# CORE REACTIVE BIODEGRADABLE MULTIARM STAR POLYMERS

by

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*To my sister*

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# LIST OF SYMBOLS/ ABBREVIATIONS

| | |
|---|---|
| ATRP | Atom transfer radical polymerization |
| CCS | Core crosslinked star |
| $CDCl_3$ | Deuterated chloroform |
| $CH_2Cl_2$ | Dichloromethane |
| D | Dendron |
| DA | Diels Alder |
| DBU | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| DMAEMA | (N,N-dimethylamino)ethyl methacrylate |
| DMAP | Dimethylamino pyridine |
| DVB | Divinylbenzene |
| EGDA | Ethylene glycol diacrylate |
| EGDMA | Ethylene glycol dimethacrylate |
| FT-IR | Fourier Transform Infrared |
| G | Generation |
| GPC | Gel Permeation Chromotography |
| L-LA | L-lactide |
| LPLLA | Linear poly (L-lactide) |
| MeOH | Methanol |
| MHz | Mega hertz |
| MI | Macroinitiator |
| MMA | Methylmetacrylate |
| P | Polymer |
| PCL | Polycaprolactone |
| PDLA | Poly (D- Lactide) |
| PLA | Polylactide |
| PMMA | Polymethyl methacrylate |
| PSt | Polystyrene |
| rDA | Retro Diels-Alder |
| ROP | Ring Opening Polymerization |
| TEA | Triethylamine |

| | |
|---|---|
| THF | Tetrahydrofuran |
| TLC | Thin Layer Chromatography |
| TU | Thiourea |
| UV | Ultraviolet |

# ABSTRACT

## CORE
## REACTIVE BIODEGRADABLE MULTIARM STAR POLYMERS

Functionalizable macromolecules have attracted increasing attention as polymeric materials due to their wide application in material and biological sciences. Although a lot of work has been done in this area, little attention has been paid towards the synthesis of both functionalizable and biodegradable polymers. In this study, we synthesized functional biodegradable polymers with multiarm star architecture. The number of arms in the final polymer can be pre-determined by using an appropriate multifunctional initiator core. To meet this goal, core functional polyester dendrons containing furan protected maleimide group were synthesized as initiators of multiarm star polymers. DL-Lactide was chosen as biodegradable monomer because of advantages and widespread of application area of biomedical applications. Multiarm star polymers were produced via Ring Opening Polymerization (ROP) which provides good control on the molecular weight and polydispersity. After the polymerization, furan protected maleimide core of star polymer was deprotected to their thiol reactive form via retro Diels Alder reaction. Thiol containing molecule was attached to demonstrate reactivity of the polymer core.

# ÖZET

## REAKTİF MERKEZLİ BİYOBOZUNUR ÇOK KOLLU BÜYÜK MOLEKÜLLER

Fonksiyonelleştirilebilen büyük moleküller, malzeme ve biyoloji bilimi alanındaki geniş uygulamalarından dolayı polimerik malzeme olarak artan bir ilgi görmektedirler. Bu alanda birçok çalışma yapılmış olmasına rağmen, hem fonksiyonelleştirilebilen ve hem de biyobozunur polimerlerin sentezi üzerinde fazla durulmamıştır. Bu projede, biz fonksiyonelleştirilebilen, biyobozunur, çok kollu büyük moleküler yapıda polimerleri sentezledik. Sonuçta oluşan polimer kollarının sayısı uygun fonksiyonelli başlatıcıların kullanılmasıyla önceden belirlenebilir. Bu hedefe ulaşmak için başlatıcı olarak furan koruması altındaki maleimid grubu içeren fonksiyonel merkezli poliester dendronlar sentezlendi. DL-laktat monomeri, avantajları ve geniş biyomedikal uygulama alanı dolayısıyla biyobozunur monomer olarak seçildi. Çok kollu polimerlerin sentezinde polimerin molekül ağırlığı ve molakül ağırlığı dağılımı değerlerinde iyi kontrol sağladığı için halka açılma polimerleşmesi (ROP) kullanıldı. Polimerleşme ve koruma altındaki maleimid merkezinin aktifleştirilmesinden sonra, polimerin maleimid merkezinin reaktifliğini göstermek için tiyol içeren bir molekül bağlandı.

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# 1. INTRODUCTION

## 1.1. Biodegradable Polymers

Type of polymers, that can be degraded and catabolised by microorganisms (bacteria, fungi, etc.) under natural environment are called biodegradable polymers. These polymers do not generate any harmful products to the natural environment after degradation. Abiotic reactions (photodegradation, oxidation and hydrolysis) may also change the polymer before, during or in place of biodegradation because of environmental factors. The usual mechanism of degradation is through hydrolysis or enzymatic cleavage of the labile heteroatomic bonds, resulting in scission of the polymer backbone [1]. The cleavage mechanism of a polyester polymer backbone through hydrolysis is shown in Figure 1.1 [1].

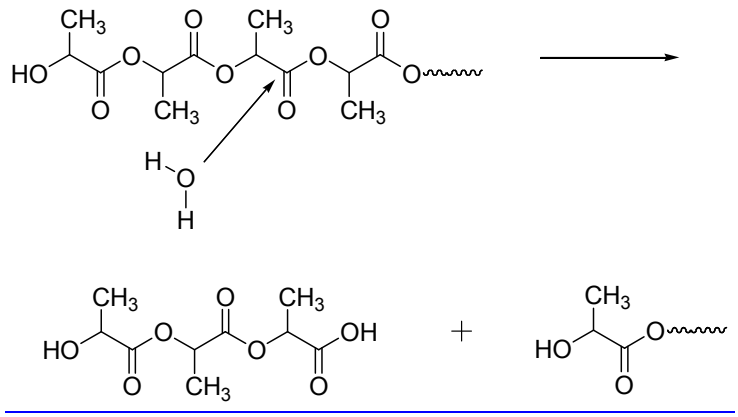

Figure 1.1. Hydrolysis and cleavage of the ester linkage [1]

### 1.1.1. Natural Biodegradable Polymers

Biodegradable polymers are mainly grouped into two categories: natural and synthetic polymers. Natural biodegradable polymers are produced from renewable resources such as plants, microorganisms and animals. Chain growth polymerization reactions which are catalyzed by enzymes are the main synthesis procedures of natural biodegradable polymers. Activated monomers are mostly produced by complicated

metabolic processes in cells. Microorganisms are able to produce the more widespread natural biodegradable polymers such as polyesters, polysaccharides, proteins. For natural biodegradable polymers, hydrolysis and enzymatic cleavage mechanisms are more predominant degradation pathways [2]. Fructan, as an example, is a linear branched natural polymer and function in carbohydrate storage. In catabolism of fructan, fructan exohydrolases, degradation enzyme of fructan, degrade polymer backbone by cleaving terminal fructose residues. (Figure 1.2) [3].

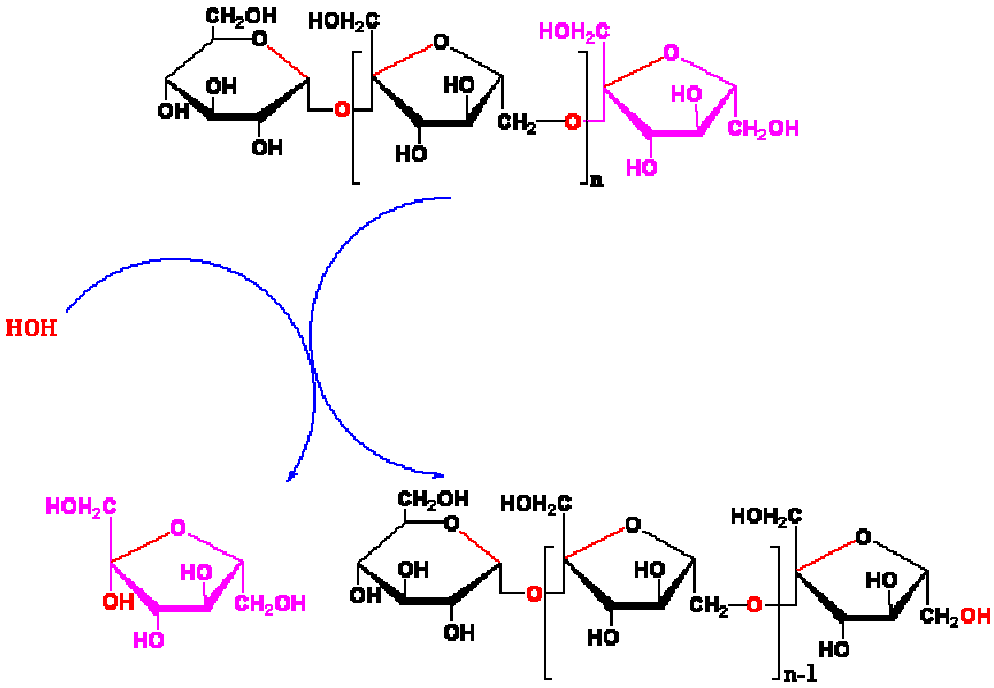


Figure 1.2. Degradation mechanism of fructan [3]

### 1.1.2. Synthetic Biodegradable Polymers

The most attractive feature of synthetic biodegradable polymers is the ability to modify their properties by tailoring appropriate monomers and altering synthetic protocols. With the help of these controllable changes, specific polymers can be obtained with specific properties and functionality. Because of their adaptable properties like hydrophobicity, crystallinity, degradability, solubility and mechanical- thermal features, synthetic biodegradable polymers have widespread application areas (Figure 1.3) [2].

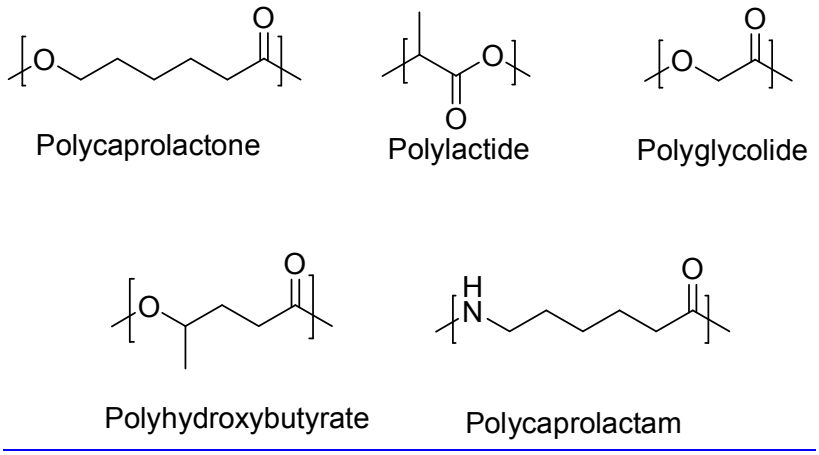


Figure 1.3. Examples of synthetic biodegradable polymers

### 1.1.3. Applications of Biodegradable Polymers

In recent years, there has been a growing interest in biodegradable polymer research both in fundamental settings and chemical industry. Biodegradable polymers are clearly more natural and environmental friendly alternatives compared to other polymeric systems because of their degradability. Moreover, non-toxic degradation byproducts allow the use of biodegradable polymers towards several applications. For researchers, it is possible to modify traditional materials into new polymer composites out of naturally occurring materials. In addition, biodegradable materials decrease the need of synthetic polymer production which causes high cost and environmental pollution. Thus, using biodegradable materials have considerable advantages in terms of both environmental and economical reasons. Medical and environmental applications are two of the most important utilizations of biodegradable polymers. [4-6]

One of medical application area of synthetic biodegradable polymers is tissue engineering. The biodegradable materials can form a support, which encourages and supports growing tissue while slowly degrading. This means that polymers will eventually break down and dissolve in the body, leaving only the healthy tissue that was engineered. This application can be used in many different ways, wherever tissue engineering is needed in the application.

Green biodegradable drug delivery systems have provided great improvement in medical applications. These systems have been constructed by utilizing synthetic and biodegradable polymers. Researchers have been able to increase the retention time of the drugs to many hours, days or months by modifying these polymers. Moreover, it is possible to release specific amounts of the drug over a certain time period in these drug releasing systems. This controllable drug release provides much more effective treatment with lower side effects (Figure 1.4) [7]. Unlike to nondegradable ones, using biodegradable materials will allow the material to stay in the body and then degraded slowly over time without needing a second surgery to remove them, when they are used as sutures and vascular stents.

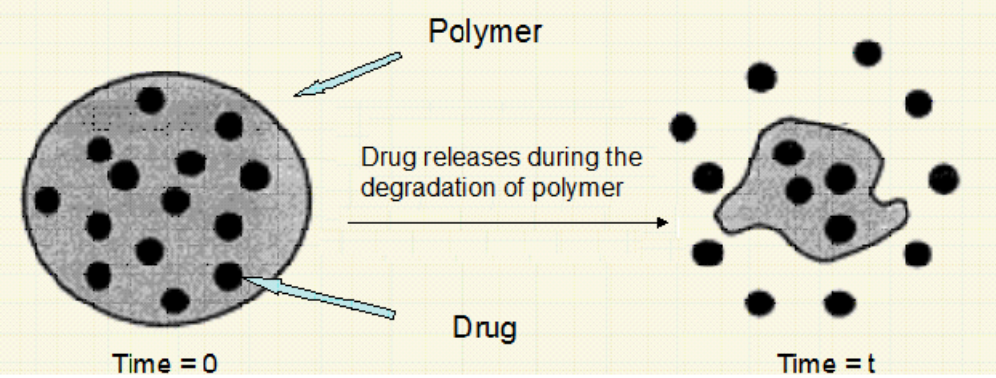


Figure 1.4. Schematic representation of drug delivery [7]

### 1.2. Multiarm Star Polymers

Polymers can be grouped into four classes by means of architectures: linear, cross-linked, branched and dendritic polymers. Multiarm star polymers are one of the six subclasses of dendritic polymers. (Figure 1.5) [8]. A multiarm star polymer is a macromolecule, which has a central core that many linear arms extended from. These linear arms have similar molecular weights and narrow molecular weight distributions. This gives the star shape to the macromolecule. Multiarm star polymers have been one of the most attractive kinds of macromolecules due to their prominent bulk and solution properties. The number of arms in the final polymer can be pre-determined by using a needed multifunctional initiator core. Moreover, further functionalizations allow additional modifications or cross-linkings. This provides macromolecule to have a considerable

property that they can be engineered through the needs. Thus, they are usable in many areas like biotechnology and material sciences.

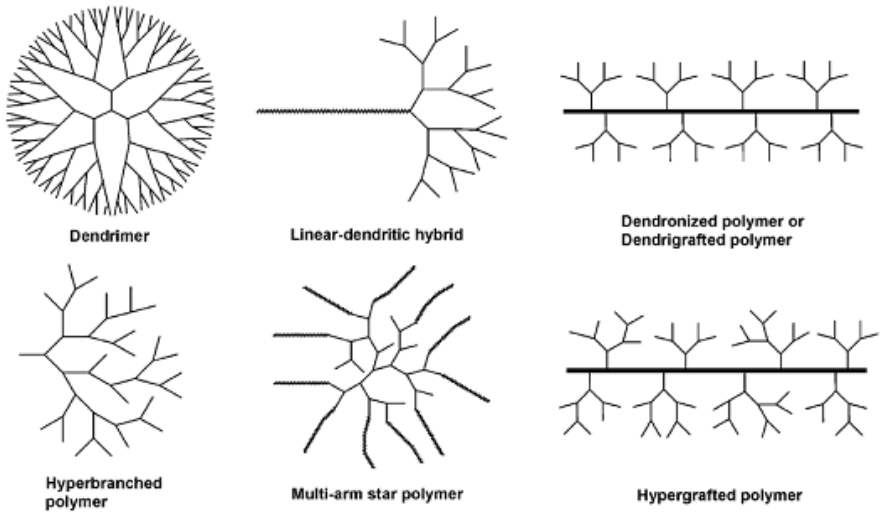


Figure 1.5. Classes of dendritically architectured polymers [8]

Multiarm star polymers are obtained by two common approaches. In the first one, the 'arm-first' method, end-reactive living polymers are synthesized first. Then polymers can be either quenched via a multifunctional coupling agent to form the core part or combined to each other. In the other procedure, the 'core first' method, a multifunctional core that synthesized in the first place is used as the initiator of living polymerization. Here, the resultant star polymer has arms with the same number of initiators in the structure of the core, which leads to more organized arms around the core. Figure (1.6).

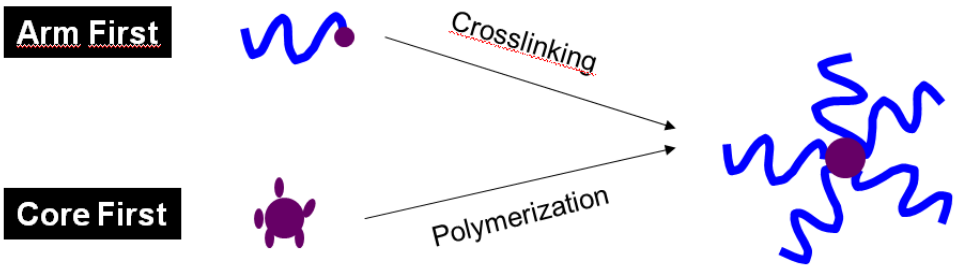


Figure 1.6. Common approaches to synthesize multiarm star polymers

### 1.2.1. Literature Examples of Multiarm Star Polymers

Gao and Matyjaszewski [9] in 2008, synthesized star block copolymers containing a highly cross-linked core and many arms, via a novel method, termed as "star from in situ generated core". To illustrate this new concept, atom transfer radical polymerization was applied for homopolymerization of ethylene glycol diacrylate (EGDA) to generate a multifunctional cross-linked core (nanogel). Monovinyl monomers were added into the system and polymerized from the polyEGDA nanogel macroinitiator (MI) to form the star arms. The star polymers preserved the initiating sites at the chain ends, and they were further used as star MIs for arm extension by polymerization of a second monovinyl monomer to form a star block copolymer. Figure 1.7 demonstrates the steps of in situ generated core method used in study. [9]

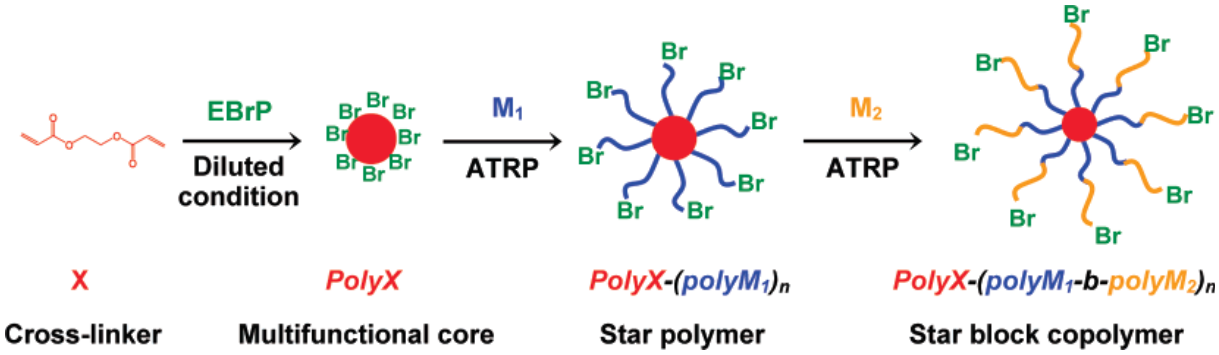


Figure 1.7. Illustration for synthesis of star and star block copolymers by the "star from in situ generated core method" [9]

In 2006, Wiltshire and Qiao [10] investigated the synthesis of selectively degradable core cross-linked star (CCS) polymer. Degradable polycaprolactone (PCL), nondegradable polystyrene (PSt) and polymethyl methacrylate (PMMA) were used as macroinitiators. ATRP of nondegradable monomers were combined with ROP of degradable monomers used for synthesis of CCS polymers via arm-first method. Degradable CCS polymers were synthesized with PCL macroinitiators and both ethylene glycol dimethacrylate (EGDMA) and divinylbenzene (DVB) crosslinkers. Hydrolysis experiments showed that the PCL arms could be selectively degraded to yield EGDMA and DVB cores. Second CCS polymer was synthesized in a similar fashion with a mixture

of degradable PCL and nondegradable PMMA arms. Hydrolysis of this CCS polymer resulted in degradation of the core and full recovery of the original linear arms. Hydrolysis study of the polymer that is synthesized with degradable PCL macroinitiator and bislactone monomer shows fully degradability of this CCS polymer. Figure 1.8 illustrates the study [10].

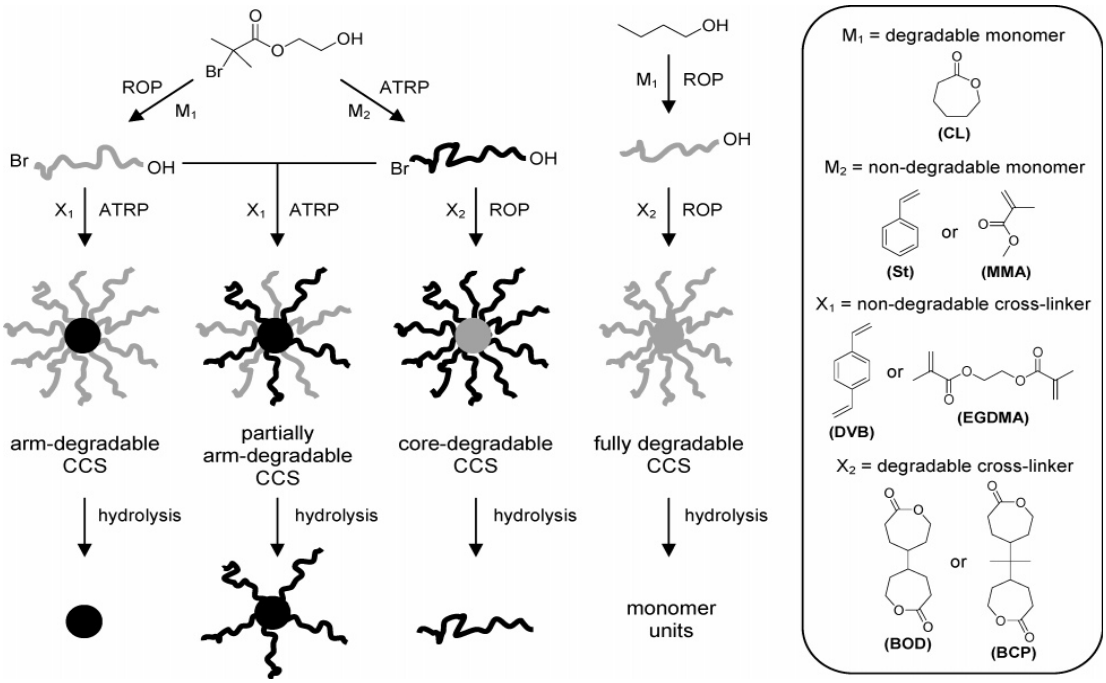


Figure 1.8. Generalized schematic of core cross-linked star polymer formation [10]

Because of several potential areas of application, particularly in the electronic materials and drug delivery areas, a need has arisen for core cross-linked star (CCS) polymers that can be degraded under mild conditions.

Wiltshire and Qiao [11] reported the first example of the synthesis of a fully degradable CCS polymer in another study (2006). This new type of star polymer was synthesized from lactone-based monomers using a controlled polymerization technique known as ring-opening polymerization (ROP) that has not previously been reported for the synthesis of CCS polymers. In this work, CCS polymers were synthesized via a two-step one-pot process involving the synthesis of living linear arms followed by a cross-linking step to generate CCS polymers. Figure (1.9) [11].

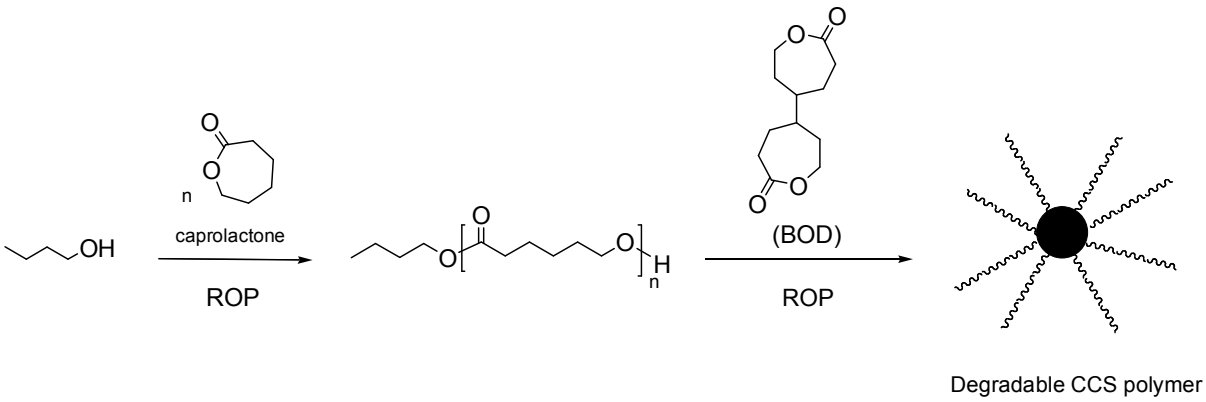


Figure 1.9. Synthesis of degradable core cross linked star polymers via ring opening polymerization [11]

In the study of Aryal [12] in 2009 novel type of biodegradable and biocompatible multi-arm star amphiphilic block copolymers, H40-PCL-b-MPEG, were synthesized by ROP of ε-CL using H40 as a macroinitiator. Results indicate that the micelles formed from the H40-PCLb-MPEG copolymer could be a suitable candidate for drug delivery applications due to their unimolecular nature, stability, biocompatibility, higher drug loading, and controlled release ability (Figure 1.10) [12].

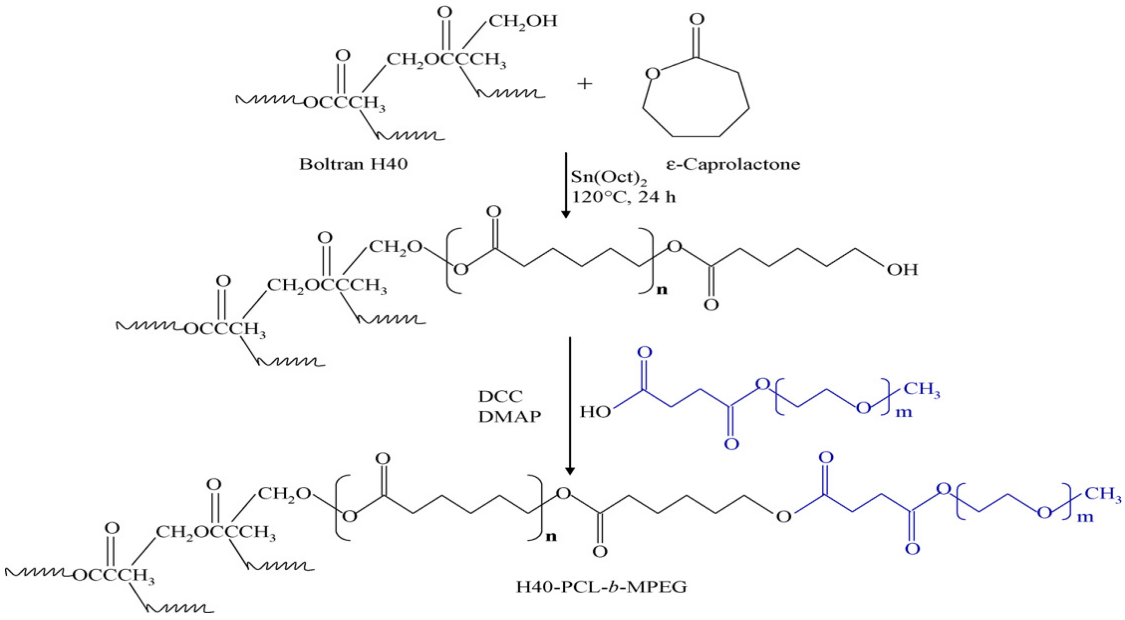


Figure 1.10. Synthesis of a biodegradable and biocompatible multi-arm star amphiphilic block copolymer H40-PCL-b-MPEG [12]

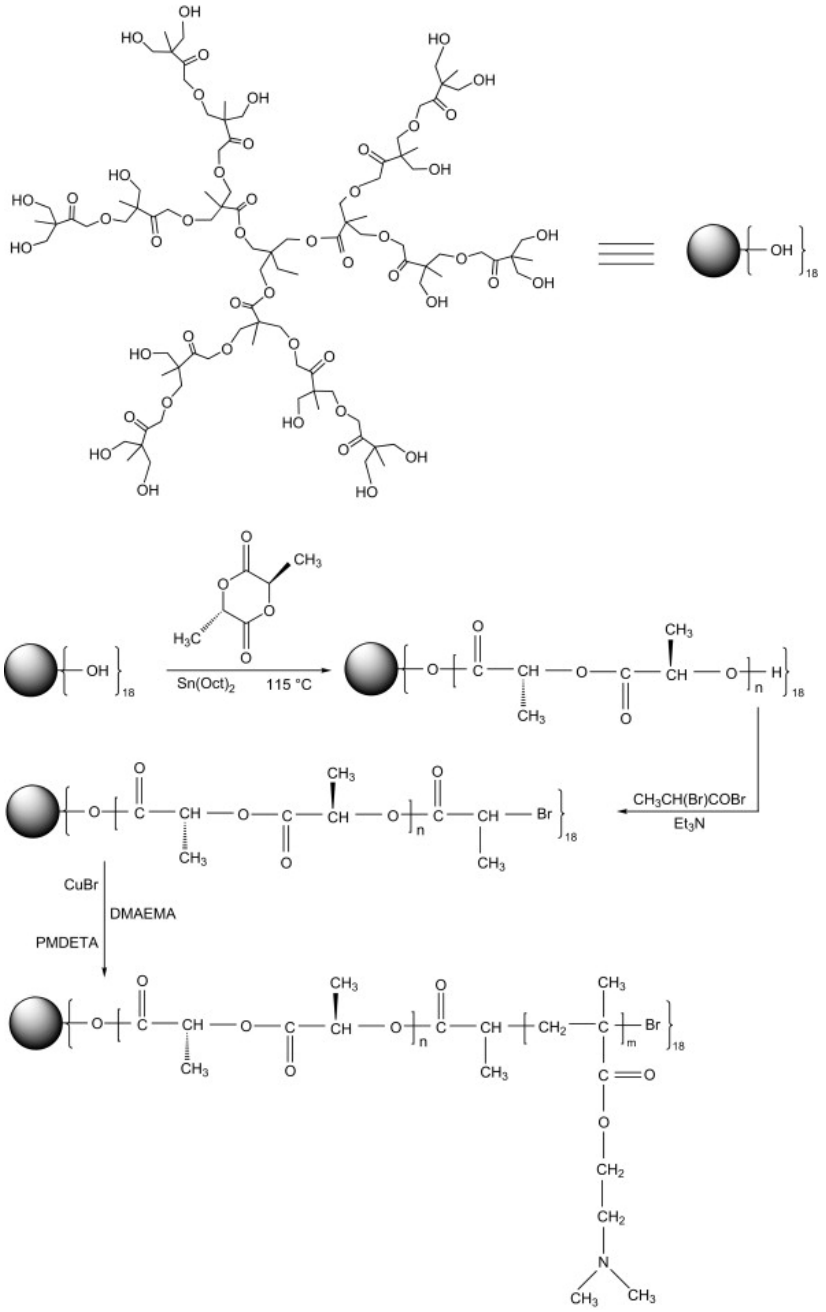


Figure 1.11. Synthesis of ( PLLA-b-PDMAEMA)s via association of living ring-opening polymerization (ROP) and atom transfer radical polymerization (ATRP) [13]

W. Yuan and co-workers [13] successfully obtained novel dendritic star-shaped PLLAs and amphiphilic dendritic star-block poly(L-lactide)-b-poly(2-(N,N-dimethylamino) ethyl methacrylate) (PLLA-b-PDMAEMA)s via association of living ring-opening polymerization (ROP) and atom transfer radical polymerization (ATRP). Dendritic star-shaped poly(L-lactide)s (PLLAs) were prepared by bulk polymerization of L-lactide (L-

LA) with the initiation of polyester dendrimer and catalization of tin 2 ethylhexanoate catalyst. Then dendritic star-shaped PLLA was converted into PLLABr macroinitiator for the preparation of amphiphilic dendritic star-block PLLAb-PDMAEMA copolymer via ATRP of 2-(N,N-dimethylamino)ethyl methacrylate (DMAEMA). Figure (1.11) demonstrates the polyester dendrimer with its eighteen hydroxyl groups that initiate the lactide polymerization, synthesis of PLLA from this initiator, conversion of PLLA to an ATRP macroinitiator for obtaining the copolymer. The thermal properties of these polymers were investigated. Moreover, study on drug release from the copolymer was done with the drug model chlorambucil. The study showed that the rate of drug release could be effectively controlled by altering the pH values of the environment [13].

Aliphatic polyester dendrons have some significant advantages such as high biodegradability, well-defined architecture with their branching and monodisperse unique shape and controlled surface properties to linear ones. These attractive properties received much interest especially in medical applications like drug delivery.

The study by Gong and coworkers (2009) is a good illustration on attractive aliphatic polyester dendrons. In this work dumbbell-shaped tri-block well-defined copolymers with narrow molecular weight distributions consisting of comb-like poly(L-lactide) (PLLA) and linear poly(ethylene glycol) (PEG) with and varied PLLA arm lengths were obtained. The reaction between NHS end functionalized linear poly(ethylene glycol) (PEG) and amine-terminated fourth-generation polyester dendron yields tri block PEG G4 dendron with deprotected branches. After deprotection of acetonide groups, dumbbell shaped tri-block PLLA was synthesized via ring-opening polymerization (ROP) of L-lactide (LA) (Figure 1.12) [14].

According to the results of study; (Tg), melting point (Tm), degree of crystallinity (cc), and onset decomposition temperature (Td) of the copolymers are lower than those of the linear polylactide (LPLLA). Surface chemistry of the copolymer films such as surface hydrophobicity and the capability of adsorbing protein increase with the length of PLLA arms. The cell proliferation has been enhanced significantly on the surfaces of the copolymers with longer PLLA arm lengths because of more favorable surface

physicochemical properties. No cytotoxicity of dumbbell-shaped copolymers has been reported using rabbit bone marrow [14].

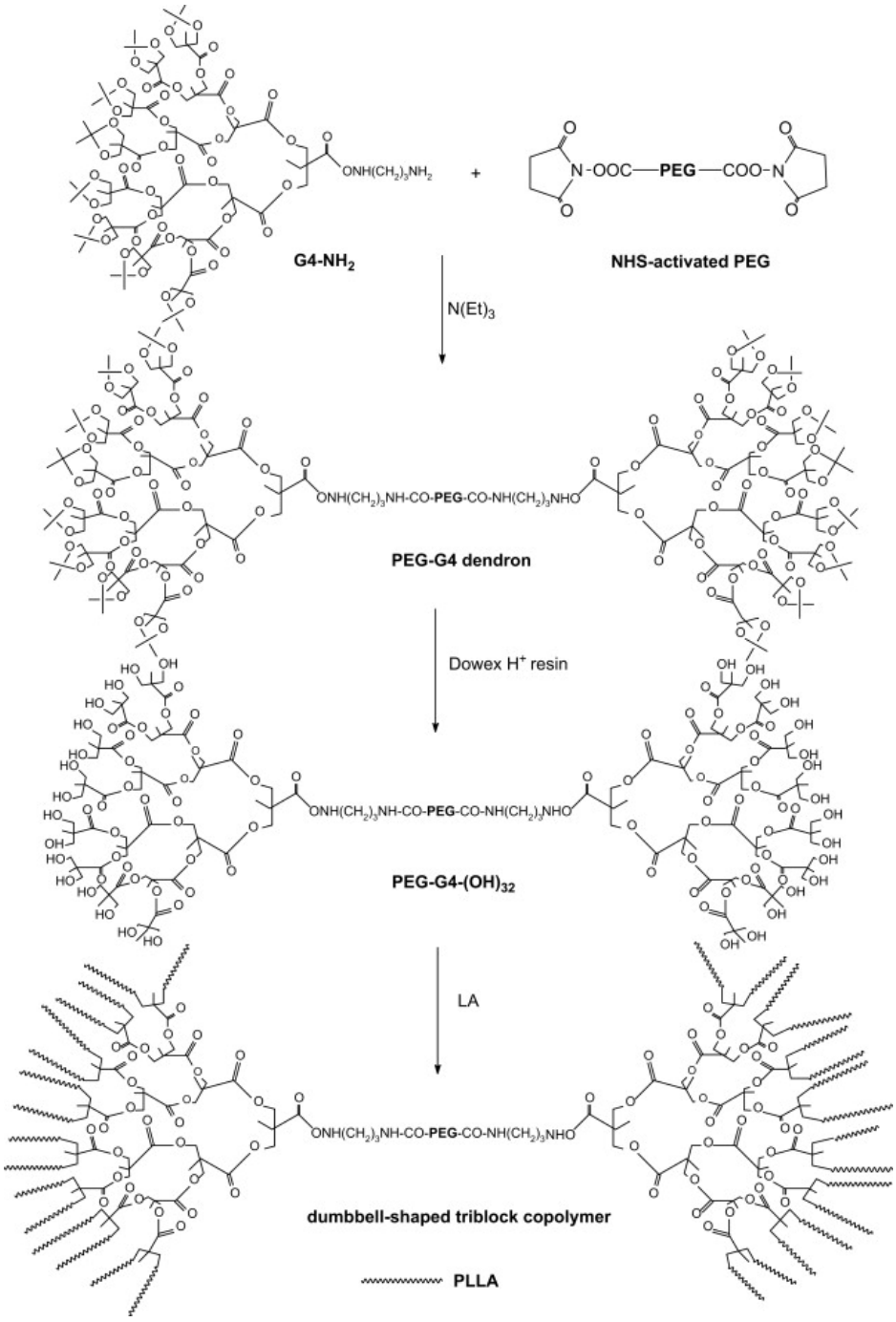


Figure 1.12. Usage of a polyester dendron to obtain comb-like poly(L-lactide) (PLLA) and linear poly(ethylene glycol) (PEG) [14]

### 1.3. Ring Opening Polymerization

Ring opening polymerization (ROP) is an important polymerization technique to polymerize certain cyclic monomers. A wide variety of polymers have been successfully synthesized via ring opening polymerization. Thus, studies of ROP have constituted an active area of industrial and academic research. Although there are other polymerization processes to acquire these polymers, high control in molecular weights and low polydispercity values that can be provided by ROP, are necessary for advance applications. [15]. In Figure 1.13 most common monomers and polymerized forms are shown

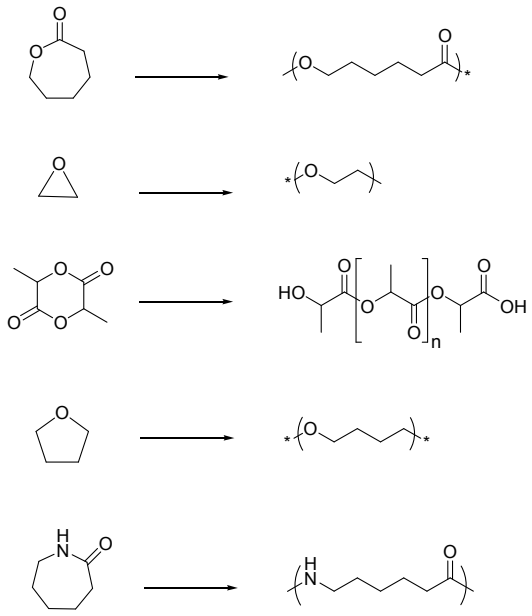

Figure 1.13. Some monomers that are polymerized via ROP

The success of ROP depends on both thermodynamic and kinetic conditions. Thermodynamically, the stability of cyclic monomer should allow the reaction. While the instability of small rings gets easier the polymerization, reaction is no longer favorable for less strained stable rings. Even if the ring opening reaction is thermodynamically favorable, there must be a reasonable mechanism kinetically. [16]

The ROP of cyclic monomers requires a convenient catalyst system to proceed in rational conditions and obtain polymers with controlled properties. Different catalytic systems have been utilized to reach desired polymer via ROP technique.

In organometallic catalytic system, which means metal-based catalytic system, polymerization takes advantage of transition metals complexes. These systems have been the focus of considerable attention for ROP, and numerous researches have been carried out extensive research to clarify the mechanism of such polymerizations. The most widely used complex in organometallic ROP tin (II) octanoate [Sn(Oct)2], is commercially available, easy to handle, and soluble in common organic solvents. The chemical structure of Sn(Oct)2 is shown in Figure 1.14 [17] as an example of metal complexes used in ROP. Moreover, Figure 1.15 [17] illustrates the expected mechanism of polymerization with tin(II) octanoate, as an example of metal catalyzed process [17].

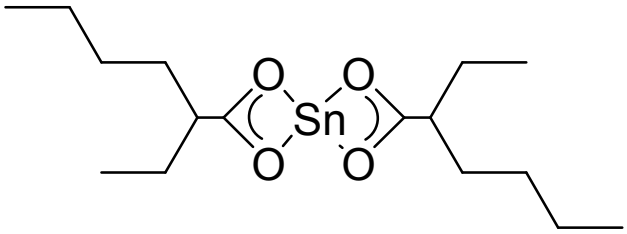


Figure 1.14. Structure of Sn(Oct) [17]

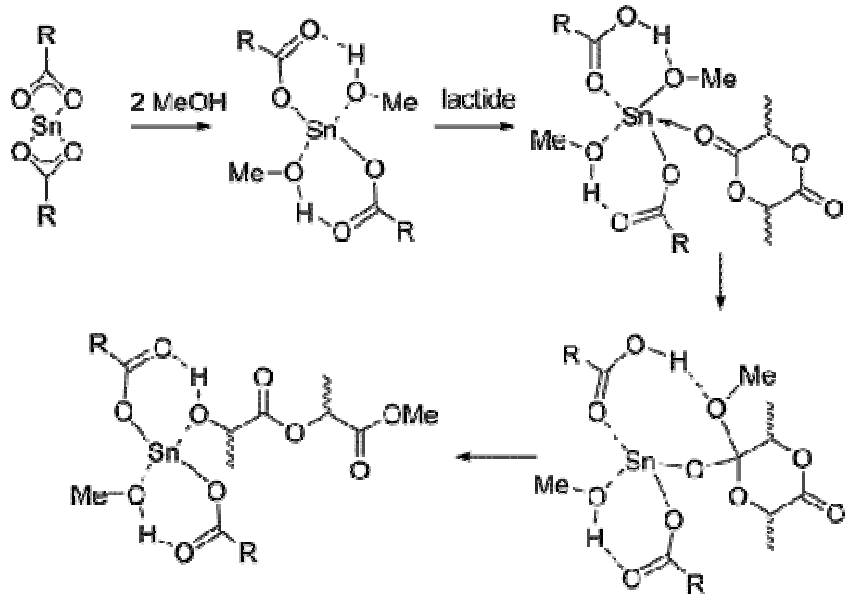


Figure 1.15 Predicted Mechanism for the Sn(Oct)2,-Catalyzed ROP [17]

Organometallic techniques have been used successfully to polymerize cyclic monomers, however, possible remainders of heavy metals may cause significant difficulties, especially in microelectronics and medical applications. Moreover, metallic residues in the polymers can influence environmental problems. For this reason, researchers have been interested in alternative processes.

Enzyme catalyst polymerization is another technique to polymerize various kinds of cyclic monomers. Desired polymers can be synthesized with the advantage of enzyme diversity. However, catalysis process of enzymes is quite long with the compare of other systems [18].

Other catalytic system of ROP process uses organic molecules as catalysts. Figure 1.16 shows the three main structures of these organic molecules [19].

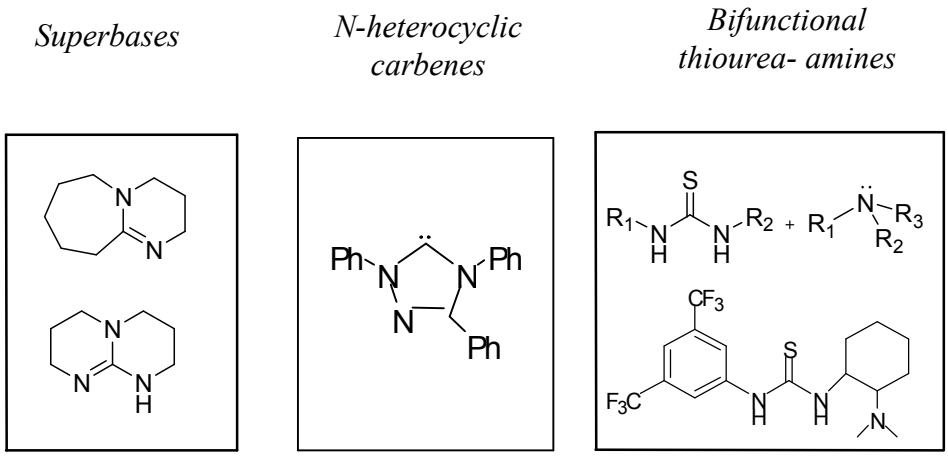


Figure 1.16 Organocatalytic groups which have been used in ROP [19].

Organocatalytic System is based on the activation of monomer or initiator, or both, with the help of H bonding. Figure 1.17 explains the catalytic process [20].The carbonyl oxygen of heterocyclic monomer, lactide, interact with hydrogens of thiourea type catalyst. Thus, carbon atom of this carbonyl group becomes more electrophilic. On the other hand, because of the H bonding between H atom of alcohol initiator and N atom of catalyst, oxygen of initiator becomes more nucleophilic. As a result, initiator can easily react with monomer and polymerization runs [18].

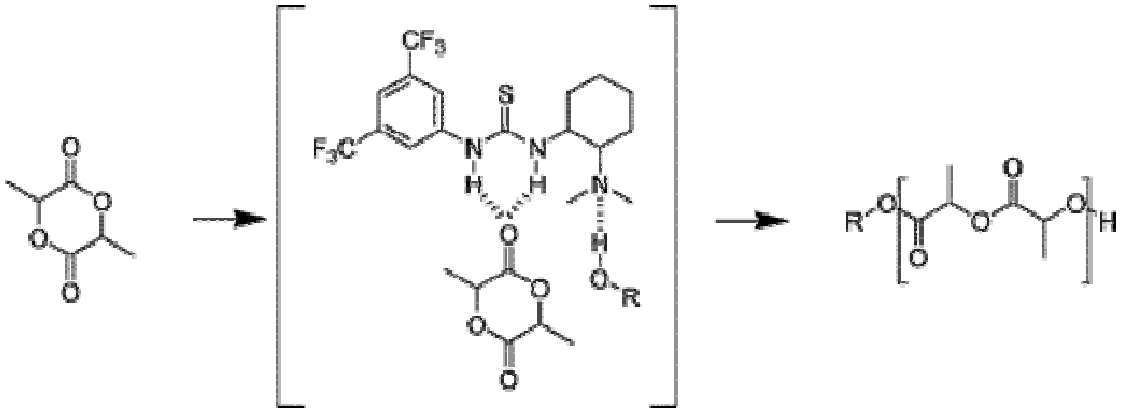

Figure 1.17 The Catalytic effect of the organocatalyst in polymerization of lactide [20]

### 1.4. Dendritic Initiators

Dendrimers are regularly branched macromolecules, which have well-defined, monodisperse globular architectures. Structure of a dendrimer includes a core, repeating units and surface groups. Branching units are symmetrically placed around the core and form the dendrimer's uniform shape (Figure 1.18).

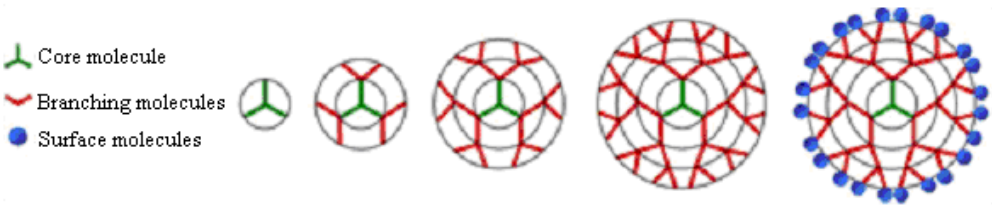


Figure 1.18. Structure of dendrimers

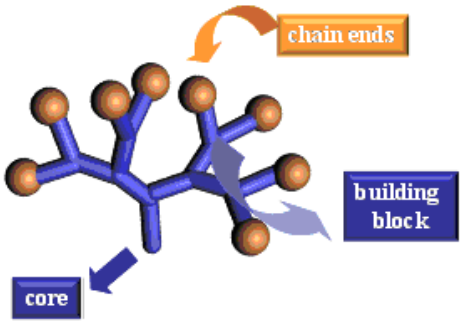


Figure 1.19. Structure of dendrons

Branching units are the building blocks of the dendrimer. Surface groups at the periphery are mostly functional to react with other molecules. Dendron is a part of the dendrimer that starts from a core and ends at the periphery. Dendrons do not include the 'core' part. The focal point, which may also have chemically reactive groups, is starting point from which repeating units construct the dendron (Figure 1.19).

Dendrons are synthesized by two approaches, one of which involves the growth of a dendron starting from the core. After the attachment of branching units, the surface groups are placed on the periphery. This is called as divergent synthesis (Figure 1.20). In the other method, convergent approach, firstly surface groups are attached onto the branching units and via a multivalent core, these small dendron pieces are combined (Figure 1.21). Synthesize dendrons are combined either via covalent bond forming reaction between their focal points or via non-covalent interactions [21].

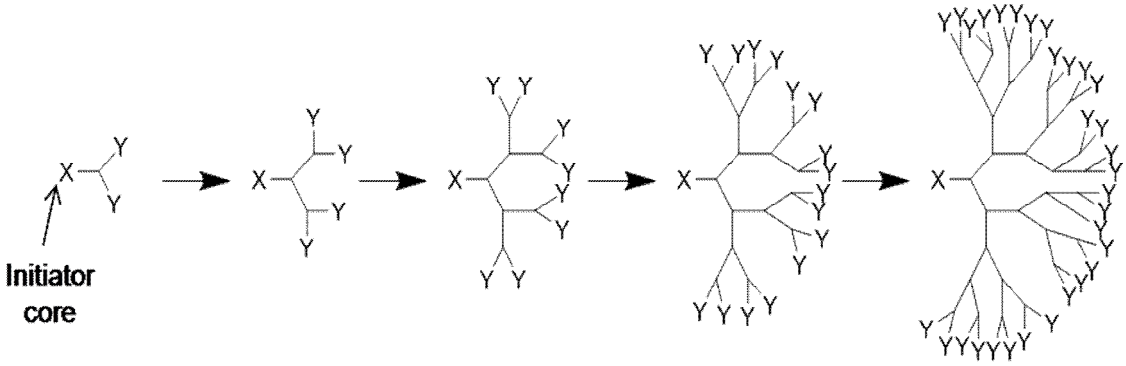


Figure 1.20. Schematic representation of divergent synthesis of dendrons [21]

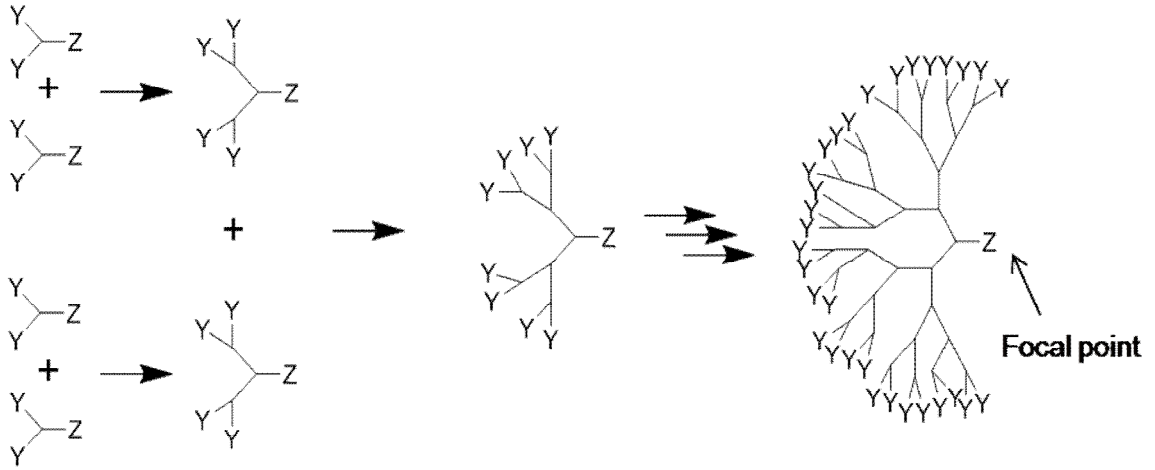


Figure 1.21. Schematic representation of convergent synthesis of dendrons [21]

## 1.5. Click Chemistry

Click chemistry processes are uncomplicated reactions with simple reaction conditions, available starting materials and easy purification. A click chemistry reaction must give very high chemical yields, generate only harmless by products, be stereo specific, physiologically stable and exhibit a large thermodynamic driving force. There are four main types of "click" reactions which are;

- Nucleophilic opening of highly strained rings such as epoxides, aziridines
- Protecting group reactions such as acetals, ketals and their aza-analogs
- Cycloaddition reactions such as Diels-Alder [4+2]
- Copper catalyzed Huisgen [3+2] or Huisgen 1,3 dipolar cycloadditon reactions [22].

### 1.5.1. Diels Alder Reaction

In Diels Alder reaction (DA) an electron rich diene group reacts with an electron poor dienophile. Furan and anthracene derivatives have been widely utilized as diene components. In addition, maleimides are mostly preferred as dienophile group, due to their high reactivity and wide structural variability through the nature of the nitrogen substituents. Products of Diels Adler reactions can be obtained in high yields without formation of offensive by-products. Some of the Diels–Alder reactions are reversible; the decomposition reaction of the cyclic system is called a retro-Diels-Alder reaction (rDA) (Figure 1.22).

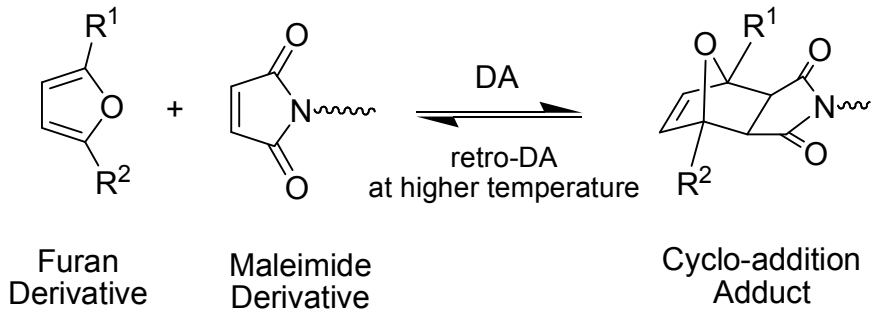


Figure 1.22. Representation of the DA and rDA reactions [23]

1.5.1.1. Uses of Diels Alder Reaction in Polymerizations: Either linear polymers or cross linked structures can be synthesized by Diels Alder reaction. In the generation of linear polymers by Diels Alder cycloadditions, multifunctional diene and dienophiles are used as monomers. Diels Alder reactions have been utilized to obtain the cross-linking of polymer structure via taking the advantage of the inter-macro-molecular couplings with a bifunctional reagent. The thermal sensitivity of the DA can be used to obtain cross-linked polymers that can reversibly back to their monomers.

Recently Sanyal and coworkers [23] utilized the potential of these elegant, versatile and powerful transformations: the Diels–Alder cycloaddition and the retro Diels–Alder cycloreversion reactions, individually or as a combination in the synthesis of polymeric materials. In a short period, the methodologies based on these reactions have enabled the synthesis of various macromolecular constructs difficult to realize otherwise. In addition, the DA cycloaddition offers a reagent-free 'click' reaction to construct various macromolecular architectures. Furthermore, the thermally reversible natures of the DA adducts make them attractive building blocks for the design of thermo reversible materials (Figure 1.23) [23]

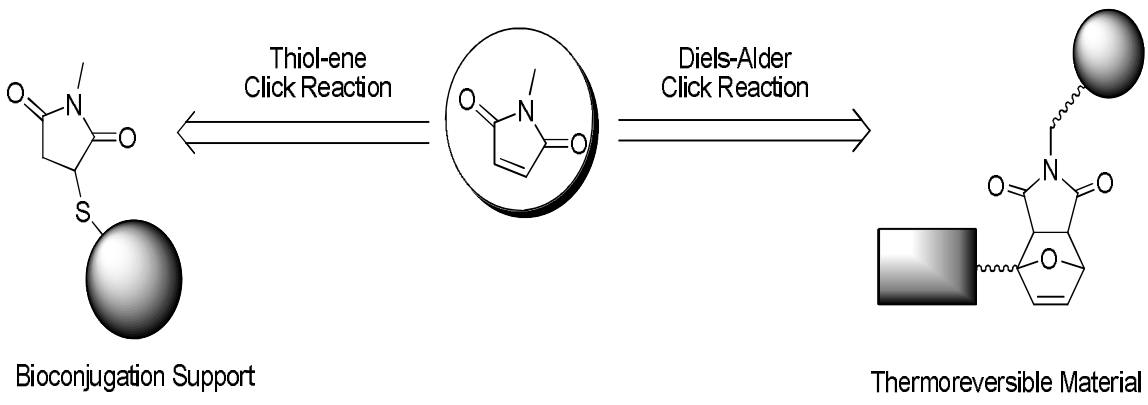


Figure 1.23. Maleimide functional group: An ideal 'click' substrate [23]

Recently O. GOK and coworkers [24] synthesized multiarm star polymers containing thiol-reactive maleimide groups at their core by atom transfer radical polymerization (ATRP). In the procedure used, one end of the initiator contains multiple halogen groups that produce the star architecture upon polymerization and the other end

contains a masked maleimide functional group. Unmasking of the maleimide group after the polymerization provides the thiol reactive maleimide core that widely used in bioconjugation. (Figure 1.24) [24].

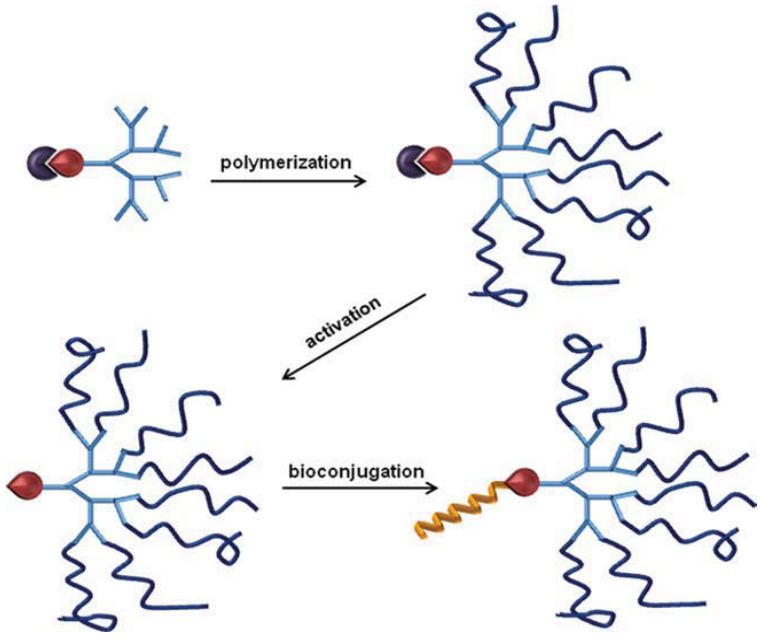


Figure 1.24. The approach to synthesis of thiol reactive multiarm polymers [24]

After obtaining the multiarm star polymer, masked maleimide group was converted to its reactive form. (retro-G2-PEGMA) upon subjecting to the retro-Diels–Alder reaction by heating (Figure 1.25) [24].

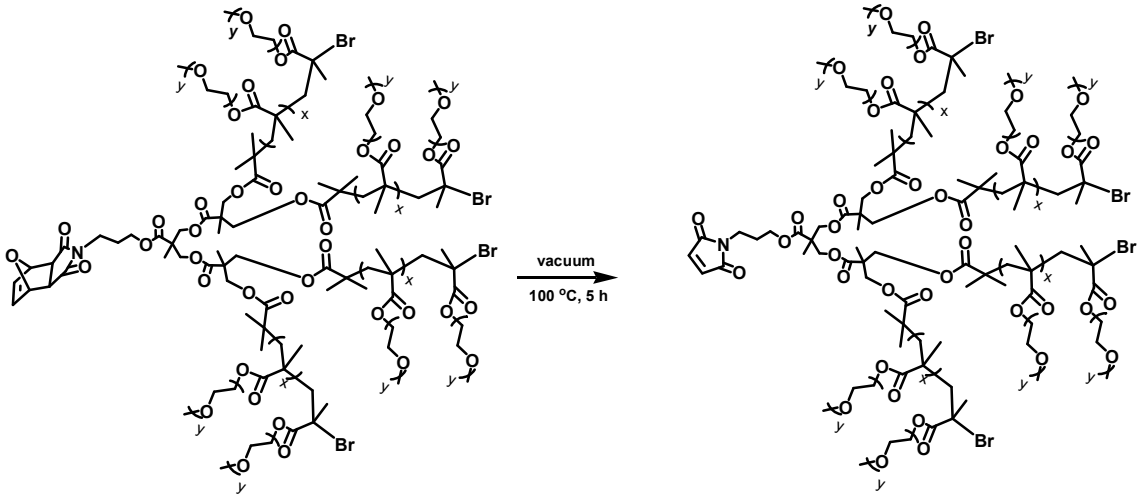


Figure 1.25. Synthesis of the reactive-core polymer (retro-G2-PEGMA) via the retro Diels–Alder cycloreversion [24]

Functionalization of the core maleimide group with a thiol containing tripeptide glutathione was used to demonstrate facile reactivity of the core of these multiarm polymers under reagent-free conditions. The conjugate addition was carried out by treatment of the polymer with glutathione in water at room temperature. (Figure 1.26) [24].

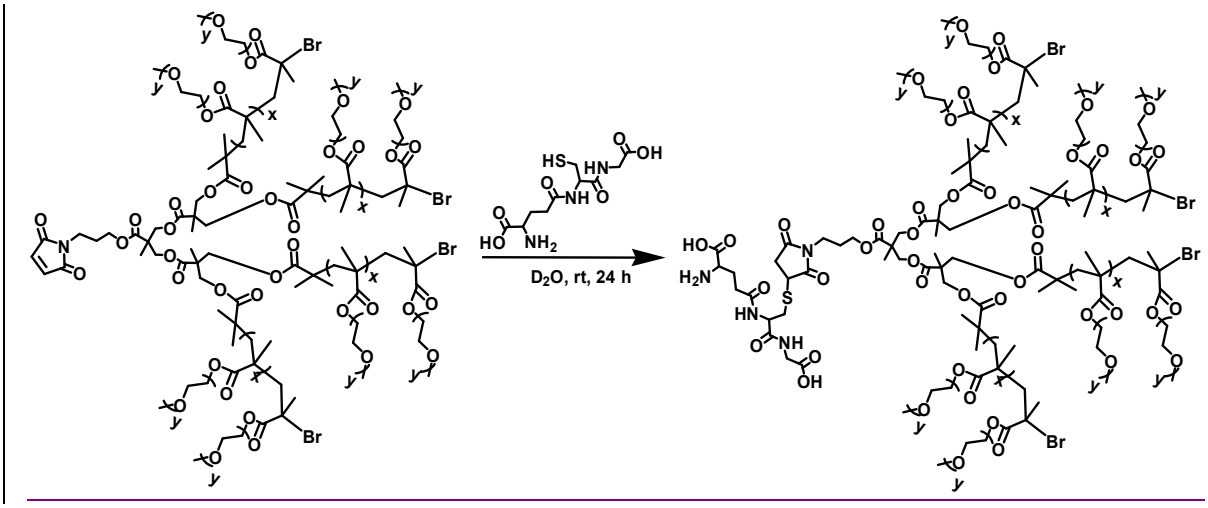


Figure 1.26. Synthesis of the glutathione-conjugated polymer [26]

# 2. AIM OF THE STUDY

In recent years, there has been a growing interest in biodegradable polymer research both in fundamental settings and chemical industry because of their degradability and non toxic degradation products. Although a lot of work has been done in this area, little attention has been paid towards the synthesis of functionalizable biodegradable polymers. To the best of our knowledge there are in fact no studies that report the synthesis of functionalizable biodegradable multiarm polymers. The aim of this study is to synthesize and characterize multiarm biodegradable polymers with a functional core. We synthesized biodegradable polymers in multiarm star architecture because of the advanced bulk and solution properties that make multiarm type polymers attractive candidates for especially biomedical applications like drug delivery.

The unique property of synthesized multiarm biodegradable polymer are their functional core . This core functionality makes polymer reactive and provides the ability of attaching desired molecules to the polymer. By this way, functional materials may be synthesized for any application or the molecules that reacted to the core may be carried to a target. The overall synthetic strategy is outlined in Figure 2.1.

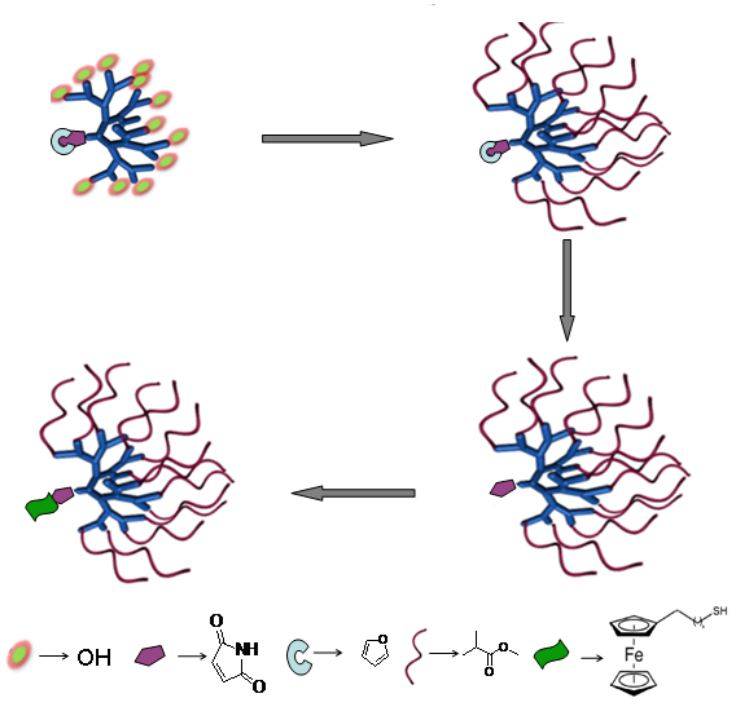


Figure 2.1. Synthetic approach for core reactive biodegradable multiarm star polymers

# 3. RESULT AND DISCUSSION

Biodegradable multiarm star polymers which are bearing furan protected maleimide core were synthesized using the ring opening polymerization technique. Polyester dendrons which have hydroxyl functional groups at their periphery and protected maleimide group at the core were synthesized as macro initiators of polymers. Ring opening polymerization technique was used to obtain biodegradable multiarm star polymers. Deprotection of these dendritic polymers was achieved by retro Diels-Alder reaction. Then, the activity of maleimide moiety at the core is verified by Michael addition reaction with a thiol containing molecule. Synthesis of dendritic initiators, polymerization via ROP, activation of maleimide group and thiol attachment to the core is shown in Figure 3.1.

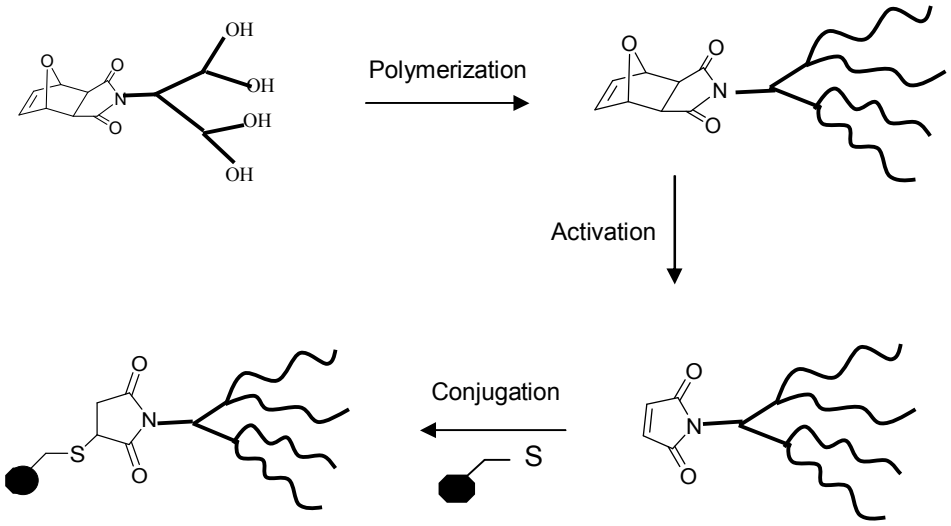


Figure 3.1. General representation of synthesis of biodegradable core reactive multiarm star polymers

## 3.1 Dendrons

As the multiarm initiator for the polymerization, biodegradable polyester dendron with maleimide functionality at the core was chosen and three different generations of dendrons were synthesized according to the literature procedures [24, 25]. Ester groups in dendron structure make its hydrolysis easier in aqueous media. Thus not only the polylactide arms, but also the dendron initiator becomes biodegradable. Dendrons are

synthesized by the divergent method, meaning that the growth of the repeating units of the dendron starts from the core towards the periphery (Figure 1.20).

To prevent the interference of double bond of maleimide group from participating into the polymerization reactions, starting from the dendron synthesis it is protected by a furan moiety. The repeating unit (a) is synthesized and converted to its anhydride form (b) according to literature protocols (Figure 3.2) [26,27].

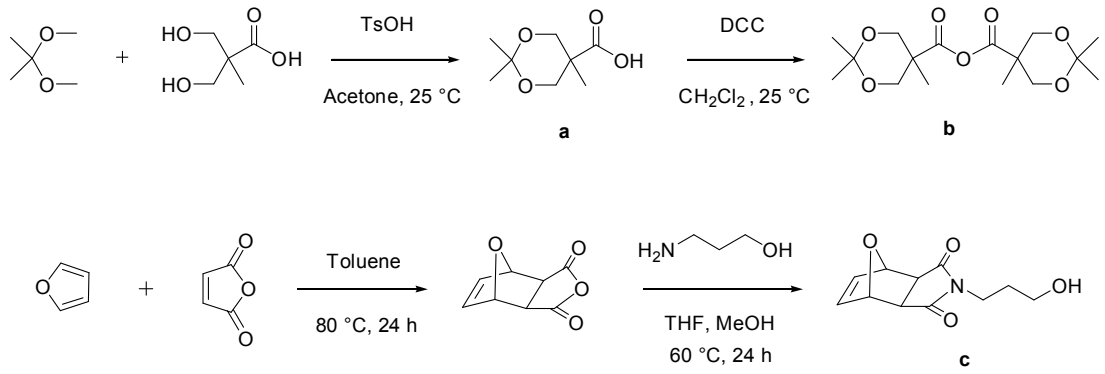


Figure 3.2. Synthesis of (b) and (c)

Anhydride reacted with furan protected maleimide propanol (c) to obtain 1st generation dendron bearing furan protected maleimide group at its core (d). The acetonide groups of this G1 dendron is achieved via treatment with DOWEX, $H^+$ (Figure 3.3).

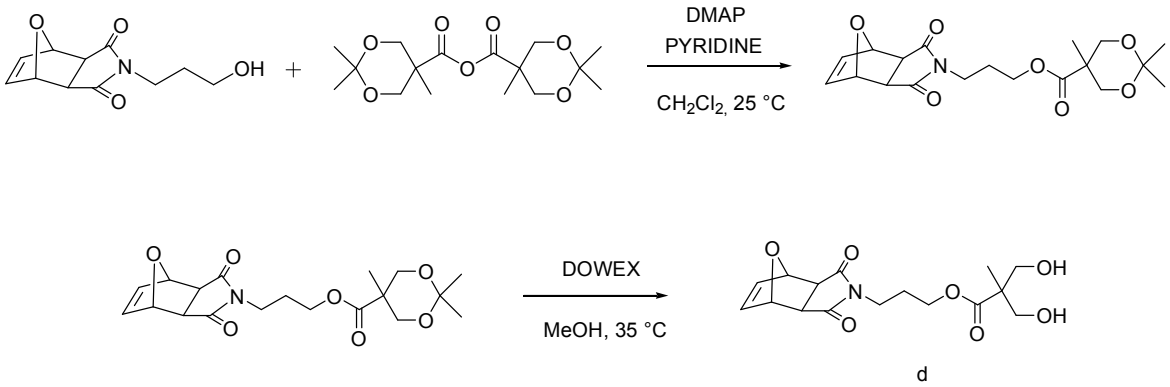


Figure 3.3. Synthesis of 1st generation dendron with furan protected maleimide group at its core

After synthesizing first generation dendron with free alcohol groups, 2nd and 3rd generation dendrons were synthesized in the same manner (Figure 3.4).

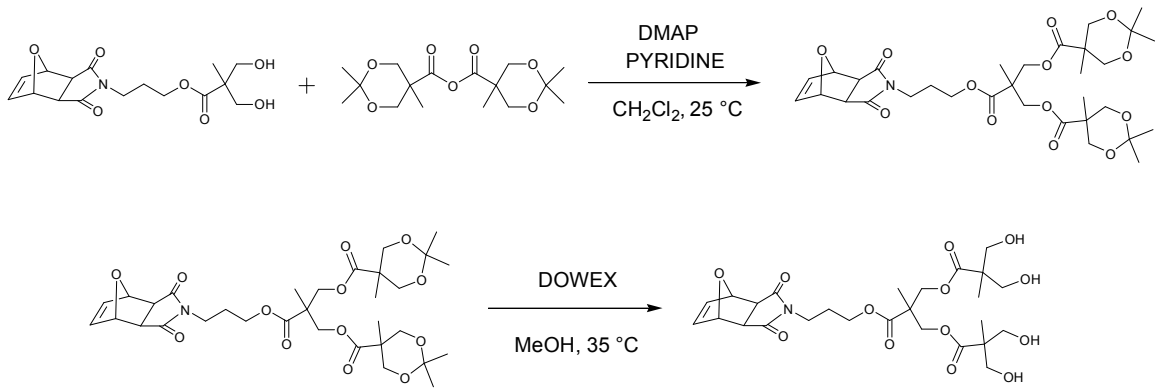


Figure 3.4. Synthesis of 2nd and 3rd generation dendrons

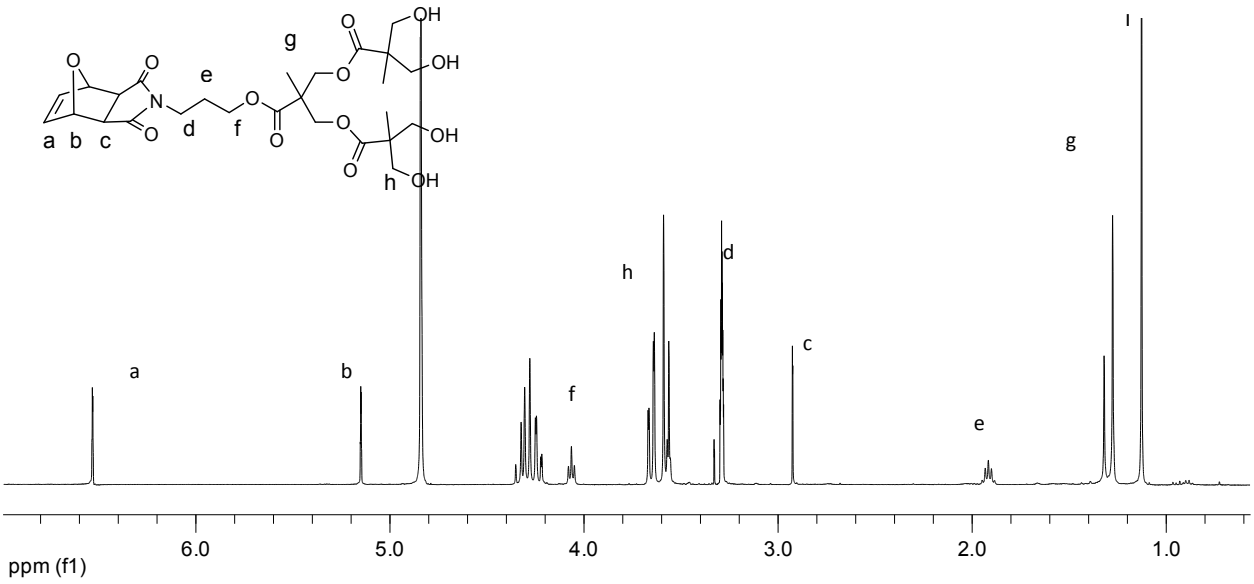


Figure 3.5. $^{1}$H NMR spectrum of 2nd Generation Dendron in deuterated methanol

The dendritic multiarm initiators were obtained in pure form after column chromatography. All dendritic initiators were characterized with $^{1}$H NMR, $^{13}$C NMR and elemental analysis for their structural assignments and purity. For example, the presence of the bicyclic unit composed of the furan protected maleimide unit was evident from the proton resonances at 2.91, 5.16 and 6.54 ppm for the second generation dendritic initiator

(Figure 3.5). The carbon NMR provides further support of the structure due to the presence of four different carbonyl peaks as expected. It is very important to obtain the multiarm initiators in very high purity in order to synthesize polymers with monomodal molecular weight distribution. (Figure 3.6)

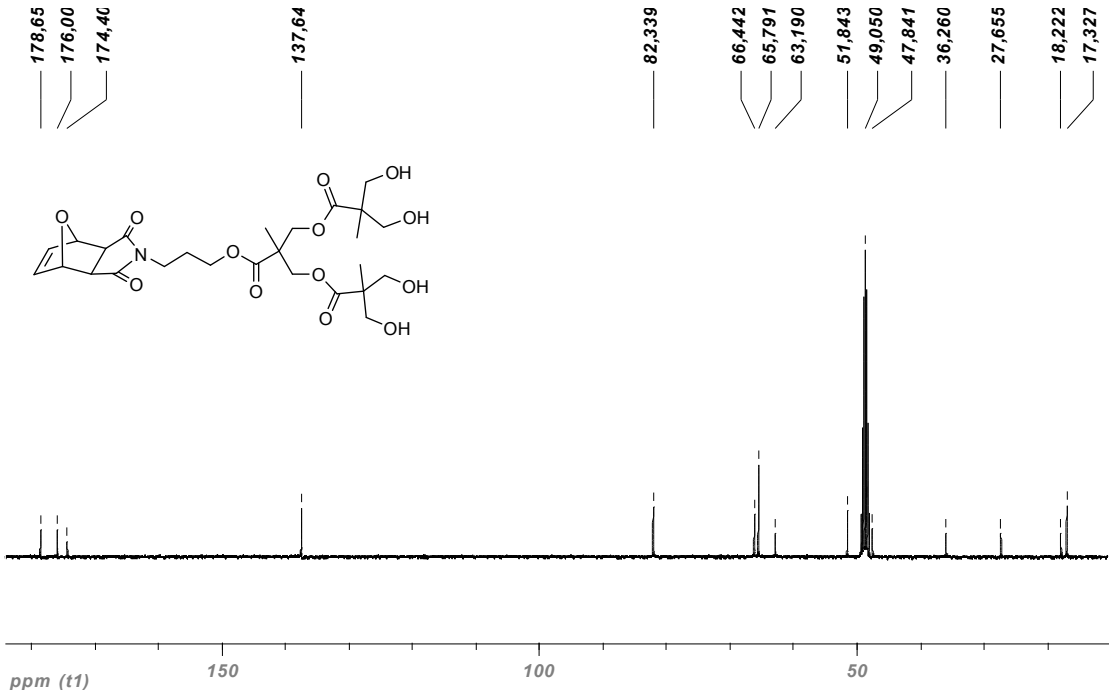


Figure 3.6. $^{13}C$ NMR spectrum of 2nd Generation Dendron in deuterated methanol

### 3.2 Multiarm Star Polymers

The linear polymer arms of multiarm star polymer consist of polylactide (PLA) which is a biodegradable polyester. It has been used in widespread of area with increasing interest because of its characteristics. PLA has a non aggressive degradability which is simple hydrolysis of the ester bond and not require the presence of enzymes to catalyze. Because of its nontoxic degradation products, it has been used in especially medical applications like drug delivery, tissue engineering and sutures. It has a unique crystallinity arising from its stereoregular form. For all these reasons, we synthesized multiarm star Poly D Lactide (PDLA) in this study. [2]

The synthesis of PLA can be categorized into two polymerization techniques which are direct condensation polymerization of lactic acid to (PLA) and Ring Opening Polymerization (ROP) of lactide to PLA. The first method is not used much anymore because of some disadvantages like low control on yielded polymer and need of high temperature and long reaction time. On the other hand, predictable molecular weights, low polydispersities and high end group fidelity are necessities for advance applications of lactide. We synthesized multiarm star polylactide polymers by ROP that can meet these requirements. Moreover, organocatalytic ROP has been chosen to avoid of possible metal remainders which may come from metal complex catalyses used in organometallic ROP. Figure 3.7 shows the general representation of polymerization. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) and thiourea amine (TU) were used as organocatalysts (Figure 3.7) [15, 18, 20].

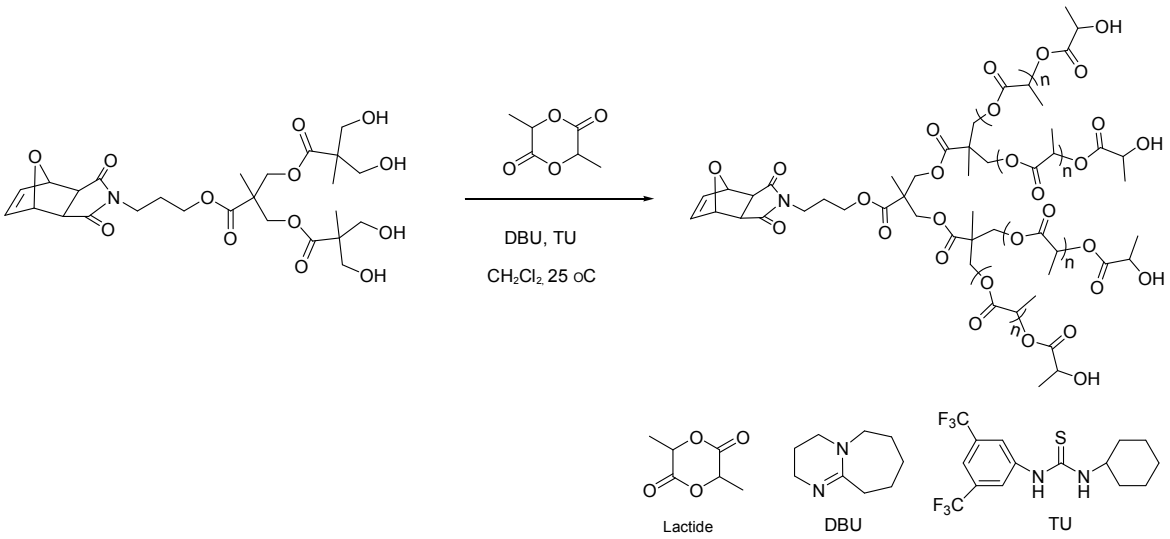


Figure 3.7. Synthesis of multiarm star polymer

Resulted polymers purified via precipitation in cold methanol. After purification, polymers were characterized with $^{1}$H NMR . Peaks at 6.48, 5.22 and 2.81 ppm corresponding to the oxabicyclic moiety observed in analysis proved the presence of the maleimide group (Figure 3.8). Also the molecular weight difference between gpc traces of dendritic initiator and polymer, is evidence of the polymerization (Figure 3.9). The polymerization conditions and the results of $^{1}$H NMR GPC analysis are given in Table 3.1.

Table 3.1 Synthesis and Characterization of Maleimide-Core Polymers

| Polymer | $[M]_0/[I]_0$ | [I] | Time (min) | Temp. ($^oC$) | Conv. (%) | GPC [a] | | $M_{n,theo}$ | $M_{n,NMR}$ |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | $M_n$ (g/mol) | $M_w/M_n$ | | |
| G1-PDLA | 30 | **G1** | 90 | 25 | 82 | 4400 | 1.09 | 3823 | 3936 |
| G1-PDLA | 60 | **G1** | 90 | 25 | 81 | 9600 | 1.07 | 7280 | 9322 |
| G1-PDLA | 80 | **G1** | 90 | 25 | 79 | 15200 | 1.07 | 9377 | 13128 |
| G1-PDLA | 100 | **G1** | 90 | 25 | 78 | 18700 | 1.08 | 11359 | 16915 |
| G2-PDLA | 60 | **G2** | 90 | 25 | 75 | 13400 | 1.07 | 7419 | 7257 |
| G2-PDLA | 120 | **G2** | 90 | 25 | 83 | 21200 | 1.05 | 14830 | 13255 |
| G3-PDLA | 160 | **G3** | 360 | 25 | 83 | 21700 | 1.18 | 20000 | 27296 |

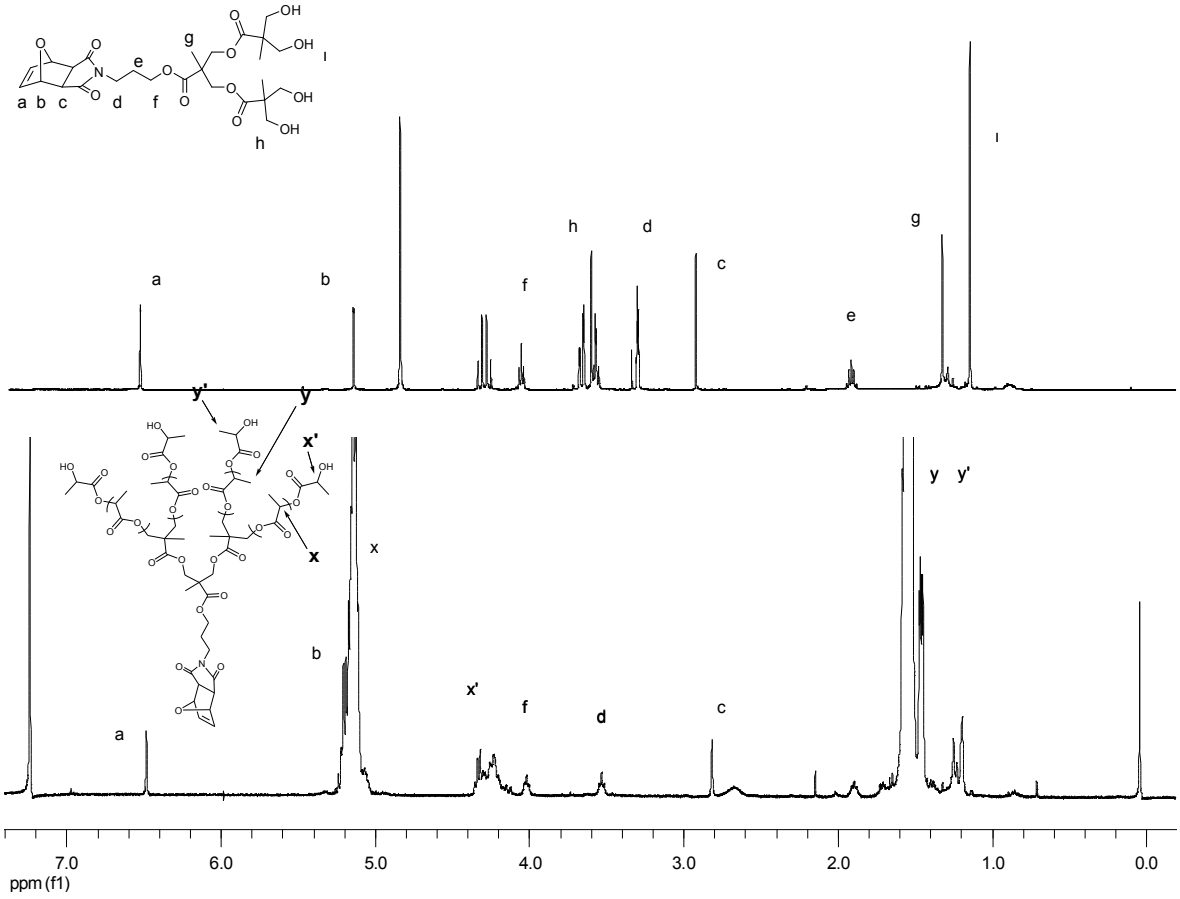


Figure 3.8. $^1$H NMR spectrum of 2$^{nd}$ generation dendron (D2) in deuterated methanol and 2$^{nd}$ Generation Polymer in deuterated chloroform.

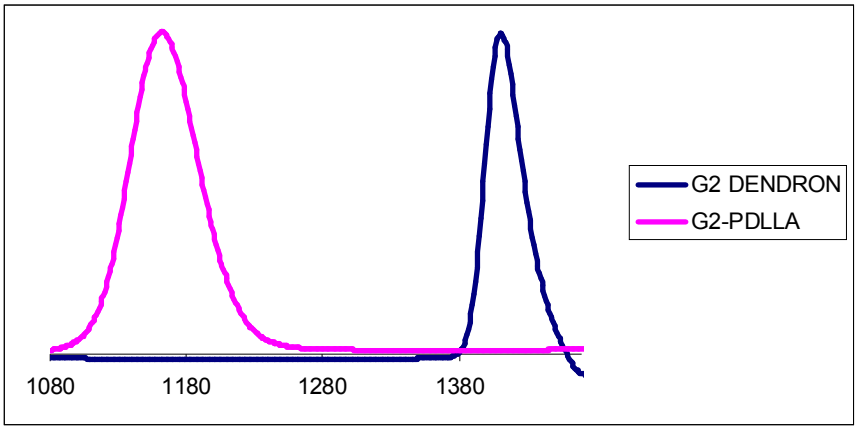


Figure 3.9. Gpc traces of dendritic initiator and polymer

Maleimide group was chosen as the functional group of dendritic initiators because of its reactivity and tendency to Diels Alder reaction. Moreover, maleimide group was in furan protected form to block other possible reactions. After polymerization, polymers containing the masked maleimide group were converted to their reactive form via retro Diels-Alder reaction. Polymer was heated under vacuum at 100 $^{o}$C for 12 h to achieve this goal (Figure 3.10).

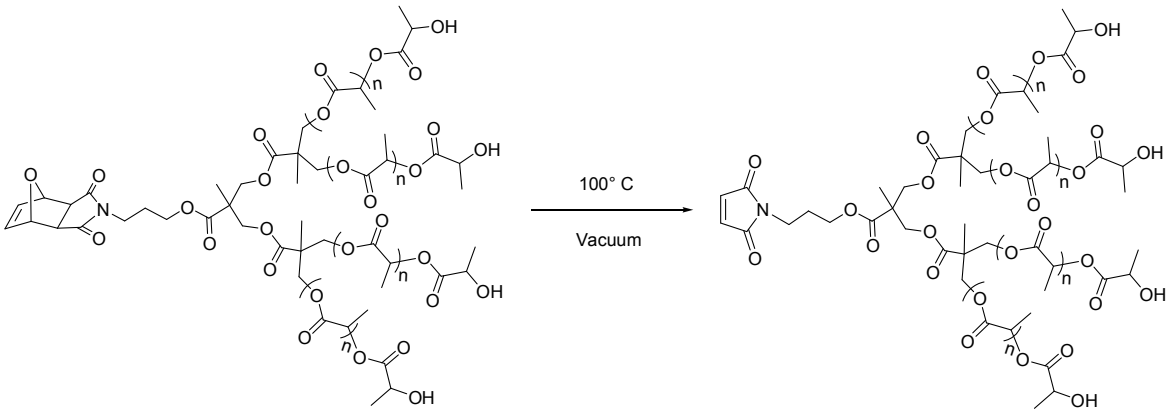


Figure 3.10. Activation of polymer via retro Diels-Alder reaction

Disappearance of proton resonances at 2.83, 5.23 and 6.48 ppm due to the bicyclic core, and appearance of a new proton resonance at 6.73 ppm prove the deprotection reaction of maleimide. Figure 3.11 shows the $^{1}$H NMR spectrum of polymer before and after activation via retro Diels-Alder reaction.

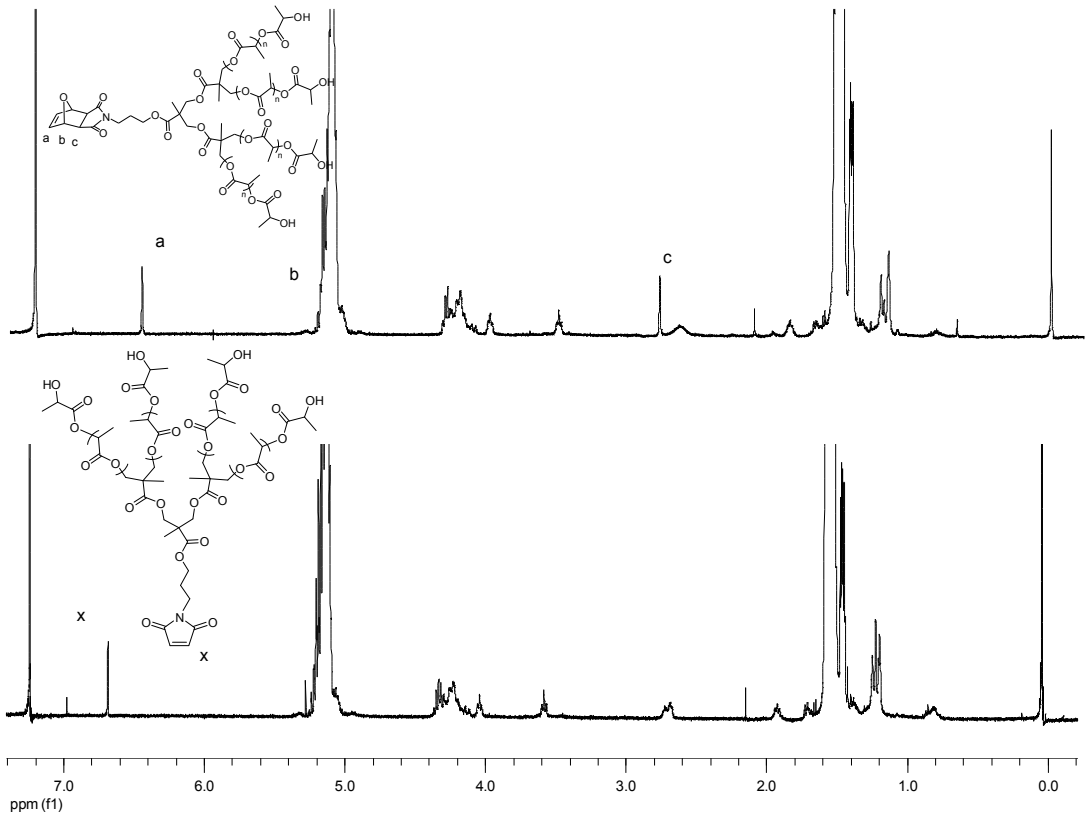


Figure 3.11. $^{1}$H NMR spectrum of polymer before and afteractivation via retro Diels-Alder reaction

Maleimide group also enables the functionalization of polymers via Michael-type addition since it readily reacts with thiol containing molecules. Oftentimes the reaction goes to very high conversions without the need of additional reagents. [24, 28] Conjugation of thiol containing molecules to the maleimide core of the biodegradable multiarm star polymer was utilized to show the efficiency of core reactivity (Figure 3.12) [27]. Precipitation of polymer in methanol was utilized as purification method to get rid of any residual unbound thiol.

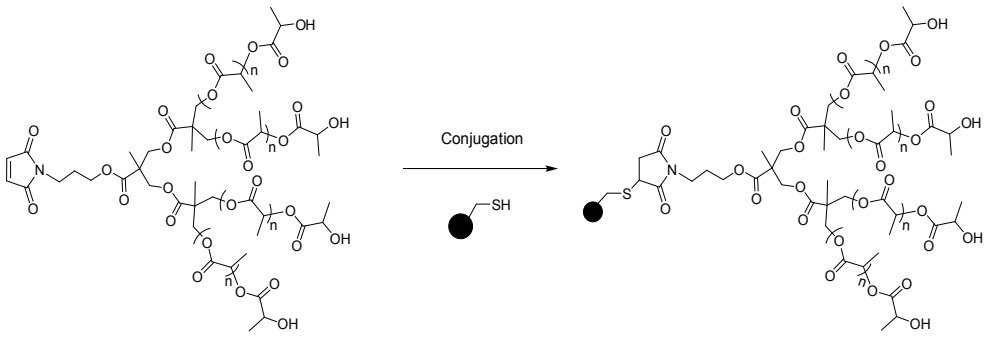


Figure 3.12. Conjugation of thiol containing molecule to the active core of polymer [27]

# 4. EXPERIMENTAL

## 4.1. Materials and Methods

All reagents were obtained from commercial sources (Merck, Aldrich and Alfa Aesar) and were used as received unless otherwise stated. Dry solvents ($CH_2Cl_2$, THF, toluene) was obtained from ScimatCo Purification System, other dry solvents were dried over molecular sieves. DL-lactide (Purac) were recrystallized three times from toluene and dried in a vacuum prior to use. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (98%) was used as received (Aldrich) and stored over molecular sieves (3Å). Thiourea (TU) was prepared according to literature procedure [1]. Dendrons were dried under vacuum after azeotropic distillation with toluene before use. The dendron and polymer characterizations involved $^1H$ solution NMR spectroscopy (Varian 400 MHz and Bruker 260 MHz), FlashEA$^R$ 1112 Series Elemental Analyzer (CHNS Separation Column, PTFE; 2m; 6x5mm), UV-Vis spectroscopy and Fourier transform infrared (FTIR) spectroscopy (Perkin Elmer 1600 Series). The molecular weights were estimated by gel permeation chromatography (GPC) analysis using a Viscotek GPCmax VE-2001 analysis system. PLgel (length/ID 300 mm 3 7.5 mm, 5 lm particle size) Mixed-C column was calibrated with polystyrene standards, using refractive index detector. THF was used as elutent at a flow rate of 1 mL/min at 30 $^oC$.

## 4.2 Synthesis of Dendrons

### 4.2.1 Synthesis of 1st Generation Dendron (D1)

Compound 1 was synthesized according to the previously reported literature procedure. [2]. Anhydride 2 was also synthesized according to the previously reported literature procedure starting from commercially available 2,2-bishydroxymethylpropionic acid. [3]. To a solution of 1 (8.70 g, 26.3 mmol) in dry $CH_2Cl_2$ (40 mL), 2 (3.96 g, 17.5 mmol), 4-(dimethylamino) pyridine (DMAP; 0.86 g, 7.00 mmol), and pyridine (5.5 mL) were added. The mixture was stirred at ambient temperature for 12 h followed by quenching of excess anhydride with (1:1) mixture of pyridine and water (6.6 mL) for 12 h. The reaction mixture was extracted with 1 M $NaHSO_4$ (3 × 20 mL), 10% $Na_2CO_3$ (3 × 20

mL), and brine (1 × 20 mL). Then the combined organic layers were dried over anhydrous $Na_2SO_4$. The residue was concentrated *in vacuo*. The crude product was purified by column chromatography to give protected G1-dendron as a white solid. Then, 1st generation protected dendron was dissolved in MeOH (30 mL) and to this solution Dowex $H^+$ resin was added with a tip of spatula. The resulting mixture was stirred at room temperature until the consumption of protected G1-dendron was observed via TLC. The resin was then filtered off and washed with MeOH. The crude product (D1) was purified by recrystallization with $CHCl_3$ and obtained by filtration to give (7.45 g 84 %) as a white solid. (Figure 4.1).$^1$H NMR ($CDCl_3$, δ, ppm) 6.49 (s, 2H, C*H*=C*H*), 5.24 (s, 2H, C*H* bridgehead protons), 4.59 (t, 2H, *J* = 5.8 Hz, OC$H_2$), 3.86 (dd, 2H, *J* = 8.8, 2.4 Hz, $CH_2$ ester protons), 3.74 (d, 2H, *J* = 8.4, 2.8 Hz, C$H_2$ ester protons), 3.59 (t, 2H, *J*= 6.6 Hz, NC$H_2$), 3.11 (t, 2H, *J*= 6.2 Hz, OH), 2.84 (s, 2H, C*H*-C*H* bridge protons), 1.97-1.91 (m, 2H, $NCH_2CH_2CH_2O$), 1.09 (s, 3H, C(C$H_3$)). $^{13}$C NMR ($CDCl_3$, δ, ppm) = 176.45, 175.57, 136.44, 80.89, 67.66, 60.90, 49.64, 47.37, 35.21, 26.40, 17.18. ELEM. ANAL. Calcd. for $C_{19}H_{25}N_1O_7$: C, 57.65%; H, 6.55%; N, 4.03%. Found: C, 57.74%; H, 6.82%; N, 3.54%.

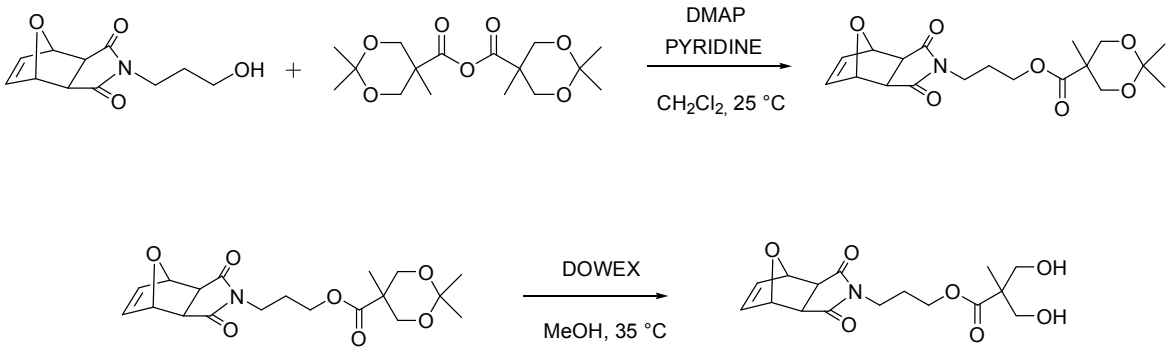


Figure 4.1 Synthesis of 1st Generation Dendron (D1)

### 4.2.2 Synthesis of 2nd Generation-Dendron (D2)

G1-Dendron D1 (2.0 g, 5.3 mmol) was dissolved in MeOH (30 mL). To this solution, Dowex $H^+$ resin was added with a tip of spatula. The resulting mixture was stirred at ambient temperature until the consumption of G1-Dendron was observed via TLC. The resin was then filtered off and washed with MeOH. The filtrate was concentrated *invacuo* to give a white solid (1.78 g, 99% yield). The solid (1.97 g, 4.9 mmol) was then added to a solution of DMAP (0.56 g, 4.6 mmol), pyridine (3.5 mL), and anhydride 2 (5.71 g, 17.3

mmol) in dry $CH_2Cl_2$ (9 mL). The mixture was then stirred at room temperature for 12 h. Excess anhydride was quenched with (1:1) mixture of pyridine and water (4.4 mL) for 12 h. The reaction mixture was diluted with 50 mL $CH_2Cl_2$ and extracted with 1 M $NaHSO_4$ (3 × 20 mL), 10% $Na_2CO_3$ (3 × 20 mL), and brine (1 × 20 mL). Then the combined organic layers were dried over anhydrous $Na_2SO_4$ and concentrated *invacuo*. The crude product was purified by column chromatography to give protected G2-dendron as a colorless viscous liquid. Then, 2nd generation dendron was dissolved in MeOH (30 mL) and to this solution Dowex $H^+$ resin was added with a tip of spatula. The resulting mixture was stirred at room temperature until the consumption of protected G2-dendron was observed via TLC. The resin was then filtered off and washed with MeOH. The crude product (D2) was purified by column chromatography. The product was obtained by filtration to give (2.69 g, 89 %)as a white solid (Figure 4.2). $^1$H NMR ($CD_3OD$, δ, ppm) 6.47 (s, 2H, C*H*=C*H*), 5.08 (s, 2H, C*H* bridgehead protons), 3.99 (t, 2H, *J*= 6.2 Hz, O$CH_2$), 3.60 (dd, 4H, *J* = 6.4, 4.4 Hz, $CH_2$ ester protons), 3.54-3.47 (m, 10H, $CH_2$ ester protons and N$CH_2$), 3.24-3.23 (m, 4H, OH), 2.85 (s, 2H, C*H*-C*H* bridge protons), 1.87-1.81 (m, 2H, $NCH_2CH_2CH_2O$), 1.25 (s, 3H, C($CH_3$)), 1.07 (s, 6H, C($CH_3$)$_2$).$^{13}$C NMR ($CDCl_3$, δ, ppm) = 178.65, 176.01, 174.41, 137.64, 82.34, 66.44, 65.79, 63.19, 51.84, 47.84, 36.26, 27.66, 18.22, 17.33. ELEM. ANAL. Calcd. for $C_{32}H_{45}N_1O_{13}$: C, 58.98%; H, 6.96%; N, 2.15%. Found: C, 58.91%; H, 7.05%; N, 1.78%.

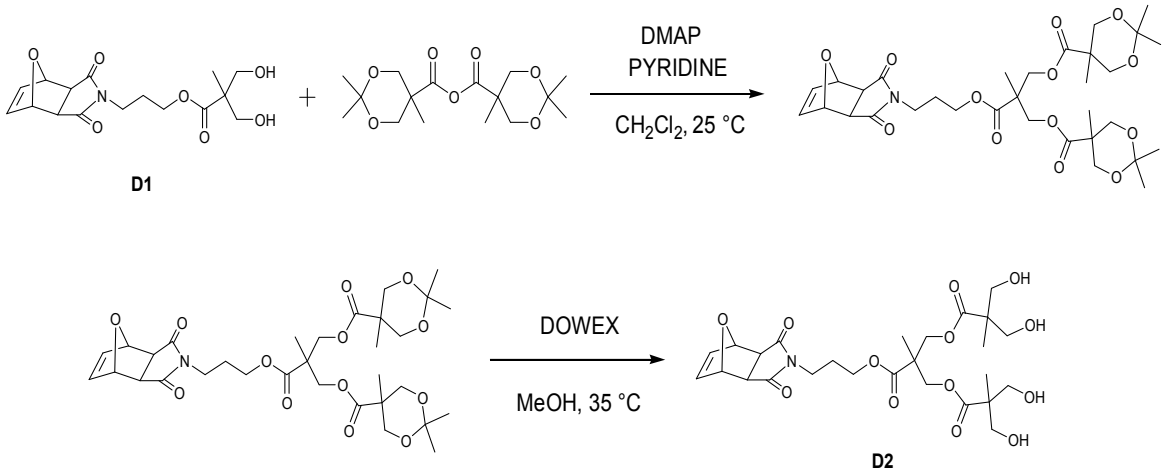


Figure 4.2. Synthesis of 2nd Generation Dendron (D2)

### 4.2.3 Synthesis of 3rd Generation-Dendron (D3)

G2-Dendron D2 (0.52 g, 0.79 mmol) was dissolved in MeOH (10 mL) and Dowex $H^+$ resin was added to this solution,with a tip of spatula. The resulting mixture was stirred at ambient temperature until the consumption of G2-Dendron was observed via TLC. The resin was then filtered off and washed with MeOH. The filtrate was concentrated *in vacuo* to give a white solid (0.44 g, 98% yield). The solid (0.42 g, 0.74 mmol) was then added to a solution of DMAP (0.19 g, 1.55 mmol), pyridine (2.7 mL), and Compound 2 (1.96 g, 5.90 mmol) in dry $CH_2Cl_2$ (10 mL). The mixture was then stirred at room temperature for 12 h. Excess anhydride was quenched with (1:1) mixture of pyridine and water (9 mL) for 12 h. The reaction mixture was diluted with 20 mL of $CH_2Cl_2$ and then extracted with 1 M $NaHSO_4$ (3 × 20 mL), 10% $Na_2CO_3$ (3 × 20 mL), and with brine (1 × 20 mL). Then the combined organic layers were dried over anhydrous $Na_2SO_4$. The residue was concentrated *in vacuo*. The crude product was purified by column chromatography to give of protected G3-dendron as a colorless viscous liquid 95 %).

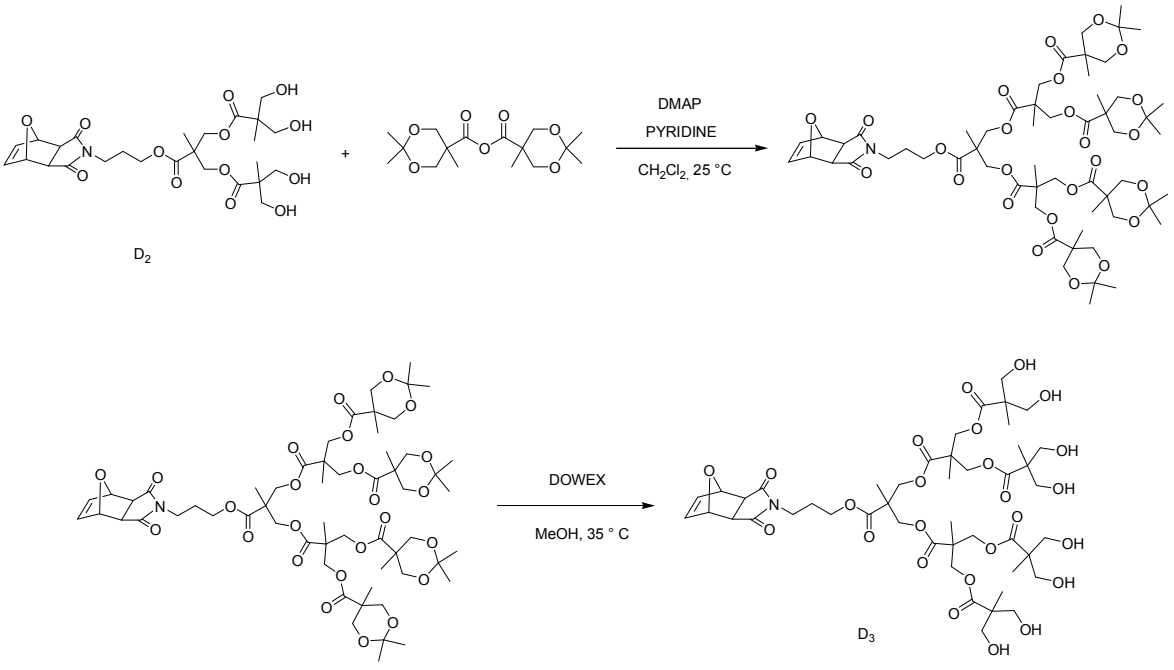


Figure 4.3 Synthesis of 3rd Generation Dendron (D3)

Protected G3-dendron was dissolved in MeOH (20 mL) and to this solution Dowex $H^+$ resin was added with a tip of spatula. The resulting mixture was stirred at room temperature until the consumption of protected G3-dendron was observed via TLC. The

resin was then filtered off and washed with MeOH. The crude product was purified by recrystallization with $CHCl_3$. The product was obtained by filtration to give D3 as a yellow solid (0.66 g, 80.75 %) (Figure 4.3). $^1$H NMR ($CD_3OD$, δ, ppm) 6.47 (s, 2H, C*H*=C*H*), 5.09 (s, 2H, C*H* bridgehead protons), 4.00 (t, 2H, *J* = 6.4 Hz, OC$H_2$), 3.61-3.50 (m, 30H, C$H_2$ ester protons and NC$H_2$), 3.24-3.23 (m, 4H, OH), 2.87 (s, 2H, C*H*-C*H* bridge protons), 1.84-1.82 (m, 2H, $NCH_2CH_2CH_2O$), 1.26 (s, 3H, C(C$H_3$)), 1.22 (s, 6H, C(C$H_3$)$_2$),1.07 (s, 12H, C(C$H_3$)$_3$).$^{13}$C NMR ($CDCl_3$, δ, ppm) = 178.57, 175.93, 173.82, 137.64, 82.34, 67.33, 66.24, 65.84, 63.33, 51.80, 47.95, 36.20, 27.72, 18.28, 17.83, 17.36. ELEM. ANAL. Calcd. for $C_{58}H_{85}N_1O_{25}$: C, 57.07%; H, 7.24%; N, 1.15%. Found: C, 57.07%; H, 7.12%; N, 1.04%.

## 4.3 Synthesis of Polymers

### 4.3.1 Synthesis of 1st Generation Poly (DL-Lactide) (PDLLA) (P1)

D-LA (300 mg, 2.08 mmol) and first generation dendron initiator (D1) (12 mg 0.035 mmol) were dried under vacuum for 12 hours after three times azeotropic distillation with toluene. Thiourea (co-catalyst) (15mg, 0.041 mmol) was added. This solid mixture was dissolved in dry $CH_2Cl_2$ (3 mL) under nitrogen atmosphere. DBU was injected to the solution to initiate the polymerization. Polymerization was quenched after 90 minutes by addition of benzoic acid (8 mg). After terminating to the polymerization, solvent was evaporated and polymer purified via precipitation into cold methanol (Figure 4.4). The polymer (P1) was analyzed after filtration. $[M]_0/[I]_0$= 60 ; conversion = 81 %. $M_{n,theo}$=7280, $M_{n,NMR}$= 9322, $M_{n,GPC}$= 9600, $M_w/M_n$= 1.07, relative to PS. $^1$H NMR ($CDCl_3$, δ, ppm) 6.49 (s, 2H, C*H*=C*H*), 5.24-5.08 (m, 3H, C*H* bridgehead protons and CH-O of lactide), 4.37-4.19 (m, 5H, $CH_2$ ester protons and CH-OH of lactide), 4.05-4.01 (m, 2H, OC$H_2$), 3.53 (t, 2H, *J*= 6.6 Hz, NC$H_2$), 2.82 (s, 2H, C*H*-C*H* bridge protons), 1.92-1.86 (m, 2H, $NCH_2CH_2CH_2O$), 1.58-1.45 (m, 6H, $OC(CH_3)$ and $HOC(CH_3)$ of lactide),1.24 (s, 3H, C(C$H_3$)).

### 4.3.2 Synthesis of 2nd Generation PDLLA (P2)

D-LA (300 mg, 2.08 mmol) and second generation dendron initiator (D2) (19.8 mg 0.035 mmol) were dried under vacuum for 12 hours after three times azeotropic distillation

with toluene. Thiourea co-catalyst (15mg, 0.041 mmol) was added. This solid mixture was dissolved in dry $CH_2Cl_2$ (3 mL) under nitrogen atmosphere. DBU was injected to the solution to initiate the polymerization. Polymerization was quenched after 90 minutes by addition of benzoic acid (8 mg). After terminating to the polymerization, solvent was evaporated and polymer purified via precipitation into cold methanol (Figure 4.5). The polymer (P2) was analyzed after filtration. $[M]_0/[I]_0$= 60 ; conversion = 75 %. $M_{n,theo}$=7419, $M_{n,NMR}$= 7257, $M_{n,GPC}$= 13400, $M_w/M_n$= 1.07, relative to PS. $^1$H NMR ($CDCl_3$, δ, ppm) 6.48 (s, 2H, CH=CH), 5.24-5.05 (m, 3H, CH bridgehead protons and CH-O of lactide), 4.36-4.12 (m, 13H, $CH_2$ ester protons and CH-OH of lactide), 4.02 (t, 2H, J= 5.2 Hz, $OCH_2$), 3.53 (t, 2H, J= 6.8 Hz, $NCH_2$), 2.82 (s, 2H, CH-CH bridge protons), 1.91-1.86 (m, 2H, $NCH_2CH_2CH_2O$), 1.73-1.23 (m, 9H, $OC(CH_3)$ and $HOC(CH_3)$ of lactide, $C(CH_3)$ of dendron),1.20 (s, 6H, $C(CH_3)_2$)

### 4.3.3 Synthesis of 3rd Generation PDLLA (P3)

D-LA (300 mg, 2.08 mmol) and first generation dendron initiator (D1) (12 mg 0.035 mmol) were dried under vacuum for 12 hours after three times azeotropic distillation with toluene. Thiourea co-catalyst (15mg, 0.041 mmol) was added. This solid mixture was dissolved in dry $CH_2Cl_2$ (3 mL) under nitrogen atmosphere. DBU was injected to the solution to initiate the polymerization. Polymerization was quenched after 90 minutes by addition of benzoic acid (8 mg). After terminating to the polymerization, solvent was evaporated and polymer purified via precipitation into cold methanol (Figure 4.6). The polymer (P3) was analyzed after filtration. $[M]_0/[I]_0$= 120; conversion = 83 %. $M_{n,theo}$=20000, $M_{n,NMR}$= 27296, $M_{n,GPC}$= 23000, $M_w/M_n$= 1.18, relative to PS. $^1$H NMR ($CDCl_3$, δ, ppm) 6.48 (s, 2H, CH=CH), 5.22-5.04 (m, 3H, CH bridgehead protons and CH-O of lactide), 4.36-4.12 (m, 31H, $CH_2$ ester protons, CH-OH of lactide and $OCH_2$), 3.52 (t, 2H, J= 6.2 Hz, $NCH_2$), 2.82 (s, 2H, CH-CH bridge protons), 1.93-1.86 (m, 2H, $NCH_2CH_2CH_2O$), 1.73-1.36 (m, 6H, $OC(CH_3)$ and $HOC(CH_3)$ of lactide), 1.27 (s, 3H, $C(CH_3)$), 1.23 (s, 6H, $C(CH_3)_2$),1.20 (s, 12H, $C(CH_3)_3$).

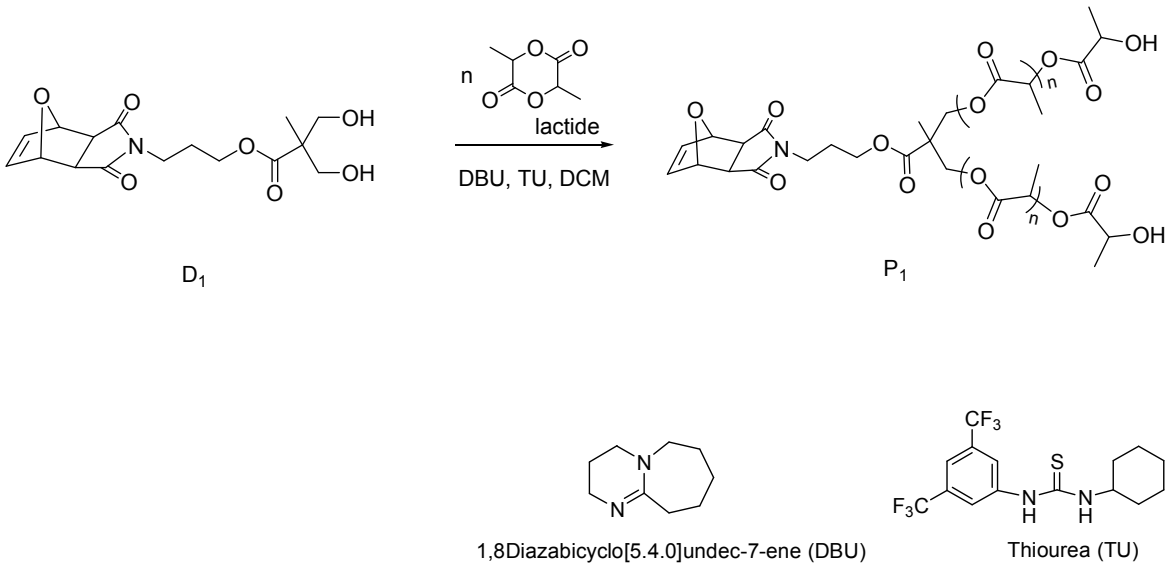


Figure 4.4 Synthesis of 1st Generation Poly (DL-Lactide) (P1)

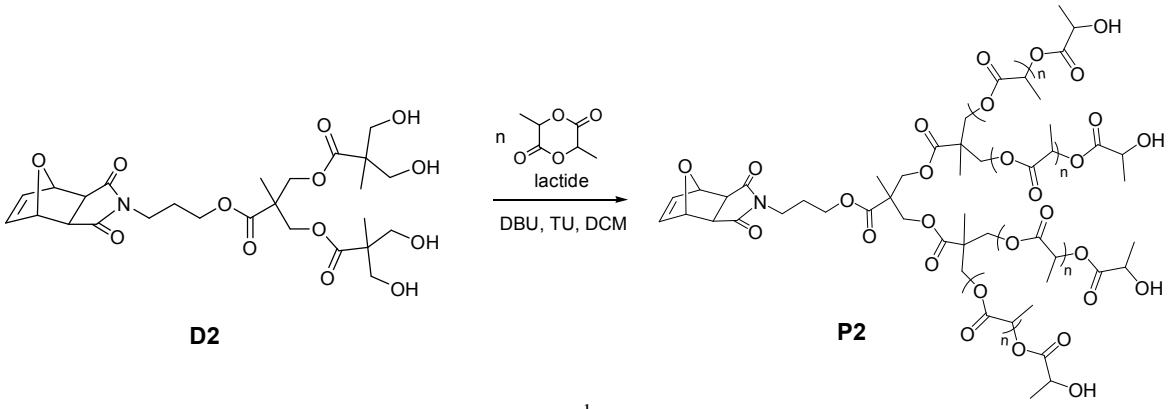


Figure 4.5 Synthesis of 2nd Generation PDLL A (P2)

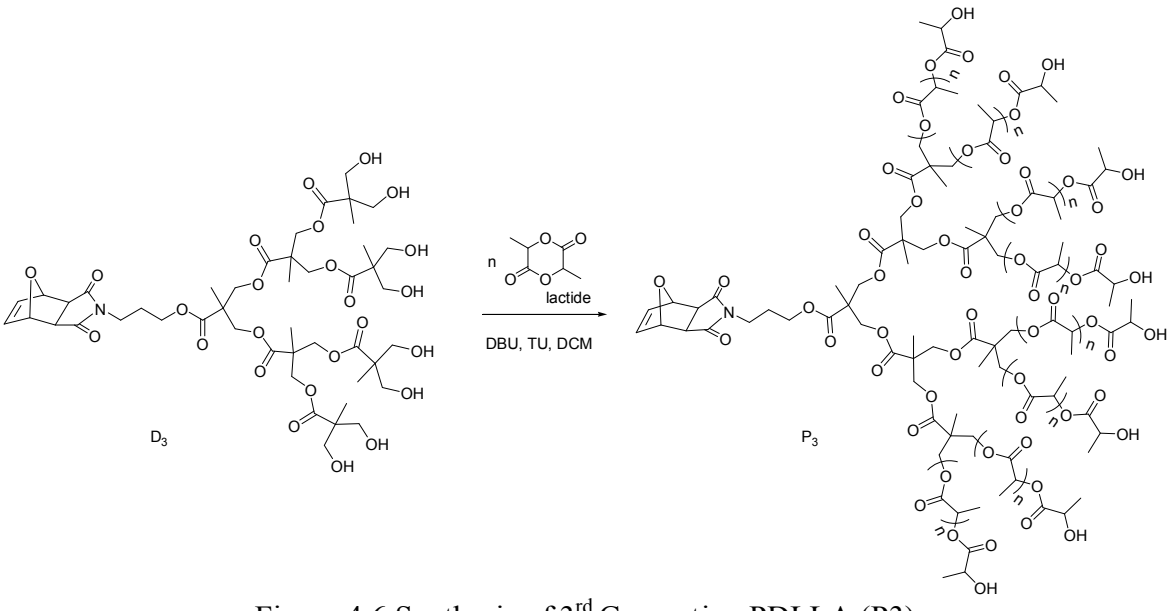


Figure 4.6 Synthesis of 3rd Generation PDLLA (P3)

## 4.4 Activation of Polymers

### 4.4.1 Activation of P1 via Retro Diels Alder Reaction

P1 (70 mg, 0.2 mmol) was heated at 100 °C for 12 hours under high vacuum. NMR analysis proved quantitative conversion of the oxabicyclic moiety to the maleimide functional group (Figure 4.7). $^1$H NMR ($CDCl_3$, δ, ppm) 6.68 (s, 2H, C*H*=C*H*), 5.23-5.10 (m, 1H CH-O of lactide), 4.35-4.19 (m, 5H, $CH_2$ ester protons and CH-OH of lactide), 4.08-4.02 (m, 2H, OC$H_2$), 3.57 (t, 2H, *J*= 6.6 Hz, NC$H_2$), 1.96-1.89 (m, 2H, $NCH_2CH_2CH_2O$), 1.58-1.38 (m, 6H, $OC(CH_3)$ and $HOC(CH_3)$ of lactide),1.24 (s, 3H, $C(CH_3)$).

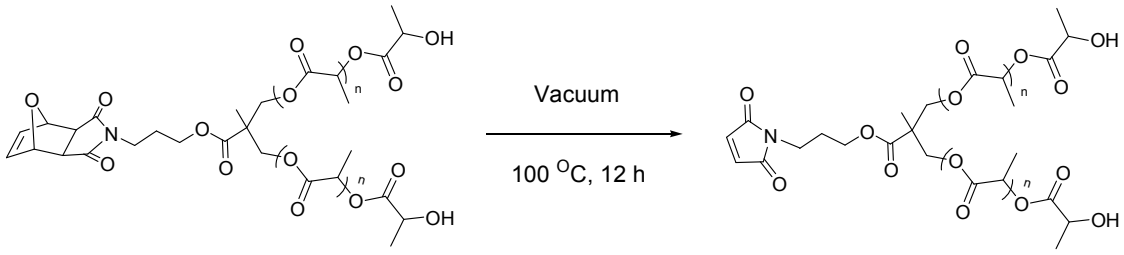


Figure 4.7. Activation of P1.

### 4.4.2 Activation of P2 via Retro Diels Alder Reaction

P1 (200 mg, 0.35 mmol) was heated at 100 °C for 12 hours under high vacuum. NMR analysis proved quantitative conversion of the oxabicyclic moiety to the maleimide functional group (Figure 4.8) . $^1$H NMR ($CDCl_3$, δ, ppm) 6.48 (s, 2H, C*H*=C*H*), 5.26-5.04 (m, 1H, CH-O of lactide), 4.37-4.12 (m, 13H, $CH_2$ ester protons and CH-OH of lactide), 4.04 (t, 2H, *J*= 5.6 Hz, OC$H_2$), 3.58 (t, 2H, *J*= 6.6 Hz, NC$H_2$), 1.94-1.90 (m, 2H, $NCH_2CH_2CH_2O$), 1.73-1.36 (m, 9H, $OC(CH_3)$ and $HOC(CH_3)$ of lactide), 1.25 (s, 3H, $C(CH_3)$), 1.23 (s, 6H, $C(CH_3)_2$).

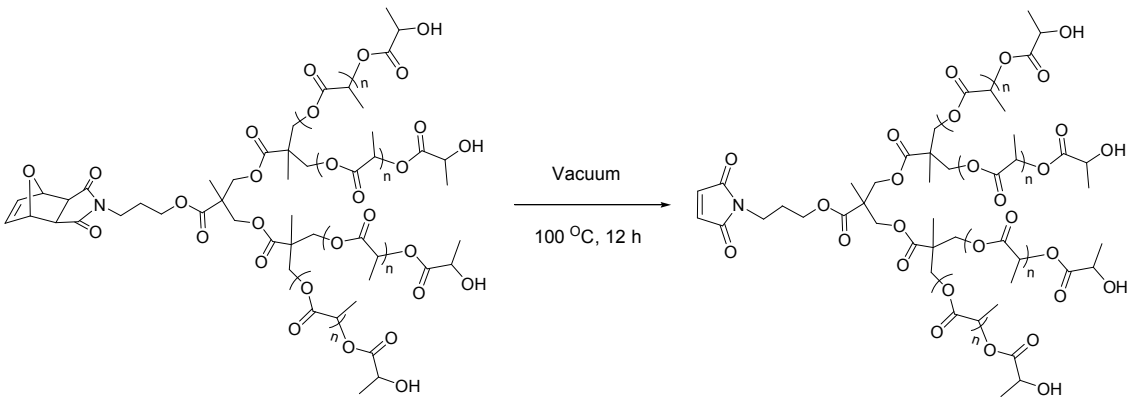


Figure 4.8. Activation of P2

## 4.5 Functionalization of Polymers with 6-(Ferrocenyl) hexanethiol

### 4.5.1 Functionalization of (P1)

P1 (20 mg, 2.1 μmol) was dissolved in $CH_2Cl_2$ (0.65 mL) under nitrogen atmosphere. 6-Ferrocenyl hexanethiol (1.26 mg 4.2 μmol) was dissolved in dry $CH_2Cl_2$ (0.2 mL). This solution was then transferred to polymer solution. TEA (0.665μL, 0.42 μmol) added lastly for catalyzation of reaction. The solution was stirred at room temperature for 24 hours. After evaporation of solvent, product was purified via precipitation in cold 1:3 ether: methanol mixture. (Figure 4.9).

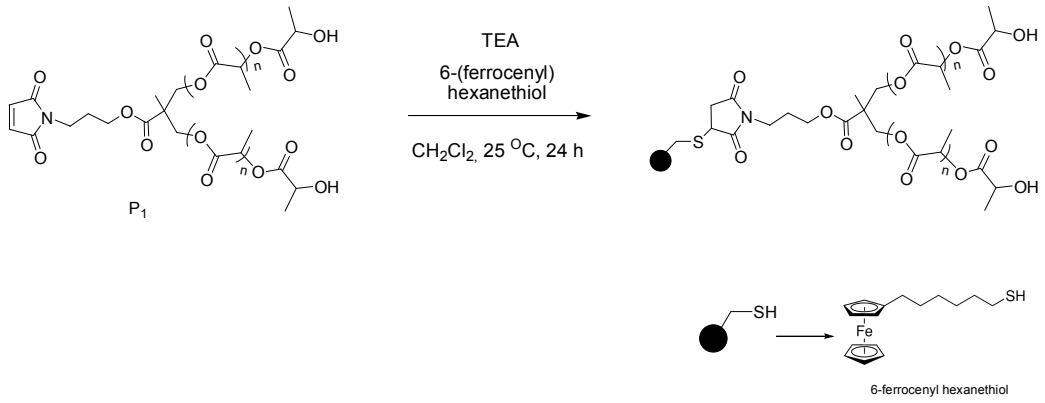


Figure 4.9. Functionalization of P1

### 4.5.2 Functionalization of (P2)

P1 (53 mg, 4.1 μmol) was dissolved in $CH_2Cl_2$ (2 mL) under nitrogen atmosphere. 6-Ferrocenyl hexanethiol (2.49 mg 8.2 μmol) was dissolved in dry $CH_2Cl_2$ (1 mL). This solution was then transferred to polymer solution. TEA (1.3 μL, 8.4 μmol) added lastly for catalyzation of reaction. The solution was stirred at room temperature for 24 hours. After evaporation of solvent, product was purified via precipitation in cold 1:3 ether : methanol mixture.(Figure4.10).

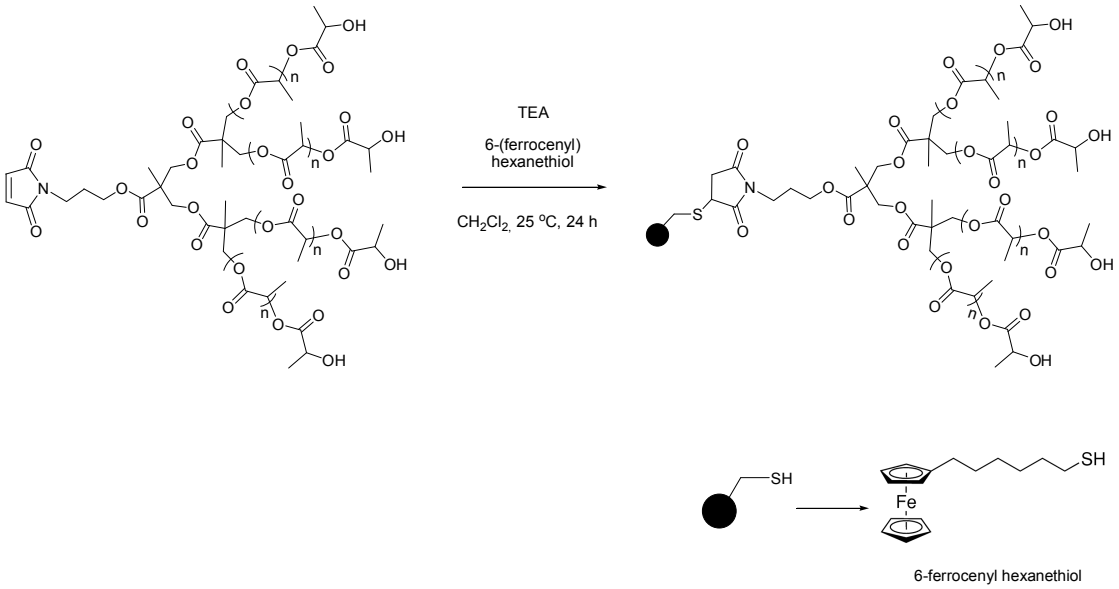


Figure 4.10. Functionalization of P2

# 5. CONCLUSION

In this study, core reactive biodegradable multiarm star polymers were synthesized for the first time in literature. Three generations of polyester dendrons which contain furan protected maleimide unit at the core were synthesized using furan-maleimide based cycloadducts. Poly lactide arms of the star polymer were grown by using organo-catalyzed ring opening polymerization. After synthesizing biodegradable multiarm star polymer with furan protected maleimide core, the maleimide groups were obtained quantitatively in their native form by heating the polymer. This polymer could be functionalized with desired small molecules or biomolecules containing a thiol based nucleophile that will participate in Michael addition reaction with the maleimide groups. We attached active maleimide core a thiol containing molecule to demonstrate the functionality of polymer.

# APPENDIX

$^{1}H$ and $^{13}C$ NMR spectra of the synthesized products are included.

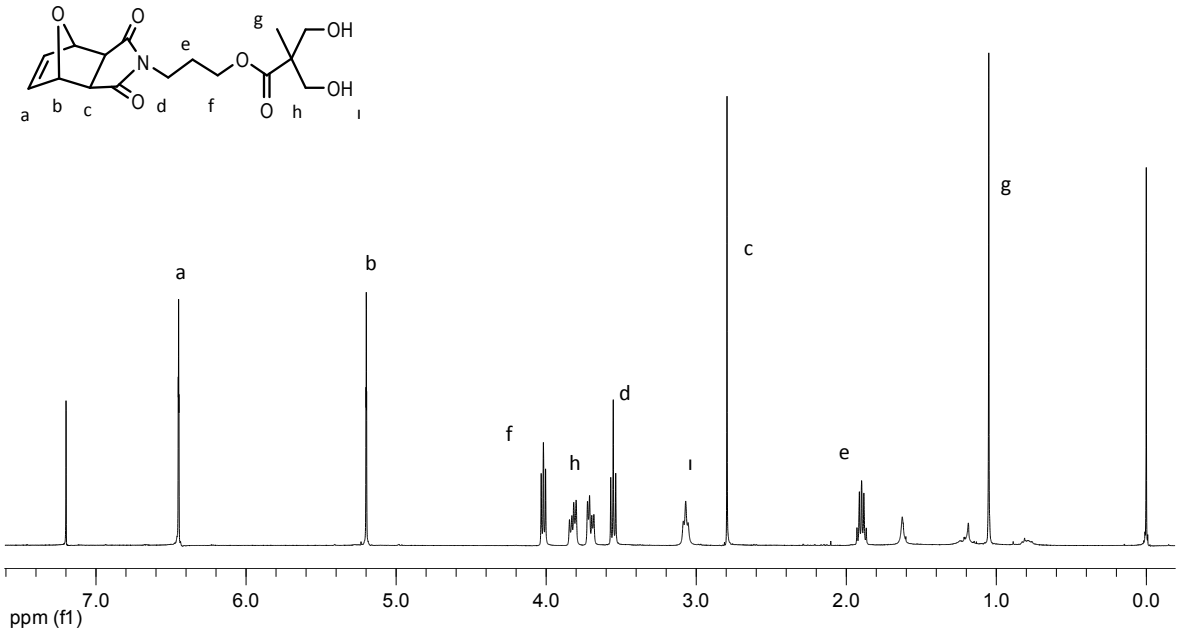


Figure A.1. $^{1}H$ NMR Spectrum of D1

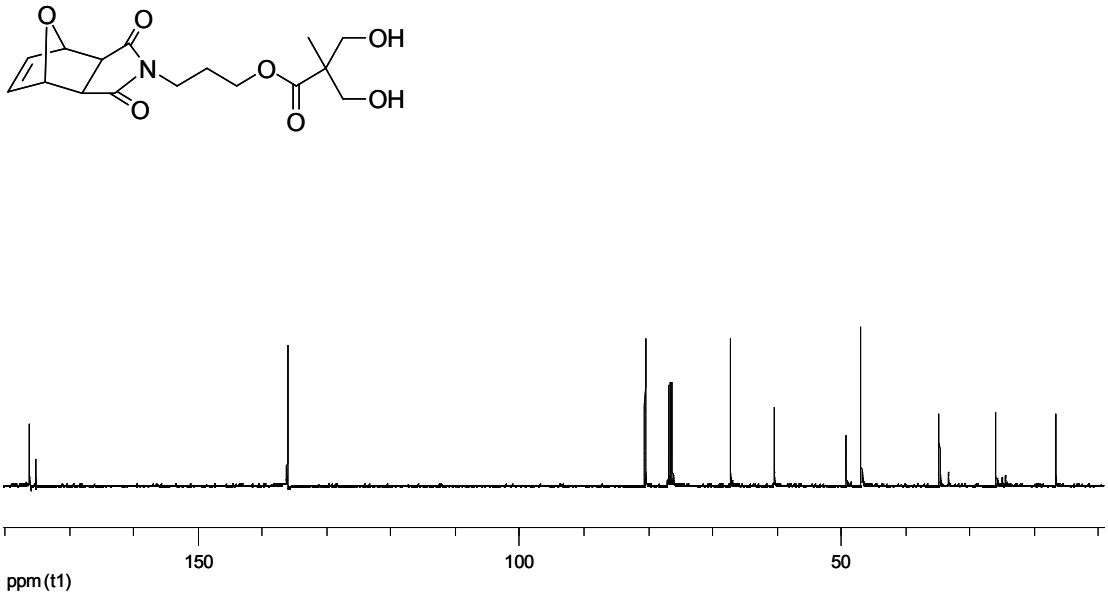


Figure A.2. $^{13}C$ NMR Spectrum of D1

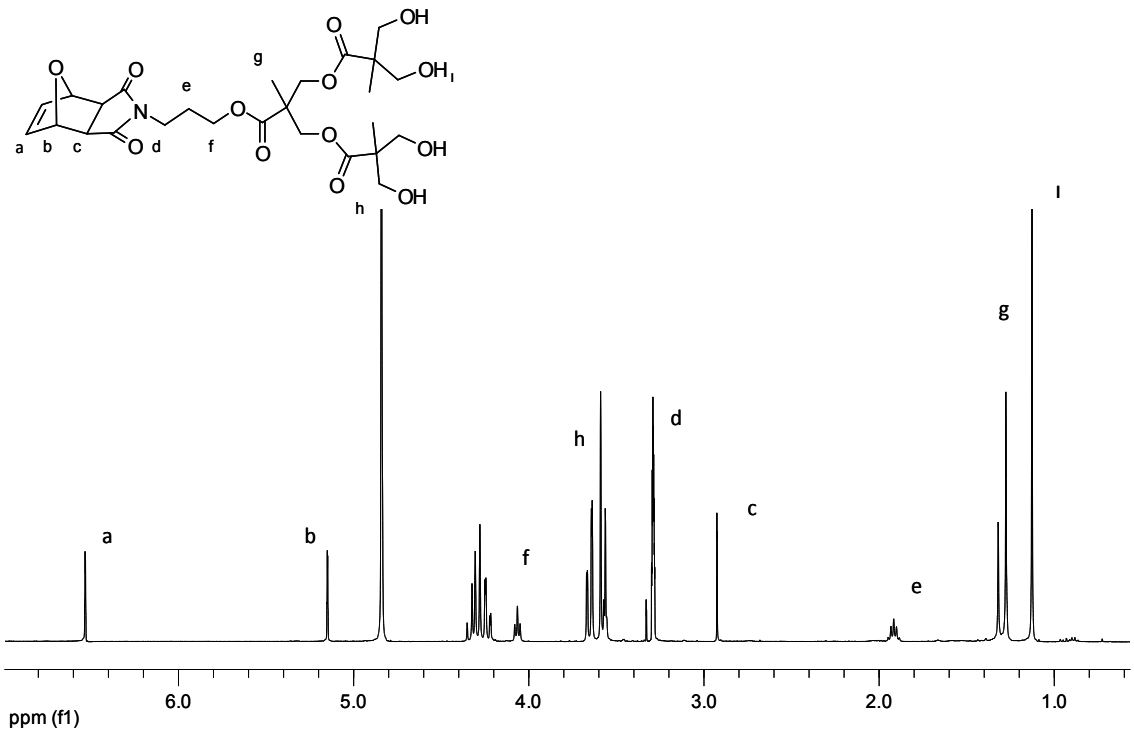


Figure A.3. $^{1}$H NMR Spectrum of D2 ( MeOH)

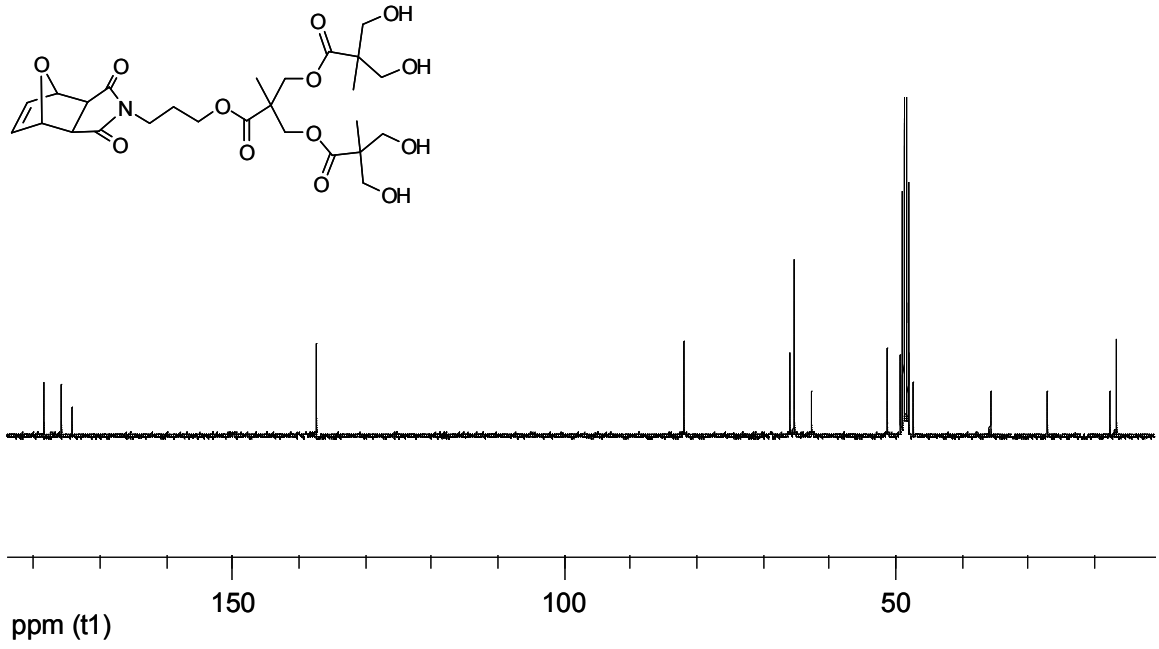


Figure A.4. $^{13}$C NMR Spectrum of D2

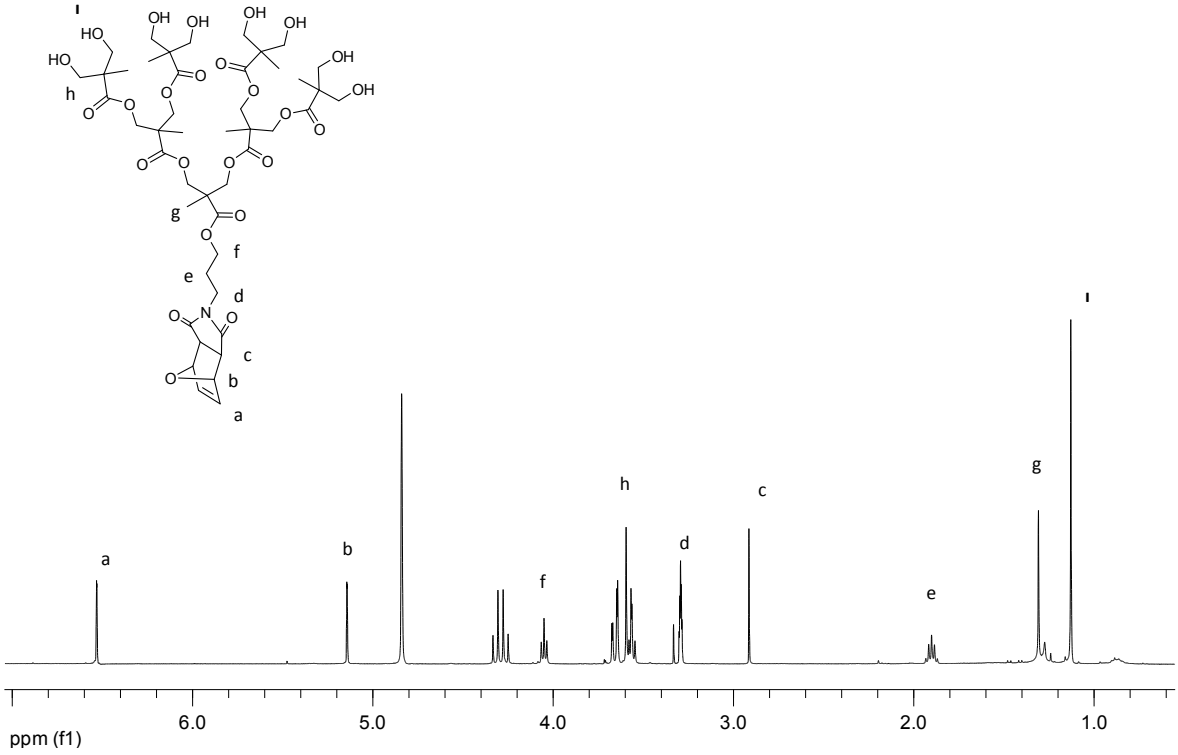


Figure A.5. $^{1}$H NMR Spectrum of D3

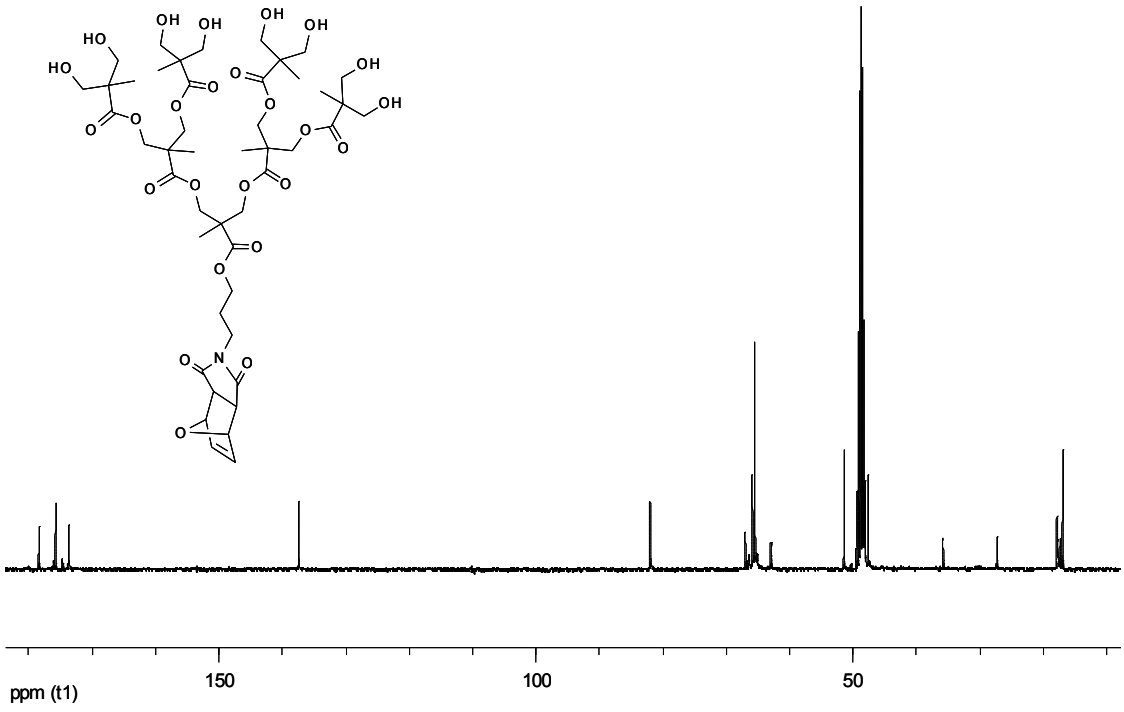


Figure A.6. $^{13}$C NMR Spectrum of D3

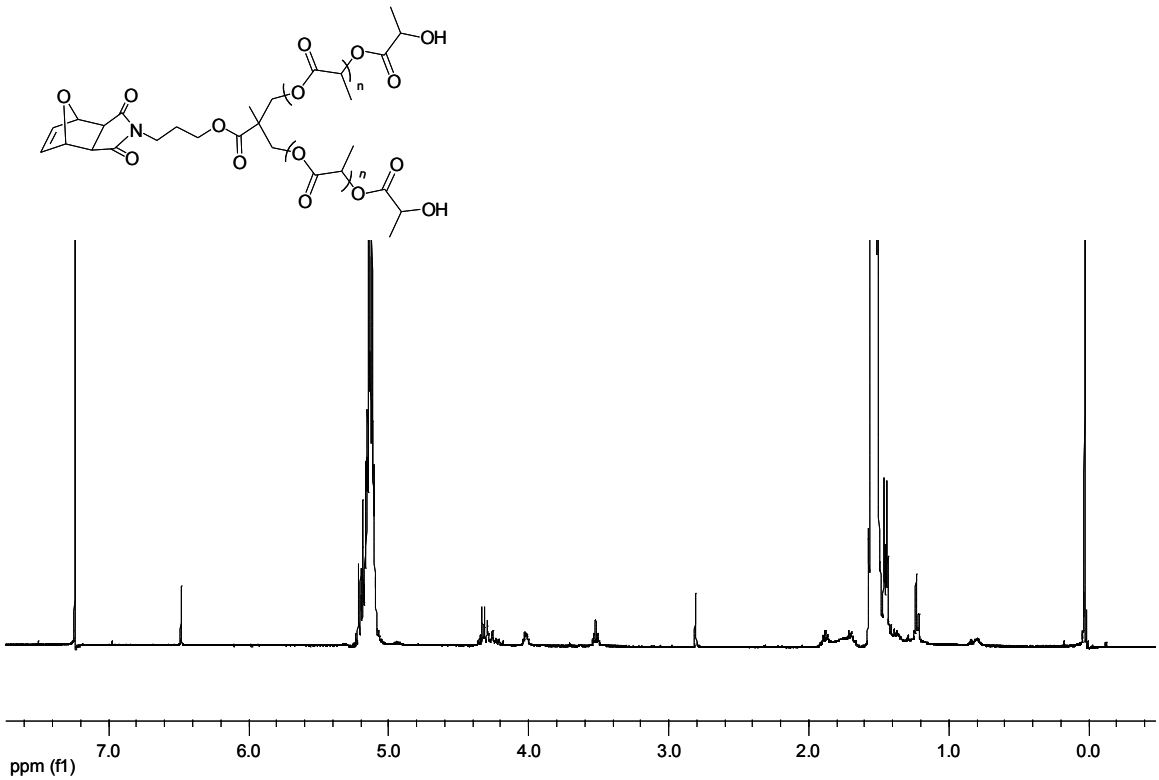


Figure A.7. $^{1}$H NMR Spectrum of P1, $[M]_0/[I]_0 = 60$

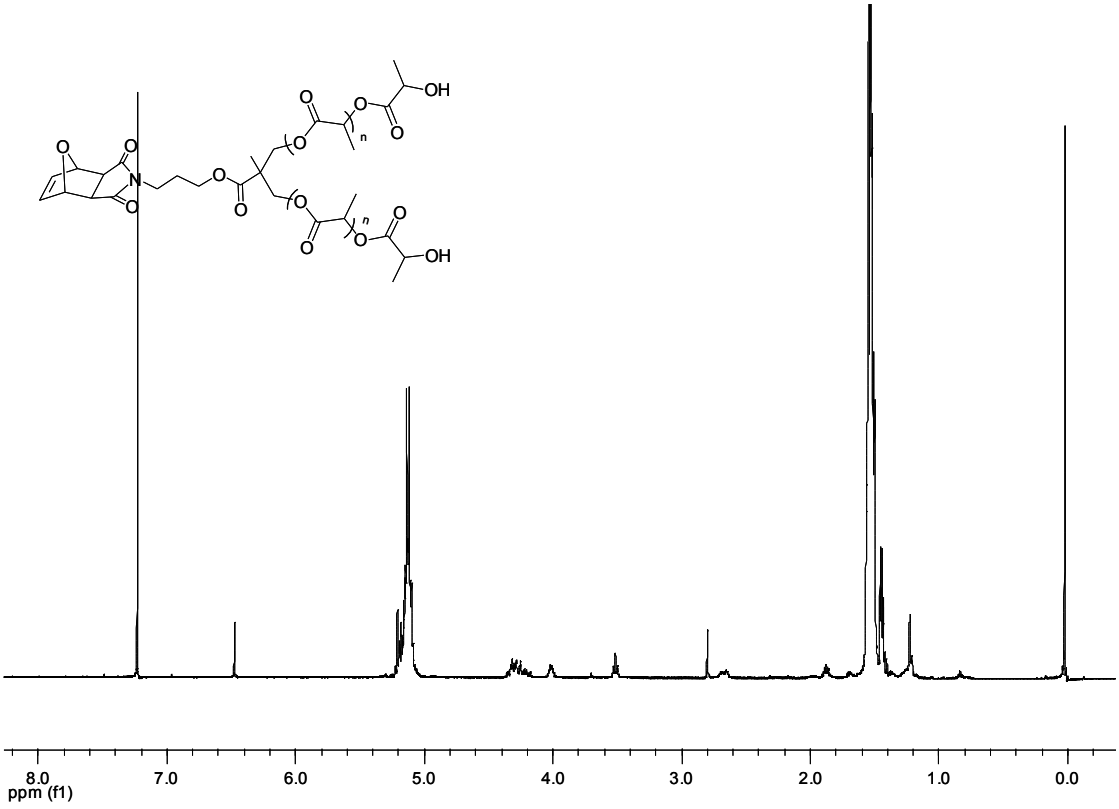


Figure A.8. $^{1}$H NMR Spectrum of P1, $[M]_0/[I]_0 = 30$

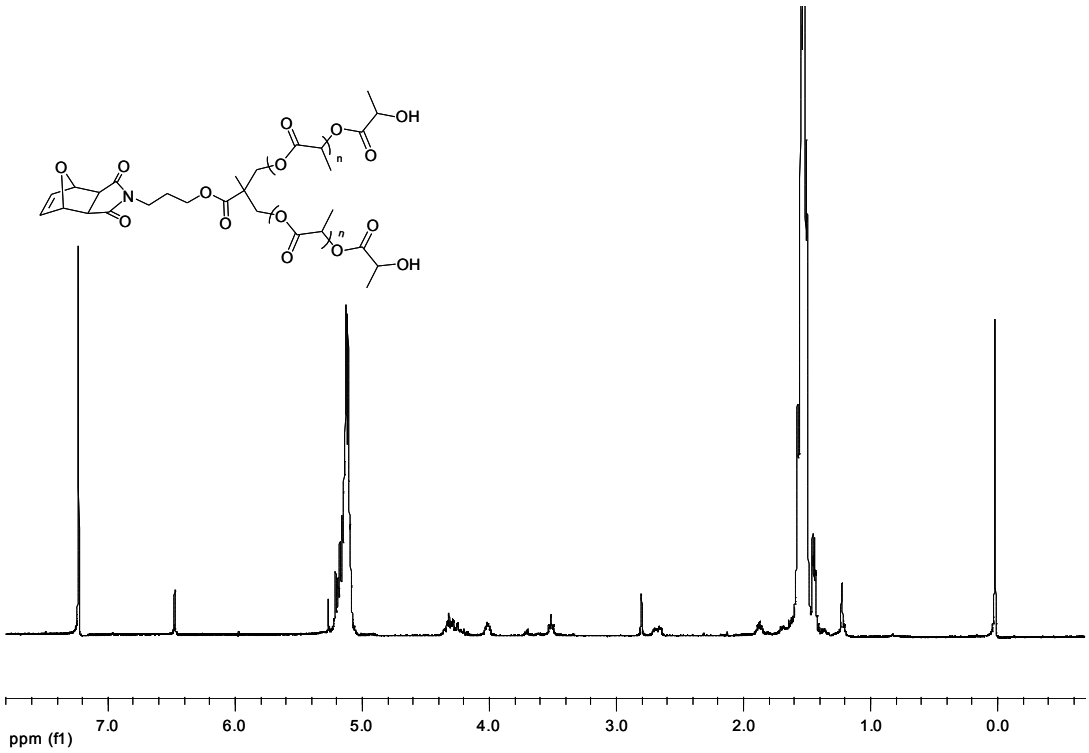


Figure A.9. $^{1}$H NMR Spectrum of P1, $[M]_0/[I]_0 = 100$

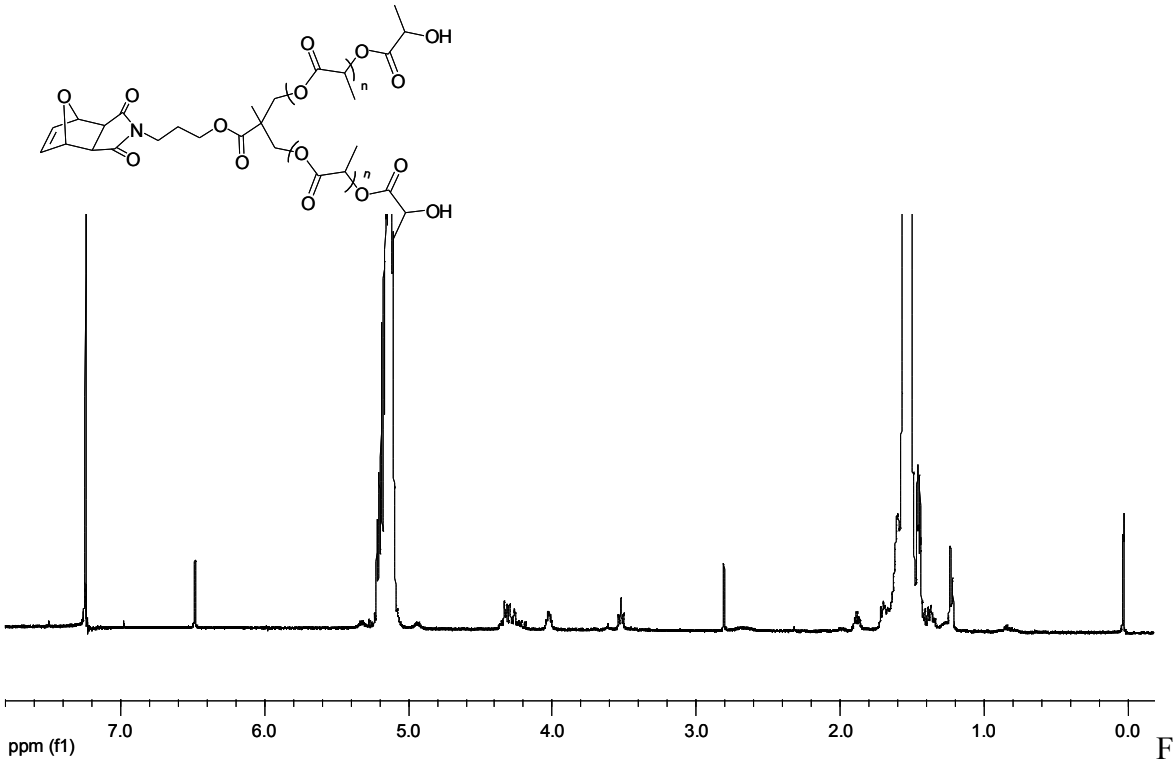


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Figure A.10. $^{1}$H NMR Spectrum of P1, $[M]_0/[I]_0 = 80$

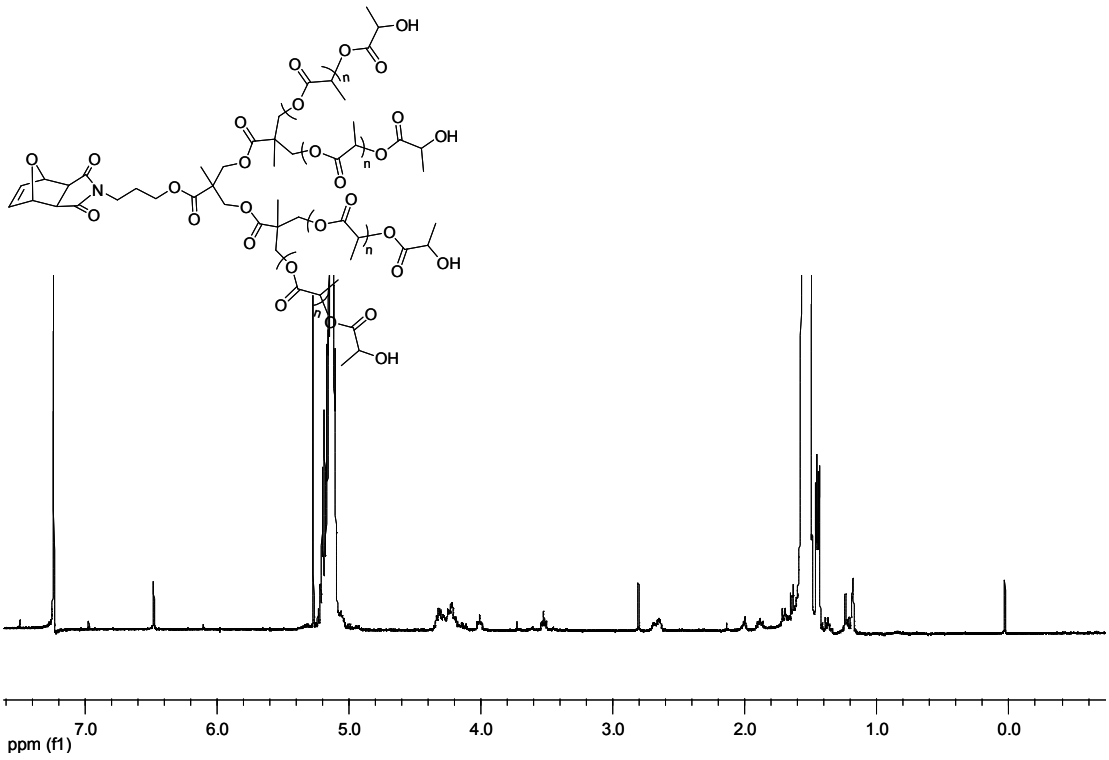


Figure A.11. $^{1}$H NMR Spectrum of P2, $[M]_0/[I]_0 = 120$

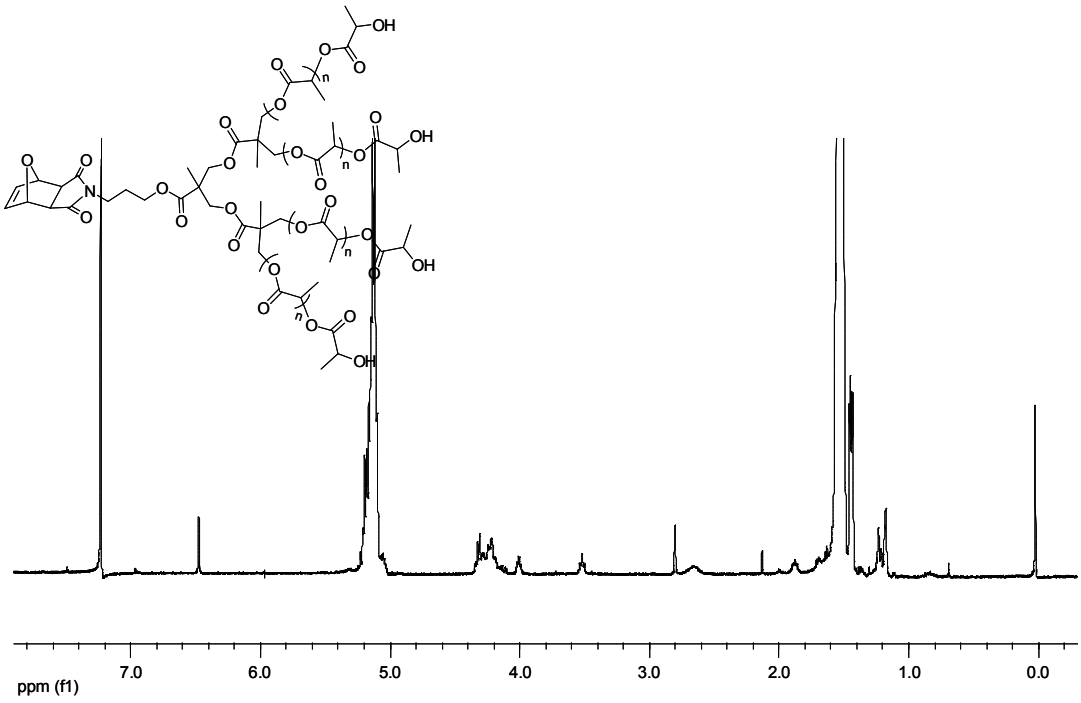


Figure A.12. $^{1}$H NMR Spectrum of P2, $[M]_0/[I]_0 = 60$

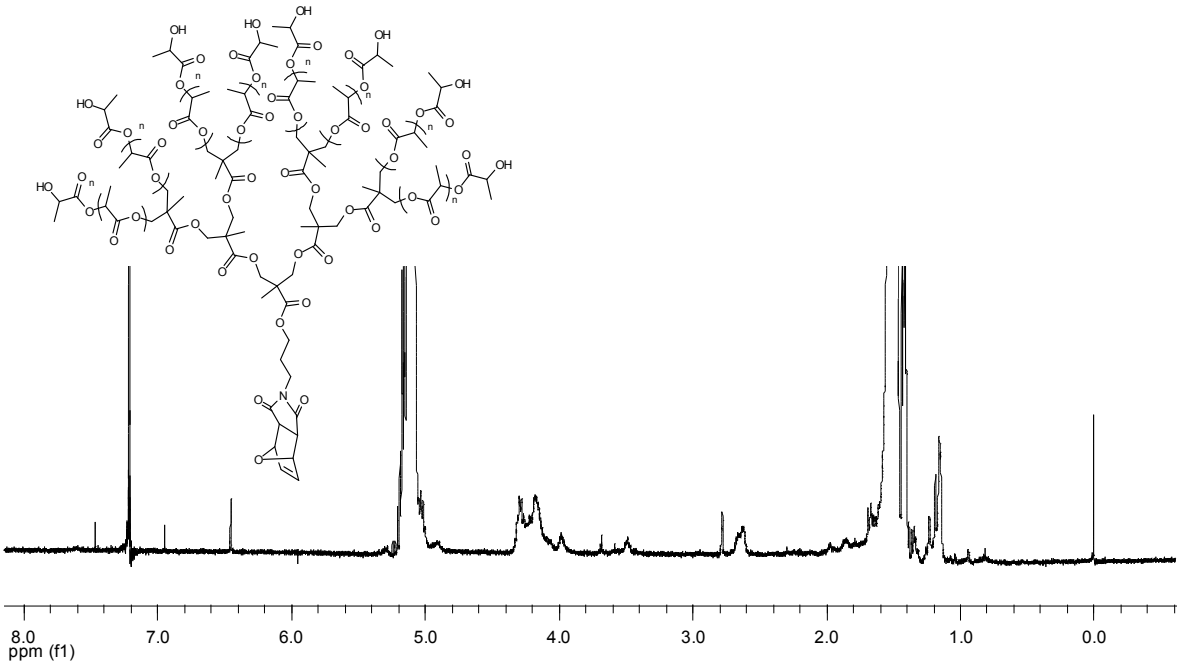


Figure A.13. $^{1}$H NMR Spectrum of P3, $[M]_0/[I]_0 = 150$

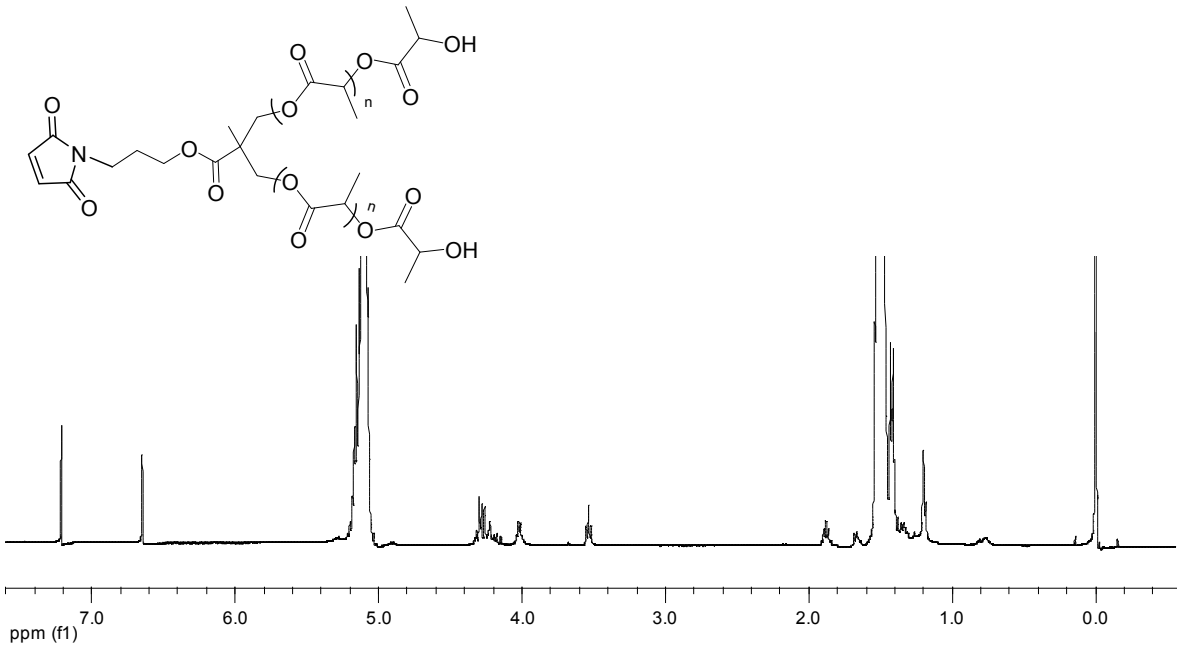


Figure A.14. $^{1}$H NMR Spectrum of P1 after retro (R1)

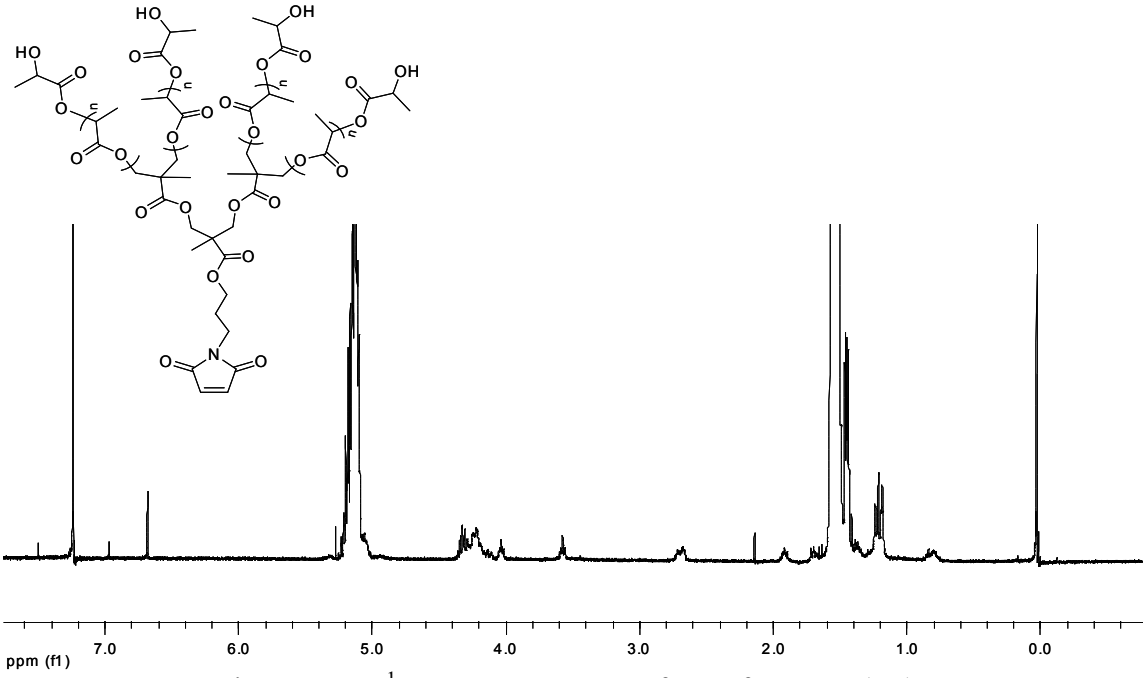


Figure A.15. $^{1}$H NMR Spectrum of P2 after retro (R2)

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