OLEFIN METATHESIS IN CARBOHYDRATE AND NORBORNENE APPLICATIONS

By

KALYAN MONDAL

DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

2007
ACKNOWLEDGMENTS

The rewards associated with completing this dissertation and earning my Ph.D. would not be a nearly as great if it hadn’t been for the very special people who gave me their support along the way. I would like to extend my sincere appreciation to my research advisor, Dr. Eric Enholm, for his support, patience, understanding and invaluable help throughout my graduate career at the University of Florida. I am forever grateful for his patience during my ever-developing skill in the lab. His enthusiasm and knowledge have been motivating, and his instruction has not only given me the technical abilities, but also the confidence needed for a successful career. Looking back I have come a long way with regards to chemical knowledge and problem solving. It has been a real pleasure for me to conduct and discuss research with Dr. Enholm. He provided me all the necessary guidance to complete my dissertation and allowed me the research freedom to develop my own ideas. He has been a great advisor and I will never forget his encouragement and kindness.

I would like to thank my committee members for their constructive feedback and advice. Special thanks go to Dr. William Dolbier. He is one of the most sincere and helpful professors I have ever met, who shows true concern and interest toward his students. I would also like to thank Dr. Ronald Castellano. His excellent teaching style and well organized lectures gave me a great start to the PhD program. I sincerely thank Dr. Ion Ghiviriga for helping with the elucidation of the structure of my organic compounds and for sharing his vast NMR expertise, more than I thought I could ever learn about NMR. I also appreciate Dr. Kenneth Sloan for being on my committee and providing valuable feedback during my oral qualifier and the preparation of this dissertation. I truly have been fortunate to have these individuals on my committee.
Graduate school would not have been enjoyable without my fellow Enholm group members—Jed Hastings, Sophie Klein, Tammy Low, and Ryan Martin. It has been a blessing to work in a cooperative environment, where laboratory discussions are open and free, and everyone is so helpful and genuinely friendly. I especially like to thank Jed for his patience in helping with my lab experiments early on, for exchanging knowledge and for providing feedback as I prepared for my oral qualifier. Not only has it been a joy working with these individuals, I also appreciate their friendship outside of lab.

Special thanks go to Dr. Tammy Davidson, my M.S. adviser from my previous school East Tennessee State University and currently working at University of Florida for her consistent mental support throughout my PhD career. Finally, my most heartfelt acknowledgement must go to my parents, sisters and my wife Debalina for their continuous support, encouragement and kindness. I specially thank my parents for their inspiration, infinite love and faith. They have made me a better person by being my role models and instilling me with strong values. I would not have been in the position to write this dissertation without my parents. Last and not the least, I would like to thank my wife Debalina for her consistent support for the last one year. Words alone cannot express my gratitude, especially for their tremendous love and belief in me during the PhD period.

Special acknowledgement foes to the faculty and staff of the Department of Chemistry at the University of Florida for providing an excellent environment for graduate study that has helped me to make my stay here quite enjoyable and rewarding.
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Olefin metathesis is a convenient route for the synthesis of functionalized higher alkenes from simple alkene precursors. Our research goals are comprised of developing olefin metathesis in ring opening metathesis polymerization (ROMP) of norbornene scaffold, in self-metathesis reactions of carbohydrates, which can be used as precursors for the generation of dynamic combinatorial libraries (DCLs), and in employing for the first time to study the acyclic diene metathesis (ADMET) polymerization of carbohydrates.

Functionalized norbornene monomers have been the subject of interest due to facile preparation and high reactivity in ROMP. We choose norbornene aldehyde as the starting material for synthesizing the norbornene polymer scaffold, which can later be crosslinked using a diyl and by the release of nitrogen gas.

Olefin metathesis is an important methodology for the generation of library members in dynamic combinatorial chemistry. We have synthesized a series of carbohydrate based homodimers by self metathesis reaction using Grubbs’ second generation catalyst. Sophisticated products were observed bearing a variety of functional and protecting groups on the carbohydrates. The carbohydrate-linked alkenes were trans with several versions examined. Products yields were dependent on the type of carbohydrate groups, and whether the ester group
possessed an allyl or pentenyl moiety at the carboxylate side. In addition, several carbohydrate derivatives were made containing diene functionality. When subjected to the self-metathesis condition, such diene carbohydrate system generated cyclic dimer.

The utility of ADMET chemistry for the polymerization of dienes containing silyl, aromatic, and ester functional groups have been investigate. We have synthesized the diesters of carbohydrates (D)-mannitol, (D)-ribose, (D)-isomannide, and (D)-isosorbide. We performed the ADMET chemistry for those carbohydrates. To our best knowledge, we are the first to report the ADMET chemistry of carbohydrates.
CHAPTER 1
HISTORICAL BACKGROUND

1.1 Olefin Metathesis

Throughout the history of chemistry, any reaction that has the ability to form carbon-carbon bonds receives a significant amount of attention; and olefin metathesis is not an exception to it. Olefin metathesis is a powerful synthetic tool that has found its way into the vast array of scientific disciplines, starting from the development of small molecular drug candidates to the industrial sized synthesis of petrochemicals.1-7 The word, “metathesis”, derived from the Greek words meta (change) and tithemi (place), means an exchange; thus the term “olefin metathesis”, originally introduced by Calderon in 1967,9 refers to the interchange of carbon atoms (with their substituents) between a pair of alkene bonds.10 This catalytic organic reaction is unlike other carbon-carbon bond forming strategies due to the versatility of synthetic transformations it promotes, such as the synthesis of various sized cycloalkenes from dienes and specialized polymers by the ring opening metathesis polymerization of the cyclic molecules. Olefin metathesis has opened efficient synthetic routes for the synthesis of complex natural products, medicinal drugs, and new materials as demonstrated by the explosion of the metathesis related applications found in literature during the past decade. In 2005, the importance of this organic reaction was prestigiously recognized by the Nobel Prize Award in Chemistry to the major contributors of olefin metathesis–Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock.

1.1.1 Development of Olefin Metathesis and Catalyst

Olefin metathesis was first discovered accidentally by researchers in petrochemical companies in the 1950s when they were searching for heterogeneous catalyst to produce high-octane gasoline products from olefins.7,8 Instead of their expected products, the chemists
observed newly developed olefins. It was not until the 1960s, when researchers at Goodyear Tire & Rubber determined that these new products were the result of exchange of substituents on different olefins, which they officially referred to as “olefin metathesis” (Scheme 1-1).\textsuperscript{11}

![Scheme 1-1. Olefin metathesis.](image)

For several years, chemist tried to explain the mechanism involved in this novel reaction that involves a skeletal transformation of olefins. Calderon,\textsuperscript{12} Pettit,\textsuperscript{13} and Grubbs and Brunck\textsuperscript{14} initially suggested cyclobutane, tetramethylene complex, and a rearranging metallacyclopentane intermediate as part of the mechanism, respectively, but all of the proposals were later found to be incorrect (Scheme 1-2).\textsuperscript{8} It was in the year 1971 when French chemist Yves Chauvin proposed a metal-carbene mechanism, which involved the formation of a metallacyclobutane intermediate (Scheme 1-3).\textsuperscript{8,15} However, the mechanism for the olefin metathesis was not to be established for years yet. The independent works of Katz, Schrock, and Tebbe supported the mechanism proposed by Chauvin and is now accepted widely.\textsuperscript{1,8}

Several groups had tried to develop transition metal carbene complexes. These include Fischer carbenes (involving low oxidation state metals and electron deficiency at the carbon center) and Schrock carbenes (involving high oxidation state metals and electron deficiency at the metal center).\textsuperscript{1,8} The Fischer carbenes involved little activity for the olefin metathesis, while Schrock’s tantalum and niobium metal complexes were also proved unsuccessful.\textsuperscript{1,8} The propagating species could not be obtained, isolated, or structurally characterized and the metal catalysts involved in the olefin metathesis are often referred as “classical” or “ill-defined”
catalysts. However, all these initial studies helped to improve the synthesis of alkylidene complexes that eventually demonstrated improved reactivity for olefin metathesis.

Scheme 1-2. Proposed intermediates for olefin metathesis.²

Despite of all these early developments, Olefin metathesis did not find any practical application due to the following reasons:

1. Low reactivity of the metal catalyst.
2. Lack of stability and tolerance toward the functional group of the alkene involved.

In the 1990s, Schrock introduced first a well-defined alkoxy imidomolybdenum-based catalytic system 1-1, which allowed successful application of olefin metathesis (Figure 1-1). In contrast to the earlier developed catalysts, the molybdenum alkylidene complex is highly reactive and leads to the desired product with higher percentage of yield including starting materials with sterically hindered alkenes. However, the catalyst was found to be ineffective for the starting materials containing polar functional groups like alcohols and carboxylic acids. Also, this catalyst is highly air and moisture sensitive and needs absolute dry conditions to carry out the olefin reaction.

![Shrock’s catalyst](image)

Figure 1-1. Alkoxy imidomolybdenum-based Schrock’s catalyst.

To improve the moisture-air and the functional group sensitivity, Grubbs and coworkers examined ruthenium based catalysts having an oxidation state higher than the Fischer carbenes but lower than Schrock’s catalyst. The first Grubbs’ catalyst [(PPh₃)₂Cl₂Ru=CHCH=C(Ph)₂] (1-2) was developed in 1992 and was stable in protic and aqueous solvents. However, the catalyst exhibited limited reactivity in comparison with Schrock’s carbene complex (Figure 1-2). In 1996 Grubbs and coworkers introduced a modified form of their earlier ruthenium based catalyst (Figure 1-2, Grubbs’ catalyst 1-3), and is commonly known as Grubbs’ first generation catalyst. It not only displayed better functional group tolerance but also was observed
to be 20–10,000 times more reactive than the earlier version of the ruthenium catalyst 1-2 (Figure 1-2). Based on Herrmann’s studies on N-heterocyclic carbenes Grubbs replaced one of the tricyclohexyl phosphine (PCy3) ligands with a mesityl N-heterocyclic ligand to afford a more stable ruthenium catalyst 1-4, which is commonly referred as “Grubbs’ second generation catalyst”. This second generation catalyst shows far more superiority in terms of its tolerance towards moisture, air, and a wide variety of functional groups (Figure 1-2). As a result of this enhanced reactivity our research efforts were focused on olefin metathesis using Grubbs’ second generation catalyst 1-4 along with the use of Grubbs’ first generation catalyst 1-3.

Figure 1-2. Ruthenium catalysts.

1.1.2 Mechanism of Olefin Metathesis

The commercial availability of ruthenium catalysts 1-3 and 1-4 has made them a practical and standard organic tool. The synthesis of this metal alkylidene complexes will not be discussed here. However, to better apply olefin metathesis towards the synthesis of target compounds and polymers, it is helpful to examine the mechanism that was first introduced by Chauvin. When utilizing Grubbs’ catalysts 1-3 and 1-4, the first step of the mechanism involves the dissociation of the PCy3 ligand, followed by the binding of the alkene to the carbene (Scheme 1-4). The next step is a [2+2] cycloaddition with the metal catalyst to form the metallacyclobutane intermediate, which can then undergo a cycloreversion process to produce a new metal
alkylidene complex (Scheme 1-5). The mechanism proceeds as a catalytic cycle where the metal alkylidene undergoes another [2+2] cycloaddition with a second alkene, followed by the cycloreversion leaving the newly formed olefin with \( R_1 \) and \( R_2 \) groups and the metal alkylidene for further catalytic use.

Scheme 1-4. Dissociative substitution of ruthenium catalyst.

Because ethylene gas is released as a byproduct, it is possible to shift the equilibrium towards the desired products by deliberately evacuating or flushing the headspace with argon to remove ethylene. The cycle continues until the reaction is quenched. Ethyl vinyl ether (EVE) reacts with the ruthenium catalyst and forms the Fischer carbene \( \text{L(PCy}_3\text{)(Cl)}_2\text{Ru=CHOEt} \)
This new, electron rich carbene complex formed by the reaction between ruthenium catalyst and EVE is virtually irreversible in nature and significantly less reactive than the ruthenium alkylidenes. \cite{26, 29}

![Scheme 1-6](image)

Scheme 1-6. Quenching of ruthenium catalyst with ethyl vinyl ether (EVE). \cite{29}

### 1.1.3 Important Types of Metathesis Reactions and Applications

As highlighted many times, olefin metathesis is a versatile technique which includes ring-closing metathesis (RCM), ring-opening metathesis (ROM), cross-metathesis (CM), ring-opening metathesis polymerization (ROMP), and acyclic diene metathesis (ADMET) (Scheme 1-7). \cite{6} The three main metathesis reactions, used in our studies, RCM, ROMP, and ADMET will be discussed in greater detail.

RCM is olefin metathesis involving the cyclization of a diene to generate various sized cycloalkenes, from small 5-membered rings to macrocycles. \cite{18} The stereochemistry of the cycloalkene products are dependent on the substrates; for example, small and medium sized rings formed from RCM are in a less strained \textit{cis} conformation while in contrast, the stereochemistry of the non-rigid RCM derived macrocyclic compounds is difficult to predict and can encompass a mixture of \textit{cis} and \textit{trans} stereoisomers. \cite{30}

RCM reactions are conducted under highly dilute conditions to prevent ADMET polymerization. In addition, heat is often employed to improve ring closures due to the entropy of activation required to bring the two ends of the chain together. \cite{31} However, higher temperatures can cause the catalyst to decompose, thus a greater catalyst loading is required. \cite{5}
Despite this requirement, RCM has provided a shorter, more efficient synthetic route to natural products, medicinal drugs, and new materials compared to conventional methods, as attested by the numerous studies found in literature. An example is shown in Scheme 1-8 in which Danishefsky and coworkers utilized RCM to synthesize Epothilones using different alcohol protection groups.

Scheme 1-7. Different types of olefin metathesis.

The reverse reaction of the RCM is called ROM, where the cycloalkene breaks open to form terminal diene, which can be followed by a CM reaction with other acyclic alkenes to form new products. Similar to RCM, ROM requires dilute conditions due to the resulting dienes undergoing polymerization, referred to as ROMP. The polymerization is quite practical and is more widely used than the ROM itself. Cycloalkenes, which possess ring strain, such as norbornene, cyclopentene and cyclooctene, favor ROMP. Removing ring strain leads to a reversible reaction that is driven forward, and is not reversible anymore.
Scheme 1-8. Utilizing RCM for the synthesis of Epothilones using different alcohol protection and different solvents.\textsuperscript{32}

Grubb’s second generation catalyst \textbf{1-4} has high functional group tolerance and has been demonstrated in ROMP to generate functionalized, telechelic and trisubstituted polymers.\textsuperscript{33} ROMP is responsible for the synthesis of a variety of new materials, starting from the development of nonlinear optics to biologically relevant polymers.\textsuperscript{32} A recent application of this polymerization is shown in Scheme 1-9, where a polymer was synthesized to create biomaterials that can undergo a [2+2] cycloaddition when irradiated with UV light.\textsuperscript{35}


RCM and ROMP started as the most popular types of metathesis reactions, but due to recent studies and a better understanding of the selectivity and stereoselectivity of CM, the later
has become a more useful and versatile synthetic technique over the years. The concerns over selectivity arise from the mixture of heterodimers, homodimers, \textit{cis} and \textit{trans} stereoisomers that can be generated from CM reactions. In addition, employing internal olefins in CM can also lead to a greater number of product mixtures (Scheme 1-10). Factors such as steric and electronic effects may also affect CM reactivity and selectivity, and must be considered when planning reactions. For example, olefins possessing electron withdrawing or bulky substituents often lead to little or no CM products because of the poor reactivity with the catalyst, but steric effects nearly always favor \textit{trans} selectivity.\textsuperscript{34}

Scheme 1-10. Cross-metathesis of asymmetric internal olefins.

Fortunately, new models and methodology were developed to improve selective CM. For instance, Grubbs categorized olefin metathesis as Type I, II, III and IV based on their reactivity to form homodimers by CM with catalyst 1-3 and 1-4. Primary allylic alcohols, protected amines and esters are the examples of Type I alkenes (sterically unhindered, and electron-rich) because they readily form homodimers by CM and also undergo secondary metathesis reactions.\textsuperscript{28, 36, 37} The more sterically hindered Type II alkenes (i.e., secondary alcohols and vinyl ketones) are less reactive and Type III alkenes are nonreactive (i.e., tertiary allylic carbons). Type IV alkenes (i.e., protected trisubstituted allyl alcohols) are spectators and do not participate in the CM reaction. The examples given above are based on the utilization of catalyst 1-4. One strategy towards selective CM involves a two steps procedure in which homodimers of Type I
alkenes are generated, followed by a secondary metathesis reaction with Type II / III alkenes to preferentially form the heterodimer product with trans favored in the presence of selected functional groups (Scheme 1-11). CM is more widely used now and an example of a recent application of CM is shown in Scheme 1-12, where Roy and coworkers were able to carry out cross-metathesis of O- and C- galactopyranosides in good to excellent yields with predominantly trans selectivity.

![Scheme 1-11](image1)

Scheme 1-11. Primary and secondary CM reactions.

![Scheme 1-12](image2)


### 1.2 Ring Opening Metathesis Polymerization (ROMP)

Ring opening metathesis polymerization (ROMP) (Scheme 1-13) involves a chain growth process resulting in the formation of linear high molecular weight polymers. Norbornene is often used in these studies, due to a small strain release.

![Scheme 1-13](image3)

Scheme 1-13. Ring opening metathesis polymerization of norbornene.

Like all olefin metathesis reactions, ROMP is governed by competing equilibrium. The thermodynamics of the ring-chain equilibrium dictate the polymerizability of cyclic olefins.
\[ \Delta G = -RT \ln K_{eq} = \Delta H - T\Delta S \quad (1) \]

Polymerization is governed by the enthalpy (\(\Delta H\)) since with the polymerization the ring strain of the monomer unit gets released. The bond-angle strain in 3, 4, and 8-membered rings as well as in bicyclic monomers like norbornene provides the necessary energy for the polymerization process. The inherent ring strain in these monomer units allow the equilibrium to be shifted from the cyclic monomer towards the linear polymer. The polymerization of the strain free (i.e., \(\Delta H = 0\)) macrocyclic olefin is an entropically (\(\Delta S\)) driven process as a result of the formation of linear polymer. The ROMP of 5, 6, and 7-membered rings, however, presents a thermodynamic uncertainty. Due to comparable entropy and enthalpy (\(\Delta H - T\Delta S \approx 0\)) values, such stable cyclic olefin monomers can undergo polymerization at \(T_c\), the polymerization ceiling temperature (the temperature above which no polymerization can take place for any cyclic monomer).\(^{50, 51}\) Patton and McCarthy demonstrated that at a temperature of -23°C cyclohexene could polymerize.\(^{51}\) In general, monomers with greater ring strain (i.e., larger negative value of \(\Delta H\) of the reaction) are more prone to undergo ring-opening polymerization reactions.

The mechanism of ROMP chemistry is outlined in Scheme 1-14 using norbornene as the monomer and Grubbs’ catalyst. The catalyst, \(M\), is a transition metal carbene complex. The first step of polymerization involves coordination of the monomer unit to the metal to form an initial \(\pi\)-complex [A]. The monomer then undergoes an insertion process through a [2+2]-like cycloaddition to form the metallacyclobutane intermediate [B]. The double bond of the cyclic intermediate is highly strained and is energetically unfavorable. The successive cleavage of the metallacyclobutane by a retro [2+2] addition generates a chain extended \(\pi\)-complex [C]. The final step involves the dissociation of the \(\pi\)-complex. This whole process repeats itself and
thereby creating potentially high molecular weight polymers, until the reaction is halted by the addition of a capping reagent like EVE.

Scheme 1-14. Mechanism of the ROMP of norbornene using Grubbs’ catalyst.

Ring opening polymerization is controlled by a chain growth mechanism, as shown in the above mentioned mechanism (Scheme 1-14). Polymerization or chain propagation continues at the reactive, growing chain end until secondary metathesis reactions, called chain transfer or cyclization, become significant. When this secondary reaction predominates over the primary chain propagation reaction, the thermodynamics of the polymerization is controlled by the ring-chain equilibria.52

1.3 Dynamic Combinatorial Chemistry

For the discovery of biologically active substances, especially drugs, it is necessary to find molecules that react selectively with the given biological targets. Within less than one decade, combinatorial chemistry has established itself as a versatile and attractive approach for the synthesis of libraries of compounds that are able to be tested for their biological activities and desirable properties.54,55 It was first developed for the synthesis of peptide libraries for screening against antibodies or receptors. However, the technology has evolved rapidly to become a
powerful technique primarily in the drug discovery processes. The goal of combinatorial chemistry is to synthesize a large number of products via condensation of a small numbers of starting materials in all possible combinations. For example, let us consider a chemical reaction in which there are three different reactants: A, B, C. If we start with only one type of each reagent, and then the reaction will result in \(1 \times 1 \times 1 = 1\) product as the result of a total of three reactions. On the other hand, if we use 10 types of each reagent, then there will be a total 30 reactions which would result in the formation of \(10 \times 10 \times 10 = 1000\) products, while 100 types of each reagent would result in the formation of \(1,000,000\) products as a result of 300 total reactions only.

Traditional combinatorial chemistry involves sequential and irreversible syntheses irrespective of whether they are performed individually in parallel, or concertedly in the same compartment. Another characteristic feature is that all constituents of the library are more or less robust molecules. The major disadvantage of this process is the lack of flexibility or limited flexibility in the generation of the library, since almost all structures have to be designed distinctly and synthesized separately. In contrast to the static approaches involved in traditional combinatorial chemistry, the library may be produced from a set of reversibly interchanging reactants. This technique introduces a dynamic equilibrium into the system. The interesting feature of dynamic combinatorial chemistry (DCC) is that each library member affects all other surrounding constituents and components. Also, DCC combines the generation of the library and the screening processes in a single step. There is a continuous interchange of building blocks between different members, and hence the composition of a dynamic combinatorial library (DCL) is governed by thermodynamics rather than kinetics. The major advantage of DCC over the traditional or static combinatorial chemistry is that the desired compound is amplified at the
expense of the undesired compounds. This is due to the fact that the molecular recognition events are specific for a particular member, and thus will stabilize that particular substance only. This induces a shift in equilibrium towards the formation of recognized species at the expense of unrecognized species.\textsuperscript{59}

Figure 1-3. Schematic representation of the concept involved in DCC.\textsuperscript{73}

In the simplest fashion, we can describe the principle involved in dynamic combinatorial chemistry by means of Emil Fischer’s lock-and-key metaphor.\textsuperscript{74} The whole process can be divided into three steps. The first step involves selection of initial building blocks, which are capable of interacting with each other in a reversible fashion. The second step involves the development of the conditions for the generation of the library, where the building blocks can form interchanging, individual molecular “keys” (for example, ligands). In the last step, the library is subjected to a selection process, which results from binding strength to a molecular “lock” (for example, a receptor).\textsuperscript{73} With this concept, two situations can arise. In the first case, the receptor can itself act as the trap for the given ligand. Under this condition the ensemble of candidates will be forced to rearrange in order to produce that species. In the second case, a
specific synthetic receptor is selected from a series of interconverting receptors by addition of a certain ligand. These two cases have been termed as “substrate casting” and “receptor molding” respectively. Figure 1-4 shows the schematic representation of the casting and the molding process.

Thus, in DCC, there are two concepts, depending on whether a receptor or a substance acts as a target-template for the assembly of the other partners. Casting involves the receptor-induced assembly of a substrate that fits the receptor; whereas, the molding involves substrate-induced assembly of a receptor that fits the substrate.

There are three steps involved in a dynamic combinatorial approach. These are:

1. synthesis of a mixture of inter-converting molecules;
2. amplification of the best binder(s) through non-covalent interactions with a template; and
3. isolation (or re-synthesis) of the best binder(s). The success of each step depends upon the type of reversible reaction used to connect the building blocks. Under ideal conditions, we look for a rapid reversible reaction which is tolerant towards a wide-range of functional groups, proceeds under mild conditions, and does not interfere with the recognition events. A series of different types of reversible reactions have
been studied for their use in DCC. Table 1-1 shows a series of such reactions. These include disulfide exchange,\textsuperscript{77} metal-ligand coordination,\textsuperscript{78} exchange of oximes,\textsuperscript{79} and hydrazones,\textsuperscript{80} and olefin metathesis.\textsuperscript{81, 82} There are two basic procedures involved in the implementation of the DCC approach, depending on whether library generation and screening are performed in a single step or in two steps. This result in two types of dynamic libraries: adoptive combinatorial libraries and pre-equilibrated dynamic combinatorial libraries.\textsuperscript{77}

Earlier using the reversible chemistry, diverse libraries were generated. However, recent emphasis in combinatorial chemistry is to shift the equilibrium towards templating by exposing those libraries to targets.\textsuperscript{59} These targets can either be a receptor or ligand molecules. The most significant examples of templating have been observed when a molecule selects its best receptor from small dynamic libraries of macrocycles of different sizes.\textsuperscript{80, 86, 87} Figure 1-5 shows an example of hydrogen-bond based dynamic system prepared from a building block derived from L-proline. Acid catalyzed cyclization results in the formation of 15 macrocycles initially, which changes mainly into cyclic dimers. At equilibrium, the library comprises 88\% of the dimers and 11\% of trimers. Addition of template acetylcholine to the reaction mixture significantly changes the equilibrium to produce a 50-fold amplification of the cyclic trimer.\textsuperscript{59}
Table 1-1. Potential application of different dynamic process in DCC systems.59

(a) \[
\begin{array}{c}
\text{O} \\
R^1\text{O} \rightarrow \text{O} \rightarrow R^1 \\
\begin{array}{c}
\text{O} \\
R^2\text{O} \rightarrow \text{O} \rightarrow R^2 \\
\text{O} \\
R^1\text{O} \rightarrow \text{O} \rightarrow R^1
\end{array}
\end{array}
\xrightleftharpoons{\text{Base}} \begin{array}{c}
\text{O} \\
R^1\text{O} \rightarrow \text{O} \rightarrow R^1 \\
\begin{array}{c}
\text{O} \\
R^2\text{O} \rightarrow \text{O} \rightarrow R^2 \\
\text{O} \\
R^2\text{O} \rightarrow \text{O} \rightarrow R^1
\end{array}
\end{array}
\]

(b) \[
\begin{array}{c}
\text{O} \\
R^1\text{O} \rightarrow \text{O} \rightarrow R^1 \\
\begin{array}{c}
\text{O} \\
R^2\text{O} \rightarrow \text{O} \rightarrow R^2 \\
\text{O} \\
R^1\text{O} \rightarrow \text{O} \rightarrow R^1
\end{array}
\end{array}
\xrightleftharpoons{\text{Pd(0)}} \begin{array}{c}
\text{O} \\
R^1\text{O} \rightarrow \text{O} \rightarrow R^1 \\
\begin{array}{c}
\text{O} \\
R^2\text{O} \rightarrow \text{O} \rightarrow R^2 \\
\text{O} \\
R^1\text{O} \rightarrow \text{O} \rightarrow R^1
\end{array}
\end{array}
\]

(c) \[
\begin{array}{c}
\text{O} \\
R^1\text{N} \rightarrow \text{N} \rightarrow R^1 \\
\begin{array}{c}
\text{O} \\
R^2\text{N} \rightarrow \text{N} \rightarrow R^2 \\
\text{O} \\
R^1\text{N} \rightarrow \text{N} \rightarrow R^1
\end{array}
\end{array}
\xrightleftharpoons{\text{Protease}} \begin{array}{c}
\text{O} \\
R^1\text{N} \rightarrow \text{N} \rightarrow R^1 \\
\begin{array}{c}
\text{O} \\
R^2\text{N} \rightarrow \text{N} \rightarrow R^2 \\
\text{O} \\
R^1\text{N} \rightarrow \text{N} \rightarrow R^1
\end{array}
\end{array}
\]

(d) \[
\begin{array}{c}
\text{H} \\
R^1\text{C} \rightarrow \text{N} \rightarrow R^1 \\
\begin{array}{c}
\text{H} \\
R^2\text{C} \rightarrow \text{N} \rightarrow R^2 \\
\text{H} \\
R^1\text{C} \rightarrow \text{N} \rightarrow R^1
\end{array}
\end{array}
\xrightleftharpoons{\text{Acid}} \begin{array}{c}
\text{H} \\
R^1\text{C} \rightarrow \text{N} \rightarrow R^1 \\
\begin{array}{c}
\text{H} \\
R^2\text{C} \rightarrow \text{N} \rightarrow R^2 \\
\text{H} \\
R^2\text{C} \rightarrow \text{N} \rightarrow R^1
\end{array}
\end{array}
\]

(e) \[
\begin{array}{c}
\text{H} \\
R^1\text{C} \rightarrow \text{N} \rightarrow R^1 \\
\begin{array}{c}
\text{H} \\
R^2\text{C} \rightarrow \text{N} \rightarrow R^2 \\
\text{H} \\
R^2\text{C} \rightarrow \text{N} \rightarrow R^1
\end{array}
\end{array}
\xrightleftharpoons{\text{Acid}} \begin{array}{c}
\text{H} \\
R^1\text{C} \rightarrow \text{N} \rightarrow R^1 \\
\begin{array}{c}
\text{H} \\
R^2\text{C} \rightarrow \text{N} \rightarrow R^2 \\
\text{H} \\
R^2\text{C} \rightarrow \text{N} \rightarrow R^1
\end{array}
\end{array}
\]

(f) \[
\begin{array}{c}
\text{H} \\
R^1\text{C} \rightarrow \text{N} \rightarrow R^1 \\
\begin{array}{c}
\text{H} \\
R^2\text{C} \rightarrow \text{N} \rightarrow R^2 \\
\text{H} \\
R^2\text{C} \rightarrow \text{N} \rightarrow R^1
\end{array}
\end{array}
\xrightleftharpoons{\text{Acid}} \begin{array}{c}
\text{H} \\
R^1\text{C} \rightarrow \text{N} \rightarrow R^1 \\
\begin{array}{c}
\text{H} \\
R^2\text{C} \rightarrow \text{N} \rightarrow R^2 \\
\text{H} \\
R^2\text{C} \rightarrow \text{N} \rightarrow R^1
\end{array}
\end{array}
\]

(g) \[
\begin{array}{c}
\text{R}^1\text{S} \rightarrow \text{S} \rightarrow R^1 \\
\begin{array}{c}
\text{R}^2\text{S} \rightarrow \text{S} \rightarrow R^2 \\
\text{R}^1\text{S} \rightarrow \text{S} \rightarrow R^1
\end{array}
\end{array}
\xrightleftharpoons{\text{Grubbs catalyst}} \begin{array}{c}
\text{R}^1\text{S} \rightarrow \text{S} \rightarrow R^1 \\
\begin{array}{c}
\text{R}^2\text{S} \rightarrow \text{S} \rightarrow R^2 \\
\text{R}^2\text{S} \rightarrow \text{S} \rightarrow R^1
\end{array}
\end{array}
\]

(h) \[
\begin{array}{c}
\text{R}^1\text{C} \rightarrow \text{C} \rightarrow R^1 \\
\begin{array}{c}
\text{R}^2\text{C} \rightarrow \text{C} \rightarrow R^2 \\
\text{R}^1\text{C} \rightarrow \text{C} \rightarrow R^1
\end{array}
\end{array}
\xrightleftharpoons{\text{Grubbs catalyst}} \begin{array}{c}
\text{R}^1\text{C} \rightarrow \text{C} \rightarrow R^1 \\
\begin{array}{c}
\text{R}^2\text{C} \rightarrow \text{C} \rightarrow R^2 \\
\text{R}^1\text{C} \rightarrow \text{C} \rightarrow R^1
\end{array}
\end{array}
\]
1.4 Carbohydrate chemistry

The study of carbohydrates began in the late nineteenth century with the work of Emil Fischer. Carbohydrate ring structure was elucidated in the 1930s by Haworth and colleagues. Polysaccharides were discovered soon after and appeared to be present in every living organism, such as vegetables and animals. In addition to determining the structure of this new category of molecules, chemists and biologists focused on the functions of these ubiquitous polymers. Polysaccharides display a very wide range of biological functions from acting as nature’s source of energy (such as starch and glycogen), to providing structural materials (cellulose, chitin, collagen, and proteoglycans) 1-3 (Figure 1-6). Carbohydrates are now known to assume wider variety of biological roles. For example, the sulfated polysaccharide, heparin plays an essential role in blood coagulation, while hyaluronan acting as a lubricant in joints has been used in the implantation of plastic intra-ocular lenses in the 1980s.
Moreover, hyaluronan, as well as another sulfated polysaccharide, chondroitin sulfate, exhibit anti-inflammatory activity and were investigated for the treatment of osteoarthritis and rheumatoid arthritis. A large number of syntheses involving carbohydrate chemistry are directed increasingly toward the preparation of artificial glycoconjugates. Such glycoconjugates contain sugars and/or naturally occurring compounds. However, it has been recognized that it is not necessary to have actual glycoconjugates in order to study and understand various biological processes. Several artificial carbohydrate compounds exhibiting parallel or even improved biological interactions can be synthesized. Carbohydrate recognition plays an important role in many biological processes like, cell-cell interaction, cell communication, and others. They are also used as ligands for endogenous lectins, used to mediate various regulatory processes. Therefore, carbohydrate groups are highly attractive tools for the generation of mimics and analogues. Eventually, by identifying and tailoring potent new ligands, medicinal application in drug designing and glycohistochemistry can be accomplished.
Unlike other compound groups, synthesis of carbohydrate libraries using classical methods have never witnessed identical rapid progress. In spite of suffering identical problems, DCC still offers a complementary route for the synthesis of carbohydrate libraries, especially, the synthesis of dynamically interchanging carbohydrates “clusters”.\(^{58}\) Only a few examples of DCLs containing carbohydrates are reported and none of them involve metathesis.\(^ {58, 77, 88-91}\)

Multicovalent neoglycoconjugates have been extensively utilized to probe and enhance carbohydrate-protein interactions at the molecular level.\(^ {92-94}\) Moreover, glycoclusters\(^ {92}\) and dendrimers\(^ {93}\) are also emerging as potential carbohydrates therapeutic agents.\(^ {94}\) Several examples exist in which ligand-induced receptor and protein dimerization occurred as a general mechanism for signal transduction.\(^ {95}\) It is conceivable that signal transduction and receptor shedding could be triggered by carbohydrate oligomers.\(^ {96}\)

Cross-metathesis of a hydrocarbon chain having terminal double bond involves elimination of ethylene gas. If elimination of the ethylene gas can shift the equilibrium towards the product side, then the addition of the gas can shift the equilibrium towards the reactant side. This is the basic concept involved in developing carbohydrate based dynamic combinatorial library using the cross-metathesis method. We examined the reactivity of various types of sugars in the self-metathesis reactions. Roy and coworkers employed Grubbs’ catalyst based cross-metathesis for \(O\)- and \(C\)- allyl and \(O\)-pentenyl galactopyranosides.\(^ {150}\) Considering the growing importance of carbohydrates in the study of carbohydrate-protein interactions, our research goal is to generate a series of \(O\)-esters of furanose and pyranose with pendant terminal double bonds and examine their applications in the olefin metathesis reaction.
1.5 Tissue Engineering

Peppas and Langer defined biomedical engineering as an extension of chemical engineering towards biomaterials.\textsuperscript{39} Tissue engineering is one of its main branches. Various disciplines, such as materials science, cell biology, chemistry, reactor engineering, as well as clinical research contribute to tissue engineering. It requires a balanced combination of cell culture growth with biomaterials to support it and with bioactive molecules to enhance and direct it.\textsuperscript{40} A quite successful approach in tissue engineering involves replacement or repair of damaged or failed tissues with viable ones by creation of an environment, which promotes the native capacity of cell to integrate, differentiate, and proliferate.\textsuperscript{41-43}

Every year, millions of patients suffer the loss, or failure of an organ or tissue as a result of accidents or disease. Similarly, traumatic injuries, cancer treatment, and congenital abnormalities are often associated with abnormal bone shape or segmental bone loss. Restoration of normal structure and function in these cases requires replacement of the missing bone that may be accomplished by surgical transfer of natural tissue from an uninjured location elsewhere in the body. However, these approaches are extremely limited and have several drawbacks including shortage of donor, infection or pain of patients due to second surgery for the removal of implanted metal plate, inadequate blood supply, and secondary deformities at the donor site.\textsuperscript{44}

Recently, tissue engineering has found enormous applications in generating artificial constructs to direct tissue regeneration.\textsuperscript{45} Scaffolds made from synthetic and natural polymers and ceramics have been investigated extensively for orthopedic treatment. This approach has several advantages including ability to generate desired pore structures with matching size, shape and mechanical properties. The major disadvantages it has include shaping them to fit in cavities or defects, bonding to the bone tissues, and requirement of an open surgery to get rid of it.\textsuperscript{46}
A material that can be employed as a scaffold in tissue engineering must satisfy a number of requirements. These include biocompatibility, biodegradation to non-toxic products within the time frame required for the application, processability to complicated shapes with appropriate porosity, ability to support cell growth and proliferation, and appropriate mechanical strength during the major part of the tissue regeneration process. Biodegradable synthetic polymers offer a number of advantages over other materials for developing scaffolds in tissue engineering. The ideal biomaterial must be biocompatible, promote cellular interaction and tissue development, and possess proper physical and mechanical properties. The key advantages include the ability to tailor mechanical properties and degradation kinetics to suit various applications. However, in addition to the main requirements mentioned earlier, an injectable polymer composition must be in liquid or paste form, sterilizable without causing any chemical change, and must have the capacity to incorporate biological matrix components. Upon injection the prepolymer composition should bond to the biological surface and cure to the solid and porous structural form with appropriate mechanical properties. The curing process should take place with minimum heat generation and chemical reactions involved in curing should not damage the cells and adjacent tissues. The cured polymer while facilitating the cell-in-growth proliferation and migration should ideally be degraded into biocompatible materials that are either absorbed within the body or released from the body without any side reaction or damage to the body.46

Among the families of synthetic polymers, polyesters have been found attractive due to the ease of degradation by hydrolysis of ester linkage (degradation products being reabsorbed through the metabolic pathways in some cases) and the potential to tailor the structure to alter degradation rates. Biodegradable synthetic polymers such as polyglycolides, polylactides, polycaprolactone (PCL) and their copolymers, poly(p-dioxanone), and copolymers of
trimethylene carbonate and glycolide have been used in a number of clinical applications for the preparation of the scaffolds. However, the hydrophobicity of such polyester based biodegradable polymers, acidity of the decomposed material; and self acceleration of degradation are the major drawbacks they have.40

Attempts to find tissue-engineered materials to cure orthopedic injuries/diseases have made necessary the development of new polymers that meet a number of demanding requirements. Such requirements include ability of scaffold to provide mechanical support during tissue growth and gradually degrade to biocompatible products, to withstand several requirements including ability to incorporate cells, growth factors etc. and to provide osteoconductive and osteoinductive environments. Recent studies in tissue engineering involve development of in-situ polymerization of the biocompatible compositions. This can function as cell delivery systems in the form of an injectable liquid/paste. Many of the currently available degradable polymers do not comply with all of these necessary requirements and significant chemical changes are required to their structure to achieve their role for the desired applications.46 One strategy to overcome these problems is to develop living tissue substitutes based on synthetic biodegradable polymers. We hope our research efforts to synthesize the biomaterials for tissue engineering from norbornenemethanol will satisfy the criteria mentioned above.

1.6 Hydrogels

A hydrogel is a network of polymer chains that are water-insoluble, sometimes found as a colloidal gel in which water is the dispersion medium. Hydrogels are superabsorbent (they can contain over 99% water) natural or synthetic polymers. Hydrogels possess also a degree of flexibility very similar to natural tissue, due to their significant water content. Common uses of hydrogels are--
• Currently used as scaffolds in tissue engineering. When used as scaffolds, hydrogels may contain human cells in order to repair tissue.

• Environmentally sensitive hydrogels. These hydrogels have the ability to sense changes of pH, temperature, or the concentration of metabolite and release their contents as result of such a change.

• As sustained-release delivery system.

• Hydrogels that are responsive to specific molecules, such as glucose or antigens, can be used as biosensors as well as in DDS.

• In disposable diapers where they "capture" urine, or in sanitary towels.

• Contact lenses (silicone hydrogels, polyacrylamides).

• Medical electrodes using hydrogels composed of cross linked polymers (polyethylene oxide, polyAMPS and polyvinylpyrrolidone).

• Water gel explosives.

Other, less common applications include---

• Breast implants.

• Granules for holding soil moisture in arid areas.

• Dressings for healing of burn or other hard-to-heal wounds. Wound GEL are excellent for helping to create or maintain environment.

  Common ingredients are e.g., polyvinyl alcohol, sodium polyacrylate, acrylate polymers and copolymers with an abundance of hydrophilic groups. Natural hydrogel materials are being investigated for tissue engineering. These materials include agarose, methylcellulose, hyaluronan, and other naturally derived polymers.

  Hydrogels swell strongly in aqueous media, and are composed of hydrophilic organic polymer components that are cross-linked into a three-dimensional network either by covalent or non-covalent interactions. The cross-linking nature of hydrogels provides it with dimensional stability, whereas the high solvent content gives rise to fluid-like transportation properties.

  Physical properties of hydrogels make it suitable for various applications. Initially it was used as
superabsorbent where it can act as an absorber entrapping water and are used where a large volume of aqueous media needs to be removed from a localized source. With an eye to applying those in several areas like in vivo diagnostics, drug/gene delivery, chemical separations, and chemical and biological sensors scientists have now started to synthesize more complex polymer architectures. Such materials must satisfy conditions like biocompatibility, biodegradation, encapsulation, and biorecognition etc.

Based on the type of cross-links hydrogels are classified into two different categories—(a) Physically cross-linked hydrogels, and (b) Chemically cross-linked hydrogels.\textsuperscript{108}

**Physically Cross-linked Hydrogels**

This class of hydrogels is classified by its reversibility or by its degradation properties. These hydrogels are mostly used to encapsulate proteins,\textsuperscript{109} cells,\textsuperscript{110} or drugs,\textsuperscript{111} followed by dissolution of the structure to release them. The noncovalent attractive forces like hydrophobic interactions, hydrogen bonding, or ionic interactions between the polymer chains are responsible for the cross-linking here (Figure 1-7).

![Hydrogel Network](image)

**Figure 1-7.** Physical cross-linking by noncovalent interactions.\textsuperscript{108}

Hydrogel formation is based on the pH value of the medium as the hydrogen bonds, the main source of such noncovalent bonding, are formed only when the acid groups are protonated.\textsuperscript{112,113}
Chemically Cross-linked Hydrogels

These kinds of hydrogels are more stable because the cross-links are covalent bonds.\(^{114}\) They have permanent structures unlike the physically cross-linked hydrogels. Such hydrogels are made by polymerizing monomers containing the cross-linking agent. One example is the chemically cross-linked hydrogel poly(2-hydroxyethyl methacrylate). It is typically synthesized by polymerizing 2-hydroxy methacrylate (\(\text{H}_2\text{C}=\text{C}-(\text{CH}_3)\text{COOCH}_2\text{CH}_2\text{OH}\)) with ethylene glycol dimethacrylate (\(\text{CH}_2=\text{C}(\text{CH}_3)\text{COOCH}_2\text{CH}_2\text{OCO}(\text{CH}_2)\text{C}=\text{CH}_2\)) as the cross-linking agent. Hydrogels can also be formed by cross-linking of the various functional groups present on the polymer backbone.

1.7 Acyclic Diene Metathesis (ADMET)

The introduction of the well-defined alkylidene metal catalysts by Schrock and Grubbs continues to have profound impact on the viability of ring opening metathesis polymerization (ROMP) reactions. However, it was the early contributions made specifically by Schrock that introduced a new metathesis polymerization reaction. Acyclic diene metathesis (ADMET) polymerization has been an area of intermittent study for the last 30 years. However, the discovery of Schrock’s alkylidines was the first practical reality.

Acyclic diene metathesis (ADMET) polymerization (Figure 1-8) has proven to be a viable synthetic route for the synthesis of high molecular weight unsaturated polymers and copolymers, including polymers possessing various functionalities.\(^{98}\) ADMET represents a unique equilibrium step condensation route for the synthesis of polyalkenylenes. The ADMET condensation, like the cross metathesis, is a reversible reaction which is driven by the continuous production and removal of ethylene gas.\(^{100}\)
In order to understand the ADMET chemistry, structure-reactivity studies have been done. The mechanism of ADMET chemistry is shown in Scheme 1-15. By examining the mechanism of both the ADMET and ROMP chemistry, it is found that the reaction intermediate, the metallacyclobutane ring, is common to both and this is the only common feature between them as one is a chain growth polymerization and the other is step growth polymerization. In ADMET chemistry, two metallacyclobutane rings must be proposed in a propagation step (whereas only one is needed in ROMP chemistry). The first metallacyclobutane ring is the result of joining two monomers together followed by cleavage of methylidene carbene, which becomes the active catalyst entity during the polymerization itself. The methylidene carbene continues to react with either monomer or polymer, leading to a new metallacyclobutane ring acting as the precursor of ethylene evolution. Once the ethylene is evolved and removed from the reaction system, the cycle repeats itself, and further connection with monomers results in the formation of high molecular weight polymer.

The utility of ADMET chemistry for the polymerization of dienes containing silyl, aromatic, and ester functional groups has been investigated. ADMET has been shown to be an efficient technique for the preparation of unsaturated polyethers, unsaturated polyesters, as well as a variety of functionalized polyethylenes and polyalkenylenes containing heteroatoms (N, Si) in the polymer main chain.
Scheme 1-15. Representative ADMET polymerization cycle.

To our best knowledge no ADMET chemistry has been reported for the polymerization of dienes containing carbohydrates. Shown later in this dissertation, we have for the first time, synthesized a number of carbohydrate based dienes, which can be subjected to the ADMET chemistry.

1.8 Scope of the Thesis

Olefin metathesis is a powerful organic synthetic tool, as attested by the large volume of research found in literature. Grubbs’ second generation catalyst 1-4 and its tolerance for functional groups have made this methodology even more useful. However, there are still areas
of olefin metathesis that require more studies: peptidomimetics and carbohydrates. The work presented here will examine the use of olefin metathesis in several applications.

1. Development of ROMP reactions on a norbornene scaffold as a means to later crosslink the polymers using a diyl and release of nitrogen gas.

2. Self-metathesis of carbohydrates to make homodimers could be prepared and used as precursors of DCLs bearing a variety of functions and protecting groups on the carbohydrates. The carbohydrate-linking alkene was trans with several versions examined.

3. ADMET reactions of carbohydrates. The preliminary work is seen in this dissertation for the first time. Very complex products with new protecting group, strategies, and numerous asymmetric centers are produced.
CHAPTER 2
RING OPENING METATHESIS POLYMERIZATION OF NORBORNENE DERIVATIVES

2.1 Introduction

Synthetic biopolymers are designed with unique properties and biodegradability. A vast majority of biodegradable polymers belongs to the polyester family, including polyglycolides, and polylactides. Biodegradable synthetic polymers offer a number of advantages over the other materials in respect to developing scaffolds in tissue engineering. Key advantages include ability to modify the mechanical properties, and the degradation kinetics facilitating their application in different fields.\textsuperscript{46} Another major advantage of synthetic polymers include fabrication to the different shapes with desired pore morphology. Major disadvantages of such polymers include poor biocompatibility, poor processability, release of acidic degradation product, and loss of mechanical properties during the early stages of degradation.\textsuperscript{46}

Major research efforts have been directed to the development of medically applicable biomaterials.\textsuperscript{169} Photopolymerization of multifunctional monomers allows the synthesis of highly cross-linked polymer networks, which is useful for applications like contact lenses, dental restorative materials, and coatings for optical fibers.\textsuperscript{170-172} Numerous groups are involved in developing advanced experimental techniques and models in order to understand the polymerization of such multifunctional monomers to develop biomaterials.\textsuperscript{173-177} Of particular interest discussed here is an exploration into the use of multifunctional monomers for orthopedic biomaterial applications. One of the traditional treatments of many fractures is the application of metal plates for fixing the joints. However, it has several drawbacks like surgery for removing the plates, stress shielding during healing, fatigue, loosening of implants etc. Synthesis of degradable polymers as biologically useful materials is an area of great interest. The major advantage of using a degradable polymer is its ability to provide temporary mechanical support
as well as the elimination of the requirement of second surgery. Our research group was interested in synthesizing new biomaterials with increased mechanical strength.\textsuperscript{77}

Our goal is to apply ring opening metathesis polymerization (ROMP) as a tool to photocrosslink a polymer. Since this cross-linking is covalent, better mechanical strength is possible. Earlier work done by previous group member Aarti Joshi had developed new biomaterials using cinnamate esters and coumarin esters as functional groups and ROMP, combined with [2+2] cross-linking as the methodology. The advantages include flexibility caused by the mild polymerization and ability to accommodate different functional groups giving better mechanical strength obtained by the linear ladder-like cross-linking throughout the polymer chain length.

Our approach is to incorporate the elimination of nitrogen into the photo-crosslinking reaction to prepare a porous architecture within the hard polymers that should permit the flow of water, nutrients, and other biomolecules throughout the new artificial tissue. We aim to use a free radical nitrogen release reaction to introduce the holes and open architecture. Our research group had developed the following novel approach (Scheme 2-1, 2-2) to developing a cross-link while simultaneously releasing nitrogen gas to synthesize the desired cross-linked polymer.

![Scheme 2-1. Nitrogen aerosol through elimination.](image)
Scheme 2-2. ROMP to synthesize polymer scaffold.

We extend our research in order to increase the size of pores within the cross-linked polymers in order to allow passage of tissue fluid and achieving the goal with fewer numbers of steps, thus minimizing the time and cost factor for the synthesis of such biomaterials. Scheme 2-3 shows several other nitrogen releasing methods that could be investigated. Each example lead to slightly different intermediate with \( 2-7 \), \( 2-8 \), \( 2-9 \) leading to a carbone, nitrene, and diradical species, respectively.

Scheme 2-3. Other nitrogen-releasing products.
We used the method (a) for the synthesis of nitrogen-releasing system. Scheme 2-4 shows the basic concept of the development of diazoester, which when exposed to light can undergo nitrogen elimination. Thus a polymer of norbornene diazoesters can undergo photocross-linking to generate the hard polymer with pores for the flow of the fluid.

Scheme 2-4. Synthesis of norbornene diazoester.

**2.2 Results and Discussion**

We started with commercially available norbornene aldehyde 2-12, which was a mixture and *exo* and *endo* isomers. First step involves the synthesis of norbornenemethanol by treating the aldehyde in methanol with sodium borohydride and sodium hydroxide at 0°C with an overall yield of 80% (Scheme 2-5). This gives a mixture of *exo* and *endo* isomers of norbornenemethanol.

Scheme 2-5. Synthesis of norbornenemethanol.
The norbornene alcohol was then treated with \( N \)-t-Boc glycine in dichloromethane (CH\(_2\)Cl\(_2\)) in presence of diisopropylcarbodiimide (DIC) and 4-\( N \), \( N \)-dimethylaminopyridine (DMAP) to generate the corresponding ester carbamate of norbornene \( 2-14 \) with a yield of 71\%.

The next step was the deprotection of the amine group to generate the amino acetate of norbornene \( 2-15 \) (25\% yield one time only) (Scheme 2-6). t-BOC Deprotection was carried out in the presence of acid trifluoroacetic acid (TFA) using different concentration and different solvents. Table 3-1 shows the t-BOC cleavage using different reaction conditions.

![Scheme 2-6. Deprotection of t-Boc protected ester carbamate of norbornene.](image)

However, the deprotection work of \( 2-14 \) to generate the corresponding amino acetate of norbornene did not proceed as expected. The TLC of the reaction showed several spots and purification of the crude product resulted in a very poor yield (less than 10\%). Presence of acid like TFA might be responsible for the poor recovery of the deprotected product \( 2-15 \). Also the deprotected amino acetate is highly reactive and can undergo a possible reaction with each other to generate the dimer. This factor might also be responsible for having undesired results during the acid catalyzed deprotection of \( 2-14 \).
Table 2-1. t-Boc Cleavage of the compound 2-14.

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Starting Material (SM)</th>
<th>SM : TFA</th>
<th>Solvent</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-14</td>
<td>1:8</td>
<td>-</td>
<td>Several spots</td>
</tr>
<tr>
<td>2</td>
<td>2-14</td>
<td>1:4</td>
<td>-</td>
<td>Several spots</td>
</tr>
<tr>
<td>3</td>
<td>2-14</td>
<td>1:3</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt; (0.5 equiv)</td>
<td>25%</td>
</tr>
<tr>
<td>4</td>
<td>2-14</td>
<td>1:2.5</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt; (0.5 equiv)</td>
<td>10%</td>
</tr>
<tr>
<td>5</td>
<td>2-14</td>
<td>1:2.0</td>
<td>CHCl&lt;sub&gt;3&lt;/sub&gt; (1 equiv)</td>
<td>10%</td>
</tr>
<tr>
<td>6</td>
<td>2-14</td>
<td>1:1.4</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN (0.5 equiv)</td>
<td>15%</td>
</tr>
</tbody>
</table>

Our aim was to synthesize the amino acetate of norbornene, which could be converted to the corresponding diazoester. Considering the fact that acid deprotection of a t-Boc group lead to either several products or a poor yield, we changed the path to generate 2-16 (yield 75%) by treating the norbornenemethanol with Fmoc glycine in anhydrous tetrahydrofuran (THF) using DIC, and DMAP as the catalyst. Fmoc functional group is stable under acidic condition, but undergoes deprotection under basic condition. The Fmoc protected ester carbamate can be subjected to the base catalyzed deprotection to generate the desired amino acetate 2-15 (Scheme 2-8). Table 2-2 shows a series of reactions involved in the deprotection of the Fmoc group to get 2-15. In one method, 2-16 was added to the solution of piperidine in DMF (20%).<sup>179, 180</sup> In another method 2-16 was treated with 0.10 M TBAF in DMF (10 equiv). Scheme 2-7 shows the possible product of the deprotection of Fmoc protecting group in presence of TBAF in DMF along with the side product dibenzofulvene.<sup>181</sup>

![Scheme 2-7. Deprotection of Fmoc group.](image)

However, the deprotection of Fmoc did not provide the necessary results. The possible reason for the failure of piperidine catalyzed Fmoc deprotection is that the piperidine prefers to...
attack at the ester carbonyl compared to the attack to the amide carbonyl as the former (ester carbonyl) is more reactive than the later. The $^1H$ NMR of the deprotected product showed mostly the norbornenemethanol and not the desired compound 2-15.

![Synthesis of norbornene amino acetate using Fmoc protecting group.](image)

Scheme 2-8. Synthesis of norbornene amino acetate using Fmoc protecting group.

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Starting Material</th>
<th>Reagent</th>
<th>Quenching</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.16</td>
<td>0.1 TBAF in DMF</td>
<td>CH$_2$Cl$_2$</td>
<td>Major yield was Norbornenemethanol</td>
</tr>
<tr>
<td>2</td>
<td>2.16</td>
<td>0.1 TBAF in DMF</td>
<td>H$_2$O</td>
<td>Norbornenemethanol</td>
</tr>
<tr>
<td>3</td>
<td>2.16</td>
<td>50% piperidine in DMF</td>
<td>H$_2$O</td>
<td>Norbornenemethanol</td>
</tr>
<tr>
<td>4</td>
<td>2.16</td>
<td>20% piperidine in DMF</td>
<td>H$_2$O</td>
<td>Norbornenemethanol</td>
</tr>
</tbody>
</table>

The base catalyzed deprotection of Fmoc ester carbamate of norbornene did not work either. So we changed the route of making the diazoester from the amino acetate of norbornene. We use a new intermediate ketoester for this purpose. In this method, we synthesized the ketoester 2-17 from norbornenemethanol (Scheme 2-9) with an overall yield of 75%.

Ketoester 2-17 was then subjected to diazotization by treating it with \( p \)-TsN\(_3\) to make the corresponding diazoester 2-18 with an overall yield of 70% (Scheme 2-10).\(^{182, 183}\) This diazoacetate product is potentially explosive material and proper care was taken in making the product as well as preserving it for future use.

Scheme 2-10. Synthesis of diazoester 2-19.

The next step was the synthesis of the polymer containing the diazo functional group using ROMP methodology (Scheme 2-11). However, the reaction was unsuccessful employed under several reaction conditions due to the formation of insoluble polymer of the diazoester of norbornene.

Scheme 2-11. Attempt to make polymer by ROMP.
The reason behind the formation of the insoluble polymer is the possible cross-linking reaction was the diazoketone likely reacted faster than the ROMP with the catalyst. Also there could be a possibility that the release of nitrogen can cause the formation of new metal-alkyledene with the ruthenium catalyst causing a complicated ring opening metathesis reaction. Similar kind of cyclization reaction was observed by Padwa for a series of α-diazo ketones in presence of rhodium catalyst. We checked whether the norbornene with ketoester pendent functional group (compound 2-17) is capable of undergoing polymerization or not (Scheme 2-12). The reaction took place successfully giving the corresponding ROMP product. In our next step we tried to make copolymer using different ratio of norbornene and norbornene diazoester without any success (Scheme 2-13). We have also successfully polymerized the keto hexanoate of norbornene using Grubbs’ first generation catalyst (Scheme 2-14).

Scheme 2-12. ROMP of the ketoester of norbornene.

Scheme 2-13. Unsuccessful attempt to make co-polymer using ROMP.
2.3 Conclusion

We successfully synthesized the monomer 2-19 for the synthesis of the polymer 2-20. However, polymerization of 2-19 was not successful as the resultant polymerization using ROMP generated an insoluble cross-linked polymer. We have synthesized the polymer of the norbornene ketoesters, both the compound 2-17 and the compound 2-24. We have now observed the diazoketone group is not compatible with the Grubbs’ catalyst and metathesis. Compound 2-19 will need to be modified. So we proposed the polymerization of the compound 2-17 followed by the incorporation if the diazoo functional group into the polymer (Scheme 2-15 and 2-16). This approach will be studied later.

Scheme 2-16. Diazotization of the co-polymer 2-27.
CHAPTER 3
METATHESIS OF CARBOHYDRATES

3.1 Introduction

In the current era of proteomics, genomics, and glycomics, there is an exponential increase in potential therapeutic targets, which in turn increases the demand to access novel and diverse chemical libraries.\textsuperscript{130} Molecular diversity\textsuperscript{131,132} is based on the “similar property principle”\textsuperscript{133}, which suggests that structurally similar molecules should have similar physiological and biological properties. One way to interpret the molecular diversity is to split it into the functional and structural parts, and then reduce the structural part into the rigid portion of the scaffold. For example, some libraries can be described in terms of (a) functional diversity, (b) structural diversity, (c) type of side chains and/or substituents, or (d) relative orientation of the side chains.\textsuperscript{134,135} Such orientations are defined by the carbon-carbon (C\textsubscript{\alpha}-C\textsubscript{\beta}) bonds linking the side chain to the backbone. A variety of scaffolds have been examined. These scaffolds are basically controlled by the orientation of the functional group and have lower impact on the biological properties of the compound.\textsuperscript{130}

Monosaccharide-based scaffolds that contain several chiral centers were targeted in this work. In principle we can incorporate various alkoxy substituents at each position and not alter the chirality at that center. Sugar scaffolds provide an unparalleled opportunity to generate libraries of high functional and structural diversity. For example, three different pharmacophore groups in glucose generates up to 60 unique products of similar molecular properties but with different orientations of the pharmacophore groups (Scheme 3-1).\textsuperscript{130}
Scheme 3-1. Illustration of the structural diversity in pyranose scaffolds.\textsuperscript{130}

A great deal of synthesis in carbohydrate chemistry is increasingly directed towards the synthesis of artificial glycoconjugates containing the sugars and/or naturally occurring compounds instead of the natural compounds itself.\textsuperscript{117, 118} The artificial carbohydrate compounds can be synthesized to exhibit parallel or even improved biological interactions. Many biological interactions require two or more carbohydrate moieties.\textsuperscript{118} Many combinatorial approaches involving carbohydrates have been investigated. For example the structural diversity of carbohydrates has been coupled with the Ugi four component condensation reactions in both solid and solution phase.\textsuperscript{130, 160} There are no DCL libraries that use solid phase synthesis. In spite of this drawback solid phase organic synthesis is still an attractive and powerful tool for the development of compound libraries. Little is known about static libraries using sugars. Sofia et al.\textsuperscript{136} demonstrated this by generating a large library of disaccharide-based moenomycin mimetics and identified several compounds which displayed high activity against Gram-positive bacteria. Orthogonally protected scaffolds of D-glucose\textsuperscript{137} and D-galactose\textsuperscript{138} have been used by Kunz’s group to exploit the concept of regioselective introduction of a variety of substituents...
using solid support chemistry. However, none are used to make dynamic combinatorial libraries and none use metathesis.

It is therefore clear that sugars possess a great deal of potential as medical compounds. However, the application of combinatorial chemistry to the carbohydrate class of biomolecules has arrived “late to the party” with only recent consideration of these compounds as potential therapeutic agents.\textsuperscript{121-123} Carbohydrates are biological information molecules with the possibility of dense functionalization and stereochemistry, thereby potentially could lead to excellent libraries.\textsuperscript{124} Only a few example of DCLs containing carbohydrates are available and none of them involves a metathesis method.\textsuperscript{57, 117-118, 125-126, 162} A few classes of biomolecules have been used with DCLs, including lectins, enzymes, polynucleotides, etc., and libraries have been constructed using a variety of elements. Most of these are associated with non-natural cores and connectors. Efforts are now being made to develop strategies that can join the carbohydrates through this synthetic linkages.\textsuperscript{118, 127} Several chemical reactions including the aldol condensation,\textsuperscript{128} and free-radical couplings\textsuperscript{129, 162} are used to synthesize these connectors. Such linkages are more resistant towards acids and enzymes.

The concept of employing homodimeric compounds\textsuperscript{139} to increase the ligand-binding affinity\textsuperscript{140} and ultimately shed light on enzymatic and cellular processes has generated considerable interest in the drug discovery arena.\textsuperscript{141, 142} Such homodimeric compounds prepared by metathesis are discussed below. The use of naturally occurring compounds like peptides,\textsuperscript{143} steroids,\textsuperscript{144} and carbohydrates\textsuperscript{145} as scaffolds in combinatorial synthesis has received considerable attention. In spite of their good qualities, carbohydrate molecules have an unfortunate drawback of being water soluble.
Olefin metathesis has emerged as a versatile technology for the synthesis of combinatorial libraries in respect to scaffold creation and embellishment.\textsuperscript{146} The advantages of olefin metathesis over the other transition-metal-catalyzed reactions can be seen in catalyst efficiency, accessibility and functional group compatibility.\textsuperscript{116} Cross-metathesis also opens the door to DCLs. In spite of having advantages like unique properties, high reactivity, stability to air and remarkable functional group tolerance, ruthenium carbene catalysts (Grubbs’ first and second generation catalyst) have scarcely been used in carbohydrate chemistry.\textsuperscript{148} The example of carbohydrate homodimerization was reported by Descotes \textit{et.al.}\textsuperscript{149} in his sugar syntheses using a tungsten aryloxo complex such as 3-1 (Figure 3-1).

\begin{化学式}
\begin{center}
\includegraphics[width=0.5\textwidth]{3-1.png}
\end{center}
\end{化学式}

Figure 3-1. Tungsten aryloxo complex used by Descotes.\textsuperscript{150}

However, such tungsten-catalyzed alkenyl glycoside homodimerizations were unsuccessful with \textit{O}-allyl glycosides as well as benzyl-protected sugar derivatives. Roy and coworkers first prepared a range of “homodimers” starting from peracetylated or perbenzylated \textit{O}- and \textit{C}-allyl as well as \textit{O}-pentenyl galactopyranosides using ruthenium benzylidene complex 1-3 (Scheme 3-2).\textsuperscript{150} Table 3-1 shows a series of \textit{O}- and \textit{C}-allyl and \textit{O}-pentenyl (entry 3-6) galactopyranosides using ruthenium catalyst 1-3.\textsuperscript{150} Such carbohydrate dimers represent appealing tools to quickly titrate distances between carbohydrate binding sites in polyvalent recognition. Moreover, they can represent potent noncovalent cross-linking reagents.\textsuperscript{163}
The examples above demonstrate the importance of ruthenium catalyzed cross-metathesis reaction in carbohydrate chemistry. As part of the continuing interest in the application of cross-metathesis in carbohydrates we envisioned ring closing metathesis (RCM) as a means to generate the homodimer 3-19 (Scheme 3-3). We envisioned the self-metathesis products possessing several anchoring groups where pharmacophoric groups can be attached. Also some carbohydrates can have two hydroxyl groups (primary, and secondary hydroxyl groups), which can be protected in different ways. Such carbohydrates can also be subjected to different olefin metathesis reactions.
Table 3-1. Olefin self-metathesis of alkenyl \( O\) - and \( C\)-glycopyranosides.\textsuperscript{150}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R</th>
<th>Product (E/Z)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-2</td>
<td>( OAc, OAc )</td>
<td>3-3 (5/1)</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>3-4</td>
<td>( OAc, OAc )</td>
<td>3-5 (4/1)</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>3-6</td>
<td>( OAc, OAc )</td>
<td>3-10 (5/1)</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>3-7</td>
<td>( OAc, OAc )</td>
<td>3-11 (4/1)</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>3-8</td>
<td>( OAc, OAc )</td>
<td>3-12 (2/1)</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>3-9</td>
<td>( OAc, OAc )</td>
<td>3-13 (1/1)</td>
<td>75</td>
</tr>
<tr>
<td>7</td>
<td>3-12</td>
<td>( OBn, OBn )</td>
<td>3-15 (3/1)</td>
<td>76</td>
</tr>
</tbody>
</table>

\[ R \rightarrow R \quad \text{10 mol\%}, \ 1-3 \quad \text{CH}_2\text{Cl}_2, \text{reflux, 6h} \]
Scheme 3-4. Protecting group and hydroxyl reactivity strategy.

3.2 Results and Discussion

3.2.1 Metathesis of the monoester of carbohydrates

In order to study the viability of olefin metathesis for DCC, we first required synthesis of the various monomers and ester derivatives. It was then necessary to react the monomers with Grubbs’ second generation catalyst 1-4 to study the selectivity and reactivity of olefin metathesis. A series of 5- and 6- member carbohydrate derivatives (furanosides and pyranosides) were synthesized by coupling acetone, benzyl, and TBDMS protected carbohydrates with allyl chloroformate and 4-pentenoic acid using DIC, DMAP, or/and HOBT. The starting material was typically consumed within the next 3 h as indicated by TLC. Purification by column
chromatography gave the 4-pentenoic esters of the 5- and 6-member carbohydrates in moderate
to high yield (Table 3-2) with the exception of 3-41 (26% only).

Table 3-2. Yields, and optical properties of carbohydrate derivatives.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Carbohydrates</th>
<th>Protecting group</th>
<th>Product</th>
<th>Yield (%)</th>
<th>$[\alpha]_{D}^{25}$ (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>D-Mannose</td>
<td>Acetone protected</td>
<td>3-26</td>
<td>71</td>
<td>+59.82 (C=1.57, MeOH)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3-29</td>
<td>76</td>
<td>+49.55 (C=1.91, MeOH)</td>
</tr>
<tr>
<td>2</td>
<td>D-Glucose</td>
<td>Acetone protected</td>
<td>3-32</td>
<td>71</td>
<td>-27.50 (C=1.19, MeOH)</td>
</tr>
<tr>
<td>3</td>
<td>D-Galactose</td>
<td>Acetone protected</td>
<td>3-36</td>
<td>87</td>
<td>-48.22 (C=2.71, MeOH)</td>
</tr>
<tr>
<td>4</td>
<td>D-Ribose</td>
<td>Acetone protected</td>
<td>3-41</td>
<td>26</td>
<td>-60.34 (C=1.46, MeOH)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TMS protected</td>
<td>3-45</td>
<td>89</td>
<td>-51.16 (C=2.05, MeOH)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Benzyl protected</td>
<td>3-46</td>
<td>81</td>
<td>-71.55 (C=1.57, CH2Cl2)</td>
</tr>
<tr>
<td>5</td>
<td>D-Isomannide</td>
<td>Benzyl protected</td>
<td>3-52</td>
<td>84</td>
<td>+168.51 (C=1.66, CH2Cl2)</td>
</tr>
<tr>
<td>6</td>
<td>D-Isosorbide</td>
<td>Benzyl protected</td>
<td>3-56</td>
<td>71</td>
<td>+74.19 (C=1.87, CH2Cl2)</td>
</tr>
</tbody>
</table>

The resultant 4-pentenoate monomers of the protected carbohydrates were then subjected
to olefin metathesis in presence of Grubbs’ second generation catalyst in anhydrous CH2Cl2 or
CHCl3 under reflux condition. Table 3-3 shows the olefin metathesis of the monomers of
different carbohydrates.

We started with commercially available D-mannose (3-24). The first step was the
protection of four out of five hydroxyl groups available in the furanose form of the sugar. The
protection of the D-mannofuranose (3-24) (mannose) was performed in presence of acetone and
2, 2-dimethoxy propane (2, 2 DMP). Catalytic amount of p-toluenesulfonic acid (p-TsOH) was
added to facilitate the reaction, resulting in the formation of 71% of the diacetone D-mannose (3-
25). This protected mannose was then treated with allylchloroformate in presence of DMAP to
obtain the corresponding carbonate 3-26 with an overall yield of 67%. Scheme 3-5 shows the
Table 3-3. Yields, and optical properties of the metathesis products.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Carbohydrates</th>
<th>Protecting group</th>
<th>Product</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>[α]25 ( \text{D} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>D-Mannose</td>
<td>Acetone protected</td>
<td>3-27</td>
<td>61</td>
<td>Oil</td>
<td>+15.6 ( \text{C}=1.04, \text{CH}_2\text{Cl}_2 )</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3-30</td>
<td>72</td>
<td>88.5-90.0</td>
<td>+28.88 ( \text{C}=1.04, \text{CH}_2\text{Cl}_2 )</td>
</tr>
<tr>
<td>2</td>
<td>D-Glucose</td>
<td>Acetone protected</td>
<td>3-33</td>
<td>83</td>
<td>Oil</td>
<td>0° ( \text{C}=1.28, \text{CH}_2\text{Cl}_2 )</td>
</tr>
<tr>
<td>3</td>
<td>D-Galactose</td>
<td>Acetone protected</td>
<td>3-37</td>
<td>74</td>
<td>86.0-87.0</td>
<td>-1.35° ( \text{C}=1.11, \text{CH}_2\text{Cl}_2 )</td>
</tr>
<tr>
<td>4</td>
<td>D-Ribose</td>
<td>Acetone protected</td>
<td>3-44</td>
<td>81</td>
<td>Oil</td>
<td>-6.60° ( \text{C}=1.51, \text{CH}_2\text{Cl}_2 )</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TBDMS protected</td>
<td>3-48</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Benzyl protected</td>
<td>3-49</td>
<td>81</td>
<td>Oil</td>
<td>+0.13° ( \text{C}=1.68, \text{CH}_2\text{Cl}_2 )</td>
</tr>
<tr>
<td>5</td>
<td>D-Isomannide</td>
<td>Benzyl protected</td>
<td>3-53</td>
<td>82</td>
<td>Oil</td>
<td>+0.23° ( \text{C}=1.87, \text{CH}_2\text{Cl}_2 )</td>
</tr>
<tr>
<td>6</td>
<td>D-Isosorbide</td>
<td>Benzyl protected</td>
<td>3-57</td>
<td>80</td>
<td>Oil</td>
<td>-</td>
</tr>
</tbody>
</table>

Scheme 3-5. Synthesis of the carbonate of diacetone (D)-mannose.
The metathesis of the carbonate of (D)-mannose was carried out in presence of Grubbs’ first and second generation catalysts. Prior to the addition of Grubbs’ catalyst (both first and second generation), butylated hydroxytoluene (BHT) was added to prevent any possible atom transfer radical polymerization (ATRP). All reactions were refluxed either in anhydrous chloroform or in anhydrous methylene chloride overnight. The reaction was quenched with EVE. EVE reacts with the catalyst (both first and second generation) in an irreversible manner, making it inactive to other kind of olefins.\textsuperscript{152} Metathesis of compound 3-26 resulted in the formation of metathesis product 3-27 with an overall yield of 61%. Use of methylene chloride as the solvent helps to maintain the reactivity of Grubbs’ catalyst during the reflux. The reaction was expected to result in the formation of both \(E\) and \(Z\) isomer, with the \(E\) isomer having a well-known preference over the \(Z\) due to steric hindrance. Once the metathesis product was formed, it was subjected to hydrogenation via Pd on activated carbon (10\% Pd) under \(H_2\) atmosphere to give compound 3-28 in good yield (90\%). Scheme 3-6 shows the formation of the saturated metathesis product 3-28.

To increase the yield of the metathesis product, we had increased the chain by one methylene and removed the carbonate. Instead of allyl chloroformate, the diacetone (D)-mannose 3-25 was treated with 4-pentenoic acid in the presence of DIC and DMAP to give the ester 3-29 with a yield of 76\%. The ester of mannose was then subjected to metathesis with Grubbs’ first generation catalyst (10 \text{ mol\%}) in anhydrous dichloromethane (0.50 M) resulting in the formation of the self-metathesis product 3-30 with a yield of 72\%. A series of self metathesis of (D) mannose carbonate were done and everytime the yield was around 74\% (varying from 72\% - 76\%).
Scheme 3-6. Metathesis followed by hydrogenation to obtain saturated homodimer.

Thus, with the use of new terminal alkene with longer chain length, there is an improvement in the overall metathesis yield. Scheme 3-7 shows the metathesis reaction involving the longer terminal alkene chain. Only a single trans isomer was produced.
The next sugar used for the metathesis was glucose. The diacetone D-glucofuranose (3-31) is commercially available. It was subjected to esterification with 4-pentenoic acid in presence of DIC and catalytic amount of DMAP. The yield was 70%. The metathesis of ester 3-32 under identical conditions to those used for the mannose derivative 3-29 resulted in the formation of compound 3-33, with a yield of 83%. Scheme 3-8 shows the overall reactions involved in the metathesis of glucose.

Both the sugars, (D)-mannose and (D)-glucose are chiral in nature and the esterification may lead to possible isomerization of the product. In order to find out whether actual racemization took place during the esterification or not, we did the esterification of both (D)-mannose and (D)-glucose in presence and absence of hydroxybenzotriazole (HOBT). The C₁ of the ester compound is particularly labile, especially in the presence of acids or HOBT. Since no change in the NMR as well as the optical rotational properties was observed, we were
convinced that C₁ epimerization had not occurred. Table 3-4 shows the optical properties of the ester of sugars in presence and absence of HOBT.

Table 3-4. Comparison of the optical property of the esters of (D)-mannose and (D)-glucose.

<table>
<thead>
<tr>
<th>Type of ester</th>
<th>$[\alpha]^{25}_D$ of the ester without HOBT</th>
<th>$[\alpha]^{25}_D$ of the ester with HOBT</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Mannose Ester" /></td>
<td>$+49.55^\circ$</td>
<td>$+49.25^\circ$</td>
</tr>
<tr>
<td><img src="image2" alt="Glucose Ester" /></td>
<td>$-27.50^\circ$</td>
<td>$-27.03^\circ$</td>
</tr>
</tbody>
</table>

Scheme 3-8. Metathesis of the ester of diacetone (D)-glucose.
The NMR of the metathesis of D-mannose indicates that the product is mostly \textit{trans} isomer. However, in the case of D-glucose, the metathesis product contains both \textit{cis} and \textit{trans} isomers. Considering the steric factor, the \textit{trans} isomer is expected to predominate over the \textit{cis} isomer. However, a combination of \textsuperscript{1}H NMR and 2-D NMR of the product give the ratio of \textit{cis} and \textit{trans} isomers.

The third sugar we used was D-galactose. Like mannose, the commercially available D-galactose was first protected by treating it with acetone in the presence of a catalytic amount of anhydrous copper sulfate to give compound \textbf{3-34} with an overall yield of 43\%.\textsuperscript{153} However, the protected D-galactopyranose is also available commercially. This protected galactose was then subjected to esterification with 4-pentenoic acid (\textbf{3-18}) to give the ester with a yield of 87\%. It was subjected to metathesis with 10 mol\% of Grubbs’ first generation catalyst, using anhydrous methylene chloride (0.50 M), resulting in the formation of 74\% of the metathesis product \textbf{3-37}. In fact, we noticed some double bond isomerization with the galactose system when the ester of the D-galactopyranose was subjected to the metathesis with Grubbs’ second generation catalyst using chloroform during reflux. We used Grubbs’ second generation catalyst and the chloroform system for the metathesis of the ester of D-mannose and the D-glucose also without any evidence of double bond isomerization. Again, a single geometric isomer of \textbf{3-37}, was observed and it was \textit{trans}. As a result we have shifted to the Grubbs’ first generation catalyst and dichloromethane system for all metathesis reaction conditions applied in later part of the project. Scheme 3-9 shows the formation of the metathesis product of (D)-galactose \textbf{3-37}. 
Scheme 3-9. Metathesis of the protected (D)-galactose.

The fourth sugar we used was D-ribose. Unlike the first three sugars, D-mannose, D-glucose, and D-galactose, protection of the D-ribose resulted in the formation of compound 3-39, which has two hydroxyl groups. One of the hydroxyl groups is 1° (primary), while the other hydroxyl group is 2° (secondary). From the steric hindrance point of view, a primary alcohol is expected to be more reactive than a secondary one. However, when the monoacetone D-ribose was subjected to monoesterification with 4-pentenoic acid, using the same conditions, the esterification took place not only at the desired 1° alcohol to give 3-41, but also at the other available position 3-42, 3-43, resulting into an overall poor yield (26%) of the desired sugar derivative 3-41. We changed the concentration of the reaction medium using 0.50 M, 1.0 M, and 0.10 M of dichloromethane without any significant improvement in the percentage yield of the desired product 3-41.
Scheme 3-10. Monoesterification of the monoacetone (D)-ribose.

Metathesis of compound 3-41 using standard reaction conditions resulted in the formation of compound 3-47 with an overall yield of 81% (Scheme 3-11).

Scheme 3-11. Metathesis of compound 3-41.

Even the less reactive alcohol site (2⁰ hydroxyl site) of the monoacetone D-ribose took part in esterification (compound 3-42), yet the overall yield was low (no significant amount was recovered after column chromatography each time). So, our next attempt was to protect the most reactive alcohol site, so that the esterification of the corresponding ribose would lead to the incorporation of the ester group exclusively in the less reactive site. We used both tert-butyl
dimethylsilyl chloride, (TBDMSCl)\textsuperscript{154} and benzyl chloride for the protection of the primary hydroxyl site of monoacetone (D)-ribose. Scheme 3-12 shows the synthesis of TBDMS protected monoacetone (D)-ribose \textit{3-40} (52%), and benzyl protected monoacetone (D)-ribose \textit{3-44} (47%).

![Chemical structure of TBDMS and benzyl protected monoacetone (D)-ribose]

Scheme 3-12. Synthesis of TBDMS and benzyl protected monoacetone (D)-ribose.

Compounds \textit{3-40} and \textit{3-44} were then subjected to the esterification reaction with 4-pentenoic acid, using DIC and catalytic amount of DMAP. Esterification of TBDMS protected monoacetone (D)-ribose resulted in the formation of compound \textit{3-45} with an 89% yield. Esterification of the benzyl protected monoacetone (D)-ribose resulted in the formation of compound \textit{3-46} with an overall yield of 81%. Scheme 3-13 shows the esters of the two di-protected (D)-ribose \textit{3-45} (benzyl protected) and \textit{3-46} (TBDMS protected).

When the ester of TBDMS protected monoacetone (D)-ribose 3-45, was subjected to the metathesis reaction, no significant result was obtained. Our attempt of the metathesis of compound 3-45 did not yield the desired self-metathesis product. The ester of benzyl monoacetone (D)-ribose, 3-46, was then subjected to the metathesis reaction with Grubbs’ first generation catalyst using methylene chloride as the reflux solvent with a concentration of 0.50 M. Scheme 3-15 shows the metathesis of the compound 3-46, which resulted in the formation of the self-metathesis compound 3-49 with an overall yield of 81%.

The last two sugars we used are commercially available (D)-isomannide and (D)-isosorbide, which are diastereoisomers. In the case of (D)-isomannide (3-50), both the hydroxyl groups are cis, whereas for (D)-isosorbide (3-54), they are trans with respect to each other.
Scheme 3-14. Metathesis of the ester of TBDMS protected monoacetone (D)-ribose.

Scheme 3-15. Metathesis of the ester of benzyl protected monoacetone (D)-ribose.

Scheme 3-16 shows the metathesis of the ester of benzyl protected (D)-isomannide, where the first step involved the synthesis mono benzylated (D)-isomannide 3-51 by following the literature procedure. This was then subjected to esterification to get 3-52 (84%) followed by metathesis reaction using Grubbs’ first generation catalyst to get the self-metathesis product 3-53 (82%).
Scheme 3-16. Synthesis of metathesis product of benzylated (D)-isomannide.

However, in case of (D)-isosorbide the two hydroxyl groups are trans to each other. Due to the cis-fused bicyclic system, one hydroxyl group is in the exo position while the other one is in the endo position. From a steric point of view, the hydroxyl group in the exo position is expected to be more reactive than the hydroxyl group in the endo position. Benzylation of the (D)-isosorbide with KOH, water, and benzyl bromide resulted in the formation of mostly exo protected (D)-isosorbide 3-55, following the literature procedure. It was then subjected to the esterification reaction to give the product 3-56, followed by the self-metathesis reaction in presence of Grubbs’ first generation catalyst to give the metathesis product 3-57 with an yield of 80%. Scheme 3-17 shows the metathesis of the exo-benzylated (D)-isosorbide.
Scheme 3-17. Metathesis of the benzylated (D)-isosorbide in the *exo* position.

Table 3-3 shows the all the homodimers made from esters of different *o*-oligosaccharides

### 3.2.2 Metathesis of Tri-esters of Phloroglucinol

We diversify the concept of making library of metathesis products of carbohydrates. In this approach we tried the cross metathesis reaction between the ester of phloroglucinol with the ester of different carbohydrates to generate a second library (Scheme 3-18).

The first step involves the synthesis of the tri-ester of phloroglucinol 3-62 using the usual esterification reaction conditions between phloroglucinol 3-61 and 4-pentenoic acid 3-18 (Scheme 3-19). The second step involves the cross-metathesis reaction between the ester of diacetone (D)-glucose and the ester of phloroglucinol using Grubbs’ first-generation catalyst (Scheme 3-20). The reaction gives a whole bunch of possible cross-metathesis as well as self-metathesis products as observed from the TLC of the crude product. However, the major product
isolated from the crude mixture was the compound 3-63 with a yield of 58%. Using a preparative column chromatography, it is possible to separate each fraction as well as identify them by NMR.

Scheme 3-18. Schematic representation of the cross-metathesis between carbohydrate and phloroglucinol esters.

3.4 Conclusion

Our main objective in this project was to examine the olefin self-metathesis reactivity and selectivity of the esters of pentose and fructose. The extension of carbon skeletons by the construction of carbon-carbon bonds represents one of the most important areas in synthetic organic chemistry. We applied this self-metathesis technique on different carbohydrates in their 5-membered as well as 6-membered ring formations. We synthesized the olefin metathesis products of functionalized carbohydrate derivatives in good yields with the Grubbs’ first
generation catalyst used mostly. It is considered that having the olefin moiety further from the ester functional groups increased the yields of the homodimer products. The stereochemistry of the homodimers was found to be predominantly trans. The flexibility of our route is illustrated by the different types of O-glycoside that have been prepared from the commercially available monosaccharides (Table 3-2). Our metathesis-based approach to O-saccharide formation allows for structural diversity in the olefin.
CHAPTER 4
ACYCLIC DIENE METATHESIS REACTIONS OF CARBOHYDRATES

4.1 Introduction

Hydrogels have increased popularity as scaffolds for tissue engineering due to their high water content, good biocompatibility, and consistency similar to soft tissue. Natural and synthetic hydrogels retain water in a three-dimensional network of polymer chains. Examples of such degradable polymers include series of polyesters such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and their copolymers. But these have their own problems like early loss of mechanical properties, generation of acidic products during degradation creating harsh environments that are not compatible with cells and tissues.

Carbohydrates are mostly present in nature in the form of glycoconjugates (glycoproteins and glycolipids). Their role is unambiguously important but remains often vague. If the understanding of the biological role of carbohydrates is to approach that of nucleic acids and proteins, access to well-defined pure oligosaccharide structures will have to be improved. While the sequencing of samples of oligonucleotides and proteins is routine and has been automated, carbohydrate sequencing has been particularly challenging. Glycopolymers, synthetic sugar-containing macromolecules, are attracting ever-increasing interest from the chemistry community due to their role as biomimetic analogues and their potential for commercial applications. Recent developments in polymerization techniques have enabled the synthesis of glycopolymers featuring a wide range of controlled architectures and functionalities.

Condensation polymers and the corresponding monomers and macrocycles can generally be interconverted by a series of closely related reactions, where the nature of the major reaction product(s) depends greatly on the concentration of reactants. Acyclic Diene Metathesis chemistry is used to produce polymers of unique and fixed architecture utilizing diene
monomers. ADMET is a condensation polymerization reaction that connects molecules through terminal alkenes with the release of small molecules ethylene. The release of this gaseous molecule is the driving force for this reaction and allows high molecular weight to be reached with a variety of monomers. Essentially this is an example of self-metathesis with a diene.

The use of monosaccharides in hydrogels for soft tissues has not been investigated. This is somewhat unusual because sugars are nontoxic food to most animal forms and highly hydroxylated. Absorption with time as new tissue grows into the biomaterial will not be problematic in this case. Traditionally, carbohydrate substituted polymers have been synthesized by polymerization of acrylamide derivatives. The naturally occurring carbohydrates are chiral molecules. The racemizations of chiral centers are of great concern when polymerization method requires the use of basic or highly thermal conditions. ADMET is a thermally and chemically neutral polymerization method. These conditions make ADMET an ideal candidate for studying polymers that are sensitive to harsher polymerization methods. These polymers (4-14, 4-15, 4-16, and 4-17) made by ADMET chemistry therefore represent an opportunity to develop hydrogel from them.

In connection with our interest in the potential applications of such reactions, in particular the preparation of combinatorial libraries of either macrocycles and/or polymers, we decided to polymerize a series of carbohydrate based pentenoic ester with pendent terminal double bond by ADMET polymerization method using Grubbs’ first generation catalyst. Scheme 4-1 shows the basic idea behind the ADMET of functionalized carbohydrate derivatives.
Another interesting feature of ADMET chemistry is the regiochemistry of the polymer, i.e., the structural arrangements of the monomer units. When ethylene is polymerized into linear chains, only one arrangement of atoms is possible. However, the incorporation of substituents into the olefin monomer introduces the opportunity for some structural variability. For example, when propylene is polymerized, the monomers can arrange themselves along the chain in three different ways. If we call the CH₂ end of the propylene the "head" and the CH(CH₃) end the "tail", then a head-to-tail (HT) polymerization would lead to a polymer chain with a methyl group (CH₃) located on every other carbon (Figure 4-1). On the other hand, if the polymerization occurred in a head-to-head (HH), tail-to-tail (TT) fashion, methyl groups would be located on adjacent carbons in pairs.
A third possibility involves random orientation of monomer units along the polymer chain. These three different structural forms of polypropylene would be expected to have different physical properties. Generally, the head-to-tail polymer is produced using heterogeneous Ziegler-Natta or homogeneous cyclopentadienyl-zirconium catalysts. Ring closing metathesis polymerization of the diester of (D)-ribose results in the formation of a cyclic structure with a possibility of the formation of the HH/TT or HT structure pattern (Figure 4-3). If the H and T monomer units are equally reactive the repeat units would be linked statistically. In that case the expected proportions of HT: HH: TT linkages are 50:25:25. On the other if the head groups are much more reactive than the tail group, then HH link would be formed first, followed later by TT linkages and polymer would contain only HH and TT linkages. \(^{178}\)

Scheme 4-2 shows an example how the carbohydrate D-mannitol \(\text{4-4}\) might be incorporated into the backbone of a metathesis polymer. Instead of placing the sugar into the polymer lengthwise where it is a major structural unit, this time the polymer is placed across the carbohydrate (Figure 4-2).
Scheme 4-2. Diacetone D-mannitol as a hydrogel precursor.

Figure 4-2. Hydrogels with carbohydrates lengthwise, crosswise or rings.
Adding two alkenes as ester linkages for the construction of 4-9 serves two purposes. First, it allows for the ADMET reaction to occur by providing two alkenes to build on. Secondly, the esters provide a point for natural degradation in time by esterases in the cells.

**4.2 Results and Discussion**

In order to study the viability of olefin metathesis for ADMET, we first required to synthesize a number of monomers—ester derivatives with pendent diene. It was then necessary to allow the monomers to undergo metathesis reaction in presence of Grubbs’ first generation catalyst 1-3. A series of carbohydrate derivatives were synthesized by coupling acetone protected carbohydrates with 4-pentenoic acid using DIC, DMAP. The starting material was typically consumed within 3 h as indicated by TLC. Purification by column chromatography gave the 4-pentenoic esters of the protected carbohydrates in moderate to high yield (Table 4-1).

<table>
<thead>
<tr>
<th>Enter</th>
<th>Carbohydrate</th>
<th>Product</th>
<th>Yield (%)</th>
<th>$[\alpha]_{D}^{25}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>D-Mannitol</td>
<td>4-9</td>
<td>71</td>
<td>$+13.88^\circ$ (C = 2.33, MeOH)</td>
</tr>
<tr>
<td>2</td>
<td>D-Ribose</td>
<td>4-10</td>
<td>72</td>
<td>$-44.25^\circ$ (C = 2.13, MeOH)</td>
</tr>
<tr>
<td>3</td>
<td>D-Isomannide</td>
<td>4-11</td>
<td>65</td>
<td>$+142.68^\circ$ (C = 2.20, CH$_2$Cl$_2$)</td>
</tr>
<tr>
<td>4</td>
<td>D-Isosorbide</td>
<td>4-12</td>
<td>70</td>
<td>$+87.39^\circ$ (C = 2.06, CH$_2$Cl$_2$)</td>
</tr>
</tbody>
</table>

The resultant monomers with two pendent alkene groups were then subjected to ADMET in presence of Grubbs’ first generation catalyst in anhydrous CHCl$_3$ under vacuum condition resulting in the formation of the polymers in high yield. Table 4-2 shows the acyclic diene metathesis polymerization of different carbohydrates monomers.
Table 4-2. ADMET of the carbohydrates.

<table>
<thead>
<tr>
<th>Enter</th>
<th>Carbohydrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>D-Mannitol</td>
<td>4-13</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>D-Ribose</td>
<td>4-15</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>D-Isosorbide</td>
<td>4-16</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>D-Isomannide</td>
<td>4-17</td>
<td>94</td>
</tr>
</tbody>
</table>

Monoacetone protected sugars, used for the preparation of dynamic combinatorial libraries, like (D)-ribose (4-6) (similar to the compound earlier named as (3-38)), (D)-isomannide (4-7) (similar to the compound earlier named as (3-50)), (D)-isosorbide (4-8) (similar to the compound earlier named as (3-54)) have two hydroxyl groups and therefore, can be subjected to diesterification reaction, resulting in the synthesis of dienes. Also we have synthesized the diester of diacetone (D)-mannitol (4-9). All these dienes can be subjected to ADMET chemistry. Depending on the reaction condition available, it is possible to obtain either a ring closing metathesis product or an ADMET product as observed with the diene of monoacetone D-ribose 4-10 (similar to the compound earlier named as 3-39). A high concentration of catalyst (monomer: catalyst, 10:1) can lead to RCM product 4-14, whereas a much lower concentration of catalyst (monomer: catalyst, 100:1) gives rise to the formation of the ADMET polymer 4-15.

The first diene subjected to ADMET was based on the sugar (D)-mannitol (4-4). Scheme 4-3 shows the synthesis of the diester of diacetone D-mannitol 4-9. The first step involves the protection of the (D)-mannitol using the literature procedure126 4-5 with an overall yield of 51%. Compound 4-5 was then been subjected to esterification using the normal esterification reaction conditions to make the compound 4-9 with an overall yield of 70%.
Scheme 4-3. Synthesis of the diester of diacetone (D)-mannitol.

The monoacetone (D)-ribose (4-6) has two hydroxyl groups. Therefore, esterification of the monoacetone D-ribose (4-6) with 4-pentenoic acid (using 2.10 equivalents with respect to the moles of the carbohydrate 4-6) results in the formation of the diester of the monoacetone (D)-ribose 4-10 with an overall yield of 72%. Scheme 4-4 shows the synthesis of the diester of monoacetone (D)-ribose.

Scheme 4-4. Synthesis of the diester of the monoacetone (D)-ribose.

The other two carbohydrates used for ADMET polymerization are (D)-isomannide (4-7) and (D)-isosorbide (4-8). Scheme 4-5 shows the synthetic route for the synthesis of compound
4-11 (65%). Scheme 4-6 shows the synthesis of diester of (D)-isosorbide 4-12 with a yield of 70%.

Scheme 4-5. Synthesis of the diester of monoacetone (D)-isomannide.

Scheme 4-6. Synthesis of the diester of monoacetone (D)-isosorbide.

First ADMET chemistry was performed with diester of (D)-mannitol following the usual ADMET reaction condition (Scheme 4-7). First attempt resulted in the formation of expected polymer product, which was insoluble in almost all common organic solvents. No further characterization of the highly viscous, gluey material could be done. In our second attempt, we carried out the ADMET polymerization in presence of BHT. The product so obtained was soluble in dichloromethane. It appeared to be highly viscous liquid and could not be precipitated, unlike usual ADMET products.
Carbohydrates with two terminal double bonds can undergo either self-metathesis (like the one mentioned earlier in chapter 3) to make a homodimer with linear structure or ADMET polymerization reaction to give a polymer depending upon the reaction conditions employed. However, when the diene of monoacetone (D) ribose \textbf{4-10} was subjected to the metathesis reaction condition using 10 mol\% of Grubbs’ first generation catalyst in anhydrous dichloromethane (0.50 M), a new compound \textbf{4-14} was synthesized. In case of the diester of D-ribose \textbf{4-10}, the $^1$H NMR shows specific peak at $\delta = 5.0$ ppm for the hydrogen at the terminal double bond and a peak at $\delta = 5.8$ ppm due to hydrogen at the internal double bond, whereas for the ADMET product of the diester of monoacetone D-ribose \textbf{4-15} there is no peak either at $\delta = 5.8$ ppm or at $\delta = 5.0$ ppm, instead a new broad multiplet has appeared at $\delta = 6.0-5.0$ ppm. The $^1$H NMR of the compound \textbf{4-14} shows two multiplets at $\delta = 5.52-5.42$ ppm (2H) and at $\delta = 5.38-5.26$ ppm (2H). If the compound \textbf{4-14} is a regular self-metathesis product then we would see the peak for the hydrogens at the terminal carbon of the double bond. The HRMS analysis shows that it is a dimer [calcd 653.2809 against found 653.2783]. The absence of any peak corresponding to the terminal double bond hydrogen suggests that it is a cyclic dimer product (Figure 4-3) and not a polymer or linear dimer.
Figure 4-3. Schematic representation of the HH or HT cyclic dimer of diacetone (D)-ribose.

Such a variation in the possible structure of the cyclic dimer 4-14(HH)/4-14(HT) is due to the presence of two different hydroxyl groups as the two ester functional groups are not equivalent. In the Figure 4-3 the pentenoate end attached to the 1\textsuperscript{st} hydroxyl end is assumed to be the head whereas the pentenoate end attached to the 2\textsuperscript{nd} hydroxyl end is assumed to be the tail. Further analysis of the product 4-14(HH)/4-14(HT) by 2-D NMR, and crystallography will help to determine the actual structure of the compound.

The next carbohydrate used for ADMET is (D)-ribose. It is the concentration of the catalyst used for the reaction which determines whether the reaction would be ADMET type or
RCM. ADMET polymerization requires much less amount of ruthenium catalyst compared to that for the RCM reaction. The usual ratio of monomer to catalyst ratio for ADMET is 100:1 or even less than that, whereas the ratio for the RCM reaction is 10:1. Scheme 4-8 shows the synthesis of the ADMET polymer for the carbohydrate (D)-ribose. Scheme 4-9, and 4-10 show the synthesis of the ADMET of carbohydrates (D)-isomannide and (D)-isosorbide respectively.

Scheme 4-8. ADMET of the diester of (D)-ribose.

Scheme 4-9. ADMET of the diester of (D)-isomannide.

Scheme 4-10. ADMET of the diester of (D)-isosorbide.
Also for the carbohydrate (D)-isosorbide, the two hydroxyl groups are \textit{trans} to each other. Even though the hydroxyl groups for (D)-isosorbide are not of $1^0/2^0$ type, but their reactivity are different. One of the hydroxyl groups occupies the \textit{exo} orientation while the other occupies the \textit{endo} orientation. From the steric point of view hydroxyl group at \textit{exo} orientation is more reactive than the hydroxyl group at the \textit{endo} orientation. Hence the polymer 4-17 formed by ADMET polymerization method will be of different type compared to the polymer of (D)-mannitol or (D)-isomannide. Thus we have a possibility of having a mixture of HH/TT as well as HT polymer linkages in both polymers 4-15 and 4-17.

The molecular weight of the polymers ($M_n$) was determined by GPC with respect to polystyrene as the standard. Table 4-3 shows the $M_n$ of the polymers 4-13, 4-15, 4-16, and 4-17.

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>ADMET</th>
<th>Mn</th>
<th>DPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-13</td>
<td>5000</td>
<td>1.11</td>
</tr>
<tr>
<td>2</td>
<td>4-15</td>
<td>4500</td>
<td>1.10</td>
</tr>
<tr>
<td>3</td>
<td>4-16</td>
<td>7000</td>
<td>1.14</td>
</tr>
<tr>
<td>4</td>
<td>4-17</td>
<td>6250</td>
<td>1.13</td>
</tr>
</tbody>
</table>

4.3 Conclusion

We have successfully developed ADMET chemistry for carbohydrates for the first time. This opens up a new field of chemistry. Of the four carbohydrates we used, monoacetone (D)-ribose has two different reactive sites, primary and secondary hydroxyl groups. Similarly the hydroxyl groups of (D) isosorbide are different in reactivity based on the steric factor. So we expect to get polymers with a mixture of head-to-head or tail-to-tail and head-to-tail linkages.
CHAPTER 5
EXPERIMENTAL METHODS

5.1 General Methods and Instrumentation

All moisture and air-sensitive reactions were performed under argon atmosphere in flame-dried glassware. Solvents were distilled under N₂ from appropriate drying agents according to the established procedures. Rₐ values were obtained by using thin-layer chromatography. Analytical thin-layer chromatography (TLC) was performed using Kiesel gel 20 F-254 pre-coated 0.25 mm silica gel plates. UV light, phosphomolybdic acid in ethanol, anisaldehyde in ethanol, permanganate, and vanillin were used as indicators for spot identification in TLC. Proton nuclear magnetic resonance (¹H NMR) spectra were recorded on a Gemini, VXR, and Mercury 300MHz spectrometer. Carbon nuclear magnetic resonance (¹³C) spectra were recorded at 75 MHz on the same spectrometers. Some of the chemical shifts were reported in ppm downfield with respect to trimethylsilane (TMS) as an internal standard, while in other cases the chemical shift of the solvent (for example, the chemical shift of solvent CDCl₃ is 7.27 ppm) was used for standardization. Infrared spectra were obtained from KBr-pellets using a Bruker Vector 22 IR and are reported in wavelength (cm⁻¹). Unless reported all yields refer to the isolated materials, determined by TLC and NMR. High-resolution mass spectroscopy (HRMS) was performed by the Mass Spectroscopy Laboratory at the University of Florida. Optical rotations were recorded on a Perkin-Elmer 241 digital polarimeter (10⁻¹ deg cm² g⁻¹). Melting points were obtained on a Thomas-Hoover capillary melting point apparatus.
5.2 Experimental Procedure and Data

Norbornenemethanol 2-13

\[
\text{\begin{center}
\includegraphics[width=1cm]{norbornenemethanol.png}
\end{center}}
\)

A solution of norbornene-1-carboxaldehyde (11.67 gm, 96 mmol) in MeOH (58 mL) was added dropwise over 1 h to a suspension of NaBH₄ (1.74 gm, 46 mmol) in 2N NaOH (20 mL) at 0°C under Ar. The reaction mixture was stirred at room temperature for further 3 h, monitored by TLC. The pH of the reaction medium was brought back to 6 at 0°C with 30% H₂SO₄ (30 mL). The methanol was evaporated, and the resulting residue was extracted with diethyl ether (3 x 70 mL). The combined organic layers were washed with saturated NaHCO₃ and brine (3 x 100 mL with each), dried over anhydrous MgSO₄, and concentrated under reduce pressure, affording 2-13 as a white liquid (9.50 g, 80%).

2-13: Rₓ = 0.71 (CH₂Cl₂/MeOH, 9:1); IR (film) \(\nu_{\text{max}}\) 3333, 2967, 1682, 1570, 1337, 1252, 1146 cm\(^{-1}\); \(^1\)H NMR (300MHz, CDCl₃) \(\delta\) 6.20–5.90 (m, 2H, CH=CH), 3.70–3.20 (m, 2H, CH₂OH), 2.90–2.70 (m, 2H, C=CCH, C=CCH), 2.40–2.20 (m, 1H), 2.10–1.90 (s, 1H, OH), 1.85–1.70 (m, 1H), 1.50–1.40 (m, 1H), 1.40–1.10 (m, 2H); \(^{13}\)C NMR \(\delta\) 137.3, 136.8, 136.6, 132.3, 64.2, 66.2, 49.5, 44.9, 43.6, 43.3, 42.2, 41.74, 41.6, 41.6, 29.6, 28.9. This compound is commercially available from Aldrich.

Ester carbamate of norbornene 2-14

\[
\text{\begin{center}
\includegraphics[width=1cm]{ester_carbamate.png}
\end{center}}
\)

A solution of N-tertiary-butoxycarbonyl-glycine (N-tBoc) (1.34 g, 0.01 mol) in anhydrous CH₂Cl₂ (3 mL) was added to a solution of the norbornenemethanol 2-13 (1 g, 8 mmol), catalytic amount of DMAP, and DIC (1.10 g, 9 mmol) in anhydrous CH₂Cl₂ (13 mL) over a period of 20 min at 0°C under Ar. The reaction mixture was then stirred for an additional 3 h at room
temperature monitored by TLC. The precipitate was filtered and the organic phase was washed with saturated NaHCO₃ and brine (3 x 30 mL each), dried over anhydrous MgSO₄ and concentrated under reduce pressure. The crude product was then purified by silica gel column chromatography using hexane and ethyl acetate (90:10) as eluent to afford the pure product 2-14 as colorless oil (1.60 g, 71%).

2-14: Rₕ = 0.52 (CH₂Cl₂/MeOH, 9:1); IR (film) ν_max, 3067, 2978, 1692, 1575, 1347, 1258, 1146 cm⁻¹; ¹H NMR (300MHz, CDCl₃) δ 6.20-5.85 (m, 2H, CH=CH), 5.22-5.00 (s, 1H, -NH), 4.25-3.72 (m, 4H, CH₂OH, OCOCH₂NH), 2.90–2.70 (m, 2H, C=CCH, C=CCH), 2.45–2.30 (m, 1H), 1.90-1.80 (m, 1H), 1.50-1.40 (s, 9H, C(CH₃)₃), 1.30-1.10 (m, 3H); ¹³C NMR δ 170.6, 170.5, 155.9, 137.9, 137.1, 136.3, 132.2, 80.0, 69.5, 68.8, 49.5, 45.0, 43.9, 43.7, 42.6, 42.3, 41.7, 38.0, 37.9, 31.7, 29.6, 29.1, 28.5, 22.8, 14.3.

Amino acetate of norbornene 2-15

In a 5 mL round bottom flask under argon, 0.26 g (0.93 mmol) of 2-14 in 1 mL of anhydrous CH₂Cl₂ was taken. 0.10 mL of TFA was added into it at 0°C under Ar over 15 min. The reaction mixture was stirred for an additional 2 h at 0°C and was followed by overnight stirring under Ar at room temperature. The volatilities were removed under reduced pressure and the residue was treated with saturated NaHCO₃, and extracted with ethyl acetate (3 x 10 mL). The pooled organic extracts were then dried over anhydrous MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using hexane and ethyl acetate (40:60) as eluent to afford the pure product 2-15 (45 mg, 25% yields) as colorless oil. Possible reason for the low yield could be the use of high concentrated acid TFA. Also a possible dimerization of the amino acetate of norbornene 2-15 may also be responsible for
the low yield. Reaction conditions had been changed with the change in concentration of acid TFA and the solvent (Table 2-1) without any significant change in yield.

**2-15:** Rf = 0.52 (CH2Cl2/MeOH, 9:1); IR (film) νmax 3054, 2975, 1698, 1625, 1578, 1378, 1244, 1048 cm⁻¹; ¹H NMR (300MHz, CDCl₃) δ 6.80-6.20 (m, 2H, CH=CH), 4.60-3.90 (m, 2H), 3.40-3.20 (m, 2H), 3.00-2.80 (m, 1H), 2.60-2.40 (s, 2H), 2.40-2.30 (m, 1H), 2.10-1.90 (m, 1H), 1.90-1.60 (m, 2H); ¹³C NMR δ170.8, 170.4, 170.3, 137.9, 137.1, 136.3, 132.2, 69.5, 68.9, 49.5, 45.1, 43.9, 43.7, 42.3, 41.7, 41.5, 38.0, 37.8, 29.6, 29.1, 22.94.

**Fmoc protected ester carbamate of norbornene 2-16**

A solution of N-Fmoc-glycine (3.95 g, 13 mmol) in anhydrous THF (13 mL) was added at 0°C under Ar over a period of 20 min into a solution of norbornenemethanol (1.50 g, 12 mmol) in anhydrous THF (9 mL) along with DIC (1.59 g, 13 mmol) and DMAP (0.14 g, 1.10 mmol). After completion of addition, the reaction mixture was warmed to room temperature and stirred for an additional 3 h. The reaction was monitored by TLC (hexane/EtOAc, 6:4). The product was then filtered to remove the precipitate. The organic phase was then washed with aqueous saturated NaHCO₃ and brine solution (3 x 50 mL each), dried over anhydrous MgSO₄, and concentrated over reduced pressure. The crude product was then purified by silica gel column chromatography using hexane and ethyl acetate (90:10) as eluent to afford the pure product as highly viscous oil (3.82, 79%).

**2-16:** Rf = 0.72 (hexane/EtOAc, 6:4); IR (film) νmax 3033, 2967, 1685, 1572, 1347, 1250, 1151 cm⁻¹; ¹H NMR (300MHZ, CDCl₃) δ 7.8-7.2 (m, 8H, CH=CH of benzene ring part), 6.2-5.8 (m, 2H, CH=CH of norbornene part), 4.42-4.34 (d, J = 8.1 Hz, 2H), 4.26-4.16 (t, J = 7.2 Hz,
2H); 4.06–3.86 (m, 3H), 3.78–3.66 (t, J = 7.2 Hz, 1H), 2.88–2.74 (m, 2H), 2.44–2.28 (m, 1H), 1.88–1.76 (m, 1H), 1.48–1.18 (m, 2H); \(^{13}\)C NMR δ 170.2, 156.5, 147.3, 143.9, 141.4, 137.9, 137.2, 136.2, 132.2, 127.8, 127.1, 125.2, 120.1, 69.7, 69.0, 67.3, 49.5, 47.2, 45.0, 43.9, 43.7, 42.9, 42.3, 41.7, 38.0, 37.8, 29.6, 29.0.

**Deprotection of the Fmoc group**

![Deprotection of the Fmoc group](image)

2-16 (1.61 g, 2.75 mmol) was added to a solution of piperidine in DMF (20%). The mixture was heated for 30 min or until disappearance of starting material by TLC (CHCl\(_3\)/MeOH, 9:1). The solution was cooled back to room temperature and poured into cold water (50 mL). The white solid of dibenzofulvene was removed by vacuum filtration. The filtrate was then extracted with diethyl ether (3 x 50 mL), washed with water, dried under anhydrous MgSO\(_4\), and concentrated under reduced pressure to get the deprotected compound, which is mostly the norbornenemethanol (0.12 g, 25%).

2-13: R\(_f\) = 0.71 (CH\(_2\)Cl\(_2\)/MeOH, 9:1); IR (film) \(\nu\)max 3333, 2967, 1682, 1570, 1337, 1252, 1146 cm\(^{-1}\); \(^1\)H NMR (300MHZ, CDCl\(_3\)) δ 6.20–5.90 (m, 2H, CH=C)H, 3.70–3.20 (m, 2H, \(\mathrm{CH_2OH}\)), 2.90–2.70 (m, 2H, C=CCH, C=CCH), 2.40–2.20 (m, 1H), 2.10–1.90 (s, 1H, \(\mathrm{OH}\)), 1.85–1.70 (m, 1H), 1.50–1.40 (m, 1H), 1.40–1.10 (m, 2H); \(^{13}\)C NMR δ 137.3, 136.8, 136.6, 132.3, 64.2, 66.2, 49.5, 44.9, 43.6, 43.3, 42.2, 41.74, 41.6, 41.6, 29.6, 28.9.

**Norbornene ketoester 2-17**

![Norbornene ketoester 2-17](image)

5.30 g of the norbornenemethanol 2-13 (43 mmol) was taken in a round bottom flask under Ar and was dissolved in 86 mL of anhydrous benzene. 7.82 g of DMAP (64 mmol, 1.50 equiv)
was added into it. 14.87 g of methyl acetoacetate (13 mmol, 3 equiv) was added and the reaction mixture was refluxed overnight under Ar. The crude product was then washed with water and brine (3 x 50 mL each) and dried over anhydrous MgSO4. The pooled organic layers were then concentrated under reduced pressure and purified by silica gel column chromatography using hexane and ethyl acetate (70:30) as eluent affording the pure compound 2-17 (6.67g, 75%) as a colorless oil.

2-17: Rf = 0.54 (hexane:EtOAc, 4:6); IR (film) νmax 3053, 2965, 1715, 1655, 1568, 1357, 1256, 1149 cm⁻¹; ¹H NMR (300MHZ, CDCl₃) δ 6.18-5.86 (m, 2H, CH=CH), 4.22-3.64 (m, 2H, CH₃O), 3.46-3.40 (s, 2H, COCH₂CO), 2.87-2.64 (d, 2H, C=CC₃H, C=CC₃H), 2.26–2.22 (s, 3H, COCH₃), 1.90-1.60 (m, 1H), 1.50-1.10 (m, 3H); ¹³C NMR δ 200.9, 167.2, 137.8, 137.0, 136.2, 132.1, 69.5, 68.8, 50.2, 49.4, 44.9, 43.9, 43.6, 42.3, 41.6, 37.9, 37.7, 30.2, 29.6, 28.9.

p-Toluene sulfonyl azide (2-18)

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \\
\text{S} & \quad \text{N}_2\text{N} \quad \text{O} \\
\end{align*}
\]

Sodium azide (3.34 g, 51 mmol) was added into a 20 mL of ethanol. To this solution was added 8.89 gm (50 mmol) of p-toluene sulfonyl chloride in 40 mL acetone. A precipitate of NaCl was formed. The reaction mixture was then stirred for an additional 15 h and then filtered. Acetone was removed by rotary evaporation and the organic phase was separated and diluted with CH₂Cl₂. The solution was then washed with distilled water (3 x 50 mL) and dried over anhydrous MgSO₄. Removal of the solvent was left 8.24 gm of p-toluene sulfonyl azide (2-18) (90% yields) as colorless oil. Spectral data are in agreement with literature.¹⁸² Necessary precautions were taken to preserve this highly explosive compound in a sealed vial.
**2-18**: $R_f = 0.21$ (hexane/CH$_2$Cl$_2$, 6:4); IR (film) $\nu_{max}$ 3238, 3067, 2927, 2100, 1595, 1494, 1451.5 cm$^{-1}$; $^1$H NMR (300MHZ, CDCl$_3$) $\delta$ 7.90-7.20 (d, $J = 8.4$ Hz, 4H), 2.60-2.40 (s, 3H, tosyl CH$_3$); $^{13}$C NMR $\delta$ 141.2, 139.5, 128.3, 125.6, 14.4.

**Diazoe-ester of norbornene 2-19**

![Diazoe-ester of norbornene 2-19](image)

To a stirred solution of the norbornene keto ester 2-17 (1.33 g, 6 mmol) in 7 mL of anhydrous acetonitrile and p-TsN$_3$ (1.52 g, 8 mmol), triethyl amine (3.60 mL, 4 equiv) was added at 0°C under Ar over 10 min. The reaction mixture was stirred for additional 2 h at 0°C. It was then warmed to room temperature and was stirred for another additional 5 h. Then 1M NaOH (60 mL) was added to the stirred solution. The reaction mixture was stirred for additional 12 h. It was extracted with dichloromethane (3 x 50 mL). The combined extracts were washed with 1M NaOH (3 x 75 mL), dried over anhydrous MgSO$_4$ and concentrated under reduced pressure to obtain a yellow crude oil. The product was purified by silica gel column chromatography using hexane and ethyl acetate (60:40) as eluent to afford a pure product 2-19 (0.93 g, 81%).

**2-19**: $R_f = 0.56$ (hexane/EtOAc, 6:4); IR (film) $\nu_{max}$ 3123, 2968, 2111, 1696, 1549, 1363, 1241, 1185 cm$^{-1}$; $^1$H NMR (300MHZ, CDCl$_3$) $\delta$ 6.18-5.88 (m, 2H, CH=CH), $\delta$ 4.82-4.66 (s, 1H, COCHN$_2$), 4.24-3.66 (m, 2H, CH$_2$O), 2.92-2.72 (m, 2H, C=CCH, C=CCH), 2.44-2.28 (1H), 1.86-1.74 (m, 1H), 1.48-1.10 (m, 3H); $^{13}$C NMR $\delta$ 177.1, 166.4, 137.3, 136.6, 135.8, 131.8, 68.9, 68.5, 37.9, 49.0, 45.7, 44.6, 43.6, 43.5, 43.2, 41.9, 41.2, 38.0, 37.8, 37.6, 37.4, 36.5, 29.1, 28.5;
Norbornene oxohexanoate 2-22

To an ice-cooled solution of norbornenemethanol 2-13 (6.13 g, 50 mmol), DIC (9.64 g, 74 mmol) and catalytic amount of DMAP (0.86 g, 7 mmol) in 99 mL anhydrous CH₂Cl₂, 4-acetyl butyric acid (9.64 g, 70 mmol) was added over 20 min. After completion of addition, the reaction mixture was stirred at room temperature for an additional 4 h until there was no more starting material monitored by TLC (hexane/EtOAc, 6:4). It was then filtered and washed with water (2 x 75 mL) and brine (1 x 50 mL). The organic layer was dried over anhydrous MgSO₄ and concentrated under reduced pressure. The crude was then purified by silica gel column chromatography using hexane and ethyl acetate (90:10) as eluent affording the pure product 2-22 (8.50 g, 73%) as colorless oil.

2-22: Rf = 0.65 (hexane/EtOAc, 6:4); IR (film) νmax 3053, 2967, 2667, 1714, 1669, 1573, 1424, 1343, 1266, 1158 cm⁻¹; ¹H NMR (300MHZ, CDCl₃) δ 6.20-5.60 (m, 2H, CH=CH), δ 4.20-3.50 (m, 2H, CH₂O), δ 2.80-2.68 (m, 2H, C=CH₂, C=CH₂), δ 2.45-2.38 (m, 2H), 2.35-2.20 (m, 3H), δ 2.10-2.05 (s, 3H, CH₃), δ 1.85-1.70 (m, 3H), δ 1.40-1.00 (m, 3H); ¹³C NMR δ 207.8, 172.9, 137.6, 136.9, 136.1, 132.1, 68.4, 67.7, 49., 44.9, 43.8, 43.6, 42.4, 42.2, 41.5, 37.9, 37.8, 33.2, 29.8, 29.54, 28.96, 18.9, 18.9.
ROMP of the Compound 2-17

A 50 mL round bottom flask, equipped with a magnetic stirring bar under Ar, was flame dried and cooled under vacuum. The flask was flushed with Ar and charged with 0.61 g (2.90 mmol) of the keto-ester of the norbornenemethanol and 4-acetyl butyric acid 2-17, catalytic amount of BHT and 20 mg of the Grubbs’ first-generation catalyst (0.01 equiv.) in 15 mL of anhydrous CH₂Cl₂ (0.20 equiv). The mixture was stirred rapidly for an additional 15 min at the room temperature and then quenched with ethyl vinyl ether to afford the ROMP product 2-23 (0.51 g).

2-26: Rf = 0.21 (CHCl₃/MeOH, 9:1); IR νmax 3015, 2985, 2678, 1725, 1661, 1575, 1428, 1353, 1265, 1163 cm⁻¹; ¹H NMR (300MHz, CDCl₃) δ 5.80-5.40 (m, 2H), 4.60-4.20 (m, 2H), 3.80-3.60 (m, 2H), 3.50-2.50 (m, 6H), 2.40-2.20 (m, 2H), 2.20-1.60 (m, 12H); ¹³C NMR δ 205.6, 205.3, 172.7, 172.3, 137.5, 136.3, 135.9, 133.1, 69.5, 68.6, 67.3, 50.2, 49.5, 45.3, 44.8, 43.7, 43.5, 42.8, 42.6, 41.8, 38.2, 37.9, 33.7, 30.2, 29.7, 29.2.
ROMP of the Compound 2-22

A 50 mL round bottom flask, equipped with a magnetic stirring bar under Ar, was flame dried and cooled under vacuum. The flask was flushed with Ar and charged with 0.51 g (2.10 mmol) of the keto-ester of the norbornenemethanol and 4-acetyl butyric acid 2-22, catalytic amount of BHT and 18 mg of the Grubbs’ first-generation catalyst (0.01 equiv.) in 10 mL of anhydrous CH₂Cl₂ (0.20 equiv). The mixture was stirred rapidly for the next 15 min at the room temperature and then quenched with ethyl vinyl ether to afford the ROMP product 2-24 (0.44g) as a highly viscous oil.

2-24: Rf = 0.23 (CHCl₃/MeOH, 9:1); IR νmax 3013, 2965, 2678, 1725, 1669, 1573, 1423, 1344, 1264, 1157 cm⁻¹; ¹H NMR (300MHz, CDCl₃) δ 5.30-5.20 (m, 2H), 4.05-3.70 (m, 2H), 2.55-2.40 (m, 4H), 2.30-2.15 (m, 4H), 2.10-2.05 (m, 5H), 1.95-1.70 (m, 6H); ¹³C NMR δ 207.6, 172.7, 137.5, 136.3, 135.9, 133.1, 68.4, 67.3, 49.5, 44.8, 43.7, 43.5, 42.8, 42.6, 41.8, 38.2, 37.9, 33.7, 30.2, 29.7, 29.2, 19.5, 19.2.
Diacetone D-mannose (3-25)

A solution of D-mannose (3-24) (10 g, 0.06 mol) and 2,2 DMP (31 mL) in acetone (74 mL) was placed in a round bottom flask under Ar. Catalytic amount of p-toluenesulfonic acid (p-TsOH) (80 mg, 0.46 mmol) was added. The reaction mixture was stirred at r.t. overnight. The reaction was monitored by TLC (hexane/EtOAc, 6:4). After 10 h of reaction, the solvent was removed under reduced pressure to afford a pure white solid product (m.p. 119.0 – 121.0 °C) of diacetone D-mannose (3-25) (10.11g, 71% yield).

3-25: Rf = 0.25 (hexane/EtOAc, 6:4); m.p. 119.0-121.0 °C (lit 123-124 °C); α25D +17.16 ° (C = 1.35, MeOH); IR (KBr) νmax 3435, 2988, 2948, 2901, 1459,1439, 1319 cm⁻¹; ¹H NMR (300MHz, CDCl₃) δ 5.39-5.36 (d, J = 5.84 Hz, 1H), 4.83-4.78 (dd, J = 5.88 Hz, 3.69 Hz, 1H), 4.63-4.58 (d, J = 5.88 Hz, 1H), 4.44-4.37 (m, 1H), 4.21-4.16 (dd, J = 6.99 Hz, 3.72 Hz, 1H), 4.20-4.02 (m, 2H), 3.14-3.18 (d, 1H, hydroxyl OH), 1.48-1.44 (s, 6H), 1.4.-1.30 (s, 3H, 3H); ¹³C NMR δ 112.8, 109.3, 101.4, 85.7, 80.4, 79.8, 73.5, 66.1, 26.9, 26.0, 25.3, 24.6. Spectral data and m.p. are in agreement with literature.¹⁵⁹

Carbonate of diacetone (D)-mannose 3-26
To a solution of the diacetone-D-mannose (3-25) (4 g, 15 mmol) together with DMAP (5.63 g, 46 mmol) in CHCl₃ (31 mL, 0.5 M), allyl chloroformate (5.57 g, 46 mmol) was added. The reaction mixture was then refluxed for an additional 3 h under Ar until the complete consumption of the starting material. Reaction was monitored by TLC (hexane/EtOAc, 6:4). The crude product was filtered, washed with water (3 x 100 mL) and brine (3 x 100 mL). The organic layer was then dried over anhydrous MgSO₄, concentrated under reduced pressure, and purified by silica gel column chromatography using hexane and ethyl acetate (90:10) to afford the product 3-26 (3.55 g, 67%) as a colorless oil.

3-26: Rf = 0.51 (hexane/EtOAc, 6:4); [α]²⁵_D +59.82 ° (C = 1.57, MeOH); IR (neat) ν_max 3643, 3087, 2987, 2338, 1754, 1456, 1381, 1296 cm⁻¹; ¹H NMR (300MHz, CDCl₃) δ 6.02-5.99 (s, 1H), 5.98-5.84 (ddt, J = 17.33 Hz, 10.28 Hz, 7.34 Hz, 1H), 5.40-5.24 (m, 2H), 4.86-4.80 (dd, J = 5.88 Hz, 3.69 Hz, 1H), 4.76-4.72 (d, J = 5.88 Hz, 1H), 4.65-4.60 (m, 2H), 4.42-4.34 (m, 1H), 4.10-3.98 (m, 3H), 1.48-1.44 (s, 3H), 1.44-1.40 (s, 3H), 1.36-1.34 (s, 3H), 1.34-1.30 (s, 3H); ¹³C NMR (CDCl₃) δ 153.3, 131.3, 119.6, 113.5, 109.6, 103.9, 84.9, 82.5, 79.4, 72.9, 68.9, 66.9, 27.1, 26.1, 25.3, 24.8; HRMS (CI pos) for C₁₆H₂₅O₈ [M+H]+=, calcd 345.1549, found 345.1539.

Metathesis of the carbonate of D-mannose 3-27

A 50 mL round bottom flask, equipped with a magnetic stirring bar under Ar, was flame dried and cooled under vacuum. The flask was flushed with Ar and charged with 0.50 g (2
mmol) of the carbonate of protected (D)-mannose 3-26, 167 mg of the Grubbs’ first-generation catalyst (10 mol %) in 4.0 mL of CH₂Cl₂ (0.50 M). The reaction mixture was stirred and refluxed for 18 h. Ethyl vinyl ether (1 mL) was added to quench the metathesis reaction. The crude product was then concentrated under reduced pressure, and purified by silica gel column chromatography using hexane and ethyl acetate (70/30) as eluent to afford the metathesis product 3-27 (0.41 g, 61%) as a highly viscous oil.

3-27: Rᵥ = 0.35 (hexane/EtOAc, 6:4); IR (neat) νₘₐₓ 3643, 3087, 2987, 1754, 1640, 1456, 1381, 1296 cm⁻¹; ¹H NMR (300MHz, CDCl₃) δ 6.04-6.00 (s, 2H), δ 5.96-5.90 (m, 2H), δ 4.88-4.82 (dd, J = 5.85 Hz, 3.67 Hz, 2H), 4.78-4.74 (dd, J = 5.98 Hz, 2.19 Hz, 2H), δ 4.70-4.64 (m, 4H), 4.44-4.36 (m, 2H), δ 4.14-4.02 (m, 6H), 1.50-1.42 (two s, 6H, 6H), 1.38-1.32 (two s, 6H, 6H); ¹³C NMR (CDCl₃) 187.8, 183.7, 173.2, 154.3, 154.5, 131.3, 131.5, 113.7, 109.8, 103.9, 103.4, 84.9, 82.5, 79.4, 72.9, 68.9, 66.9, 27.1, 26.1, 25.3, 24.8, 24.6.

**Hydrogenation of the metathesis product of carbonate of diacetone (D)-mannose 3-28**

![Metathesis product of carbonic acid allyl ester 3-26](image)

Metathesis product of carbonic acid allyl ester 3-26 (102 mg, 0.15 mmol) was hydrogenated in presence of Pd catalyst. The product 3-28 was used directly for the NMR analysis in CDCl₃.

3-28: Rᵥ = 0.56 (hexane/EtOAc, 6:4); IR (neat) νₘₐₓ 3087, 2987, 2338, 1754, 1640, 1456, 1381, 1296 cm⁻¹; ¹H NMR (300MHz, CDCl₃) δ 6.06-6.02 (s, 2H), 4.90-4.84 (dd, J = 5.81 Hz,
2.13 Hz, 2H), 4.80-4.74 (dd, $J = 6.32$ Hz, 1.9 Hz, 2H), 4.46-4.36 (m, 4H), 4.26-4.18 (m, 2H),
4.12-4.02 (m, 6H), 1.60-1.54 (m, 4H), 1.50-1.42 (two s, 6H, 6H), 1.38-1.32 (two s, 6H, 6H); $^{13}$C
NMR (CDCl$_3$) 154.3, 154.5, 131.3, 131.5, 113.7, 109.8, 103.9, 103.4, 84.9, 82.5, 79.4, 72.9,
68.9, 66.9, 27.1, 26.1, 25.3, 24.8, 24.6, 23.6, 23.8.

**Esterification of diacetone D-mannose 3-29**

![Chemical Structure](image)

To a solution of the diacetone D-mannose (3-25) (5.17 g, 0.02 mol) was added DIC (3.01 g, 24 mmol) and a catalytic amount of DMAP (0.49 g, 4 mmol) in anhydrous CH$_2$Cl$_2$ (40 mL, 0.50 M) in a round bottom flask under Ar. 4-Pentenoic acid (2.39 g, 24 mmol) at 0°C over the 10 min. After completion of the addition, the reaction mixture was warmed to the room temperature and stirred for an additional 3.5 h. Reaction was monitored by TLC (hexane/EtOAc, 6:4). After the completion of the reaction, the product was filtered, and washed with water (2 x 100 mL) and brine (1 x 75 mL). The crude product was then dried over anhydrous MgSO$_4$, concentrated under reduced pressure, and purified by silica gel column chromatography using hexane and ethyl acetate (90:10) as eluent to afford the desired product 3-29 (5.12 g, 76 %) as a colorless oil.

3-29: $R_f = 0.47$ (hexane/EtOAc, 6:4); [$\alpha$]$^D_{25}$ $+49.55^\circ$ (C = 1.19, MeOH); IR (neat) $\nu$ max
3080.17, 2987.39, 1747.39, 1642.32, 1455.96, 1373.83, 1071.79 cm$^{-1}$; $^1$H NMR (300MHz,
CDCl$_3$) $\delta$ 6.14-6.08 (s, 1H), 5.86-5.72 (ddt, $J = 17.33$, Hz, 10.28, 7.34, 1H), 5.08-4.97 (m, 2H),
4.85-4.80 (dd, $J = 5.88$ Hz, 2.69 Hz, 1H), 4.69-4.64 (d, $J = 5.88$ Hz, 1H), 4.42-4.32 (m, 1H),
4.10-3.96 (m, 3H), 2.44-2.30 (m, 4H), 1.46-1.44 (s, 3H), 1.44-1.41 (s, 3H), 1.36-1.32 (s, 3H),
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1.32-1.28 (s, 3H); $^{13}$C NMR (CDCl$_3$) $\delta$ 171.5, 136.4, 115.9, 113.4, 109.5, 100.9, 85.2, 82.4, 79.5, 73.0, 66.9, 33.6, 28.7, 27.1, 26.1, 25.3, 24.8; HRMS (CI pos) for C$_{17}$H$_{27}$O$_7$ [M+H]$^+$, calcd 343.1757, found 343.1762.

**Metathesis of the ester of D-mannose 3-30**

A 50 mL round bottom flask, equipped with a magnetic stirring bar under Ar, was flame dried and cooled under vacuum. The flask was flushed with argon and charged with 0.63 g (1.80 mmol) of the ester of diacetonated (D)-mannose 3-29, 150 mg of the Grubbs’ first-generation catalyst (10 mol %) in 4.0 mL of CH$_2$Cl$_2$ (0.50 M). The reaction mixture was stirred and refluxed for 18 h. Ethyl vinyl ether (1 mL) was added to quench the metathesis reaction. The crude product was then concentrated under reduced pressure, and purified by silica gel column chromatography using hexane and ethyl acetate (70:30) as eluent to afford the solid metathesis product 3-30 (0.43 g, 72%) (m.p. 88.5 – 90.0 °C).

3-30: $R_f = 0.26$ (hexane/EtOAc, 6:4); m.p. 88.5 °C – 90.0 °C; [$\alpha$]$^\text{25}_\text{D} + 28.88$ ° (C = 1.04, CH$_2$Cl$_2$); IR (KBr) $\nu_{\text{max}}$ 2987, 2671, 1742, 1459, 1382, 1250 cm$^{-1}$; $^1$H NMR (300MHz, CDCl$_3$) $\delta$ 6.02-6.00 (s, 2H), 5.48-5.34 (m, 2H), 4.88-4.80 (dd, $J = 7.55$ Hz, 4.63 Hz, 2H), 4.70-4.64 (dd, $J = 5.49$ Hz, 3.69 Hz, 2H), 4.42-4.34 (m, 2H), 4.12-4.06 (m, 6H), 2.40-2.24 (m, 8H), 1.50-1.46 (s, 6H), 1.46-1.42 (s, 6H), 1.38-1.34 (s, 6H), 1.34-1.30 (s, 6H); $^{13}$C NMR (CDCl$_3$) $\delta$ 171.5, 171.5, 129.5, 129.0, 113.4, 109.4, 100.9, 100.9, 85.2, 82.4, 79.5, 73.0, 66.9, 34.2, 27.6,
27.1, 26.1, 25.3, 24.8, 22.6; HRMS (Cl pos) C_{32}H_{49}O_{14} [M+H]^+, calcd 657.3122, found 657.3118.

**Ester of diacetone D-glucose 3-32**

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \\
\text{H}_3\text{C} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{O} \\
\text{H}_3\text{C} & \quad \text{H}_3\text{C} \\
\end{align*}
\]

To a solution of the diacetone-D-glucose (3-31) (6 g, 0.02 mol) at 0°C was added DCC (2.30 g, 0.02 mol) and a catalytic amount of DMAP (0.47 g, 4 mmol) in anhydrous CH$_2$Cl$_2$ (40 mL, 0.50 M) taken in a round bottom flask under Ar. 4-Pentenoic acid (2.31 g, 0.02 mol) was then added at 0°C over the 10 min. After completion of the addition, the reaction mixture was warmed to the room temperature and stirred for 3.5 h. Reaction was monitored by TLC (hexane/EtOAc, 6:4). At the end of the reaction, the product was filtered, and washed with water (2 x 50 mL) and brine (1 x 50 mL). The crude product was then dried over anhydrous MgSO$_4$, concentrated under reduced pressure, and purified by silica gel column chromatography using hexane and ethyl acetate (95:5) as eluent to afford the desired product 3-32 (5.60 g, 71 %) as a colorless oil.

3-32: R$_f$ = 0.51 (hexane/EtOAc, 6:4); [\(\alpha\)]$_{D}^{25}$ -27.50 $^\circ$ (C = 1.19, MeOH); IR (neat) $\nu_{\text{max}}$ 3080, 2988, 1748, 1642, 1455, 1374, 1163, 1076 cm$^{-1}$; $^1$H NMR (300MHz, CDCl$_3$) $\delta$ 5.85-5.70 (m, 2H), 5.30-5.20 (m, 1H), 5.10-4.90 (m, 2H), 4.45-4.35 (d, $J$ = 7.1 Hz, 1H), 4.20-4.10 (m, 2H), 4.10-4.00 (m, 1H), 4.00-3.90 (m, 1H), 2.50-2.30 (m, 4H), 1.50-1.40 (s, 3H), 1.40-1.30 (s, 3H), 1.20-1.30 (s, 6H); $^{13}$C NMR (CDCl$_3$) $\delta$ 171.4, 136.3, 115.7, 112.2, 109.3, 105.1, 83.4, 79.9, 76.0, 72.4, 67.2, 33.4, 28.7, 26.8, 26.7, 16.2, 25.3; HRMS (Cl pos) for C$_{16}$H$_{23}$O$_7$ [M-CH$_3$]$^+$, calcd 327.1444, found 327.1448.
Metathesis of the glucose ester 3-33

A 50 mL round bottom flask, equipped with a magnetic stirring bar under Ar, was flame dried and cooled under vacuum. The flask was flushed with argon and charged with 0.56 g (2 mmol) of the monoester of diacetone (D)-glucose 3-32, 0.25 g of the Grubbs’ first-generation catalyst (10 mol %) in 6 mL of anhydrous CH2Cl2 (0.5 M). The reaction mixture was stirred and refluxed for 18 h. The metathesis reaction was then brought back to room temperature and quenched with ethyl vinyl ether (1 mL). The crude product was concentrated under reduced pressure, and purified by silica gel column chromatography using hexane and ethyl acetate (70:30) as eluent to afford the desired metathesis product 3-33 (0.45 g, 83%) as a highly viscous oil.

3-33: Rf = 0.34 (hexane/EtOAc, 6:4); [α]25D 0° (C = 1.28, CH2Cl2); IR (neat) νmax 3627, 2988, 2254, 1747, 1455, 1374, 1075 cm⁻¹; 1H NMR (300MHz, CDCl3) δ 5.85-5.78 (m, 2H), 5.48-5.34 (m, 2H), 5.24-5.18 (m, 2H), 4.60-4.40 (m, 2H), 4.22-4.12 (m, 4H), 4.06-3.92 (m, 4H), 2.42-2.22 (m, 8H), 1.50-1.46 (s, 6H), 1.38-1.34 (s, 6H), 1.29-1.24 (s, 12H); 13C NMR (CDCl3) δ 171.5, 129.5, 129.0, 112.3, 109.4, 105.1, 83.5, 79.9, 79.9, 76.1, 72.5, 67.3, 37.1, 34.0, 27.7, 26.9, 26.9, 26.8, 26.3, 25.4, 25.4, 22.7; HRMS (Cl pos) for C31H45O14 [M-CH3]+, calcld 641.2809, found 641.2824.
Synthesis of diacetone D-galactose 3-35

Anhydrous CuSO₄ (3.0 g, 19 mmol) (dried at 110 °C for 24 h) and (D)-galactose (3-34) (1.35 g, 7 mmol) were suspended in dry acetone (30 mL) in a 50 mL round bottom flask under Ar, and were treated with catalytic amount of conc. H₂SO₄ (0.50 mL). The resulting mixture was stirred at room temperature for 24 h. The cupric sulfate was then removed by filtration and washed with acetone. The combined organic phases were then neutralized by addition of K₂CO₃. The resulting mixture was then filtered, washed with brine (3 x 50 mL) and dried over anhydrous MgSO₄. The organic layer was then evaporated under reduced pressure, and purified by silica gel column chromatography using hexane and ethyl acetate (40:60) affording the desired diacetone D-galactose (3-35) (0.83 g, 43 % yield). Spectral data are in agreement with literature.¹⁵³

3-35: Rₜ = 0.18 (hexane/EtOAc, 6:4); [α]²⁵D -48.22 ° (C = 2.71, MeOH); IR (neat) ν max, 3489, 2996, 1713, 1645, 1388, 1309, 1260 cm⁻¹; ¹H NMR (300MHz, CDCl₃) δ 5.50-5.44 (d, J = 5.1 Hz, 1H), 4.60-4.52 (dd, J = 7.8 Hz, 2.4 Hz, 1H), 4.28-4.24 (dd, J = 5.1 Hz, 2.4 Hz, 1H), 4.24-4.18 (dd, J = 8.1 Hz, 1.8 Hz, 1H), 3.80-3.65 (m, 3H), 2.45-2.25 (br s, 1H, hydroxyl OH), 1.48-1.42 (s, 3H), 1.38-134 (s, 3H), 1.28-1.24 (s, 6H); ¹³C NMR (CDCl₃) δ 109.6, 108.9, 96.5, 71.7, 70.9, 70.8, 68.3, 62.4, 26.2, 26.1, 25.1, 24.5.
Ester of protected D-galactose 3-36

To a solution of the diacetone D-galactose (3-35) at 0°C (1.85 g, 7 mmol) was added DIC (1.35 g, 11 mmol) and a catalytic amount of DMAP (0.12 g, 1 mmol) in anhydrous CH₂Cl₂ (15 mL, 0.50 M) taken in a round bottom flask under Ar. 4-Pentenoic acid (1.10 g, 11 mmol) was added at 0°C over the next 10 min. After completion of the addition, the reaction mixture was brought back to the room temperature and stirred for an additional 3 h. Reaction was monitored by TLC (hexane/EtOAc, 6:4). At the end of the 3 h, the product was filtered, and washed with water (2 x 50 mL) and brine (1 x 50 mL). The crude product was then dried over anhydrous MgSO₄, concentrated under reduce pressure, and purified by silica gel column chromatography using hexane and ethyl acetate (90:10) as eluent to give the desired product 3-36 (2.11g, 87 %) as a colorless oil.

3-36: R_f = 0.51 (hexane/EtOAc, 6:4); [α]_25^D -38.03 ° (C = 2.08, MeOH); IR (neat) ν_{max} 3080, 2988, 2937, 1738, 1642, 1455, 1383, 1071 cm⁻¹; \(^1\)H NMR (300MHz, CDCl₃) δ 5.86-5.70 (m, 1H), 5.52-5.46 (d, J = 5.1 Hz, 1H), 5.06-4.90 (m, 2H), 4.62-4.54 (d, J = 7.2 Hz, 1H), 4.32-4.02 (m, 4H), 4.02-3.92 (m, 1H), 2.46-2.27 (m, 4H), 1.48-1.44 (s, 3H), 1.42-1.38 (s, 3H), 1.32-1.25 (s, 6H); \(^1^C NMR (CDCl₃) δ 172.86, 136.7, 115.5, 109.6, 108.7, 96.4, 71.1, 70.8, 70.5, 66.1, 63.4, 33.5, 28.9, 26.1, 26.0, 25.0, 24.5; HRMS [CI pos] for C₁₇H₂₇O₇ [M+H]⁺, calcd 343.1757, found 373.1748.
Metathesis of the ester of (D)-galactose 3-37

A 50 mL round bottom flask, equipped with a magnetic stirring bar under Ar, was flame dried and cooled under vacuum. The flask was flushed with argon and charged with 0.48 g (0.001 mol) of the ester of protected diacetone-D-galactose 3-36, 115 mg of the first-generation Grubbs’ catalyst (10 mol %) in 3 mL of anhydrous CH$_2$Cl$_2$ (0.50 M). The reaction mixture was stirred and refluxed for next 18 h. Ethyl vinyl ether (1 mL) was added to quench the metathesis. The crude product was concentrated under reduced pressure, and purified by silica gel column chromatography using hexane and ethyl acetate (70:30) as eluent to afford the desired solid metathesis product 3-37 (0.34 g, 74%) (m.p. 86-87 °C).

3-37: R$_f$ = 0.34 (hexane/EtOAc, 6:4); m.p. 86-87 °C; $[\alpha]_D^{25}$ = -43.81 ° (C = 1.00, CH$_2$Cl$_2$); IR (KBr) $\tilde{\nu}$$_{max}$ 2994, 2943, 1736, 1451, 1381, 1250 cm$^{-1}$; $^1$H NMR (300MHz, CDCl$_3$) $\delta$ 5.56-5.51 (d, $J$ = 8.1 Hz, 2H), 5.50-5.36 (m, 2H), 4.65-4.58 (dd, $J$ = 9.2 Hz, 2.5 Hz, 2H), 4.36-3.99 (m, 10H), 2.44-2.26 (m, 8 H), 1.52-1.48 (s, 6H), 1.46-1.42 (s, 6H), 1.36-1.31 (dd, 12H); $^{13}$C NMR (CDCl$_3$) $\delta$ 172.7, 129.2, 128.8, 109.4, 108.5, 96.1, 70.9, 70.5, 70.3, 65.8, 63.2, 63.1, 33.8, 27.5, 25.8, 25.7, 24.8, 24.3, 22.5; HRMS (CI pos) for C$_{32}$H$_{49}$O$_{14}$ [M+H]$^+$, calcd 657.3122, found 657.3099.
Protected monoacetone -D-ribose 3-39

\[
\begin{align*}
\text{HO} & \quad \text{O} & \quad \text{OH} \\
\text{O} & \quad \overset{\text{C}}{\text{O}} & \quad \overset{\text{H}}{\text{H}_3\text{C}} \\
\text{H}_3\text{C} & \quad \overset{\text{O}}{\text{C}} & \quad \overset{\text{O}}{\text{C}} \\
\end{align*}
\]

Catalytic amount of conc. H$_2$SO$_4$ was added to a stirring mixture of D-ribose (3-38) (5 g, 33 mmol) in dry acetone (33 mL, 1M) at room temperature under Ar. A clear solution was obtained within 10 minutes. Stirring was continued for the next 5 minutes. The reaction medium was then neutralized by adding NaHCO$_3$, filtered, and extracted with ether. The combined organic medium was then washed by water (3 x 50 mL) and brine (3 x 50 mL), dried over anhydrous MgSO$_4$, and concentrated under reduced pressure. The crude product was then purified by silica gel column chromatography using hexane and ethyl acetate (60:40) as eluent affording a pure product of 3-39 (4.20 g, 67%) as a colorless oil.

3-39: $R_f = 0.38$ (CH$_2$Cl$_2$/MeOH, 9:1); $[\alpha]_{D}^{25} = -35.57^\circ$ (C = 1.69, MeOH); IR (neat) $\nu_{\text{max}}$ 3385, 2942, 1736, 1459, 1377, 1325 cm$^{-1}$; $^1$H NMR (300MHz, CDCl$_3$) $\delta$ 5.68-5.62 (d, $J = 6$ Hz, 1H), 5.38-5.32 (d, $J = 6$ Hz, 1H), 4.79-4.73 (d, $J = 6.0$ Hz, 1H), 4.56-4.50 (d, $J = 6.0$ Hz, 1H), 4.38-4.26 (br m, 2H, two hydroxyl O), 3.372-3.62 (m, 2H), 1.56-1.42 (s, 3H), 1.30-1.24 (s, 3H); $^{13}$C NMR (CDCl$_3$) $\delta$ 112.3, 102.8, 87.7, 86.8, 81.7, 63.5, 26.4, 24.8.

TBDMS protected monoacetone-D-ribose 3-40

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{Si} & \quad \text{CH}_3 \\
\text{H}_3\text{C} & \quad \text{O} & \quad \text{OH} \\
\text{O} & \quad \overset{\text{C}}{\text{O}} & \quad \overset{\text{C}}{\text{O}} \\
\text{H}_3\text{C} & \quad \overset{\text{O}}{\text{C}} & \quad \overset{\text{O}}{\text{C}} \\
\text{H}_3\text{C} & \quad \overset{\text{O}}{\text{C}} & \quad \overset{\text{O}}{\text{C}} \\
\end{align*}
\]

To a solution of 2,3-o-isopropylidene-D-ribofuranose (3-39) (2.25 g, 12 mmol) and imidazole (2.25 g, 33 mmol) in anhydrous DMF (6 mL, 2M) was added TBDMS chloride (2.05
g, 14 mmol) in one portion. The resulting solution was then stirred at room temperature for 3.5 h and was subsequently diluted in water (30 mL). The product was then extracted with ethyl acetate (3 x 30 mL). The combined extract was washed with water (2 x 50 mL) and brine (1 x 50 mL), dried over anhydrous MgSO₄, and purified by silica gel column chromatography with hexane and ethyl acetate (90:10) as eluent affording the pure white solid 3-40 (1.86g, 52% yield) (m.p. 54-57°C). Spectral data and melting point are in agreement with literature.¹⁵⁴

3-40: R_f = 0.51 (hexane/EtOAc, 6:4); m.p. 54.0-55.0 °C (lit 55.0-57.0 °C)²⁴ [α]²⁵_D -14.02 ° (C = 1.64, MeOH), lit C = -13.4 ° (C = 1.0, CHCl₃);²⁴ IR (neat) ν_max 3422, 2935, 2859, 1472, 1374 cm⁻¹;¹ H NMR (300MHz, CDCl₃) δ 5.20-5.12 (d, J = 12 Hz, 1H), 4.70-4.62 (d, J = 6.2 Hz, 1H), 4.62-4.56 (d, J = 6 Hz, 1H), 4.42-4.36 (d, J = 8.1 Hz, 1H), 4.24-4.18 (m, 1H, hydroxyl OH), 3.65-3.62 (d, 2H), 1.80-1.34 (s, 3H), 1.24-1.20 (s, 3H), 0.85-0.80 (s, 9H), 0.01-0.05 (s, 6H);¹³C NMR (CDCl₃) δ 111.9, 103.4, 87.5, 86.9, 81.9, 64.8, 26.5, 26.1, 25.9, 25.8, 25.6, 24.9, 24.7, 18.3, -5.6, -5.7.

Esterification of monoacetone (D)-ribose 3-41

To a solution of the monoacetone-D-ribose (3-39) (3.00 g, 16 mmol) at 0°C was added DIC (2.39 g, 19 mmol) and a catalytic amount of DMAP (0.48 g, 4 mmol) in anhydrous CH₂Cl₂ (32 mL, 0.50 mol) taken in a round bottom flask under Ar. 4-Pentenoic acid (1.58 g, 16 mmol) was added at 0°C over the next 20 min. After completion of the addition, the reaction mixture was warmed to the room temperature and stirred for 4 h. Reaction was monitored by TLC (hexane/EtOAc, 6:4). The crude product was filtered, and washed with water (2 x 50 mL) and
brine (1 x 50 mL). It was then dried over anhydrous MgSO₄, concentrated under reduced pressure, and purified by silica gel column chromatography using hexane and ethyl acetate (60:40) as eluent to give the desired product 3-41 (1.15 g, 26 %). Majority of the product is the diester of the monoacetone (D)-ribose. All products were colorless oil.

3-41: Rₚ = 0.28 (hexane/EtOAc, 6:4); [α]D²⁵ -60.34 ° (C = 1.46, MeOH); IR (neat) νmax 3494, 3080, 2986, 1744, 1642, 1417, 1382 cm⁻¹; ¹H NMR (300MHz, CDCl₃) δ 6.20-6.15 (s, 1H), 5.82-5.68 (m, 1H), 5.06-4.94 (m, 2H), 4.73-4.68 (d, J = 8.1 Hz, 1H), 4.65-4.60 (d, J = 8.1 Hz, 1H), 4.36-4.28 (t, J = 7.1 Hz, 1H), 3.62-3.52 (m, 2H), 2.64-2.54 (br s, 1H, hydroxyl OH), 2.40-2.26 (m, 4H), 1.46-1.42 (s, 3H), 1.28-1.24 (s, 3H); ¹³C NMR (CDCl₃) δ171.3, 136.2, 115.9, 112.9, 102.6, 88.8, 85.5, 81.2, 63.4, 33.6, 28.5, 26.5, 24.9; HRMS [CI pos] for C₁₃H₂₁O₆ [M+H]⁺, calcd 273.1338, found 273.1336.

**Esterification of TBDMS protected monoacetone-D-ribose 3-45**

![Structural formula of TBDMS protected monoacetone-D-ribose 3-45](image)

To a solution of the TBDMS protected monoacetone-D-ribose 3-40, (1.20 g, 4 mmol) was added DIC (0.60 g, 5 mmol) and DMAP (0.14 g, 12 mmol) in anhydrous CH₂Cl₂ (8 mL, 0.50 M) taken in a round bottom flask under Ar. 4-Pentenoic acid (0.47 g, 5 mmol) was added at 0°C over the next 10 minutes. After completion of the addition, the reaction mixture was warmed to the room temperature, and stirred for an additional 3 h. Reaction was monitored by TLC (hexane/EtOAc, 6:4). At the end of 3 h, the product was filtered, washed with water (2 x 50 mL) and brine (1 x 50 mL). The crude product was then dried over anhydrous MgSO₄, concentrated
under reduce pressure, and purified by silica gel column chromatography using hexane and ethyl acetate (95:5) as eluent to give the desired product \textbf{3-45} (1.36 g, 89 \%) as a colorless oil.

\textbf{3-45}: \( R_f = 0.65 \) (hexane/EtOAc, 6:4); \( [\alpha]_{D}^{25} \) -51.16 ° (C = 2.05, MeOH); IR (neat) \( \nu_{\text{max}} \) 3081, 2956, 1752, 1472, 1417, 1374, 1105 cm\(^{-1}\); \( ^1\text{H NMR (300MHz, CDCl}_3 \) \( \delta \) 6.18-6.14 (s, 1H), 5.84-5.70 (m, 1H), 5.08-4.94 (m, 2H), 4.78-4.72 (d, \( J = 5.1 \) Hz, 1H), 4.66-4.62 (d, \( J = 5.1 \) Hz, 1H), 4.30-4.22 (dd, \( J = 8.1 \) Hz, 2.3 Hz, 1H), 3.68-3.60 (dd, \( J = 8.1 \) Hz, 2.3 Hz, 1H), 3.56-3.46 (dd, \( J = 8.1 \) Hz, 2.3 Hz, 1H), 2.38-2.32 (m, 4H), 1.48-1.44 (s, 3H), 1.32-1.28 (s, 3H), 0.90-0.86 (s, 9H), 0.06--1.02 (s, 6H); \( ^{13}\text{C NMR (CDCl}_3 \) \( \delta \) 171.4, 136.4, 115.8, 112.9, 102.7, 88.2, 85.3, 81.8, 63.7, 33.8, 28.6, 26.6, 25.9, 25.2, 18.4, -5.3, -5.3; HRMS [Cl pos] for \( \text{C}_{18}\text{H}_{31}\text{O}_6\text{Si} \) [\( \text{M-Me}_3 \)]+, calcd 371.1890, found 371.1882.

\begin{center}
\textbf{Monobenzylation of monoacetone (D)-ribose 3-44}
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\[
\begin{array}{c}
\text{Ph} \\
\text{O} \\
\text{O} \\
\text{OH} \\
\text{O} \\
\text{H}_3\text{C} \\
\text{CH}_3
\end{array}
\]
\end{center}

In a 100 mL oven-dried round bottom flask, 4.06 g of acetone D-ribose (3-39) (21 mmol) was taken in 11 mL of anhydrous \( \text{CH}_2\text{Cl}_2 \) (2M) and was stirred for the next 10 min. 0.90 g of NaH (60\% in oil dispersion) was added to it and the reaction mixture was stirred for the next 15 min under Ar, till no more hydrogen gas was evaporated, as noticed by the absence of an bubbling. This was followed by the addition of TBAI (0.80 g, 2 mmol). Then 2.70 g of benzyl chloride (21 mmol) was added over the next 15 min under Ar. The reaction mixture was stirred for overnight. At the end of 12 h stirring it was quenched with water and the organic layer was extracted with \( \text{CH}_2\text{Cl}_2 \). The combined organic medium were then washed with water (3 x 20 mL) and brine (3 x 20 mL), dried over anhydrous \( \text{MgSO}_4 \), and concentrated under reduced pressure.
The crude product was then purified by silica gel column chromatography using hexane and ethyl acetate (80:20) as eluent affording the pure product **3-44** (2.80 g, 47 %) as a white solid (m.p. 98.5 – 100.0 °C).

**3-44**: \( R_f = 0.35 \) (hexane/EtOAc, 6:4); \( [\alpha]^{25}_D -82.08 ^\circ \) (C = 1.08, CH\(_2\)Cl\(_2\)); m.p. 98.5 – 100.0 °C; IR (neat) \( \nu_{\text{max}} 3476, 3032, 2930, 1947, 1892, 1498 \text{ cm}^{-1}; \) \( ^1H \) NMR (300MHz, CDCl\(_3\)) \( \delta 7.38-7.28 \text{ (m, 5H)}, 5.22-5.16 \text{ (s, 1H)}, 4.88-4.84 \text{ (d, } J = 6 \text{ Hz, 1H)}, 4.80-4.73 \text{ (d, } J = 6 \text{ Hz, 1H)}, 4.70-4.64 \text{ (d, } J = 6 \text{ Hz, 1H)}, 4.60-4.53 \text{ (d, } J = 7.1 \text{ Hz, 1H)}, 4.47-4.42 \text{ (t, } J = 7.1 \text{ Hz, 1H)}, 3.75-3.56 \text{ (m, 2H)}, 3.20-3.12 \text{ (dd, } J = 10.1 \text{ Hz, 5.1 Hz, 1H)}, 1.50-1.46 \text{ (s, 3H)}, 1.34-1.28 \text{ (s, 3H)}; \) \( ^{13}C \) NMR (CDCl\(_3\)) \( \delta 136.5, 128.8, 128.4, 128.4, 112.3, 108.2, 88.6, 86.1, 81.7, 70.3, 64.2, 26.5, 24.8; \) HRMS (ESI FT-ICR) for C\(_{15}\)H\(_{20}\)O\(_5\)Na \([M+Na]^+\), calcd 303.1203, found 303.1210.

**Esterification of benzylated monoacetone-D-ribose 3-46**

To a solution of the benzylated monoacetone-D-ribose **3-44** (2.20 g, 8 mmol) was added DIC (1.19 g, 9 mmol) and a catalytic amount of DMAP (0.29 g, 2 mmol) in anhydrous CH\(_2\)Cl\(_2\) (79 mL, 0.10 M) taken in a round bottom flask under argon atmosphere, 4-pentenoic acid (0.94 g, 9 mmol) was added at 0°C over the next 15 min. After completion of the addition, the reaction mixture was warmed to the room temperature and stirred for 3 h. Reaction was monitored by TLC (hexane/EtOAc, 6:4). At the end of 3 h, the product was filtered, and washed with water (2 x 50 mL) and brine (1 x 50 mL). The crude product was then dried over anhydrous MgSO\(_4\), concentrated under reduce pressure, and purified by silica gel column chromatography using
hexane and ethyl acetate (70:30) as eluent to give the desired product 3-46 (2.30 g, 81%) as a colorless oil.

3-46: $R_f = 0.61$ (hexane/EtOAc, 1:2); $[\alpha]^D_{25} -71.55^\circ$ (C = 1.57, CH$_2$Cl$_2$); IR (neat) $\nu_{\text{max}}$ 3067, 3033, 2941, 1740, 1642, 1498, 1455, 1374, 1078 cm$^{-1}$; $^1$H NMR (300MHz, CDCl$_3$) $\delta$ 7.37-7.24 (m, 5H), 5.87-5.72 (m, 1H), 5.18-5.16 (m, 1H), 5.09-4.96 (m, 2H), 4.72-4.66 (t, $J$ = 7.1 Hz, 3H), 4.46-4.37 (m, 2H), 4.24-4.12 (m, 2H), 2.46-2.30 (m, 4H), 1.49-1.46 (s, 3H), 1.33-1.29 (s, 3H); $^{13}$C NMR (CDCl$_3$) $\delta$ 172.7, 137.2, 136.8, 128.7, 128.4, 128.2, 115.9, 112.8, 107.6, 85.6, 84.7, 82.2, 69.5, 64.9, 33.6, 28.9, 26.7, 25.2; HRMS (ESI FT-ICR) for C$_{20}$H$_{26}$O$_6$Na [M+Na]$^+$, calcd 385.1622, found 385.1623.

**Metathesis of the monoacetone (D)-ribose 3-47**

![Diagram of 3-47]

A 50 mL round bottom flask, equipped with a magnetic stirring bar under Ar, was flame dried and cooled under vacuum. The flask was flushed with argon and charged with 0.51 g (1 mmol) of the ester of monoacetone (D)-ribose 3-41, 0.15 g of the Grubbs’ first-generation catalyst (10 mol %) in 4 mL of anhydrous CH$_2$Cl$_2$ (0.50 M). The reaction mixture was stirred and refluxed for 18 h. The metathesis reaction was then brought back to room temperature and quenched with ethyl vinyl ether (1 mL). The crude product was concentrated under reduced pressure, and purified by silica gel column chromatography using hexane and ethyl acetate (40:60) as eluent to afford the desired metathesis product 3-47 (0.39 g, 81%).
**3-47** \( R_f = 0.23 \) (hexane/EtOAc, 1:2); \([\alpha]^{25}_{D} \) -1.35 ° (C = 1.11, CH₂Cl₂); IR (neat) \( \nu_{\text{max}} \) 3492, 2941, 1743, 1377, 1111 cm⁻¹; \(^1\)H NMR (300MHz, CDCl₃) \( \delta \) 6.22-6.18 (s, 2H), 5.46-5.14 (m, 2H), 4.70-4.62 (m, 2H), 4.40-3.62 (m, 2H), 3.68-3.54 (m, 4H), 2.72-2.52 (br s, 2H), 2.40-2.22 (m, 8H), 1.48-1.44 (s, 6H), 1.32-1.26 (s, 6H); \(^1^3\)C NMR (CDCl₃) \( \delta \) 171.5, 171.4, 129.4, 129.1, 113.0, 102.7, 88.8, 85.5, 85.5, 81.3, 63.5, 34.3, 34.2, 27.4, 26.5, 24.9, 22.5; HRMS (ESI FT-ICR) for C₂₄H₃₆O₁₂Na \([M+Na]^+\), calcd 539.2099, found 539.2102.

**Metathesis of benzylated monoacetone (D)-ribose 3-49**

![Chemical Structure](image)

A 50 mL round bottom flask, equipped with a magnetic stirring bar under Ar, was flame dried and cooled under vacuum. The flask was flushed with argon and charged with 0.66 g (2 mmol) of the ester of benzylated monoacetone (D)-ribose 3-46, 0.15 g of the Grubbs’ first-generation catalyst (10 mol %) in 4 mL of anhydrous CH₂Cl₂ (0.50 M). The reaction mixture was stirred and refluxed for 18 h. The metathesis reaction was then brought back to room temperature and quenched with ethyl vinyl ether (1 mL). The crude product was concentrated under reduced pressure, and purified by silica gel column chromatography using hexane and ethyl acetate (70:30) as eluent to afford the desired metathesis product **3-49** (0.51 g, 74%).

**3-49** \( R_f = 0.64 \) (hexane/EtOAc, 1:2); \([\alpha]^{25}_{D} \) -6.60 ° (C = 1.51, CH₂Cl₂); IR (neat) \( \nu_{\text{max}} \) 3065, 3032, 2940, 1952, 1739, 1607, 1498, 1455 cm⁻¹; \(^1\)H NMR (300MHz, CDCl₃) \( \delta \) 7.38-7.28 (m, 10H), 5.46-5.32 (m, 2H), 5.18-5.16 (s, 2H), 4.72-4.66 (t, \( J = 7.3 \) Hz, 6H), 4.47-4.41 (d, \( J = \) \( \ldots \))
8.1 Hz, 2H), 4.40-4.36 (m, 2H), 4.20-4.15 (dd, J = 7.1 Hz, 2.1 Hz, 4H), 2.42-2.22 (m, 8H), 1.49-1.46 (s, 6H), 1.34-1.30 (s, 6H); $^{13}$C NMR (CDCl$_3$) $\delta$ 172.3, 136.7, 129.0, 128.2, 127.9, 127.7, 112.3, 107.1, 85.1, 84.2, 81.7, 69.1, 64.4, 64.3, 33.6, 27.4, 26.2, 24.7; HRMS (ESI FT-ICR) for C$_{38}$H$_{48}$O$_{12}$Na [M+Na]$^+$, calcd 719.3055, found 719.3038.

**Metathesis of the diester of monoacetone (D)-ribose 4-14(HH/HT)**

![Chemical Structure]

A 50 mL round bottom flask, equipped with a magnetic stirring bar under Ar, was flame dried and cooled under vacuum. The flask was flushed with argon and charged with 0.51 g (2 mmol) of the diester of monoacetone (D)-ribose 3-43, 0.12 g of the Grubbs’ first-generation catalyst (10 mol %) in 15 mL of anhydrous CH$_2$Cl$_2$ (0.10 M). The reaction mixture was stirred and refluxed for 18 h. The metathesis reaction was then brought back to room temperature and quenched with ethyl vinyl ether (1 mL). The crude product was concentrated under reduced pressure, and purified by silica gel column chromatography using hexane and ethyl acetate (70:30) as eluent to afford the desired metathesis product 4-14 (HH/HT) (0.47 g, 74%).

4-14: R$_f$ = 0.34 (hexane/EtOAc, 6:4); $[\alpha]_{D}^{25}$ -59.47 o (C = 1.48, CH$_2$Cl$_2$); IR (neat) $\nu$$_{\text{max}}$ 2989, 2863, 1736, 1427, 1357 cm$^{-1}$; $^1$H NMR (300MHz, CDCl$_3$) $\delta$ 6.18-6.12 (s, 2H), 5.52-5.42 (m, 2H), 5.38-5.26 (m, 2H), 4.76-4.70 (d, J = 5.1 Hz, 2H), 4.60-4.44 (m, 4H), 4.00-3.80 (m, 4H), 2.44-2.34 (m, 8H), 2.32-2.22 (m, 4H), 2.18-2.02 (m, 4H), 1.50-1.40 (s, 6H), 1.32-1.24 (s, 6H);
**Benzylation of D-isomannide 3-51**

D-Isomannide (3-50) (5.20 g, 36 mmol), potassium hydroxide (5.20 g, 36 mmol) were dissolved in water (18 mL) and the resulting solution was heated to reflux for 20 min. The mixture was cooled to room temperature, benzyl chloride (4.51 g, 36 mmol) was added. The solution was refluxed for additional 3h. The reaction was quenched with acid (HCl, 2N, 15 mL), followed by extraction with ethyl acetate (3 x 15 mL). The combined organic layers were dried over anhydrous MgSO₄ and concentrated under vacuum. The crude product was then purified by silica gel column chromatography using hexane and ethyl acetate (30:70) as eluent to afford the pure product 3-51 with a yield of 3.36 g (40% yield) as a white solid (m.p. 90-92.0°C). Spectral data and m. p. are in agreement with literature.¹⁵⁵

**3-51**: R<sub>f</sub> = 0.22 (hexane/EtOAc, 6:4); m.p. 90-92 °C (lit. reported m.p. 93 °C), [α]<sup>25</sup> <sub>D</sub> +122.25 ° (C = 1.03, CH₂Cl₂) (lit reported [α]<sup>20</sup> <sub>D</sub> +138 ° (C = 1.00, CHCl₃)); IR (neat) ν<sub>max</sub> 3423, 3063, 3031, 2875, 1496, 1455, 1405 cm⁻¹; <sup>1</sup>H NMR (300MHz, CDCl₃) δ 7.34-7.16 (m, 5H), 4.70-4.62 (d, <i>J</i> = 11.8 Hz, 1H), 4.50-4.40 (dd, <i>J</i> = 8.5 Hz, 5.5 Hz, 2H), 4.38-4.32 (t, <i>J</i> = 7.1 Hz, 1H), 4.20-4.10 (dq, <i>J</i> = 8.5 Hz, 5.5 Hz, 1H), 4.14-3.94 (m, 3H), 3.77-3.66 (m, 2H), 3.00-2.84 (dd, <i>J</i> = 8.5 Hz, 2.1 Hz, 1H); <sup>13</sup>C NMR (CDCl₃) δ 137.6, 128.4, 127.9, 81.7, 80.5, 79.0, 74.5, 72.5, 72.3, 71.3.

¹⁵⁵
Esterification of monobenzylated (D)-Isomannide 3-52

To a solution of benzylated-D-isomannide (3-51) (0.53 g, 2 mmol) was added DIC (0.34 g, 2.70 mmol) and catalytic amount of DMAP (70 mg, 6 mmol) in anhydrous CH₂Cl₂ (6 mL, 0.5 mol) taken in a round bottom flask under Ar. 4-Pentenoic acid (0.28 g, 3 mmol) was added at 0°C over the next 5 min. After completion of the addition, the reaction mixture was warmed to the room temperature, and stirred for an additional 2.5 h. Reaction was monitored by TLC (hexane/EtOAc, 6:4). After the completion of the reaction, the product was filtered, washed with water (2 x 20 mL) and brine (1 x 20 mL). The crude product was then dried over anhydrous MgSO₄, concentrated under reduce pressure and purified by silica gel column chromatography using hexane and ethyl acetate (90:10) as eluent to afford the pure product 3-52 with a yield of 3.24 g (84%).

3-52: R_f = 0.31 (hexane/EtOAc, 6:4); [α]_{D}^{25} +168.51 ° (C = 1.66, CH₂Cl₂); IR (neat) ν_max
3067, 3031, 2879, 1740, 1642, 1500, 1455, 1367 cm⁻¹; ¹H NMR (300MHz, CDCl₃) δ 7.40-7.20 (m, 5H), 5.90-5.74 (m, 1H), 5.12-5.07 (m, 2H), 5.06-4.96 (m, 2H), 4.78-4.71 (d, J = 8.1 Hz, 1H), 4.70-4.65 (t, J = 7.1 Hz, 1H), 4.50-4.45 (t, J = 7.1 Hz, 1H), 4.08-3.98 (m, 2H), 3.96-3.88 (dd, J = 8.5 Hz, 5.5 Hz, 2H), 3.68-3.60 (t, J = 7.1 Hz, 1H), 2.52-2.44 (m, 1H), 2.42-2.34 (m, 2H); ¹³C NMR (CDCl₃) δ 172.4, 137.6, 136.5, 128.4, 127.9, 115.5, 80.7, 80.2, 78.8, 70.5, 38.1, 28.7; HRMS (ESI FT-ICR) for C₁₈H₂₄O₅Na [M+Na]⁺, calcd 343.1359, found 343.1359.
Metathesis of the ester of benzylated (D)-Isomannide 3-53

A 50 mL round bottom flask, equipped with a magnetic stirring bar under Ar, was flame dried and cooled under vacuum. The flask was flushed with Ar and charged with 0.52 g (16 mmol) of the ester of benzylated (D)-isomannide 3-52, 0.13 g of the Grubbs’ first-generation catalyst (10 mol %) in 5 mL of anhydrous CH₂Cl₂ (0.50 M). The reaction mixture was stirred and refluxed for 18 h. The metathesis reaction was then brought back to room temperature and quenched with ethyl vinyl ether (1 mL). The crude product was then concentrated under reduced pressure, and purified by silica gel column chromatography using hexane and ethyl acetate (70:30) as eluent to afford the desired metathesis product 3-53 (0.41 g, 82%) as a highly viscous oil.

3-53: Rᵣ = 0.35 (hexane/EtOAc, 1:2); [α]²⁵ᵣ +0.13 ⁰ (C = 1.68, CH₂Cl₂); IR (neat) νₘₐₓ 3031, 2878, 1739, 1497, 1455, 1367 cm⁻¹; ¹H NMR (300MHz, CDCl₃) δ 7.40-7.26 (m, 12H), 5.50-5.36 (m, 2H), 5.16-5.06 (dd, J = 5.1 Hz, 2.1 Hz, 2H), 4.78-4.72 (d, J = 7.1 Hz, 2H), 4.70-4.64 (t, J = 7.1 Hz, 2H), 4.60-4.54 (d, J = 7.2 Hz, 2H), 4.51-4.46 (t, J = 7.1 Hz, 2H), 4.10-3.98 (m, 4H), 3.96-3.88 (m, 4H), 3.68-3.59 (t, J = 7.1 Hz, 2H), 2.46-2.26 (m, 8H); ¹³C NMR (CDCl₃) δ 172.7, 137.7, 129.4, 129.0, 128.6, 128.1, 80.8, 80.3, 78.9, 74.3, 74.2, 72.7, 71.2, 70.6, 33.8, 27.8, 22.7; HRMS (ESI FT-ICR) for C₃₄H₄₀O₁₀Na [M+Na]+, calcd 631.2514, found 631.2518.
Benzylation of D-isosorbide (exo) 3-55

D-Isosorbide (3-54) (5.20 g, 36 mmol), potassium hydroxide (2 g, 36 mmol) were dissolved in water (18 mL) and the resulting solution was heated to reflux for 20 min. The mixture was cooled to r.t., benzyl chloride (4.51 g, 36 mmol) was added. The solution was refluxed for an additional 3 h followed by an acid quench (HCl, 2 N, 15 mL), and extraction with ethyl acetate (3 x 25 mL). The combined organic layers were dried over anhydrous MgSO₄ and concentrated under vacuum. The crude product was then precipitated in cold diethyl ether (30 mL) to obtain the final product 3-55 with a yield of 40%. Spectral data are in agreement with literature.¹⁵⁵

3-55: R_f = 0.18 (hexane/EtOAc, 6:4); [α]²⁵_D +29.76 ° (C = 1.32, CH₂Cl₂), (lit, [α]²⁷_D +27.60 ° (C = 0.51, CHCl₃)²⁶, IR (neat) νmax 3489, 2996, 1713, 1645, 1458, 1388, 1309, 1260 cm⁻¹; ¹H NMR (300 MHZ, CDCl₃) δ 7.38-7.26 (m, 5H), 4.65-4.60 (t, J = 7.1 Hz, 1H), 4.60-4.55 (d, J = 8.1 Hz, 2H), 4.54-4.48 (d, J = 8.1 Hz, 1H), 4.34-4.21 (m, 1H), 4.14-4.04 (m, 2H), 3.92-3.80 (m, 2H), 3.58-3.50 (m, 1H), 2.84-2.76 (d, J = 8.1 Hz, 1H); ¹³C NMR (CDCl₃) δ 137.6, 128.6, 128.0, 127.8, 86.1, 83.6, 81.9, 75.5, 73.5, 72.4, 71.6.

Esterification of benzylated (D)-isosorbide (exo) 3-56
To a solution of benzylationated (D)-isosorbide (exo) **3-55** (1.2 g, 0.005 mol) at 0°C was added DIC (0.69 g, 5 mmol) and a catalytic amount of DMAP (0.21 g, 2 mmol) in anhydrous CH$_2$Cl$_2$ (50 mL, 0.10 M) taken in a round bottom flask under Ar. 4-Pentenoic acid (0.55 g, 6 mmol) was added at 0°C over the next 10 min. After completion of the addition, the reaction mixture was warmed to the room temperature, and stirred for an additional 3 h. Reaction was monitored by TLC (hexane/EtOAc, 6:4). At the end of 3h, the product was filtered, washed with water (2 x 35 mL) and brine (2 x 35 mL). The crude product was then dried over anhydrous MgSO$_4$, concentrated under reduce pressure and purified by silica gel column chromatography using hexane and ethyl acetate (90:10) as eluent to afford the pure product **3-56** with a 71 % yield (1.15 g) as a colorless oil.

**3-56**: R$_f$ = 0.47 (hexane/EtOAc, 6:4); [α]$^25_{D}$+74.19 ° (C = 1.87, CH$_2$Cl$_2$); IR (neat) ν$_{max}$ 3489, 2996, 1713, 1645, 1458, 1388, 1309, 1260 cm$^{-1}$; $^1$H NMR (300MHz, CDCl$_3$) δ 7.36-7.22 (m, 5H), 5.88-5.72 (m, 1H), 5.14-5.04 (m, 2H), 5.02-4.94 (m, 2H), 4.83-4.74 (t, $J$ = 7.1 Hz, 1H), 4.58-4.54 (s, 2H), 4.54-4.49 (d, $J$ = 5.1 Hz, 1H), 4.10-4.06 (m, 1H), 4.06-3.98 (m, 1H), 3.95-3.82 (m, 2H), 3.77-3.69 (dd, $J$ = 5.1 Hz, 1.9 Hz, 1H), 2.49-2.42 (m, 2H), 2.41-2.34 (m, 2H); $^{13}$C NMR (CDCl$_3$) δ 172.6, 137.6, 136.5, 128.4, 127.1, 127.6, 115.5, 86.1, 83.2, 80.5, 73.9, 73.0, 71.3, 69.9, 33.1, 28.7; HRMS (ESI FT-ICR) for C$_{18}$H$_{22}$O$_5$Na [M+Na]$^+$, calcd 343.1359, found 343.1369.
Metathesis of the ester of benzylated (D)-isosorbide (exo) 3-57

A 25 mL round bottom flask, equipped with a magnetic stirring bar under Ar, was flame dried and cooled under vacuum. The flask was flushed with argon and charged with 0.47 g (15 mmol) of the ester of benzylated (D)-isosorbide (exo) 3-56, 0.12 g of the Grubbs’ first-generation catalyst (10 mol %) in 5 mL of anhydrous CH₂Cl₂ (0.30 M). The reaction mixture was stirred and refluxed for 18 h. The metathesis reaction was then brought back to room temperature and quenched with ethyl vinyl ether (1 mL). The crude product was concentrated under reduced pressure, and purified by silica gel column chromatography using hexane and ethyl acetate (70:30) as eluent to afford the desired metathesis product 3-57 (0.37 g, 82%) as a colorless oil.

3-57: R<sub>f</sub> = 0.35 (hexane/EtOAc, 1:2); IR (neat) ν<sub>max</sub> 3031, 2878, 1739, 1657, 1497, 1455, 1367 cm<sup>-1</sup>;<sup>1</sup>H NMR (300MHz, CDCl₃) δ 7.38-7.26 (m, 10H), 5.52-5.38 (m, 2H), 5.16-5.09 (m, 2H), 4.84-4.78 (t, J = 7.1 Hz, 2H), 4.58-4.55 (m, 2H), 4.54-4.51 (d, J = 7.1 Hz, 2H), 4.12-4.06 (m, 2H), 4.05-3.99 (m, 2H), 3.96-3.85 (m, 4H), 3.77-3.70 (m, 2H), 2.47-2.28 (m, 8H);<sup>13</sup>C NMR (CDCl₃) δ 172.9, 138.1, 129.9, 129.4, 128.9, 128.4, 128.2, 86.7, 86.7, 81.1, 74.5, 74.4, 73.6, 71.89, 70.5, 34.3, 28.2, 23.2.
Ester of phloroglucinol 3-62

To a solution of the phloroglucinol 3-61 (2.30 g, 0.018 mol) taken in a round bottom flask was added DIC (7.10 g, 56 mmol) and DMAP (2.97 g, 24 mmol) in anhydrous THF (37 mL, 0.50 M) under Ar. 4-Pentenoic acid (5.65 g, 56 mmol) was added at 0 °C over the next 15 minutes. After completion of the addition, the reaction mixture was warmed to the room temperature and stirred for an additional 3 h. Reaction was monitored by TLC (hexane/EtOAc, 6:4). After the completion of the reaction, the product was filtered, and washed with water (2 x 50 mL) and brine (1 x 50 mL). As observed from the TLC plate, a significant portion of the crude product was the di-ester of phloroglucinol. The crude product was then dried over anhydrous MgSO4, concentrated under reduce pressure, and purified by silica gel column chromatography using hexane and ethyl acetate (95:5) as eluent to afford the desired product 3-62 (5.03 g, 75 %) as a colorless oil.

3-62: Rf = 0.62 (hexane/EtOAc, 6:4); IR (neat) νmax 3081, 2981, 2922, 1767, 1642, 1608, 1457, 1363, 1126, 1004 cm⁻¹; ¹H NMR (300MHz, CDCl3) δ 6.84-6.81 (m, 3H), 5.96-5.81 (m, 3H), 5.18-5.04 (m, 6H), 2.68-2.62 (t, J = 7.1 Hz, 6H), 2.53-2.44 (q, J = 12.1 Hz, 6H); ¹³C NMR (CDCl3) δ 170.8, 151.3, 136.2, 116.2, 112.7, 33.6, 28.8; HRMS [ESI-FTICR-MS] for C_{21}H_{24}O_{6}Na [M+Na]^+, calcd 395.1465, found 395.1459.
A 50 mL round bottom flask, equipped with a magnetic stirring bar under Ar, was flame dried and cooled under vacuum. The flask was flushed with argon and charged with 0.16 g (0.43 mmol) of the ester of phloroglucinol 3-62 and 0.51 g (1.49 mmol) of the ester of diacetone-D-glucose 3-32, 37 mg of the first-generation Grubbs’ catalyst (10 mol %) in 17 mL of anhydrous CH₂Cl₂ (0.50 M). The reaction mixture was stirred and refluxed for 18 h. The cross metathesis reaction was then brought back to room temperature and quenched with ethyl vinyl ether (1 mL). The crude product was concentrated under reduced pressure, and purified by silica gel column chromatography using hexane and ethyl acetate (70:30) as eluent to afford the desired metathesis product 3-63 (0.11 g, 58%) as a highly viscous oil.

3-63: Rₔ = 0.35 (hexane/EtOAc, 1:2); [α]ᵣ<sup>25</sup> +0.15 ° (C = 1.68, CH₂Cl₂); IR (neat) ν<sub>max</sub> 3081, 2981, 2922, 1767, 1642, 1608, 1457, 1363, 1126, 1004 cm⁻¹; ¹H NMR (300MHz, CDCl₃) δ 7.40-7.26 (m, 3H), 5.90-5.80 (m, 4H), 5.7-5.0 (m, 12H), 4.5-4.4 (m, 4H), 4.3-4.1 (m,
8H), 4.1-3.9 (m, 8H), 2.5-2.2 (m, 18H), 1.6-1.4 (s, 12H), 1.4-1.3 (s, 12H), 1.30-1.25 (m, 12H);

$^{13}$C NMR (CDCl$_3$) δ 172.7, 137.7, 129.4, 129.0, 128.6, 128.1, 80.8, 80.3, 78.9, 74.3, 74.2, 72.7, 71.2, 70.6, 33.8, 27.8, 22.7.

**Formation of diacetone D-mannitol (4-5)**

![Chemical structure](image)

Anhydrous zinc chloride (28.0 g) was placed in an oven-dried 500 mL round bottom flask and 141 mL of acetone was added. The mixture was stirred under argon atmosphere until the salt had dissolved completely. The suspension was filtered into another round-bottom flask containing 16.0 g of D-mannitol (4-4) and stirred in a bath of cool water until it had just dissolved (several hours). The solution was poured with stirring into a beaker containing a solution of 35 g of potassium carbonate in 35 mL of water. The suspension was filtered with suction and the precipitate was stirred several times with dichloromethane. The aqueous layer was also extracted with dichloromethane two times. The combined organic extracts were dried over anhydrous MgSO$_4$, evaporated to dryness under reduced pressure. The crude product was then recrystallized with dichloromethane/n-hexane (1:10) resulting in the formation of 11.75 g (51%) of the pure product 4-5. Spectral data are in agreement with literature.$^{126}$

4-5: $R_f = 0.09$ (hexane/EtOAc, 6:4); m.p. 117.0-119.0 °C (lit 118.0 – 120.0 °C); $^{126}$ $^\alpha_{D}^{20} +2.09$ ° (C = 1.46, MeOH); IR (KBr) $\nu_{max}$ 3319, 2986, 2893, 1457, 1418, 1372, 1214, 1159, 1065 cm$^{-1}$; $^1$H NMR (300MHz, CDCl$_3$) δ 4.20-4.10 (m, 4H), 4.00-3.94 (dd, $J = 8.4$ Hz, 5.4 Hz, 2H), 3.78–3.70 (d, $J = 6.7$ Hz, 2H), 3.00-2.62 (br s, 2H, O$H$), 1.44-1.40 (s, 6H), 1.38-1.34 (s, 6H); $^{13}$C NMR δ 109.6, 76.4, 71.3, 66.9, 26.9, 25.4.
Esterification of diacetone D-mannitol 4-9

To a solution of the diacetone D-mannitol (4-5) (4 g, 15 mmol) taken in a 100 mL round bottom flask was added at 0°C DIC (5.77 g, 45 mmol) and DMAP (0.53 g, 0.28 mol) in anhydrous CH$_2$Cl$_2$ (30 mL, 0.50 equiv.) under Ar. 4-Pentenoic acid (4.60 g, 0.05 mol) was added at 0°C over the next 10 minutes. After completion of addition the reaction mixture was warmed to room temperature and stirred for the next 3.5 h. The reaction was monitored by TLC (hexane/EtOAc, 6:4). At the end of 3.5h, the product was filtered, and washed with water (2 x 50 mL) and brine (1 x 50 mL). The crude product was then dried over anhydrous MgSO$_4$, concentrated under reduced pressure; and purified by silica gel column chromatography using hexane and ethyl acetate (100:0 to 90:10) as eluent to give the desired product 4-9 (4.60 g, 71%).

4-9: $R_f = 0.53$ (hexane/EtOAc, 6:4); $[\alpha]_{D}^{25} +13.88^\circ$ (C = 2.33, MeOH); IR (KBr) $\nu_{max}$ 3081, 2987, 1747, 1642, 1455, 1418, 1372, 1156 cm$^{-1}$; $^1$H NMR (300MHz, CDCl$_3$) $\delta$ 5.95-5.85 (m, 2H), 5.40-5.30 (m, 2H), 5.10-4.90 (m, 4H), 4.20-4.10 (dd, $J = 8.2$ Hz, 5.4 Hz, 2H), 3.94-3.84 (dd, $J = 9.5$ Hz, 5.4 Hz, 2H), 3.82-3.76 (dd, $J = 12.5$ Hz, 4.5 Hz, 2H), 2.50-2.30 (m, 8H), 1.38-1.30 (s, 6H), 1.28-1.20 (s, 6H); $^{13}$C NMR $\delta$ 171.8, 136.4, 115.9, 109.5, 74.4, 71.5, 68.1, 33.5, 28.8, 26.6, 25.3.
Diester of the monoacetone (D)-ribose 3-43 or 4-10

To a solution of monoacetone (D)-ribose 3-39 (or 4-6) (2.10 g, 0.011 mol) at 0°C was added DIC (2.30 g, 25 mmol) and a catalytic amount of DMAP (0.34 g, 3 mmol) in anhydrous CH$_2$Cl$_2$ (22 mL) taken in a round bottom flask under Ar. 4-Pentenoic acid (2.54 g, 25 mmol) was added dropwise at 0 °C over the next 15 minutes. After completion of the addition, the reaction mixture was warmed to the room temperature and stirred for the next 3.5 h. Reaction was monitored by TLC (hexane/EtOAc, 6:4). At the end of 3.5 h, the product was filtered, and washed with water (2 x 50 mL) and brine (1 x 50 mL). The crude product was then dried over anhydrous MgSO$_4$, concentrated under reduce pressure, and purified by silica gel column chromatography using hexane and ethyl acetate (90:10) as eluent to give the desired product 3-43 (or 4-10) (2.83 g, 72 %).

4-10: R$_f$ = 0.52 (hexane/EtOAc, 6:4); $[\alpha]^{25}_D$ -44.25 ° (C = 2.13, MeOH); IR (neat) $\nu$ max 3079, 2979, 2881, 1743, 1703, 1642, 1520, 1419, 1366, 1066 cm$^{-1}$; $^1$H NMR (300MHz, CDCl$_3$) $\delta$ 6.20-6.18 (s, 1H), 5.84-5.70 (m, 2H), 5.06-4.94 (m, 4H), 4.68-4.64 (s, 2H), 4.44-4.38 (t, J = 7.1 Hz, 1H), 4.14-4.02 (m, 2H), 2.46-2.26 (m, 8H), 1.48-1.44 (s, 3H), 1.32-1.28 (s, 3H); $^{13}$C NMR (CDCl$_3$) $\delta$ 172.9, 171.7, 136.9, 136.8, 116.3, 116.2, 113.7, 102.6, 85.8, 85.6, 82.1, 64.5, 34.1, 33.8, 29.2, 28.9, 26.9, 25.5; HRMS [CI pos] for C$_{18}$H$_{26}$O$_7$ [M]$^+$, calcd 354.1679, found 354.1691.
Esterification of D-isomannide 4-11

To a solution of D-isomannide (4-7) (or compound 3-50) (6 g, 0.04 mol) in anhydrous THF (82 mL, 0.50 equiv) was added DIC (11.41 g, 0.09 mol) and DMAP (3.80 g, 31 mmol) at 0°C under Ar. 4-Pentenoic acid (8.65 g, 90 mmol) was added at 0°C under Ar over the next 20 min. The reaction mixture was warmed to room temperature and stirred for the next 4h. The crude product was then filtered, washed with water (2 x 50 mL) and brine (1 x 50 mL). The combined organic layer were then dried over anhydrous MgSO₄, concentrated under reduced pressure, and purified by silica gel column chromatography using hexane and ethyl acetate (90:10) as eluent to afford the pure product 4-11 (8.28 g, 65%) as a colorless oil.

4-11: $R_f = 0.39$ (hexane/EtOAc, 6:4); $[\alpha]_{D}^{25} +142.68^\circ$ (C = 2.20, CH₂Cl₂); IR (neat) $\nu_{\text{max}}$ 3079, 2979, 2881, 1743, 1703, 1642, 1520, 1419, 1366, 1066 cm⁻¹; $^1$H NMR (300MHz, CDCl₃) $\delta$ 5.80-5.64 (m, 2H), 5.02-4.94 (m, 3H), 4.94-4.88 (m, 2H), 4.88-4.84 (dd, $J = 10.1$ Hz, 5.1 Hz, 1H), 4.60-4.54 (m, 2H), 3.94-3.86 (dd, $J = 8.1$ Hz, 2.1 Hz, 2H), 3.71-3.64 (dd, $J = 5.1$ Hz, 2.1 Hz, 2H), 2.42-2.34 (m, 2H), 2.32-2.22 (m, 2H); $^{13}$C NMR (CDCl₃) $\delta$ 172.4, 136.5, 115.6, 80.4, 73.7, 70.4, 22.1, 28.8; HRMS (ESI FT-ICR) for C₁₆H₂₂O₆Na $[M+Na]^+$, calcd 333.1309, found 333.1310.
Diesterification of (D)-Isosorbide 4-12

To a solution of (D)-isosorbide (4-8) (or compound 3-54) (2.06 g, 0.01 mol) at 0°C was added DIC (3.73 g, 0.03 mol), and DMAP (1.03 g, 8 mmol) in anhydrous THF (30 mL, 0.50 M) taken in a round-bottom flask under Ar. 4-Pentenoic acid (3.03 g, 0.03 mol) was added over the next 10 min at 0°C. After completion of addition the reaction medium was warmed to room temperature and was stirred for the next 6 h. The reaction was monitored by TLC (hexane/EtOAc, 6:4). At the end of 6 h, the reaction medium was diluted with EtOAc (30 mL), and washed with water (2 x 30 mL), and brine (2 x 30 mL). The combined organic layer were then dried over anhydrous MgSO₄, and concentrated under reduced pressure followed by purification by column chromatography, using ethyl acetate and hexane as eluent (90:10) to afford the pure product 4-12 (3.06 g, 70%) as a colorless oil.

4-12: Rf = 0.42 (hexane/EtOAc, 6:4); [α]D²⁵ +153.71.39 ⁰ (C = 2.10, CH₂Cl₂); IR (neat) νmax 3060, 2980, 2877, 1741, 1703, 1542, 1419, 1365 cm⁻¹; ¹H NMR (300MHz, CDCl₃) δ 5.86-5.68 (m, 2H), 5.17-5.14 (m, 1H), 5.14-5.08 (m, 1H), 5.07-5.03 (m, 1H), 5.01-4.97 (m, 2H), 4.97-4.94 (m, 1H), 4.81-4.76 (t, J = 7.2 Hz, 1H), 4.44-4.40 (d, J = 5.1 Hz, 1H), 3.94-3.91 (m, 1H), 3.91-3.86 (m, 1H), 3.79-3.72 (dd, J = 8.1 Hz, 5.1 Hz, 1H), 2.48-2.28 (m, 8H); ¹³C NMR (CDCl₃) δ 172.3, 172.0, 136.5, 136.3, 115.8, 115.6, 85.9, 80.8, 78.0, 73.9, 73.4, 70.4, 33.4, 33.2, 31.6, 28.8, 22.7, 14.1.
ADMET of the diacetone (D)-mannitol 4-13

A 25 mL round bottom flask equipped with stir-bar was placed under argon atmosphere.

Ester of diacetone protected (D)-mannitol 4-9 (2.86 g, 7 mmol) in anhydrous chloroform (7 mL) was added to it. Grubb’s second-generation catalyst (56.93 mg) was added to the monomer and stirred (monomer: catalyst ratio 100:1). The reaction system was placed under argon atmosphere and vacuum alternatively. With the first addition of the catalyst, there was little evolution of ethylene gas as observed from the bubbles formed. As the reaction progressed the medium became more and more viscous and it had been changed from alternate argon vacuum state to total vacuum condition. It was kept under this condition for next 48 hours with two more addition of 1 equivalent CHCl₃ and subsequent vacuuming. After 48 hours of reaction, half of the amount of Grubbs’ second generation catalyst used initially was added. With the second addition of catalyst, there were formation huge bubbles and the system was kept under total vacuum for the next 24 hours. The reaction was monitored by taking NMR of the crude time to time, as there was no significant information available from the TLC monitoring. The NMR of the crude taken after first 24, 48 and 72 hours showed disappearance of the hydrogen of the terminal double bond. The polymerization was terminated by adding ethyl vinyl ether. Any further purification of the polymer could not be performed due its inability to be precipitated in an appropriate cold solvent.
4-13: R_f = 0.22 (CHCl3/MeOH, 9:1); [α]^{25}_D +15.65 ° (C = 2.02, MeOH); IR (neat) ν_{max} 3071, 2977, 1767, 1465, 1438, 1382, 1186 cm^{-1}; \(^1\)H NMR (300MHz, CDCl3) δ 6.0-5.2 (m, 11H), δ 4.2-4.0 (m, 7H), δ 4.0-3.7 (m, 14 H), δ 3.2-3.0 (m, 14H), δ 2.6-2.2 (m, 16H), δ 1.4-1.2 (m, 45H); \(^13\)C NMR: δ 172.3, 130.1, 110.0, 109.5, 74.5, 74.2, 71.7, 71.5, 65.9, 65.6, 34.9, 34.0, 33.7, 30.42, 29.0, 27.7, 26.6, 26.2, 25.7, 25.3. 

ADMET of the diester of (D)-ribose 4-15

A 25 mL round bottom flask equipped with stir-bar was placed under Ar. Diester of diacetone protected (D)-ribose 4-10 (2.86 g, 7 mmol) in anhydrous chloroform (8 mL) was added to it. Grubb’s second-generation catalyst (57 mg) was added to the monomer and stirred (monomer: catalyst ratio 100:1). The reaction system was placed under argon atmosphere and vacuum alternatively. With the first addition of the catalyst, there was little evolution of ethylene gas as observed from the bubbles formed. As the reaction progressed the medium became more and more viscous and it had been changed from alternate argon vacuum state to total vacuum condition. It was kept under this condition for next 48 hours with two more addition of 1 equivalent CHCl3 and subsequent vacuuming. After 48 hours of reaction, half of the amount of Grubbs’ second generation catalyst used initially was added. With the second addition of catalyst, there were formation huge bubbles and the system was kept under total vacuum for the next 24 h. The reaction was monitored by taking NMR of the crude time to time, as there was no significant information available from the TLC monitoring. The NMR of the crude taken after first 24, 48 and 72 hours showed disappearance of the hydrogen of the terminal double bond. The
polymerization was terminated by adding ethyl vinyl ether. Any further purification of the polymer could not be performed due its inability to be precipitated in an appropriate cold solvent.

4-15: \( R_f = 0.21 \) (CHCl3/MeOH, 9:1); \( [\alpha]^{25}_D +141.65^\circ \) (C = 1.76, MeOH); IR (neat) \( \nu_{\text{max}} \) 3058, 2983, 1745, 1646, 1523, 1420, 1375, 1123 cm\(^{-1}\); \( ^1\)H NMR (300MHz, CDCl3) \( \delta \) 6.20-6.18 (m, 6H), 5.0-4.0 (m, 22H), 2.46-2.26 (m, 30H), 1.5-1.1 (m, 10H); \( ^{13}\)C NMR: \( \delta \) 172.9, 172.7, 172.3, 171.5, 136.9, 136.7, 136.2, 136.1, 135.9, 134.7, 102.1, 101.9, 101.5, 85.8, 85.7, 85.5, 85.3, 85.1, 84.9, 82.7, 82.5, 82.1, 64.5, 64.3, 64.2, 63.9, 34.5, 33.7, 27.4, 26.3, 25.3, 24.9.

**ADMET of the diester of (D)-isomannide 4-16**

![Structure](image)

A 25 mL round bottom flask equipped with stir-bar was flamed dried and placed under Ar. Ester of diacetone protected (D)-isomannide 4-10 (2.56 g, 8 mmol) in anhydrous chloroform (10 mL) was added to it. Grubb’s second-generation catalyst (58 mg) was added to the monomer and stirred (monomer: catalyst ratio 100:1). The reaction system was placed under argon atmosphere and vacuum alternatively. With the first addition of the catalyst, there was little evolution of ethylene gas as observed from the bubbles formed. As the reaction progressed the medium became more and more viscous and it had been changed from alternate argon vacuum state to total vacuum condition. It was kept under this condition for next 48 hours with two more addition of 1 equivalent CHCl3 and subsequent vacuuming. After 48 hours of reaction, half of the amount of Grubbs’ second generation catalyst used initially was added. With the second addition of catalyst, there were formation huge bubbles and the system was kept under total
vacuum for the next 24 hours. The reaction was monitored by taking NMR of the crude time to
time, as there was no significant information available from the TLC monitoring. The NMR of
the crude taken after first 24, 48 and 72 hours showed disappearance of the hydrogen of the
terminal double bond. The polymerization was terminated by adding ethyl vinyl ether. Any
further purification of the polymer could not be performed due its inability to be precipitated in
an appropriate cold solvent.

4-16: Rf = 0.23 (CHCl3/MeOH, 9:1); [α]D +148.39 ° (C = 2.01, MeOH); IR (neat) νmax
3078, 2971, 2885, 1763, 1698, 1632, 1516 cm⁻¹; ¹H NMR (300MHz, CDCl₃) δ 5.3-
5.0 (m, 6H), δ 4.4-4.0 (m, 6H), δ 4.0-3.5 (m, 16H), δ 3.4-3.0 (m, 16H), δ 2.50-2.20 (m, 32H), δ
1.6-1.1 (m, 32H); ¹³C NMR: δ 109.1, 74.0, 71.2, 65.6, 34.5, 33.7, 27.4, 26.3, 25.3, 24.9.

ADMET of the diester of (D)-isosorbide 4-17

![Diagram]

A 25 mL round bottom flask equipped with stir-bar was flame dried and placed under Ar.
Ester of diacetone protected (D)-isosorbide 4-11 (2.76 g, 9 mmol) in anhydrous chloroform (8
mL) was added to it. Grubb’s second-generation catalyst (57 mg) was added to the monomer and
stirred (monomer: catalyst ratio 100:1). The reaction system was placed under argon atmosphere
and vacuum alternatively. With the first addition of the catalyst, there was little evolution of
ethylene gas as observed from the bubbles formed. As the reaction progressed the medium
became more and more viscous and it had been changed from alternate argon vacuum state to
total vacuum condition. It was kept under this condition for next 48 hours with two more
addition of 1 equivalent CHCl₃ and subsequent vacuuming. After 48 hours of reaction, half of the amount of Grubbs’ second generation catalyst used initially was added. With the second addition of catalyst, there were formation huge bubbles and the system was kept under total vacuum for the next 24 hours. The reaction was monitored by taking NMR of the crude time to time, as there was no significant information available from the TLC monitoring. The NMR of the crude taken after first 24, 48 and 72 hours showed disappearance of the hydrogen of the terminal double bond. The polymerization was terminated by adding ethyl vinyl ether. Any further purification of the polymer could not be performed due its inability to be precipitated in an appropriate cold solvent.

4-17: Rf = 0.25 (CHCl₃/MeOH, 9:1); [α]²⁵ₓ +154.39 ° (C = 2.26, MeOH); IR (film) νₘₐₓ 3061, 2988, 2857, 1743, 1709, 1644, 1412, 1375 cm⁻¹; ¹H NMR (300MHz, CDCl₃) δ 5.3-5.0 (m, 6H), δ 4.4-4.0 (m, 6H), δ 4.0-3.5 (m, 18H), δ 3.4-3.0 (m, 18H), δ 2.50-2.20 (m, 28H), δ 1.6-1.1 (m, 34H); ¹³C NMR: δ 172.3, 172.0, 171.6, 170.9, 136.4, 135.8, 135.4, 135.2, 86.9, 86.5, 81.2, 80.8, 78.5, 78.3, 77.8, 77.4, 73.9, 73.6, 73.1, 70.6, 70.3, 69.8, 69.5, 69.1, 68.8, 33.7, 33.3, 33.1, 32.9, 31.9, 31.7, 31.5, 31.3, 28.9, 28.7, 28.3, 27.9, 22.9, 22.5, 22.2, 21.7.
APPENDIX A
SELECTED NMR SPECTRAL DATA

The $^1$H NMR spectra of selected compounds from Chapter 2-4 are illustrated in this appendix. The spectra along with the proposed structure are shown.

Figure A-1. $^1$H NMR of diacetone (D)-mannitol.
Figure A-2. $^1$H NMR of the ADMET of diacetone (D)-mannitol.
Figure A-3. $^1$H NMR of the t-Boc amino acetate of norbornene.
Figure A-4. $^1$H NMR of ketoester of norbornene.
Figure A-5. $^1$H NMR of diazo-ketoester of norbornene.
Figure A-6. $^1$H NMR of the homodimer of diacetone (D)-mannose.
Figure A-7. $^1$H NMR of the homodimer of diaceton (D)-glucose.
Figure A-8. $^1$H NMR of the homodimer of the diacetoned (D)-galactose.
Figure A-9. $^1$H NMR of the homodimer of the benzylated monoacetoned (D)-ribose.
Figure A-10. $^1$H NMR of the homodimer of monoaceton (D)-ribose.
Figure A-11. $^1$H NMR of the diester of monoacetonated (D)-ribose.
Figure A-12. $^1$H NMR of the homodimer of benzylated (D)-isomannide.
Figure A-13. $^1$H NMR of the diester of (D)-isomannide.
Figure A-14. $^1$H NMR of the diester of (D)-isosorbide.
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BIOGRAPHICAL SKETCH

Kalyan Mondal was born in 1974, in Calcutta, India. He completed his schooling from Taki High School, Calcutta with Science as major. He received his bachelor’s degree from the University of Calcutta. Dr. S. P. Basak inspired him in organic chemistry throughout his teaching. Kalyan gladly recognizes his contribution for his basic chemistry knowledge. He then joined B.Tech course under University of Calcutta and studied about Reverse Engineering on Rubber based products. This Graduation course introduced him with new prospects of study in Polymer Science. Dr. S. N. Gupta, Advisor had helped him to enrich his knowledge in Polymer Science. After graduation, he decided to do further research work in synthesizing of Prostate specific Antigen field and thus did his M.Tech from the same University under the guidance of Dr. P. Sarkar. He always wanted to carry on his research work to develop his knowledge. This passion of knowledge brought him to USA and opened new scopes and opportunities before him. He received his second M.S. degree in chemistry from East Tennessee State University under the guidance of Dr. Tammy Davidson, working on the synthesis of Chiral Surfactants for Enantioselective Organic Synthesis. He always wanted to be innovative and versatile and get every possible knowledge from various fields of synthesis. He joined Dr. Eric Enholm’s group to enrich his knowledge on synthetic chemistry for PhD program at University of Florida. Kalyan has learned much about the field of synthetic organic chemistry, especially chemistry related to developing new methodology and multi-step synthesis. His graduate career is reached to a pinnacle from where he is eager to step forward to apply his knowledge in practical field of various industries engaged in different research & development works.