohols (discussed in Chapter 3 and applied in Chapters 4 and 5) will also be applied in some examples.
2.3. Experimental Section

2.3.1. General

$^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance-500 NMR spectrometer operating at 500.13 and 125.7 MHz respectively using the solvent resonances as secondary chemical shift references. The signals of carbon and hydrogen nuclei of new compounds were assigned from the analysis of their one dimensional ($^1$H, $^{13}$C, and DEPT-135) and two dimensional (COSY, HSQC, and HMBC) NMR spectral data. The $^1$H and $^{13}$C NMR spectra may be found in Appendix B. High-resolution mass spectra were recorded using electrospray ionization with Bruker Microtof time of flight mass analyser. Melting points were determined on a Fisher-John's melting point apparatus and are uncorrected.

Acetone was refluxed over K$_2$CO$_3$ and distilled over molecular sieves. Dichloromethane was refluxed over calcium hydride and distilled onto molecular sieves. Benzene was refluxed over CaCl$_2$ and distilled over molecular sieves. Methanol was refluxed over calcium oxide and distilled over molecular sieves. Tetrahydrofuran was refluxed over LiAlH$_4$ and distilled over molecular sieves. Unless otherwise noted, non-aqueous reactions were carried out under a nitrogen atmosphere. Jones reagent (0.56 M) was prepared by dissolving sodium dichromate dihydrate (Na$_2$Cr$_2$O$_7$.2H$_2$O, 300 g, 1.01 mol) in 1.5 L of water followed by slowly adding conc. sulfuric acid (300 mL) to the cooled solution (0 °C). Compounds were visualized/ located by spraying the TLC plate with a solution of 2 % ceric ammonium sulfate in 0.5 M H$_2$SO$_4$ followed by heating on a hot plate until color developed. Solid compounds were purified on silica gel using flash column chromatography and specified eluents, or by crystallization. Liquids and oils were purified using flash column chromatography. The sodium phosphate buffer stock solution
was made by dissolving sodium phosphate monobasic (803 mg, 6.7 mmol) and sodium phosphate dibasic (950 mg, 6.7 mmol) in water (20 mL).

2.3.2. Synthesis of Core Molecules

2.3.2.1. 1-Allyl-4-bromobenzene (86).

\[ \text{\begin{tikzpicture}
\draw (-0.5,0) -- (0.5,0) -- (0.5,1) -- (-0.5,1) -- cycle;
\draw (-0.5,0.5) -- (0.5,0.5) -- (0.5,-0.5) -- (-0.5,-0.5) -- cycle;
\node at (0,0) {\text{Br}};
\end{tikzpicture}} \]

A stirred mixture of magnesium turnings (3.62 g, 0.149 mol) and dry THF (150 mL) in a two-neck round-bottomed flask was flushed with N\(_2\) for 10 min then heated to 40 °C when two drops of 1,2-dibromoethane were added. A 10 % of a solution of 1,4-dibromobenzene (29.3 g, 0.124 mol) in THF (50 mL) was added and when the magnesium had started to react, the rest of this solution was added slowly over 0.5 h. Stirring was continued until the magnesium turnings were completely consumed. The flask was cooled to 0 °C and a solution of allyl bromide (16.5 g, 0.136 mol) in dry THF (30 mL) was added slowly over 0.5 h. The mixture was heated under reflux for 12 h, and then allowed to cool to rt. Water (60 mL) was carefully added and the mixture was extracted using diethyl ether (40 mL x 3). The combined extracts were dried (MgSO\(_4\)), filtered, and concentrated. Purification using column chromatography (hexanes/EtOAc; 2: 1, R\(_F\) 0.44) afforded a colorless syrup (15.4 g, 63 % yield). \(^1\)H NMR and \(^{13}\)C NMR data were more or less similar to lit.\(^{189}\)

2.3.2.2. 1,4-Diallylbenzene (85).
An oven-dried two-neck round-bottomed flask charged with diiodide 88 (48.0 g, 0.134 mol), Cul (2.55 g, 0.013 mol), and 2,2’-dipyridyl (2.10 g, 0.013 mol) was evacuated and flushed with N₂. Anhydrous THF (700 mL) was added and the stirred reaction mixture was cooled to 0 °C. A 1 M solution of vinyl magnesium bromide in THF (540 mL, 0.536 mol) was added quickly via cannula, and the reaction mixture was allowed to warm to rt. After 1 h, saturated NH₄Cl (200 mL) and 28% NH₃ (150 mL) were added and the mixture was stirred for 1h at rt. The product was extracted using hexanes (100 mL × 3) and the combined extracts were washed with brine (60 mL × 2), dried (MgSO₄), filtered, and concentrated. Purification using column chromatography (hexanes, R$_F$ 0.37) gave a colorless oily syrup (17.2 g, 81% yield); $^1$H and $^{13}$C NMR data were similar to lit.$^{139,142}$

2.3.2.3. 1,3,5-Triallylbenzene (89).

A tube was charged with allyltributylstannane$^{148}$ (3.10 mL, 0.010 mol), 1,3,5-tribromobenzene (1.00 g, 0.003 mol), tetrakis(triphenylphosphine)palladium(0) (0.280 g, 0.242 mmol), dry benzene (5 mL), and a stirring bar. The tube was evacuated and back-filled with N₂ three times. The reaction mixture was stirred in the sealed tube at a bath temperature of 120 °C for 24 h and then allowed to cool to rt. After carefully releasing the pressure, the reaction mixture was diluted with diethyl ether (15 mL) and stirred for 15 min with saturated aqueous KF (10 mL). The organic layer was separated and stirred with 10% NH₄OH (10 mL) for 20 min. The organic layer was separated, washed with brine (10 mL), dried (MgSO₄), and concentrated to
give crude triallylbenzene that was distilled (bp 125 ºC/ 1.5 torr) to give the pure product as a colorless syrup (0.47 g, 75% yield): $^1$H NMR (500.13 MHz, CDCl$_3$) $\delta$ 3.35 (d, $J = 6.5$ Hz, 6H, 3CH$_2$ sp$^3$), 5.05 – 5.11 (m, 6H, 3CH$_2$CH=CH$_2$), 5.92 – 6.01 (m, 3H, 3CH$_2$CH=CH$_2$), 6.87 (s, 3H, PhH); $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$ 140.3 (PhC), 137.6 (3CH$_2$CH=CH$_2$), 126.6 (PhC), 115.7 (3CH$_2$CH=CH$_2$), 40.2 (3CH$_2$ sp$^3$). HR-EI MS $m/z$ calcd for C$_{15}$H$_{18}$ 198.1409, found 198.1419.

### 2.3.2.4. General method for forming allyl ethers: 1,4-diallyloxybenzene (90).

[Diagram of 90]

Allyl bromide (220 g, 1.82 mol) and anhydrous DMF (200 mL) were cooled to -10 ºC and sodium hydride (60% oil dispersion, 17.6 g, 0.440 mol) was added. The resulting mixture was stirred for 10 min, and a solution of hydroquinone (20.0 g, 0.182 mol) in DMF (200 mL) was added dropwise over 30 min. The reaction mixture was stirred for 15 min after which TLC confirmed the disappearance of hydroquinone. The flask was allowed to warm to 0 ºC and water (150 mL) was carefully added. The product was extracted using diethyl ether (150 mL) and the aqueous layer was extracted with ether ($2 \times 60$ mL). The organic layers were combined, dried (MgSO$_4$), filtered, and concentrated under vacuum. The crude product was obtained as a pale yellow oily liquid and crystallized out of hexanes at -10 ºC to give colorless crystals (34.2 g, 99% yield): mp 38 - 40 ºC; lit.$^{190}$ mp 31.9 – 32.4 ºC; $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$ 153.1 (PhC), 133.8 (CH sp$^2$), 117.6 (CH$_2$ sp$^3$), 115.8 (PhC), 69.6 (CH$_2$ sp$^3$); $^1$H NMR more or less similar to lit.$^{191}$
2.3.2.5. 1-Allyloxy-4-bromobenzene (91).

\[ \text{prepared from allyl bromide (70.0 g, 0.580 mol) in anhydrous DMF (200 mL), sodium hydride (60\% oil dispersion, 5.60 g, 0.140 mol), and a solution of 4-bromophenol (20.0 g, 0.116 mol) in DMF (100 mL) as for 90. The product was obtained as a colorless oily liquid after purification using column chromatography (24 g, 97\% yield): (EtOAc/hexanes; 1:2, R_f 0.52); }^{1} \text{H NMR and }^{13} \text{C NMR spectra similar to lit.}^{192} \]

2.3.2.6. 1-Allyloxy-4-iodobenzene (92).

\[ \text{the general method for allylation with allyl bromide (68.7 g, 0.568 mol) in DMF (200 mL), sodium hydride (60\% oil dispersion, 5.45 g, 0.136 mol), and a solution of 4-iodophenol (25.0 g, 0.114 mol) in DMF (100 mL) gave after purification using column chromatography (hexanes, R_f 0.43), the title compound as a yellow oil (28.3 g, 96 \% yield): }^{1} \text{H NMR (500.13 MHz, CDCl}_3) \delta 4.49 (dt, J = 5.0, 1.5 Hz, 2H, OCH}_2), 5.33 (dq, J = 10.5 Hz, 1.5 Hz, 1H, H}_\text{cis}), 5.44 (dq, J = 17.5 Hz, 1.5 Hz, 1H, H}_\text{trans}), 6.05 (ddt, J = 17.5 Hz, 10.5 Hz, 5 Hz, 1H, CH}_2\text{CH=CH}_2), 6.69 - 6.72 (m, 2H, PhH), 7.55 - 7.58 (m, 2H, PhH); }^{13} \text{C NMR (125.7 MHz, CDCl}_3) \delta 158.3, 138.1 (PhC), 132.8 (vinyl CH) 117.8 (vinyl CH}_2), 117.1 (PhCH), 83.0 (PhCl), 68.6 (CH}_2\text{sp}^3); HR EIMS m/z calculated for C}_9\text{H}_9\text{IO 259.9698, found 259.9690. Note that the }^{1} \text{H NMR data are more or less similar to those of Taskinen,}^{193} \text{ but neither the }^{1} \text{H NMR nor }^{13} \text{C NMR data match those in the characterization of 92 provided by Qu et al.}^{194} \]
2.3.2.7. General method for one pot reductive ozonolysis and reduction: 1,4-benzenediethanol (79).

Ozone was bubbled through a solution of 85 (4.65 g, 29.4 mmol) maintained at –78 ºC in a 1:1 mixture of methanol (100 mL) and dichloromethane (100 mL) until TLC confirmed the disappearance of the olefin. N₂ was then bubbled through the reaction mixture for 15 min. Excess dimethyl sulfide was added at -78 ºC, and the reaction mixture was allowed to warm to rt with stirring. The reaction mixture was concentrated under vacuum, and the resulting syrup was dissolved in absolute ethanol (100 mL). The reaction flask was cooled to 0 ºC and excess NaBH₄ was added in portions with stirring. Stirring was continued at rt for 20 h and water (20 mL) was added. The reaction mixture was acidified to pH ~ 6 (20% HCl) and filtered. Concentration of the filtrate under vacuum gave a thick oily residue, which was then dissolved in EtOAc (65 mL) and water (15 mL). The organic layer was collected, dried (MgSO₄), and concentrated. The product was obtained as a colorless solid and was purified using column chromatography (EtOAc, RF 0.52) to give colorless crystals (3.86 g, 79% yield): mp 84 - 86 °C; lit.¹³⁸ mp 85 °C.

2.3.2.8. 1,3,5-Benzenetriethanol (80).

Compound 80 was prepared from 89 (4.26 g, 0.022 mol) by the general method and purified using column chromatography to give colorless crystals (3.52 g, 78% yield): mp 74 - 76 °C; lit.¹⁴³ mp 75 °C. ¹H and ¹³C NMR data were similar to lit.¹⁴⁷
2.3.2.9. 1,4-Bis-(2-hydroxyethoxy)benzene (81).

\[
\begin{align*}
\text{HO} & \quad \text{O} & \quad \text{O} & \quad \text{OH} \\
81
\end{align*}
\]

Prepared from 90 (4.68 g, 0.025 mol) as for 79 and purified using column chromatography (EtOAc; R_f 0.51) to give the product as a colorless crystalline powder (3.87 g, 79% yield): mp 102 - 104 °C; lit.\textsuperscript{161} mp 103 - 104 °C.

2.3.2.10. 2-(4-Bromophenoxy)ethanol (82).

\[
\begin{align*}
\text{HO} & \quad \text{O} & \quad \text{Br} \\
82
\end{align*}
\]

The general method with 91 (12.5 g, 0.058 mol) gave the product as a thick residue that was purified using column chromatography (EtOAc, R_f 0.31). The product solidified on cooling (fridge) to give colorless crystals (10 g, 79% yield): mp 54 - 56 °C; lit.\textsuperscript{150} mp 55 °C.

2.3.2.11. 2-(4-Iodophenoxy)ethanol (83).

\[
\begin{align*}
\text{HO} & \quad \text{O} & \quad \text{I} \\
83
\end{align*}
\]

The general method with 92 (5.00 g, 0.019 mol) gave the product as a colorless solid that was purified using column chromatography (EtOAc, R_f 0.31) to give a colorless crystalline solid (3.96 g, 78% yield): mp 75 - 76 °C; lit.\textsuperscript{154} mp 73.5 - 74.5 °C.
2.3.3. Synthesis of Dendrons

2.3.3.1. General procedure for mono-O-benzylation of diols

*trans*-5-Benzylxoxymethyl-cis-5-hydroxymethyl-2-phenyl-1,3-dioxane and

cis-5-benzylxoxymethyl-trans-5-hydroxymethyl-2-phenyl-1,3-dioxane (95, 96)

Mono-O-benzylidine pentaerythritol 94\(^{164}\) (5.00 g, 0.022 mol) and dibutyltin oxide (5.55 g, 0.022 mol) were dissolved in dry toluene (300 mL) in a 500 mL round bottom flask. The flask was fitted with a Dean-Stark apparatus, and the mixture was heated at reflux (115 °C) for 12 h. The mixture was then allowed to cool to rt, and benzyl bromide (3.81 g, 0.223 mol) and tetrabutylammonium bromide (1.00 g, 3.10 mmol) were added. Heating at reflux temperature (115 °C) was continued for another 12 h. The reaction mixture was allowed to cool to rt and then concentrated under vacuum. The concentrated residue was dissolved in CH\(_2\)Cl\(_2\) (150 mL) and this organic layer was washed repeatedly with water until the aqueous layer became clear. The organic layer was dried (MgSO\(_4\)), filtered, and concentrated to give a crude mixture of 95 and 96 as a pale yellow syrup. Purification was achieved using column chromatography (EtOAc/hexanes, 1:2). First to elute was compound 95 as a thick colorless syrup (3.40 g, 49 %); (EtOAc/hexanes, 1:2, R\(_F\) 0.51); \(^1\)H and \(^{13}\)C NMR spectra similar to lit.\(^{171}\) The second component 96 was also a thick colorless syrup (2.41, 35 %); (EtOAc/hexanes, 1:2, R\(_F\) 0.41); \(^1\)H and \(^{13}\)C NMR more or less similar to lit.\(^{171}\)
2.3.3.2. *trans*-5-Benzyloxymethyl-*cis*-5-hydroxymethyl-2-(4-methoxyphenyl)-1,3-dioxane and *cis*-5-benzyloxymethyl-*trans*-5-hydroxymethyl-2-(4-methoxyphenyl)-1,3-dioxane (98, 99)

The general procedure using 5,5-bis(hydroxymethyl)-2-(4-methoxyphenyl)-1,3-dioxane (97)\(^{195,196}\) (6.00 g, 0.024 mol) gave a mixture of 98 and 99 as a colorless solid. Purification was achieved using column chromatography (EtOAc/ hexanes, 1:2). First to elute was compound 98 as a colorless crystalline solid (3.90 g, 48 %); (EtOAc/ hexanes, 1:2, R\(_f\) 0.38): mp 90 – 91 °C; \(^1\)H NMR (500.13 MHz, CDCl\(_3\)) \(\delta\) 2.55 (s, br, 1H), 3.52 (s, 2H), 3.75 (d, \(J = 11.5\) Hz, 2H), 3.81 (s, 3H), 3.97 (s, 2H) 4.18 (d, \(J = 11.5\) Hz, 2H), 4.62 (s, 2H), 5.38 (s, 1H), 6.88 – 6.91 (m, 2H), 7.30 – 7.39 (m, 7H); \(^13\)C NMR (125.7 MHz, CDCl\(_3\)) \(\delta\) 160.2, 138.0, 130.8, 128.7, 128.0, 127.8, 127.5, 113.8, 102.1, 73.9, 72.2, 70.5, 66.1, 55.4, 38.7. HR ESI MS: \(m/z\) calcd for C\(_{20}\)H\(_{24}\)NaO\(_5\) 367.1516, found 367.1524. The second component 99 was also a colorless crystalline solid (2.93 g, 36 %); (EtOAc/hexanes, 1:2, R\(_f\) 0.33); mp 101 – 102 °C; \(^1\)H NMR (500.13 MHz, acetone-\(d_6\)) \(\delta\) 3.49 (d, \(J = 5.5\) Hz, 2H), 3.73 (t, \(J = 5.5\) Hz, 1H), 3.79 (s, 3H), 3.85 (s, 2H), 3.87 (d, \(J = 12\) Hz, 2H), 4.07 (d, \(J = 12\) Hz, 2H), 4.60 (s, 2H), 5.39 (s, 1H), 6.88 – 6.91 (m, 2H), 7.27 – 7.40 (m, 7H); \(^13\)C NMR (125.7 MHz, acetone-\(d_6\)) \(\delta\) 160.8, 139.9, 132.5, 129.0, 128.4, 128.1, 114.0, 102.2, 73.8, 70.5, 70.0, 63.1, 55.5, 39.9. HR ESI MS: \(m/z\) calcd for C\(_{20}\)H\(_{24}\)NaO\(_5\) 367.1516, found 367.1518.
2.3.3.3. General procedure for Merck oxidation of alcohols

*trans*-5-Benzylxymethyl-*cis*-2-phenyl-1,3-dioxane-5-carboxylic acid and
*cis*-5-benzyloxymethyl-*trans*-2-phenyl-1,3-dioxane-5-carboxylic acid (100, 101)

Benzyl alcohol (95) (8.56 g, 27.2 mmol), 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) (0.300 g, 1.91 mmol), and sodium phosphate buffer (pH 6.7) (105 mL) were dissolved in acetonitrile (140 mL). The resulting mixture was stirred and heated to 38 ºC for 5 min. About 20 % of a solution of 80% sodium chlorite (6.22 g, 54.5 mmol) in water (28 mL) was added to the mixture through a pressure-equalizing funnel. Via another pressure-equalizing funnel, 20 % of a solution of household bleach (6% sodium hypochlorite) (0.64 mL) in water (13 mL) was also added. The remaining bleach and sodium chlorite solutions were added simultaneously over a period of 0.5 h. Stirring at 38 ºC was continued for another 10 to 12 h. The reaction mixture was allowed to cool to rt, water was added (140 mL), and the pH was adjusted to 8 using a 0.5 M NaOH solution. The reaction flask was cooled with a water-ice bath, and an ice-cold solution of sodium sulfite (8.30 g, 66.0 mmol) in water (136 mL) was added. The resulting mixture was stirred for 45 min, diluted with CH2Cl2 (150 mL), and stirring was continued for a further 20 min. The organic layer was separated, discarded, and more CH2Cl2 (150 mL) was added. After stirring for 10 min, this organic layer was also separated and discarded. The aqueous layer was acidified (pH = 5- 6) using 20 % HCl and CH2Cl2 (150 mL) was added. The organic layer was collected, and the aqueous layer extracted with CH2Cl2 (2 x 100 mL). The organic layers were combined, dried (MgSO4), filtered, and concentrated to give a
crude colorless solid. The product was purified using crystallization (EtOAc/hexanes) to afford **100** as colorless crystals (7.06 g, 79 %): mp 113 - 114 ºC; $^1$H NMR (500.13 MHz, CDCl$_3$) $\delta$ 3.46 (s, 2H), 3.92 (d, $J = 11.5$ Hz, 2H), 4.49 (s, 2H), 4.67 (d, $J = 11.5$ Hz, 2H), 5.46 (s, 1H), 7.24 - 7.47 (m, 10H); $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$ 176.8, 137.6, 137.4, 129.3, 128.7, 128.5, 128.1, 127.8, 126.3, 102.1, 73.8, 70.32, 70.28, 47.2. HR ESI MS: $m/z$ calcd for C$_{19}$H$_{19}$O$_5$ 327.1238, found 327.1233.

In a similar fashion, 7.25 g of **96** was oxidized and afforded **101** also as colorless crystals (5.76 g, 76 %): mp 134 – 135 ºC; $^1$H NMR (500.13 MHz, CDCl$_3$) $\delta$ 4.10 (s, 2H), 4.15 (d, $J = 12$ Hz, 2H), 4.38 (d, $J = 12$ Hz, 2H), 4.65 (s, 2H), 5.45 (s, 1H), 7.29 - 7.43 (m, 10H); $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$ 175.3, 137.7, 137.6, 129.4, 128.6, 128.5, 128.0, 127.8, 126.2, 102.0, 73.9, 69.3, 68.7, 46.0. HR ESI MS: $m/z$ calcd for C$_{19}$H$_{19}$O$_5$ 327.1238, found 327.1238.

2.3.3.4. trans-5-Benzylxymethyl-cis-2-(4-methoxyphenyl)-1,3-dioxane-5-carboxylic acid (102)

![Structure of 102](image)

The general procedure using **98** (1.38 g, 4.01 mmol) at 35 ºC for 11 h (see table 2.1) gave a colorless solid which was crystallized (EtOAc/ hexanes) to afford **102** as colorless crystals (0.57 g, 40 %): mp 125 – 126 ºC; $^1$H NMR (500.13 MHz, CDCl$_3$) $\delta$ 3.47 (s, 2H), 3.78 (s, 3H), 3.91 (d, $J = 12$ Hz, 2H), 4.50 (s, 2H), 4.66 (d, $J = 12$ Hz, 2H), 5.43 (s, 1H), 6.85 - 6.88 (m, 2H), 7.27 – 7.41 (m, 7H); $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$ 177.6, 160.2, 137.4, 130.2, 128.7, 128.1, 127.73, 127.66, 113.8, 102.0, 73.7, 70.3, 70.2, 55.4, 47.3. HR ESI MS: $m/z$ calcd for C$_{20}$H$_{21}$O$_6$ 357.1333, found 327.1336.
2.3.3.5. cis-5-Methyl-2-phenyl-1,3-dioxane-5-carboxylic acid (43)

![cis-5-Methyl-2-phenyl-1,3-dioxane-5-carboxylic acid (43)](image)

2,2-Bis(hydroxymethyl)propanoic acid (30.0 g, 0.224 mol) was dissolved in water (300 mL). Under vigorous stirring, conc. HCl (3 mL) was added, and benzaldehyde (23.7 g, 0.224 mol) was added dropwise over a period of 2 h at 38 °C. When the addition was complete, stirring was continued for 12 h at 40 ºC. The reaction mixture was allowed to cool to rt, and the precipitated solid product was collected using suction filtration and was washed with water (2 x 50 mL), then crystallized (EtOAc) to give colorless needles (27 g, 54% yield): mp 149 - 151 °C; lit. mp 185 - 187 °C, 197 - 198 °C; ¹H NMR (500.13 MHz, CDCl₃) δ 1.11 (s, 3H, CH₃), 3.71 (d, J = 11.5 Hz, 2H, H-4ax, H-6ax), 4.62 (d, J = 11.5 Hz, 2H, H-4eq, H-6eq), 5.49 (s, 1H, H-2), 7.32 - 7.37 (m, 3H, PhH), 7.44 - 7.48 (m, 2H, PhH); ¹H NMR (500.13 MHz, acetone-d₆): δ 1.05 (s, 3H, CH₃), 1.11 (s, 3H, CH₃), 3.74 (d, J = 11.5 Hz, 2H, H-4ax, H-6ax), 4.57 (d, J = 11.5 Hz, 2H, H-4eq, H-6eq), 5.53 (s, 1H, H-2), 7.31 - 7.44 (m, 5H, PhH); ¹³C NMR (125.7 MHz, acetone-d₆): δ 175.7 (C=O), 139.8, 129.4, 128.7, 127.1 (PhC), 102.1 (C-2), 74.0 (C-4, C-6), 42.6 (C-5), 18.2 (CH₃). HR ESI MS: m/z calcd for C₁₂H₁₃O₄ 221.0819, found 221.0834.

2.3.3.6. 5,5-Bis(benzyloxymethyl)-2-phenyl-1,3-dioxane (105)

![5,5-Bis(benzyloxymethyl)-2-phenyl-1,3-dioxane (105)](image)

Mono-O-benzylidene pentaerythritol (94) (0.740 g, 3.30 mmol) and benzyl bromide (1.35 g, 7.89 mmol) were dissolved in dry DMF (15 mL) at 0 °C. NaH (60%) (0.318 g, 7.95...
mmol) was then added in portions, and the reaction mixture was allowed to warm to rt with stirring for 12 h. Water (3 mL) and CH₂Cl₂ (20 mL) were added and the resulting mixture was stirred for 10 min. The organic layer was collected, washed with water (3 x 7 mL), dried (MgSO₄), filtered, and concentrated to give a crude colorless solid. Purification using column chromatography (hexanes/EtOAc; 5:1, Rf 0.45) gave 105 as a colorless crystalline solid (1.15 g, 86 % yield): mp 79 °C; lit.¹⁷⁷ mp 72 °C; ¹H NMR (500.13 MHz, CDCl₃) δ 3.46 (s, 2H, CH₂eq), 3.99 (s, 2H, CH₂ax), 4.03 (d, J = 11.5 Hz, 2H, H-4ax, H-6ax), 4.31 (d, J = 11.5 Hz, 2H, H-4eq, H-6eq), 4.58 (s, 2H, OCH₂Pheq), 4.70 (s, 2H, OCH₂Phax), 5.54 (s, 1H, H-2), 7.38 – 7.50 (m, 13H, PhH), 7.57 – 7.59 (m, 2H, PhH); ¹³C NMR (125.7 MHz, CDCl₃) δ 138.7, 138.4, 138.3, 129.0, 128.4, 128.33, 128.30, 127.7, 127.52, 127.46, 126.2 (PhC), 101.8 (C-2), 73.4 (OCH₂Phax), 73.3 (OCH₂Pheq), 70.3 (CH₂ax), 70.2 (C-4, C-6), 68.9 (CH₂eq), 39.0 (C-5). HR ESI MS: m/z calcd for C₂₆H₂₈NaO₄ 427.1880, found 427.1852.

2.3.3.7. General procedure for reductive opening of benzylidene acetals

3-(Benzyloxy)-2,2-bis(benzyloxymethyl)propan-1-ol (106)

To a solution of benzylidene acetal (105) (2.00 g, 4.94 mmol) in anhydrous THF (10 mL) was added a 1 M solution of BH₃·THF complex (9.88 mL, 9.88 mmol) under nitrogen. Anhydrous CoCl₂ (1.28 g, 9.88 mmol) was added in one portion and the reaction mixture was stirred at rt for 20 min when TLC confirmed the disappearance of the starting material. The reaction mixture was diluted using EtOAc (40 mL) and undissolved CoCl₂ was filtered off. The blue solution was cooled to 0 °C and aqueous NaBH₄ solution was added dropwise with stirring

62
until the blue color disappeared and there was formation of a black precipitate. The precipitate
was filtered off and the organic layer was separated, washed with NaHCO₃ (1 M, 10 mL), water
(10 mL) and dried (MgSO₄). Concentration followed by column chromatography (hexanes/
EtOAc; 3:1, Rf 0.39) gave the product as a colorless syrup (1.83 g, 91% yield): ¹H and ¹³C NMR
spectra similar to lit.¹⁷⁸

2.3.3.8. 3-(Benzyloxy)-2,2-bis(methoxymethyl)propan-1-ol (110)

Using the general procedure with benzylidene acetal (109)¹⁷⁷ (16.4 g, 65.1 mmol), 110
was obtained as colorless syrup (15.4 g, 93% yield) after purification using column
chromatography (hexanes/EtOAc; 2:1, Rf 0.33). ¹H and ¹³C NMR spectra similar to lit.¹⁹⁷

2.3.3.9. 3-(Benzyloxy)-2-(benzyloxymethyl)-2-((4-methoxybenzyloxy)methyl)propan-1-ol
(115)

Acetal 113 (8.61 g, 19.8 mmol) was dissolved in dichloromethane (15 mL) and the
reaction flask was cooled to -78 °C. Diisobutylaluminum hydride (DIBAL-H) (40 mL, 39.6
mmol) (1 M in CH₂Cl₂) was added dropwise to the cooled solution with stirring. The reaction
mixture was stirred for 6 h at - 78 °C or for 3 h at - 10 °C when TLC confirmed the
disappearance of the starting material. The mixture was diluted using dichloromethane (15 mL)
and quenched using methanol at 0 °C. To the reaction mixture was then added 10 % KOH (10 mL) and the mixture was stirred for 10 min at rt. The organic layer was collected, dried (MgSO₄), filtered, and concentrated. Purification using column chromatography (hexanes/EtOAc; 3:1, R_f = 0.23) gave the product as a colorless syrup (8.04 g, 93% yield): ^1^H NMR (500.13 MHz, CDCl₃) δ 3.13 (t, J = 6.0 Hz, 1H, OH), 3.69 (s, 2H, OCH₂C₅H₄), 3.70 (s, 4H, C₅H₄CH₂OBn), 3.84 (s, 3H, OCH₃), 3.92 (d, J = 6.0 Hz, 2H, CH₂OH), 4.53 (s, 2H, OCH₂PMP), 4.59 (s, 2H, 2OCH₂Ph), 6.96 – 6.99 (m, 2H, PhH), 7.32 – 7.34 (m, 2H, PhH), 7.36 – 7.45 (m, 10H, PhH); ^1^C NMR (125.7 MHz, CDCl₃) δ 159.0, 138.3, 130.3, 129.0, 128.2, 127.4, 127.3, 113.6 (PhC), 73.30 (2OCH₂Ph), 73.0 (OCH₂PMP), 70.6 (C₅H₄CH₂OBn), 70.3 (C₅H₄CH₂OCH₂PMP), 65.6 (CH₂OH), 55.0 (OCH₃), 45.0 (C₅H₄). HR ESI MS: m/z calculated for C₂₇H₃₂NaO₅ 459.2142, found 459.2152.

2.3.3.10. General oxidation procedure using Jones reagent

3-(Benzyloxy)-2,2-bis(benzyloxy)methyl)propanoic acid (107)

Alcohol 106 (1.13 g, 2.80 mmol) was dissolved in acetone (12 mL) and the Jones reagent (0.56 M, 7.5 mL, 4.20 mmol) was added dropwise at 0 °C with stirring over a 1 h period. The ice-water bath was removed and stirring was continued for 8 h at rt. Acetone was removed under vacuum and water (12 mL) was added. The aqueous layer was extracted using diethyl ether (12 mL x 3). The combined organic layers were washed with water (9 mL x 3), dried (MgSO₄), and concentrated. Purification using column chromatography (hexanes/ EtOAc; 3:1, R_f 0.27) gave the acid as a colorless solid (0.87 g, 74 % yield). Purification was also achieved using
crystallization (hexanes/ EtOAc) in 61 % yield: mp 94 - 95 °C; \(^{1}\)H NMR (500.13 MHz, acetone-
\(d_6\)) \(\delta\) 3.77 (s, 6H, 3C\textsubscript{quat}CH\textsubscript{2} O), 4.53 (s, 6H, 3OCH\textsubscript{2}Ph), 7.25 - 7.34 (m, 15H, PhH), 10.89 (br, 1H, OH); \(^{13}\)C NMR (125.7 MHz, acetone-
\(d_6\)) \(\delta\) 173.9 (C=O), 139.5, 129.0, 128.14, 128.10 (PhC), 73.7 (3CH\textsubscript{2}Ph), 68.8 (3C\textsubscript{quat}CH\textsubscript{2}O), 53.8 (C\textsubscript{quat}). HR ESI MS: \(m/z\) calcd for C\textsubscript{26}H\textsubscript{27}O\textsubscript{5} (M-H) 419.1864, found 419.1850.

2.3.3.11. 3-(Benzyloxy)-2,2-bis(methoxymethyl)propanoic acid (111)

According to the general procedure, alcohol 110 (1.53 g, 6.02 mmol) and the Jones reagent (0.56 M, 16 mL, 9.00 mmol) in acetone (15 mL) were reacted for 8 h. After work up as above, a pure product was obtained as a colorless syrup (1.40 g, 87 % yield). \(^{1}\)H NMR (500.13 MHz, CDCl\textsubscript{3}) \(\delta\) 3.36 (s, 6H), 3.63 (s, 4H), 3.70 (s, 2H), 4.56 (s, 2H), 7.27 - 7.37 (m, 5H), 11.80 (br, 1H); \(^{13}\)C NMR (125.7 MHz, CDCl\textsubscript{3}) \(\delta\) 178.3, 138.2, 128.3, 127.6, 127.5, 73.3, 70.4, 67.8, 59.4, 53.4. HR ESI MS: \(m/z\) calcd for C\textsubscript{14}H\textsubscript{19}O\textsubscript{5} (M-H) 267.1238, found 267.1236.

2.3.3.12. General procedure for anhydride formation

A carboxylic acid (9.14 mmol) and DCC (1.04 g, 5.02 mmol) were dissolved in dry CH\textsubscript{2}Cl\textsubscript{2} (25 mL), and the mixture was stirred at rt until TLC confirmed the disappearance of the acid (6 – 10 h). The precipitated urea by-product was filtered off, and the organic layer was concentrated to give the crude product, which was purified as indicated below for individual anhydrides.
2.3.3.13. trans-5-Benzylloxymethyl-cis-2-phenyl-1,3-dioxane-5-carboxylic anhydride and cis-5-benzylloxymethyl-trans-2-phenyl-1,3-dioxane-5-carboxylic anhydride (103 and 104)

According to the general procedure, carboxylic acid 100 (3.00 g, 9.14 mmol) and DCC in dry CH₂Cl₂ were stirred at rt for 6 h to give crude 103 as a colorless solid. Crystallization (EtOAc/ hexanes) afforded colorless crystals (2.60 g, 89% yield): mp 121 – 122 °C; ¹H NMR (500.13 MHz, CDCl₃) δ 3.45 (s, 4H), 3.86 (d, J = 11.5Hz, 4H), 4.40 (s, 4H), 4.72 (d, J = 11.5 Hz, 4H), 5.46 (s, 2H), 7.23 - 7.47 (m, 20H); ¹³C NMR (125.7 MHz, CDCl₃) δ 167.0, 137.8, 137.3, 129.2, 128.6, 128.3, 128.0, 127.8, 126.5, 102.2, 73.7, 70.1, 70.0, 49.3. HR ESI MS: m/z calcd for C₃₈H₃₈NaO₉ 661.2408, found 661.2418.

In a similar manner, carboxylic acid 101 (4.36 g, 13.3 mmol) and DCC (1.51 g, 7.29 mmol) afforded anhydride 104 as colorless crystals (3.86 g, 91% yield): mp 129 - 131 °C; ¹H NMR (500.13 MHz, CDCl₃) δ 4.08 (s, 4H), 4.14 (d, J = 11.5 Hz, 4H), 4.37 (d, J = 11.5 Hz, 4H), 4.64 (s, 4H), 5.44 (s, 2H), 7.27 - 7.42 (m, 20H); ¹³C NMR (125.7 MHz, CDCl₃) δ 166.6, 137.4, 136.9, 128.8, 128.2, 128.0, 127.6, 127.4, 126.1, 101.8, 73.3, 69.7, 69.6, 48.9. HR ESI MS: m/z calcd for C₃₈H₃₈NaO₉ 661.2408, found 661.2403.

2.3.3.14. 3-(Benzyloxy)-2,2-bis(benzyloxymethyl)propanoic anhydride (108)
According to the general procedure, carboxylic acid 107 (3.84 g, 9.14 mmol) and DCC in dry CH₂Cl₂ were stirred at rt for 8 h and gave the crude product as a colorless solid. Purification using column chromatography (hexanes/ EtOAc; 3:1; RF 0.45) gave a colorless crystalline solid (3.34 g, 89% yield). Purification was also achieved using crystallization (MeOH, - 10 °C) to give colorless crystals: mp 69 - 70 °C; ¹H NMR (500.13 MHz, acetone-d₆) δ 3.70 (s, 12H, 6C₄H₂O), 4.46 (s, 12H, 6OCH₂Ph), 7.24 - 7.32 (m, 30H, PhH); ¹³C NMR (125.7 MHz, acetone-d₆) δ 167.4 (C=O), 139.2, 129.1, 128.4, 128.3 (PhC), 73.9 (CH₂Ph), 68.1 (C₄H₂O), 55.8 (C₄H₂O). HR ESI MS: m/z calcd for C₅₂H₅₄NaO₉ 845.3660, found 845.3651.

2.3.3.15. 3-(Benzyloxy)-2,2-bis(methoxymethyl)propanoic anhydride (112)

According to the general procedure, carboxylic acid 111 (2.45 g, 9.14 mmol) and DCC in dry CH₂Cl₂ were stirred at rt for 7 h and gave the crude product as a pale yellow oil. The oil was then purified using column chromatography (hexanes/ EtOAc; 3:1; RF 0.30) to give a colorless oil (2.23 g, 94 % yield): ¹H NMR (500.13 MHz, CDCl₃) δ 3.34 (s, 12H), 3.62 (s, 8H), 3.69 (s, 4H), 4.54 (s, 4H), 7.29 - 7.37 (m, 10H); ¹³C NMR (125.7 MHz, CDCl₃) δ 166.9 (C=O), 138.1, 128.2, 127.5, 127.4 (PhC), 73.3 (CH₂Ph), 69.7 (C₄H₂OBn), 67.4 (C₄H₂OMe), 59.2 (C₄H₂OMe), 54.9 (OMe). HR ESI MS: m/z calcd for C₂₈H₃₈NaO₉ 541.2419, found 541.2414.

2.3.3.16 3-(Allyloxy)-2,2-bis(allyloxymethyl)propanoic anhydride (119)
According to the general procedure, carboxylic acid 118 (2.47 g, 9.14 mmol) and DCC in dry CH$_2$Cl$_2$ were stirred at rt for 9 h and gave the crude product as a thick oil. The oil was then purified using column chromatography (hexanes/ EtOAc; 3:1; R$_f$ 0.58) to give a colorless oil (2.22 g, 93 % yield). $^1$H NMR (500.13 MHz, CDCl$_3$) $\delta$ 3.63 (s, 12H), 3.96 (dt, $J = 5.5$ Hz, 1.5 Hz, 12H), 5.12 (dtd, $J = 10.5$, 3.0, 1.5 Hz, 6H), 5.23 (dtd, $J = 17.3$, 3.0, 1.5 Hz, 6H), 5.79 - 5.87 (m, 6H); $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$ 167.0 (C=O), 134.6 (CH$_{sp2}$), 116.7 (CH$_{2sp2}$), 72.4 (OCH$_2$), 67.4 (C$_{quat}$CH$_2$O), 55.0 (C$_{quat}$). HR ESI MS: m/z calcd for C$_{28}$H$_{42}$NaO$_9$ 545.2721, found 545.2747.
Chapter 3. Efficient and Controllably Selective Preparation of Esters

3.1. Introductory Remarks

A very large number of methods are available for the formation of esters from carboxylic acids and alcohols.\textsuperscript{199-202} When both the carboxylic acid and the alcohol are large and acid or base-sensitive, fewer options are available but these are still numerous. The methods used most commonly include dehydration using DCC and DMAP\textsuperscript{203,204} or 4-(1-pyrrolidinyl)-pyridine,\textsuperscript{205} reaction with 2-halopyridinium salts\textsuperscript{206,207} or sterically hindered aromatic acid anhydrides\textsuperscript{208-210} or chlorides.\textsuperscript{211} Some newer reagents include dimethyl-sulfamoyl chloride,\textsuperscript{212} triphenylphosphine dihalides,\textsuperscript{213} 1-tosylimidazole,\textsuperscript{214} and O-alkylisoureas.\textsuperscript{215}

3.2. The Use of Uronium-based Coupling Agents

We wanted conditions for ester formation that could be used for the efficient convergent synthesis of polyester dendrimers under very mild conditions.\textsuperscript{91} The ester groups present in both the divergently assembled polyalcoholic core and the carboxylic acid-terminated dendron, ruled out transesterification conditions and either strong Brønsted or Lewis acids or bases. Agents for formation of amides from amino acids under mild conditions meet these requirements.\textsuperscript{216-220} Many of these reagents are commercially available compounds that are stable in air at room temperature. They are very effective at promoting amide formation at room temperature but only scattered reports\textsuperscript{221-224} have appeared about their application to ester formation and those concerned formation of phenolic esters\textsuperscript{221} and primary aliphatic esters\textsuperscript{221-224} using TBTU and HBTU. An alternative approach only employed with primary alcohols is to use the uronium salt precursor, 1-hydroxybenzotriazole, with DCC and DMAP.\textsuperscript{225-227}
Uronium-based coupling agents, namely, 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (120),\(^{217}\) 2-(1H-7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TATU) (121),\(^ {220}\) and 1-[(1-(cyano-2-ethoxy-2-oxoethylideneaminoxy)dimethylaminomorpholinomethylene)]methanaminium hexafluorophosphate (COMU) (122)\(^ {218}\) depicted in Figure 9 and commercially available were used in this study. The acids and alcohols used are shown in Figure 10.

3.3. Esterification Using COMU

Reactions were initially performed using COMU and equivalent amounts of acid and alcohol at room temperature with two equivalents of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the non-nucleophilic base. Table 2 shows the results obtained under these conditions, with the yields given being of isolated products. In DMF, ester formation with small or phenolic alcohols
occurred rapidly and in good yields. Secondary alcohols showed slow reactivity and tertiary alcohols did not react even after 36 hours.

**Table 2** Esterification results using COMU (equimolar conditions)

<table>
<thead>
<tr>
<th>entry</th>
<th>acid</th>
<th>alcohol</th>
<th>reaction time (h)</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Acid 1" /></td>
<td><img src="image2.png" alt="Alcohol 1" /></td>
<td>12</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Acid 2" /></td>
<td><img src="image4.png" alt="Alcohol 2" /></td>
<td>14</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Acid 3" /></td>
<td><img src="image6.png" alt="Alcohol 3" /></td>
<td>2</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Acid 4" /></td>
<td><img src="image8.png" alt="Alcohol 4" /></td>
<td>2</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9.png" alt="Acid 5" /></td>
<td><img src="image10.png" alt="Alcohol 5" /></td>
<td>2.5</td>
<td>89</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11.png" alt="Acid 6" /></td>
<td><img src="image12.png" alt="Alcohol 6" /></td>
<td>4.5</td>
<td>74</td>
</tr>
<tr>
<td>7</td>
<td><img src="image13.png" alt="Acid 7" /></td>
<td><img src="image14.png" alt="Alcohol 7" /></td>
<td>5</td>
<td>69</td>
</tr>
<tr>
<td>8</td>
<td><img src="image15.png" alt="Acid 8" /></td>
<td><img src="image16.png" alt="Alcohol 8" /></td>
<td>3</td>
<td>78</td>
</tr>
<tr>
<td>9</td>
<td><img src="image17.png" alt="Acid 9" /></td>
<td><img src="image18.png" alt="Alcohol 9" /></td>
<td>16</td>
<td>71</td>
</tr>
<tr>
<td>10</td>
<td><img src="image19.png" alt="Acid 10" /></td>
<td><img src="image20.png" alt="Alcohol 10" /></td>
<td>16</td>
<td>68</td>
</tr>
<tr>
<td>11</td>
<td><img src="image21.png" alt="Acid 11" /></td>
<td><img src="image22.png" alt="Alcohol 11" /></td>
<td>36</td>
<td>no rxn</td>
</tr>
<tr>
<td>12</td>
<td><img src="image23.png" alt="Acid 12" /></td>
<td><img src="image24.png" alt="Alcohol 12" /></td>
<td>3</td>
<td>81</td>
</tr>
<tr>
<td>13</td>
<td><img src="image25.png" alt="Acid 13" /></td>
<td><img src="image26.png" alt="Alcohol 13" /></td>
<td>4</td>
<td>67</td>
</tr>
<tr>
<td>14</td>
<td><img src="image27.png" alt="Acid 14" /></td>
<td><img src="image28.png" alt="Alcohol 14" /></td>
<td>4</td>
<td>83</td>
</tr>
</tbody>
</table>
The reactions worked equally well in acetonitrile but were much slower in tetrahydrofuran because of poor solubility of the coupling agent in the solvent. Table 3 shows the results obtained using benzoic acid.

**Table 3** Solvent flexibility with COMU

<table>
<thead>
<tr>
<th>entry</th>
<th>acid</th>
<th>alcohol</th>
<th>solvent</th>
<th>reaction time (h)</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>CH₃CN</td>
<td>3</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>DMF</td>
<td>3</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>THF</td>
<td>24</td>
<td>69</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>CH₃CN</td>
<td>4.5</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>DMF</td>
<td>4.5</td>
<td>74</td>
</tr>
</tbody>
</table>

To test whether the base has an effect on the rate of the reaction with COMU, a set of parallel reactions was performed using both DBU and N,N-diisopropylethyl amine (DIEA) as non-nucleophilic bases. The results in Table 4 show that the two bases performed in a similar manner with this coupling agent.

As seen in Table 2, reactions of secondary alcohols were observed to be slow with moderate yields when equimolar amounts of the acid, alcohol, and coupling agent were used. To find optimum conditions for these, reactions were carried out using different equivalents of benzoic acid/ 2° alcohol and the coupling agent in DMF or in acetonitrile. When excess amounts of the acid or alcohol and the coupling agent were used, reactions reached completion faster and
yields up to 81% were obtained. For example, using 1.2 equiv of acid and 1.5 equiv of coupling agent increased the yield of esterification of benzoic acid with cyclopentanol from 68% in 16 h to 81% in 10 h. (Table 5).

**Table 4** Base flexibility with COMU

<table>
<thead>
<tr>
<th>entry</th>
<th>acid</th>
<th>alcohol</th>
<th>base 2 equiv</th>
<th>reaction time (h)</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>DBU</td>
<td>3</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>DIEA</td>
<td>3</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>DBU</td>
<td>4.5</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>DIEA</td>
<td>6</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>DBU</td>
<td>16</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>DIEA</td>
<td>18</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>DBU</td>
<td>16</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>DIEA</td>
<td>18</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>DBU</td>
<td>36</td>
<td>no rxn</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>DIEA</td>
<td>36</td>
<td>no rxn</td>
<td></td>
</tr>
</tbody>
</table>

**Table 5** Optimization for secondary alcohols with COMU

<table>
<thead>
<tr>
<th>entry</th>
<th>acid (equiv)</th>
<th>alcohol (equiv)</th>
<th>COMU (equiv)</th>
<th>reaction time (h)</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>16</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1.5</td>
<td>16</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>1.2</td>
<td>1</td>
<td>1.5</td>
<td>10</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>co-solvent</td>
<td>1.5</td>
<td>7</td>
<td>80</td>
</tr>
</tbody>
</table>
3.4. Esterification Using TBTU

The next coupling agent that was closely examined is TBTU. Initial investigation was to see whether esterification using this coupling agent was base-sensitive, using equimolar amounts of the acid, the alcohol, and the coupling agent in DMF. Surprisingly, secondary alcohols did not react when the weaker base DIEA was used (Table 6).

**Table 6** Base flexibility with TBTU

<table>
<thead>
<tr>
<th>entry</th>
<th>acid</th>
<th>alcohol</th>
<th>base (2 equiv)</th>
<th>reaction time (h)</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td></td>
<td></td>
<td>DBU</td>
<td>0.25</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DIEA</td>
<td>0.25</td>
<td>86</td>
</tr>
<tr>
<td>3-4</td>
<td></td>
<td></td>
<td>DBU</td>
<td>0.50</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DIEA</td>
<td>0.50</td>
<td>78</td>
</tr>
<tr>
<td>5-6</td>
<td></td>
<td></td>
<td>DBU</td>
<td>4</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DIEA</td>
<td>12</td>
<td>no rxn</td>
</tr>
<tr>
<td>7-8</td>
<td></td>
<td></td>
<td>DBU</td>
<td>4</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DIEA</td>
<td>12</td>
<td>no rxn</td>
</tr>
<tr>
<td>9-10</td>
<td></td>
<td></td>
<td>DBU</td>
<td>36</td>
<td>no rxn</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DIEA</td>
<td>36</td>
<td>no rxn</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td>DBU</td>
<td>1</td>
<td>72</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td>DBU</td>
<td>3</td>
<td>60</td>
</tr>
</tbody>
</table>

Even though TBTU required about 30 minutes of activation time between the acid and the coupling agent before the alcohol could be added, reactions reached completion much faster than
in the case of COMU. Here also, tertiary alcohols did not react. These observations are summarized in Table 6.

As in the case of COMU, the reactions worked equally well in acetonitrile but were much slower in tetrahydrofuran because of poor solubility of the coupling agent in the solvent. Table 7 illustrates the results obtained for esterification between benzoic acid and 2-propanol. Esterification using secondary alcohols resulted in lower yields compared to yields obtained when primary or phenolic alcohols were used (Tables 6 and 7). It was found that using excess amounts of the acid or the alcohol and the coupling agent resulted in substantial improvement of the yields. Table 8 illustrates the optimum conditions.

**Table 7** Solvent flexibility with TBTU

<table>
<thead>
<tr>
<th>entry</th>
<th>acid</th>
<th>alcohol</th>
<th>solvent</th>
<th>reaction time (h)</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 8** Optimization for secondary alcohols with TBTU

<table>
<thead>
<tr>
<th>entry</th>
<th>acid (equiv)</th>
<th>alcohol (equiv)</th>
<th>TBTU (equiv)</th>
<th>reaction time (h)</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1.5</td>
<td>4</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>1.2</td>
<td>1</td>
<td>1.5</td>
<td>4</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>co-solvent</td>
<td>1.5</td>
<td>2-3</td>
<td>96</td>
</tr>
</tbody>
</table>
3.5. Esterification Using TATU

This coupling agent is relatively expensive, which is a disadvantage especially for large-scale applications. Here, only one single reaction between every different type of alcohol (phenolic, 1°, 2°, 3°) and benzoic acid was carried out using conditions that had been found to be optimum for TBTU. As summarized in Table 9, it can be concluded that TATU and TBTU give comparable results concerning short reaction times and yields. In addition, esterification using TATU also required about 30 minutes to activate the carboxylic acid and when esterification between cyclopentanol and benzoic acid was tried using the weaker base DIEA, no reaction was observed. Esterification using tert-butanol, a tertiary alcohol, was unsuccessful, just as in the cases of both TBTU and COMU.

Table 9 Esterification results using TATU

<table>
<thead>
<tr>
<th>entry</th>
<th>acid</th>
<th>alcohol</th>
<th>reaction time (h)</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>I-phenol</td>
<td>0.25</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>benzoic acid</td>
<td>I-20-mono</td>
<td>0.5</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>cyclopentanol</td>
<td>3 - 4</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>tert-butanol</td>
<td>36</td>
<td>no rxn</td>
</tr>
</tbody>
</table>
TBTU and TATU had been observed to be base-sensitive for esterification of secondary alcohols, requiring the strength of the base to be at least similar to that of DBU for the reaction to proceed. For this reason, it was interesting to find out what kind of observations if any, would be made when a stronger base such as 7-methyl-1,5,7-triazabicyclo-[4.4.0]dec-5-ene (MTBD) was used. To study this point, all three coupling agents were examined. Interestingly, only COMU gave successful results for esterification between tert-butanol and benzoic acid. There was no reaction in case of both TBTU and TATU. Additionally, MTBD did not improve the reaction with secondary alcohols. These observations are illustrated in Table 10.

**Table 10** Esterification results with MTBD

<table>
<thead>
<tr>
<th>entry</th>
<th>acid</th>
<th>alcohol</th>
<th>coupling agent</th>
<th>reaction time (h)</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>TBTU</td>
<td>16</td>
<td>no rxn</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>TATU</td>
<td>16</td>
<td>no rxn</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>COMU</td>
<td>16</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>TBTU</td>
<td>4 -5</td>
<td>91</td>
</tr>
</tbody>
</table>

3.6. Mechanistic Considerations

Mechanisms have been proposed for the reactions involving COMU and amines228 and for TBTU and alcohols (Scheme 41).221 These mechanisms have the following steps: addition of the carboxylate salt to the uronium reagent, decomposition of the resulting tetrahedral intermediate I, addition of the released anion II to the carbonyl center followed by loss of a urea
derivative, and alcohol addition to the activated carbonyl group III. The base sensitivity of the reaction with secondary alcohols performed with the benzotriazole-derived coupling agents (TBTU and TATU) indicates that the last step is rate determining in this case. To investigate the validity of this observation, the activation of a hindered carboxylic acid-terminated second generation dendron was attempted using TBTU in the presence of the weaker base DIEA (Scheme 42). After 30 minutes, the desired reactive intermediate complex IV whose $^{13}$C NMR spectrum is shown in Figure 11 was isolated. Therefore, the fact that secondary alcohols do not react when DIEA is used means that without a doubt, the alcohol addition to the activated complex, which is the last step, is rate determining. It appears that the base must partially deprotonate the alcohol before the nucleophile attacks the activated complex.

Scheme 41 Proposed reaction mechanisms: top level on each line, TBTU mechanism; bottom level, COMU mechanism
Scheme 42 Reactive intermediate IV forms quickly even in the presence of DIEA

Figure 11 125.7 MHz $^{13}$C NMR spectrum of the reactive intermediate IV in CDCl$_3$

For the slower base-insensitive COMU reactions, an earlier step must be rate determining for primary and secondary alcohols, either the decomposition of the initial tetrahedral
intermediate or the readdition of the stable anion. However, with the tertiary alcohol, tert-butanol, ester formation only occurs with the strong organic base MTBD using COMU. Clearly, the rate-determining step for COMU has switched to being the last step for this hindered alcohol. The relative acidities in DMSO and acetonitrile of alcohols and the conjugate acids of the organic bases employed indicate that the alcohol will only be slightly ionized under the reaction conditions. The difference in pKa between isopropanol and tert-butanol is similar to that between DBU and MTBD. It appears that the tetrahedral intermediate for alcohol addition is lower in energy relative to starting materials for COMU than for the benzotriazole-derived coupling agents, either for electronic or steric reasons.

3.7. Convergent Synthesis

Scheme 43 Divergent growth of second generation acid dendron

Having established that these conditions were effective for ester formation, we tested whether they could be used for the convergent synthesis of polyester dendrimers. The
preparation of diol 81 was discussed in Chapter 2. The addition of tribranched dendrons to compound 81 to form ester linkages when the carboxylic acid of the dendron is preactivated as the anhydride will be discussed in Chapter 6. As shown in Scheme 44, peptide-coupling agents can also be used for this purpose, forming the two ester linkages between 81 and 136 in good yield under mild conditions. The divergent synthesis of dendron 136 proceeding through two dendron growth steps is described in Scheme 43 while the formation of other esters from this acid dendron with simple alcohols is summarized in Scheme 45 and Table 11.

Scheme 44 TBTU-promoted convergent synthesis of a 2nd generation dendrimer

Scheme 45 TBTU-promoted ester formation
3.8. Regioselective Esterification of Diols and Polyols

An evaluation of whether the base sensitivity of reaction outcome to alcohol structure could be used to obtain regioselectivity was tested with a diol (134) and a polyol (135) using TBTU and DIEA with an aryl (124) and an aliphatic acid (107). The reactions were highly selective for the primary hydroxyls; in only one reaction was a small amount of the secondary product obtained, that is for 1,3-butanediol (134) (see Scheme 46), where benzylation gave 5% of the secondary product in addition to the major primary product (90%). Most other selective esterification methods are less selective in benzylation of 134 than this method. When a pure sample of 144 was mixed with DIEA and stirred at room temperature for 2 h in DMF, the resulting mixture contained compound 144 and 10% of the secondary product. This observation clearly shows that the secondary product forms because of migration of benzoic acid from the primary position to the secondary position (Scheme 47). The migration product was not observed when the hindered acid 107 was employed possibly for steric reasons.

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Base (2 equiv)</th>
<th>Reaction time (h)</th>
<th>% Yield</th>
<th>Ester</th>
</tr>
</thead>
<tbody>
<tr>
<td>HO</td>
<td>DBU</td>
<td>1</td>
<td>92</td>
<td>142</td>
</tr>
<tr>
<td></td>
<td>DIEA</td>
<td>1</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>I-</td>
<td>DBU</td>
<td>1.5</td>
<td>91</td>
<td>143</td>
</tr>
<tr>
<td></td>
<td>DIEA</td>
<td>1.5</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>DBU</td>
<td>3</td>
<td>82</td>
<td>141</td>
</tr>
</tbody>
</table>
3.9. Concluding Remarks

Peptide coupling reagents, COMU, TBTU, and TATU can be used to prepare esters in excellent yields from all types of alcohols at room temperature under mild conditions using organic bases and short reaction times. Esterification of secondary alcohols promoted by TBTU and TATU require a base, such as DBU, that is stronger than tertiary amines. Only COMU is effective for the preparation of esters from tertiary alcohols, and then only when the still stronger base, MTBD is used. The base sensitivity of the TBTU and TATU promoted reactions can be used for the regioselective esterification of primary hydroxyls in diols and polyols. This protecting group-free esterification method is an important discovery, which has a significant advantage over the protection/deprotection methods, especially in carbohydrate chemistry. The following two chapters illustrate some applications for this.
3.10. Experimental Section

3.10.1. General

$^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance 500 NMR spectrometer operating at 500.13 and 125.7 MHz respectively using the solvent resonances as secondary standards. The carbon and hydrogen atoms of new compounds were assigned following the analysis of their one dimensional ($^1$H, $^{13}$C, and DEPT-135) and two dimensional (COSY, HSQC, and HMBC) NMR spectral data. The $^1$H and $^{13}$C NMR spectra of all compounds may be found in Appendix A. High-resolution mass spectra were recorded on a Bruker Micro-TOF mass spectrometer using electrospray ionization. Melting points were determined on a Fisher-John's melting point apparatus and are uncorrected.

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), and $N,N$-diisopropylethylamine (DIEA), tetrahydrofuran, acetonitrile, and dichloromethane were refluxed over calcium hydride and distilled onto molecular sieves. Methanol, ethanol, $t$-butanol, cyclopentanol, and 2-propanol were dried over calcium oxide and distilled over molecular sieves. Pyridine was dried over potassium hydroxide and was stored over molecular sieves. All reactions were carried out under a nitrogen atmosphere. Compounds were visualized/ located by spraying the TLC plate with a solution of 2 % ceric ammonium sulfate in 0.5 M H$_2$SO$_4$ followed by heating on a hot plate until color developed. Jones reagent (0.56 M) was prepared by dissolving sodium dichromate dihydrate (Na$_2$Cr$_2$O$_7$.2H$_2$O, 300 g, 1.01 mol) in 1.5 L of water followed by slowly adding conc. sulfuric acid (300 mL) to the cooled solution (0 °C).
3.10.2. Synthesis

3.10.2.1. 3-Allyloxy-2,2'-bis(benzyloxymethyl)propan-1-ol (149).

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Allyl bromide (10.5 mL, 121 mmol) and 3-(benzyloxy)-2,2'-
bis(benzyloxymethyl)propan-1-ol\textsuperscript{91,178} (16.4 g, 40.3 mmol) were dissolved in anhydrous DMF
(150 mL) and the mixture was cooled to 0 °C. Sodium hydride (60 % oil dispersion, 1.94 g, 48.5
mmol) was then added in portions with stirring at 0 °C. The mixture was allowed to warm to rt
with stirring for 12 h. The mixture was diluted using Et\textsubscript{2}O (100 mL), cooled to 0 °C, and ice-
water (50 mL) was added slowly with stirring. The organic layer was separated and the aqueous
layer was extracted using Et\textsubscript{2}O (60 mL x 2). Organic layers were combined, washed with brine
(50 mL x 2), and water (50 mL x 2), then dried (MgSO\textsubscript{4}), filtered, and concentrated. Purification
using column chromatography (hexanes/ EtOAc; 5:1; R\textsubscript{f} 0.60) gave the product as a colorless
syrup (16.8 g, 93 %): \textsuperscript{1}H NMR (500.13 MHz, CDCl\textsubscript{3}) \( \delta \) 3.57 (s, 2H, OCH\textsubscript{2}C\textsubscript{quat}), 3.60 (s, 6H,
C\textsubscript{quat}(CH\textsubscript{2}O)\textsubscript{3}), 3.98 (dt, \( J = 5.5, 1.5 \) Hz, 2H, CH\textsubscript{2} (sp\textsubscript{3}, allyl)), 4.53 (s, 6H, 3CH\textsubscript{2}Ph), 5.16 (ddt, \( J = 10.5, 2, 1.5 \) Hz, 1H, cis, allyl), 5.27 (ddt, \( J = 17, 2, 1.5 \) Hz, 1H, trans, allyl), 5.90 (m, 1H, CH
(sp2, allyl), 7.27 - 7.36 (m, 15H, PhH); \textsuperscript{13}C NMR (125.7 MHz, CDCl\textsubscript{3}) \( \delta \) 139.1 (PhC), 135.3 (CH
sp2, allyl), 128.3, 127.4 (PhC), 116.3 (CH\textsubscript{2}, sp2, allyl), 73.4 (3CH\textsubscript{2}Ph), 72.4 (CH\textsubscript{2}, sp3, allyl),
69.6 C\textsubscript{quat}(CH\textsubscript{2}O)\textsubscript{3}, 69.5 (OCH\textsubscript{2}C\textsubscript{quat}), 45.7 (C\textsubscript{quat}). HR ESI MS: m/z calcd for C\textsubscript{29}H\textsubscript{34}NaO\textsubscript{4}
(M+Na) 469.2354, found 469.2352.
3.10.2.2. (3-Benzylxyloxy-2,2-bis(benzyloxymethyl)propoxy)acetaldehyde (150)

Ozone was bubbled through a solution of olefin 149 (2.56 g, 5.73 mmol) maintained at –78 ºC in a 1:1 mixture of methanol (8 mL) and dichloromethane (8 mL) until TLC confirmed the disappearance of the starting material. N₂ was then bubbled through the mixture for 15 min. Excess dimethyl sulfide was added at -78 ºC and the mixture was allowed to warm to rt with stirring. The reaction mixture was concentrated under vacuum and the resulting yellow syrup was purified using column chromatography (hexanes/ EtOAc: 3:1; R_f 0.35) to give the product as a colorless syrup: yield 2.03 g (79 %); ^1H NMR (500.13 MHz, CDCl₃) δ 3.74 (s, 6H, 3CquatCH₂O), 3.77 (s, 2H, CquatCH₂O), 4.05 (d, J = 1 Hz, 2H, CH₂C=O), 4.64 (s, 6H, 3CH₂Ph), 7.38 – 7.47 (m, 15H, PhH), 9.73 (t, J = 1 Hz, 1H, O=CH); ^13C NMR (125.7 MHz, CDCl₃) δ 201.6 (C=O), 138.7, 128.2, 127.4, 127.4 (PhC), 76.7(CC=O), 73.3 (3CH₂Ph), 71.0 (CquatCH₂O), 69.0 (3CquatCH₂O), 45.7 (Cquat). HR ESI MS: m/z calcd for C₂₈H₃₂NaO₅ (M+Na) 471.2142, found 471.2137.

3.10.2.3. (3-Benzylxyloxy-2,2-bis(benzyloxymethyl)propoxy)acetic acid (126)

Aldehyde 150 (1.70 g, 3.79 mmol) was dissolved in acetone (8 mL) in a round-bottomed flask maintained at 0 ºC. The Jones reagent (16.3 mL, 10.9 mmol) was then added drop wise during a period of 30 min. When the addition was complete, the ice-water bath was removed and stirring was continued for another 40 min when TLC confirmed the disappearance of the
aldehyde. Water (20 mL) and ether (25 mL) were added and the resulting mixture was stirred for 10 min. The organic layer was collected, washed with water (9 mL x 3), dried (MgSO₄), filtered, and concentrated. The resulting syrup was purified using column chromatography (hexanes/EtOAc; 2:1; R_f 0.2) to give 126 as a colorless syrup: yield 1.43 g (81 %): ¹H NMR (500.13 MHz, CDCl₃) δ 3.67 (s, 6H, 3C_quatCH₂O), 3.69 (s, 2H, C_quatCH₂O), 4.11 (s, 2H, CH₂C=O), 4.56 (s, 6H, 3CH₂Ph), 7.34 – 7.42 (m, 15H, PhH), 10.88 (br, 1H, OH); ¹³C NMR (125.7 MHz, CDCl₃) δ 173.0 (C=O), 138.0, 128.4, 127.7 (PhC), 73.5 (3CH₂Ph), 72.2 (C_quatCH₂O), 69.5 (3C_quatCH₂O), 68.5 (OCH₂C=O), 45.1 (C_quat). HR ESI MS: m/z calcd for C₂₈H₃₁O₆ (M-H) 463.2126, found 463.2109.

3.10.2.4. General esterification procedure using COMU

In an oven-dried round-bottomed flask equipped with a magnetic stir bar, an acid (0.724 mmol), COMU (0.310 g, 0.724 mmol), and the base specified in the Table or the procedure below, for instance 1,8-diazabicyclo[5.4.0]undec-7-ene (0.22 mL, 1.45 mmol), were dissolved in anhydrous DMF (3 mL) and the resulting orange-red solution was stirred at rt for 10 min under a nitrogen atmosphere. An alcohol (0.724 mmol of hydroxyl groups) in DMF (1 mL) was then injected into the reaction mixture via syringe and vigorous stirring at rt was continued until there was a noticeable color change or until TLC confirmed the completion of the reaction (1 - 16 h). The reaction mixture was diluted with CH₂Cl₂ (15 mL) and the resulting mixture was washed with 5% HCl (2 x 3 mL), 1M NaHCO₃ (3 x 3 mL) and water (2 x 3 mL). The organic layer was collected, dried (MgSO₄), filtered and concentrated to give a crude ester product. Solid crude products were purified using precipitation out of cold methanol or cold hexanes/EtOAc, or
column chromatography to give colorless solids. Liquids or oils crude products were purified using column chromatography to give colorless products.

3.10.2.5. General esterification procedure using TBTU or TATU

In an oven-dried round-bottomed flask equipped with a magnetic stir bar, an acid (1.25 mmol), TBTU (0.40 g, 1.25 mmol), and the base specified in the Table or the procedure below, for instance 1,8-diazabicyclo[5.4.0]undec-7-ene (0.38 mL, 2.49 mmol) were dissolved in anhydrous DMF (3 mL) and the resulting mixture was stirred at rt for 30 min. under a nitrogen atmosphere. An alcohol (1.25 mmol of hydroxyl groups) in DMF (1 mL) was then injected into the reaction mixture via syringe and stirring was continued at rt until TLC confirmed the completion of the reaction (0.25 – 5 h). The reaction mixture was diluted with CH₂Cl₂ (15 mL) and the resulting mixture was washed with 5% HCl (2 x 3 mL), 1 M NaHCO₃ (3 x 3 mL) and water (2 x 3 mL). The organic layer was collected, dried (MgSO₄), filtered and concentrated to give a crude ester product, which was purified as described above for the COMU procedure.

3.10.2.6. General procedure for dendron growth

In an oven-dried round-bottomed flask equipped with a magnetic stir bar under a nitrogen atmosphere, the benzylidene or benzyl protected anhydride, the hydroxyl-terminated dendron or 2(p-toluenesulfonyl)ethanol, and N,N-dimethyl-4-aminopyridine (DMAP) were dissolved in a 3:1 mixture of CH₂Cl₂/ pyridine (v/v). The reaction mixture was stirred at rt for 10 - 12 h and diluted with water (3 mL) in pyridine (3 mL). Stirring was continued overnight to quench the excess anhydride. The mixture was diluted using CH₂Cl₂ (150 mL) and washed with NaHCO₃ (1 M, 30 mL x 3), 10% aq. Na₂CO₃ (30 mL x 3), brine (30 mL x 2), and water (30 mL), then dried (MgSO₄), filtered, and concentrated. The crude product was then purified using column
chromatography to give the desired product (> 93% yield). The NaHCO₃ layers were combined, acidified (pH = 5-6), and the precipitated carboxylic acid by-product was recovered.

3.10.2.7. 2-(4-Iodophenoxy)ethyl 5-methyl-2-phenyl-1,3-dioxane-5-carboxylate (151)

Synthesized using the COMU procedure (base in Table 3.1): a colorless solid; Rₜ 0.35 (hexanes/ EtOAc; 3:1); mp 128 – 130 °C; ¹H NMR (500.13 MHz, CDCl₃) δ 1.04 (s, 3H, CH₃), 3.65 (d, J = 11.5 Hz, 2H, H-4ax, H-6ax), 4.17 (t, J = 5 Hz, 2H, IPhOC₂H₂), 4.54 (t, J = 5 Hz, 2H, CH₂O), 4.66 (d, J = 11.5 Hz, 2H, H-4eq, H-6eq), 5.45 (s, 1H, H-2), 6.66 – 6.68 (m, 2H, PhH), 7.28 – 7.54 (m, 7H, PhH); ¹³C NMR (125.7 MHz, CDCl₃) δ 174.1,(C=O), 158.6, 138.4, 137.9, 129.1, 128.3, 126.3, 117.3 (PhC), 101.9 (C-2), 83.4 (PhC), 73.6 (C-4, C-6), 66.2 (IPhOC), 63.3 (CH₂OC=O), 42.7 (Cquat), 18.0 (CH₃). HR ESI MS m/z calcd for C₂₀H₂₁INaO₅ 491.0326, found 491.0322.

3.10.2.8. 2-(4-Bromophenoxy)ethyl 5-methyl-2-phenyl-1,3-dioxane-5-carboxylate (152)

Synthesized using the TBTU procedure (base in Table 3.5): a colorless solid; Rₜ 0.41 (hexanes/ EtOAc; 3:1); mp 121 – 122 °C; ¹H NMR (500.13 MHz, CDCl₃) δ 1.04 (s, 3H, CH₃), 3.65 (d, J = 11.5 Hz, 2H, H-4ax, H-6ax), 4.18 (t, J = 5 Hz, 2H, BrPhOCH₂H₂), 4.55 (t, J = 5 Hz, 2H,
3.10.2.9. 2-(4-Iodophenoxy)ethyl 5-benzyloxyethyl-2-phenyl-1,3-dioxane-5-carboxylate (153)

Synthesized using the COMU procedure (base in Table 3.1): a colorless solid; Rf 0.39 (hexanes/ EtOAc; 3:1); mp 67 – 69 °C; \(^1\)H NMR (500.13 MHz, CDCl\(_3\)) \(\delta\) 4.09 – 4.11 (m, 6H (2H-5', H-4\text{ax}, H-6\text{ax}, 2H-IPhOCH\(_2\))), 4.41 (d, \(J = 11.5\) Hz, 2H, H-4\text{eq}, H-6\text{eq}), 4.48 (t, \(J = 4.5\) Hz, 2H, CH\(_2\)O), 4.57 (s, 2H, CH\(_2\)Ph), 5.44 (s, 1H, H-2), 6.65 (d, \(J = 9\) Hz, PhH), 7.29 – 7.46 (m, 10H, PhH), 7.56 (d, \(J = 9\) Hz, 2H, PhH); \(^1\)C NMR (125.7 MHz, CDCl\(_3\)) \(\delta\) 171.2 (C=O), 138.4, 138.1, 137.7, 129.2, 128.4, 127.6, 127.5, 126.2, 117.1 (PhC), 101.9 (C-2), 83.5 (PhC), 73.4 (CH\(_2\)Ph), 69.8 (CH\(_2\)ax), 68.8 (C-4, C-6), 65.8 (IPhOC), 63.0 (CH\(_2\)OC=O), 46.1 (C\text{quat}). HR ESI MS \(m/z\) calcd for C\(_{27}\)H\(_{27}\)I\(_2\)NaO\(_6\) 597.0741, found 507.0749.

3.10.2.10. Methyl 2-(3-(benzyloxy)-2,2-bis(benzyloxyethyl)propoxy)acetate (154).
Synthesized using the COMU procedure (base in Table 3.1): a colorless syrup; Rf 0.58 (hexanes/ EtOAc; 3:1); $^1$H NMR (500.13 MHz, CDCl$_3$) $\delta$ 3.72 (s, 6 H, C$_{quat}$CH$_2$O), 3.78 (s, 2H, C$_{quat}$CH$_2$O), 3.78 (s, 3H, OCH$_3$), 4.16 (s, 2H, OCH$_2$C=O), 4.61 (s, 6H, 3CH$_2$Ph), 7.34 – 7.43 (m, 15H, PhH); $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$ 171.0 (C=O), 138.8, 128.2, 127.3 (PhC), 73.3 (3CH$_2$Ph), 71.2 (C$_{quat}$CH$_2$O), 69.3 (3C$_{quat}$CH$_2$O), 69.0 (OCH$_2$C=O), 51.6 (OCH$_3$), 45.7 (C$_{quat}$). HR ESI MS: m/z calcd for C$_{29}$H$_{34}$NaO$_6$ 501.2248, found 501.2238.

3.10.2.11. 2-(4-Iodophenoxy)ethyl acetate (155)

![Chemical structure of 2-(4-Iodophenoxy)ethyl acetate (155)]

Synthesized using the COMU procedure (base in Table 3.1): a pale yellow solid; Rf 0.39 (hexanes/ EtOAc; 4:1); mp 50 – 51 °C; $^1$H NMR (500.13 MHz, CDCl$_3$) $\delta$ 2.08 (s, 3H, CH$_3$), 4.10 (t, $J$ = 5 Hz, 2H, IPhOC$_2$H), 4.38 (t, $J$ = 5 Hz, 2H, CH$_2$OC=O), 6.65 – 6.68 (m, 2H, PhH), 7.52 – 7.55 (m, 2H, PhH); $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$ 170.9 (C=O), 158.3, 138.3, 117.0, 83.4 (PhC), 66.0 (IPhOC), 62.6 (CH$_2$OC=O), 20.9 (CH$_3$). HR ESI MS m/z calcd for C$_{10}$H$_{11}$INaO$_3$ 328.9645, found 328.9635.

3.10.2.12. 2-(4-Iodophenoxy)ethyl benzoate (156)

![Chemical structure of 2-(4-Iodophenoxy)ethyl benzoate (156)]

Synthesized using both the COMU and TBTU procedures (bases in Tables 3.1, 3.3, and 3.5): a cotton-like colorless solid; Rf 0.40 (hexanes/ EtOAc; 3:1); mp 84 – 85 °C; $^1$H NMR (500.13 MHz, CDCl$_3$) $\delta$ 4.28 (t, $J$ = 4.5 Hz, 2H, IPhOCH$_2$), 4.66 (t, $J$ = 4.5 Hz, 2H, CH$_2$OC=O), 4.66 (t, $J$ = 4.5 Hz, 2H, CH$_2$OC=O),
6.71 – 6.74 (m, 2H, PhH), 7.43 – 7.46 (m, 2H, PhH), 7.55 – 7.58 (m, 3H, PhH), 8.04 – 8.05 (m, 2H, PhH); $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$ 166.6 (C=O), 158.6, 138.4, 133.3, 129.89, 129.85, 128.5, 117.2, 83.5 (PhC), 66.3 (IPhOC), 63.3 (CH$_2$OC=O). HR ESI MS $m/z$ calcd for C$_{15}$H$_{13}$INaO$_3$ 390.9802, found 390.9809.

3.10.2.13. 1,4-Bis(2-benzoyloxyethoxy)benzene (157)

![1,4-Bis(2-benzoyloxyethoxy)benzene (157)]

Synthesized using the COMU procedure (base in Table 3.1): a colorless crystalline solid; $R_f$ 0.41 (hexanes/ EtOAc; 2:1); mp 130 - 131 °C; $^1$H NMR (500.13 MHz, CDCl$_3$) $\delta$ 4.27 (t, $J = 5$ Hz, 4H, PhOC$_2$H$_2$), 4.65 (t, $J = 5$ Hz, 4H, CH$_2$OC=O), 6.90 (s, 4H, PhH), 7.42 – 7.45 (m, 4H, PhH), 7.54 – 7.58 (m, 2H, PhH), 8.05 – 8.07 (m, 4H, PhH); $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$ 166.6 (C=O), 153.2, 133.2, 130.0, 129.8, 128.5, 116.0 (PhC), 66.9 (PhOC), 63.6 (CH$_2$OC=O). HR ESI MS $m/z$ calcd for C$_{24}$H$_{22}$NaO$_6$ 429.1309, found 429.1318.

3.10.2.14. 4-Iodophenyl benzoate (158)

![4-Iodophenyl benzoate (158)]

Synthesized using both the COMU and TBTU procedures (bases in Table 3.1, 3.3, and 3.5): a colorless crystalline solid; $R_f$ 0.50 (hexanes/ EtOAc; 6:1); mp 123 – 124 °C; lit. $^{237}$ mp 115 -117 °C; lit. $^{238}$ mp 118.5 -119.5 °C; $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$ 164.8 (C=O), 150.9, 138.6, 133.9, 130.3, 129.2, 128.7, 124.0, 90.0 (PhC). $^1$H NMR spectrum similar to lit.$^{237}$ HR ESI MS $m/z$ calcd for C$_{13}$H$_{9}$INaO$_2$ 346.9539, found 346.9544.
3.10.2.15. Isopropyl benzoate (159)

![Isopropyl benzoate](image)

Synthesized using both the COMU and TBTU procedures; a colorless syrup: $R_f$ 0.68 (hexanes/ EtOAc; 6:1); $^1$H NMR and $^{13}$C NMR data were similar to lit.239

3.10.2.16. Cyclopentyl benzoate (160)

![Cyclopentyl benzoate](image)

Synthesized using both the COMU and TBTU procedures; a colorless syrup: $R_f$ 0.57 (hexanes/ EtOAc; 10:1); $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$ 166.3, 132.7, 130.9, 129.5, 128.3 (PhC), 77.7 (OCH), 32.8 (OCH(CH$_2$)$_2$), 23.8 (2CH$_2$); $^1$H NMR data were similar to lit.240

3.10.2.17. 4-Iodophenyl 2-phenylacetate (161)

![4-Iodophenyl 2-phenylacetate](image)

Synthesized using the COMU procedure, a colorless crystalline solid: $R_f$ 0.53 (hexanes/ EtOAc; 4:1); mp 60 – 61 °C; $^1$H NMR (500.13 MHz, CDCl$_3$) $\delta$ 3.86 (s, 2H, CH$_2$), 6.84 – 6.86 (m, 2H, PhH), 7.31 – 7.41 (m, 5H, PhH), 7.66 – 7.69 (m, 2H, PhH); $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$ 169.7 (C=O), 150.7 138.5, 133.3, 129.4, 128.9, 127.6, 123.8, 90.0 (PhC), 41.5 (CH$_2$). HR ESI MS $m/z$ calcd for C$_{14}$H$_{11}$INaO$_2$ 360.9696, found 360.9685.
3.10.2.18. 1,4-Bis(2-(2-phenylacetyloxy)ethoxy)benzene (162)

![Chemical Structure Image]

Synthesized using both the COMU procedure; a cotton-like colorless solid: R_f 0.38 (hexanes/ EtOAc; 3:1); mp 82 – 84 °C; \(^1\)H NMR (500.13 MHz, CDCl\(_3\)) \(\delta\) 3.68 (s, 4H, CH\(_2\)Ph), 4.13 (t, \(J = 5\) Hz, 4H, PhOC\(_H2\)), 4.44 (t, \(J = 5\) Hz, 4H, CH\(_2\)OC=O), 6.83 (s, 4H, PhH), 7.26 – 7.34 (m, 10H, PhH); \(^1^3\)C NMR (125.7 MHz, CDCl\(_3\)) \(\delta\) 171.7 (C=O), 153.2, 133.9, 129.4, 128.7, 127.3, 115.9 (PhC), 66.8 (PhOC), 63.4 (CH\(_2\)OC=O), 41.3 (CH\(_2\)Ph). HR ESI MS \(m/z\) calcd for C\(_{26}\)H\(_{26}\)NaO\(_6\) 457.1622, found 457.1620.

3.10.2.19. 1,4-Bis(2-phenylacetyloxy)butane (163)

![Chemical Structure Image]

Synthesized using both the COMU procedure; a colorless syrup: R_f 0.42 (hexanes/ EtOAc; 4:1); \(^1\)H NMR (500.13 MHz, CDCl\(_3\)) \(\delta\) 1.32 (m, 4H, Ha), 1.62 (quin, \(J = 7\) Hz, 4H, H\(_b\)), 3.63 (s, 4H, H\(_c\)), 4.10 (t, \(J = 7\) Hz, 4H, H\(_d\)), 7.27 – 7.37 (m, 10H, PhH); \(^1^3\)C NMR (125.7 MHz, CDCl\(_3\)) \(\delta\) 171.5 (C=O), 134.2, 129.2, 128.5, 127.0 (PhC), 64.5 (C\(_D\)), 41.4 (C\(_C\)), 28.4 (C\(_B\)), 25.4 (C\(_A\)). HR ESI MS \(m/z\) calcd for C\(_{22}\)H\(_{26}\)NaO\(_4\) 377.1723, found 377.1724.

3.10.2.20. Tert-butyl benzoate (164)

![Chemical Structure Image]
Synthesized using the COMU procedure: a colorless syrup; R_f 0.68 (hexanes/ EtOAc; 9:1); ^1^H NMR and ^13^C NMR spectral data were similar to lit.\textsuperscript{241}

3.10.2.21. 2-Tosylethyl 3-(benzyloxy)-2,2-bis(benzyloxy)methyl)propanoate (137)

\begin{center}
\includegraphics[width=0.2\textwidth]{137.png}
\end{center}

2(p-Toluenesulfonyl)ethanol (4.00 g, 20.0 mmol), dry pyridine (30 mL), CH\textsubscript{2}Cl\textsubscript{2} (90 mL), DMAP (0.489 g, 4.00 mmol), and the anhydride 108 (20.6, g, 25.0 mmol) were stirred at rt for 12 h under nitrogen, and diluted with water (∼ 3 mL) in pyridine (3 mL). Stirring was continued overnight to quench the excess anhydride. The mixture was diluted with CH\textsubscript{2}Cl\textsubscript{2} (150 mL) and the organic layer was washed with NaHCO\textsubscript{3} (1 M, 30 mL × 3), 10% aq. Na\textsubscript{2}CO\textsubscript{3} (30 mL × 3), brine (30 mL × 2), and water (30 mL), then dried (MgSO\textsubscript{4}), filtered, and concentrated. The crude product was then purified using column chromatography to give 137 as a thick colorless syrup (11.3 g, 94% yield): R_f 0.44 (hexanes/ EtOAc; 2:1); ^1^H NMR (500.13 MHz, acetone-\textit{d}_6) δ 2.41 (s, 3H, ArCH\textsubscript{3}), 3.45 (t, J = 6 Hz, 2H, SCH\textsubscript{2}−), 3.60 (s, 6H, C\textsubscript{quat}(CH\textsubscript{2})\textsubscript{3}), 4.40 (t, J = 6 Hz, 2H, -CH\textsubscript{2}OC=O), 4.49 (s, 6H, CH\textsubscript{2}Ph), 7.26 – 7.35 (m, 15H, PhH), 7.37 (d, 2H, J = 8 Hz, PhH), 7.75 (d, 2H, J = 8 Hz, PhH); ^13^C NMR (125.7 MHz, acetone-\textit{d}_6) δ 172.1 (C=O), 145.4, 139.3, 137.7, 130.7, 128.9, 128.8, 128.14, 128.12 (PhC), 73.6 (CH\textsubscript{2}Ph), 68.1 (C\textsubscript{quat}CH\textsubscript{2}), 58.3 (-CH\textsubscript{2}OC=O), 55.5 (SCH\textsubscript{2}−), 54.1 (C\textsubscript{quat}), 21.5 (CH\textsubscript{3}Ar). HR ESI MS m/z calcd for C\textsubscript{35}H\textsubscript{38}NaO\textsubscript{7}S 625.2230, found 625.2214.
3.10.2.22. 2-Tosylethyl 3-hydroxy-2,2-bis(hydroxymethyl)propanoate (138)

Compound 137 (8.00 g, 13.3 mmol) was dissolved in a 1:2 mixture of CH₂Cl₂/MeOH (v/v) in an oven-dried round-bottomed flask equipped with a magnetic stir bar and a catalytic amount of Pd/C was added. The flask was evacuated and back-filled with hydrogen three times. After stirring the mixture overnight under H₂ atmosphere, the catalyst was removed via filtration using celite and this celite was washed with MeOH. The filtrate was concentrated to dryness to afford the product as a colorless solid (4.32 g, 98% yield): mp 103 – 104 °C; ¹H NMR (500.13 MHz, acetone-d₆) δ 2.46 (s, 3H, ArCH₃), 3.60 (t, J = 6 Hz, 2H, SCH₂-), 3.70 (s, 6H, Cₜₐₜ(CH₂)₃), 4.40 (t, J = 6 Hz, 2H, -CH₂OC=O), 7.50 (d, 2H, J = 8 Hz, PhH), 7.85 (d, 2H, J = 8 Hz, PhH); ¹³C NMR (125.7 MHz, acetone-d₆) δ 173.6 (C=O), 145.9, 137.5, 130.9, 129.0 (PhC), 61.7 (CₜₐₜCH₂), 58.2 (-CH₂OC=O), 56.7 (Cₜₐₜ), 55.5 (SCH₂), 21.5 (CH₃Ar). HR ESI MS m/z calcd for C₁₄H₂₀NaO₇S 355.0822, found 355.0829.

3.10.2.23. 2-(Toluenesulfonyl)ethyl-protected second generation dendron (139)

First generation dendron 138 (2.05 g, 6.17 mmol), dry pyridine (20 mL), CH₂Cl₂ (60 mL), DMAP (0.452 g, 3.70 mmol), and anhydride 35 (9.86 g, 23.12 mmol) were stirred at rt for 10 h
under nitrogen. After work up and purification as described above for 137, the product was obtained as a colorless crystalline solid (5.42 g, 93% yield): R<sub>f</sub> 0.41 (hexanes/ EtOAc; 1:1); mp 127 - 128 °C; <sup>1</sup>H NMR (500.13 MHz, CDCl<sub>3</sub>) δ 0.89 (s, 9H, 3CH<sub>3</sub>), 2.33 (s, 3H, CH<sub>3</sub>Ar), 2.93 (t, J = 5.5 Hz, 2H, -CH<sub>2</sub>OC=O), 3.58 (d, J = 11 Hz, 6H, 3H-4<sub>ax</sub>, 3H-6<sub>ax</sub>), 4.14 (t, J = 5.5 Hz, 2H, -CH<sub>2</sub>OC=O), 4.22 (s, 6H, C<sub>quat</sub>(CH<sub>2</sub>)<sub>3</sub>), 4.54 (d, J = 11 Hz, 3H-4<sub>eq</sub>, 3H-6<sub>eq</sub>), 7.23 – 7.64 (m, 19H, PhH); <sup>13</sup>C NMR (125.7 MHz, CDCl<sub>3</sub>) δ 173.0 (3C=O), 169.3 (C=O), 145.0, 137.9, 136.4, 130.1, 129.0, 128.3, 128.1, 126.2 (PhC), 101.7 (C-2), 73.6 (C-4, C-6), 61.3 (C<sub>quat</sub>(CH<sub>2</sub>)<sub>3</sub>), 58.7 (-CH<sub>2</sub>OC=O), 54.5 (SCH<sub>2</sub>-), 51.0 (C<sub>quat</sub>), 42.7 (C-5), 21.6 (CH<sub>3</sub>Ar), 17.7 (3CH<sub>3</sub>). HR ESI MS m/z calcd for C<sub>50</sub>H<sub>56</sub>NaO<sub>16</sub>S 967.3181, found 967.3219.

3.10.2.24. 1,8-Diazabicyclo[5.4.0]undec-7-ene-8-ium salt of second generation dendron (140)

Compound 139 (4.27 g, 4.52 mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (85 mL) in an oven-dried round-bottom flask equipped with a magnetic stir bar. The system was closed and flushed with nitrogen for 5 min. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (2.40 mL, 15.8 mmol) was added via syringe, the mixture was stirred at rt for 9 h and then concentrated to give a thick syrup. Crystallization from hexanes/ CH<sub>2</sub>Cl<sub>2</sub> gave the title compound as colorless crystals (4.0 g, 97% yield): mp 175 – 177 °C; <sup>1</sup>H NMR (500.13 MHz, CDCl<sub>3</sub>) δ 0.88 (s, 9H, 3CH<sub>3</sub>), 1.47 – 1.66 (m, 8H, 4(CH<sub>2</sub>), DBU), 2.65 (t, J = 5 Hz, 2H, DBU), 3.07 (t, J = 5.5 Hz, 2H, DBU), 3.12 – 3.13
(m, 2H, DBU), 3.21 (t, J = 5.5 Hz, 2H), 3.52 (d, J = 11 Hz, 6H, 3H-4ax, 3H-6ax), 4.49 (s, 6H, 
C\text{quat}(\text{CH}_2)_3), 4.60 (d, J = 11 Hz, 6H, 3H-4eq, 3H-6eq), 5.36 (s, 3H, H-2), 7.25 – 7.41 (m, 15H, 
PhH), 13.04 (br, 1H, N-H-O); \textsuperscript{13}C NMR (125.7 MHz, CDCl\textsubscript{3}) \delta 174.1 (C=O), 173.4 (3C=O), 
165.9 (C, sp\textsuperscript{2}, DBU), 138.2, 128.7, 128.1, 126.5 (PhC), 101.8 (C-2), 73.6 (C-4, C-6), 64.1 
(C\text{quat}(\text{CH}_2)_3), 53.9, 50.8 (2\text{CH}_2), DBU), 48.4 (C\text{quat}), 42.4 (C-5), 37.9, 31.9, 29.0, 27.0, 24.1, 19.5 
(6\text{CH}_2), DBU), 18.0 (3\text{CH}_3).

3.10.2.25. Protected second generation acid dendron (136)

Salt 140 (2.15 g, 2.35 mmol) was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (60 mL) in a separatory funnel and 
this organic layer was washed with a 0.5 M HCl solution (15 mL x 3). The organic layer was 
collected, dried (MgSO\textsubscript{4}), filtered, and concentrated to give acid 136 as a colorless crystalline 
solid in quantitative yield: mp 197 – 199 °C; \textsuperscript{1}H NMR (500.13 MHz, DMSO-d\textsubscript{6}) \delta 0.86 (s, 9H, 
3\text{CH}_3), 3.69 (d, J = 11 Hz, 6H, 3H-4ax, 3H-6ax), 4.37 (s, 6H, C\text{quat}(\text{CH}_2)_3), 4.38 (d, J = 11 Hz, 6H, 
3H-4eq, 3H-6eq), 5.48 (s, 3H, H-2), 7.29 – 7.34 (m, 15H, PhH), 13.43 (br, 1H, COOH); \textsuperscript{13}C NMR 
(125.7 MHz, DMSO-d\textsubscript{6}) \delta 173.0 (3C=O), 171.5 (C=O), 138.1, 128.7, 128.0, 126.2 (PhC), 100.6 
(C-2), 72.3 (C-4, C-6), 61.5 (C\text{quat}(\text{CH}_2)_3), 50.0 (C\text{quat}), 42.4 (C-5), 17.2 (3\text{CH}_3). \textsuperscript{13}) HR ESI MS 
m/z calcd for C\textsubscript{41}H\textsubscript{45}O\textsubscript{14} 761.2815, found 761.2776.
3.10.2.26. Formation of esters from protected second generation acid dendron (136)

![Chemical structures](image)

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<th>% Yield</th>
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<td>82</td>
<td>141</td>
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</table>

3.10.2.27. Ethyl bis-2,2'-((5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)methyl-3-((5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)propanoate (142) (table above)

![Chemical structure](image)

Synthesized using the TBTU procedure; a colorless solid: \( R_f \) 0.55 (hexanes/ EtOAc; 1:1); mp 159 – 160 ºC; \(^1\)H NMR (500.13 MHz, CDCl\(_3\)) \( \delta \) 0.91 (s, 9H, 3CH\(_3\)), 1.02 (t, \( J = 7 \) Hz, 3H, CH\(_3\)), 3.58 (d, \( J = 11.5 \) Hz, 6H, 3H-4\(_{ax}\), 3H-6\(_{ax}\)), 3.98 (q, \( J = 7 \) Hz, 2H, CH\(_2\)OC=O), 4.48 (s, 6H,
C_{quat(CH_2)_3}, 4.56 (d, J = 11.5 Hz, 6H, 3H-4_{eq}, 3H-6_{eq}), 5.41 (s, 3H, H-2), 7.28 – 7.43 (m, 15H, PhH); $^{13}$C NMR (125.7 MHz, CDCl$_3$) δ 173.0 (3C=O), 169.9 (C=O), 137.8, 128.8, 128.1, 126.2 (PhC), 101.7 (C-2), 73.5 (C-4, C-6), 61.78 (CH$_2$OC=O), 61.77 (C_{quat(CH_2)_3}), 50.9 (C_{quat}), 42.6 (C-5), 17.6 (3CH$_3$), 13.9 (CH$_3$). HR ESI MS m/z calcd for C$_{43}$H$_{50}$NaO$_{14}$ 813.3093, found 813.3150.

3.10.2.28. 2-(4-Iodophenoxy)ethyl bis-2,2’-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)propanoate (143)

![Chemical Structure](image)

Synthesized using both the COMU and TBTU procedures; a colorless solid: R$_f$ 0.55 (hexanes/ EtOAc; 1:1); mp 155 – 157 °C; $^1$H NMR (500.13 MHz, CDCl$_3$) δ 0.89 (s, 9H, 3CH$_3$), 3.56 (d, J = 11.5 Hz, 6H, 3H-4$_{ax}$, 3H-6$_{ax}$), 3.68 (t, J = 4.5 Hz, 2H, ArOCH$_2$), 4.13 (t, J = 4.5 Hz, 2H, CH$_2$OC=O), 4.47 (s, 6H, C_{quat(CH_2)_3}), 4.55 (d, J = 11.5 Hz, 6H, 3H-4$_{eq}$, 3H-6$_{eq}$), 5.40 (s, 3H, H-2), 6.48 (d, J = 8.5 Hz, 2H, PhH), 7.28 - 7.46 (m, 15H, PhH), 7.47 (d, J = 7 Hz, 2H, PhH); $^{13}$C NMR (125.7 MHz, CDCl$_3$) δ 173.0 (3C=O), 170.0 (C=O), 158.3, 138.3, 137.9, 128.9, 128.2, 126.2, 117.1 (PhC), 101.7 (C-2), 73.5 (C-4, C-6), 65.4 (ArOCH$_2$), 63.8 (CH$_2$OC=O), 61.7 (C_{quat(CH_2)_3}), 51.2 (C_{quat}), 42.7 (C-5), 17.7 (3CH$_3$). HR ESI MS m/z calcd for C$_{49}$H$_{53}$INaO$_{15}$ 1031.2321, found 1031.2413.
3.10.2.29. Benzylidene-protected hydroquinone-cored second generation dendrimer (141)

Synthesized using the TBTU procedure; a colorless crystalline solid: R$_f$ 0.14 (hexanes/EtOAc; 1:1); mp 183 – 185 °C; $^1$H NMR (500.13 MHz, acetone-$d_6$/DMSO-$d_6$) $\delta$ 3.70 (d, $J = 11.5$ Hz, 12H, 6H-4$_{ax}$, 6H-6$_{ax}$), 3.93 (t, $J = 4.5$ Hz, 4H, 2PhOCH$_2$), 4.27 (t, $J = 4.5$ Hz, 4H, 2CH$_2$OC=O), 4.44 (d, $J = 11.5$ Hz, 12H, 6H-4$_{eq}$, 6H-6$_{eq}$), 4.47 (s, 12H, 2Cquat(CH$_2$)$_3$), 5.50 (s, 6H, H-2), 6.73 (s, 4H, PhH), 7.30 – 7.38 (m, 30H, PhH); $^{13}$C NMR (125.7 MHz, acetone-$d_6$/DMSO-$d_6$) $\delta$ 173.4 (6C=O), 170.5 (2C=O), 153.2, 138.9, 129.1, 128.4, 126.7, 116.0 (PhC), 101.5 (6C-2), 73.2 (6C-4, 6C-6), 66.4 (2PhOC), 64.4 (2CH$_2$OC=O), 62.0 (2Cquat(CH$_2$)$_3$), 51.4 (2Cquat), 42.9 (6C-5), 17.5 (6CH$_3$). HR EI MS: m/z calcd for C$_{92}$H$_{102}$Na$_2$O$_{30}$ 866.3120, found 866.3048.

3.10.2.30. 3-Hydroxylbut-1-yl benzoate (144)

Synthesized using the TBTU procedure with diisopropylethylamine (DIEA) as base, a colorless syrup, a 95/5 mixture of the primary and secondary benzoates: R$_f$ 0.32 (hexanes/EtOAc; 2:1), $^1$H and $^{13}$C NMR spectra similar to lit.$^{233}$
3.10.2.31. 3-Hydroxybutyl 3-benzyloxy-2,2'-bis(benzoyloxymethyl)propanoate (145)

Synthesized using the TBTU procedure with diisopropylethylamine (DIEA) as base, 1,3-butanediol (134) and 3-benzyloxy-2,2'-bis(benzoyloxymethyl)propanoic acid (107): a colorless syrup; Rf 0.36 (hexanes/ EtOAc; 2:1); $^1$H NMR (500.13 MHz, DMSO-$d_6$/ methanol-$d_4$) $\delta$ 1.91 (d, $J = 6.5$ Hz, 3H, CH$_3$), 2.32 – 2.37 (m, 2H, CHCH$_2$CH$_2$), 4.35 – 4.42 (m, 2H, CH$_2$OC=O), 4.42 (s, 6H, C$_{quat}$(CH$_2$)$_3$), 4.59 – 4.65 (m, 1H, CH), 5.23 (s, 6H, CH$_2$Ph), 8.00 – 8.09 (m, 15H, PhH); $^{13}$C NMR (125.7 MHz, DMSO-$d_6$/ methanol-$d_4$) $\delta$ 174.8 (C=O), 139.2, 128.9, 128.1, 128.0 (PhC), 73.5 (CH$_2$Ph), 68.6 (C$_{quat}$CH$_2$), 65.1 (C$_a$), 59.5 (C$_b$), 53.6 (C$_{quat}$), 42.2 (C$_d$), 23.8 (C$_e$). HR ESI MS $m/z$ calcd for C$_{30}$H$_{36}$NaO$_6$ 515.2411, found 515.2402.

3.10.2.32. Methyl 6-$O$-benzoyl-$\alpha$-D-glucopyranoside (146)

Synthesized using the TBTU procedure with diisopropylethylamine (DIEA) as base: a thick colorless oil; $^1$H NMR data similar to lit.$^{242}$ $^{13}$C NMR (125.7 MHz, DMSO-$d_6$/ methanol-$d_4$) $\delta$ 168.9 (C=O), 134.1, 131.9, 130.6, 129.7 (PhC), 101.0 (C-1), 74.8 (C-3), 73.6 (C-5), 73.3 (C-2), 71.6 (C-4), 62.4 (C-6), 55.5 (OCH$_3$).
3.10.2.33. Methyl 6-O-(3-benzyloxy-2,2'-bis(benzyloxymethyl)propanoyloxy)-α-D-glucopyranoside (147)

Synthesized using the TBTU procedure with diisopropylethylamine (DIEA) as base: a viscous colorless oil; $^1$H NMR (500.13 MHz, DMSO-$d_6$/methanol-$d_4$) δ 3.28 (t, $J_{3,4} = J_{4,5} = 9.3$ Hz, H-4), 3.35 (s, 3H, OCH$_3$), 3.38 (dd, $J_{1,2} = 3.7$ Hz, $J_{2,3} = 9.6$ Hz, H-2), 3.48 – 3.51 (m, 1H, H-5), 3.61 (t, $J_{2,3} = J_{3,4} = 9.3$ Hz, H-3), 3.63 (s, 6H, C$_{quat}$(CH$_2$)$_3$), 3.65 (dd, $J_{5,6a} = 5.5$ Hz, $J_{6a,6b} = 12.1$ Hz, H-6a), 3.78 (dd, $J_{5,6b} = 1.5$ Hz, $J_{6a,6b} = 11.5$ Hz, H-6b), 4.41 (s, 6H, CH$_2$Ph), 4.65 (d, $J_{1,2} = 3.5$ Hz, H-1); $^{13}$C NMR (125.7 MHz, DMSO-$d_6$/methanol-$d_4$) δ 175.3 (C=O), 139.5, 129.1, 128.3 (PhC), 100.1 (C-1), 74.7 (C-3), 73.8 (CH$_2$Ph), 73.3 (C-5), 73.1 (C-2), 71.4 (C-4), 68.9 (C$_{quat}$(CH$_2$)$_3$) 62.3 (C-6), 55.3 (OCH$_3$), 53.9 (C$_{quat}$). HR ESI MS m/z calcd for C$_{33}$H$_{40}$NaO$_{10}$ 619.2518, found 619.2519.
Chapter 4: Synthesis of Lyme Disease Glycolipid Antigens

4.1. Introductory Remarks

Lyme disease (LD) is a rapidly expanding multi-system illness that is the most common tick-bourne disease in the northern hemisphere.\textsuperscript{243-246} It is caused by species of the spirochete *Borrelia burgdorferi sensu lato*; at least three species cause the disease in Europe, *Borrelia afzelii*, *Borrelia garinii*, and *Borrelia burgdorferi sensu stricto* but only the latter is important in North America.\textsuperscript{246-248} The bacteria are transmitted to humans by bites of ticks of species of the genus *Ixodes*.\textsuperscript{248} These ticks have a three-host life cycle where the larvae feed on small rodents and birds that act as reservoirs for the bacteria.\textsuperscript{248-250} The larvae leave the initial host then molt into nymphs that feed on a second host, primarily small rodents but also humans, then leave the second host and molt into adults that feed on large mammals, primarily deer but including dogs and occasionally humans.\textsuperscript{248,250} The bacteria reside in the mid-gut of the ticks and only migrate to the salivary glands after changes in surface protein expression (OspA to OspC) occur induced by a mammalian blood meal. These changes require at least 17 h of feeding.\textsuperscript{243}

4.2. Antigens Against Lyme Disease

A vaccine against Lyme disease based on the outer surface protein OspA was introduced in 1998 but withdrawn in 2002 for several reasons among which was the recognition that the change in surface protein expression made it an unusual transmission-blocking vaccine.\textsuperscript{251} Other possible antigens include two glycolipids first isolated from *Borrelia burgdorferi* in 2001\textsuperscript{252} and shown to be cholesteryl 6-\(\alpha\)-acyl-\(\beta\)-D-galactopyranoside (BbGL1) and 1,2-di-\(\alpha\)-acyl-3-\(\alpha\)-D-galactopyranosyl-\(\alpha\)-glycerol (BbGL2) (see Figure 12),\textsuperscript{253,254} abundant in the outer membranes of the LD-causing *Borrelia burgdorferi* species.\textsuperscript{255} The acyl groups in both BbGL1 and BbGL2 are
a mixture of palmitoyl and oleoyl groups and it was recently shown that at least one of the acyl
groups in BbGL2 must contain a cis-alkene for antigenicity to be maintained.\textsuperscript{256}

\begin{center}
\includegraphics[width=\textwidth]{figure12.png}
\end{center}

\textbf{Figure 12} \textit{Borrelia burdorferi} glycolipid antigens

In this chapter, the synthesis of a library of BbGL1 derivatives is discussed. This short
and efficient synthesis makes use of the primary-selective synthesis of esters described in
Chapter 3 for the acylation step. BbGL1 and its derivatives have been synthesized five times
since its structure was determined in 2003.\textsuperscript{253,254} Pozsgay \textit{et al.} outlined a twelve-step synthesis
from D-galactose using pivaloyl groups to achieve $\beta$-selective glycosylation via neighbouring
group participation and protecting group chemistry to introduce the ester group at O-6 in 11%
overall yield.\textsuperscript{257} This group also reported the synthesis of a derivative allowing conjugation to
protein using a similar pathway.\textsuperscript{258} Wu \textit{et al.} prepared the palmitoyl version of BbGL1 in low
yield (38\%) on a small scale enzymically but did not indicate how they prepared the cholesterol
glycoside.\textsuperscript{259} Kulkarni and Gervay-Hague reported a short synthesis but the yield in the
glycosylation step was moderate (56\% $\beta/\alpha$ 9/1) and that in the esterification step was worse
(43\%).\textsuperscript{260} In addition, Stübs \textit{et al.} were unable to repeat the carbodiimide-promoted selective
esterification reaction, despite extensive studies.\textsuperscript{261} This latter group synthesized the cholesteryl
glycoside in four steps from D-galactose then added a number of different acyl groups
enzymically using acyl transfer from acetone oxime esters catalysed by a lipase in low yields (5 to 31%).\textsuperscript{261}

Two key steps are required for the synthesis of BbGL1 analogues from D-galactose: a β-selective glycosylation and regioselective esterification. We opted to perform the glycosylation using the single step Lewis acid catalysed reaction of cholesterol with easily accessible β-D-galactose pentaacetate (167) even though the yield is expected to be lower than two or three step processes involving more active glycosyl leaving groups. Lewis acid catalysis of glycosylation of pentaacetates has been known for some time using acids such as tin tetrachloride\textsuperscript{262-265} and zinc chloride,\textsuperscript{266,267} but we choose to investigate boron trifluoride etherate to avoid the use of toxic or solid hydroscopic metal catalysts. This activator has been used before but only with primary alcohols for preparative purposes as far as we are aware.\textsuperscript{268,269} Ellervik \textit{et al.} demonstrated that these reactions proceed rapidly with glycosyl acetates under equimolar conditions to give the desired product accompanied by slower anomerization and equilibration.\textsuperscript{270}

\textbf{Scheme 48 Synthesis of cholesteryl β-D-galactopyranoside (168)}

The effects of changing conditions were investigated as outlined in Table 12. Increasing the relative amount of cholesterol increased the yield. Increasing the amount of BF\textsubscript{3}-Et\textsubscript{2}O increased the rate but decreased the β/α ratio. Adding acetonitrile slowed the reaction rate but
improved the $\beta/\alpha$ ratio, although we could not find conditions that eliminated the need for separation of the anomers by column chromatography. The best conditions were in DCM with 1.5 equiv of BF$_3$·Et$_2$O, which gave an acceptable 73% yield ($\beta/\alpha$ 6:1).

Cholesterol had an $R_F$ that was similar to that of the product. We found it convenient to separate excess cholesterol by acetylation followed by silica gel chromatography, which also allowed separation of the minor amount of the $\alpha$-glycoside. De-O-acetylation gave cholesteryl $\beta$-D-galactopyranoside (168) (Scheme 48).

Table 12 Effect of variation of conditions on glycosylation

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<td>3.0</td>
<td>48</td>
<td>62</td>
<td>5/1</td>
</tr>
<tr>
<td>0.032</td>
<td>10</td>
<td>DCM</td>
<td>4.5</td>
<td>48</td>
<td>59</td>
<td>3/1</td>
</tr>
<tr>
<td>0.01</td>
<td>3</td>
<td>DCM/MeCN 6:1</td>
<td>1.5</td>
<td>96</td>
<td>51</td>
<td>12/1</td>
</tr>
<tr>
<td>0.01</td>
<td>10</td>
<td>DCM/MeCN 6:1</td>
<td>1.5</td>
<td>96</td>
<td>66</td>
<td>11/1</td>
</tr>
</tbody>
</table>

The critical step is the regioselective addition of fatty acid esters at O-6 of compound 168. We found that the TBTU-promoted esterification procedure described in Chapter 3 worked well with a variety of fatty acids as shown in Table 13 with yields in the 78 to 84% range. Three changes were made to the conditions previously used for the regioselective acylation of primary hydroxyls in the presence of secondary hydroxyls. The poor solubility of 168 in DMF required a change of solvent and the reaction was found to proceed well in pyridine. The much longer chain lengths in the fatty acids used here required longer reaction times and 36 h was found to give
reasonable yields. Reactions performed in pyridine without the addition of the more basic tertiary amine, DIEA, gave approximately the same yields as those with DIEA added. This latter observation provides more information about the cause of the selectivity of this TBTU-promoted esterification of primary hydroxyls. The pKa of the conjugate acid of pyridine in water is 5.25. The smallest pKa of the non-anomeric secondary hydroxyls of glucose derivatives is about 12.3. That of the primary hydroxyl is about 1.5 to 2 pKa units larger, approximately 14, and those of galactose are similar. Possible pathways for the last step in the esterification reaction promoted by TBTU are shown in Scheme 49. The amount of alkoxide present with DIEA as the base would be approximately 0.001 [alcohol] because the pKa of DIEA is about 11. If alkoxide were the nucleophile (lower pathway in Scheme 49), the reaction rate would slow drastically on removal of DIEA because it is approximately 6 pKa units more basic than pyridine. The absence of marked effects on rates indicates that the base serves only to remove protons after a rate-determining addition of the primary alcohols (upper pathway in Scheme 49).

![Scheme 49](image)

**Table 13** Regioselective esterification results

<table>
<thead>
<tr>
<th>fatty acid</th>
<th>DIEA (equiv)</th>
<th>time (h)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>palmitic</td>
<td>2</td>
<td>12</td>
<td>49</td>
</tr>
<tr>
<td>palmitic</td>
<td>2</td>
<td>24</td>
<td>67</td>
</tr>
<tr>
<td>palmitic</td>
<td>2</td>
<td>36</td>
<td>82</td>
</tr>
<tr>
<td>stearic</td>
<td>2</td>
<td>36</td>
<td>84</td>
</tr>
<tr>
<td>stearic</td>
<td>0</td>
<td>36</td>
<td>80</td>
</tr>
<tr>
<td>myristic</td>
<td>2</td>
<td>36</td>
<td>79</td>
</tr>
<tr>
<td>lauric</td>
<td>2</td>
<td>36</td>
<td>78</td>
</tr>
<tr>
<td>oleic</td>
<td>2</td>
<td>36</td>
<td>83</td>
</tr>
<tr>
<td>erucic</td>
<td>2</td>
<td>36</td>
<td>81</td>
</tr>
<tr>
<td>erucic</td>
<td>0</td>
<td>36</td>
<td>77</td>
</tr>
</tbody>
</table>
Secondary alcohols do not form esters under TBTU-promoted conditions unless the stronger base DBU is present (Chapter 3).\textsuperscript{274,275} Since a stronger base would have little effect on the rate of the upper pathway of Scheme 49, the pathway followed when the base is changed to DBU must involve alkoxide ions. Apparently, primary alcohols are sufficiently less hindered and more nucleophilic to permit their direct addition to the carbonyl group of the benzotriazole-activated ester whereas secondary alcohols need to be activated as alkoxides before they can add.

\textbf{Scheme 49} Possible pathways for the last step of TBTU-promoted esterification. B = base

\textbf{4.3. Concluding Remarks}

Regioselective esterification of primary hydroxyls promoted by the peptide coupling agent TBTU is an efficient method for the O-6 acylation on carbohydrates. This method was used in the development of short and efficient syntheses of a library of one of the two glycolipid antigens against Lyme disease, BbGL1. The reduction in synthetic steps means less cost for the final product and in addition, the elimination of protection/ deprotection steps leads to minimized chemical wastes, which is important as we move towards a greener chemistry and a greener
world. Overall yields for the three steps from β-d-galactopyranose pentaacetate ranged from 48 to 52% for the different fatty acids.

4.4. Experimental Section

4.4.1. General

$^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance-500 MHz NMR spectrometer operating at 500.13 and 125.7 MHz respectively using the solvent resonances as secondary chemical shift references. The carbon and hydrogen atoms of new compounds were assigned following the analysis of their one dimensional ($^1$H, $^{13}$C, and DEPT-135) and two dimensional (COSY, HSQC, and HMBC) NMR spectral data. The $^1$H and $^{13}$C NMR spectra of all compounds may be found in Appendix A. Coupling constant ($J$) values are reported in Hertz. High-resolution mass spectra were recorded using electrospray ionization with a time of flight mass analyser. Melting points are uncorrected. Acetonitrile, dichloromethane, and $N,N$-diisopropylethylamine (DIEA) were refluxed over calcium hydride and distilled onto molecular sieves. Methanol was dried over calcium oxide and distilled over molecular sieves. Unless otherwise noted, non-aqueous reactions were carried out under a nitrogen atmosphere. Pyridine was dried over potassium hydroxide and was stored over molecular sieves. Compounds were visualized/ located by spraying the TLC plate with a solution of 2 % ceric ammonium sulfate in 0.5 M H$_2$SO$_4$ followed by heating on a hot plate until color developed.
4.4.2. Synthesis

4.4.2.1. Cholesteryl 2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside (170) and cholesteryl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside (171)

\[
\begin{align*}
\alpha & \quad \text{AcO} \quad \text{AcO} \quad \text{AcO} \quad \text{AcO} \\
\beta & \quad \text{AcO} \quad \text{AcO} \quad \text{AcO} \\
\end{align*}
\]

β-D-Galactose pentacetate (167)\(^{276}\) (2.00 g, 5.12 mmol) and cholesterol (19.8 g, 51.2 mmol) were dissolved in anhydrous dichloromethane (160 mL), and the mixture was stirred for 30 min with 4 Å molecular sieves at rt under a nitrogen atmosphere. The solution was slowly treated with boron trifluoride diethyl etherate at rt. After the addition was complete, stirring at rt was continued for a further 72 h when TLC confirmed the disappearance of the sugar. The solution was washed with NaHCO\(_3\) (1 M, 30 mL \(\times\) 3) and water (30 mL \(\times\) 2), then dried (MgSO\(_4\)), filtered, and concentrated. The resulting dry solid was dissolved in anhydrous dichloromethane (100 mL) and dry pyridine (100 mL). Excess acetic anhydride was slowly added and the mixture was stirred under nitrogen for 6 h at rt. The mixture was diluted with dichloromethane (60 mL), poured in ice and stirred for 4 h. The organic layer was separated and washed with NaHCO\(_3\) (1 M, 30 mL \(\times\) 3), 10% aq. Na\(_2\)CO\(_3\) (30 mL \(\times\) 3), brine (30 mL \(\times\) 2), water (30 mL), dried (MgSO\(_4\)), filtered, and concentrated. The crude solid was then purified using column chromatography (EtOAc/ hexanes, 1: 3). First to elute was the α anomer (170) as a colorless crystalline solid (0.29 g, 8%); (EtOAc/ hexanes, 1: 3, R\(_F\) 0.32); mp 192 – 194 °C; lit.\(^{277}\) 193 – 195 °C; \(^1\)H and \(^{13}\)C NMR spectra similar to lit.\(^{260}\) The second component was the β anomer (171) also as a colorless crystalline solid: yield 2.39 g (65%); R\(_F\) 0.24 (EtOAc/hexanes,
1: 3); mp 164 - 166 °C; lit.278 152 - 154 °C; lit.277 157 - 159 °C; \(^1\)H and \(^{13}\)C NMR data similar to lit.260,279

4.4.2.2. Cholesteryl β-D-galactopyranoside (168)

![Compound 168](image)

Compound 168 was prepared following a literature procedure280 and was obtained as a colorless solid: mp 271 – 271 °C; lit.278 265 – 267 °C; \(^1\)H and \(^{13}\)C NMR data similar to lit.260,279

4.4.2.3. General regioselective esterification procedure using TBTU

In an oven-dried round-bottomed flask equipped with a magnetic stir bar, an acid (0.722 mmol), TBTU (0.230 g, 0.722 mmol), and diisopropyl ethylamine (DIEA) (0.210 mL) were dissolved in anhydrous pyridine (10 mL) and the resulting mixture was stirred at rt for 30 min. under a nitrogen atmosphere. Cholesteryl β-D-galactopyranoside (168) (0.330 g, 0.601 mmol) in pyridine (3 mL) was then injected into the reaction mixture via syringe and stirring was continued at rt for 36 h. Pyridine was removed under vacuum and the resulting solid was purified using column chromatography (hexane/ EtOAc) to give colorless solids.

4.4.2.3.1. Cholesteryl 6-O-palmitoyl-β-D-galactopyranoside (169a)

![Compound 169a](image)
A colorless solid: Rf 0.15 (hexanes/EtOAc; 1: 2); $^1$H NMR (500.13 MHz, CDCl$_3$) $\delta$ 5.35 - 5.36 (m, 1H, H-6 Chol), 4.27 - 4.37 (m, 3H, H-1, H-6a, H-6b), 3.88 (br, 1H, H-4), 3.61 - 3.68 (m, 3H, H-2, H-3, H-5), 3.55 (m, 1H, H-3 Chol), 2.85 (br, 1H, HO-2), 2.68 (br, 1H, HO-3), 2.58 (br, 1H, HO-4), 0.85 - 2.37 (m, 71H, aliphatic FA and Chol), 0.67 (s, 3H, H-18 Chol); $^{13}$C NMR data similar to lit. HR ESI MS m/z calcd for C$_{49}$H$_{86}$NaO$_7$ 809.6266, found 809.6235.

**4.4.2.3.2. Cholesteryl 6-O-stearoyl-$\beta$-D-galactopyranoside (169b)**

A colorless solid: Rf 0.29 (hexanes/EtOAc; 1: 3); $^1$H NMR (500.13 MHz, CDCl$_3$) $\delta$ 5.32 (br, 1H, H-6 Chol), 4.73 (br, 1H, HO-2), 4.33 – 4.37 (m, 1H, H-6a), 4.32 (br, 1H, HO-3), 4.30 (d, $J$ = 7.5 Hz, 1H, H-1), 4.19 – 4.23 (m, 1H, H-6b), 4.04 (br, 1H, HO-4), 3.89 (br, 1H, H-4), 3.59 – 3.68 (m, 3H, H-2, H-3, H-5), 3.51 (m, 1H, H-3 Chol), 2.24 – 2.36 (m, 4H, H-2 FA, H-4a, H-4b Chol), 1.80 – 2.02 (m, 5H, Chol), 0.79 – 1.59 (m, 67H, aliphatic FA and Chol), 0.67 (3H, H-18 Chol); $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$ 173.7 (C=O), 140.5 (C-5 Chol), 122.1 (C-6 Chol), 101.9 (C-1), 79.9 (C-3 Chol), 73.6 (C-5), 72.6 (C-3), 71.1 (C-2), 69.0 (C-4), 63.3 (C-6), 56.9 (C-14 Chol), 56.4 (C-17 Chol), 50.3 (C-9 Chol), 42.5 (C-13 Chol), 39.9 (C-4 Chol), 39.7 (C-24 Chol), 39.0 (C-12 Chol), 37.5 (C-10 Chol), 36.8 (C-1 Chol), 36.3 (C-22 Chol), 36.0 (C-20 Chol), 34.4 (C-2 FA), 32.1 (C-7 Chol), 32.0 (C-8 Chol), 30.0 (C-2 Chol), 29.97, 29.9, 29.84, 29.78, 29.7, 29.6, 29.5 (C-4 – C-15 FA), 28.4 (C-25 Chol), 28.1 (C-15 Chol), 25.1 (C-16 Chol), 24.4 (C-3 FA), 24.1 (C-23 Chol), 23.0 (C-27 Chol), 22.8 (C-26 Chol), 22.7 (C-17 FA), 21.2 (C-11 Chol), 113.
19.5 (C-21 Chol), 18.9 (C-19 Chol), 14.3 (C-18 FA), 12.0 (C-18 Chol). HR ESI MS m/z calcd for C_{51}H_{90}NaO_{7} 837.6579, found 837.6598.

4.4.2.3.3. Cholesteryl 6-O-myristoyl-β-D-galactopyranoside (169c)

A colorless solid: R_{f} 0.28 (hexanes/EtOAc; 1: 3); 1H NMR (500.13 MHz, pyridine-d_{5}) δ 7.07 (br, 1H, HO-2), 6.89 (br, 1H, HO-3), 6.62 (br, 1H, HO-4), 5.34 -5.35 (m, 1H, H-6 Chol), 4.95 (dd, J_{5,6a} = 7.5 Hz, J_{6a,6b} = 11 Hz, H-6a), 4.87 (d, J_{1,2} = 8 Hz, 1H, H-1), 4.70 (dd, J_{5,6b} = 4.5 Hz, J_{6a,6b} = 11 Hz, 1H, H-6b), 4.39 (t, J = 9 Hz, 1H, H-5), 4.35 (d, J = 2.5 Hz, 1H, H-4), 4.11 -4.16 (m, 2H, H-2, H-3), 3.90 (tt, J = 4.5 Hz, 11.5 Hz, 1H, H-3 Chol), 2.42 (m, 1H, H-4a Chol), 2.38 (t, J = 7.5 Hz, 2H, H-2 FA), 1.71 – 2.03 (m, 6H, Chol), 0.90 – 1.60 (m, 48H, aliphatic FA and Chol), 0.77 – 0.89 (m, 9H, aliphatic FA and Chol), 0.66 (s, 3H, H-18 Chol); 13C NMR (125.7 MHz, pyridine-d_{5}) δ 173.5 (C=O), 141.0 (C-5 Chol), 121.9 (C-6 Chol), 103.3 (C-1), 78.6 (C-3 Chol), 75.1 (C-5), 73.6 (C-3), 72.3 (C-2), 70.1 (C-4), 64.7 (C-6), 56.9 (C-14 Chol), 56.4 (C-17 Chol), 50.4 (C-9 Chol), 42.5 (C-13 Chol), 40.0 (C-4 Chol), 39.7 (C-24 Chol), 39.4 (C-12 Chol), 37.6 (C-10 Chol), 36.96 (C-1 Chol), 36.5 (C-22 Chol), 36.1 (C-20 Chol), 34.5 (C-2 FA), 32.21, 32.16, 32.1 (3C, C-7, C-8 Chol, C-12 FA), 30.4, 30.1, 30.04, 30.01, 29.99, 29.9, 29.68, 29.66, 29.5 (9C, C-2 Chol, C-4 – C-22 FA), 28.5 (C-25 Chol), 28.2 (C-15 Chol), 25.4 (C-16 Chol), 24.5 (C-3 FA), 24.2 (C-23 Chol), 23.0 (2C, C-26, C-27 Chol), 22.7 (C-13 FA), 21.3 (C-11 Chol), 19.4 (C-21 Chol), 18.9 (C-19 Chol), 14.3 (C-12 FA), 12.0 (C-18 Chol). HR ESI MS m/z calcd for C_{47}H_{82}NaO_{7} 781.5953, found 781.5929.
4.4.2.3.4. Cholesteryl 6-O-lauroyl-β-D-galactopyranoside (169d)

A colorless solid: R_f 0.16 (hexanes/EtOAc; 1: 3); {superscript}1H NMR (500.13 MHz, pyridine-\textit{d}_5) δ 5.32 - 5.33 (m, 1H, H-6 Chol), 4.91(dd, \textit{J}_{5,6a} = 7.5 Hz, \textit{J}_{6a,6b} = 11 Hz, H-6a), 4.85 (d, \textit{J}_{1,2} = 7.5 Hz, 1H, H-1), 4.64 (dd, \textit{J}_{5,6b} = 4.5 Hz, \textit{J}_{6a,6b} = 11.5 Hz, 1H, H-6b), 4.36 (m, 1H, H-5), 4.35 (br, 1H, H-4), 4.16 (dd, \textit{J}_{3,4} = 3 Hz, \textit{J}_{2,3} = 9.5 Hz, 1H, H-3), 4.10 (dd, \textit{J} = 4.5 Hz, 7 Hz, 1H, H-2), 3.87 (tt, \textit{J} = 4.5 Hz, 11.5 Hz, 1H, H-3 Chol), 2.39 (br, 1H, H-4a Chol), 2.36 (t, \textit{J} = 7.5 Hz, 2H, H-2 FA), 2.14 (d, \textit{J} = 12 Hz, 1H, H-4b Chol), 1.37 – 2.00 (m, 16H, aliphatic FA and Chol), 0.84 - 1.26 (m, 43H, aliphatic FA and Chol), 0.65 (s, 3H, H-18 Chol); {superscript}13C NMR (125.7 MHz, pyridine-\textit{d}_5) δ 173.4 (C=O), 140.9 (C-5 Chol), 121.8 (C-6 Chol), 103.1 (C-1), 78.6 (C-3 Chol), 74.7 (C-5), 73.5 (C-3), 72.2 (C-2), 70.0 (C-4), 64.5 (C-6), 56.8 (C-14 Chol), 56.4 (C-17 Chol), 50.4 (C-9 Chol), 42.5 (C-13 Chol), 40.0 (C-4 Chol), 39.7 (C-24 Chol), 39.2 (C-12 Chol), 37.6 (C-10 Chol), 36.9 (C-1 Chol), 36.4 (C-22 Chol), 36.0 (C-20 Chol), 34.4 (C-2 FA), 32.1, 32.0 (3C, C-7, C-8 Chol, C-10 FA), 30.2, (C-2 Chol), 29.9, 29.8, 29.6, 29.4 (C-4 – C-9 FA), 28.5 (C-25 Chol), 28.2 (C-15 Chol), 25.3 (C-16 Chol), 24.5 (C-3 FA), 24.1 (C-23 Chol), 22.9 (2C, C-26, C-27 Chol), 22.6 (C-11 FA), 21.3 (C-11 Chol), 19.4 (C-21 Chol), 18.9 (C-19 Chol), 14.3 (C-12 FA), 11.9 (C-18 Chol). HR ESI MS \textit{m/z} calcd for C_{45}H_{78}NaO_{7} 753.5640, found 753.5626.
4.4.2.3.5. Cholesteryl 6-O-oleoyl-β-D-galactopyranoside (169e)

A colorless solid: $R_f$ 0.38 (hexanes/EtOAc; 1: 3); $^1$H NMR (500.13 MHz, pyridine-$d_5$) δ 6.75 (br, 1H, HO-2), 6.30 (br, 1H, HO-3), 5.48 (m, 2H, FA H-9, H-10), 5.37 (m, 1H, H-6 Chol), 4.92 (dd, $J_{5,6a} = 7.5$ Hz, $J_{6a,6b} = 11$ Hz, H-6a), 4.87 (d, $J_{1,2} = 8$ Hz, 1H, H-1), 4.72 (dd, $J_{5,6b} = 4.5$ Hz, $J_{6a,6b} = 11$ Hz, 1H, H-6b), 4.62 (br, 1H, HO-4), 4.37 (t, $J = 9$ Hz, 1H, H-5), 4.35 (d, $J_{3,4} = 3$ Hz, 1H, H-4), 4.11 – 4.15 (m, 2H, H-2, H-3), 3.91 (tt, $J = 6.5$ Hz, 11 Hz, 1H, H-3 Chol), 2.38 – 2.41 (m, 3H), 0.86 – 2.12 (m, 68H, aliphatic FA and Chol), 0.69 (s, 3H, H-18 Chol); $^{13}$C NMR data similar to lit.$^{279}$ HR ESI MS $m/z$ calcd for C$_{51}$H$_{88}$NaO$_7$ 835.6422, found 835.6403.

4.4.2.3.6. Cholesteryl 6-O-erucoyl-β-D-galactopyranoside (169f)

A colorless solid; $R_f$ 0.29 (hexanes/EtOAc; 1: 2); $^1$H NMR (500.13 MHz, CDCl$_3$) δ 5.31 – 5.37 (m, 3H, H-6 Chol, H-13, H-14 FA), 3.25 – 4.55 (br, 3H, HO-2, HO-3, HO-4), 4.26 – 4.35 (m, 3H, H-1, H-6a, H-6b), 3.88 (s, 1H, H-4), 3.50 – 3.68 (m, 4H, H-2, H-3, H-5 Gal, H-3 Chol), 2.26 – 2.34 (m, 4H, H-2 FA, H-4a, H-4b Chol), 1.88 – 2.08 (m, 7H, Chol), 0.85 - 1.70 (m, 66H, aliphatic FA and Chol), 0.67 (s, 3H, H-18 Chol); $^{13}$C NMR (125.7 MHz, CDCl$_3$) δ 173.8 (C=O), 140.5 (C-5 Chol), 130.1 (C-13 FA), 130.0 (C-14 FA), 122.2 (C-6 Chol), 101.8 (C-1), 79.8 (C-3
Chol), 73.6 (C-5), 72.5 (C-3), 71.4 (C-2), 68.9 (C-4), 63.0 (C-6), 56.9 (C-14 Chol), 56.4 (C-17 Chol), 50.3 (C-9 Chol), 42.5 (C-13 Chol), 39.9 (C-4 Chol), 39.7 (C-24 Chol), 39.0 (C-12 Chol), 37.5 (C-10 Chol), 36.8 (C-1 Chol), 36.3 (C-22 Chol), 36.0 (C-20 Chol), 34.4 (C-2 FA), 32.1 (C-12 FA), 32.0 (C-15 FA), 29.97, 29.9, 29.82, 29.79, 29.7, 29.6, 29.5 (10C, C-2 Chol, C-6 – C-11 FA, C-16 – C-18 FA), 28.2 (C-25 Chol), 27.38 (C-15 Chol), 27.37 (C-16 Chol), 25.1 (C-3 FA), 24.0 (C-23 Chol), 23.0, 22.8 (2C, C-26, C-27 Chol), 22.7 (C-21 FA), 21.2 (C-11 Chol), 19.5 (C-21 Chol), 18.9 (C-19 Chol), 14.3 (C-22 FA), 12.0 (C-18 Chol). HR ESI MS m/z calcd for C_{55}H_{96}NaO_{7} 891.7048, found 891.7074.
Chapter 5: Direct Synthesis of Maradolipids and Other Trehalose 6-monoesters and 6,6'-diesters

5.1. Introductory Remarks

Primary monoesters and diesters of trehalose (Figure 13) have been of interest since the recognition\textsuperscript{281} that they are important components of the outer membranes of mycobacteria in which the carboxylic acids are mycolic acids, complex long-chain $\beta$-hydroxy acids.\textsuperscript{282-284} They are also of interest for many diverse biological activities.\textsuperscript{283,285,286} Recently, they have been identified as components of the outer membrane of dauer (enduring) larva of the well-known nematode, \textit{Caenorhabditis elegans}.\textsuperscript{287} This form of larva appears when the nematode is exposed to extremely dry conditions and the altered membrane allows the nematode to survive extreme desiccation.\textsuperscript{288} The mixture of fatty acids present in the outer membrane, the "maradolipids",\textsuperscript{287} is extremely complex, with about 38\% of the fatty acids being monomethyl branched fatty acids and about 16\% containing cyclopropyl groups. The most abundant component is a nonsymmetric 6,6'-trehalose diester, 6-\textit{O}-(13-methylmyristoyl)-6'\textit{-O}-oleoyltrehalose (176b).\textsuperscript{287} The only monomethyl branched fatty acids that have been identified in \textit{C. elegans} are branched next to the terminal carbon, that is, they are iso fatty acids.\textsuperscript{287,289-291} Nevertheless, ante monomethyl branched fatty acids, that is, fatty acids branched on the carbon second from the terminal carbon, are common in nature.\textsuperscript{290}

![Figure 13 Trehalose 6,6'-diesters](image_url)
5.2. Trehalose Primary Esters

There has been extensive effort directed at the synthesis of trehalose primary esters.\textsuperscript{283,292,293} Most authors have chosen to use protecting group strategies. One approach has been to use temporary protection of the primary hydroxyls with trityl or tert-butyldimethylsilyl or tert-butyldiphenylsilyl groups before benzylation, removal of the primary protecting groups and acylation.\textsuperscript{294-300} The discovery\textsuperscript{301} that primary trimethylsilyl groups can be selectively removed by mild aqueous base has led to the extensive use of the 2,2',3,3',4,4'-hexa-O-trimethylsilyl derivative for acylation studies.\textsuperscript{301-311} An alternative strategy has been to selectively convert the primary hydroxyls into leaving groups, either sulfonates\textsuperscript{312} or halides,\textsuperscript{301} before introducing acyl groups via $S_N2$ substitution with carboxylate salts.\textsuperscript{294,295,302} Trehalose has also been monoesterified at O-6 enzymically using a variety of vinyl fatty acid esters in dimethyl formamide by a protease from \textit{Bacillus subtilis} in good yields.\textsuperscript{313} Very recently, the major trehalose diester (176b) has been synthesized chemoenzymatically using vinyl esters as acyl donors, and using the commercially available Alcalase from \textit{Bacillus licheniformis} to do the initial monoacylation in 18 days with vinyl oleoate, then performing the second acylation under Mitsunobu conditions.\textsuperscript{314} Protecting-group-free strategies are inherently attractive but few have been disclosed to this point. Transesterification gave quite low yields.\textsuperscript{285,315} Tributylstannylation gave moderate yields only when the conditions using the toxic tributylstannyl ethers were carefully optimized.\textsuperscript{316} Mitsunobu reactions are more attractive but again the yields are in the 50 to 60\% range and the best solvent is toxic hexamethylphosphoramide.\textsuperscript{317,318} The following section discusses the protecting-group-free synthesis of 6-monoesters and 6,6'-diesters of trehalose using the primary-selective acylation procedure which was discussed in Chapter 3.\textsuperscript{275}
5.3. Synthesis of Trehalose 6-monoesters and 6,6'-diesters

The conditions developed for the regioselective acylation of primary alcohols in the presence of secondary alcohols involved reaction of the diol or polyol with the carboxylic acid in N,N-dimethylformamide (DMF) with at least 2 equiv of diisopropylethylamine (DIEA) and 1.2 equiv of TBTU (Chapter 3). Trehalose is relatively insoluble in DMF but it was found that pyridine was a good solvent for this reaction as it was for the selective acylation of galactosides in Chapter 4.\textsuperscript{319} Reaction of trehalose (172) with a slight excess of the fatty acid at room temperature gave good yields (65-69%) of the 6-O-monoacylated products as pictured in Scheme 50 and shown in entries 1, 5 and 9 of Table 14. Under these conditions, small amounts of the 6,6'-di-O-acylated products were also obtained, consistent with the first substitution having little effect on the reactivity of the second primary hydroxyl group. The long chains of the fatty acids caused these reactions to be considerably slower than the corresponding reactions with simple acids, such as benzoic acid, and longer reaction times were required to achieve complete reaction of the fatty acids. As noted in the reactions with galactose derivatives (Chapter 4)\textsuperscript{319} the added base was unnecessary if the solvent is pyridine (compare entries 1, 5, and 9 in Table 14), consistent with the role of the base in the reactions of primary alcohols being to accept protons released from the initial reaction of the acid with the uronium salt (TBTU) and from the addition of the alcohol to the active ester. Use of two or more equivalents of fatty acids gives reasonable yields of the 6,6-di-O-acyl products (see entries 2, 3, 7, and 10 in Table 14). Neither increasing the relative amount of fatty acid beyond 2.1 equiv nor raising the reaction temperature improved the yields of the disubstituted products. Instead, additional products were obtained of which the 2,6,6'-triester (Figure 14) was the most prominent, isolated in 20% yield from the reaction of trehalose with 3.5 equiv of hexanoic acid for 48 h and in 40% yield from the reaction with 5
equiv of oleic acid for 168 h. No products of esterification on secondary oxygen atoms have previously been observed in reactions of this type with monosaccharides. Perhaps the hydroxyl group at O-2 of trehalose is more acidic than hydroxyls of monosaccharides because the anomeric oxygen is more electron withdrawing in a non-reducing disaccharide.

![Scheme 50 Synthesis of trehalose 6-monoesters and 6,6'-diesters](image)

**Table 14** Conditions and outcomes for the reactions of trehalose (172) with fatty acids

<table>
<thead>
<tr>
<th>entry</th>
<th>fatty acid (equiv)</th>
<th>TBTU (equiv)</th>
<th>DIEA (equiv)</th>
<th>time (h)</th>
<th>temp</th>
<th>product, yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6-mono 6,6'-di</td>
</tr>
<tr>
<td>1</td>
<td>hexanoic (1.1)</td>
<td>1.1</td>
<td>2.1</td>
<td>36</td>
<td>rt</td>
<td>173a, 69; 174a, 14</td>
</tr>
<tr>
<td>2</td>
<td>hexanoic (2.1)</td>
<td>2.1</td>
<td>2.1</td>
<td>36</td>
<td>rt</td>
<td>173a, 20; 174a, 63</td>
</tr>
<tr>
<td>3</td>
<td>hexanoic (2.1)</td>
<td>2.1</td>
<td>0</td>
<td>36</td>
<td>rt</td>
<td>173a, 19; 174a, 63</td>
</tr>
<tr>
<td>4</td>
<td>hexanoic (3.5)</td>
<td>3.5</td>
<td>3.5</td>
<td>48</td>
<td>rt</td>
<td>173a, 10; 174a, 48a</td>
</tr>
<tr>
<td>5</td>
<td>palmitic (1.1)</td>
<td>1.1</td>
<td>0</td>
<td>72</td>
<td>rt</td>
<td>173b, 67; 174b, 14</td>
</tr>
<tr>
<td>6</td>
<td>palmitic (1.1)</td>
<td>1.1</td>
<td>2.1</td>
<td>48</td>
<td>40 °C</td>
<td>173b, 37; 174b, 32</td>
</tr>
<tr>
<td>7</td>
<td>palmitic (2.1)</td>
<td>2.1</td>
<td>0</td>
<td>72</td>
<td>rt</td>
<td>173b, 16; 174b, 66</td>
</tr>
<tr>
<td>8</td>
<td>palmitic (2.2)</td>
<td>2.2</td>
<td>0</td>
<td>168</td>
<td>rt</td>
<td>173b, 18; 174b, 69</td>
</tr>
<tr>
<td>9</td>
<td>oleic (1.1)</td>
<td>1.1</td>
<td>0</td>
<td>60</td>
<td>rt</td>
<td>173c, 65; 174c, 15</td>
</tr>
</tbody>
</table>
The most abundant component in the maradolipid mixture is 6-O-(13-methylmyristoyl)-6’-O-oleoyltrehalose \((176b)\).\(^{287}\) It was found that unsymmetrical derivatives of this type could be synthesized in good yields by reacting the monooleoyl derivative \(173c\) with 1.1 equiv of the fatty acid for extended reaction times at room temperature (see Scheme 51 and entries 4 and 6 of Table 15). Branched fatty acids such as 13-methylmyristic acid are available commercially from specialized companies at great expense for the amounts necessary for synthetic purposes but here this acid was synthesized using the method of Foglia and Vail.\(^{320}\) Compound \(176b\) (maradolipid) had been synthesized twice previously in five-step routes using TMS ethers as temporary protecting groups.\(^{309,310}\)
The ante derivative 6-\textit{O}-(12-methyltetradecanoyl)-6\textsuperscript{'-}\textit{O}-oleoyltrehalose (176c) was prepared in the same way (see Scheme 51) from 173c and 12-methylmyristic acid. This fatty acid was prepared in racemic form using a Wittig reaction of the Wittig reagent derived from 11-bromoundecanoic acid with 2-butanone followed by hydrogenation as previously described.\textsuperscript{321} Compound 176c had never been synthesized previously and provides a sample for examining whether such compounds are part of the complex maradolipid mixture.

**Table 15** Conditions and outcomes for the reactions of 6-\textit{O}-oleoyltrehalose with fatty acids

<table>
<thead>
<tr>
<th>Entry</th>
<th>fatty acid (equiv)</th>
<th>TBTU (equiv)</th>
<th>time (h)</th>
<th>temp</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>hexanoic (1.1)</td>
<td>1.1</td>
<td>72</td>
<td>rt</td>
<td>59\textsuperscript{a}</td>
</tr>
<tr>
<td>2</td>
<td>13-methyltetradecanoic (1.1)</td>
<td>1.1</td>
<td>72</td>
<td>rt</td>
<td>62\textsuperscript{b}</td>
</tr>
<tr>
<td>3</td>
<td>13-methyltetradecanoic (1.1)</td>
<td>1.1</td>
<td>120</td>
<td>rt</td>
<td>72\textsuperscript{c}</td>
</tr>
<tr>
<td>4</td>
<td>13-methyltetradecanoic (1.1)</td>
<td>1.1</td>
<td>170</td>
<td>rt</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>12-methyltetradecanoic (1.1)</td>
<td>1.1</td>
<td>72</td>
<td>rt</td>
<td>54\textsuperscript{d}</td>
</tr>
<tr>
<td>6</td>
<td>12-methyltetradecanoic (1.1)</td>
<td>1.1</td>
<td>170</td>
<td>rt</td>
<td>79</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Plus 26\% of 173c also isolated. \textsuperscript{b} Plus 22\% of 173c. \textsuperscript{c} Plus 10\% of 173c. \textsuperscript{d} Plus 27\% of 173c.
5.4. Conformational Analysis

It was also of interest to determine whether the diverse biological activities of these compounds is influenced by alteration of the populations of the rotameric conformations adopted by the hydroxymethyl groups of trehalose caused by the interactions of the hydrophobic fatty acid alkyl groups. Trehalose itself adopts a conformation with both anomeric linkages adopting normal exo-anomeric conformations both in the solid state\cite{322-324} and in solution.\cite{325-327} Hydroxymethyl rotameric populations have been discussed extensively\cite{328-331} and have been determined carefully for glucose derivatives by making use of all H,H and C,H coupling constants of isotopically enriched derivatives.\cite{332-334} 4,6-Unsubstituted derivatives slightly prefer the $gt$ conformer over the $gg$ conformer with the $tg$ conformer having a population of about 10% or slightly less.\cite{331-334} Barnett and Naidoo suggest that the preference for the $gt$ conformer is due to direct and water-mediated hydrogen bonds between the O6 hydroxyl hydrogen and O5.\cite{330} In the solid state, trehalose and its dihydrate are present in conformations where the two hydroxymethyl groups each adopt one of the two rotamers populated in solution, the $gg$ and $gt$ rotamers, giving rise to $^{13}$C CP/MAS spectra with one signal for each of the 12 carbon atoms. H5-H6 vicinal coupling constants were determined for the three monoesters (173), the three symmetrical diesters (174), and the two 2,6,6’- triesters (175) making the reasonable (all $\Delta \nu/J > 6$) assumption that the coupling patterns were first order. The values obtained are reported in Table 16. The hydroxymethyl groups can adopt three energy minima conformers, termed the $gg$, $gt$, and $tg$ rotamers, according to whether O5 and C4, respectively, are gauche or trans to O6. The coupling constants for the C6 protons were used to calculate rotameric populations using the values of the coupling constants for each rotamer calculated by Stennutz et al.\cite{332} Fractional
rotameric populations $\rho_{gg}$, $\rho_{gt}$, $\rho_{tg}$, were obtained by solving the following three linear equations:

$J_{5,6R} = \rho_{gg} (0.8) + \rho_{gt} (9.9) + \rho_{tg} (4.5)$.  
$J_{5,6S} = \rho_{gg} (1.3) + \rho_{gt} (1.5) + \rho_{tg} (10.8)$.  
$\rho_{gg} + \rho_{gt} + \rho_{tg} = 1$.

![Figure 15](image)

**Figure 15** Newman projection from C5 to C6 illustrating the three rotamers and atom labeling

<table>
<thead>
<tr>
<th>Table 16</th>
<th>Three-bond coupling constants observed for C6 protons (CD$_3$OD, 22 °C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound</td>
<td>$^3J_{5,6R}$ (Hz)</td>
</tr>
<tr>
<td>173a</td>
<td>4.98</td>
</tr>
<tr>
<td>173b</td>
<td>5.08</td>
</tr>
<tr>
<td>173c</td>
<td>5.05</td>
</tr>
<tr>
<td>174a</td>
<td>5.20</td>
</tr>
<tr>
<td>174b</td>
<td>5.29</td>
</tr>
<tr>
<td>174c</td>
<td>5.28</td>
</tr>
<tr>
<td>175a</td>
<td>4.96</td>
</tr>
<tr>
<td>175c</td>
<td>4.87</td>
</tr>
</tbody>
</table>

The percentage populations for each rotamer are listed in Table 17. The percentage populations for the monoesters and diesters are similar to those obtained for glucose previously\textsuperscript{331,332} although the relative amounts of the $gg$ rotamer appears to have increased slightly at the expense of the $gt$ conformer. This is consistent with loss of the stabilizing effect for the $gt$ isomer rotamer of direct and hydroxylic solvent mediated hydrogen bonds between the
O6 hydroxyl hydrogen and O5. Therefore, aggregation of the long lipophilic groups on O6 does not appear to influence the rotameric populations for the hydroxymethyl groups of these two classes of compounds significantly.

**Table 17** Percentage population of rotamers (CD$_3$OD, 22 $^\circ$C)

<table>
<thead>
<tr>
<th>Compound</th>
<th>% $gt$ for C5C6 bond</th>
<th>% $gg$ for C5C6 bond</th>
<th>% $tg$ for C5C6 bond</th>
<th>% $gt$ for C5'C6' bond</th>
<th>% $gg$ for C5'C6' bond</th>
<th>% $tg$ for C5'C6' bond</th>
</tr>
</thead>
<tbody>
<tr>
<td>173a</td>
<td>43</td>
<td>50</td>
<td>6.6</td>
<td>48</td>
<td>47</td>
<td>5.0</td>
</tr>
<tr>
<td>173b</td>
<td>45</td>
<td>49</td>
<td>6.4</td>
<td>41</td>
<td>52</td>
<td>6.9</td>
</tr>
<tr>
<td>173c</td>
<td>44</td>
<td>49</td>
<td>7.1</td>
<td>48</td>
<td>44</td>
<td>8.4</td>
</tr>
<tr>
<td>174a</td>
<td>45</td>
<td>47</td>
<td>7.6</td>
<td>45</td>
<td>47</td>
<td>7.6</td>
</tr>
<tr>
<td>174b</td>
<td>47</td>
<td>47</td>
<td>6.9</td>
<td>47</td>
<td>47</td>
<td>6.9</td>
</tr>
<tr>
<td>174c</td>
<td>46</td>
<td>46</td>
<td>7.6</td>
<td>46</td>
<td>46</td>
<td>7.6</td>
</tr>
<tr>
<td>175a</td>
<td>43</td>
<td>50</td>
<td>7.4</td>
<td>70</td>
<td>23</td>
<td>6.6</td>
</tr>
<tr>
<td>175c</td>
<td>42</td>
<td>51</td>
<td>7.4</td>
<td>76</td>
<td>19</td>
<td>4.6</td>
</tr>
</tbody>
</table>

In contrast, for the 2,6,6'-triesters, the two sets of H5,H6 coupling constants were different; the set for the disubstituted glucose unit was similar to those observed for the mono and diesters but for the monosubstituted glucose residue, the $J_{5,6R}$ value was between 2.2 and 2.7 Hz bigger than those observed for all other residues. For this residue, the $gt$ conformer was calculated to be more favored, to the extent of 70 and 76% of the rotamers for 175a and 175c, respectively, mostly at the expense of the $gg$ conformer. This change is probably caused by
intramolecular van der Waals interactions between the long chains of the 6’-ester and the 2-ester, favoring the rotamer where the C6’ ester is turned toward the disubstituted glucose residue, as illustrated in Figure 16.

**Figure 16** A conformation illustrating how adopting the $gt$ conformation for C5-C6 bond in the monosubstituted glucose ring allows van der Waals between the long chains of the 6'-ester and the 2-ester

5.5. Concluding Remarks

The regioselective esterification of primary hydroxyls promoted by TBTU is an excellent way for the direct synthesis of trehalose 6-monoesters, and other trehalose 6,6’-diesters. One equiv of fatty acid provides 6-O-monoesters in one step in good yields (~70%) accompanied by small amounts of the diprimary ester; two equiv provides symmetrical 6,6'-diesters in fair yields. In comparison, enzymatic esterification using commercially available protease from *Bacillus subtilis* gave the monopalmitate 173b in 84% yield and the monooleaoate 173c in 55% yield after 12 days. Other protecting-group-free chemical transformations give monoesters in lower yields, of which, the Mitsunobu reaction is most efficient (47 - 61%). The monoesters can be again be monoesterified in the same way to provide non-symmetric 6,6'-O-diesters in two steps from trehalose in very good yields. This method allows expeditious synthesis of any desired structure. Compounds synthesized include the most abundant component of the very complex
maradolipid mixture, 6-O-(13-methyltetradecanoyl)-6’-O-oleoyltrehalose, and a component potentially present in this mixture, 6-O-(12-methyltetradecanoyl)-6’-O-oleoyltrehalose, a derivative of an ante fatty acid. The C5-C6 rotameric populations of 6-O-monoesters, symmetrical 6,6’-diesters, and 2,6,6’-triesters of fatty acids were calculated from the values of the H5-H6R and H5-H6S coupling constants and found to be similar to those found for glucose. The rotameric population of the monosubstituted glucose residue was altered considerably in the 2,6,6’-triesters to favor the gt rotamer, presumably because of attraction between the 2- and 6’-fatty acid chains.

5.6. Experimental Section

5.6.1. General

1H and 13C NMR spectra were recorded on a Bruker Avance-500 MHz NMR spectrometer operating at 500.13 and 125.7 MHz respectively using the solvent resonances as secondary chemical shift references. The carbon and hydrogen atoms were assigned following analysis of their one dimensional (1H, 13C) and two dimensional (COSY, HSQC, HMBC, and TOCSY) NMR spectral data. Coupling constant (J) values are reported in Hertz. High-resolution mass spectra were recorded using electrospray ionization with a time of flight mass analyzer. Melting points are uncorrected. N,N-Diisopropylethylamine (DIEA) was refluxed over calcium hydride and distilled onto molecular sieves. All non-aqueous reactions were performed under a nitrogen atmosphere. Pyridine was refluxed over potassium hydroxide and distilled onto molecular sieves. Compounds were visualized/located by spraying the TLC plate with a solution of 5 % H2SO4 in ethanol followed by heating on a hot plate until color developed.
5.6.2. Synthesis

5.6.2.1. General esterification procedure using TBTU

A. Use of trehalose (172)

In an oven-dried round-bottomed flask equipped with a magnetic stir bar, a fatty acid (number of equiv given in Table 5.1) and TBTU (number of equiv given in Table 5.1) were dissolved in anhydrous pyridine (5 mL) and the resulting mixture was stirred at rt for 30 min under a nitrogen atmosphere. A solution of trehalose (amount used listed with the individual products) in dry pyridine (3 mL) was then injected into the reaction mixture via syringe and stirring was continued at rt for a time given in Table 5.1. Pyridine was removed under vacuum and the resulting residue was purified using silica gel column chromatography with elution using a solvent gradient of 5 - 25% methanol in EtOAc - DCM (1:1).

B. Use of 6-O-oleoyl-\(\alpha,\alpha\)-trehalose (173c)

In an oven-dried round-bottomed flask equipped with a magnetic stir bar, a fatty acid (1.1 equiv) and TBTU (1.1 equiv) were dissolved in anhydrous pyridine (5 mL), and the resulting mixture was stirred at rt for 30 min under a nitrogen atmosphere. 6-O-Oleoyl-\(\alpha,\alpha\)-trehalose (173c) (amount used given with individual products) in dry pyridine (3 mL) was then injected into the reaction mixture via syringe and stirring was continued at rt for the time given in Table 5.2. Pyridine was removed under vacuum and the resulting residue was dissolved in EtOAc-THF (3:1, 20 mL). After washing the mixture using saturated aq. NaHCO\(_3\) (2 x 3 mL), the organic layer was collected, dried (MgSO\(_4\)), filtered and concentrated to give a crude product, which was purified using silica gel column chromatography with elution using a gradient of 5 - 25% methanol in EtOAc - DCM (1:1).
5.6.2.1.1. 6-O-Hexanoyl-\(\alpha,\alpha\)-trehalose (173a)

The title compound was synthesized using procedure A above with trehalose (1) (200 mg, 0.58 mmol) and hexanoic acid under conditions listed in Table 5.1, entry 1 and was obtained as a colorless solid (178 mg, 69% yield): R₆ 0.20 [25% MeOH in EtOAc-DCM(1:1), v/v], mp 136 – 138 °C, lit\(^{300}\) mp 135-137 °C; \(^1\)H NMR (500.13 MHz, CD₃OD) \(\delta\) 0.91 (t, 3H, \(J = 7.0\) Hz, Me), 1.28 - 1.36 (m, 4H, 2 x CH₂), 1.61 (m, 2H, CH₂CH₃), 2.33 (t, 2H, \(J = 7.5\) Hz, CH₂CO), 3.34 - 3.38 (m, 2H, H-4, H-4'), 3.49 (dd, 2H, \(J = 3.9, 7.9\) Hz, H-2, H-2'), 3.67 (dd, 1H, \(J = 5.2, 11.7\) Hz, H-6'R), 3.79 - 3.83 (m, 4H, H-3, H-3', H-6', H-5'), 4.02 (ddd, 1H, \(J_{4,5} = 10.1\) Hz, \(J_{5,6R} = 5.2\) Hz, \(J_{5,6S} = 2.1\) Hz, H-5), 4.20 (dd, 1H, \(J = 5.2, 11.9\) Hz, H-6R), 4.38 (dd, 1H, \(J = 2, 11.9\) Hz, H-6S), 5.08 (d, 1H, \(J = 3.8\) Hz, H-1'), 5.10 (d, 1H, \(J = 3.7\) Hz, H-1); \(^{13}\)C NMR (125.7 MHz, CD₃OD) \(\delta\) 175.6 (C=O), 95.3, 95.2 (C-1, C-1'), 74.8, 74.6, 74.0, 73.33 (C-2, C-2', C-3, C-3'), 73.3, 72.0, 71.6 (C-4, C-4', C-5, C-5'), 64.5, 62.7 (C-6, C-6'), 35.1, 32.6 (COCH₂, COCH₂CH₂), 32.5, 26.0 (hexanoyl CH₂), 23.6 (CH₂CH₃), 14.4 (Me). HR ESI MS \(m/z\) calcd for C₁₈H₃₂NaO₁₂ 463.1786, found 463.1764. In addition, compound 174a (44 mg, 14% yield) was obtained.

5.6.2.1.2. 6,6'-Di-O-hexanoyl-\(\alpha,\alpha\)-trehalose (174a)
The title compound was synthesized using procedure A above with trehalose (200 mg, 0.58 mmol) and hexanoic acid under conditions listed in Table 5.1, entry 2 and was obtained as a colorless solid (198 mg, 63% yield): R_F 0.40 [20% MeOH in EtOAc-DCM (1:1), v/v], mp = 157 - 160 °C, lit\textsuperscript{300} mp 157.7 - 159.0 °C; \textsuperscript{1}H NMR (500.13 MHz, CD\textsubscript{3}OD) δ 0.91 (t, J = 6 Hz, 6H, 2 x Me), 1.30 - 1.37 (m, 8H, 4 x CH\textsubscript{2}), 1.62 (m, 4H, CH\textsubscript{2}CH\textsubscript{3}), 2.34 (t, 4H, J = 7 Hz, CH\textsubscript{2}CO), 3.33 (dd, 2H, J = 9, 10 Hz, H-4, H-4'), 3.47 (dd, 2H, J = 3.7, 9.7 Hz, H-2, H-2'), 3.77 (dd, 2H, J = 9.1, 9.6 Hz, H-3, H-3'), 4.01 (ddd, 2H, J = 10.0 Hz, J\textsubscript{5,6R} = 5.2 Hz, J\textsubscript{5,6S} = 2.1 Hz, H-5, H-5'), 4.19 (dd, 2H, J = 5.2, 11.9 Hz, H-6R), 4.35 (dd, 2H, J = 2.1, 11.9 Hz, H-6S), 5.03 (d, 2H, J = 3.7 Hz, H-1', H-1); \textsuperscript{13}C NMR (125.7 MHz, CD\textsubscript{3}OD) δ 175.5 (C=O), 95.3 (C-1, C-1'), 74.5, 73.1 (C-2, C-2', C-3, C-3'), 71.9, 71.5 (C-4, C-4', C-5, C-5'), 64.4 (C-6, C-6'), 35.0, 32.4 (COCH\textsubscript{2}, COCH\textsubscript{2}CH\textsubscript{2}), 25.8 (hexanoyl CH\textsubscript{2}), 23.4 (CH\textsubscript{2}CH\textsubscript{3}), 14.3 (Me). HR ESI MS m/z calcd for C\textsubscript{24}H\textsubscript{42}NaO\textsubscript{13} 561.2518, found 561.2517. In addition, compound 173a (49 mg, 20% yield) was obtained.

5.6.2.1.3. 2,6,6'-Tri-O-hexanoyl-α,α-trehalose (175a)

Following procedure A above using trehalose (325 mg, 0.95 mmol) with hexanoic acid (386 mg, 3.32 mmol, 3.5 equiv) as in Table 5.1 entry 4, the reaction gave compounds 173a and 174a as listed in Table 5.1 plus the title compound as a colorless syrup (119 mg, 20% yield): R_F 0.60 [5% MeOH in EtOAc-DCM (1:1), v/v]; \textsuperscript{1}H NMR (500.13 MHz, CD\textsubscript{3}OD) δ 0.91 (t, 9H, J =
6.0 Hz, 3 x Me), 1.30 - 1.39 (m, 12H, 6 x CH₂), 1.59-1.63 (m, 6H, CH₃CH₂), 1.95-2.45 (m, 6H, CH₂CO), 3.27 (dd, 1H, J = 9.0, 10 Hz, H-4'), 3.43 (dd, 1H, J = 9.1, 10 Hz, H-4), 3.47 (dd, 1H, J = 3.8, 9.8 Hz, H-2'), 3.69 (t, 1H, J = 9.0 Hz, H-3'), 3.77 (dd, 1H, J₄,₅' = 9.6 Hz, J₅,₆'R = 7.2 Hz, J₅,₆'S = 2.0 Hz, H-5'), 3.99 (t, 1H, J = 9.1 Hz, H-3), 4.04 (dd, 1H, J₄,₅ = 7.0 Hz, J₅,₆'R = 4.9 Hz, J₅,₆'S = 2.0 Hz, H-5), 4.16 (dd, 1H, J = 7.0, 11.9 Hz, H-6'R), 4.23 (dd, 1H, J = 5, 12 Hz, H-6R), 4.29 (dd, 1H, J = 2 Hz, 11.8 Hz, H-6'S), 4.39 (dd, 1H, J = 2, Hz, 12 Hz, H-6S), 4.70 (dd, 1H, J = 3.6, 10 Hz, H-2), 5.02 (d, 1H, J = 3.7 Hz, H-1'), 5.18 (d, 1H, J = 3.6 Hz, H-1); ¹³C NMR (125.7 MHz, CD₃OD) δ 175.52, 175.44, 174.8 (C=O), 95.3, 92.6 (C-1, C-1'), 74.8, 74.2, 73.0, 72.94 (C-2, C-2', C-3, C-3'), 72.09, 72.04, 71.9, 71.6 (C-4, C-4', C-5, C-5'), 64.9, 64.2 (C-6, C-6'), 39.0, 35.1, 35.0, 34.96, 32.55, 32.52 (COCH₂, COCH₂CH₂), 25.9, 25.8, 25.76, 25.73, 25.66 (hexanoyl CH₂), 23.5 (CH₂CH₃), 14.5 (Me). HR ESI MS m/z calcd for C₃₀H₅₂NaO₁₄ 659.3249, found 659.3240.

5.6.2.1.4. 6-O-Palmitoyl-α,α-trehalose (173b)

The title compound was synthesized using procedure A above with trehalose (300 mg, 0.87 mmol) and palmitic acid under conditions listed in Table 5.1, entry 5 and was obtained as a colorless solid (341 mg, 67% yield): Rf 0.33 [20% MeOH in EtOAc-DCM (1:1)], mp 156 - 159 °C, lit³³⁵ mp 114 - 116 °C; ¹H NMR (500.13 MHz, CD₃OD) δ 0.90 (t, 3H, J = 6.0 Hz, Me), 1.29 - 1.37 (m, 24H, 12 x CH₂), 1.62 (m, 2H, CH₂CH₃), 2.34 (t, 2H, J = 7.2 Hz, CH₂CO), 3.30 - 3.33 (m, 2H, H-4, H-4'), 3.46, 3.47 (2 overlapping dd, 2H, J₁,₂ = 4.0 Hz, J₂,₃ = 9 Hz, H-2, H-2')
(dd, 1H, J = 5.7, 12.1 Hz, H-6'R), 3.76 - 3.83 (m, 4H, H-3', H-6', H-5'), 4.01 (ddd, 1H, J_{4,5} = 10.1 Hz, J_{5,6R} = 5.1 Hz, J_{5,6S} = 2.0 Hz, H-5), 4.19 (dd, 1H, J = 5.1, 11.9 Hz, H-6R), 4.35 (dd, 1H, J = 2, 11.9 Hz, H-6S), 5.07 (d, 1H, J = 3.7 Hz, H-1'), 5.10 (d, 1H, J = 3.7 Hz, H-1); \textsuperscript{13}C NMR (125.7 MHz, CD\textsubscript{3}OD) δ 175.6 (C=O), 95.4, 95.3 (C-1, C-1'), 74.8, 74.6, 74.1, 73.2 (C-2, C-2', C-3, C-3'), 73.4, 72.1, 71.6 (C-4, C-4', C-5, C-5'), 64.5, 62.8 (C-6, C-6'), 35.2 (COCH\textsubscript{2}, COCH\textsubscript{2}CH\textsubscript{2}), 33.2, 30.9, 30.8, 30.6, 30.4, 26.0 (palmitoyl CH\textsubscript{2}), 23.9 (CH\textsubscript{2}CH\textsubscript{3}), 14.6 (Me).

HR ESI MS m/z calcd for C\textsubscript{28}H\textsubscript{52}NaO\textsubscript{12} 603.3351, found 603.3335. In addition, compound 174b (71 mg, 14% yield) was obtained.

\textbf{5.6.2.1.5. 6,6'-Di-O-palmitoyl-α,α-trehalose (174b)}

![Diagram of 6,6'-Di-O-palmitoyl-α,α-trehalose (174b)]

The title compound was synthesized using procedure A above with trehalose (300 mg, 0.87 mmol) and palmitic acid under conditions listed in Table 5.1, entry 7 and was obtained as a gummy solid (480 mg, 66% yield): R\textsubscript{F} 0.62 [20% MeOH in EtOAc-DCM (1:1), v/v]; \textsuperscript{1}H NMR (500.13 MHz, CD\textsubscript{3}OD) δ 0.90 (t, 6H, J = 6.0 Hz, 2 x Me), 1.26 - 1.39 (m, 48H, 24 x CH\textsubscript{2}), 1.61 (m, 4H, CH\textsubscript{2}CH\textsubscript{3}), 2.34 (t, 4H, J = 7.2 Hz, CH\textsubscript{2}CO), 3.30 - 3.34 (m, 2H, H-4, H-4'), 3.47 (dd, 2H, J = 3.7, 9.7 Hz, H-2, H-2'), 3.77 (t, 2H, J = 9.3 Hz, H-3, H-3'), 4.02 (ddd, 2H, J_{4,5} = 10.0 Hz, J_{5,6R} = 5.3 Hz, J_{5,6S} = 2.1 Hz, H-5, H-5'), 4.19 (dd, 2H, J = 5.3, 11.9 Hz, H-6R, H-6'R), 4.35 (dd, 2H, J = 2.1, 11.9 Hz, H-6S, H-6'S), 5.04 (d, 2H, J = 3.7 Hz, H-1,H-1'); \textsuperscript{13}C NMR (125.7 MHz, CD\textsubscript{3}OD) δ 175.5 (C=O), 95.4 (C-1, C-1'), 74.7, 73.3 (C-2, C-2', C-3, C-3'), 72.1, 71.7 (C-4, C-4', C-5, C-5'), 64.6 (C-6, C-6'), 35.2, 33.2 (COCH\textsubscript{2}, COCH\textsubscript{2}CH\textsubscript{2}), 30.96, 30.93, 30.8, 30.6, 30.6,
30.4, 26.2 (palmitoyl CH₂), 23.9 (CH₂CH₃), 14.6 (Me). HR ESI MS m/z calcd for C₄₄H₈₂NaO₁₃
841.5648, found 841.5648. In addition, compound 173b (82.0 mg, 16% yield) was obtained.

5.6.2.1.6. 6-O-Oleoyl-α,α-trehalose (173c)

![Chemical structure of 173c]

The title compound was synthesized using procedure A above with trehalose (300 mg, 0.87 mmol) and oleic acid under conditions listed in Table 5.1, entry 9 and was obtained as a colorless solid (346 mg, 65% yield): Rf 0.37 [20 % MeOH in EtOAc-DCM (1:1), v/v], mp become transparent at 120 - 130 °C, melted at 166 - 168 °C (lit mp 165 - 167 °C); ¹H NMR (500.13 MHz, CD₃OD) δ 0.90 (t, 3H, J = 6.5 Hz, Me), 1.25 - 1.40 (m, 20H, 10 x CH₂), 1.45 - 1.61 (m, 2H, CH₂CH₃), 2.02 - 2.04 (m, 4H, 2 x CH₂CHCH), 2.34 (t, 2H, J = 7.0 Hz, CH₂CO), 3.30 - 3.32 (m, 2H, H-4, H-4'), 3.46, 3.47 (2 overlapping dd, 2H, J₁,₂ = 3.9 Hz, J₂,₃ = 8.8 Hz, J₁',₂' = 4.0 Hz, J₂',₃' = 9.2 Hz, H-2, H-2'), 3.67 (dd, 1H, J = 5.5, 12.1 Hz, H-6'R), 3.76 - 3.85 (m, 4H, H-3, H-3', H-6'S, H-5'), 4.02 (ddd, 1H, J₄,₅ = 10.1 Hz, J₅,₆ = 5.1 Hz, J₅,₆ = 2.1 Hz, H-5), 4.20 (dd, 1H, J = 5.1, 11.9 Hz, H-6R), 4.36 (dd, 1H, J = 2.1, 11.9 Hz, H-6S), 5.07 (d, 1H, J = 3.7 Hz, H-1'), 5.09 (d, 1H, J = 3.7 Hz, H-1), 5.35 (t, 2H, J = 4.8 Hz, CH=CH); ¹³C NMR (125.7 MHz, CD₃OD) δ 175.4 (C=O), 130.9, 130.8 (CH=CH), 95.2, 95.1 (C-1, C-1'), 74.6, 74.4, 73.9, 73.19, 73.16, 71.91, 71.86, 71.4 (C-2, C-2', C-3, C-3', C-4, C-4', C-5, C-5'), 64.4, 62.6 (C-6, C-6'), 35.0, 33.1 (COCH₂, COCH₂CH₂), 30.8, 30.6, 30.5, 30.3, 30.2, 28.1, 26.0 (oleoyl CH₂), 23.7 (CH₂CH₃), 14.5 (Me). HR ESI MS m/z calcd for C₃₀H₅₄NaO₁₂ 629.3507, found 629.3527. In addition, compound 174c (115 mg, 15% yield) was obtained.
The title compound was synthesized using procedure A above with trehalose (150 mg, 0.43 mmol) and oleic acid under conditions listed in Table 5.1, entry 10 and was obtained as a gummy solid (260 mg, 66% yield): R_f 0.63 [20% MeOH in EtOAc-DCM (1:1), v/v]; ^1H NMR (500.13 MHz, CD_3OD) δ 0.94 (t, 6H, J = 6.5 Hz, 2 x Me), 1.32 - 1.45 (m, 40H, 20 x CH_2), 1.64 - 1.67 (m, 4H, CH_2CH_3), 2.05 - 2.07 (m, 8H, CH_2CHCH), 2.38 (t, 4H, J = 7.0 Hz, CH_2CO), 3.33 (dd, 2H, J_3,4 = 8.9 Hz, J_4,5 = 10.1 Hz, H-4, H-4'), 3.50 (dd, 2H, J_1,2 = 3.8 Hz, J_2,3 = 9.7 Hz, H-2, H-2'), 3.81 (dd, 2H, J_3,4 = 9.1 Hz, J_2,3 = 9.5 Hz, 2H, H-3, H-3'), 4.05 (ddd, 2H, J_4,5 = 10.1 Hz, J_5,6 = 5.1 Hz, J_5,6' = 2.1 Hz, H-5, H-5'), 4.23 (dd, 2H, J = 5.1 Hz, 11.9 Hz, H-6R, H-6'R), 4.39 (dd, 2H, J = 2.1, 11.9 Hz, H-6S, H-6'S), 5.09 (d, 2H, J = 3.8 Hz, H-1',H-1), 5.35 (t, 4H, J = 4.8 Hz, 4H, CH=CH); ^13C NMR (125.7 MHz, CD_3OD) δ 175.5 (C=O), 131.1, 131.0 (CH=CH), 95.3 (C-1, C-1'), 74.7, 73.3, 72.1, 71.6 (C-2, C-2', C-3, C-3', C-4, C-4', C-5, C-5'), 64.6 (C-6, C-6'), 35.2, 33.2 (COCH_2, COCH_2CH_2), 31.0, 31.0, 30.8, 30.6, 30.5, 30.4, 28.3, 26.2 (oleoyl CH_2), 23.9 (CH_2CH_3), 14.6 (Me). HR ESI MS m/z calcd for C_{48}H_{86}NaO_{13} 893.5961, found 893.5950. In addition, compound 173c (48 mg, 18% yield) was obtained.
5.6.2.1.8. 2,6,6'-Tri-O-oleoyl-α,α-trehalose (175c)

The title compound was synthesized from trehalose (150 mg, 0.43 mmol) and oleic acid (610 mg, 2.16 mmol, 5 equiv) using procedure A under the conditions listed in Table 5.1 entry 13. Compounds 173c and 174c were obtained as listed in Table 5.1, entry 13 plus the title compound as a thick colorless syrup (198 mg, 40% yield): R_F 0.43 [1% MeOH in EtOAc-DCM (1:1), v/v]; ^1H NMR (500.13 MHz, CD_3OD) δ 0.90 (t, 9H, J = 6.5 Hz, 3 x Me), 1.19 - 1.35 (m, 60H, 30 x CH_2), 1.57-1.66 (m, 6H, CH_2CH_3), 1.99 - 2.07 (m, 12H, CH_2CHCH), 2.32-2.46 (m, 6H, CH_2CO), 3.24 (dd, 1H, J = 9.0, 10 Hz, H-4'), 3.44 (overlapped dd, 1H, H-4), 3.47 (dd, 1H, J = 9.0, 10 Hz, H-2'), 3.68 (t, 1H, J = 9.2 Hz, H-3'), 3.78 (ddd, 1H, J_4',5' = 10.0 Hz, J_5',6'R = 7.7 Hz, J_5',6'S = 2.0 Hz, H-5'), 3.99 (t, 1H, J = 9.6 Hz, H-3), 4.07 (ddd, 1H, J_4,5 = 7.0 Hz, J_5,6'R = 4.5 Hz, J_5,6'S = 2.2 Hz, H-5'), 4.15 (dd, 1H, J = 7.8, 11.7 Hz, H-6'R), 4.24 (dd, 1H, J = 5.0, 12.0 Hz, H-6R), 4.29 (dd, 1H, J = 1.9, 12.0 Hz, H-6'S), 4.39 (dd, 1H, J = 2.2, 12.0 Hz, H-6S), 4.70 (dd, 1H, J = 3.7, 10 Hz, H-2), 5.01 (d, 1H, J = 3.7 Hz, H-1'), 5.18 (d, 1H, J = 3.6 Hz, H-1), 5.33-5.36 (m, 6H, CH=CH); ^13C NMR (125.7 MHz, CD_3OD) δ 175.52, 175.38, 174.8 (C=O), 131.06, 131.02 (CH=CH), 95.3, 92.7 (C-1, C-1'), 74.9, 74.2, 73.0, 72.28 (C-2, C-2', C-3, C-3'), 72.06, 72.00, 71.9, 71.6 (C-4, C-4', C-5, C-5'), 65.0, 64.2 (C-6, C-6'), 35.3, 35.1, 35.0 (COCH_2, COCH_2CH_2), 33.2, 31.0, 30.8, 30.7, 30.6, 30.55, 30.47, 30.40, 28.3, 26.3, 26.2, 26.0 (oleoyl CH_2), 24.0 (CH_2CH_3), 14.7 (Me). HR ESI MS m/z calcd for C_66H_{118}NaO_{14} 1157.8414, found 1157.8451.
5.6.2.1.9. 6-O-Hexanoyl-6'-O-oleoyl-α,α-trehalose (176a)

![Chemical Structure](176a)

The title compound was synthesized using procedure B above with 6-O-oleoyl-α,α-trehalose (173c) (100 mg, 0.17 mmol) and hexanoic acid (21 mg, 0.18 mmol) and was obtained as a gummy solid (69 mg, 59% yield): Rf 0.46 [20% MeOH in EtOAc-DCM (1:1), v/v]; 1H NMR (500.13 MHz, CD3OD) δ 0.89 - 0.93 (m, 6H, 2 x Me), 1.25 - 1.41 (m, 24H, 12 x CH2), 1.61 - 1.64 (m, 4H, CH2CH3), 2.01 - 2.04 (m, 4H, CH2CHCH), 2.34 (t, 4H, J = 7.3 Hz, CH2CO), 3.32 - 3.35 (m, 2H, H-4, H-4'), 3.46 (dd, 2H, J = 3.8, 9.7 Hz, H-2, H2'), 3.77 (t, 2H, J = 9.3 Hz, H-3, H-3'), 3.99 - 4.03 (m, 2H, H-5, H-5'), 4.21 (dd, 2H, J = 5.4, 11.8 Hz, H-6R, H-6'R), 4.35 (dd, 2H, J = 2.0, 11.9 Hz, H-6S, H-6'S), 5.04 (d, 2H, J = 3.8 Hz, H-1',H-1), 5.35 (t, 2H, J = 4.8 Hz, CH=CH); 13C NMR (125.7 MHz, CD3OD) δ 175.62, 175.61 (C=O), 131.12, 130.97 (CH=CH), 95.4 (C-1, C-1'), 74.7, 73.3 (C-2, C-2', C-3, C-3'), 72.1, 71.6 (C-4, C-4', C-5, C-5'), 64.6 (C-6, C-6'), 35.2, 33.2 (COCH2, COCH2CH2), 32.6, 30.99, 30.95, 30.8, 30.6, 30.5, 30.4, 30.3, 28.3, 26.2, 25.9 (CH2), 23.9, 23.5 (CH2CH3), 14.6, 14.4 (Me). HR ESI MS m/z calcd for C36H64NaO13 727.4239, found 727.4216.

5.6.2.1.10. 6-O-(13-Methyltetradecanoyl)-6'-O-oleoyl-α,α-trehalose (maradolipid) (176b)

![Chemical Structure](176b)
The title compound was synthesized using procedure B above and the conditions in Table 5.2, entry 4 with 6-O-oleyl-α,α–trehalose (173c) (150 mg, 0.24 mmol) and 13-methyltetradecanoic acid (66 mg, 0.27 mmol), prepared using a literature method.320 A gummy solid (168 mg, 81% yield): Rf 0.51 [20% MeOH in EtOAc-DCM (1:1), v/v]; 1H NMR (500.13 MHz, CD3OD) δ 0.88 - 092 (m, 9H, 3 x Me), 1.06 - 1.12 (m, 2H, CH2), 1.25 - 1.35 (m, 36H, 18 x CH2), 1.53 (sept, 1H, J = 6.6 Hz, CH(CH3)2), 1.60 - 1.64 (m, 4H, CH2CH3), 2.01 - 2.05 (m, 4H, CH2CHCH), 2.34 (t, 4H, J = 7.4 Hz, CH2CO), 3.31 - 3.35 (m, 2H, H-4, H-4'), 3.43 (dd, 2H, J = 3.7 Hz, 9.8 Hz, H-2, H-2'), 3.78 (t, 2H, J = 9.5 Hz, H-3, H-3'), 3.99 - 4.03 (m, 2H, H-5, H-5'), 4.20 (dd, 2H, J = 5.3, 11.8 Hz, H-6R, H-6'R), 4.35 (dd, 2H, J = 1.7, 11.8 Hz, H-6S, H-6'S), 5.05 (d, 2H, J = 3.7 Hz, H-1, H-1'), 5.35 (t, 2H, J = 4.8 Hz, CH=CH); 13C NMR (125.7 MHz, CD3OD) δ 175.44, 175.41 (C=O), 130.9, 130.8 (CH=CH), 95.1 (C-1, C-1'), 74.5, 73.1 (C-2, C-2', C-3, C-3'), 71.9, 71.5 (C-4, C-4', C-5, C-5'), 64.4 (C-6, C-6'), 40.3 (CH), 35.1, 33.1 (COCH2, COCH2CH2), 31.1, 30.9, 30.8, 30.8, 30.6, 30.5, 30.4, 30.3, 30.2, 29.2, 28.6, 28.2, 26.1 (CH2), 23.8, 23.1 (CH2CH3), 14.9 (Me). HR ESI MS m/z calcd for C45H82NaO13 853.5648, found 853.5626.

5.6.2.1.11. 6-O-(12-Methyltetradecanoyl)-6'-O-oleyl-α,α-trehalose (176c)

The title compound was synthesized using procedure B above under the conditions in Table 2, entry 6 with 6-O-oleyl-α,α-trehalose (173c) (100 mg, 0.17 mmol) and 12-
methyltetradecanoic acid (44 mg, 0.18 mmol) and was obtained as a gummy solid (108 mg, 79%): R<sub>F</sub> 0.51 [20% MeOH in EtOAc-DCM (1:1), v/v]; <sup>1</sup>H NMR (500.13 MHz, DMSO-<sup>d<sub>6</sub></sup>) δ 0.80 - 0.90 (m, 9H, 3 x Me), 1.05 - 1.12 (m, 2H, CH<sub>2</sub>), 1.16 - 1.18 (m, 2H, CH<sub>2</sub>), 1.20 - 1.35 (m, 37H, CH<sub>2</sub>CH<sub>3</sub>, 19 x CH<sub>2</sub>), 1.48 - 1.51 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>), 1.95 - 1.99 (m, 2H, CH<sub>2</sub>CHCH), 2.26 (t, 4H, J = 7.0 Hz, CH<sub>2</sub>CO), 3.10 - 3.14 (m, 2H, H-4, H-4'), 3.22 - 3.26 (m, 2H, H-2, H-2'), 3.52 - 3.57 (m, 2H, H-3, H-3'), 3.86 - 3.90 (m, 2H, H-5, H-5'), 4.02 (dd, 2H, J = 5.7, 11.7 Hz, H-6R, H-6'R), 4.22 (m, 2H, H-6S, H-6'S), 4.70 (d, 2H, J = 5.5 Hz, OH), 4.82 (d, 2H, J = 3.6 Hz, H-1, H-1'), 4.97 (d, 2H, J = 5.5 Hz, OH), 5.07 (d, 2H, J = 5.5 Hz, OH), 5.30 (t, 2H, J = 5 Hz, CH=CH); <sup>13</sup>C NMR (125.7 MHz, DMSO-<sup>d<sub>6</sub></sup>) δ 172.70, 172.68, (C=O), 129.6 (CH=CH), 93.3 (C-1, C-1'), 72.7, 71.4, 71.3, 70.1, 70.0, 69.7 (C-2, C-2', C-3, C-3', C-4, C-4', C-5, C-5'), 63.1 (C-6, C-6'), 36.0, 33.8, 33.6, 31.3 (COCH<sub>2</sub>, COCH<sub>2</sub>CH<sub>2</sub>), 29.4, 29.0, 28.9, 28.86, 28.74, 28.70, 28.6, 28.50, 28.46, 26.6, 26.5 (CH, CH<sub>2</sub>), 24.3, 22.1 (CH<sub>2</sub>CH<sub>3</sub>), 13.9, 11.2 (Me). HR ESI MS m/z calcd for C<sub>45</sub>H<sub>82</sub>NaO<sub>13</sub> 853.5648, found 853.5620.
Chapter 6: Synthesis of Polyester Dendrimers

6.1. Introductory Remarks

Polyester dendrimers have been shown to be efficient drug carriers.$^{2,3}$ Drug molecules can be attached to the surface of the dendrimers,$^4$ or the encapsulation method, where the drug is housed inside the cavities, can be used. In both methods, the polyester dendrimer may increase solubility, cellular uptake, and cellular retention of the drug to enhance the efficacy of the drug. Slow release of drugs inside the cell is achieved because of the instability of ester bonds under acidic conditions. The activity of the dendrimer–DOX and its reduced toxicity relative to free DOX,$^{22}$ is convincing evidence of the polyester dendrimer’s ability to improve the pharmacokinetic profiles of attached drugs. Although much work needs to be performed to demonstrate that polyester dendrimers are general drug delivery systems, the possibility that a single polyester dendrimer carrier can be used to impart multiple classes of drugs, imaging agents or combinations of agents with the same improved solubilities, biodistribution, and pharmacokinetic profiles warrants further synthesis and investigation of these molecules.

The number of dendritic families that are synthetically accessible is only limited by the imagination of the synthetic chemist. The following sections discuss attempts to prepare new dendritic polyol species. This work was guided by the following considerations. Firstly, the plan was to develop the use of the new core molecules that were not sensitive to deprotection by mild acid or hydrogenolysis (Chapter 2). The next goal was to create dendrimers that were less easily hydrolyzed in vivo than the well-known bis-HMPA-based dendrimers. These latter dendrimers are hydrolyzed fairly slowly,$^{80}$ but even slower hydrolysis would improve lifetimes for use of these dendrimers as frameworks in applications such as antiadhesion drugs against urinary tract
infections or to support vaccines or as drug carriers. It was thought that incorporation of more branched dendrons would accomplish this goal.

6.2. The Use of 2,2-Bis(hydroxymethyl)propanoic Acid (bis-HMPA) Dendrons.

As part of a program to prepare polyester glycodendrimers, initial attempts were to assemble core molecules and dendrons (discussed in Chapter 2) into polyester dendrimers. Both the benzylidene-protected and the acetonide-protected dendrons of bis-HMPA (Figure 17) were prepared. As shown in Scheme 52, core 79 reacted with anhydride 44 in the presence of DMAP and pyridine to give the protected first generation dendrimer in excellent yield. Deprotection using hydrogenolysis also proceeded in excellent yield to give the deprotected first generation dendrimer. The two anhydrides 44 and 49 were then reacted with core 81 (Schemes 53 and 54). The divergent growth of a second generation dendrimer using 49 is illustrated in Scheme 53 and the synthesis of a third generation dendrimer using 44 is shown in Schemes 54 and 55.

![Figure 17](image)

**Figure 17** Benzylidene and acetonide-protected dendrons of bis-HMPA

![Scheme 52](image)

**Scheme 52** Preparation of a first-generation dendrimer with a hydroquinone core, a tetraol
These dendrimers, both protected and hydroxyl-terminated are crystalline products, and were stable over a period of several months at room temperature.
6.3. The Reactivity of Tribranched Dendrons

The successful preparation of new tribranched dendrons was discussed in Chapter 2. It was hoped that the use of these tribranched dendrons would lead to the preparation of new types of polyester dendrimers that hydrolyze more slowly. The AB₃ anhydride 108 reacted with core 81 under the standard conditions to give a protected first generation dendrimer in excellent yield.
Hydrogenolysis of the six \( O \)-benzyl groups occurred via reaction overnight under the same conditions used for removal of the benzylidene acetals to give a hexaol (Scheme 56). The same two steps using tribranched 112 produced 190, a diol as shown in Scheme 57.

First generation dendrimer 188 was then reacted with excess amount of the benzyl-protected dendron 108 but unfortunately, most of the anhydride was recovered even after 24 hours. On the other hand, reaction of the hexaol with the dibranched anhydride 44, followed by hydrogenolysis gave the second generation mixed polyester dendrimer 191, again in excellent yield (Scheme 58).
The divergent growth of a dendrimer is self-limiting, and is governed by steric hindrance arising from the introduction of numerous surface groups, particularly when sterically congested dendrons are used. Various reactions using flexible tribranched dendrons 108, 112, and 119 beyond the first generation were attempted but they all gave unsatisfactory results. For example, when anhydride 112 was reacted with dendrimer 191 under standard conditions for dendrimer growth, most of the dendron was recovered after 24 hours (Scheme 59). Similarly, the reaction of the allyl-terminated anhydride 119 and the octaol 182 did not yield successful results as shown in Scheme 60. It seems that these flexible tribranched dendrons are not versatile dendrimer building blocks. The groups at the quaternary sp³ center are flexible and can rotate around freely thereby blocking the reactive anhydride center.

Scheme 59 Potential preparation of protected third generation dendrimer

Scheme 60 Potential preparation of allyl-terminated third generation dendrimer
The other type of tribranched dendrons discussed in Chapter 2 has two hydroxyl groups of the starting pentaerythritol tied up using a benzylidene acetal linkage. Reducing the rotational freedom of the protected hydroxymethyl groups by ring formation reduces steric hindrance around the reactive center and consequently, this type of dendron has improved reactivity. For example, as shown in Scheme 61, anhydride 103 reacted with diol 192 under standard conditions for dendrimer growth to give protected second generation dendron 193 in 86% yield.

Scheme 61 Preparation of second generation mixed polyester dendron 193

6.4. Dendrimer Surface Functionalization

Following their synthesis, dendrimers are traditionally functionalized in accordance with the features the researcher wants them to display and the application they are intended for. The properties of dendrimers are heavily influenced by the type of functional groups at their periphery. For example, when water soluble crystalline dendrimers 182 and 191 were reacted with anhydride 194 (Schemes 63 and 64), the resulting compounds (195 and 196 respectively) were syrups and they dissolved in non-polar solvents like diethyl ether and dichloromethane.

Scheme 62 Preparation of anhydride 194
6.4.1. Polyester Glycodendrimers

The interactions of carbohydrates with different receptors displayed at the cell surface control a number of biological processes. The affinity of carbohydrate-receptor interactions is typically low for a single carbohydrate ligand but has been shown to increase significantly through multivalent ligand-receptor interactions. Consequently, several groups have attempted the development of well-defined macromolecules displaying a large number of carbohydrate ligands using dendrimers as carriers to achieve multivalent carbohydrate-receptor interactions and utilize them for recognition and targeting to specific cells. I am interested in the synthesis and the evaluation of polyester glycodendrimers as potential anti-
adhesion drugs. Initial work has focussed on urinary tract infections (UTIs) which are among the most frequently occurring bacterial diseases in humans.\textsuperscript{347-349}

UTIs are mainly caused by strains of uropathogenic \textit{Escherichia coli} (UPEC), a gram-negative bacterium present in most animals and humans.\textsuperscript{349} UPEC expose mannose-sensitive type 1 pili on their outer surface.\textsuperscript{350,351} Type 1 pili are heteropolymeric fibers that carry a two-domain adhesin, FimH, at their distal tip. FimH adheres via its lectin domain to terminal mannopyranose residues of uroplakin Ia and $\alpha_3\beta_1$ integrins, membrane glycoproteins that are abundantly expressed on superficial epithelial cells of the urinary tract.\textsuperscript{352,353} Early studies have shown that small compounds can hinder UPEC in different stages of their pathogenic cascade.\textsuperscript{354} Consequently, Type 1 pili and the FimH adhesion present an attractive target for the design of antibacterial species.\textsuperscript{351,355,356} It is known that to mimic the interactions of high-mannose glycans with the FimH receptor-binding site, mannosides must have $\alpha$-linked hydrophobic aglycones of considerable length ((CH$_2$)$_7$ or biphenyl) to fit in the so-called tyrosine gate.\textsuperscript{339,357-364}

Following this guide, two mannose residues (198 and 201) were prepared as shown in Scheme 65, with the idea of attaching them to dendrimer surfaces using click chemistry. These particular derivatives were selected for the following reasons. As shown in Figure 18, the original $p$-nitrophenyl glycoside\textsuperscript{339,357} and the heptyl glycoside\textsuperscript{339,357} both had nM binding constants to FimH. The hexameric 197 shown in Figure 19 had a very good Kd of 3 nM (that is a per mannose binding constant of 18 nM).\textsuperscript{339} In view of the fact that the binding constant of the heptyl glycoside is considerably better than the butyl derivative, it was considered that the closeness of the branching point to the glycosidic centre of the derivative in Figure 19 considerably hindered its binding. This led to the first set of compounds (using 198) which have
a longer chain after the triazole ring. The second set of compounds (using 201) was derived to more closely mimic heptyl α-D-mannopyranoside.\textsuperscript{355}

**Figure 18** Binding constants of two monomeric mannosides with FimH

**Figure 19** A hexameric compound with a Kd per mannose residue of 18 nM

**Scheme 65** Synthesis of mannoside residues 198 and 201
Per-\(O\)-acetylation then selective deprotection of the anomeric center followed by activation with trichloroacetonitrile gave trichloroacetimidate. Glycosylation with propargyl alcohol followed by deacetylation gave \textbf{198}. Glycosylation using 6-chlorohexanol afforded \textbf{199}, which was transformed into the corresponding azido mannose \textbf{201} after sodium azide displacement of the chloride and deacetylation (Scheme 65).

In other reactions, 6-azidohexanoic acid was prepared for attachment to click coupling partners of \textbf{198}, which must be azide-terminated. Accordingly, 6-chlorohexanol was oxidized to the corresponding acid using Jones reagent followed by an \(S_N2\) displacement with sodium azide.

![Chemical Structure](attachment:image.png)

**Scheme 66** Preparation of 6-azidohexanoic acid

The TBTU-promoted esterification using 6-azidohexanoic acid for the preparation of azide-terminated species worked well in DMF. In the case of diols, reactions were high yielding with short reaction times as expected based on the observations of Chapter 3, section 3.4. As illustrated in Scheme 67, diol \textbf{190} reacted for 4 hours to afford the corresponding azide \textbf{204} in 85% yield, while \textbf{206} yielded \textbf{207} in 94% yield after 2 hours. Similarly, third generation dendrimer \textbf{186} afforded \textbf{208} in 79% yield after reacting with 6-azidohexanoic acid for 12 hours as shown in Scheme 68.
Scheme 67 Preparation of divalent azide compounds 204 and 207

Scheme 68 Preparation of an azide-terminated third generation polyester dendrimer

Having successfully prepared both the alkyne functionalized mannoside 198 and the azide terminated species; the next step was to connect them using a click reaction. Modified versions of the click reaction have been developed that do not require toxic copper (I) so that these reactions can even be used in living cells. The reaction has also been used for the synthesis
of dendrons and dendrimer skeletons.\textsuperscript{58,368,369} Here, using this reaction, 204 and 207 reacted with mannoside 198 to give the corresponding divalent mannoside clusters 209 and 210, respectively (Scheme 69). Most often, this reaction is carried out using a mixture of water and tetrahydrofuran and this system worked well for the preparation of divalent clusters. However, this solvent system did not work for the azide terminated third generation polyester dendrimer because it precipitated whenever water was introduced into the system. After few trials, it was found that the reaction worked well in DMF. As shown in Scheme 70, dendrimer 208 reacted with mannoside 198 to give a highly mannosylated system 211 in 83\% yield.

\begin{center}
\textbf{Scheme 69} Synthesis of divalent mannoside clusters 209 and 210
\end{center}
Scheme 70 Synthesis of a highly mannosylated system 211
We have used mannoside 201 (Scheme 65) for the synthesis of non-ester glycodendrimers in this lab but this work is not discussed in this thesis. One example using 201 and an ester 212 is shown in Scheme 71. Core molecule 81 was esterified with propynoic acid to give 212 that was transformed into crystalline divalent glycodendrimer 213.

![Scheme 71 Synthesis of divalent mannoside cluster 213](image)

6.5. Concluding Remarks

As previously known, anhydride coupling was an efficient route for preparing polyester dendrimers from the core diols developed in Chapter 2. This method was used to synthesize various early generation dendritic polyols in excellent yields. The use of new cores allowed the preparation of dendrimers with new architectures. Anhydrides of the new flexible tribranched dendrons could be added to the core diols but not to first generation dendrimers bearing either dibranched or tribranched termini. Anhydrides of the new cyclic acetal protected tribranched dendrons could be added to the core diols and to dibranched termini but not to tribranched termini. It appears that dendrimers where tribranched dendrons are incorporated at one or more generations among dendrimers that are mainly formed from dibranched dendrons may be synthesized. These would meet the goal of having more slowly hydrolyzable polyester dendrimer frameworks.
TBTU-promoted esterification was an efficient method for preparing esters. Various dendrimers such as compounds 204, 205, 207, and 208 were successfully prepared following this method. Using the well-known click reaction, a number of polyester glycodendrimers including compound 211 with 16 mannose residues were efficiently prepared and characterized. It would be interesting to test if TBTU-promoted esterification can be used for the preparation of dendrimers using hindered flexible tribranched dendrons. Even though TBTU is expensive which is a disadvantage especially for large scale preparations, the reactive intermediate here would be much less hindered in comparison to the anhydride reactive center of tribranched dendrons.

6.6. Experimental Section

6.6.1. General

$^1$H and $^{13}$C NMR spectra were recorded on Bruker Avance 500 or Bruker Avance 300 NMR spectrometers operating at 500.13 and 125.7 MHz or 300.15 and 75.5 MHz respectively using the solvent resonances as secondary chemical shift references. The carbon and hydrogen atoms were assigned following analysis of their one dimensional ($^1$H, $^{13}$C) and two dimensional (COSY, HSQC, HMBC, and TOCSY) NMR spectral data. Coupling constant ($J$) values are reported in Hertz. High-resolution mass spectra were recorded on a Bruker Micro-TOF mass spectrometer using electrospray ionization. Melting points were determined on a Fisher-John's melting point apparatus and are uncorrected. Acetone was refluxed over $K_2CO_3$ and distilled over molecular sieves. Dichloromethane was refluxed over calcium hydride and distilled onto molecular sieves. Methanol was refluxed over calcium oxide and distilled over molecular sieves. Tetrahydrofuran was refluxed over LiAlH$_4$ and distilled over molecular sieves. Unless otherwise noted, non-aqueous reactions were carried out under a nitrogen atmosphere. Jones reagent (0.56 M) was prepared by dissolving sodium dichromate dihydrate ($Na_2Cr_2O_7\cdot2H_2O$, 300 g, 1.01 mol)
in 1.5 L of water followed by slowly adding conc. sulfuric acid (300 mL) to the cooled solution (0 °C). Compounds were visualized/ located by spraying the TLC plate with a solution of 2 % ceric ammonium sulfate in 0.5 M H₂SO₄ followed by heating on a hot plate until color developed. Solid compounds were purified on silica gel using flash column chromatography and specified eluents, or by crystallization. Liquids and oils were purified using flash column chromatography. Water soluble compounds were purified using size exclusion chromatography on a Sephadex LH-20 gel column with water as the eluent.

6.6.2. Synthesis

6.6.2.1. General procedures

**Formation of dendritic esters (anhydride coupling):** To an oven-dried round-bottomed flask equipped with a magnetic stir bar under nitrogen atmosphere, the benzylidene, acetonide or benzyl protected anhydride, the hydroxyl-terminated dendrimer or core, and \( N,N \)-dimethyl-4-aminopyridine (DMAP) were dissolved in a 3:1 mixture of CH₂Cl₂: pyridine (v/v). The reaction mixture was stirred at rt for 4 to 12 h and diluted with water (3 mL) in pyridine (3 mL). Stirring was continued overnight to quench the excess anhydride. The mixture was diluted with CH₂Cl₂ (150 mL) and washed using NaHCO₃ (1 M, 30 mL × 3), 10% aq. Na₂CO₃ (30 mL × 3), brine (30 mL × 2), and water (30 mL), then dried (MgSO₄), filtered, and concentrated. The crude solid was then purified using precipitation out of hexanes/ EtOAc or column chromatography to give the desired product. The NaHCO₃ layers were combined, acidified (pH = 5 – 6), and the carboxylic acid by-product was recovered. However, a different workup procedure was used for the synthesis of dendrimer 141.

**Deprotection using hydrogenolysis:** To an oven-dried round-bottomed flask equipped with a magnetic stir bar, the benzylidene or benzyl protected dendrimer was dissolved in a 1:2:1
mixture of CH₂Cl₂ : MeOH : THF (v/v/v) and a catalytic amount of Pd/C was added. The flask was evacuated and back-filled with hydrogen three times. After stirring the mixture overnight under a H₂ atmosphere, the catalyst was filtered off using celite and this celite was washed with MeOH. The filtrate was concentrated to dryness to afford the product as a colorless solid.

**Removal of isopropylidene acetals:** An acetonide-protected dendrimer was dissolved in CH₂Cl₂ (5 mL) and the mixture was diluted using methanol (15 mL). A tea spoon of DOWEX, H⁺ resin was added and the mixture was stirred for 3 h at rt when TLC confirmed complete removal of the protective groups. The resin was filtered off and carefully washed with methanol. Methanol was removed under vacuum to give hydroxyl-terminated products as colorless crystalline products.

**Esterification procedure using TBTU:** In an oven-dried round-bottomed flask equipped with a magnetic stir bar, an acid (1.20 mmol), TBTU (0.387 g, 1.20 mmol), and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.37 mL, 2.40 mmol) were dissolved in anhydrous DMF (3 mL) and the resulting mixture was stirred at rt for 30 min under a nitrogen atmosphere. An alcohol (1.00 mmol of hydroxyl groups) in DMF (1 mL) was then injected into the reaction mixture via syringe, and stirring was continued at rt until TLC confirmed the completion of the reaction (1 – 12 h). The reaction mixture was diluted with CH₂Cl₂ (15 mL) and the resulting mixture was washed with 5% HCl (2 x 3 mL), 1M NaHCO₃ (3 x 3 mL) and water (2 x 3 mL). The organic layer was collected, dried (MgSO₄), filtered and concentrated to give a crude ester product, which was purified using column chromatography and specified eluents.
6.6.2.2. Benzylidene-protected first-generation dendrimer (177)

![Diagram]

1,4-Benzenediethanol 79 (0.630 g, 3.79 mmol), dry pyridine (11 mL), CH₂Cl₂ (33 mL), DMAP (0.203 g, 1.66 mmol) and the anhydride 44 (3.88 g, 9.09 mmol) were stirred at rt for 5 h under nitrogen. After work up and purification as described above, the product was obtained as colorless flakes (2.1 g, 97% yield): mp 138 – 140 °C; ¹H NMR (500.13 MHz, CDCl₃) δ 0.95 (s, 6H, CH₃), 2.95 (t, J = 7 Hz, 4H, PhCH₂), 3.62 (d, J = 11.5 Hz, 4H, H-4ax, H-6ax), 4.38 (t, J = 7 Hz, 4H, CH₂O), 4.63 (d, J = 11.5 Hz, 4H, H-4eq, H-6eq), 5.44 (s, 2H, H-2), 7.13 (s, 4H, PhH), 7.32 – 7.34 (m, 6H, PhH), 7.42 – 7.46 (m, 4H, PhH); ¹³C NMR (125.7 MHz, CDCl₃) δ 173.9 (C=O), 137.9, 136, 129.1, 129, 128.2, 126.2 (PhC), 101.8 (C-2), 73.5 (C-4, C-6), 65.5 (CH₂O), 42.4 (Cquat), 34.7 (PhCH₂), 17.9 (CH₃). HR ESI MS: m/z calcd for C₃₄H₃₈NaO₈ 597.2459, found 597.2413.

6.6.2.3. First generation dendrimer (178)

![Diagram]

Compound 177 (1.22 g, 2.12 mmol) dissolved in dry CH₂Cl₂ (15 mL), dry methanol (30 mL) and dry THF (15 mL) was deprotected as in the general method to afford hydroxyl-terminated 178 as a colorless crystalline solid (0.84 g, 99% yield): mp 118 – 120 °C; ¹H NMR (500.13 MHz, methanol-d₄) δ 1.09 (s, 6H, CH₃), 2.92 (t, J = 7 Hz, 4H, PhCH₂), 3.61 (AB q, ΔνAB = 22.3 Hz, JAB = 10.5 Hz, 8H, CH₂OH), 4.27 (t, J = 7 Hz, 4H, CH₂O), 7.19 (s, 4H, PhH); ¹³C
NMR (125.7 MHz, methanol-$d_4$) \( \delta \) 176.6 (C=O), 137.7, 130.1 (PhC), 66.3 (CH$_2$O), 65.8 (CH$_2$OH), 51.5 (C$_{quat}$), 35.6 (PhCH$_2$), 17.3 (CH$_3$). HR ESI MS: \( m/z \) calcd for C$_{20}$H$_{30}$NaO$_8$ 421.1833, found 421.1830.

6.6.2.4. Acetone-protected hydroquinone-cored first-generation dendrimer (179)

![Diagram of 179]

1,4-Bis-(2-hydroxyethoxy)benzene \textbf{81} (0.750 g, 3.78 mmol), dry pyridine (11 mL), CH$_2$Cl$_2$ (33 mL), DMAP (0.203 g, 1.66 mmol) and the anhydride \textbf{49} (3.00 g, 9.08 mmol) were stirred at rt for 4 h under nitrogen. After work up and purification as described above, the product was obtained as a colorless crystalline solid (1.85 g, 96% yield): R$_f$ 0.50 (hexanes/EtOAc; 1:1); mp 75 – 77 °C; \(^1\)H NMR (500.13 MHz, CDCl$_3$) \( \delta \) 1.17 (s, 6H, CH$_3$), 1.35 (s, 6H, CH$_3$ax), 1.40 (s, 6H, CH$_3$eq), 3.62 (d, \( J = 12 \) Hz, 4H, H-4ax, H-6ax), 4.12 (t, \( J = 5 \) Hz, 4H, PhOC$_2$H$_2$), 4.17 (d, \( J = 11.5 \) Hz, 4H, H-4eq, H-6eq), 4.44 (t, \( J = 4.5 \) Hz, 4H, CH$_2$OC=O), 6.82 (s, 4H, PhH); \(^13\)C NMR (125.7 MHz, CDCl$_3$) \( \delta \) 174.2 (2 C=O), 153.1, 115.9 (PhC), 98.1 (C-2), 66.7 (PhOC$_2$H$_2$), 66.0 (C-4, C-6), 63.2 (CH$_2$OC=O), 41.9 (C$_{quat}$), 24.6 (CH$_3$eq), 22.8 (CH$_3$ax), 18.7 (CH$_3$). HR EI MS: \( m/z \) calcd for C$_{26}$H$_{38}$NaO$_{10}$ 533.2357, found 533.2371.

6.6.2.5. Benzylidene-protected hydroquinone-cored first-generation dendrimer (183)

![Diagram of 183]

Compound \textbf{183} was synthesized as described above in the general procedure for dendritic ester formation. 1,4-Bis-(2-hydroxyethoxy)benzene \textbf{81} (0.500 g, 2.52 mmol), dry pyridine (6
mL), CH2Cl2 (18 mL), DMAP (0.135 g, 1.11 mmol) and the anhydride 44 (2.58 g, 6.05 mmol) were stirred at rt for 4 h under nitrogen. After work up and purification as described above, the product was obtained as a colorless solid (1.48 g, 97% yield): mp 143 - 145 °C; 1H NMR (500.13 MHz, CDCl3) δ 1.04 (s, 6H, CH3), 3.65 (d, J = 11.5 Hz, 4H, H-4ax, H-6ax), 4.16 (t, J = 5 Hz, 4H, PhOCH2O), 4.53 (t, J = 5 Hz, 4H, OCH2CH2O), 4.68 (d, J = 11.5 Hz, 4H, H-4eq, H-6eq), 5.45 (s, 2H, H-2), 6.81 (s, 4H, PhH), 7.28 – 7.44 (m, 10H, PhH); 13C NMR (125.7 MHz, CDCl3) δ 174.1 (C=O), 153.2, 138, 129.1, 128.3, 126.4, 116.1 (PhC), 102 (C-2), 73.7 (C-4, C-6), 66.9 (OCH2CH2O), 63.6 (OCH2CH2O), 42.7 (Cquat), 18.0 (CH3). HR ESI MS: m/z calcd for C34H38NaO10 629.2357, found 629.2352.

6.6.2.6. Hydroquinone-cored first-generation dendrimer (180)

Method A: removal of isopropylidene acetals

Acetonide-protected first generation dendrimer 179 (1.50 g, 2.94 mmol) was deprotected as described above in the general procedure for the removal of isopropylidene acetals to give 180 as colorless crystals (1.24 g, 98% yield).

Method B: deprotection using hydrogenolysis

Using the general procedure for hydrogenolysis described above, compound 183 (1.18 g, 1.95 mmol) dissolved in dry CH2Cl2 (15 mL), dry methanol (30 mL) and dry THF (15 mL) afforded hydroxyl-terminated 180 as a colorless solid (0.83 g, 99% yield): mp 155 – 156 °C; 1H NMR (500.13 MHz, methanol-d4) δ 1.16 (s, 6H, CH3), 3.66 (AB q, ΔνAB = 29.5 Hz, JAB = 11 Hz, 8H, CH2OH), 4.16 (t, J = 5 Hz, 4H, OCH2CH2O), 4.40 (t, J = 5 Hz, 4H, OCH2CH2O), 6.89 (s,
4H, PhH); $^{13}$C NMR (125.7 MHz, methanol-$d_4$) $\delta$ 176.5 (C=O), 154.6, 116.9 (PhC), 67.9 (OCH$_2$CH$_2$O), 65.8 (CH$_2$OH), 64.3 (OCH$_2$CH$_2$O), 51.6 (C$_{quat}$), 17.3 (CH$_3$). HR ESI MS: $m/z$ calcd for C$_{20}$H$_{30}$NaO$_{10}$ 453.1731, found 453.1740.

6.6.2.7. Acetonide-protected hydroquinone-cored second-generation dendrimer (181)

First generation dendrimer 180 (0.650 g, 1.51 mmol), dry pyridine (10 mL), CH$_2$Cl$_2$ (30 mL), DMAP (0.162 g, 1.33 mmol) and anhydride 49 (2.40 g, 7.26 mmol) were stirred at rt for 5 h under nitrogen. After work up and purification as described above, the product was obtained as a colorless crystalline solid (1.50 g, 94% yield); mp 110 - 112 °C; $^1$H NMR (500.13 MHz, CDCl$_3$) $\delta$ 1.12 (s, 12H, 4 CH$_3$), 1.30 (s, 6H, 2 CH$_3$), 1.34 (s, 12H, 4 CH$_{3ax}$), 1.40 (s, 12H, 4 CH$_{3eq}$), 3.60 (d, $J = 13$ Hz, 8H, H-4$_{ax}$, H-6$_{ax}$), 4.11 – 4.15 [(m, 8H (H-4$_{eq}$, H-6$_{eq}$) and 4H (PhOC$_2$H$_2$)], 4.33 (s, 8H, 4 CH$_2$), 4.43 (t, $J = 5$ Hz, 4H, CH$_2$OC=O), 6.81 (s, 4H, PhH); $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$ 173.7 (4 C=O), 172.7 (2 C=O), 153.1, 115.9 (PhC), 98.2 (C-2), 66.4 (PhOCH$_2$), 66.10, 66.06 (C-4, C-6), 65.4 (4 CH$_2$), 63.8 (OCH$_2$CH$_2$OC=O), 46.9 (2 C$_{quat}$), 42.2 (4 C$_{quat}$), 25.3 (4 CH$_{3eq}$), 22.2 (4 CH$_{3ax}$), 18.6 (4 CH$_3$), 17.8 (2 CH$_3$). HR EI MS: $m/z$ calcd for C$_{52}$H$_{78}$NaO$_{22}$ 1077.4877, found 1077.4873.

6.6.2.8. Benzylidene-protected hydroquinone-cored second-generation dendrimer (184)
Compound 184 was synthesized as described above in the general procedure for dendritic ester synthesis. Compound 180 (0.800 g, 1.86 mmol), dry pyridine (5 mL), CH₂Cl₂ (15 mL), DMAP (0.200 g, 1.64 mmol) and the anhydride 44 (3.80 g, 8.91 mmol) were stirred at rt for 10 h under nitrogen. After work up and purification as described above, the product was obtained as a colorless solid (2.13 g, 92% yield): mp 115 - 116 °C; ¹H NMR (500.13 MHz, CDCl₃) δ 0.94 (s, 12H, 4CH₃), 1.28 (s, 6H, 2CH₃), 3.59 (d, J = 11.5 Hz, 8H, H-4ax, H-6ax), 3.89 (t, J = 5 Hz, 4H, OCH₂CH₂O), 4.27 (t, J = 5 Hz, 4H, OCH₂CH₂O), 4.41 (AB q, Δν_AB = 6 Hz, J_AB = 11 Hz, 8H, 4CH₂OC=O), 4.58 (m, 8H, H-4_eq, H-6_eq), 5.42 (s, 4H, H-2), 6.69 (s, 4H, PhH), 7.28 – 7.42 (m, 20H, PhH); ¹³C NMR (125.7 MHz, CDCl₃) δ 173.4 (4C=O), 172.8 (2C=O), 153.0, 138, 129.0, 128.3, 126.3, 115.8 (PhC), 101.8 (C-2), 73.7, 73.6 (C-4, C-6), 66.3 (OCH₂CH₂O), 65.7 (4CH₂O), 63.8 (OCH₂CH₂O), 47.0 (2C_quat), 42.7 (4C_quat), 17.9 (CH₃). HR ESI MS: m/z calcd for C₆₈H₇₈Na₂O₂₂ 1269.4877, found 1269.4877.

6.6.2.9. Second generation hydroquinone-cored dendrimer (182)

Method A: removal of isopropylidene acetals

Protected second generation dendrimer 181 (1.49 g, 1.41 mmol) was deprotected as described above in the general procedure for the removal of isopropylidene acetals to give the product as colorless crystals (1.24 g, 98% yield).
Method B: deprotection using hydrogenolysis

Using the general procedure for hydrogenolysis described above, protected second generation dendrimer 184 (1.95 g, 1.56 mmol) dissolved in dry CH₂Cl₂ (15 mL), dry methanol (30 mL), and dry THF (15 mL) afforded 182 as a colorless solid (1.36 g, 97% yield): mp 114 – 115 °C; ¹H NMR (500.13 MHz, methanol-‐d₄) δ 1.12 (s, 12H, 4CH₃), 1.28 (s, 6H, CH₃), 3.62 (m, 16H, CH₂OH), 4.17 (br m, 4H, PhOCH₂CH₂), 4.27 (AB q, ΔνAB = 19 Hz, JAB = 11 Hz, 8H, 4CH₂OC=O), 4.43 (br m, 4H, CH₂CH₂OC=O), 6.88 (s, 4H, PhH); ¹³C NMR (125.7 MHz, methanol-‐d₄) δ 175.8 (4C=O), 174.4 (2C=O), 154.4, 116.9 (PhC), 67.6 (OCH₂CH₂O), 66.3 (4CH₂OC=O), 65.7 (CH₂OH), 65.0 (OCH₂CH₂O), 51.7 (4Cquat), 47.7 (2Cquat), 18.1 (2CH₃), 17.2 (4CH₃). HR ESI MS: m/z calcd for C₄₀H₆₂NaO₂₂ 917.3625, found 917.3629.

6.6.2.10. Benzylidene-protected hydroquinone-cored third-generation dendrimer (185)

Compound 185 was synthesized as described above in the general procedure for dendritic ester synthesis. Compound 182 (1.01 g, 1.13 mmol), dry pyridine (5 mL), CH₂Cl₂ (15 mL), DMAP (0.330 g, 2.71 mmol) and the anhydride 44 (4.81 g, 11.3 mmol) were stirred at rt for 10 h under nitrogen. After work up and purification as described above, the product was obtained as a colorless solid (2.71 g, 95% yield): mp 112 - 114°C; ¹H NMR (500.13 MHz, CDCl₃) δ 0.92 (s, 24H, 8CH₃), 1.04 (s, 6H, 2CH₃), 1.19 (s, 12H, 4CH₃), 3.57 (d, J = 11.5 Hz, 16H, H-4ax, H-6ax),
3.97 (t, J = 5 Hz, 4H, ArOCH$_2$), 4.07 (AB q, $\Delta$ν$_{AB}$ = 11 Hz, $J_{AB}$ = 11 Hz, 8H, 4CH$_2$OC=O), 4.31 – 4.37 (m, 20H, 8CH$_2$OC=O, 2CH$_2$OC=O), 4.55 – 4.57 (m, 16H, H-4$_{eq}$, H-6$_{eq}$), 5.39 (s, 8H, H-2), 6.75 (s, 4H, PhH), 7.27 – 7.40 (m, 40H, PhH); $^{13}$C NMR (125.7 MHz, CDCl$_3$) δ 173.3, 172.3, 172.0 (C=O), 153.0, 137.9, 129.0, 128.3, 126.3, 115.8 (PhC), 101.8 (C-2), 73.63, 73.56 (C-4, C-6), 66.3 (ArOCH$_2$), 66.0 (4CH$_2$OC=O), 65.3 (8CH$_2$OC=O), 63.8 (OCH$_2$CH$_2$O), 47.0 (4C$_{quat}$), 46.6 (2C$_{quat}$), 42.7 (C-5), 17.82 (8CH$_3$), 17.78 (4CH$_3$), 17.4 (2CH$_3$). HR ESI MS: m/z calcd for C$_{136}$H$_{158}$Na$_2$O$_{46}$ 1286.4904, found 1286.4887.

6.6.2.11. Third generation hydroquinone-cored dendrimer (186)

Using the general procedure for hydrogenolysis described above, protected third generation dendrimer 185 (1.55 g, 0.613 mmol) dissolved in dry CH$_2$Cl$_2$ (15 mL), dry methanol (30 mL), and dry THF (15 mL) afforded 186 as a colorless solid (1.10 g, 98% yield): mp 109 – 111 °C; $^1$H NMR (500.13 MHz, DMSO-$d_6$) δ 1.00 (s, 24H, 8CH$_3$), 1.14 (s, 12H, 4CH$_3$), 1.20 (s, 6H, CH$_3$), 3.39 – 3.46 (m, 32H, 16CH$_2$OH), 4.08 – 4.23 (m, 28H, 8CH$_2$O, 4CH$_2$O, 2ArOCH$_2$), 4.36 (br, 4H, OCH$_2$CH$_2$O), 4.66 (br, 16H, OH), 4.86 (s, PhH); $^{13}$C NMR (125.7 MHz, DMSO-$d_6$) δ 174.1 (6C=O), 172.1 (2C=O), 171.9 (4C=O), 152.5, 115.6 (PhC), 66.0 (OCH$_2$CH$_2$O), 65.8 (OCH$_2$CH$_2$O), 64.5 (4CH$_2$OC=O), 63.7 (CH$_2$OH, 8CH$_2$OC=O), 50.3 (8C$_{quat}$), 46.4 (4C$_{quat}$), 46.2
(2C<sub>quat</sub>), 17.2 (4CH<sub>3</sub>), 17.0 (2CH<sub>3</sub>), 16.8 (8CH<sub>3</sub>). HR ESI MS: m/z calcd for C<sub>80</sub>H<sub>126</sub>Na<sub>2</sub>O<sub>46</sub> 934.3652, found 934.3654.

### 6.6.2.12. Benzyl-protected tribranched first-generation dendrimer (187)

![Dendrimer 187](image)

Compound 187 was synthesized as described above in the general procedure for formation of dendritic esters. The core molecule 81 (0.630 g, 3.18 mmol), dry pyridine (6 mL), CH<sub>2</sub>Cl<sub>2</sub> (18 mL), DMAP (0.210 g, 1.72 mmol) and the anhydride 108 (6.15 g, 7.47 mmol) were stirred at rt for 12 h under nitrogen. After work up and purification as described above, the product was obtained as a colorless crystalline solid (hexanes/ EtOAc; 3:1; R<sub>F</sub> 0.35) (2.99 g, 94 %): mp 70 – 71 °C; <sup>1</sup>H NMR (500.13 MHz, CDCl<sub>3</sub>) δ 3.71 (s, 12H, 6C<sub>quat</sub>CH<sub>2</sub>O), 4.01 (t, J = 5 Hz, 4H, 2PhOCH<sub>2</sub>), 4.42 (t, J = 5 Hz, 4H, 2CH<sub>2</sub>O), 4.46 (s, 12H, 6CH<sub>2</sub> benzylic), 6.69 (s, 4H, PhH), 7.21 – 7.27 (m, 30H, PhH); <sup>13</sup>C NMR (125.7 MHz, CDCl<sub>3</sub>) δ 172.6 (C=O), 153.1, 138.5, 128.4, 127.52, 127.46, 115.8 (PhC), 73.3 (6CH<sub>2</sub> benzylic), 68.0 (6C<sub>quat</sub>CO), 66.6 (2PhOC), 63.0 (2COC=O), 53.9 (C<sub>quat</sub>). HR ESI MS: m/z calcd for C<sub>62</sub>H<sub>66</sub>NaO<sub>12</sub> 1025.4446, found 1025.4429.

### 6.6.2.13. First generation tribranched dendrimer (188)

![Dendrimer 188](image)

Using the general procedure for hydrogenolysis described above, compound 187 (1.74 g, 1.73 mmol), dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (15 mL), dry MeOH (30 mL), and dry THF (15 mL) afforded 188 as a colorless crystalline solid (0.77 g, 96 % yield): mp 150 – 151 °C; <sup>1</sup>H NMR
(500.13 MHz, methanol-d$_4$) δ 3.77 (s, 12H, 6CH$_2$O), 4.17 (t, $J = 5$ Hz, 4H, 2PhOCH$_2$), 4.42 (t, $J = 5$ Hz, 4H, 2CH$_2$OC=O), 6.90 (s, 4H, PhH); $^{13}$C NMR (125.7 MHz, methanol-d$_4$) δ 175.4 (C=O), 154.7, 116.5 (PhC), 71.1 (2PhOC), 61.8 (2COC=O), 61.5 (6COH), 57.1 (C$_{quat}$). HR ESI MS: m/z calcd for C$_{26}$H$_{30}$NaO$_{12}$ 485.1629, found 485.1656.

6.6.2.14. Methyl and benzyl-protected hydroquinone-cored first-generation dendrimer (189)

![Chemical structure of compound 189]

Compound 189 was synthesized as described above in the general procedure for formation of dendritic esters. The core molecule 81 (0.50 g, 2.52 mmol), dry pyridine (5 mL), CH$_2$Cl$_2$ (15 mL), DMAP (0.185 g, 1.51 mmol) and the anhydride 112 (3.14 g, 6.05 mmol) were stirred at rt for 12 h under nitrogen. After work up and purification using column chromatography (hexanes/EtOAc; 2:1; RF 0.26), the product was obtained as colorless syrup (1.66 g, 94 % yield): $^1$H NMR (500.13 MHz, CDCl$_3$) δ 3.31 (s, 12H, 4OCH$_3$), 3.62 (s, 8H, 4CH$_2$O), 3.69 (s, 4H, 2CH$_2$O), 4.09 (t, $J = 5$ Hz, 4H, ArOCH$_2$), 4.47 (t, $J = 5$ Hz, 4H, 2CH$_2$OC=O), 4.52 (s, 4H, 2CH$_2$ benzylic), 6.82 (s, 4H, PhH), 7.27 – 7.35 (m, 10H, PhH); $^{13}$C NMR (125.7 MHz, CDCl$_3$) δ 172.4 (C=O), 153.0, 138.4, 128.2, 127.4, 127.2, 115.6 (PhC), 73.1 (2CH$_2$ benzylic), 70.2 (4C$_{quat}$CO), 67.8 (2CH$_2$OBn), 66.5 (2PhOC), 62.9 (2COC=O), 59.2 (4OCH$_3$), 53.5 (2C$_{quat}$). HR ESI MS: m/z calcd for C$_{38}$H$_{50}$NaO$_{12}$ 721.3194, found 721.3170.
6.6.2.15. Methyl and hydroxyl-terminated first-generation dendrimer (190)

Using the general procedure for hydrogenolysis described above, compound 189 (1.45 g, 2.08 mmol), dissolved in dry CH$_2$Cl$_2$ (10 mL), dry MeOH (30 mL), and dry THF (15 mL) afforded 190 as a colorless syrup (1.05 g, 98% yield): $^1$H NMR (500.13 MHz, acetone-$d_6$) $\delta$ 3.24 (s, 12H, 4OCH$_3$), 3.51 – 3.55 (m, 8H, 4CH$_2$O), 3.73 (d, $J$ = 6 Hz, 4H, 2CH$_2$O), 3.80 (t, $J$ = 6 Hz, 2H, OH), 4.14 (t, $J$ = 5 Hz, 4H, ArOCH$_2$), 4.39 (t, $J$ = 5 Hz, 4H, 2CH$_2$OC=O), 6.90 (s, 4H, PhH); $^{13}$C NMR (125.7 MHz, acetone-$d_6$) $\delta$ 173.0 (2C=O), 153.9, 116.4 (PhC), 71.0 (4Cquat CO), 67.3 (2PhOC), 63.4 (2COC=O), 61.0 (2CH$_2$OH), 59.3 (4OCH$_3$), 54.9 (2Cquat). HR ESI MS: $m/z$ calcd for C$_{24}$H$_{38}$NaO$_{12}$ 541.2255, found 541.2254.

6.6.2.16. Benzylidene-protected second-generation dendrimer with mixed branching (141)

Compound 141 was synthesized as described above in the general procedure for dendritic ester formation. Dendrimer 188 (0.550 g, 1.19 mmol), dry pyridine (4 mL), CH$_2$Cl$_2$ (12 mL), DMAP (0.262 g, 2.14 mmol) and the anhydride 44 (3.80 g, 8.91 mmol) were stirred at rt for 7 h under nitrogen. Water (4 mL) was added and the ester product precipitated out of solution immediately. The product was collected using suction filtration and was washed with methanol.
(3 x 5 mL) to afford a colorless crystalline solid (1.95 g, 97 % yield): mp 183 – 185 °C; ¹H NMR (500.13 MHz, acetone-CH3/ DMSO-CD6) δ 3.70 (d, J = 11.5 Hz, 12H, 6H-4ax, 6H-6ax), 3.93 (t, J = 4.5 Hz, 4H, 2PhOCH3), 4.27 (t, J = 4.5 Hz, 4H, 2CH2OC=O), 4.44 (d, J = 11.5 Hz, 12H, 6H-4eq, 6H-6eq), 4.47 (s, 12H, 2Cquat(CH2)3), 5.50 (s, 6H, H-2), 6.73 (s, 4H, PhH), 7.30 – 7.38 (m, 30H, PhH); ¹³C NMR (125.7 MHz, acetone-CH3/ DMSO-CD6) δ 173.4 (6C=O), 170.5 (2C=O), 153.2, 138.9, 129.1, 128.4, 126.7, 116.0 (PhC), 101.5 (6C-2), 73.2 (6C-4, 6C-6), 66.4 (2PhOC), 64.4 (2CH2OC=O), 62.0 (2Cquat(CH2)3), 51.4 (2Cquat), 42.9 (6C-5), 17.5 (6CH3). HR ESI MS: m/z calcd for C92H102Na2O30 866.3120, found 866.3048.

6.6.2.17. Second generation hydroquinone-cored dendrimer with mixed branching (191)

![Diagram of the molecule](image)

Using the general procedure for hydrogenolysis described above, compound 141 (1.50 g, 0.889 mmol), dissolved in dry CH2Cl2 (30 mL), dry MeOH (15 mL), and dry THF (15 mL) afforded 191 as a colorless crystalline solid (0.99 g, 96 % yield): mp 151 – 152 °C; ¹H NMR (500.13 MHz, DMSO-CD6) δ 3.38 – 3.46 (m, 24H, 12CH2OH), 4.12 (t, J = 5 Hz, 4H, 2PhOCH2), 4.23 (s, 12H, 2Cquat(CH2)3), 4.37 (t, J = 5 Hz, 4H, 2CH2OC=O), 4.67 (t, J = 5.5 Hz, 12H, 12OH), 6.87 (s, 4H, PhH); ¹³C NMR (125.7 MHz, DMSO-CD6) δ 174.0 (6C=O), 170.2 (2C=O), 152.5, 115.6 (PhC), 65.9 (2PhOCH2), 63.8 (2CH2OC=O), 63.6 (12CH2OH), 61.1 (2Cquat(CH2)3), 50.4 (6CH2OH), 50.3 (2Cquat), 16.7 (6CH3). HR ESI MS: m/z calcd for C50H78NaO30 1181.4470, found 1181.4470.
6.6.2.18. Protected second generation dendron with mixed branching (193)

![Diagram of compound 193]

Compound **193** was synthesized as described above in the general procedure for formation of dendritic esters. Compound **192** (1.35 g, 4.27 mmol), dry pyridine (5 mL), CH$_2$Cl$_2$ (15 mL), DMAP (0.230 g, 1.88 mmol) and the anhydride **103** (6.54 g, 10.2 mmol) were stirred at rt for 12 h under nitrogen. After work up and purification using column chromatography (hexanes/EtOAc; 2:1; R$_f$ 0.29), the product was obtained as colorless solid (3.44 g, 86% yield): mp 131 – 133 °C. $^1$H NMR (500.13 MHz, acetone-$d_6$) $\delta$ 1.06 (s, 3H, CH$_3$), 2.35 (s, 3H, PhCH$_3$), 3.28 (t, $J = 5.5$ Hz, 2H, SCH$_2$), 3.41 (s, 4H, 2C$_{quat}$CH$_2$O), 3.88 (d, $J = 11.5$ Hz, 4H, 2H-4$_{ax}$, 2H-6$_{ax}$), 4.19 (s, 4H, C$_{quat}$2CH$_2$O), 4.25 (t, $J = 5.5$ Hz, 2H, CH$_2$O), 4.40 (s, 4H, benzylic), 4.56 – 4.60 (m, 4H, 2H-4$_{eq}$, 2H-6$_{eq}$), 5.46 (s, 2H, H-2), 7.25 – 7.39 and 7.65 – 7.71 (m, 24H, PhH); $^{13}$C NMR (125.7 MHz, acetone-$d_6$) $\delta$ 172.1, 171.4 (C=O), 145.1, 137.9, 137.5, 136.4, 130.1, 129.1, 128.6, 128.3, 128.2, 128.0, 127.7 (PhC), 101.8 (C-2), 73.6 (benzylic), 70.5 (C$_{quat}$2CH$_2$O), 70.4 (C-4, C-6), 65.6 (2C$_{quat}$CH$_2$O), 58.4 (SCH$_2$CH$_2$O), 54.7 (SCH$_2$CH$_2$O), 47.8 (2C$_{quat}$), 46.9 (C$_{quat}$), 21.7 (ArCH$_3$), 17.3 (CH$_3$). HR ESI MS: m/z calcd for C$_{52}$H$_{56}$O$_{14}$NaS 959.3287, found 959.3283.

Compound 195 was synthesized as described above in the general procedure for formation of dendritic esters. Second generation dendrimer 182 (0.779 g, 0.860 mmol), dry pyridine (4 mL), CH₂Cl₂ (12 mL), DMAP (0.250 g, 2.07 mmol) and the anhydride 194 (2.95 g, 8.62 mmol) were stirred at rt for 4 h under nitrogen. After work up and purification using column chromatography (hexanes/ EtOAc; 1:1; Rf 0.31), the product was obtained as colorless syrup (1.79 g, 95% yield): ¹H NMR (500.13 MHz, CDCl₃) δ 1.27 (s, 12H, 4CH₃), 1.29 (s, 6H, 2CH₃), 2.68 (t, J = 6.5 Hz, 16H, 8CH₂OBn), 3.78 (t, J = 6.5 Hz, 16H, 8CH₂C=O), 4.14 (t, J = 4.5 Hz, 4H, 2OCH₂CH₂OC=O), 4.29 – 4.33 (m, 24H, C_quat2CH₂O), 4.48 (t, J = 4.5 Hz, 4H, ArOCH₂), 4.58 (s, 16H, benzylic), 6.89 (s, 4H, PhH), 7.33 – 7.42 (m, 40H, PhH); ¹³C NMR (125.7 MHz, CDCl₃) δ 172.1 (2C=O), 172.0 (4C=O), 171.0 (8C=O), 152.9, 138.0, 128.4, 127.6, 115.7 (PhC), 73.0 (8CH₂, benzylic), 66.2 (ArOCH₂), 65.6 (2C_quat2CH₂), 65.4 (8CH₂OBn), 65.2 (4C_quat2CH₂), 46.6 (2C_quat), 46.4 (4C_quat), 34.9 (8CH₂C=O), 17.7 (4CH₃), 17.5 (2CH₃). HR ESI MS: m/z calcd for C₁₂₀H₁₄₂NaKO₃₈ 1126.4351, found 1126.4393.
6.6.2.20. Benzyl-functionalized second-generation dendrimer with mixed branching (196)

Compound 196 was synthesized as described above in the general procedure for formation of dendritic esters. Second generation dendrimer 191 (0.350 g, 0.302 mmol), dry pyridine (4 mL), CH₂Cl₂ (12 mL), DMAP (0.133 g, 1.09 mmol) and the anhydride 194 (1.55 g, 4.53 mmol) were stirred at rt for 4 h under nitrogen. After work up and purification using column chromatography (hexanes/ EtOAc; 1:1; Rf 0.21), the product was obtained as colorless syrup (0.834 g, 89% yield): ¹H NMR (500.13 MHz, CDCl₃) δ 1.20 (s, 6CH₃), 2.62 (t, J = 6.5 Hz, 24H, 12CH₂OBn), 3.72 (t, J = 6.5 Hz, 24H, 12CH₂C=O), 4.07 (t, J = 4.0 Hz, 4H, 2OCH₂CH₂OC=O), 4.25 (s, 24H, 6Cquat2CH₂O), 4.32 (s, 12H, 2Cquat3CH₂O), 4.44 (t, J = 4.0 Hz, 4H, ArOCH₂), 4.51 (s, 24H, benzylic), 6.83 (s, 4H, PhH), 7.27 – 7.36 (m, 60H, PhH); ¹³C NMR (125.7 MHz, CDCl₃) δ 171.7 (6C=O), 170.9 (12C=O), 169.3 (2C=O), 152.8, 138.0, 128.4, 128.3, 127.6, 115.6 (PhC), 72.9 (12CH₂, benzylic), 65.9 (ArOCH₂), 65.3 (12CH₂OBn), 65.0 (6Cquat2CH₂), 64.3 (2CH₂OC=O), 61.3 (2Cquat3CH₂O), 50.8 (2Cquat), 46.4 (6Cquat), 34.8 (12CH₂C=O), 17.5 (6CH₃).
6.6.2.21. Azide-functionalized divalent first-generation dendrimer (204)

Compound 204 was synthesized using the general esterification procedure using TBTU. 6-Azidohexanoic acid 203 (0.190 g, 1.20 mmol) and diol 190 (0.260 g, 1.00 mmol (OH)) reacted for 4 h to give 204 (0.34 g, 85% yield) as a colorless syrup after purification using column chromatography (hexanes/EtOAc; 3:2; RF 0.36): \( ^1H \) NMR (300.15 MHz, CDCl\(_3\)) \( \delta \) 1.28 – 1.35 (m, 4H, H\(_c\)), 1.47 – 1.59 (m, 8H, H\(_b\), H\(_d\)), 2.21 (t, \( J = 7 \) Hz, 4H, H\(_e\)), 3.19 (t, \( J = 7 \) Hz, 4H, H\(_a\)), 3.24 (s, 12H, 4OCH\(_3\)), 3.50 (s, 8H, 2C\(_\text{quat}\)2CH\(_2\)O), 4.05 (t, \( J = 4.5 \) Hz, 4H, ArOCH\(_2\)), 4.23 (s, 4H, C\(_\text{quat}\)CH\(_2\)OC=O), 4.39 (t, \( J = 4.5 \) Hz, 4H, CH\(_2\)OC=O), 6.77 (s, 4H, PhH); \( ^{13}C \) NMR (75.5 MHz, CDCl\(_3\)) \( \delta \) 172.6, 171.5 (C=O), 153.0, 115.7 (PhC), 70.2 (4COMe), 66.5 (ArOCH\(_2\)), 63.1 (OCH\(_2\)CH\(_2\)O), 62.0 (CH\(_2\)OC=O), 59.3 (4OCH\(_3\)), 52.4 (2C\(_\text{quat}\)), 51.1 (C\(_a\)), 33.8 (C\(_e\)), 28.4, 26.1 (C\(_b\), C\(_d\)), 24.3 (C\(_c\)). HR ESI MS: \textit{m/z} calcd for C\(_{36}\)H\(_{56}\)N\(_6\)NaO\(_{14}\) 819.3747, found 819.3743.

6.6.2.22. Benzyl-functionalized divalent dendrimer (205)

Compound 205 was synthesized using the general esterification procedure using TBTU. 3-Benzylxoyproanoic acid (0.216 g, 1.20 mmol) and diol 81 (0.100 g, 1.00 mmol (OH)) reacted for 1.5 h to give 205 (0.23 g, 89% yield) as a colorless solid after purification using column
chromatography (hexanes/ EtOAc; 2:1; Rf 0.29): mp 105 – 107 °C; ¹H NMR (500.13 MHz, CDCl₃) δ 2.69 (t, J = 6.5 Hz, 4H, H_c), 3.78 (t, J = 6.5 Hz, 4H, H_d), 4.12 (t, J = 4.5 Hz, 4H, H_a), 4.44 (t, J = 4.5 Hz, 4H, H_b), 4.54 (s, 4H, benzylic), 6.85 (s, 4H, PhH), 7.29 – 7.35 (m, 10H, PhH); ¹³C NMR (125.7 MHz, CDCl₃) δ 171.5 (C=O), 153.0, 138.0, 128.4, 127.6, 115.6 (PhC), 73.0 (CH₂, benzylic), 66.5 (C_a), 65.5 (C_d), 62.9 (C_b), 35.0 (C_c). HR ESI MS: m/z calculated for C₃₀H₃₄NaO₈ 545.2146, found 545.2139.

6.6.2.23. Hydroxyl-terminated divalent dendrimer (206)

Using the general procedure for hydrogenolysis described above, compound 205 (0.75 g, 1.44 mmol), dissolved in dry CH₂Cl₂ (5 mL), dry MeOH (10 mL), and dry THF (5 mL) afforded 206 as a colorless crystalline solid (0.48 g, 98% yield): mp 118 – 120 °C ¹H NMR (500.13 MHz, methanol-d₄) δ 2.56 (t, J = 6.5 Hz, 4H, H_c), 3.82 (t, J = 6.5 Hz, 4H, H_d), 4.13 (t, J = 4.5 Hz, 4H, H_a), 4.40 (t, J = 4.5 Hz, 4H, H_b), 6.87 (s, 4H, PhH); ¹³C NMR (125.7 MHz, methanol-d₄) δ 173.5 (C=O), 154.5, 116.7 (PhC), 67.7 (C_a), 64.2 (C_b), 58.7 (C_d), 38.4 (C_c). HR ESI MS: m/z caled for C₁₆H₂₂NaO₈ 365.1207, found 365.1205.

6.6.2.24. Azide-functionalized divalent dendrimer (207)
Compound 207 was synthesized using the general esterification procedure using TBTU. 6-Azidohexanoic acid 203 (0.190 g, 1.20 mmol) and diol 206 (0.170 g, 1.00 mmol (OH)) reacted for 2 h to give 207 (0.29 g, 94% yield) as a colorless solid after purification using precipitation from diethyl ether. Purification was also achieved using column chromatography (hexanes/EtOAc; 1:1; R_F 0.53): mp 102 – 105 °C; ^1H NMR (300.15 MHz, CDCl_3) δ 1.36 – 1.40 (m, 4H, H_g), 1.51 – 1.65 (m, 8H, H_f and H_h), 2.27 (t, J = 7.4 Hz, 4H, H_e), 2.69 (t, J = 6.2 Hz, 4H, H_c) 3.23 (t, J = 6.8 Hz, 4H, H_i), 4.10 (t, J = 4.5 Hz, 4H, H_a), 4.33 (t, J = 6.2 Hz, 4H, H_d), 4.42 (t, J = 4.5 Hz, 4H, H_b), 6.82 (s, 4H, PhH); ^13C NMR (75.5 MHz, CDCl_3) δ 173.1, 170.7 (C=O), 153.1, 115.8 (PhC), 66.6 (C_a), 63.2 (C_b), 59.7 (C_d), 51.2 (C_i), 33.9 (C_c, C_e), 28.6 (C_h), 26.2 (C_f), 24.4 (C_g). HR ESI MS: m/z calcd for C_{28}H_{40}N_{6}NaO_{10} 643.2696, found 643.2701.

6.6.2.25. Azide-functionalized hydroquinone-cored third-generation dendrimer (208)

![Diagram of Compound 208](image)

Compound 208 was synthesized using the general esterification procedure using TBTU. 6-Azidohexanoic acid 203 (0.190 g, 1.20 mmol) and dendrimer 186 (0.114 g, 1.00 mmol (OH)) reacted for 12 h to give 208 (0.20 g, 79% yield) as a colorless syrup after purification using column chromatography (hexanes/EtOAc; 3:2; R_F 0.16): ^1H NMR (500.13 MHz, CDCl_3) δ 1.20 (s, 24H, 8CH\_3), 1.21 (s, 12H, 4CH\_3), 1.28 (s, 6H, 2CH\_3), 1.33 - 1.40 (m, 32H, H_e), 1.55 - 1.63 (m, 8H, H_f and H_h), 1.84 - 1.90 (m, 8H, H_c) 2.27 (t, J = 7.4 Hz, 4H, H_e), 2.69 (t, J = 6.2 Hz, 4H, H_c) 3.23 (t, J = 6.8 Hz, 4H, H_i), 4.10 (t, J = 4.5 Hz, 4H, H_a), 4.33 (t, J = 6.2 Hz, 4H, H_d), 4.42 (t, J = 4.5 Hz, 4H, H_b), 6.82 (s, 4H, PhH).
(m, 64H, H_d, H_f), 2.30 (t, J = 7.5 Hz, 32H, H_c), 3.25 (t, J = 6.9 Hz, 32H, H_g), 4.11 - 4.28 (m, 60H, H_b, 28CH_2), 4.42 (t, J = 4.5 Hz, 4H, H_a), 6.81 (s, 4H, PhH); ^13^C NMR (125.7 MHz, CDCl_3) \( \delta \) 172.8, 172.03, 172.01, 171.5 (C=O), 153.0, 115.7 (PhC), 66.3 (Ca), 66.1 (2C_{quat}2CH_2O), 65.2 (4C_{quat}2CH_2O), 64.9 (8C_{quat}2CH_2O), 63.9 (C_b), 51.2 (C_g), 46.7 (4C_{quat}), 46.6 (2C_{quat}), 46.4 (8C_{quat}), 33.8 (C_c), 28.6 (C_d), 26.2 (C_d), 24.4 (C_e), 17.8 (8CH_3), 17.6 (4CH_3), 17.5 (2CH_3).

6.6.2.26. Divalent \( \alpha \)-d-mannopyranoside-terminated dendrimer (209)

The azide functionalized divalent dendrimer 204 (0.440 g, 0.552 mmol) and propargyl \( \alpha \)-d-mannopyranoside 198 (0.280 g, 1.28 mmol) were dissolved in THF (15 mL). To the clear solution was added sodium ascorbate (0.060 g, 0.303 mmol) and a solution of copper(II) sulfate pentahydrate (0.030 g, 0.120 mmol) in water (15 mL). The mixture was then vigorously stirred overnight and concentrated under reduced pressure. Purification using size exclusion chromatography on Sephadex LH-20 column gave the product as a thick colorless syrup (0.55 g, 81% yield). \(^1^H\) NMR (500.13 MHz, D_2O) \( \delta \) 1.14 (br, 4H, H_h), 1.44 (br, 4H, H_g), 1.60 – 1.80 (br, m, 4H, H_i), 2.18 (br, 4H, H_f), 3.17 – 4.92 (m, 54H, H_a, H_b, H_c, H_d, H_e, H_j, H_l, H-1, H-2, H-3, H-4, H-5, H-6), 6.88 (s, 4H, PhH), 8.05 (br, 2H, H_k). HR ESI MS: \( m/z \) calcd for C_{54}H_{84}N_6Na_2O_{26} 639.2610, found 639.2628.
6.6.2.27. Extended α-D-mannopyranoside-terminated dendrimer (210)

![Dendrimer Structure](image)

The azide functionalized divalent dendrimer 207 (0.700 g, 1.13 mmol) and propargyl α-D-mannopyranoside 198 (0.570 g, 2.61 mmol) were dissolved in THF (20 ml). To the clear solution was added sodium ascorbate (0.120 g, 0.606 mmol) and a solution of copper(II) sulfate pentahydrate (0.060 g, 0.240 mmol) in water (15 mL). The mixture was then vigorously stirred overnight and concentrated under reduced pressure. Purification using size exclusion chromatography on Sephadex LH-20 column gave the product as a thick colorless syrup (1.03 g, 86% yield): $^1$H NMR (500.13 MHz, methanol-$d_4$) δ 1.13 – 1.28 (q, $J = 7.5$ Hz, 4H, H$_g$), 1.52 – 1.61 (q, $J = 7.5$ Hz, 4H, H$_d$), 1.81 – 1.88 (q, $J = 7.5$ Hz, 4H, H$_b$), 2.25 (t, $J = 7.5$ Hz, 4H, H$_e$), 2.69 (t, $J = 6$ Hz, 4H, H$_c$), 3.55 – 3.89 (m, 12H, H-2, H-3, H-4, H-5, H-6), 4.23 (t, $J = 4.5$ Hz, 4H, H$_d$), 4.30 (t, $J = 6$ Hz, 4H, H$_d$), 4.37 (t, $J = 7$ Hz, 4H, H$_i$), 4.41 (t, $J = 4.5$ Hz, 4H, H$_b$), 4.64 (d, $J = 12.5$ Hz, 2H, H$_k$), 4.79 (d, $J = 12.5$ Hz, 2H, H$_k$), 4.86 (br, 2H, H-1), 6.86 9s, 4H, PhH), 8.00 (s, 2H, C=CH, triazole); $^{13}$C NMR (125.7 MHz, methanol-$d_4$) δ 174.8, 172.5 (C=O), 154.4 (PhC), 145.2 (C$_{sp2}$), 125.3 (CH$_{sp2}$), 116.6 (PhC), 100.7 (C-1), 74.9 (C-5), 72.5 (C-3), 71.9 (C-2), 68.5 (C-4), 67.8 (C$_a$), 64.5 (C-6), 62.9 (C$_b$), 61.1 (C$_k$), 60.7 (C$_d$), 51.1 (C$_i$), 34.6 (C$_c$), 34.5 (C$_c$), 30.8 (C$_h$), 26.8 (C$_i$), 25.2 (C$_g$). HR ESI MS: $m/z$ calcd for C$_{46}$H$_{68}$N$_6$NaO$_{22}$ 1079.4279, found 1079.4246.
6.6.2.28. Alkyne-terminated divalent dendrimer (212)

![Dendrimer structure](image)

Compound 212 was synthesized using the general esterification procedure using TBTU. Propynoic acid (0.084 g, 1.20 mmol) and diol 81 (0.099 g, 1.00 mmol (OH)) reacted for 1 h to give the product (0.12 g, 78% yield) as a colorless solid after purification using column chromatography (hexanes/ EtOAc; 3:1; Rf 0.18): mp 99 – 102 °C; $^1$H NMR (500.13 MHz, CDCl$_3$) δ 2.92 (s, 2H, Hd), 4.16 9 (t, $J$ = 4.5 Hz, 4H, Ha) 4.52 (t, $J$ = 4.5 Hz, 4H, Hb), 6.85 (s, 4H, PhH); $^{13}$C NMR (125.7 MHz, CDCl$_3$) δ 153.1 (C=O), 152.7, 115.9 (PhC), 75.5 (C$_d$), 74.5 (C$_c$), 66.2 (C$_a$), 64.6 (C$_b$). HR ESI MS: m/z calcd for C$_{16}$H$_{14}$NaO$_6$ 325.0683, found 325.0678.

6.6.2.29. A divalent α-D-mannopyranoside-terminated dendrimer with a hexyl linker (213)

![Dendrimer structure](image)

The dialkyne 212 (0.260 g, 0.860 mmol) and 6-azidohexyl α-D-mannopyranoside 201 (0.550 g, 1.80) were dissolved in THF (15 ml). To the clear solution was added sodium ascorbate (0.090 g, 0.454) and a solution of copper(II) sulfate pentahydrate (0.045 g, 0.180 mmol) in water (15 mL). The mixture was then vigorously stirred overnight and concentrated under reduced
pressure. Purification using size exclusion chromatography on Sephadex LH-20 column gave the product as a colorless solid (0.72 g, 89% yield): mp 132 – 134 °C. ¹H NMR (500.13 MHz, DMSO-d₆/methanol-d₄) δ 1.11 – 1.40 (m, 8H, H₆, H₇), 1.41 – 1.50 (m, 4H, H₈), 1.75 – 1.85 (quint, J = 7 Hz, 4H, H₉), 3.26 – 3.67 (m, 16H, H₁₀, H₁₁, H₁₂, H₁₃, H₁₄, H₁₅, H₁₆), 4.18 (br, 4H, H₁₇), 4.36 (t, J = 7 Hz, H₁₈), 4.54 (br, 4H, H₁₉), 4.58 (br, 2H, H₁₉), 6.85 (s, 4H, PhH), 8.58 (s, 2H, H₁₆). ¹³C NMR (125.7 MHz, DMSO-d₆/methanol-d₄) δ 161.9 (C=O), 154.2 (PhC), 140.2 (C₆₃ triazole), 130.2 (Cₗ), 116.9 (PhC), 101.4 (C-I), 75.0 (C-5), 72.5 (C-3), 72.0 (C-2), 68.5 (C-4), 67.9 (Cₘ), 67.7 (Cₙ), 64.7 (Cₚ), 62.8 (C-6), 51.4 (Cₜ), 31.0 (Cₚ), 30.3 (Cₚ), 27.1 (Cₚ), 26.7 (Cₚ).

HR ESI MS: m/z calc'd for C₄₀H₆₀N₆NaO₁₈ 935.3856, found 935.3848.

6.6.2.30. Third generation dendrimer bearing 16 mannose residues (211)

The azide functionalized dendrimer 208 (1.40 g, 0.346 mmol) and propargyl α-D-mannopyranoside 198 (1.51 g, 6.92 mmol) were dissolved in DMF (35 ml). To the clear solution was added sodium ascorbate (0.290 g, 1.46 mmol) and a solution of copper(II) sulfate pentahydrate (0.145 g, 0.581 mmol) in water (3 mL). The mixture was then vigorously stirred overnight and concentrated under reduced pressure. Purification using size exclusion chromatography on Sephadex LH-20 column gave the product as a thick colorless syrup (2.16 g, 83% yield): ¹H NMR (500.13 MHz, D₂O) δ 1.09 – 1.30 (br, 74H, 14CH₃, 16CH₂ (H₉)), 1.50 (br, 32H, 16CH₂ (H₈)), 1.79 (br, 32H, 16CH₂ (H₉)), 2.25 (br, 32H, 16CH₂ (H₈)), 3.57 – 4.89 (br, m,
240H (32H, 16CH₂, H₆), (32H, 16CH₂, H₇), (112H, 16sugar x 7H), (8H, OCH₂CH₂O), (8H, 2Cquat2CH₂O), (16H, 4Cquat2CH₂O), (32H, 8Cquat2CH₂O)), 6.82 (br, 4H, PhH), 8.04 (br, 16H, H₈); ¹³C NMR (125.7 MHz, D₂O) δ 174.0, 172.7, 172.0 (C=O), 152.8 (PhC), 144.1 (Csp₂ triazole), 125.1 (Cg), 115.9 (PhC), 99.4 (C-1), 73.0 (C-5), 70.6 (C-3), 70.0 (C-2), 66.6 (C-4), 65.3 (2C, OCH₂CH₂O), 60.8 (C-6), 59.7 (C₇), 50.1 (C₈), 46.5, 46.3 (Cquat), 33.3 (Ca), 29.3 (Cd), 25.4 (Cb), 23.8 (Cc).
Chapter 7: Conclusions

7.1. Achievements Described in the Thesis

The results in Chapter 2 of this thesis detailed the preparation of core molecules. Selected cores are aromatic with non-benzylic and non-phenolic hydroxyl groups for ester stability that will not be cleaved under mild acid (for selective removal of isopropylidene acetals) or hydrogenolysis conditions (for reductive removal of benzylidene acetals and benzyl ethers). Because the selected cores (Figure 2.1) all have terminal CH₂CH₂OH groups, a single convenient route was employed for their synthesis. Chapter 2 also discussed the manipulation of the hydroxyl groups of pentaerythritol using various chemical transformations and various protection/deprotection strategies for the preparation of new types of tribranched dendrons.

Chapter 3 described an efficient esterification procedure between carboxylic and all types of alcohols using coupling reagents COMU, TBTU, and TATU in the presence of organic bases. Esterification of secondary alcohols promoted by TBTU and TATU required a base, such as DBU, that is stronger than tertiary amines. Only COMU was effective for the preparation of esters from tertiary alcohols, and then only when the still stronger base, MTBD was used. The base sensitivity of the TBTU and TATU promoted reactions was used for the regioselective esterification of primary hydroxyls in diols and polyols.

The results detailed in Chapters 4 and 5 of this thesis illustrated a facile synthesis of a library of Lyme disease glycolipid antigens and the direct synthesis of maradolipids and other trehalose 6-monoesters and 6,6'-diesters. These short syntheses were possible because of the base sensitivity of the TBTU-promoted reactions (Chapter 3), which allowed selective esterifications of primary hydroxyl groups of unprotected carbohydrates under mild conditions.
Chapter 6 discussed the assembly of cores and dendrons into polyester dendrimers. Various species were isolated here. However, dendrimers incorporating only tribranched dendrons could not be synthesized beyond the first generation because of steric hindrance. It appears that dendrimers where tribranched dendrons are incorporated at one or more generations among dendrimers that are mainly formed from dibranched dendrons can be synthesized. These would meet the goal of having more slowly hydrolyzable polyester dendrimer frameworks. The preparation of this type of layered polyester dendrimers is currently underway.

7.2. Future Work

7.2.1. Synthesis

Another avenue of investigation we are interested in is the preparation of dendronized polymers tipped with biologically active compounds and their evaluation as potential anti-adhesion drugs. Dendronized polymers are typically formed by a backbone of a linear polymer with pendant reactive anchor groups, from each of which emerges a dendron. These macromolecules are multivalent systems that integrate the two-dimensional structure of polymers and the three-dimensional structure of dendrons, to create polymers with optimized binding to the bacterial carbohydrate receptors among other important applications. Herein, dendrons like the azide-functionalized acid shown in Figure 20 have been prepared for the synthesis of functionalized dendronized polymers with polyvinyl alcohol (PVA) using the “graft-to” approach. The use of PVA is advantageous because it is commercially available in a range of molar masses, it is non-toxic, and the large number of hydroxyl groups can be readily functionalized in a variety of ways to produce diverse multivalent systems.
Esterification between acid dendron 214 and PVA would result in azide-terminated dendronized polymers, which can easily be tipped with sugar residues using click chemistry. Figure 21 depicts a potential mannose-tipped dendronized polymer based on PVA. This type of compound is designed to interact with the FimH receptors at the tip of the pili of uropathogenic *E. coli* strains. The dendrons can provide the high local concentrations of α-linked-D-mannopyranoside residues with glycosidic linkages favorable\(^\text{351}\) for binding. High local concentrations provide an entropic advantage for binding.\(^\text{340}\) The polymer provides a framework.
spanning the 100 nm distance between pili\textsuperscript{381} increasing the binding effectiveness to single bacteria and will also allow simultaneous binding of many bacteria.

7.2.2. Testing

Professor Beat Ernst of the Department of Pharmaceutical Sciences of the University of Basel in Switzerland has agreed to evaluate the polyester glycodendrimers discussed in Chapter 6 and also these mannose-tipped dendronized polymers against urinary tract infections. Professor Ernst has developed an extensive program of developing antiadhesion drugs against UTIs focusing on small molecules, and he has developed several methods for evaluating their effectiveness.\textsuperscript{361,362,382-384}


195


APPENDIX A: COPYRIGHT PERMISSION

Title: Efficient and Controllably Selective Preparation of Esters Using Uronium-Based Coupling Agents

Author: Jean-d’Amour K. Twibanire and T. Bruce Grindley

Publication: Organic Letters

Publisher: American Chemical Society

Date: Jun 1, 2011

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Title: Facile Synthesis of a Library of Lyme Disease Glycolipid Antigens

Author: Jean-d’Amour K. Twibanire, Raha Parvizi Omran, and T. Bruce Grindley

Publication: Organic Letters

Publisher: American Chemical Society

Date: Aug 1, 2012

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Department of Chemistry

Dalhousie University

Halifax, Canada
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APPENDIX B: NMR SPECTRAL DATA

500.13 MHz $^1$H NMR spectrum of 1,4-benzenediethanol (79) in chloroform-$d$

125.7 MHz $^{13}$C NMR spectrum of 1,4-benzenediethanol (79) in chloroform-$d$
500.13 MHz $^1$H NMR spectrum of 1,3,5-triallylbenzene (89) in chloroform-$d$

Expansions of the 500.13 MHz $^1$H NMR spectrum of 1,3,5-triallylbenzene (89) in chloroform-$d$
125.7 MHz $^{13}$C NMR spectrum of 1,3,5-triallylbenzene (89) in chloroform-$d$

500.13 MHz $^1$H NMR spectrum of 1,3,5-benzenetriethanol (80) in methanol-$d_4$
125.7 MHz $^{13}$C NMR spectrum of 1,3,5-triethanolbenzene (80) in methanol-$d_4$

500.13 MHz $^1$H NMR spectrum of 1,4-bis-(2-hydroxyethoxy)benzene (81) in DMSO-$d_6$
125.7 MHz $^{13}$C NMR spectrum of 1,4-bis-(2-hydroxyethoxy)benzene (81) in DMSO-$d_6$

500.1 MHz $^1$H NMR spectrum of 2-(4-bromophenoxy)ethanol (82) in chloroform-$d$
125.7 MHz $^{13}$C NMR spectrum of 2-(4-bromophenoxy)ethanol (82) in chloroform-$d$

500.13 MHz $^1$H NMR spectrum of 2-(4-iodophenoxy)ethanol (83) in chloroform-$d$
125.7 MHz $^{13}\text{C}$ NMR spectrum of 2-(4-iodophenoxy)ethanol (83) in chloroform-$d$

500.13 MHz $^1\text{H}$ NMR spectrum of 1,3,5-tris-(2-hydroxyethoxy)benzene (84) in methanol-$d_4$
125.7 MHz $^{13}$C NMR spectrum of 1,3,5-tris-(2-hydroxyethoxy)benzene (84) in methanol-$d_4$

500.13 MHz $^1$H NMR spectrum of 5-methyl-2-phenyl-1,3-dioxane-5-carboxylic acid (43) in chloroform-$d$. 
500.13 MHz $^1$H NMR spectrum of 5-methyl-2-phenyl-1,3-dioxane-5-carboxylic acid (43) in acetone-$d_6$.

125.7 MHz $^{13}$C NMR spectrum of 5-methyl-2-phenyl-1,3-dioxane-5-carboxylic acid (43) in acetone-$d_6$. 
500.13 MHz $^1$H NMR spectrum of trans-5-benzylxoyethyl-cis-5-hydroxymethyl-2-(4-methoxyphenyl)-1,3-dioxane (98) in chloroform-$d$

125.7 MHz $^{13}$C NMR spectrum of trans-5-benzylxoyethyl-cis-5-hydroxymethyl-2-(4-methoxyphenyl)-1,3-dioxane (98) in chloroform-$d$
500.13 MHz $^1$H NMR spectrum of cis-5-benzyloxymethyl-trans-5-hydroxymethyl-2-(4-methoxyphenyl)-1,3-dioxane (99) in acetone-$d_6$

125.7 MHz $^{13}$C NMR spectrum of cis-5-benzyloxymethyl-trans-5-hydroxymethyl-2-(4-methoxyphenyl)-1,3-dioxane (99) in acetone-$d_6$
500.13 MHz $^1$H NMR spectrum of cis-5-benzyloxymethyl-trans-5-hydroxymethyl-2-(4-methoxyphenyl)-1,3-dioxane (99) dissolved in chloroform-$d$ for 2 minutes

500.13 MHz $^1$H NMR spectrum of cis-5-benzyloxymethyl-trans-5-hydroxymethyl-2-(4-methoxyphenyl)-1,3-dioxane (99) dissolved in chloroform-$d$ for 2 hours
500.13 MHz $^1$H NMR spectrum of *cis*-5-benzyloxymethyl-*trans*-5-hydroxymethyl-2-(4-methoxyphenyl)-1,3-dioxane (99) dissolved in chloroform-$d$ for 36 hours

500.13 MHz $^1$H NMR spectrum of *trans*-5-benzyloxymethyl-*cis*-2-(4-methoxyphenyl)-1,3-dioxane-5-carboxylic acid (102) in chloroform-$d$
125.7 MHz $^{13}$C NMR spectrum of trans-5-benzyloxymethyl-cis-2-(4-methoxyphenyl)-1,3-dioxane-5-carboxylic acid (102) in chloroform-$d$

500.13 MHz $^1$H NMR spectrum of trans-5-benzyloxymethyl-cis-2-phenyl-1,3-dioxane-5-carboxylic acid (100) in chloroform-$d$
125.7 MHz $^{13}$C NMR spectrum of trans-5-benzyloxymethyl-cis-2-phenyl-1,3-dioxane-5-carboxylic acid (100) in chloroform-$d$

500.13 MHz $^1$H NMR spectrum of cis-5-benzyloxymethyl-trans-2-phenyl-1,3-dioxane-5-carboxylic acid (101) in chloroform-$d$
125.7 MHz $^{13}$C NMR spectrum of cis-5-benzyloxyethyl-trans-2-phenyl-1,3-dioxane-5-carboxylic acid (101) in chloroform-$d$

500.13 MHz $^1$H NMR spectrum of 3-(benzyloxy)-2,2-bis(benzyloxyethyl)propanoic acid (107) in acetone-$d_6$
125.7 MHz $^{13}$C NMR spectrum of 3-(benzyloxy)-2,2-bis(benzyloxymethyl)propanoic acid (107) in acetone-$d_6$ 

500.13 MHz $^1$H NMR spectrum of 3-(benzyloxy)-2,2-bis(methyloxymethyl)propan-1-ol (110) in chloroform-$d$
125.7 MHz $^{13}$C NMR spectrum of 3-(benzyloxy)-2,2-bis(methyloxymethyl)propan-1-ol (110) in chloroform-$d$

500.13 MHz $^1$H NMR spectrum of 3-(benzyloxy)-2,2-bis(methyloxymethyl)propanoic acid (111) in chloroform-$d$
125.7 MHz $^{13}$C NMR spectrum of 3-(benzoxo)-2,2-bis(methyloxymethyl)propanoic acid (111) in chloroform-$d$

500.13 MHz $^1$H NMR spectrum of 3-(benzoxo)-2-(benzoyxymethyl)-2-((4-methoxybenzoxo)methyl)propan-1-ol (115) in chloroform-$d$
Expansions of the 500.13 MHz $^1$H NMR spectrum of 3-(benzyloxy)-2-(benzyloxymethyl)-2-((4-methoxybenzyloxy)methyl)propan-1-ol (115) in chloroform-$d$

125.7 MHz $^{13}$C NMR spectrum of 3-(benzyloxy)-2-(benzyloxymethyl)-2-((4-methoxybenzyloxy)methyl)propan-1-ol (115) in chloroform-$d$
500.13 MHz $^1$H NMR spectrum of 3-(allyloxy)-2,2-bis(allyloxymethyl)propanoic acid (118) in chloroform-$d$

125.7 MHz $^{13}$C NMR spectrum of 3-(allyloxy)-2,2-bis(allyloxymethyl)propanoic acid (118) in chloroform-$d$
500.13 MHz $^1$H NMR spectrum of trans-5-benzyloxymethyl-cis-2-phenyl-1,3-dioxane-5-carboxylic anhydride (103) in chloroform-$d$

125.7 MHz $^{13}$C NMR spectrum of trans-5-benzyloxymethyl-cis-2-phenyl-1,3-dioxane-5-carboxylic anhydride (103)
500.13 MHz $^1$H NMR spectrum of cis-5-benzyloxymethyl-trans-2-phenyl-1,3-dioxane-5-carboxylic anhydride (104) in chloroform-$d$.

125.7 MHz $^{13}$C NMR spectrum of cis-5-benzyloxymethyl-trans-2-phenyl-1,3-dioxane-5-carboxylic anhydride (104) in chloroform-$d$. 

233
500.13 MHz $^1$H NMR spectrum of 3-(benzyloxy)-2,2-bis(benzyloxymethyl)propanoic anhydride (108) in acetone-$d_6$.

125.7 MHz $^{13}$C NMR spectrum of 3-(benzyloxy)-2,2-bis(benzyloxymethyl)propanoic anhydride (108) in acetone-$d_6$. 
500.13 MHz $^1$H NMR spectrum of 3-(benzyloxy)-2,2-bis(methoxymethyl)propanoic anhydride (112) chloroform-$d$

125.7 MHz $^{13}$C NMR spectrum of 3-(benzyloxy)-2,2-bis(methoxymethyl)propanoic anhydride (112) chloroform-$d$
500.13 MHz $^1$H NMR spectrum of 3-(allyloxy)-2,2-bis(allyloxymethyl)propanoic anhydride (119) chloroform-$d$

$\begin{array}{c}
\text{ppm} \\
\end{array}$

125.7 MHz $^{13}$C NMR spectrum of 3-(allyloxy)-2,2-bis(allyloxymethyl)propanoic anhydride (119) chloroform-$d$

$\begin{array}{c}
\text{ppm} \\
55.01 & 67.37 & 72.36 & 76.91 & 77.16 & 77.42 & 116.72 & 134.64 & 167.04
\end{array}$
500.13 MHz $^1$H NMR spectrum of allyl tribenzylpentaerythritol (149) in chloroform-$d$

125.7 MHz $^{13}$C NMR spectrum of allyl tribenzylpentaerythritol (149) in chloroform-$d$
500.13 MHz $^1$H NMR spectrum of (3-benzyloxy-2,2-bis(benzyloxymethyl)propoxy)acetaldehyde (150) in chloroform-$d$

![500.13 MHz $^1$H NMR spectrum of (3-benzyloxy-2,2-bis(benzyloxymethyl)propoxy)acetaldehyde (150) in chloroform-$d$](image)

125.7 MHz $^{13}$C NMR spectrum of (3-benzyloxy-2,2-bis(benzyloxymethyl)propoxy)acetaldehyde (150) in chloroform-$d$

![125.7 MHz $^{13}$C NMR spectrum of (3-benzyloxy-2,2-bis(benzyloxymethyl)propoxy)acetaldehyde (150) in chloroform-$d$](image)
500.13 MHz $^1$H NMR spectrum of (3-benzyloxy-2,2-bis(benzyloxymethyl)propoxy)acetic acid (126) in chloroform-$d$

125.7 MHz $^{13}$C NMR spectrum of (3-benzyloxy-2,2-bis(benzyloxymethyl)propoxy)acetic acid (126) in chloroform-$d$
500.13 MHz $^1$H NMR spectrum of 2-(4-iodophenoxy)ethyl 5-methyl-2-phenyl-1,3-dioxane-5-carboxylate (151) in chloroform-$d$

125.7 MHz $^{13}$C NMR spectrum of 2-(4-iodophenoxy)ethyl 5-methyl-2-phenyl-1,3-dioxane-5-carboxylate (151) in chloroform-$d$
500.13 MHz $^1$H NMR spectrum of 2-(4-bromophenoxy)ethyl 5-methyl-2-phenyl-1,3-dioxane-5-carboxylate (152) in chloroform-$d$

125.7 MHz $^{13}$C NMR spectrum of 2-(4-bromophenoxy)ethyl 5-methyl-2-phenyl-1,3-dioxane-5-carboxylate (152) in chloroform-$d$
500.13 MHz $^1$H NMR spectrum of 2-(4-iodophenoxy)ethyl 5-benzyloxymethyl-2-phenyl-1,3-dioxane-5-carboxylate (153) in chloroform-$d$

125.7 MHz $^{13}$C NMR spectrum of 2-(4-iodophenoxy)ethyl 5-benzyloxymethyl-2-phenyl-1,3-dioxane-5-carboxylate (153) in chloroform-$d$
500.13 MHz $^1$H NMR spectrum of methyl 2-(3-(benzyloxy)-2,2-bis(benzyloxymethyl)propoxy)acetate (154) in chloroform-$d$

125.7 MHz $^{13}$C NMR spectrum of methyl 2-(3-(benzyloxy)-2,2-bis(benzyloxymethyl)propoxy)acetate (154) in chloroform-$d$
500.13 MHz $^1$H NMR spectrum of 2-(4-iodophenoxy)ethyl acetate (155) in chloroform-$d$

125.7 MHz $^{13}$C NMR spectrum of 2-(4-iodophenoxy)ethyl acetate (155) in chloroform-$d$
500.13 MHz $^1$H NMR spectrum of 2-(4-iodophenoxy)ethyl benzoate (156) in chloroform-$d$

125.7 MHz $^{13}$C NMR spectrum of 2-(4-iodophenoxy)ethyl benzoate (156) in chloroform-$d$
500.13 MHz $^1$H NMR spectrum of 1,4-bis(2-benzoyloxyethoxy)benzene (157) in CDCl$_3$

125.7 MHz $^{13}$C NMR spectrum of 1,4-bis(2-benzoyloxyethoxy)benzene (157) in CDCl$_3$
500.13 MHz $^1$H NMR spectrum of 4-iodophenyl benzoate (158) in chloroform-$d$

125.7 MHz $^{13}$C NMR spectrum of 4-iodophenyl benzoate (158) in chloroform-$d$
500.13 MHz $^1$H NMR spectrum of isopropyl benzoate (159) in chloroform-$d$

125.7 MHz $^{13}$C NMR spectrum of isopropyl benzoate (159) in chloroform-$d$
500.13 MHz $^{1}$H NMR spectrum of cyclopentyl benzoate (160) in chloroform-$d$

125.7 MHz $^{13}$C NMR spectrum of cyclopentyl benzoate (160) in chloroform-$d$
500.13 MHz $^1$H NMR spectrum of 4-iodophenyl 2-phenylacetate (161) in chloroform-$d$

125.7 MHz $^{13}$C NMR spectrum of 4-iodophenyl 2-phenylacetate (161) in chloroform-$d$
500.13 MHz $^1$H NMR spectrum of 1,4-bis(2-(2-phenylacetyloxy)ethoxy)benzene (162) in chloroform-$d$

125.7 MHz $^{13}$C NMR spectrum of 1,4-bis(2-(2-phenylacetyloxy)ethoxy)benzene (162) in chloroform-$d$
500.13 MHz $^1$H NMR spectrum of 1,6-bis(2-phenylacetyloxy)hexane (163) in chloroform-$d$

![NMR Spectrum](image)

125.7 MHz $^{13}$C NMR spectrum of 1,6-bis(2-phenylacetyloxy)hexane (163) in chloroform-$d$

![NMR Spectrum](image)
500.13 MHz $^1$H NMR spectrum of 2-toluenesulfonylethyl 3-(benzyloxy)-2,2-bis(benzyloxymethyl)-propanoate (137) in acetone-$d_6$

125.7 MHz $^{13}$C NMR spectrum of 2-toluenesulfonylethyl 3-(benzyloxy)-2,2-bis(benzyloxymethyl)-propanoate (137) in acetone-$d_6$
500.13 MHz $^1$H NMR spectrum of 2-toluenesulfonylethyl 3-hydroxy-2,2-
  bis(hydroxymethyl)-propanoate (138) in acetone-$d_6$

125.7 MHz $^{13}$C NMR spectrum of 2-toluenesulfonylethyl 3-hydroxy-2,2-
  bis(hydroxymethyl)-propanoate (138) in acetone-$d_6$
500.13 MHz $^1$H NMR spectrum of 2-(toluenesulfonyl)ethyl bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)-methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)propanoate (139) in chloroform-$d$

Expansions of parts of the 500.13 MHz $^1$H NMR spectrum of 2-(toluenesulfonyl)ethyl bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)-methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)propanoate (139) in chloroform-$d$
125.7 MHz $^{13}$C NMR spectrum of 2-(toluenesulfonyl)ethyl bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)-methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)propanoate (139) in chloroform-$d$

Expansions of part of the 125.7 MHz $^{13}$C NMR spectrum of 2-(toluenesulfonyl)ethyl bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)-methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)propanoate (139) in chloroform-$d$
500.13 MHz $^1$H NMR spectrum of 1,8-diazabicyclo[5.4.0]undec-7-ene-8-ium bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)propanoate (140) in chloroform-$d$
125.7 MHz $^{13}$C NMR spectrum of 1,8-diazabicyclo[5.4.0]undec-7-ene-8-ium bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)propanoate (140) in chloroform-$d$

500.13 MHz $^1$H NMR spectrum of bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)-methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)propanoic acid (136) in DMSO-$d_6$
Expansions of parts of the 500.13 MHz $^1$H NMR spectrum of bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)-methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)propanoic acid (136) in DMSO-$d_6$

![NMR spectrum of bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)-methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)propanoic acid (136) in DMSO-$d_6$]

125.7 MHz $^1$H NMR spectrum of bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)-methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)propanoic acid (136) in DMSO-$d_6$

![NMR spectrum of bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)-methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)propanoic acid (136) in DMSO-$d_6$]
500.13 MHz $^1$H NMR spectrum of ethyl bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)propanoate (142) in chloroform-$d$

Expansions of parts of the 500.13 MHz $^1$H NMR spectrum of ethyl bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)propanoate (142) in chloroform-$d$
125.7 MHz $^1$H NMR spectrum of ethyl bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)-methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)propanoate (142) in chloroform-$d$

500.13 MHz $^1$H NMR spectrum of 2-(4-iodophenoxy)ethyl bis-2,2'-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)propanoate (143) in chloroform-$d$
125.7 MHz $^{13}$C NMR spectrum of 2-(4-iodophenoxy)ethyl bis-2,2’-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)methyl-3-(5-methyl-2-phenyl-1,3-dioxane-5-carbonyloxy)propanoate (143) in chloroform-$d$

500.13 MHz $^1$H NMR spectrum of 3-hydroxylbutyl benzoate (144) with 5% of the secondary product in methanol-$d_4$
Expansions of the 500.13 MHz $^1$H NMR spectrum of 3-hydroxylbutyl benzoate (144) with 5% of the secondary product in methanol-$d_4$

125.7 MHz $^{13}$C NMR spectrum of 3-hydroxylbutyl benzoate (144) with 5% of the secondary product in methanol-$d_4$
500.13 MHz $^1$H NMR spectrum of 3-hydroxybutyl 3-benzyloxy-2,2'-bis(benzyloxy)methyl)propanoate (145) in DMSO-$d_6$ methanol-$d_4$
125.7 MHz $^{13}$C NMR spectrum of 3-hydroxybutyl 3-benzyloxy-2,2'-bis(benzyloxy)methyl)propanoate (145) in DMSO-$d_6$/methanol-$d_4$

500.13 MHz $^1$H NMR spectrum of methyl 6-$O$-benzoyl-$\alpha$-D-glucopyranoside (146) in DMSO-$d_6$/methanol-$d_4$
Expansions of the 500.13 MHz $^1$H NMR spectrum of methyl 6-$O$-benzoyl-$\alpha$-$D$-glucopyranoside (146) in DMSO-$d_6$/methanol-$d_4$

125.7 MHz $^{13}$C NMR spectrum of methyl 6-$O$-benzoyl-$\alpha$-$D$-glucopyranoside (146) in DMSO-$d_6$/methanol-$d_4$
500.13 MHz $^1$H NMR spectrum of methyl 6-$O$-(3-benzyloxy-2,2'-bis(benzyloxymethyl)-propanoyloxy)-$\alpha$-$\beta$-glucopyranoside (147) in DMSO-$d_6$/methanol-$d_4$

Expansions of the 500.13 MHz $^1$H NMR spectrum methyl 6-$O$-(3-benzyloxy-2,2'-bis(benzyloxymethyl)propanoyloxy)-$\alpha$-$\beta$-glucopyranoside (147) in DMSO-$d_6$/methanol-$d_4$
125.7 MHz $^{13}$C NMR spectrum of methyl 6-$O$-(3-benzyloxy-2,2'-bis(benzyloxymethyl)propanoyloxy)-$\alpha$-$D$-glucopyranoside (147) in DMSO-$d_6$/methanol-$d_4$

500.13 MHz $^1$H NMR spectrum of cholesteryl 2,3,4,6-tetra-$O$-acetyl-$\alpha$-$D$-galactopyranoside (170) in chloroform-$d$
125.7 $^{13}$C NMR spectrum of cholesteryl 2,3,4,6-tetra-$O$-acetyl-$\alpha$-$D$-galactopyranoside (170) in chloroform-$d$

500.13 MHz $^1$H NMR spectrum of cholesteryl 2,3,4,6-tetra-$O$-acetyl-$\beta$-$D$-galactopyranoside (171) in chloroform-$d$
125.7 $^{13}$C NMR spectrum of cholesteryl 2,3,4,6-tetra-O-acetyl-$\beta$-D-galactopyranoside (171) in chloroform-$d$

500.13 MHz $^1$H NMR spectrum of cholesteryl $\beta$-D-galactopyranoside (168) in pyridine-$d_5$
125.7 MHz $^{13}$C NMR spectrum of cholesteryl β-D-galactopyranoside (168) in pyridine-$d_5$

500.13 MHz $^1$H NMR spectrum of cholesteryl 6-O-palmitoyl-β-D-galactopyranoside (169a) in chloroform-$d$
125.7 MHz $^{13}$C NMR spectrum of cholesteryl 6-$O$-palmitoyl-$\beta$-$D$-galactopyranoside (169a) in chloroform-$d$

Expansions of parts of the 125.7 MHz $^{13}$C NMR spectrum of cholesteryl 6-$O$-palmitoyl-$\beta$-$D$-galactopyranoside (169a) in chloroform-$d$
500.13 MHz $^1$H NMR spectrum of cholesteryl 6-O-stearoyl-β-D-galactopyranoside (169b) in chloroform-$d$

Expansions of parts of the 500.13 MHz $^1$H NMR spectrum of cholesteryl 6-O-stearoyl-β-D-galactopyranoside (169b) in chloroform-$d$
Expansions of parts of the 500.13 MHz $^1$H NMR spectrum of cholesteryl 6-$O$-stearoyl-\(\beta\)-D-galactopyranoside (169b) in chloroform-$d$

125.7 MHz $^{13}$C NMR spectrum of cholesteryl 6-$O$-stearoyl-\(\beta\)-D-galactopyranoside (169b) in chloroform-$d$
Expansions of parts of the 125.7 MHz $^{13}$C NMR spectrum of cholesteryl 6-$O$-stearoyl-$\beta$-$D$-galactopyranoside (169b) in chloroform-$d$.

500.13 MHz $^1$H NMR spectrum of cholesteryl 6-$O$-myristoyl-$\beta$-$D$-galactopyranoside (169c) in pyridine-$d_5$. 
Expansions of parts of the 500.13 MHz $^1$H NMR spectrum of cholesteryl 6-O-myristoyl-β-D-galactopyranoside (169c) in pyridine-$d_5$

125.7 MHz $^{13}$C NMR spectrum of cholesteryl 6-O-myristoyl-β-D-galactopyranoside (169c) in pyridine-$d_5$
Expansions of parts of the 125.7 MHz $^{13}$C NMR spectrum of cholesteryl 6-\(O\)-myristoyl-\(\beta\)-D-galactopyranoside (169c) in pyridine-\(d_5\)

500.13 MHz $^1$H NMR spectrum of cholesteryl 6-\(O\)-lauroyl-\(\beta\)-D-galactopyranoside (169d) in pyridine-\(d_5\)
Expansions of parts of the 500.13 MHz \(^1\)H NMR spectrum of cholesteryl 6-\(\text{O-lauroyl-}\beta-\text{D-galactopyranoside (169d)}\) in pyridine-\(d_5\)
125.7 MHz $^{13}$C NMR spectrum of cholesteryl 6-\(O\)-lauroyl-\(\beta\)-D-galactopyranoside (169d) in pyridine-\(d_5\)

500.13 MHz $^1$H NMR spectrum of cholesteryl 6-\(O\)-oleoyl-\(\beta\)-D-galactopyranoside (169e) in pyridine-\(d_5\)
Expansions of parts of the 500.13 MHz $^1$H NMR spectrum of cholesteryl 6-O-oleyl-β-D-galactopyranoside (169e) in pyridine-$d_5$.

125.7 MHz $^{13}$C NMR spectrum of cholesteryl 6-O-oleyl-β-D-galactopyranoside (169e) in pyridine-$d_5$. 

280
Expansions of parts of the 125.7 MHz $^{13}$C NMR spectrum of cholesteryl 6-$$O$$-oleoyl-$$\beta$$-D-galactopyranoside (169e) in pyridine-$d_5$

500.13 MHz $^1$H NMR spectrum of cholesteryl 6-$$O$$-erucoyl-$$\beta$$-D-galactopyranoside (169f) in chloroform-$d$
Expansions of parts of the 500.13 MHz $^1$H NMR spectrum of cholesteryl 6-O-erucyl-β-D-galactopyranoside (169f) in chloroform-$d$
125.7 MHz $^{13}$C NMR spectrum of cholesteryl 6-$O$-erucoyl-$\beta$-d-galactopyranoside (169f) in chloroform-$d$

Expansions of parts of the 125.7 MHz $^{13}$C NMR spectrum of cholesteryl 6-$O$-erucoyl-$\beta$-d-galactopyranoside (169f) in chloroform-$d$
500.13 MHz $^1$H NMR spectrum of 6-O-hexanoyl-$\alpha,\alpha$-trehalose (173a) in methanol-$d_4$

125.7 MHz $^{13}$C NMR spectrum of 6-O-hexanoyl-$\alpha,\alpha$-trehalose (173a) in methanol-$d_4$
500.13 MHz $^1$H NMR spectrum of 6,6'-di-O-hexanoyl-$\alpha,\alpha$-trehalose (174a) in methanol-$d_4$

Expansion of part of the 500.13 MHz $^1$H NMR spectrum of 6,6'-di-O-hexanoyl-$\alpha,\alpha$-trehalose (174a) in methanol-$d_4$
Expansion of part of the 500.13 MHz $^1$H NMR spectrum of 6,6'-di-O-hexanoyl-$\alpha,\alpha$-trehalose (174a) in methanol-$d_4$

125.7 MHz $^{13}$C NMR spectrum of 6,6'-di-O-hexanoyl-$\alpha,\alpha$-trehalose (174a) in methanol-$d_4$
Expansion of part of the 125.7 MHz $^{13}$C NMR spectrum of 6,6'-di-O-hexanoyl-$\alpha,\alpha$-trehalose (174a) in methanol-$d_4$

500.13 MHz $^1$H NMR spectrum of 2,6,6'-tri-O-hexanoyl-$\alpha,\alpha$-trehalose (175a) in methanol-$d_4$
125.7.13 MHz $^{13}$C NMR spectrum of 2,6,6'-tri-O-hexanoyl-$\alpha$,$\alpha$-trehalose (175a) in methanol-$d_4$

Expansion of part of the 125.7 MHz $^{13}$C NMR spectrum of 2,6,6'-tri-O-hexanoyl-$\alpha$,$\alpha$-trehalose (175a) in methanol-$d_4$
500.13 MHz $^1$H NMR spectrum of 6-O-palmitoyl-$\alpha,\alpha$-trehalose (173b) in methanol-$d_4$

Expansion of part of the 500.13 MHz $^1$H NMR spectrum of 6-O-palmitoyl-$\alpha,\alpha$-trehalose (173b) in methanol-$d_4$
Expansion of part of the 500.13 MHz $^1$H NMR spectrum of 6-\textit{O}-palmitoyl-\textit{\alpha,\alpha}-trehalose (173b) in methanol-$d_4$

125.7 MHz $^{13}$C NMR spectrum of 6-\textit{O}-palmitoyl-\textit{\alpha,\alpha}-trehalose (173b) in methanol-$d_4$
Expansion of part of the 125.7 MHz $^{13}$C NMR spectrum of 6-$O$-palmitoyl-$\alpha,\alpha$-trehalose (173b) in methanol-$d_4$

500.13 MHz $^1$H NMR spectrum of 6,6'$-O$-palmitoyl-$\alpha,\alpha$-trehalose (174b) in methanol-$d_4$
Expansion of part of the 500.13 MHz 1H NMR spectrum of 6,6'-di-O-palmitoyl-α,α–trehalose (174b) in methanol-\(d_4\)
125.7 MHz $^{13}$C NMR spectrum of 6,6'-di-\textit{O}-palmitoyl-\textit{\alpha},\textit{\alpha}–trehalose (174b) in chloroform-\textit{d} and methanol-\textit{d$_4$}

Expansion of part of the 125.7 MHz $^{13}$C NMR spectrum of 6,6'-di-\textit{O}-palmitoyl-\textit{\alpha},\textit{\alpha}–trehalose (174b) in chloroform-\textit{d} and methanol-\textit{d$_4$}
500.13 MHz $^1$H NMR spectrum of 6-\textit{O}-oleoyl-\textit{\alpha,\alpha}-trehalose (173c) in methanol-$d_4$

Expansion of part of the 500.13 MHz $^1$H NMR spectrum of 6-\textit{O}-oleoyl-\textit{\alpha,\alpha}-trehalose (173c) in methanol-$d_4$
Expansion of part of the 500.13 MHz $^1$H NMR spectrum of 6-\textit{O}-oleoyl-$\alpha,\alpha$-trehalose (173c) in methanol-$d_4$.

125.7 MHz $^{13}$C NMR spectrum of 6-\textit{O}-oleoyl-$\alpha,\alpha$-trehalose (173c) in methanol-$d_4$. 

295
Expansion of part of the 125.7 MHz $^{13}$C NMR spectrum of 6-$O$-oleoyl-$\alpha,\alpha$-trehalose (173c) in methanol-$d_4$

500.13 MHz $^1$H NMR spectrum of 6,6'-di-$O$-oleoyl-$\alpha,\alpha$-trehalose (174c) in methanol-$d_4$
Expansion of part of the 500.13 MHz $^1$H NMR spectrum of 6,6'-di-O-oleoyl-$\alpha,\alpha$-trehalose (174c) in methanol-$d_4$
500.13 MHz $^1$H NMR spectrum of 2,6,6'-tri-O-oleoyl-$\alpha,\alpha$-trehalose (175c) in methanol-$d_4$

Expansion of part of the 500.13 MHz $^1$H NMR spectrum of 2,6,6'-tri-O-oleoyl-$\alpha,\alpha$-trehalose (175c) in methanol-$d_4$
Expansion of part of the 500.13 MHz $^1$H NMR spectrum of 2,6,6'-tri-$O$-oleoyl-$\alpha,\alpha$-trehalose (175c) in methanol-$d_4$
125.7.13 MHz $^{13}$C NMR spectrum of 2,6,6'-tri-O-oleoyl-α,α-trehalose (175c) in methanol-$d_4$

Expansion of part of the 125.7 MHz $^{13}$C NMR spectrum of 2,6,6'-tri-O-oleoyl-α,α-trehalose (175c) in methanol-$d_4$
125.7 MHz DEPT spectrum of 2,6,6'-tri-O-oleoyl-α,α-trehalose (175c) in methanol-$d_4$

Expansion of part of the 125.7 MHz DEPT spectrum of 2,6,6'-tri-O-oleoyl-α,α-trehalose (175c) in methanol-$d_4$
500.13 MHz $^1$H NMR spectrum of 6-\textit{O}-hexanoyl-6'$-\textit{O}$-oleoyl-$\alpha,\alpha$-trehalose (176a) in methanol-$d_4$

Expansion of part of the 500.13 MHz $^1$H NMR spectrum of 6-\textit{O}-hexanoyl-6'$-\textit{O}$-oleoyl-$\alpha,\alpha$-trehalose (176a) in methanol-$d_4$
Expansion of part of the 500.13 MHz $^1$H NMR spectrum of 6-$O$-hexanoyl-6'$-O$-oleoyl-$\alpha$,$\alpha$-trehalose (176a) in methanol-$d_4$
125.7 MHz $^{13}$C NMR spectrum of 6-$O$-hexanoyl-6$'$-$O$-oleoyl-$\alpha,\alpha$-trehalose (176a) in methanol-$d_4$

Expansion of part of the 125.7 MHz $^{13}$C NMR spectrum of 6-$O$-hexanoyl-6$'$-$O$-oleoyl-$\alpha,\alpha$-trehalose (176a) in methanol-$d_4$
500.13 MHz $^1$H NMR spectrum of 6-O-(13-methyltetradecanoyl)-6'-O-oleoyl-$\alpha$,$\alpha$–trehalose (176b) in methanol-$d_4$

Expansion of part of the 500.13 MHz $^1$H NMR spectrum of 6-O-(13-methyltetradecanoyl)-6'-O-oleoyl-$\alpha$,$\alpha$–trehalose (176b) in methanol-$d_4$
Expansion of part of the 500.13 MHz $^1$H NMR spectrum of 6-O-(13-methyltetradecanoyl)-6'-O-oleoyl-$\alpha,\alpha$–trehalose (176b) in methanol-$d_4$

125.7 MHz $^{13}$C NMR spectrum of 6-O-(13-methyltetradecanoyl)-6'-O-oleoyl-$\alpha,\alpha$–trehalose (176b) in methanol-$d_4$
Expansion of part of the 125.7 MHz $^{13}$C NMR spectrum of 6-$O$-(13-methyltetradecanoyl)-6'$-O$-oleoyl-$\alpha,\alpha$–trehalose (176b) in methanol-$d_4$.

500.13 MHz $^1$H NMR spectrum of 6-$O$-(12-methyltetradecanoyl)-6'$-O$-oleoyl-$\alpha,\alpha$–trehalose (176c) in methanol-$d_4$. 

307
Expansion of part of the 500.13 MHz $^1$H NMR spectrum of 6-\(O\)-(12-methyltetradecanoyl)-6'-\(O\)-oleoyl-\(\alpha\),\(\alpha\)–trehalose (176c) in methanol-\(d_4\)
125.7 MHz $^{13}$C NMR spectrum of 6-\(O\)-(12-methyltetradecanoyl)-6\(^{'\prime}\)-\(O\)-oleoyl-\(\alpha,\alpha\)-trehalose (176c) in methanol-\(d_4\)

Expansion of part of the 125.7.13 MHz $^{13}$C NMR spectrum of 6-\(O\)-(12-methyltetradecanoyl)-6\(^{'\prime}\)-\(O\)-oleoyl-\(\alpha,\alpha\)-trehalose (176c) in methanol-\(d_4\)
500.13 MHz $^1$H NMR spectrum of benzylidene-protected first generation dendrimer (177) in chloroform-$d$.

125.7 MHz $^{13}$C NMR spectrum of benzylidene-protected first generation dendrimer (177) in chloroform-$d$. 
500.13 MHz $^1$H NMR spectrum of first generation dendrimer (178) in methanol-$d_4$.

Expansion of part of the 500.13 MHz $^1$H NMR spectrum of first generation dendrimer (178) in methanol-$d_4$. 
125.7 MHz $^{13}$C NMR spectrum of first generation dendrimer (178) in methanol-$d_4$.

500.13 MHz $^1$H NMR spectrum of acetonide-protected hydroquinone-cored first generation dendrimer (179) in chloroform-$d$.
125.7 MHz $^{13}$C NMR spectrum of acetonide-protected hydroquinone-cored first generation dendrimer (179) in chloroform-$d$

500.13 MHz $^1$H NMR spectrum of benzylidene-protected hydroquinone-cored first generation dendrimer (183) in chloroform-$d$
125.7 MHz $^{13}$C NMR spectrum of benzylidene-protected hydroquinone-cored first generation dendrimer (183) in chloroform-$d$

500.13 MHz $^1$H NMR spectrum of hydroquinone-cored first generation dendrimer (180) in methanol-$d_4$. 
Expansion of part of the 500.13 MHz $^1$H NMR spectrum of hydroquinone-cored first generation dendrimer (180) in methanol-$d_4$.

125.7 MHz $^{13}$C NMR spectrum of hydroquinone-cored first generation dendrimer (180) in methanol-$d_4$. 

315
500.13 MHz $^1$H NMR spectrum of acetonide-protected hydroquinone-cored second generation dendrimer (181) in chloroform-$d$

Expansion of part of the 500.13 MHz $^1$H NMR spectrum of acetonide-protected hydroquinone-cored second generation dendrimer (181) in chloroform-$d$
125.7 MHz $^{13}$C NMR spectrum of acetonide-protected hydroquinone-cored second generation dendrimer (181) in chloroform-$d$

500.13 MHz $^1$H NMR spectrum of benzylidene-protected hydroquinone-cored second generation dendrimer (184) in chloroform-$d$
Expansion of part of the 500.13 MHz $^1$H NMR spectrum of benzylidene-protected hydroquinone-cored second generation dendrimer (184) in chloroform-$d$

125.7 MHz $^{13}$C NMR spectrum of benzylidene-protected hydroquinone-cored second generation dendrimer (184) in chloroform-$d$
500.13 MHz $^1$H NMR spectrum of hydroquinone-cored second generation dendrimer (182) in methanol-$d_4$

Expansion of part of the 500.13 MHz $^1$H NMR spectrum of hydroquinone-cored second generation dendrimer (182) in methanol-$d_4$
125.7 MHz $^{13}$C NMR spectrum of hydroquinone-cored second generation dendrimer (182) in methanol-$d_4$

\[
\begin{align*}
17.22 & \\
18.14 & \\
47.73 & \\
48.49 & \\
48.66 & \\
48.83 & \\
49.00 & \\
49.17 & \\
49.34 & \\
49.51 & \\
51.65 & \\
65.02 & \\
65.70 & \\
66.31 & \\
67.60 & \\
116.87 & \\
154.40 & \\
174.35 & \\
175.81 & \\
\end{align*}
\]

500.13 MHz $^1$H NMR spectrum of benzylidene-protected hydroquinone-cored third generation dendrimer (185) in chloroform-$d$

\[
\begin{align*}
0.000 & \\
0.917 & \\
0.920 & \\
1.037 & \\
1.192 & \\
1.616 & \\
3.563 & \\
3.586 & \\
3.955 & \\
3.965 & \\
3.974 & \\
4.028 & \\
4.050 & \\
4.080 & \\
4.102 & \\
4.312 & \\
4.321 & \\
4.335 & \\
4.348 & \\
4.359 & \\
4.370 & \\
4.548 & \\
4.554 & \\
4.565 & \\
4.572 & \\
5.394 & \\
6.748 & \\
7.258 & \\
7.274 & \\
7.283 & \\
7.298 & \\
7.305 & \\
7.309 & \\
7.312 & \\
7.315 & \\
7.385 & \\
7.386 & \\
7.398 & \\
7.401 & \\
\end{align*}
\]
Expansion of part of the 500.13 MHz $^1$H NMR spectrum of benzylidene-protected hydroquinone-cored third generation dendrimer (185) in chloroform-$d$

125.7 MHz $^{13}$C NMR spectrum of benzylidene-protected hydroquinone-cored third generation dendrimer (185) in chloroform-$d$
Expansions of parts of the 125.7 MHz $^{13}$C NMR spectrum of benzyldiene-protected hydroquinone-cored third generation dendrimer (185) in chloroform-$d$

500.13 MHz $^1$H NMR spectrum of third generation dendrimer (186) in DMSO-$d_6$
Expansion of part of the 500.13 MHz $^1$H NMR spectrum of third generation dendrimer (186) in DMSO-$d_6$

125.7 MHz $^{13}$C NMR spectrum of third generation dendrimer (186) in DMSO-$d_6$
500.13 MHz $^1$H NMR spectrum of benzyl-protected tribranched first generation dendrimer (187) in chloroform-$d$

$^{13}$C NMR spectrum of benzyl-protected tribranched first generation dendrimer (187) in chloroform-$d$
500.13 MHz $^1$H NMR spectrum of tribranched first generation dendrimer (188) in methanol-$d_4$

125.7 MHz $^{13}$C NMR spectrum of tribranched first generation dendrimer (188) in methanol-$d_4$
500.13 MHz $^1$H NMR spectrum of methyl and benzyl-protected hydroquinone-cored first generation dendrimer (189) in chloroform-$d$

125.7 MHz $^{13}$C NMR spectrum of methyl and benzyl-protected hydroquinone-cored first generation dendrimer (189) in chloroform-$d$
500.13 MHz $^1$H NMR spectrum of hydroquinone-cored first generation dendrimer (190) in acetone-$d_6$
500.13 MHz $^1$H NMR spectrum of benzylidene-protected second generation dendrimer with mixed branching (141) in acetone-$d_6$/DMSO-$d_6$

Expansion of part of the 500.13 MHz $^1$H NMR spectrum of benzylidene-protected second generation dendrimer with mixed branching (141) in acetone-$d_6$/DMSO-$d_6$
125.7 MHz $^{13}$C NMR spectrum of benzylidene-protected second generation dendrimer with mixed branching (141) in acetone-$d_6$/ DMSO-$d_6$

500.13 MHz $^1$H NMR spectrum of second generation dendrimer with mixed branching (191) in DMSO-$d_6$
Expansions of parts of the 500.13 MHz $^1$H NMR spectrum of second generation dendrimer with mixed branching (191) in DMSO-$d_6$

125.7 MHz $^{13}$C NMR spectrum of second generation dendrimer with mixed branching (191) in DMSO-$d_6$
Expansion of parts of the 125.7 MHz $^{13}$C NMR spectrum of second generation dendrimer with mixed branching (191) in DMSO-$d_6$

500.13 MHz $^1$H NMR spectrum of protected second generation dendron with mixed branching (193) in acetone-$d_6$
125.7 MHz $^{13}$C NMR spectrum of protected second generation dendron with mixed branching (193) in acetone-$d_6$

500.13 MHz $^1$H NMR spectrum of benzyl-functionalized hydroquinone-cored second generation dendrimer (195) in chloroform-$d_6$
Expansions of parts of the 500.13 MHz $^1$H NMR spectrum of benzyl-functionalized hydroquinone-cored second generation dendrimer (195) in chloroform-$d$

125.7 MHz $^{13}$C NMR spectrum of benzyl-functionalized hydroquinone-cored second generation dendrimer (195) in chloroform-$d$
500.13 MHz $^1$H NMR spectrum of benzyl-functionalized hydroquinone-cored second generation dendrimer with mixed branching (196) in chloroform-$d$

Expansions of parts of the 500.13 MHz $^1$H NMR spectrum of benzyl-functionalized hydroquinone-cored second generation dendrimer with mixed branching (196) in chloroform-$d$
125.7 MHz $^{13}$C NMR spectrum of benzyl-functionalized hydroquinone-cored second generation dendrimer (196) in chloroform-$d$

300.15 MHz $^1$H NMR spectrum of azide-functionalized divalent first generation dendrimer (204) in chloroform-$d$
Expansion of part of the 300.15 MHz $^1$H NMR spectrum of azide-functionalized divalent first generation dendrimer (204) in chloroform-$d$

75.5 MHz $^{13}$C NMR spectrum of azide-functionalized divalent first generation dendrimer (204) in chloroform-$d$
500.13 MHz $^1$H NMR spectrum of benzyl-functionalized divalent dendrimer (205) in chloroform-$d$

Expansion of part of the 500.13 MHz $^1$H NMR spectrum of benzyl-functionalized divalent dendrimer (205) in chloroform-$d$
125.7 MHz $^{13}$C NMR spectrum of benzyl-functionalized divalent dendrimer (205) in chloroform-$d$

500.13 MHz $^1$H NMR spectrum of hydroxyl-terminated divalent dendrimer (206) in methanol-$d_4$
Expansion of part of the 500.13 MHz $^1$H NMR spectrum of hydroxyl-terminated divalent dendrimer (206) in methanol-$d_4$

![NMR Spectrum](image1)

125.7 MHz $^{13}$C NMR spectrum of hydroxyl-terminated divalent dendrimer (206) in methanol-$d_4$
300.15 MHz $^1$H NMR spectrum of azide-functionalized divalent dendrimer (207) in chloroform-$d$

Expansion of part of the 300.15 MHz $^1$H NMR spectrum of azide-functionalized divalent dendrimer (207) in chloroform-$d$
75.5 $^{13}$C NMR spectrum of azide-functionalized divalent dendrimer (207) in chloroform-$d$

500.13 MHz $^1$H NMR spectrum of azide-functionalized hydroquinone-cored third generation dendrimer (208) in chloroform-$d$
Expansions of parts of the 500.13 MHz $^1$H NMR spectrum of azide-functionalized hydroquinone-cored third generation dendrimer (208) in chloroform-\textit{d}.

125.7 MHz $^{13}$C NMR spectrum of azide-functionalized hydroquinone-cored third generation dendrimer (208) in chloroform-\textit{d}.
Expansions of the 125.7 MHz $^{13}$C NMR spectrum of azide-functionalized hydroquinone-cored third generation dendrimer (208) in chloroform-\textit{d}.

500.13 MHz $^1$H NMR spectrum of 2-propynyl 2,3,4,6-tetra-O-acetyl-$\alpha$-D-mannopyranoside in chloroform-\textit{d}.
Expansions of parts of the 500.13 MHz $^1$H NMR spectrum of 2-propynyl 2,3,4,6-tetra-O-acetyl-$\alpha$-D-mannopyranoside in chloroform-$d$

125.7 MHz $^{13}$C NMR spectrum of 2-propynyl 2,3,4,6-tetra-O-acetyl-$\alpha$-D-mannopyranoside in chloroform-$d$
300.15 MHz $^1$H NMR spectrum of 2-propynyl $\alpha$-D-mannopyranoside (198) in methanol-$d_4$

Expansions of part of the 300.15 MHz $^1$H NMR spectrum of 2-propynyl $\alpha$-D-mannopyranoside (198) in methanol-$d_4$
75.5 MHz $^{13}$C NMR spectrum of 2-propynyl $\alpha$-d-mannopyranoside (198) in methanol-$d_4$

500.13 MHz $^1$H NMR spectrum of 6-azidohexyl 2,3,4,6-tetra-$O$-acetyl-$\alpha$-d-mannopyranoside (200) in chloroform-$d$
Expansions of part of the 500.13 MHz $^1$H NMR spectrum of 6-azidohexyl 2,3,4,6-tetra-$O$-acetyl-$\alpha$-$D$-mannopyranoside (200) in chloroform-$d$

125.7 MHz $^{13}$C NMR spectrum of 6-azidohexyl 2,3,4,6-tetra-$O$-acetyl-$\alpha$-$D$-mannopyranoside (200) in chloroform-$d$
500.13 MHz $^1$H NMR spectrum of 6-azidohexyl α-D-mannopyranoside (201) in methanol-$d_{10}$

Expansion of part of the 500.13 MHz $^1$H NMR spectrum of 6-azidohexyl α-D-mannopyranoside (201) in methanol-$d_{10}$
125.7 MHz $^{13}$C NMR spectrum of 6-azidohexyl $\alpha$-D-mannopyranoside (201) in methanol-$d$

Expansion of part of the 125.7 MHz $^{13}$C NMR spectrum of 6-azidohexyl $\alpha$-D-mannopyranoside (201) in methanol-$d$
500.13 MHz $^1$H NMR spectrum of extended divalent $\alpha$-D-mannopyranoside-terminated dendrimer (210) in methanol-$d_4$

Expansion of part of the 500.13 MHz $^1$H NMR spectrum of extended divalent $\alpha$-D-mannopyranoside-terminated dendrimer (210) in methanol-$d_4$
125.7 MHz $^{13}$C NMR spectrum of extended divalent $\alpha$-D-mannopyranoside-terminated dendrimer (210) in methanol-$d_4$

Expansion of part of the 125.7 MHz $^{13}$C NMR spectrum of extended divalent $\alpha$-D-mannopyranoside-terminated dendrimer (210) in methanol-$d_4$
500.13 MHz $^1$H NMR spectrum of alkyne-terminated divalent dendrimer (212) in chloroform-$d$

125.7 MHz $^{13}$C NMR spectrum of alkyne-terminated divalent dendrimer (212) in chloroform-$d$
500.13 MHz $^1$H NMR spectrum of divalent $\alpha$-D-mannopyranoside-terminated dendrimer with a hexyl linker (213) in DMSO-$d_6$/methanol-$d_4$

Expansion of part of the 500.13 MHz $^1$H NMR spectrum of divalent $\alpha$-D-mannopyranoside-terminated dendrimer with a hexyl linker (213) in DMSO-$d_6$/methanol-$d_4$
125.7 MHz $^{13}$C NMR spectrum of divalent α-D-mannopyranoside-terminated dendrimer with a hexyl linker (213) in DMSO-$d_6$/methanol-$d_4$
500.13 MHz $^1$H NMR spectrum of third generation dendrimer bearing 16 mannose residues (211) in water-$d_2$

125.7 MHz $^{13}$C NMR spectrum of third generation dendrimer bearing 16 mannose residues (211) in water-$d_2$