DIELS-ALDER “CLICK” CYCLOADDITIONS: A TOOL FOR SYNTHESIS OF MACROMOLECULES

by
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To My Family

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ABSTRACT

DIELS-ALDER “CLICK” CYCLOADDITIONS: A TOOL FOR SYNTHESIS OF MACROMOLECULES

Diels-Alder reaction is a well known [4+2] cycloaddition reaction between a diene and a dienophile. The fact that Diels-Alder reaction takes place even at room temperature without use of any other reagents and catalysts and formed products are obtained in good purity and yields makes this reaction a widely used method in synthetic organic chemistry. These properties had lead to classification of Diels-Alder reaction among ‘click’ reactions. In this study, this reaction is employed in order to synthesize unsymmetrical dendrons. Synthesis of unsymmetrical dendrons allows formation of dendrimers which can be furnished with more than one functional group and a structure like this, allows formation of targeted drug carrying macromolecules by attachment of targeting groups and drug molecules.

The methodology employed in this research serves as a demonstration for efficient synthesis of segment block dendrimers. The strategy is mainly based on synthesis of three generations of furan functionalized Fréchet type dendrons and synthesis of maleimide functionalized poly (ester) dendrons which are then brought together with Diels-Alder reaction to yield unsymmetrical dendrimers in good yields. The formed dendrimers were further investigated for their stereochemical composition. Moreover the thermo reversible nature of the formed products was also demonstrated.

As an extension of this project, surface of biodegradable poly (ester) dendrons with a maleimide core were furnished with alkyne moieties at their peripheries. These bifunctional macromolecules enable orthogonal functionalization and hence allow attachment of different molecules to the core and surface in a selective and efficient manner.

ÖZET

MAKROMOLEKÜL SENTEZİNDE METOT OLARAK DİELS-ALDER “CLİCK” HALKASAL KATILIM REAKSİYONU

Diels-Alder tepkimesi bir dien ve dienofil arasında gerçekleşen [4+2] halkasal katılım reaksiyonudur. Diels-Alder tepkimesinin, oda sıcaklığında, herhangi bir katalizör veya kimyasala ihtiyaç duymadan, yüksek verimle gerçekleşmesi, onu sentetik organik kimyada sıklıkla kullanılan bir metot haline getirmiştir. Tüm bu sayılan özellikler Diels-Alder tepkimesinin, kolay reaksiyon şartları ve yüksek verimliliğiyle ünlü “click” reaksiyonları sınıfına girmesini sağlamıştır. Bu çalışmada, Diels-Alder tepkimesi dilimli blok dendrimerlerin sentezinde kullanılmıştır. Dilimli blok dendrimer sentezi, birden fazla fonksiyonel grupla donatılmaya müsait makromoleküllerin oluşumunu sağlar ve bu tür bir yapı ilaç molekülleri ve hedeflendirici gruplarla donatılarak, hedeflendirilmis bir taşıyıcı molekül oluşumuna olanak tanır.

Bu araştırmada uygulanan metodoloji, dilimli blok dendrimerlerin verimli bir şekilde sentezlenişini göstermeyi amaçlamaktadır. Merkezinde furan grubu bulunan Fréchet dendronlarının üç jenerasyonu, merkezinde maleimid grubu bulunan poli (ester) dendronlarının üç jenerasyonuyla Diels-Alder tepkimesi kullanılarak birleştirilmiş ve bunun sonucunda oluşan dilimli blok dendrimerler yüksek verimle elde edilmiştir. Oluşan dendrimerler stereokimyasal özellikleri açısından incelenmiştir. Ayrıca, oluşan yapının geri dönüşümlülük özelliği de gösterilmiştir.

Projenin devamı olarak merkezinde maleimid grubu bulunduran biyobozunur poli (ester) dendronların yüzeyi alkin gruplarıyla donatılmıştır. Çift reaktif gruba sahip olan bu moleküller, dendronun birden fazla fonksiyonel grupla seçici olarak tepkimeye girmesine ve dolayısıyla birden fazla fonksiyonel grubun aynı molekül üzerinde yer almasina olanak sağlamaktadır.

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LIST OF SYMBOLS / ABBREVIATIONS

J	Coupling constant
υ	Frequency

DA	Diels Alder
DCC	N,N’-Dicyclohexylcarbodiimide
DCU	Dicyclohexylurea
DMAP	4-Dimethylaminopyridine
FTIR	Fourier transform infrared
G	Generation
GPC	Gel Permeation Chromatography
HRMS	High Resolution Mass Spectrometry
MHz	Mega hertz
NMR	Nuclear Magnetic Resonance
PAMAM	Poly (amido amine)
rDA	retro Diels Alder
SEC	Size-Exclusion Chromatography
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
UV	Ultraviolet

1. INTRODUCTION

Dendrimers, being a sub-class of polymers, consist of repeating units arranged in a branched manner (Figure 1.1). They are highly ordered, regularly branched globular macromolecules as a result of being synthesized with stepwise organic reactions [1]. The first paper in this area was published in 1985 by Tomalia *et al.* [2] and since then many others with several different repeating units have been published. The fact that they are synthesized with iterative step-wise organic synthesis gives them the property of being monodisperse which makes them highly attractive building blocks for applications such as targeted drug delivery [3], formation of enzyme mimicking cavities [4], etc.

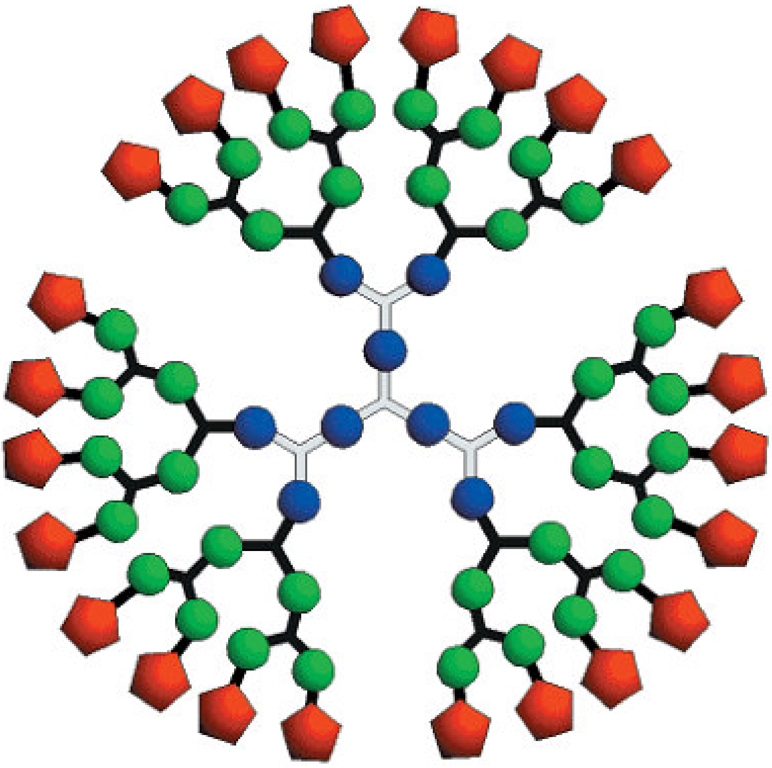


Figure 1.1. Schematic representation of a dendrimers [1]

1.1. Structure of Dendrimers

A dendrimer consists of three main parts, namely: a core, branching repeat units and surface groups which are often referred to as peripheral groups (Figure 1.2). Multiplicities of the dendrimers are determined by the core via the number of functional groups on it. Usually focal point of a dendron bears reactive groups which can be used to add repeating units and hence grow the dendrimers. Branching units are responsible from the growth of the dendritic structure and giving it the unique 3-D shape. Since the inner layers and the core are sterically hindered, the functional groups at the surface interact with surroundings and govern the physical and chemical properties of the dendrimers.

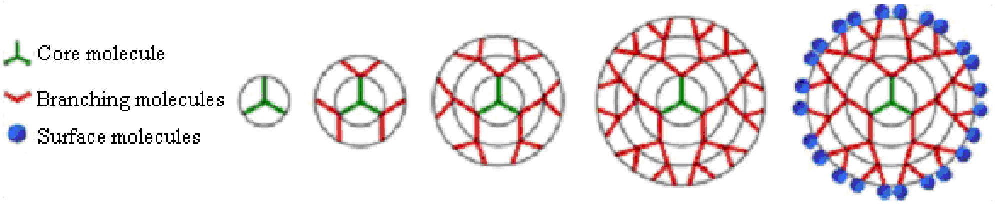


Figure 1.2. Schematic representation showing subunits of dendrimers and dendrons

Each branching point at a dendrimer is named as a new generation. As the number of branching points increases the generation of the dendrimers also increases.

1.2. Historical Development

Work published by Vögtle *et al.* in 1978 is considered to be the first publication in the area [5]. He named the products as “cascade molecules” and used a stepwise organic synthesis methodology to synthesize them. The word “dendrimer” was introduced to the literature by Tomalia and his coworkers in 1985 [2]. They synthesized the poly (amidoamine) dendrimer which is abbreviated as PAMAM (Figure 1.3). Soon after that Newkome and coworkers published the synthesis of molecules named as “arborols” which are known to obtain three branching units at each generation [6]. Since these pioneering publications dendrimers have gained great attention and a large number of papers have been published related to dendrimers and their different applications.

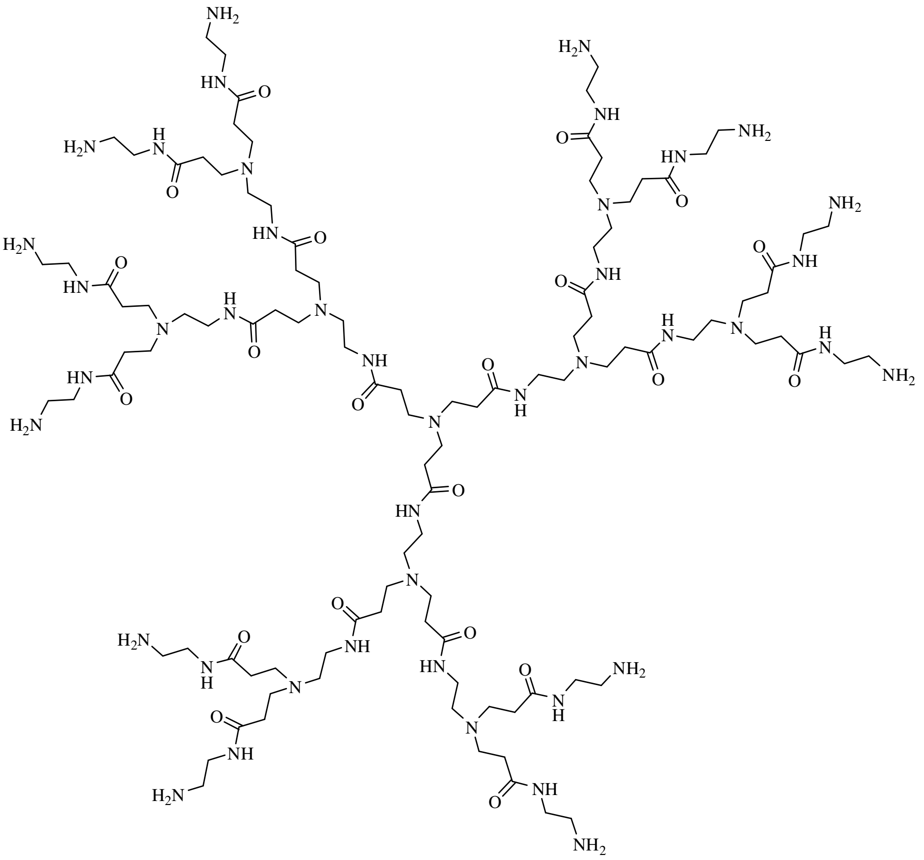


Figure 1.3. Second generation PAMAM dendrimer

1.3. Synthesis Methods

Dendrimers can be synthesized with two different methods, namely, “divergent” and “convergent” methods. First synthetic strategies described for synthesis of dendrimers have utilized the divergent method where the synthesis of the dendrimers starts from the core and followed by attachment of branching units and finally the surface groups. On the other hand convergent method starts with the attachment of surface groups onto the branching units and further coupling of these small dendrons to the multivalent core molecule results in formation of the desired dendrimer. These two methods of synthesis will be described in detail in the following sections.

1.3.1. Divergent Method

In divergent method, synthesis starts with the core molecule, which has to be a multi-functional molecule to provide the branched structure. Growth of dendrimer continues with addition of repeating units to the core molecule which, as a result, will form the final shape of the dendrimer. Monomers are chosen such that there is one active and two or more inactive sites which can be activated when needed. After the attachment of the repeating unit to the core molecule, the inactive sites on the monomer are activated and reacting the newly formed compound with the same monomer results in a higher generation dendrimer. For example polyester dendrimer, PAMAM (Figure 1.3) and poly (propylene imine) (Figure 1.4) dendrimers are usually synthesized via the divergent method [7].

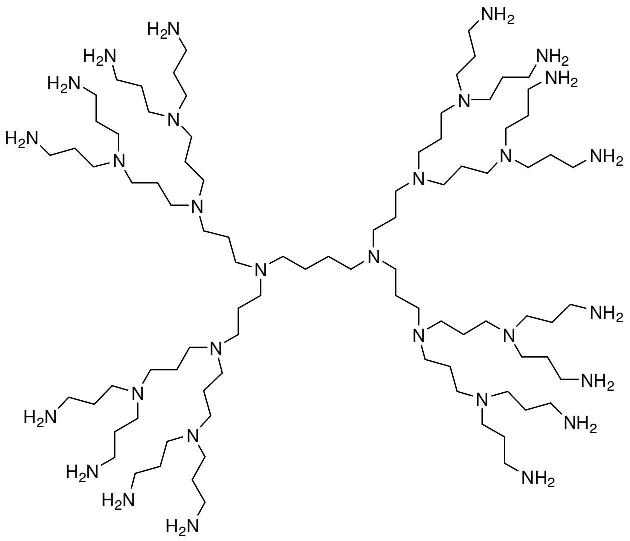


Figure 1.4. Second generation poly (propyleneimine) dendrimer

Divergent synthesis is found to be the desirable method for large scale dendrimer synthesis since the molecular weight of the dendrimer doubles with the production of each generation. This feature brings about the necessity of using a large excess of monomer in order to drive the coupling reactions to completion. Once the desired product is obtained unreacted monomers can be removed by traditional separation techniques such as distillation, crystallization, chromatography etc.

In addition to the several advantages, the method suffers from a major drawback which is the loss of structural control while reaching the higher generations. This phenomenon stems from the increasing number of couplings that needs to be accomplished as the dendrimer generation increases. For example 24 coupling reactions must be completed to convert a second generation PAMAM dendrimer into a third generation PAMAM dendrimer (Figure 1.3). Complete conversion for such high number of reactions per molecule is very difficult and hence it causes polydispersity in the formed product. As a result one obtains dendrimers with structural defects; moreover, the extent of such defects is often very difficult to detect and precisely quantify.

1.3.2. Convergent Method

First example of convergently synthesized dendrimers was disclosed by Hawker and Fréchet in 1990, where they synthesized poly (aryl ether) dendrimers (Figure 1.5) [8]. Unlike the divergent method, convergent method starts with addition of surface groups and proceeds towards the core. In other words, it consists of preparation of dendrons and coupling them with the multifunctional core molecule.

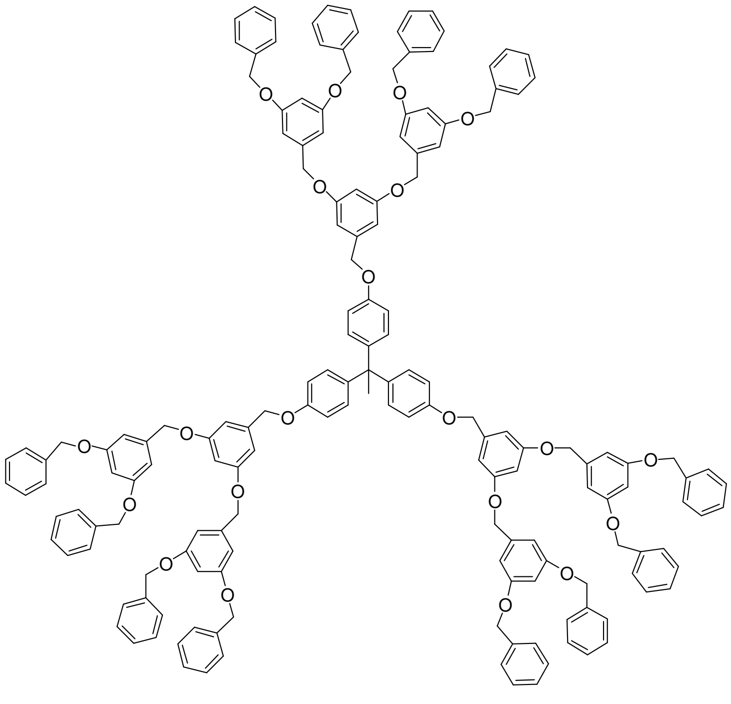


Figure 1.5. Second generation poly (aryl ether) dendrimer

According to the convergent method, synthesis begins with coupling of surface groups to a multi-functional branching unit. Branching unit must have multiple reactive groups and an inactive focal point. Once the coupling step is completed, inactive group of the monomer is activated and coupled to another branching unit in order to increase the dendron generation. By repeating the activation and coupling steps dendron can be grown until the desired generation. Attachment of the formed dendrons onto a multi-functional core molecule results in formation of the dendrimer.

In contrast to divergent method, purification of compounds requires more complex purification methods. The reason for this can be explained by taking the molecular weight difference of the starting materials and the formed compounds into account. In the divergent method the dendrimer formed at the end of reaction is 4-5 times heavier than the monomers, however, when we consider the convergent route, the molecular weight difference between the dendrons before and after the coupling reactions is very small and therefore use of column chromatography is essential for isolating the desired dendrons.

Although requirement of chromatographic techniques is a drawback of the convergent method, the advantages of the method outnumber the disadvantages. Convergent approach provides better control over the structure of the dendrimer and prevents formation of defected structures, forming monodisperse, well defined structures.

2. BLOCK DENDRIMERS

Dendrimers are attractive building blocks for a variety of applications due to the fact that they are macromolecular structures which are monodisperse and in addition to that owing to their globular branched structure they are furnished with a large number of functional groups at their periphery. A high number of surface functionality enables scientists to further react these groups with molecules of interest in order to obtain dendrimers suitable for a number of applications. Not only surface groups but also the dendrimer structure itself can be modified with different building blocks to meet the needs. Dendrimers which are made up of different building blocks are referred as block dendrimers. Block dendrimers consist of three subgroups: layer block, segment block and surface block (Figure 2.1). These different types will be explained in detail.

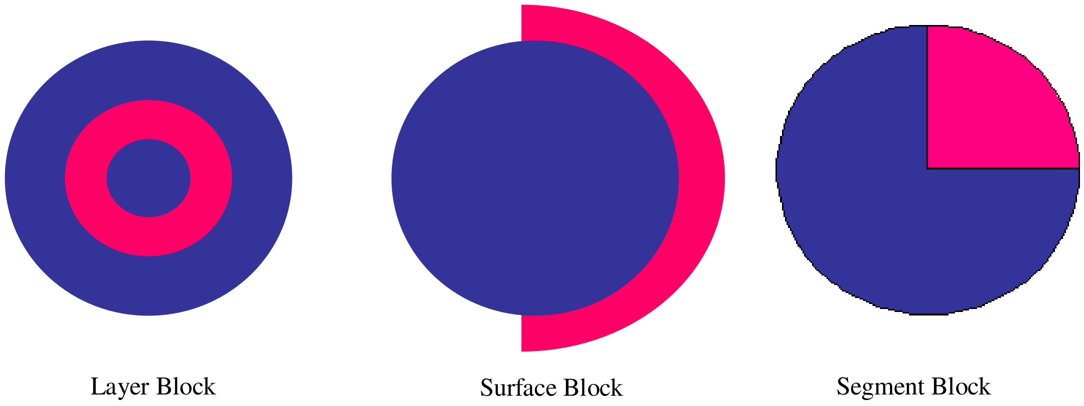


Figure 2.1. Types of block dendrimers

2.1. Layer Block Dendrimers

Layer block dendrimers are formed by attaching more then one type of repeating units to the core molecule in a layered way. Mostly these types of dendrimers are synthesized by convergent method however literature examples employing use of divergent methods also exist. The first example of a layer block dendrimer was given by Hawker and Fréchet in 1992 [9] where they have used convergent approach to attach a poly (benzyl ether) dendron **1** to a poly (benzyl ester) monomer **2** and further attachment of the formed dendron **3** to a triphenolic core **4** has resulted in formation of the layered dendrimers **5** (Figure 2.2)

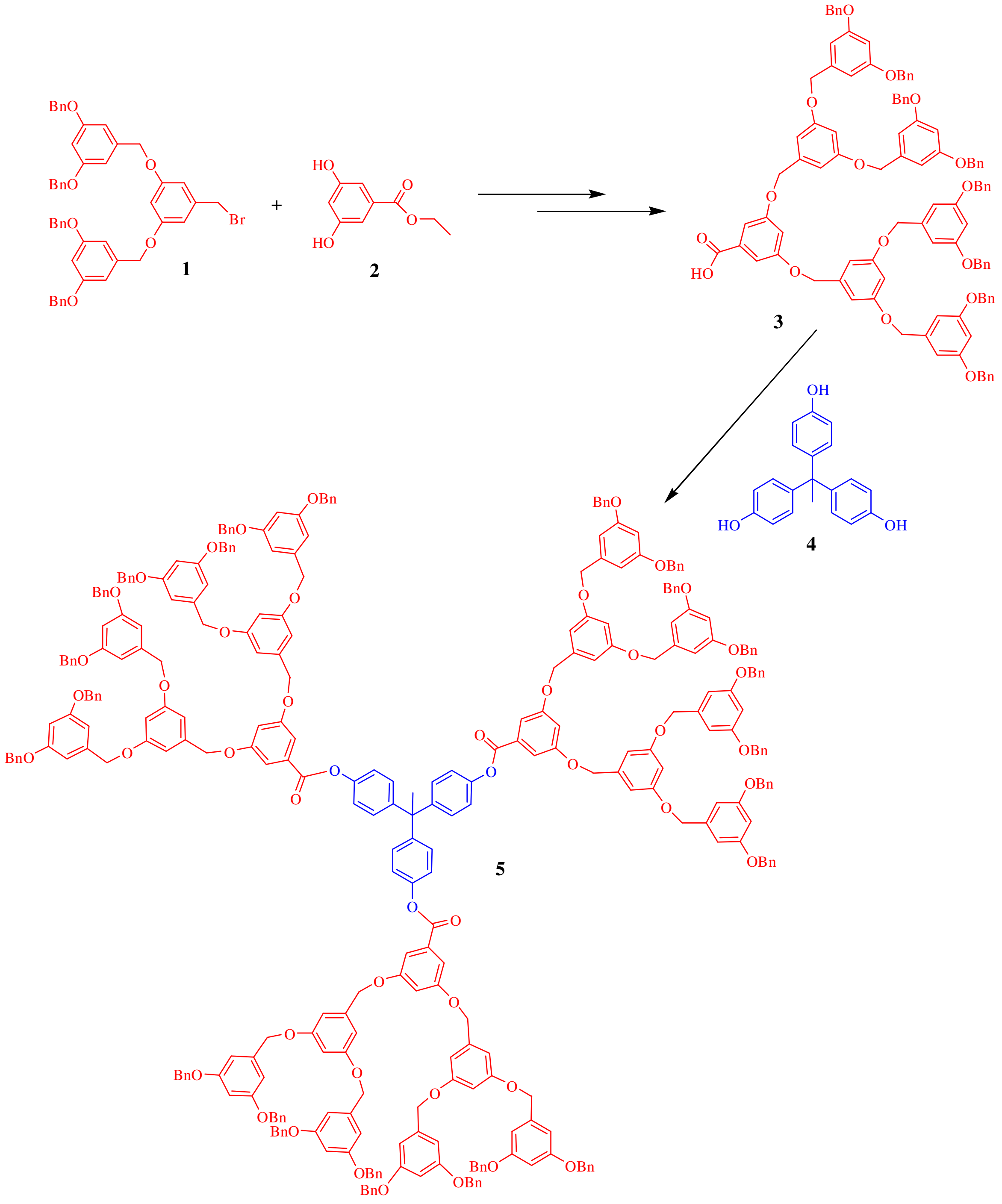


Figure 2.2. Synthesis of first layer block dendrimer

2.2. Surface Block Dendrimers

Surface block dendrimer are a class of dendrimers that possess two or more different types of peripheral groups on the dendrimer surface. A macromolecular structure of this kind can be obtained by combining dendrons bearing different end groups around a multi-functional core. In these dendrimers the dendrons that are attached to the core are formed from the same type of repeating units. In other words unlike the surface, the inner groups of the formed dendrimers are homogeneous.

One can obtain surface block dendrimers by combining two dendrons by using the reactive groups at their focal points. Hawker *et al.* [10] have synthesized orthogonally functionalizable surface block polyester dendrimers **8** by using click reaction to combine two dendrons (Figure 2.3).

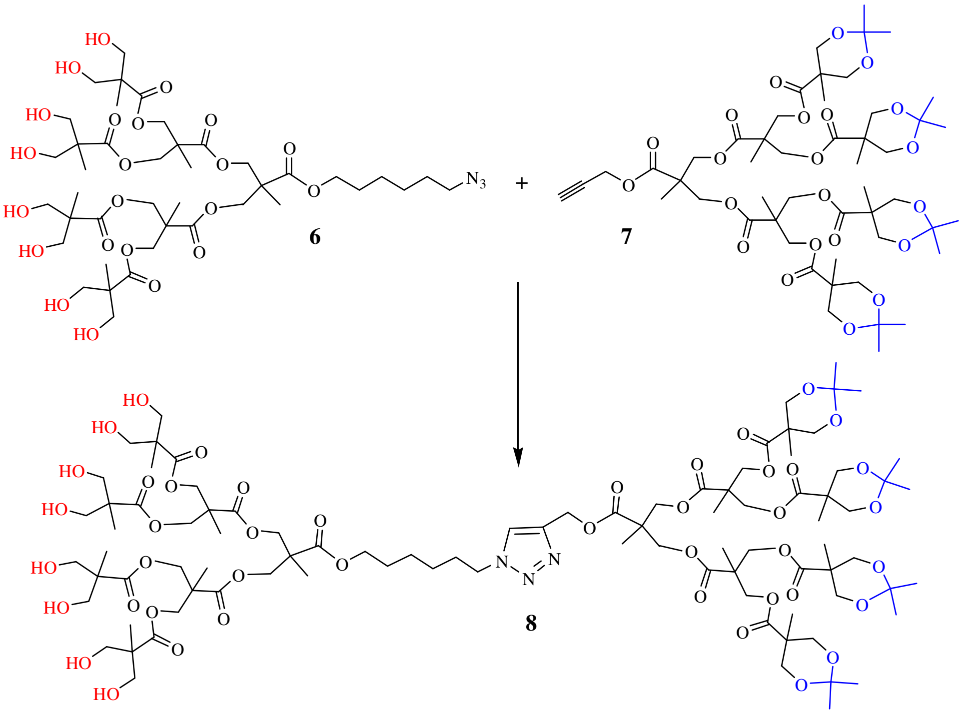


Figure 2.3. Synthesis of surface block polyester dendrimers

2.3. Segment Block Dendrimers

Segment block dendrimers are made up of two structurally different dendrons that are usually connected around a core molecule. As a result they are unsymmetrical and have different surface groups at the periphery of each dendron. Mostly they are synthesized with convergent method, and then combined around the core molecule. Trying to apply divergent method for such architectures is avoided to prevent formation of any possible side reactions which would make the synthesis more complex.

First example of this kind of structure was given by Hawker and Fréchet (Figure 2.4) [11]. The dendrimers were consisting of poly (benzyl ether) and poly (benzyl ester) dendrons. In their work, second generation Fréchet-type bromide dendron **1** was reacted with an excess of poly (benzyl ester) monomer **2**. The remaining phenol **9** was coupled to the second generation poly (benzyl ester) carboxylic acid **10** via DDC mediated esterification, yielding the unsymmetrical dendron **11**. These dendrons are then combined around a triphenolic core **4** to give final unsymmetrical dendrimers **12**.

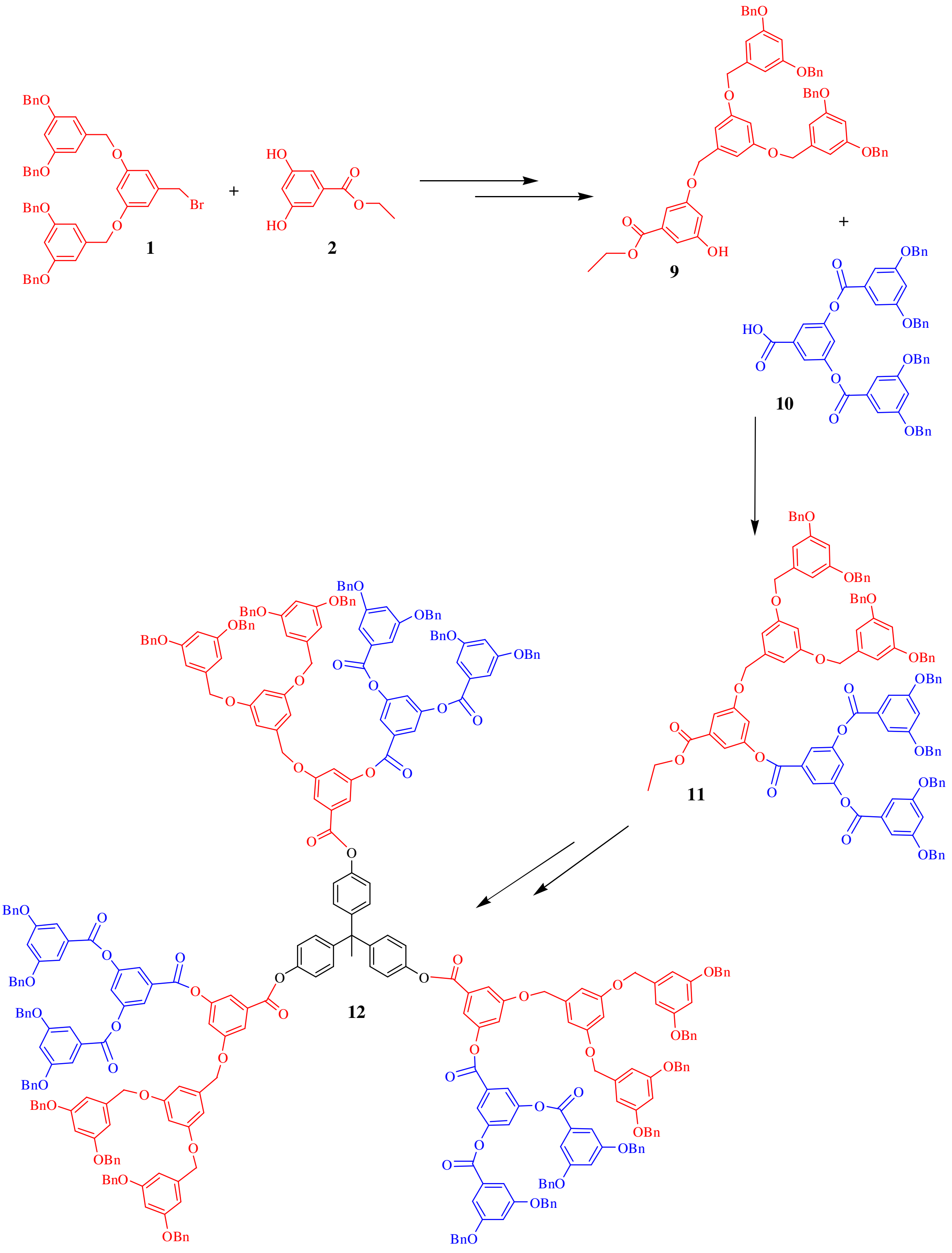


Figure 2.4. Synthesis of the first segment block dendrimer

3. DIELS – ALDER REACTION AND ITS APPLICATIONS IN MACROMOLECULAR STRUCTURES

Diels-Alder reaction (DA) is a well known [4+2] cycloaddition reaction between a conjugated diene and a dienophile [12]. The driving force of the reaction is the formation of new σ bonds which are known to be energetically more stable than π bonds . Furan and anthracene derivatives have been widely explored as diene components in macromolecular construction. Maleimides are preferred as the choice of dienophile due to their high reactivity and wide structural variability through the nature of the nitrogen substituents (Figure 3.1). Diels-Alder reaction gives the desired products in high yields without formation of offensive by-products. These properties had lead to classification of Diels-Alder reaction among “click chemistry” reactions as described by Sharpless *et al.* [13]. Highly efficient and modular nature of this reaction has made it a desirable candidate for use in macromolecular structures.

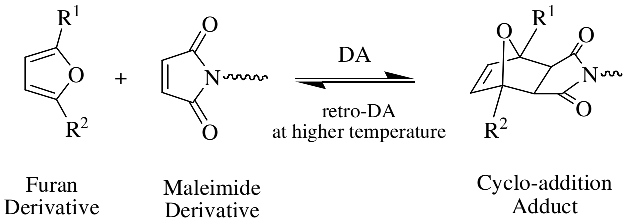


Figure 3.1. Representation of Diels-Alder reaction

In addition to the advantages stated above, it is possible to shift reaction to the side of reactants simply by increasing the heat, a process also known as “retro Diels-Alder reaction” (rDA) [14]. This property of DA reaction has been used in polymer systems to make thermo responsive polymers. Gandini used a furan containing styrene copolymer **13** and a bismaleimide cross linking agent **14** to synthesize thermally reversible cross linked materials **15** [15]. The retro-DA reaction of the cross linked material was carried out in presence of excess furan trap **16** and as a result the original polymer **14** was obtained successfully. (Figure 3.2) This study may be considered as the first systematic approach to a reversible DA - rDA cross-linking system showing the validity of the DA – rDA strategy in the synthesis of elastomeric networks.

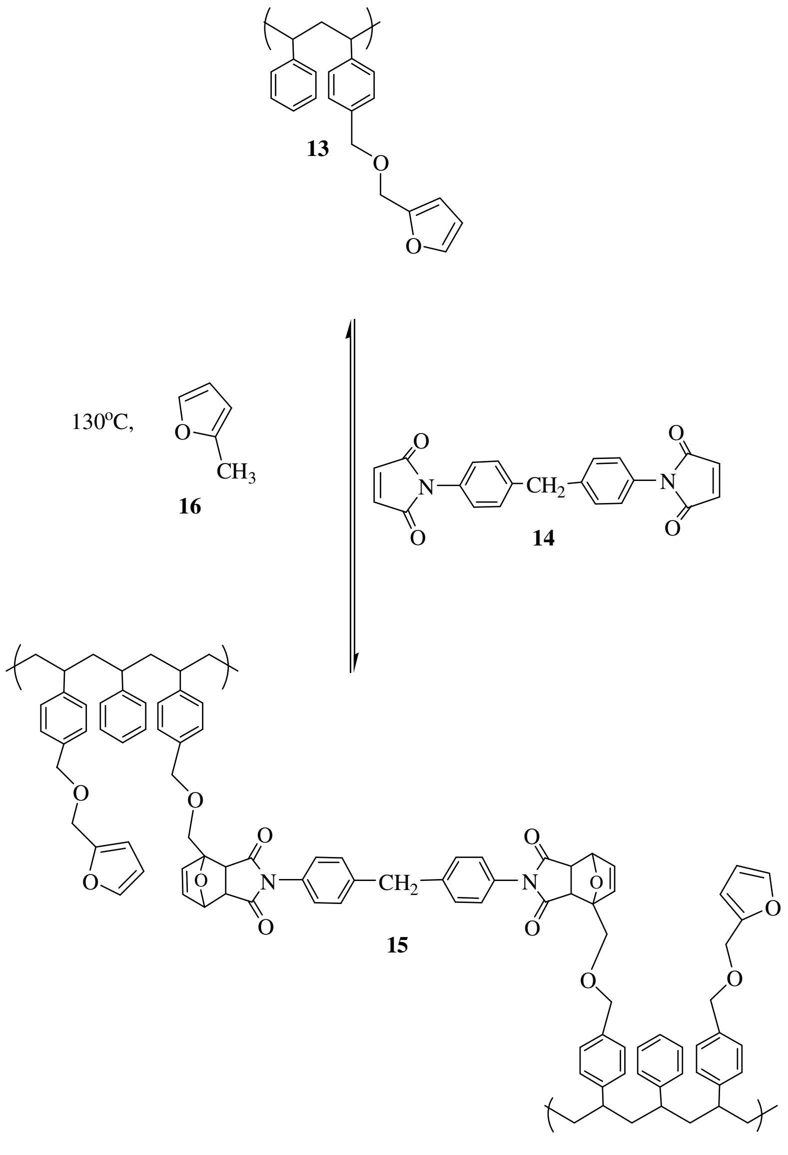


Figure 3.2. Use of Diels-Alder reaction for thermo reversible polymeric systems

Recent work from our research group disclosed a novel strategy for the synthesis of reactive polymers bearing maleimide groups as side chain units. Polymers bearing protected maleimide groups as side chain substituents were prepared from an acrylate based reactive monomer [16]. The reactive maleimide units are then activated via rDA reaction to enable post-functionalization of the formed polymer with thiol containing molecules.

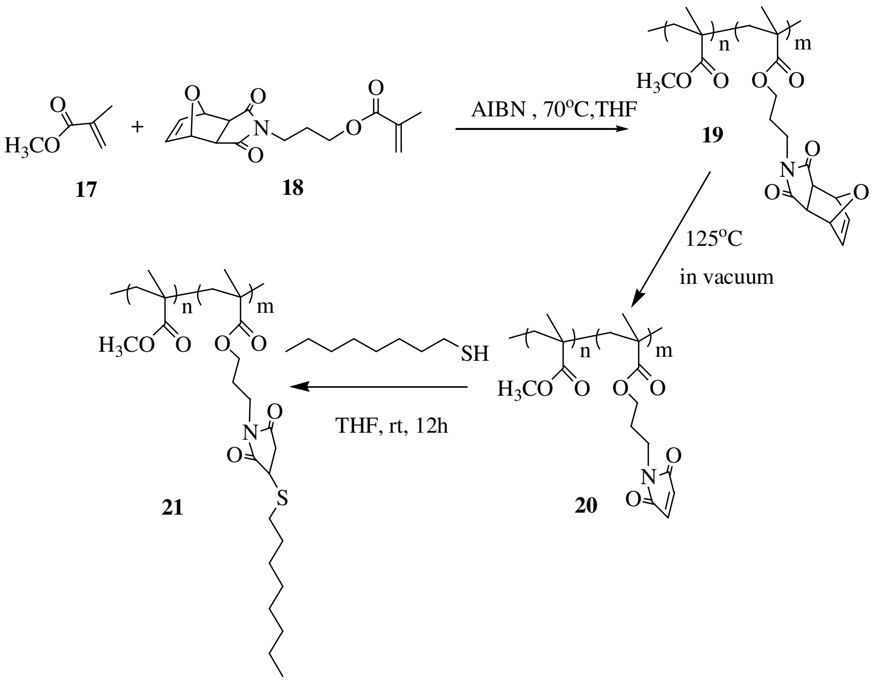


Figure 3.3. Synthesis of reactive copolymer

Diels-Alder reaction has been used in dendrimer chemistry by Müllen *et al.* for construction of poly (phenylene) dendrimers (Figure 3.4) [17].

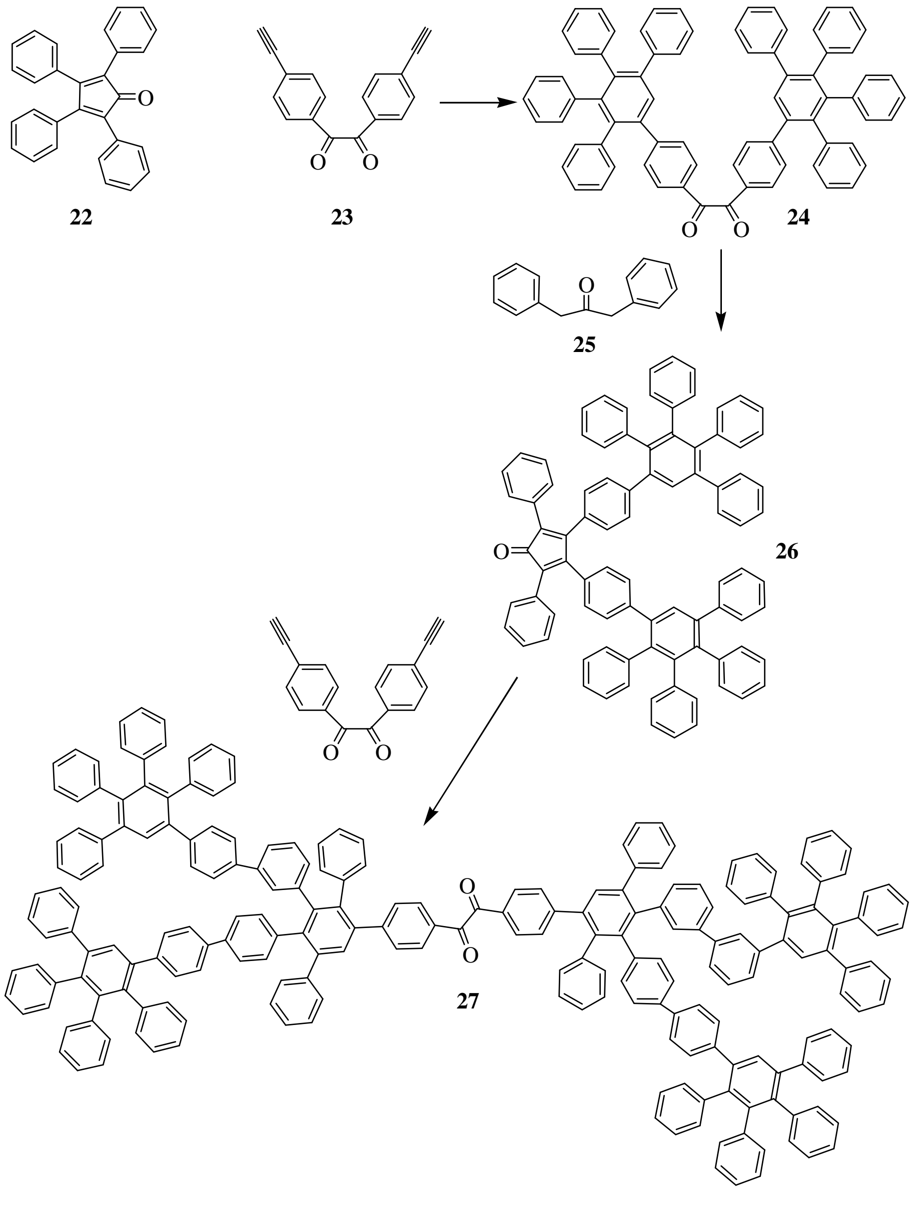


Figure 3.4. Synthesis of poly (phenylene) dendrimers

The poly (phenylene) dendrimers were synthesized with a convergent methodology by making use of repetitive Diels-Alder reaction and Knoevenagel condensations. Cyclopentadienone **22**, which is the repeating unit of the dendrimer, was reacted with 4, 4'-diethynyl benzil **23** through a Diels-Alder reaction forming the second generation dendron **24**. The formed dendron **24** was further modified with 1, 3-diphenylacetone **25** and reacted with the core molecule **23** in order to obtain a higher generation dendron **27**. The formed dendrimers were found to be chemically and thermally stable.

Diels-Alder reaction has been used for synthesis of symmetrical dendrimers. McGrath *et al.* have synthesized poly (aryl ether) dendrons bearing a furan moiety and then assembled these dendrons around a molecule containing multiple maleimide units (Figure 3.5) [18]. It was also shown that assembly of these dendrons is reversible due to the nature of the bond formed which in turn gives thermally responsive dendritic structures.

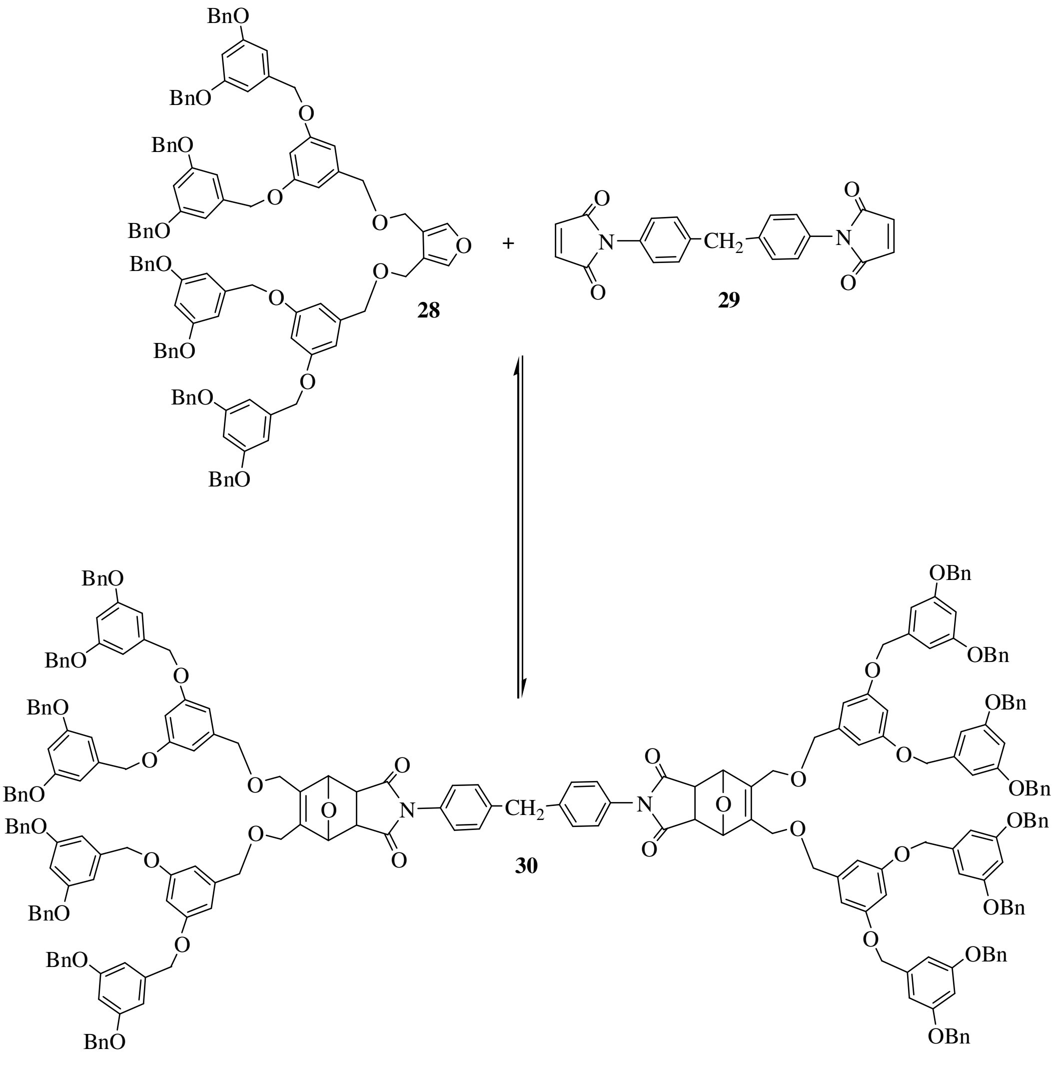


Figure 3.5. Synthesis of symmetrical dendrimers via Diels-Alder reaction

Diels-Alder reaction between Fréchet type dendron **28** and bis-maleimide linker **29** was carried out at 60 ^{0}C to give symmetrical dendrimer **30**. Retro Diels-Alder reaction was carried out at 95 ^{0}C to give parent dendron **28**. It was also shown that dendrimers which was disassembled can be reassembled simply by heating at the appropriate temperature.

4. AIM OF THE STUDY

The aim of this study is to synthesize segment block dendrimers by making use of Diels–Alder reaction (Figure 4.1). The proposed strategy not only allows synthesis of unsymmetrical dendrimers but also results in formation of thermo reversible structures. The methodology requires use of reaction conditions which is free of metal catalysts and hence provides products free of undesirable metal impurities.

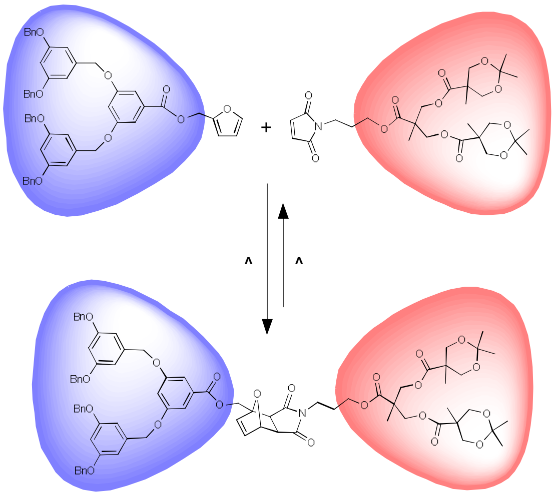


Figure 4.1. General representation of the strategy utilized

In this research three generations of poly (aryl ether) dendrons functionalized with furan moieties at the core are reacted with maleimide functionalized acetal protected poly (ester) dendrons of the same generation via Diels-Alder cycloaddition to form desired unsymmetrical dendrimers in good yields. The thermo reversible nature of these macromolecules were investigated by subjecting them to elevated temperatures in the presence of anthracene as a scavenger diene

As an extension of this research, poly (ester) dendrons that has alkyne functionalities at the periphery and a maleimide core has been synthesized to serve as an orthogonally functionalizable macromolecule which can be designed in a way to attach targeting groups or solubilizing groups and drug molecules to provide drug carrying scaffolds for targeted drug delivery. Formed dendrons were furnished with two different orthogonal reactive groups, namely, terminal alkyne functionalities at the periphery that will allow functionalization with Huisgen type click reaction, and a maleimide containing focal point that is an excellent Michael acceptor for thiolated molecules. The maleimide functional group at the core is also an excellent dienophile. This will allow handle for appending such reactive dendons onto other appropriate polymers and dendrons.

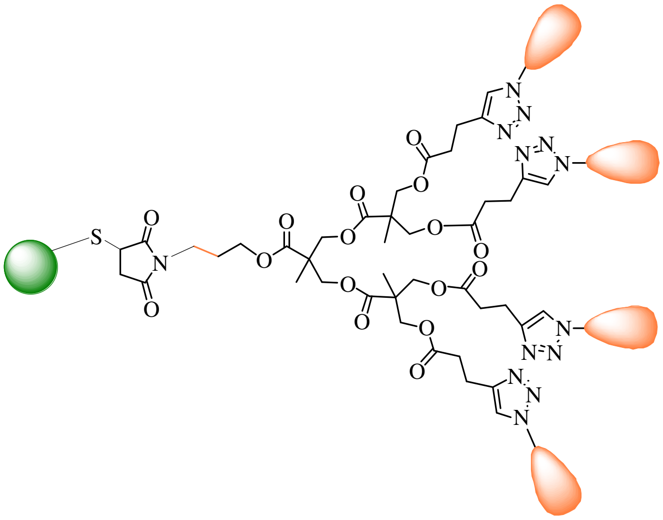


Figure 4.2. Orthogonally functionalized dendron

5. RESULTS AND DISCUSSION

5.1. General Methods and Materials

All reagents were obtained from commercial sources (Merck, Aldrich, Lancaster, Alfa Aesar, Avocado, Riedel de Haen) and were used as received unless otherwise stated. Solvents used for purification, hexane, ethyl acetate, methanol and dichloromethane were distilled prior to use (Akkimya). Characterization of compounds were carried out with ^{1}H and ^{13}C solution NMR spectroscopy (Varian 400 MHz), Fourier transform infrared (FTIR) spectroscopy (Perkin Elmer 1600 Series). Gel Permeation Chromatography (GPC) data was acquired with Viscotek GPCmax VE-2001 analysis system. PLgel (length/ID 300 mm × 7.5mm, 5µm particle size) Mixed-C column was calibrated with polystyrene standards, using refractive index detector. THF was used as eluent at a flow rate of 1mL/min at 30 ^{0}C.

5.2. Synthesis of Furan Functionalized Poly (aryl ether) Dendrons

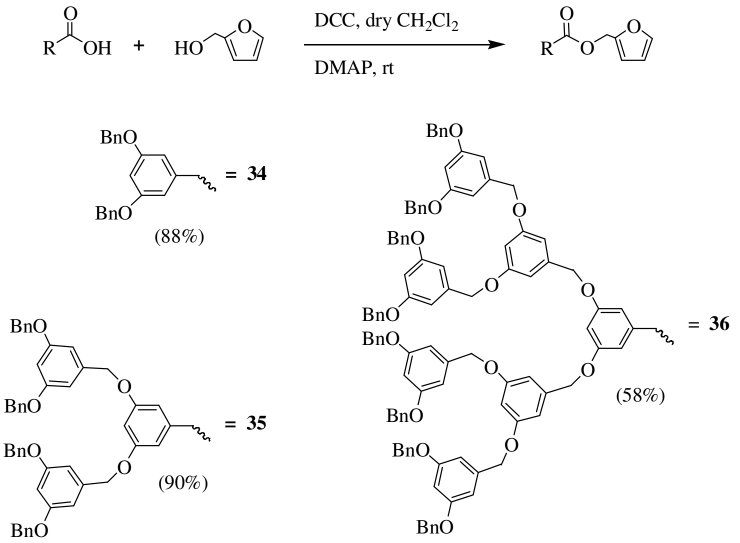


Figure 5.1. Core modification of poly (aryl ether) dendrons

5.2.1. Synthesis of 1st Generation Furan Functionalized Dendron

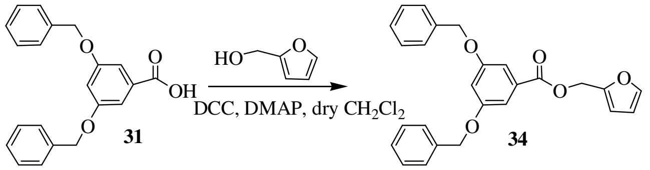


Figure 5.2. Synthesis of 1st generation furan functionalized dendron

Compound **31** was prepared according to a previously reported literature procedure [19]. Compound **31** (0.67 g, 2.0 mmol) was added to a solution of furfuryl alcohol (0.2 mL, 2.4 mmol), DCC (0.50 g, 2.4 mmol) and DMAP (0.07 g, 0.6 mmol) in dry CH_2Cl_2 (10 mL). The mixture was stirred at ambient temperature for 12 h. The by product (DCU) formed during the reaction was filtered off. The solution was concentrated in *vacuo*. The resulting compound was purified by column chromatography to give 0.73 g of **34** as a white solid (88% yield). mp: 56 °C; ^{1}H NMR ($CDCl_3$,δ, ppm) 7.43- 7.30 (m, 11H), 7.28 (d, 2H, J = 2.4 Hz), 6.77 (dd, 1H, J = 2.4, 2.4 Hz), 6.45 (d, 1H, J = 3.2 Hz), 6.36 (m, 1H), 5.27 (s, 2H), 5.04 (s, 4H), ^{13}C NMR ($CDCl_3$, δ, ppm) 165.9, 159.8, 149.5, 143.3, 136.4, 131.8, 128.6, 128.1, 127.6, 110.8, 110.6, 108.6, 107.3, 70.3, 58.7., FTIR (cm^{-1}) 1719.3, HRMS calculated for $C_{26}H_{22}O_5$ [(M + H)$^+$] 415.1546, found 415.1540.

5.2.2. Synthesis of 2nd Generation Furan Functionalized Dendron

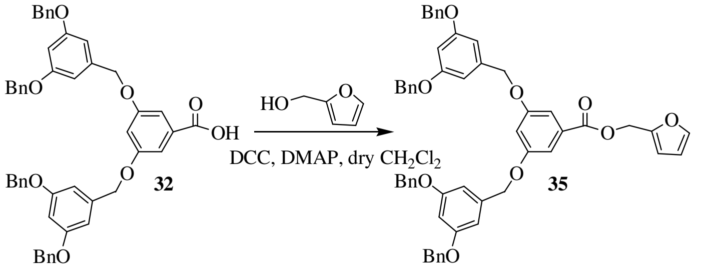


Figure 5.3. Synthesis of 2nd generation furan functionalized dendron

Compound **32** (0.45 g, 0.60 mmol) was added to a solution of furfuryl alcohol (0.06 mL, 0.72 mmol), DCC (0.15 g, 0.72 mmol) and DMAP (0.02 mg, 0.2 mmol) in dry

CH_2Cl_2 (8 mL). The mixture was stirred at ambient temperature for 12 h. The by product (DCU) formed during the reaction was filtered off. The solution was concentrated in *vacuo*. The resulting compound was purified by column chromatography to give 0.45 g of **35** as a white solid (90% yield). mp: 103 °C; ^{1}H NMR ($CDCl_3$, δ, ppm) 7.40 – 7.26 (m, 23H), 6.73 (dd, 1H, *J* = 2.1, 2.1 Hz), 6.64 (d, 4H, *J* = 1.6 Hz), 6.55 (dd, 2H, *J* = 2.1, 2.1 Hz), 6.45 (d, 1H, *J* = 3.2 Hz), 6.34 (dd, 1H, *J* = 3.2, 1.8 Hz), 5.27 (s, 2H), 5.01 (s, 8H), 4.97 (s, 4H), ^{13}C NMR ($CDCl_3$, δ, ppm) 165.8, 160.2, 159.6, 149.4, 143.2, 138.8, 136.8, 131.8, 128.5, 127.9, 127.5, 110.8, 110.6, 108.6, 107.2, 106.4, 101.7, 70.1, 58.6, FTIR (cm^{-1}) 1704.7, HRMS calculated for $C_{54}H_{46}O_9$ [$(M + H)^+$] 839.3221, found 839.3215.

5.2.3. Synthesis of 3rd Generation Furan Functionalized Dendron

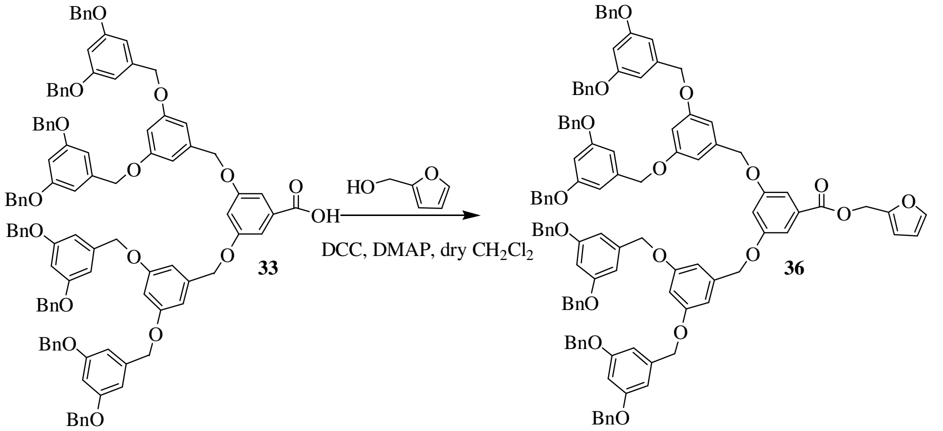


Figure 5.4. Synthesis of 3rd generation furan functionalized dendron

Compound **33** (0.24 g, 0.15 mmol) was added to a solution of furfuryl alcohol (0.03 mL, 0.3 mmol), DCC (0.04 g, 0.18 mmol) and DMAP (0.005 g, 0.04 mmol) in dry CH_2Cl_2 (4 mL). The mixture was stirred at ambient temperature for 12 h. The by product (DCU) formed during the reaction was filtered off. The solution was concentrated in *vacuo*. The resulting compound was purified by column chromatography to give 0.14 g of **36** as a white waxy solid (58 % yield). ^{1}H NMR ($CDCl_3$, δ, ppm) 7.38 - 7.25 (m, 42H), 6.76 (dd, 1H, *J* = 2.3, 2.3 Hz), 6.71 (d, 1H, *J* = 2.1 Hz), 6.63 (dd, 12H, *J* = 9.5, 2.1 Hz), 6.52 (dd, 6H, *J* = 9.5, 2.1 Hz), 6.43 (d, 1H, *J* = 3.3 Hz), 6.32 (dd, 1H, *J* = 3.2, 2.1 Hz), 5.24 (s, 2H), 4.99 (s, 16H), 4.94 (s, 4H), 4.93 (s, 8H), ^{13}C NMR ($CDCl_3$, δ, ppm) 165.8, 160.1, 160.0, 159.6, 149.4, 143.3, 139.2, 139.1, 138.8, 136.8, 131.8, 128.5, 128.0, 127.5, 110.8, 110.6, 108.6, 107.2, 106.5, 106.4, 106.4, 101.7, 101.6, 70.2, 70.1, 70.0, 58.7, FTIR (cm^{-1}) 1707.6,HRMS calculated for $C_{110}H_{94}O_{17}$ [(M+H+Na)$^{+}$] 1710.6467, found 1710.6456.

5.3. Synthesis of Maleimide Functionalized Poly (ester) Dendrons

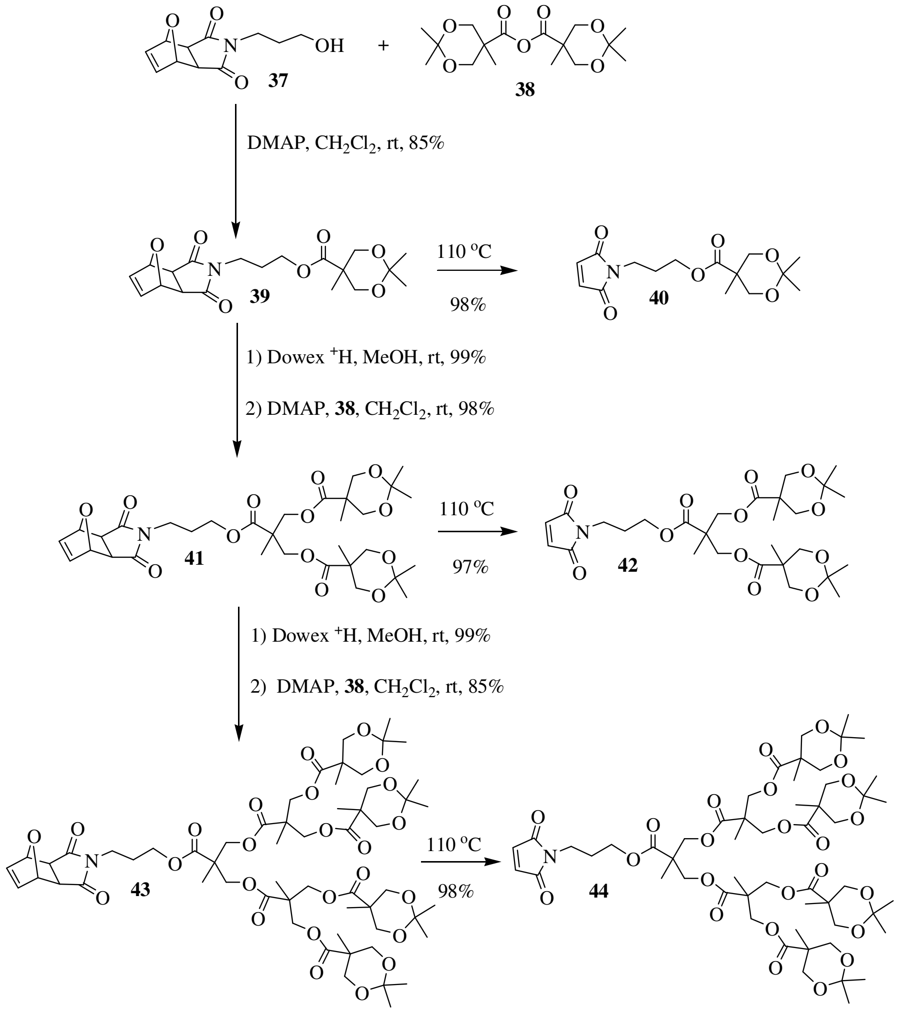


Figure 5.5. Divergent synthesis of maleimide functionalized poly (ester) dendron

5.3.1. Synthesis of 1st Generation Maleimide Functionalized Dendron

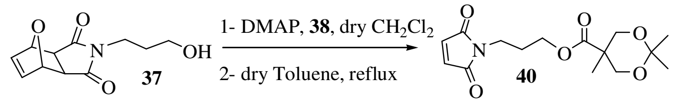


Figure 5.6. Synthesis of 1st generation maleimide functionalized dendron

Synthesis of **40**: Compounds **37** and **38** were synthesized according to the previously reported literature procedures [20], [21]. To a solution of **38** (8.70 g, 26.3 mmol) in dry CH_2Cl_2 (40 mL), **37** (3.96 g, 17.5 mmol), DMAP (0.86 g, 7.00 mmol) and pyridine (5.5 mL) was added. The mixture was stirred at ambient temperature for 12 hours followed by quenching of excess anhydride with (1:1) mixture of pyridine and water (6.6 mL) for 12 h. Reaction mixture was extracted with 1 M $NaHSO_4$ (3 x 20 mL), 10% Na_2CO_3 (3 x 20 mL) and then with brine (1 x 20 mL) combined organic layers were dried over anhydrous Na_2SO_4. The residue was concentrated in *vacuo*. Crude product was purified by column chromatography to give 5.7 g of **39** as a white solid (85 % yield). Compound **39** (0.51 g, 1.34 mmol) was then dissolved in dry toluene (6 mL) and the mixture was heated to reflux. Progress of the reaction was monitored by TLC until consumption of compound **39** is observed. The mixture was then concentrated in *vacuo* to give **40** (409 mg, 98%) as a colorless viscous liquid. ^1H NMR ($CDCl_3$,δ, ppm) 6.68 (s, 2H), 4.19 (d, 2H, J = 11.9 Hz), 4.11 (t, 2H, J = 6.0 Hz), 3.63 (d, 2H, J = 11.9 Hz), 3.61 (t, 2H, J = 7.0 Hz), 1.95 (tt, 2H, J = 6.7, 6.4 Hz), 1.41 (s, 3H), 1.38 (s, 3H), 1.21 (s, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm) 174.1, 170.6, 134.2, 98.1, 66.0, 61.7, 41.8, 34.6, 27.6, 24.3, 23.0, 18.6. FTIR (cm^{-1}) 1726.8, 1695.4, HRMS calculated for $C_{15}H_{21}NO_6$ [(M + H) $^+$] 312.1448, found 312.1442.

5.3.2. Synthesis of 2nd Generation Maleimide Functionalized Dendron

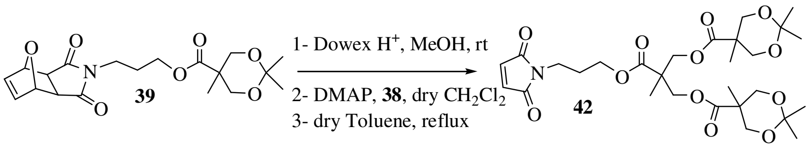


Figure 5.7. Synthesis of 2nd generation maleimide functionalized dendron

Synthesis of **42**: Compound **39** (2.0 g, 5.3 mmol) 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 ambient temperature until the consumption of **39** 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 (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 compound **38** (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. Reaction mixture was diluted with 50 mL CH_2Cl_2 and extracted with 1 M $NaHSO_4$ (3 x 20 mL), 10% Na_2CO_3 (3 x 20 mL) and then with brine (1 x 20 mL) combined organic layers were dried over anhydrous Na_2SO_4. The residue was concentrated in *vacuo*. Crude product was purified by column chromatography to give 3.14 g of **41** as a colorless viscous liquid (98% yield). Compound **41** (0.6 g, 0.71 mmol) was dissolved in dry toluene (5 mL) and the mixture was heated to reflux. Progress of the reaction was monitored by TLC until consumption of compound **41** is observed. The mixture was then concentrated in *vacuo* to give **42** (0.4 g , 97%) as a pale yellow viscous liquid. ^{1}H NMR ($CDCl_3$,δ, ppm) 6.64 (s, 2H), 4.32 (s, 4H), 4.13 (d, 4H, *J* = 11.8 Hz), 4.08 (t, 2H, *J* = 6.2 Hz), 3.62 – 3.58, (m, 6H), 1.94 (tt, 2H, *J* = 6.4, 6.2 Hz), 1.39 (s, 6H), 1.34 (s, 6H), 1.30 (s, 3H), 1.13 (s, 6H) ^{13}C NMR ($CDCl_3$, δ, ppm) 173.5, 172.4, 170.5, 134.2, 98.1, 66.0, 65.2, 62.2, 46.8, 42.0, 34.5, 27.6, 24.9, 22.3, 18.6, 17.7, FTIR (cm^{-1}) 1739.0, 1715.1, 1645.4 HRMS calculated for $C_{28}H_{41}NO_{12}$ [(M + H)$^+$] 584.2708, found 584.2702.

5.3.3. Synthesis of 3rd Generation Maleimide Functionalized Dendron

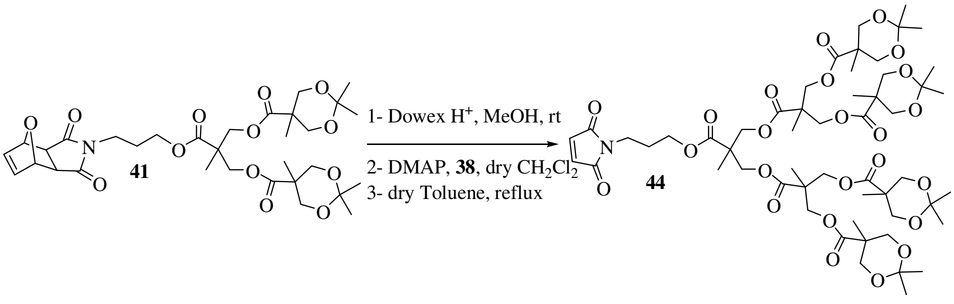
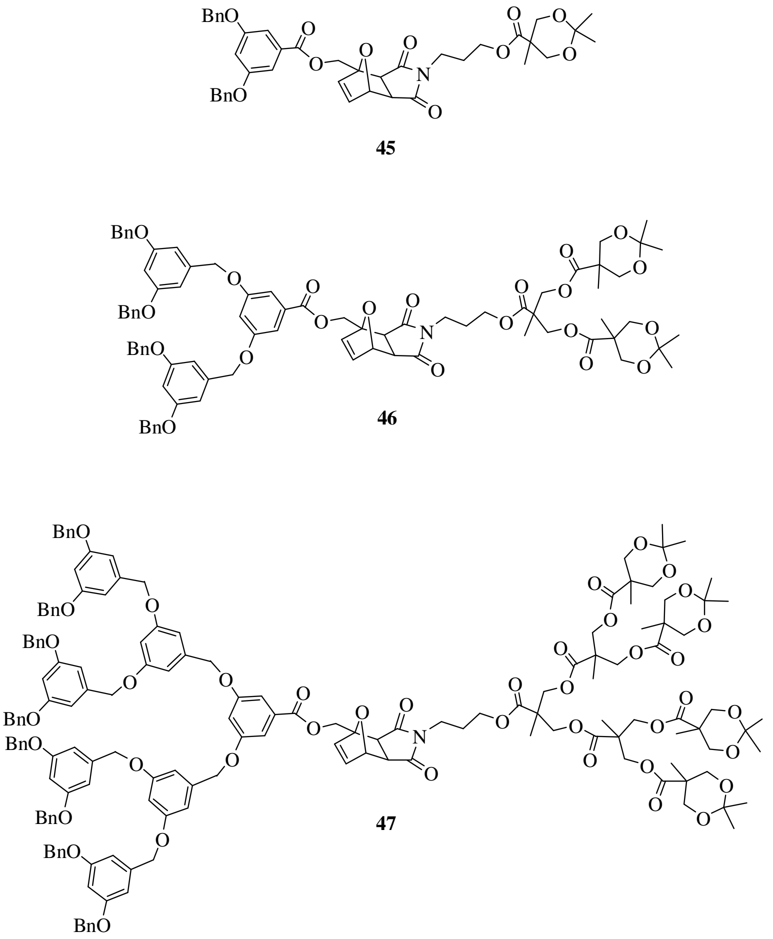


Figure 5.8. Synthesis of 3rd generation maleimide functionalized dendron

Synthesis of **44**: Compound **41** (0.52 g, 0.79 mmol) was dissolved in MeOH (10 mL) and 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 **41** 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 **38** (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. Reaction mixture was diluted with 20 mL of CH_2Cl_2 and then extracted with 1 M $NaHSO_4$ (3 x 20 mL), 10% Na_2CO_3 (3 x 20 mL) and then with brine (1 x 20 mL) combined organic layers were dried over anhydrous Na_2SO_4. The residue was concentrated in *vacuo*. Crude product was purified by column chromatography to give 0.75 g of **43** as a colorless viscous liquid (85% yield). Compound **43** (0.29 g, 0.24 mmol) was dissolved in dry toluene (3 mL) and the mixture was heated to reflux. Progress of the reaction was monitored by TLC until consumption of compound **43** is observed. The mixture was then concentrated in *vacuo* to give **44** (0.27 g, 98%) as a colorless viscous liquid. ^{1}H NMR ($CDCl_3$,δ, ppm) 6.69 (s, 2H), 4.33 - 4.23 (m, 12H), 4.12 (d, 8H, *J* = 11.8 Hz), 4.08 (t, 2H, *J* = 6.1 Hz), 3.62 - 3.58 (m, 10H), 1.96 (tt, 2H, *J* = 6.5, 6.4 Hz), 1.39 (s, 12H), 1.33 (s, 12H), 1.28 (s, 3H), 1.26 (s, 6H), 1.13 (s, 12H) ^{13}C NMR ($CDCl_3$, δ, ppm) 177.4 ,173.5, 171.9, 134.2, 98.1, 66.0, 65.9, 65.0, 62.3, 46.9, 46.7, 42.1, 34.4, 27.6, 25.0, 22.3, 18.6, 17.7, 17.6, FTIR (cm^{-1}) 1733.5, 1707.6, 1645.3, 1635.3, HRMS calculated for $C_{54}H_{81}NO_{24}$ [$(M + H)^+$] 1128.5228, found 1128.5221.

5.4. Synthesis of Segment Block Dendrimers



45

46

47

Figure 5.9. Structures of unsymmetrical dendrimers

5.4.1. Synthesis of 1st Generation Unsymmetrical Dendrimer

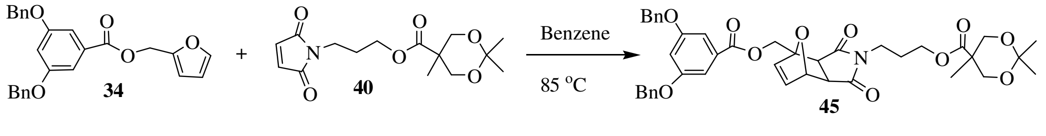


Figure 5.10. Synthesis of 1st generation unsymmetrical dendrimer

Synthesis of **45**: Compound **34** (0.06 g, 0.15 mmol) was added to a solution of **40** (0.04 g, 0.13 mmol) in benzene (0.4 mL) and was stirred for 24 h. at 85 °C. The mixture was then cooled to room temperature and solvent was evaporated in *vacuo*. The resulting compound was purified by column chromatography to give 0.09 g of **45** as a white solid (96% yield), mp: 85 °C; ^{1}H NMR ($CDCl_3$, δ, ppm) 7.41- 7.29 (m, 10H), 7.26 (d, 2H, *J* = 2.4 Hz), 6.78 (dd, 1H, *J* = 2.4, 2.4 Hz), 6.54 (dd, 1H, *J* = 5.6, 1.6 Hz), 6.45 (d, 1H, *J* = 5.7 Hz), 5.26 (d, 1H, *J* = 1.6 Hz), 5.11 (d, 1H, *J* = 12.8 Hz), 5.04 (s, 4H), 4.65 (d, 1H, *J* = 12.8 Hz), 4.21 (d, 2H, *J* = 11.8 Hz), 4.09 (t, 2H, *J* = 6.4 Hz), 3.63 (d, 2H, *J* =11.8 Hz), 3.58 (t, 2H, *J* = 6.8 Hz), 2.98 (d, 1H, *J* = 6.4 Hz), 2.92 (d, 1H, *J* = 6.4 Hz), 1.93 (tt, 2H, *J* = 6.8, 6.4 Hz), 1,41 (s, 3H), 1.38 (s, 3H), 1.22 (s, 3H) ^{13}C NMR ($CDCl_3$, δ, ppm) 175.5, 174.0, 165.7, 159.8, 135.7, 137.1, 136.4, 131.4, 128.6, 128.1, 127.6, 108.7, 107.2, 98.1, 89.7, 81.1, 70.3, 65.9, 61.9, 61.4, 49.9, 48.4, 41.8, 35.6, 26.7, 24.2, 23.1, 18.7, FTIR (cm^{-1}) 1767.9, 1694.8, 1640.0, HRMS calculated for $C_{41}H_{43}NO_{11}$ [(M + H)$^{+}$] 726.2915, found 726.2909.

5.4.2. Synthesis of 2nd Generation Unsymmetrical Dendrimer

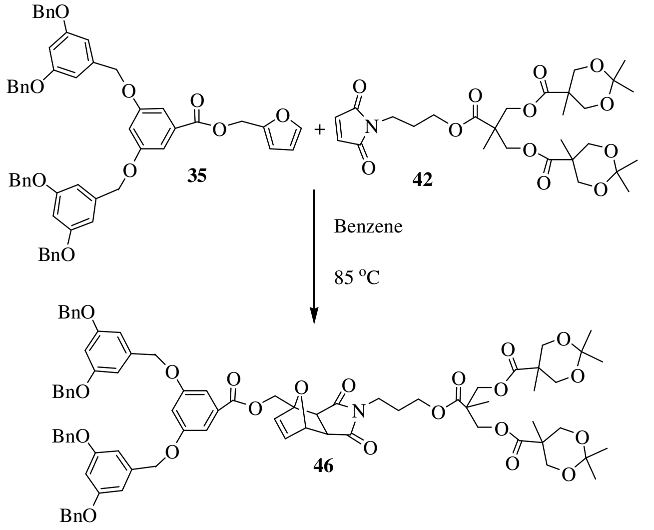


Figure 5.11. Synthesis of 2nd generation unsymmetrical dendrimer

Synthesis of **46**: Compound **35** (0.11 g, 0.13 mmol) was added to a solution of **42** (0.06 g, 0.11 mmol) in benzene (0.3 mL) and was stirred for 24 h at 85 ^{0}C. The mixture was then cooled to room temperature and solvent was evaporated in *vacuo*. The resulting mixture was purified by column chromatography to give 0.12 g of **46** as a white solid (76 % yield). mp: 64 °C; ^{1}H NMR ($CDCl_3$, δ, ppm) 7.40-7.24 (m, 22H), 6.74 (dd, 1H, *J* = 2.3, 2.3 Hz), 6.64 (d, 4H, *J* = 2.3 Hz), 6.55 (dd, 2H, *J* =2.3, 2.3 Hz), 6.50

(dd, 1H, *J* = 5.6 , 1.6 Hz), 6.44 (d, 1H, *J* = 5.7 Hz), 5.23 (d, 1H, *J* = 1.6 Hz), 5.10 (d, 1H, *J* = 12.8 Hz), 5.01 (s, 8H), 4.97 (s, 4H), 4.64 (d, 1H, *J* = 12.8 Hz), 4.34 (d, 2H, *J* = 12.8 Hz), 4.31 (d, 2H, *J* = 12.8 Hz), 4.13 (d, 4H, *J* = 11.8 Hz), 4.06 (t, 2H, *J* = 6.1 Hz), 3.60 (d, 4H, *J* = 12.4 Hz), 3.56 (t, 2H, *J* = 6.8 Hz), 2.95 (d, 1H, *J* = 6.4 Hz), 2.92 (d, 1H, *J* = 6.4 Hz), 1.91 (tt, 2H, *J* = 6.8, 6.4 Hz), 1.38 (s, 6H), 1.33 (s, 6H), 1.30 (s, 3H), 1.13 (s, 6H), ^{13}C NMR ($CDCl_3$, δ, ppm) 175.5, 174.1, 173.5, 172.4, 165.6, 160.2, 138.8, 137.6, 137.0, 136.7, 131.4, 128.6, 128.0, 127.6, 108.7, 107.2, 106.4, 101.6, 98.1, 89.6, 81.1, 70.1, 66.0, 65.9, 65.2, 62.0, 61.9, 49.9, 48.4, 46.8, 42.0, 35.5, 26.6, 25.0, 22.2, 18.5, 17.7, FTIR (cm^{-1}) 1770.0, 1732.4, 1715.7, 1699.0, HRMS calculated for $C_{82}H_{87}NO_{21}$ [$(M + H)^+$] 1422.5850, found 1422.5843

5.4.3. Synthesis of 3rd Generation Unsymmetrical Dendrimer

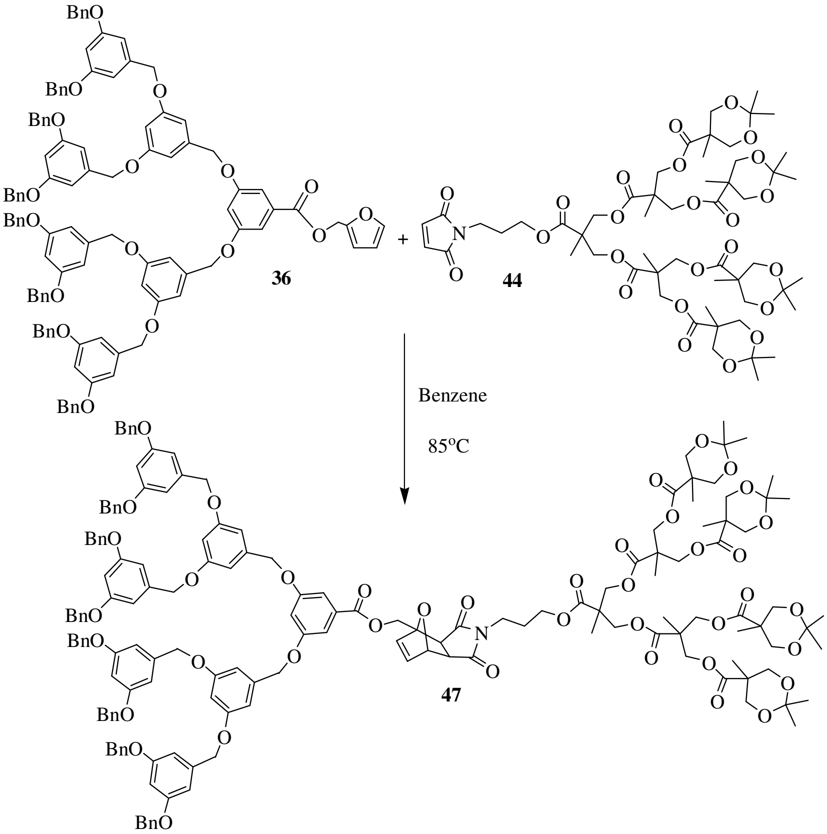


Figure 5.12. Synthesis of 3rd generation unsymmetrical dendrimer

Synthesis of **47**: Compound **36** (0.05 g, 0.03 mmol) was added to a solution of **44** (0.03 g, 0.02 mmol) in benzene (0.2 mL) and was stirred for 24 h. at 85 ^{0}C. The mixture was then cooled to room temperature and solvent was evaporated in *vacuo*. The resulting compound was purified by column chromatography to give 0.05 g of **47** as a white solid (79% yield). mp: 58 ^{o}C; ^{1}H NMR ($CDCl_3$, δ, ppm) 7.38-7.26 (m, 42H), 6.76 (dd, 1H, *J* = 2.2, 2.2 Hz), 6.64 (d, 8H, *J* = 2.2 Hz), 6.62 (d, 4H, *J* = 2.2 Hz), 6.54-6.47 (m, 7H), 6.43 (d, 1H, *J* = 5.6 Hz), 5.20 (d, 1H, *J* = 1.6 Hz), 5.08 (d, 1H, *J* = 12.9 Hz), 4.99 (s, 16H), 4.94 (s, 4H), 4.93 (s, 8H), 4.63 (d, 1H, *J* = 12.9 Hz), 4.31-4.23 (m, 12H), 4.11 (d, 8H, *J* = 11.8 Hz), 4.05 (t, 2H, *J* = 6.2 Hz), 3.58 (d, 8H, *J* = 12.0 Hz), 3.55 (t, 2H, *J* = 6.2 Hz), 2.95 (d, 1H, *J* = 6.4 Hz), 2.93 (d, 1H, *J* = 6.4 Hz), 1.91 (tt, 2H, *J* = 6.8, 6.2 Hz), 1.37 (s, 12H), 1.32 (s, 12H), 1.27 (s, 3H), 1.25 (s, 6H), 1.10 (s, 12H), ^{13}C NMR ($CDCl_3$, δ, ppm) 175.6, 174.2, 173.5, 171.8, 165.6, 160.1, 160.0, 159.6, 139.1, 138.7, 137.6, 136.9, 136.7, 131.4, 128.6, 128.0, 127.5, 108.6, 107.0, 106.5, 106.3, 101.5, 98.0, 89.6, 81.1, 70.2, 70.05, 69,96, 65.93, 65.88, 64.9, 62.1, 49.9, 48.4, 46.8, 46.6, 42.0, 35.4, 26.6, 25.2, 22.0, 18.5, 17.7, 17.5, FTIR (cm^{-1}) 1732.9, 1690.7, 1648.5, HRMS calculated for $C_{164}H_{175}NO_{41}$ [(M+ Na+K)$^{++}$] 1438.5598, found 1438.5650.

The cycloaddition reactions were very clean transformations, resulting in desired dendrimers after column chromatography. These dendrimers possess a bicyclic furan maleimide cycloadduct as a core. ^{1}H NMR data of the dendrimers shows that the two dendrons are combined together through a bicyclic core due to the appearance of new proton resonances corresponding to the bicyclic core at 5.2 and 2.9 ppm and disappearance of the characteristic resonances belonging to the maleimide and furan units at the dendron focal points (Figure 5.4).

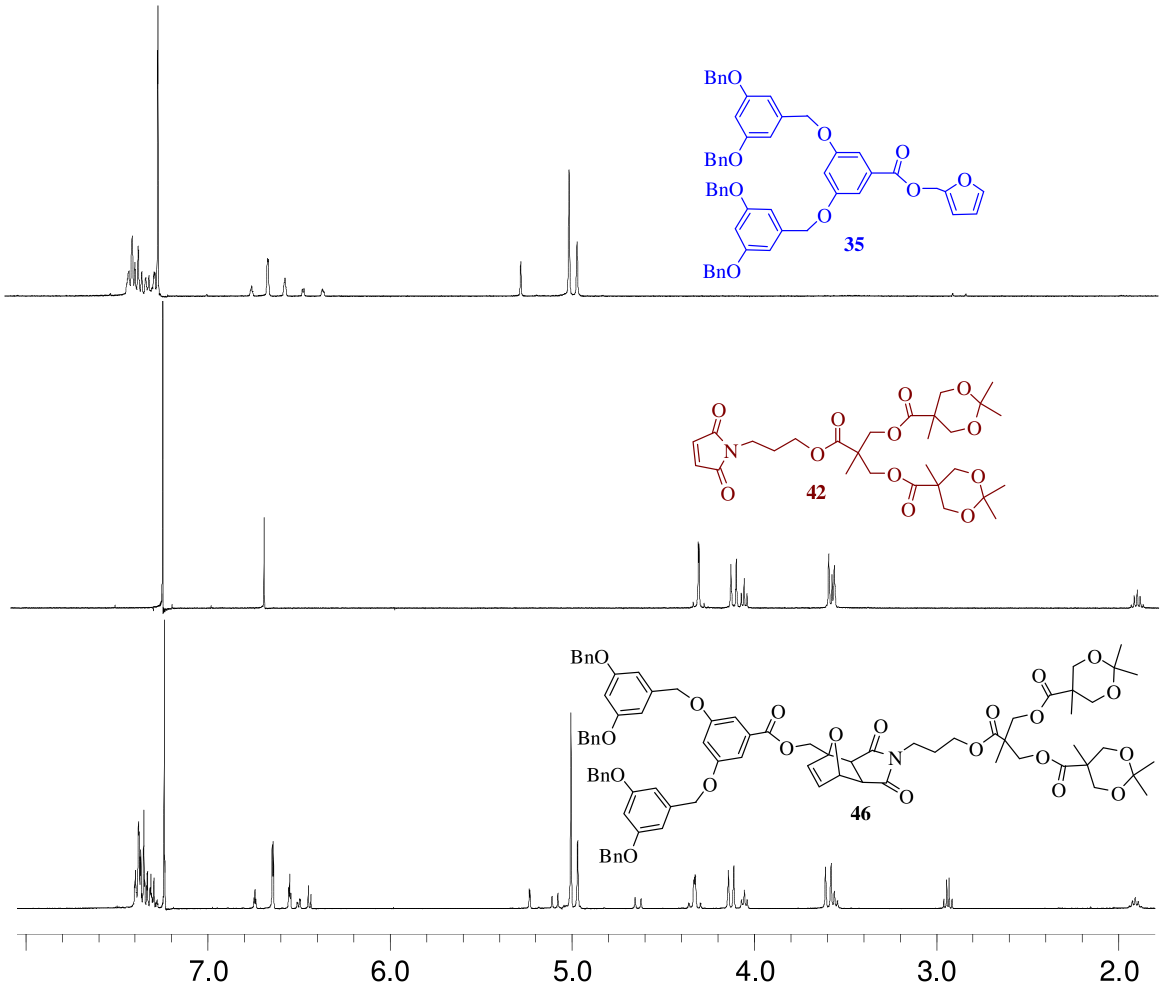


Figure 5.13. ^{1}H NMR spectra of 2nd generation dendrons **35**, **42** and dendrimer **46**

It is known that Diels-Alder reaction between a furan and a maleimide produces cycloadducts as exo and endo isomers. The endo/exo selectivity of the reaction was determined using ^{1}H NMR spectroscopy. Due to the thermoreversibility of the endo products relative to the exo adducts, a higher reaction temperature favors exo adducts. In order to investigate effect of temperature on exo-endo ratios of the formed products, a series of reactions with first generation dendrons **34** and **40** were done at rt, 45, 65 and 85 °C . The results suggest that fine tuning of the reaction temperature plays an important role for the stereoselectivity of the formed product and it is possible to obtain pure exo product at 85°C for the first generation dendrimers **45** (Figure 5.5).

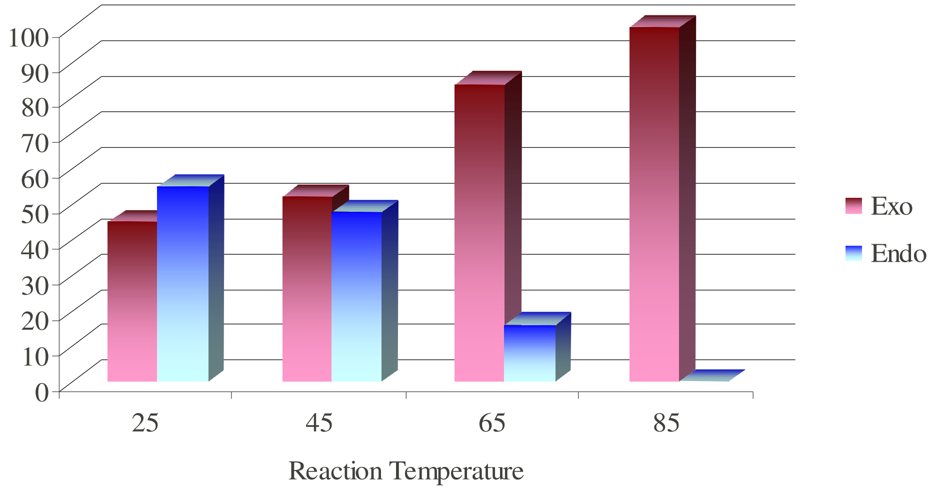


Figure 5.14. Effect of temperature on stereochemistry of **45**

However it wasn't possible to exclusively obtain exo product for the second and third generation dendrimers **46** and **47**. At this point a previous literature example was helpful for determining the peaks in the ^{1}H NMR corresponding to exo- endo isomers [22]. For example, in first generation dendrimer **45**, the benzoic ester methylene protons in the exo cycloadducts appear as doublets at 5.11 and 4.65 ppm, whereas for the endo- adducts they appear at 5.02 and 4.82 ppm (Figure 5.6).

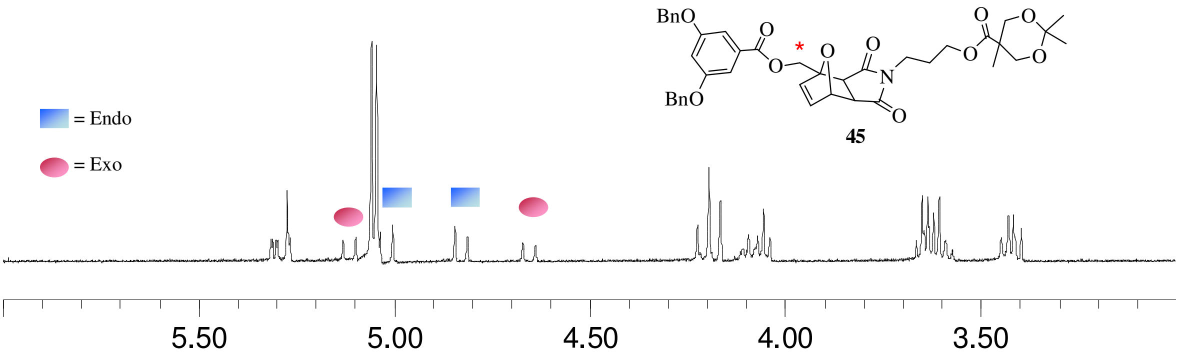


Figure 5.15. ^{1}H NMR of benzoic ester methylene protons in exo and endo adducts.

^{1}H NMR spectra of the products have shown that the second generation dendrimer **46** was obtained with an exo/endo ratio of (91:9) whereas the third generation dendrimer

47 was obtained with an exo/endo ratio of (87:13). But, thermal treatment as described later, allows one to obtain dendrimers with exo bridged cores.

To simplify the access to pure exo isomer of dendrimers **46** and **47**, we added a furan functionalized Merrifield resin to scavenge any remaining maleimide dendron that was difficult to separate from the desired dendrimer using chromatographic techniques. This thermal treatment of mixture of endo exo adducts with the scavenger resin at 50 ^{o}C also enables one to exclusively obtain exo bridged dendrimer. Resulting exo dendrimers were further characterized by GPC giving narrow polydispersity values as expected, however the molecular weights were far from the exact values due to the globular shape of the dendrimers (Figure 5.7).

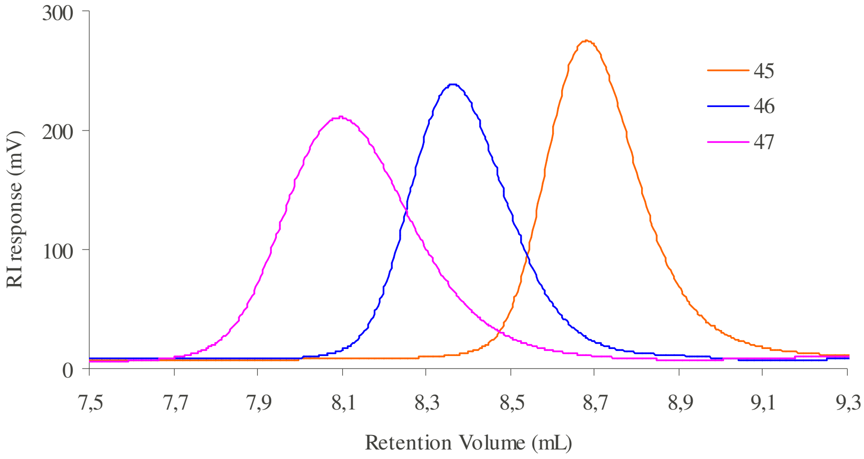


Figure 5.16. GPC results for the dendrimers **45**, **46** and **47**

In order to demonstrate the thermo reversibility property of the dendrimers formed, second generation dendrimer **46** was refluxed in toluene in the presence of anthracene. Anthracene was added as a scavenger diene to prevent reassembly of the released maleimide and furan dendrons.

Cycloaddition with anthracene under these conditions produces an adduct that is non-reversible. Disappearance of the peak at 2.94 ppm proves that the dendrimer **46** has disassembled completely. ^{1}H NMR data shows that the peaks corresponding to **34** were recovered completely. Furthermore absence of a singlet at 6.64 ppm and formation of the new multiplet at 3.16 ppm indicates that maleimide has completely reacted with the anthracene molecule forming compound **48** (Figure 5.8).

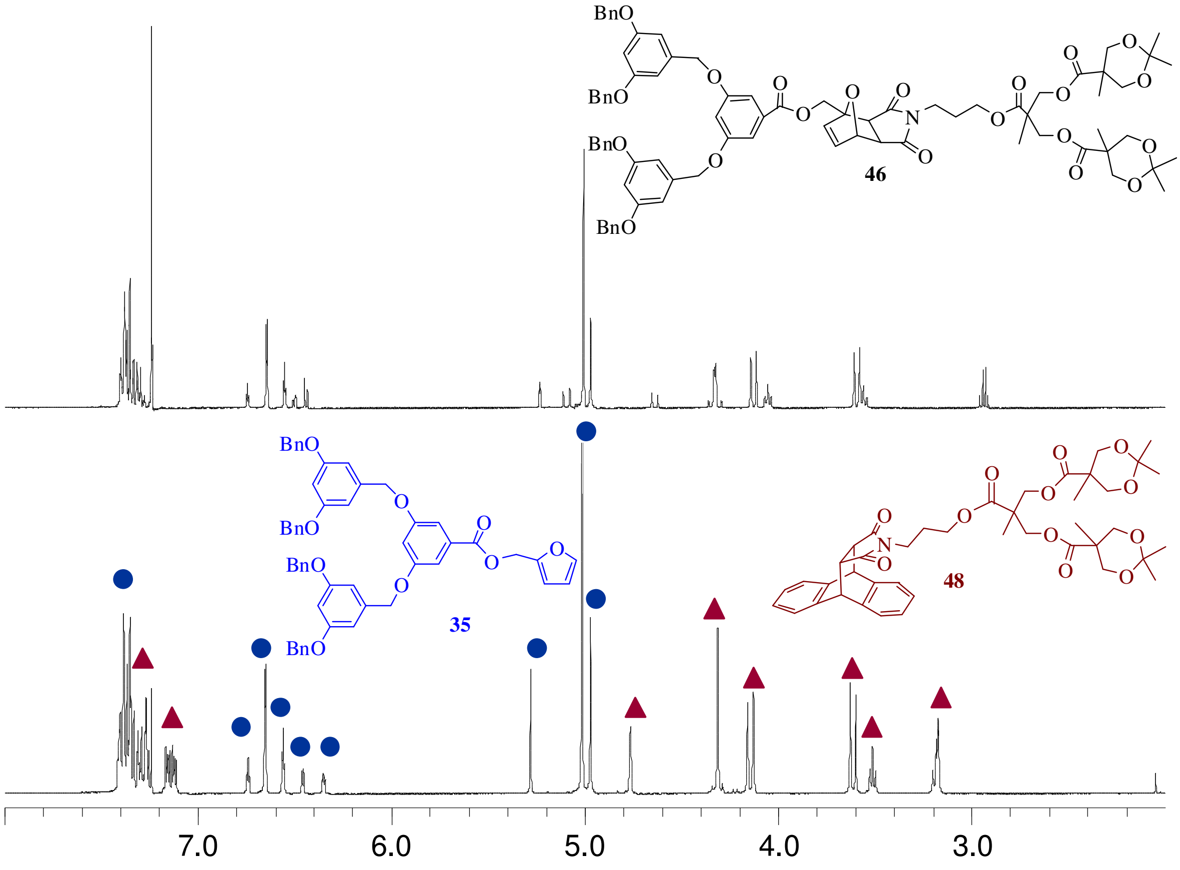


Figure 5.17. ^{1}H NMR spectra of second generation dendrimer **46** and the retro Diels-Alder products **35** and **48**

6. ORTHOGONAL FUNCTIONALIZATION OF DENDRONS

6.1. Click Chemistry

Huisgen 1, 3-dipolar cycloadditions provide easy access to a variety of five membered heterocycles by coupling two unsaturated reactants [23]. The cycloaddition reaction between azides and terminal alkynes to give disubstituted triazoles is the most ideal click reaction known to date. However this reaction generates a mixture of 1, 4 and 1, 5-disubstituted triazoles (Figure 6.1).

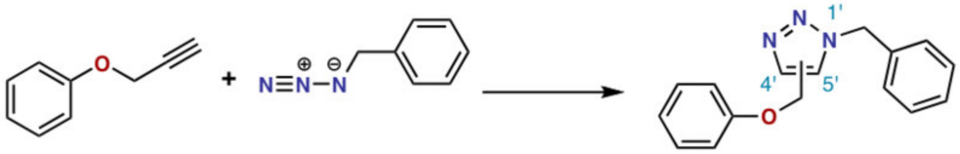


Figure 6.1. Click reaction between an azide and a terminal alkyne

In 2002 Sharpless and coworkers [24] found that Cu (I) catalyzed reaction systems regiospecifically combines azides and terminal alkynes to give only 1, 4-disustituted 1, 2, 3-triazoles. The reaction is insensitive to air and H_2O which makes it even simpler and easy to handle. Also there is virtually no byproduct and hence the purification process is easier compared to other organic transformations. All of these properties make the “click” reaction very desirable to use and therefore the reaction has found many applications in organic chemistry, drug discovery, materials science and synthesis of dendrimers and polymers.

One of the recent publications by Weck *et al.* [25] employs click reaction in order to obtain orthogonal functionalization at the polymer backbone (Figure 6.2). In this work, polymers, **49**, consisting of azide and aldehyde bearing side chains were made by ring opening metathesis polymerization (ROMP) from norbornene units modified with desired side chains. The formed polymer was then functionalized with molecules bearing a hydrazine unit **51** to form hydrazones and azide containing molecules **50** to form the triazole rings and a library of polymers, **52,** which were post functionalized with two different groups, were formed under mild conditions and high efficiencies.

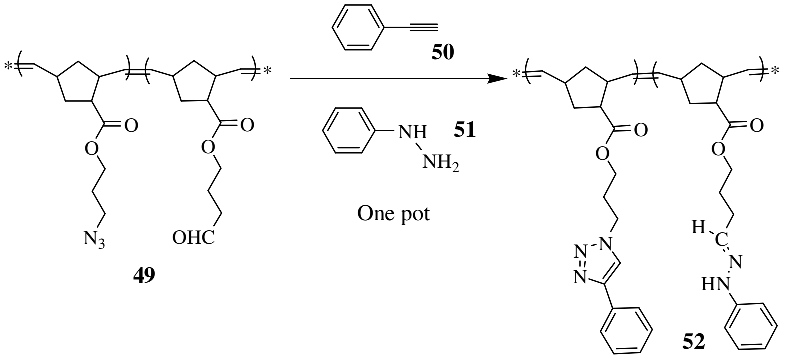


Figure 6.2. Orthogonal functionalization of polymer chain

Orthogonal multifunctionalization of macromolecular systems is highly desirable since it provides attachment sites for drugs, targeting units, sensors and therapeutics. Such orthogonal approaches can also be seen in the nature for antibody-antigen and enzyme-substrate interactions.

It is possible to obtain these orthogonal interactions in two ways. First way is to obtain them through non-covalent interactions which are desirable since they are reversible and self-assembling however poor stability of these systems makes them undesirable. On the other hand using covalent interactions provide increased stability but suffer from low efficiency. This shortage of the latter method can be overcome by employing high yielding reactions. In our work we have applied this strategy to our system and synthesized orthogonally functionalizable dendrons consisting of “clickable” surface groups and a maleimide core which serves as a Michael acceptor (Figure 6.3).

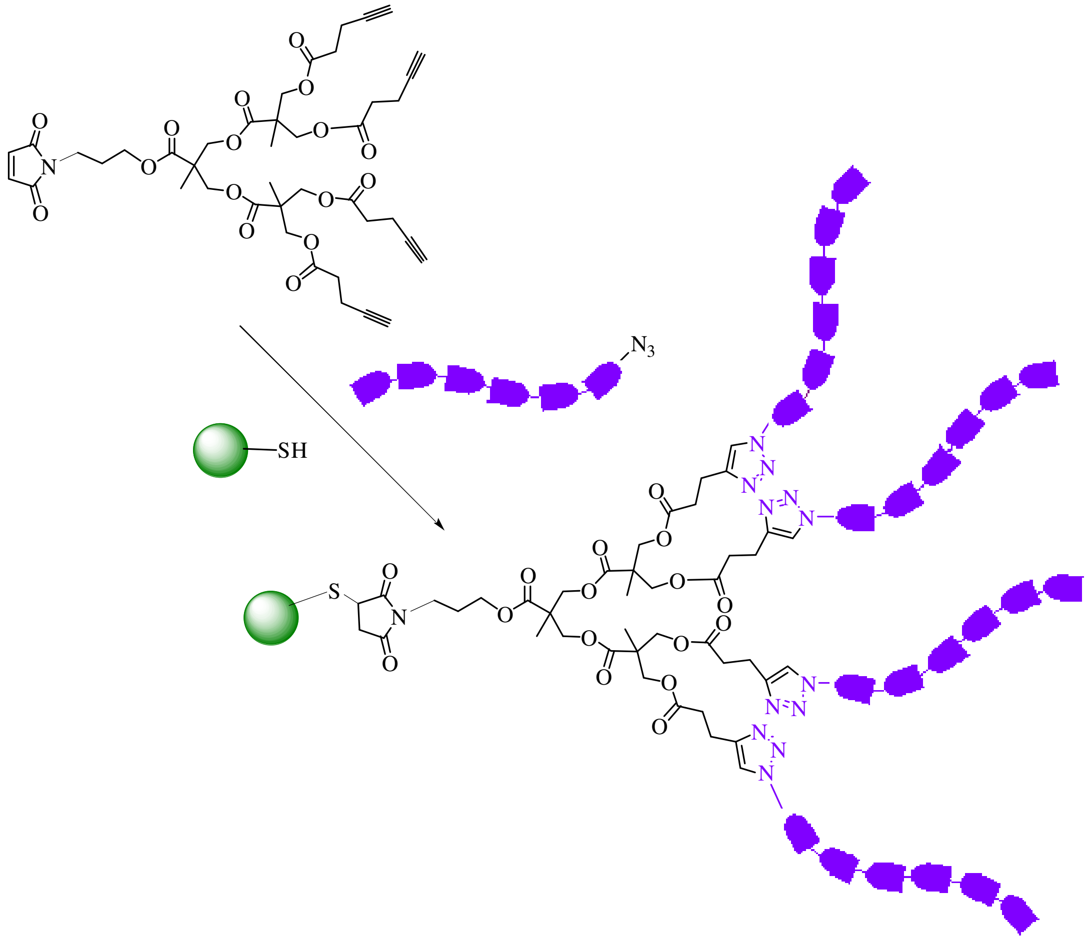


Figure 6.3. Orthogonally functionalized dendron

7. RESULTS AND DISCUSSION – B

7.1. Synthesis of Alkyne Functionalized Dendrons

In order to obtain orthogonally functionalized dendrons, three generations of poly (ester) dendrons with inactive maleimide units at the focal point were used as starting materials. Surface activation of these molecules afforded dendrons with multiple –OH groups at the periphery and further reaction of these reactive units with 4-pentynoic acid anhydride yielded alkyne appended dendrons in good yields. Activation of the core was achieved by a simple retro Diels-Alder reaction to give orthogonally bifunctional dendrons (Figure 7.1).

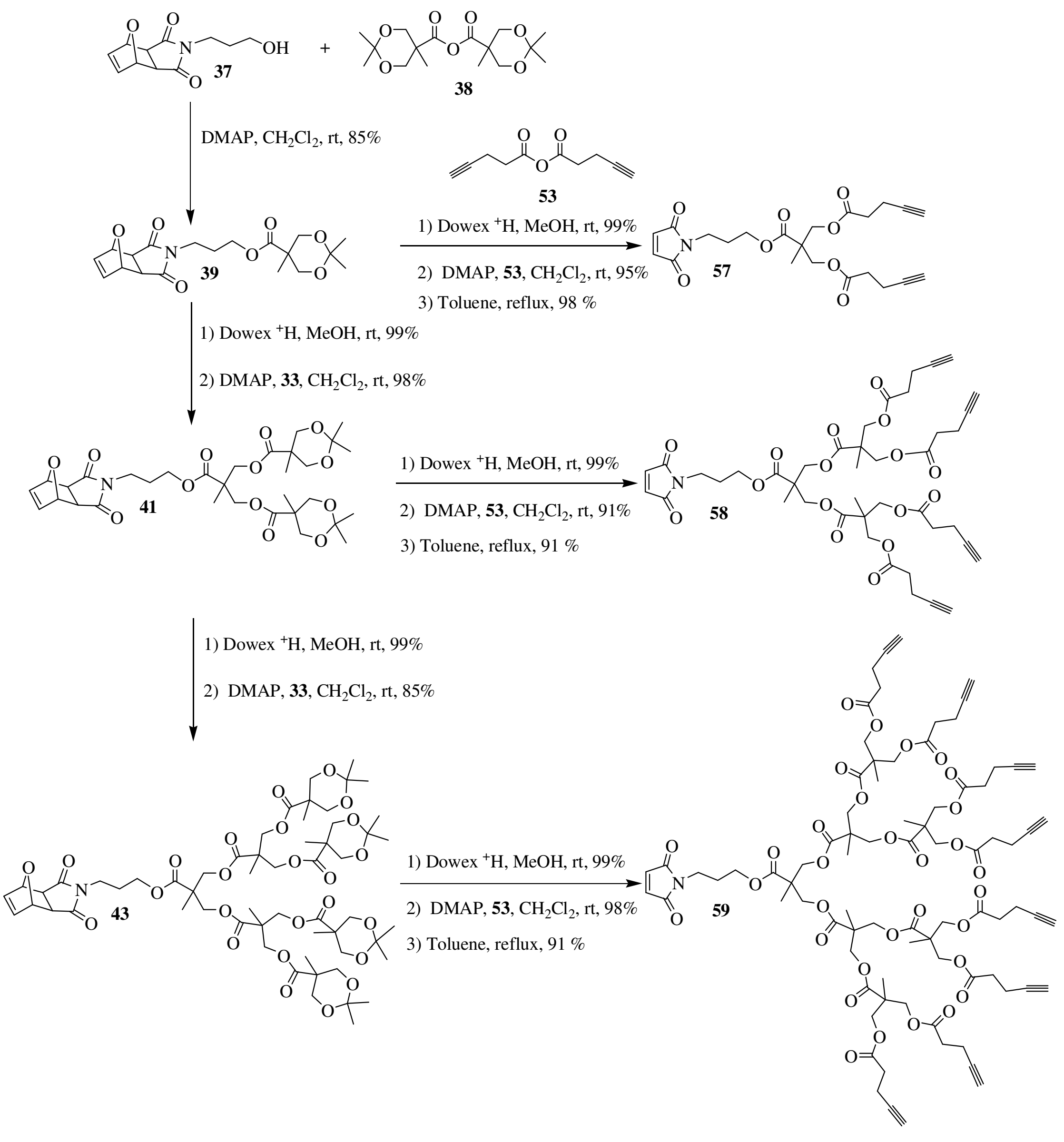


Figure 7.1. Synthesis of alkyne functionalized dendrons

7.1.1. Synthesis of 1st Generation Dendron 54

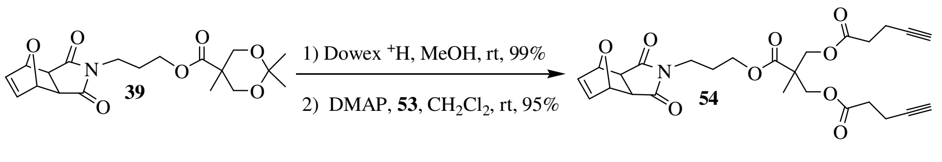


Figure 7.2. Synthesis of 1st generation dendron **54**

Compound **39** (2.00 g, 5.30 mmol) was dissolved in MeOH (30 mL) and to this solution Dowex H^+ resin was added with the tip of a spatula. The resulting mixture was stirred at ambient temperature until the consumption of **39** 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 (1.78 g, 99% yield). The solid (0.40 g, 1.10 mmol) was then added to a solution of DMAP (0.07 g, 0.60 mmol), pyridine (0.8 mL) and compound **53** (0.60 g, 3.30 mmol) in dry CH_2Cl_2 (5 mL). The mixture was then stirred at room temperature for 12 h. Excess anhydride was quenched with water (2.0 mL) for 3 h. Reaction mixture was diluted with 50 mL CH_2Cl_2 and extracted with 1 M $NaHSO_4$ (3 x 20 mL), 10% Na_2CO_3 (3 x 20 mL) and then with brine (1 x 20 mL) combined organic layers were dried over anhydrous Na_2SO_4. The residue was concentrated in *vacuo*. Crude product was purified by column chromatography to give 0.52 g of **54** as a colorless viscous liquid (95% yield). ^1H NMR ($CDCl_3$,δ, ppm) 6.49 (dd, 2H, *J* = 0.9, 0.8 Hz), 5.24 (dd, 2H, *J* = 0.9, 0.9), 4.30 (d, 2H, *J* = 11.1 Hz), 4.26 (d, 2H, J = 11.1 Hz), 4.07 (t, 2H, *J* = 6.2 Hz), 3.55 (t, 2H, *J* = 6.8 Hz), 2.82 (s, 2H), 2.57 – 2.53 (m, 4H), 2.49 – 2.45 (m, 4H), 1.96 (t, 2H, *J* = 2.54 Hz), 1.91 (tt, 2H, *J* = 6.8, 6.4 Hz), 1.27 (s, 3H), ^{13}C NMR ($CDCl_3$, δ, ppm) 176.0, 172.4, 171.1, 136.4, 82.3, 80.9, 69.2, 65.4, 61.9, 47.3, 46.2, 35.2, 33.1, 26.6, 17.8, 14.2, FTIR (cm^{-1}) 1732.0, 1695.1

7.1.2. Synthesis of 2nd Generation Dendron 55

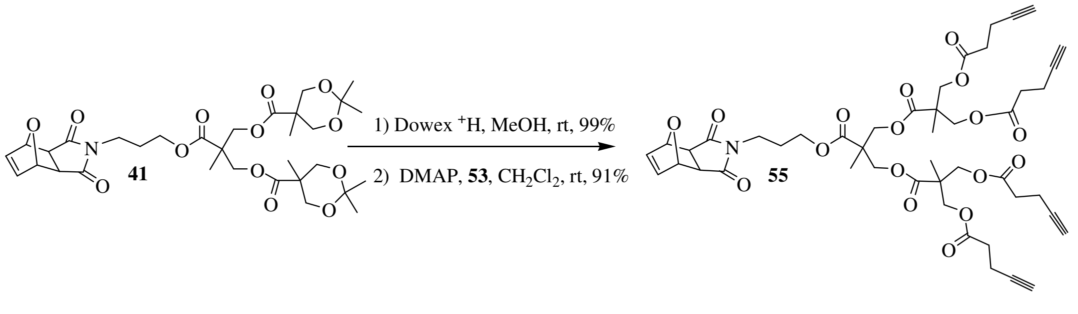


Figure 7.3. Synthesis of 2nd generation dendron **55**

Compound **41** (1.0 g, 1.5 mmol) was dissolved in MeOH (10 mL) and to this solution Dowex H^+ resin was added with the tip of a spatula. The resulting mixture was stirred at ambient temperature until the consumption of **41** 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 (0.86 g, 98% yield). The solid (0.14 g, 0.20 mmol) was then added to a solution of DMAP (0.03 g, 0.20 mmol), pyridine (0.4 mL) and compound **53** (0.26 g, 1.20 mmol) in dry CH_2Cl_2 (3 mL). The mixture was then stirred at room temperature for 12 h. Excess anhydride was quenched with water (2.0 mL) for 3 h. Reaction mixture was diluted with 20 mL CH_2Cl_2 and extracted with 1 M $NaHSO_4$ (3 x 20 mL), 10% Na_2CO_3 (3 x 20 mL) and then with brine (1 x 20 mL) combined organic layers were dried over anhydrous Na_2SO_4. The residue was concentrated in *vacuo*. Crude product was purified by column chromatography to give 0.20 g of **55** as a colorless viscous liquid (91% yield). ^1H NMR ($CDCl_3$,δ, ppm) 6.50 (s, 2H), 5.24 (s, 2H), 4.27 (s, 4H), 4.24 (d, 4H, *J* = 11.3 Hz), 4.21 (d, 4H, *J* = 11.2 Hz), 4.04 (t, 2H, *J* = 6.2 Hz), 3.56 (t, 2H, *J* = 6.8 Hz), 2.84 (s, 2H), 2.56 – 2.53 (m, 8H), 2.49-2.44 (m, 8H), 1.96 (t, 4H, *J* = 2.6 Hz), 1.92 (tt, 2H, *J* = 6.8, 6.2 Hz), 1.27 (s, 3H), 1.23 (s, 6H), ^{13}C NMR ($CDCl_3$, δ, ppm) 176.1, 171.9, 171.8, 171.1, 136.4, 82.3, 80.9, 69.2, 65.6, 65.3, 61.9, 47.4, 46.6, 46.3, 35.2, 33.1, 26.5, 17.8, 17.5, 14.2, FTIR (cm^{-1}) 1732.0, 1697.8

7.1.3. Synthesis of 3rd Generation Dendron 56

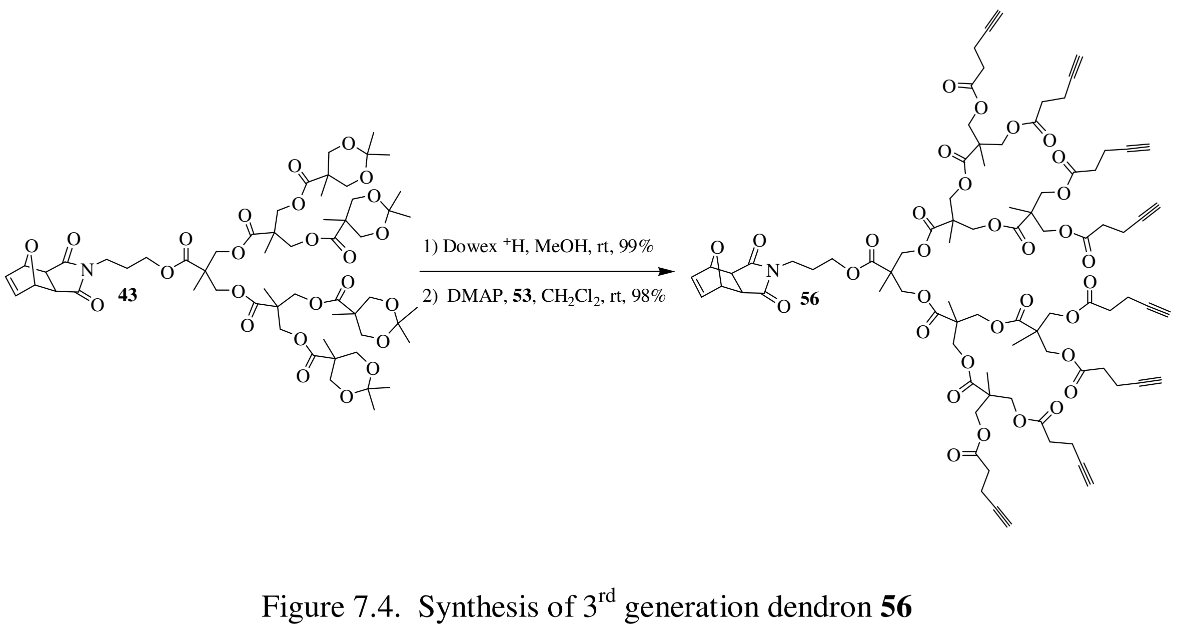


Figure 7.4. Synthesis of 3rd generation dendron **56**

Compound **43** (0.2 g, 0.2 mmol) was dissolved in MeOH (8 mL) and 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 **43** 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 (0.17 g, 98% yield). The solid (0.09 g, 0.1 mmol) was then added to a solution of DMAP (0.02 g, 0.2 mmol), pyridine (0.3 mL) and compound **53** (0.24 g, 1.4 mmol) in dry CH_2Cl_2 (5 mL). The mixture was then stirred at room temperature for 12 h. Excess anhydride was quenched with water (3.0 mL) for 12 h. Reaction mixture was diluted with 30 mL CH_2Cl_2 and extracted with 1 M $NaHSO_4$ (3 x 20 mL), 10% Na_2CO_3 (3 x 20 mL) and then with brine (1 x 20 mL) combined organic layers were dried over anhydrous Na_2SO_4. The residue was concentrated in *vacuo*. Crude product was purified by column chromatography to give 0.15 g of **56** as a colorless viscous liquid (98% yield). ^1H NMR ($CDCl_3$,δ, ppm) 6.50 (s, 2H), 5.23 (s, 2H), 4.30 – 4.19 (m, 28H), 4.05 (t, 2H, *J* = 6.0 Hz), 3.56 (t, 2H, *J* = 6.6 Hz), 2.84 (s, 2H), 2.56 – 2.53 (m, 16H), 2.48 – 2.44 (m, 16H), 1.97 (t, 8H, *J* = 2.4 Hz), 1.93 (tt, 2H, *J* = 6.6, 6.0 Hz), 1.30 (s, 3H), 1.24 (s, 6H), 1.23 (s, 12H), ^{13}C NMR ($CDCl_3$, δ, ppm) 176.1, 171.8, 171.7, 171.4, 171.0, 136.5, 82.3, 80.9, 69.3, 66.1, 65.3, 65.2, 62.1, 47.4, 46.7, 46.6, 46.3, 35.2, 33.1, 26.6, 17.7, 17.5, 17.4, 14.2, FTIR (cm^{-1}) 1731.6, 1699.0

7.1.4. Synthesis of Dendron 57

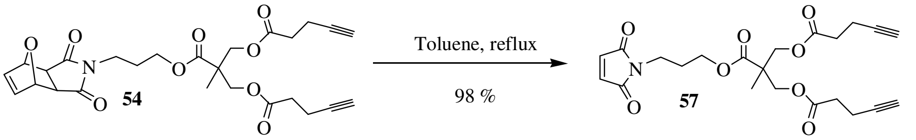


Figure 7.5. Synthesis of dendron **57**

Compound **54** (0.14 g, 0.28 mmol) was dissolved in dry toluene (15 mL) and the mixture was heated to reflux. Progress of the reaction was monitored by TLC until consumption of compound **54** is observed. The mixture was then concentrated in *vacuo* to give **57** (0.12 g , 98%) as a pale yellow viscous liquid. ^1H NMR ($CDCl_3$,δ, ppm) 6.68 (s, 2H), 4.29 (d, 2H, *J* = 11.2 Hz), 4.24 (d, 2H, *J* = 11.2 Hz), 4.08 (t, 2H, *J* = 6.2 Hz), 3.59 (t, 2H, *J* = 6.8 Hz), 2.56 – 2.53 (m, 4H), 2.48 – 2.44 (m, 4H), 1.99 – 1.90 (m, 4H), 1.26 (s, 3H), FTIR (cm^{-1}) 1732.5, 1701.8

7.1.5. Synthesis of Dendron 58

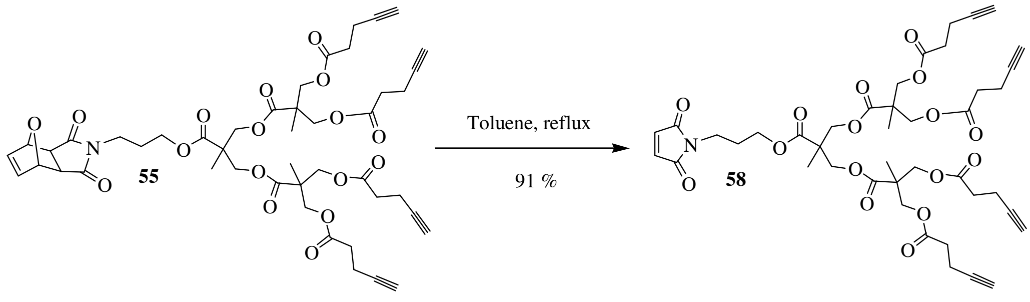


Figure 7.6. Synthesis of dendron **58**

Compound **55** (0.25 g, 0.28 mmol) was dissolved in dry toluene (15 mL) and the mixture was heated to reflux. Progress of the reaction was monitored by TLC until consumption of compound **55** is observed. The mixture was then concentrated in *vacuo* to give **58** (0.20 g , 91%) as a pale yellow viscous liquid. ^{1}H NMR ($CDCl_3$,δ, ppm) 6.70 (s, 2H), 4.26 (s, 4H), 4.25 (d, 4H, *J* = 11.2 Hz), 4.21 (d, 4H, *J* = 11.2 Hz), 4.07 (t, 2H, *J* = 6.4 Hz), 3.61 (t, 2H, *J* = 6.4 Hz), 2.56 – 2.53 (m, 8H), 2.48 – 2.44 (m, 8H), 1.98 – 1.92 (m, 6H), 1.27 (s, 3H), 1.24 (s, 6H), ^{13}C NMR ($CDCl_3$, δ, ppm) 171.6, 170.8, 170.3, 133.9, 82.1, 69.1, 65.3, 65.0, 61.9, 46.3, 46.0, 34.0, 32.8, 27.2, 17.5, 17.3, 13.9, FTIR (cm^{-1}) 1732.2, 1704.7

7.1.6. Synthesis of Dendron 59

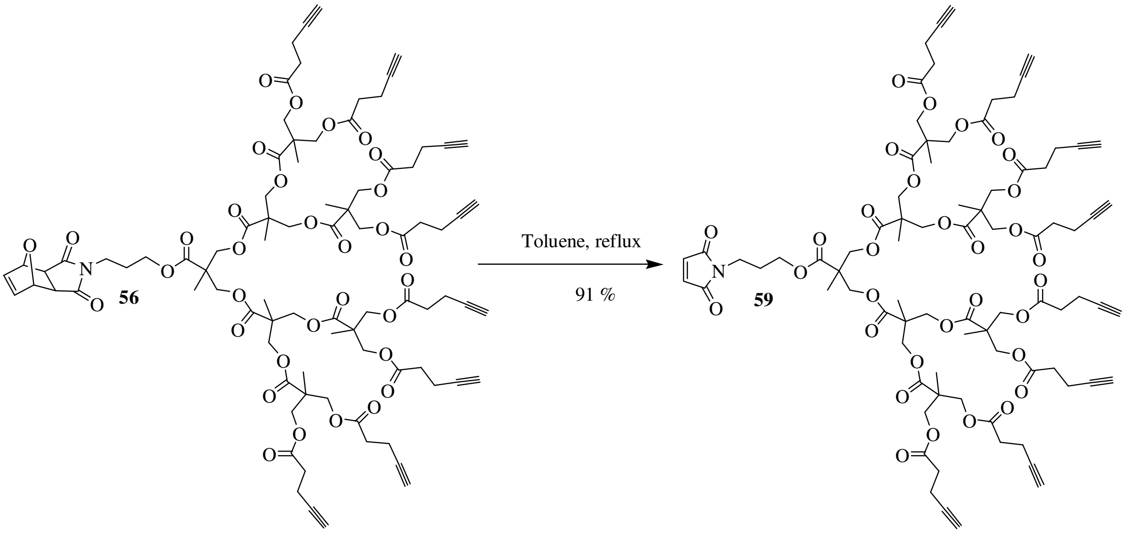


Figure 7.7. Synthesis of dendron **59**

Compound **56** (0.07 g, 0.042 mmol) was dissolved in dry toluene (10 mL) and the mixture was heated to reflux. Progress of the reaction was monitored by TLC until consumption of compound **56** is observed. The mixture was then concentrated in *vacuo* to give **59** (0.06 g , 91%) as a pale yellow viscous liquid. ^{1}H NMR ($CDCl_3$,δ, ppm) 6.71 (s, 2H), 4.30 – 4.19 (m, 28H), 4.09 (t, 2H, J = 5.6 Hz), 3.61 (t, 2H, J = 6.0 Hz), 2.56 – 2.52 (m, 16H), 2.50 – 2.44 (m, 16H), 1.97 (bs, 8H), 1.84 (bm, 2H), 1.30 (s, 3H), 1.23 (s, 18H), FTIR (cm^{-1}) 1731.1, 1707.4

Present studies are focussed upon appropriate orthogonal functionalizations of these dendrons. Attachment of water soluble near monodisperse PEG moieties at the periphery and michael addition of a thiol modified small molecules are currently being evaluated to develop a water soluble reactive multiarm PEG based polymeric scaffolds that can find potential applications in various areas such as drug delivery.

8. CONCLUSIONS

A new method for synthesis of segment block dendrimers was designed. Fréchet type poly (aryl ether) dendrons functionalized with furan moieties and maleimide functionalized poly (ester) dendrons were synthesized. Three generations of these structurally different dendrons were combined through Diels-Alder reaction. Formed dendrimers were further investigated for their stereochemical properties at different reaction temperatures and moreover the thermoreversible nature of the formed dendrimers was demonstrated by using a scavenging diene. The study was extended by surface modification of maleimide functionalized poly (ester) dendrons with pentynoic acid to provide Huisgen type “clickable” peripheral groups. Core of the formed structures were activated by rDA reaction to yield reactive maleimide units that can be efficiently functionalized by either Michael addition of thiol containing molecules or Diels-Alder based cycloaddition with a diene containing molecule.

APPENDIX A : SPECTROSCOPY DATA

^{1}H NMR and ^{13}C NMR data for the synthesized compounds are given below. Needed regions of NMR data were expanded.

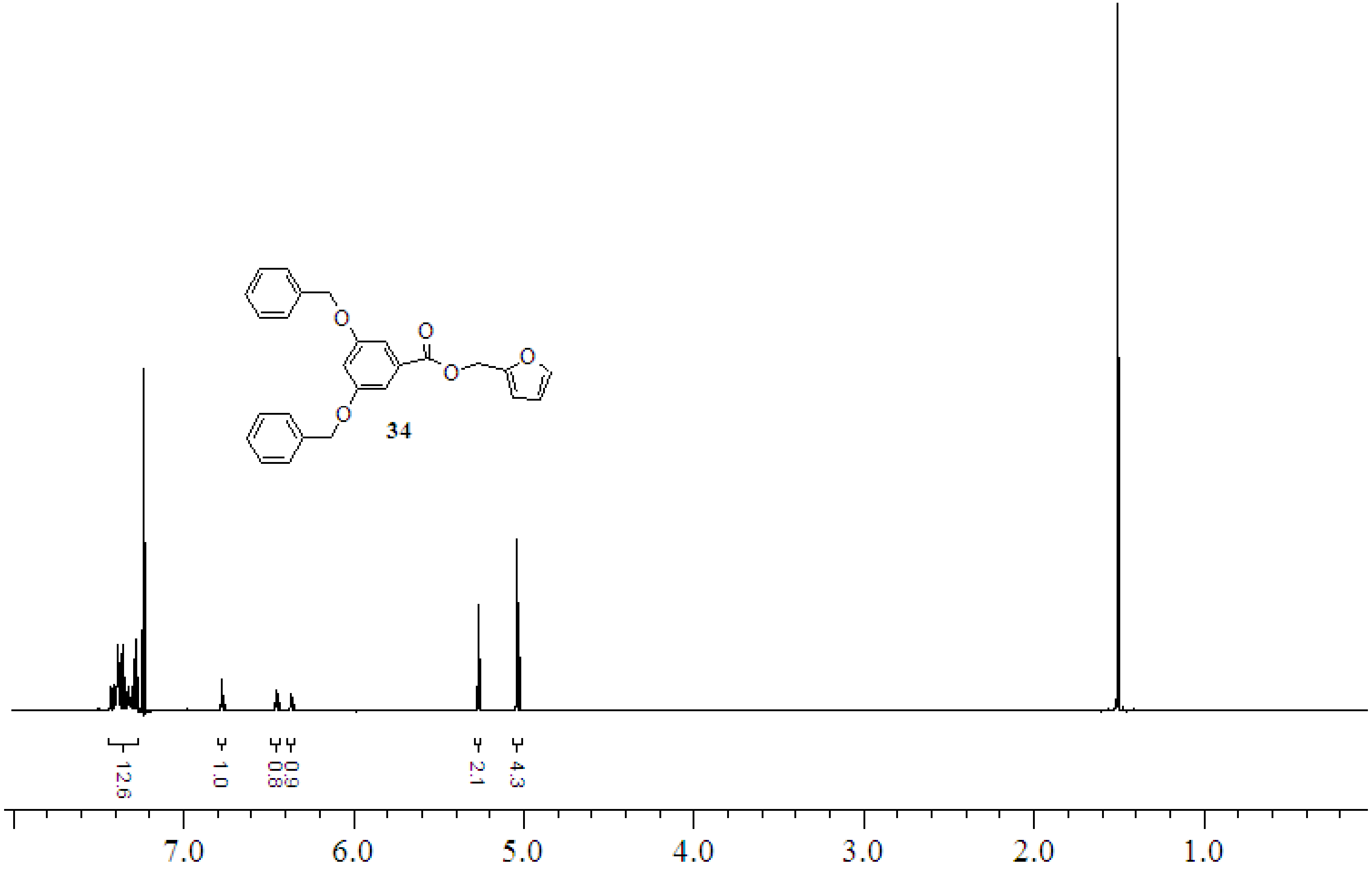


Figure A.1. ^{1}H NMR spectrum of 1st generation furan functionalized dendron **34**

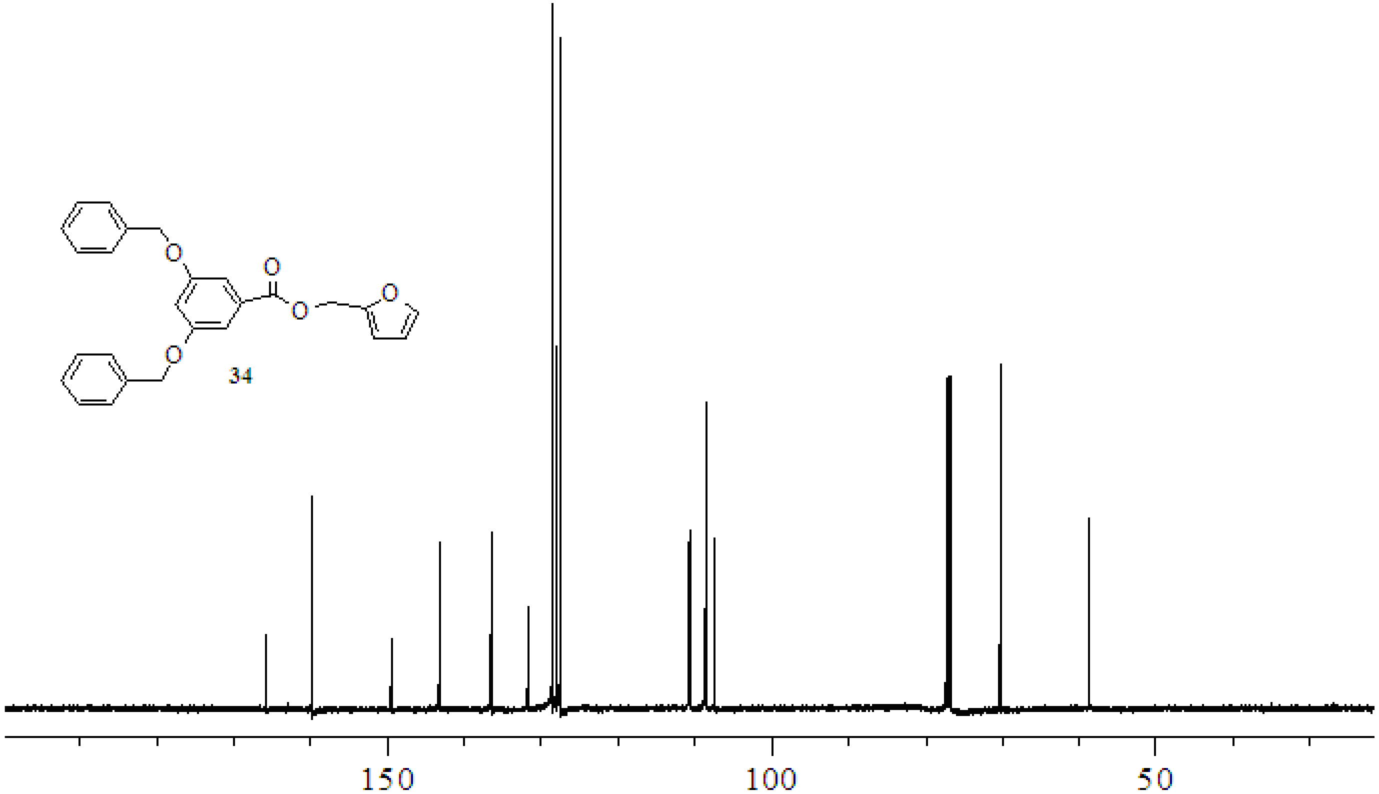


Figure A.2. ^{13}C NMR spectrum of 1st generation furan functionalized dendron **34**

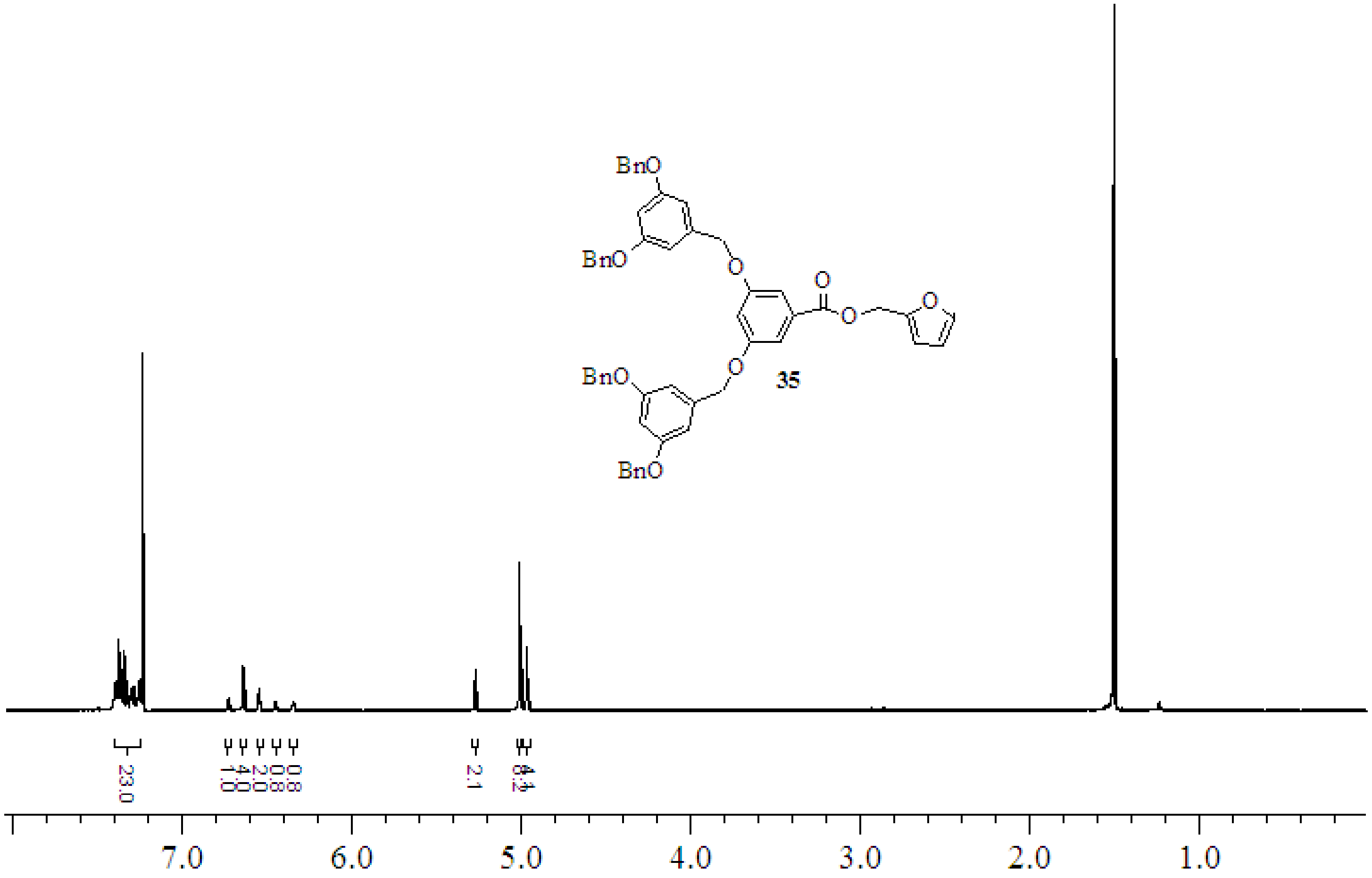


Figure A.3. ^{1}H NMR spectrum of 2nd generation furan functionalized dendron **35**

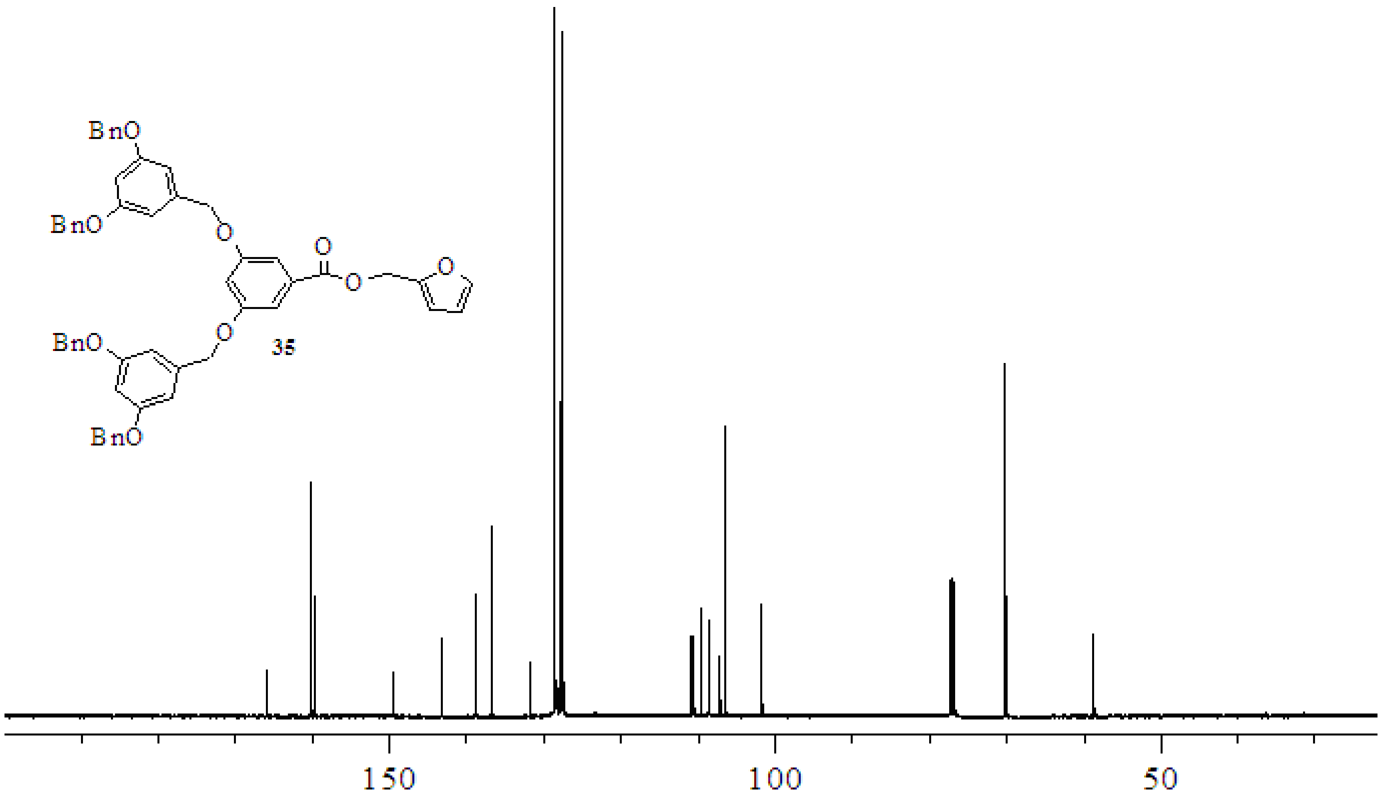


Figure A.4. ^{13}C NMR spectrum of 2nd generation furan functionalized dendron **35**

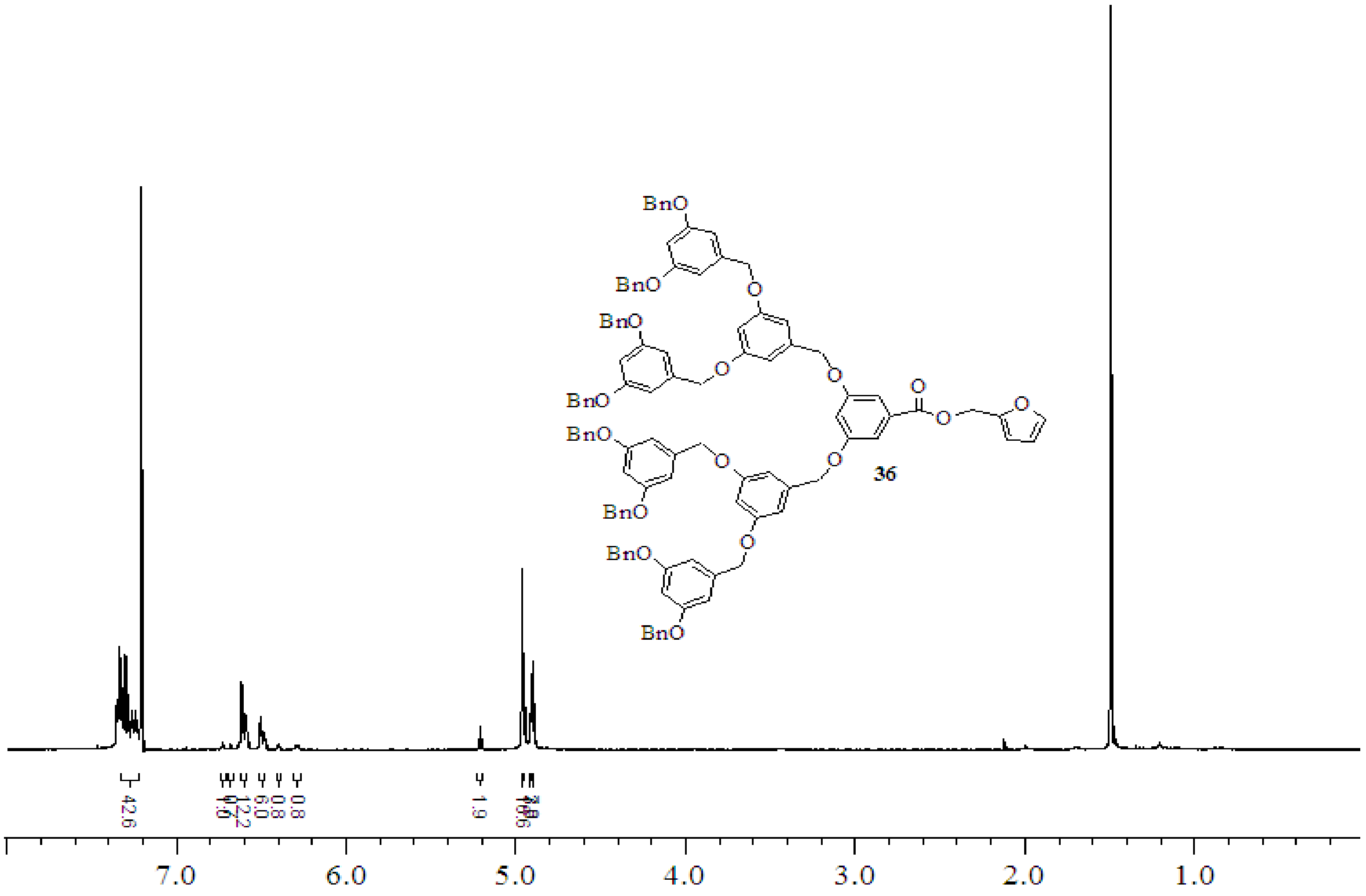


Figure A.5. ^{1}H NMR spectrum of 3rd generation furan functionalized dendron **36**

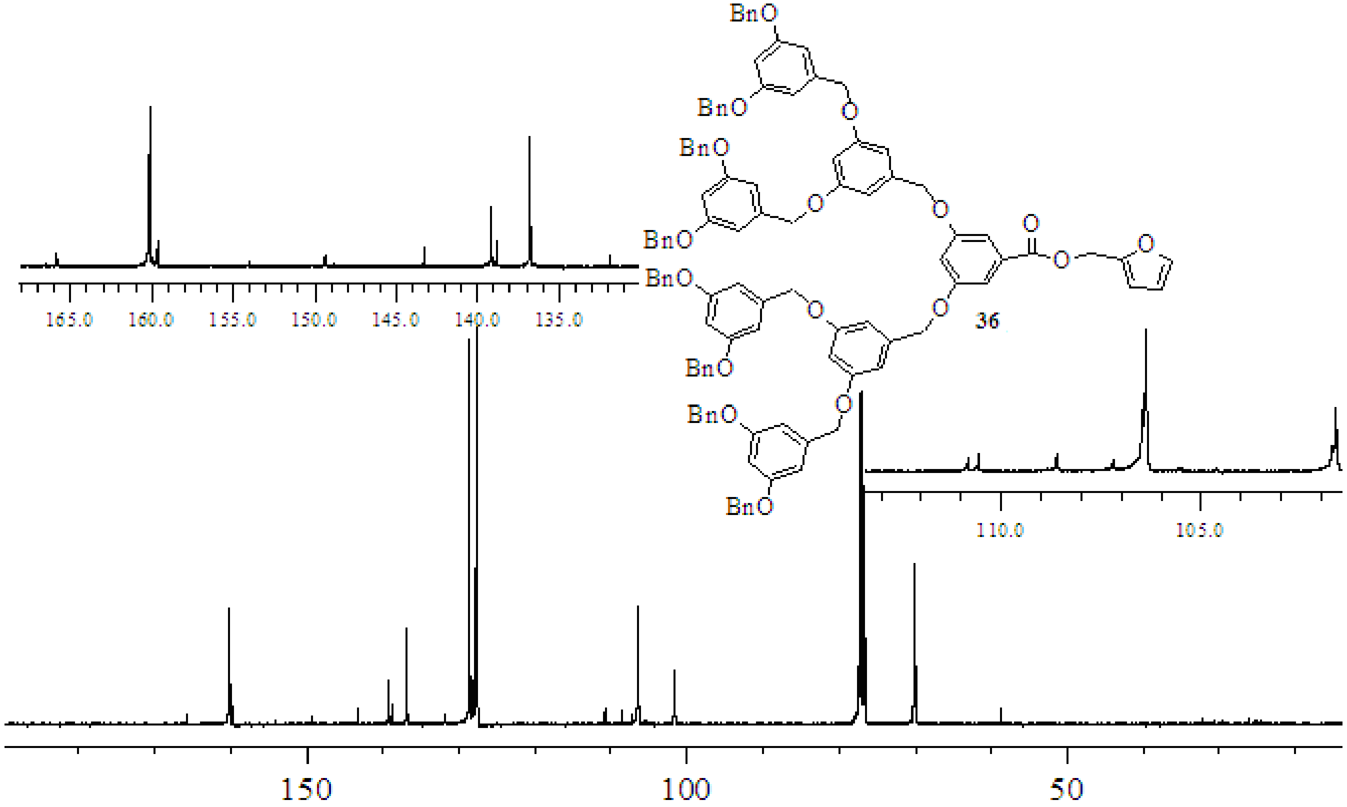


Figure A.6. ^{13}C NMR spectrum of 3rd generation furan functionalized dendron **36**

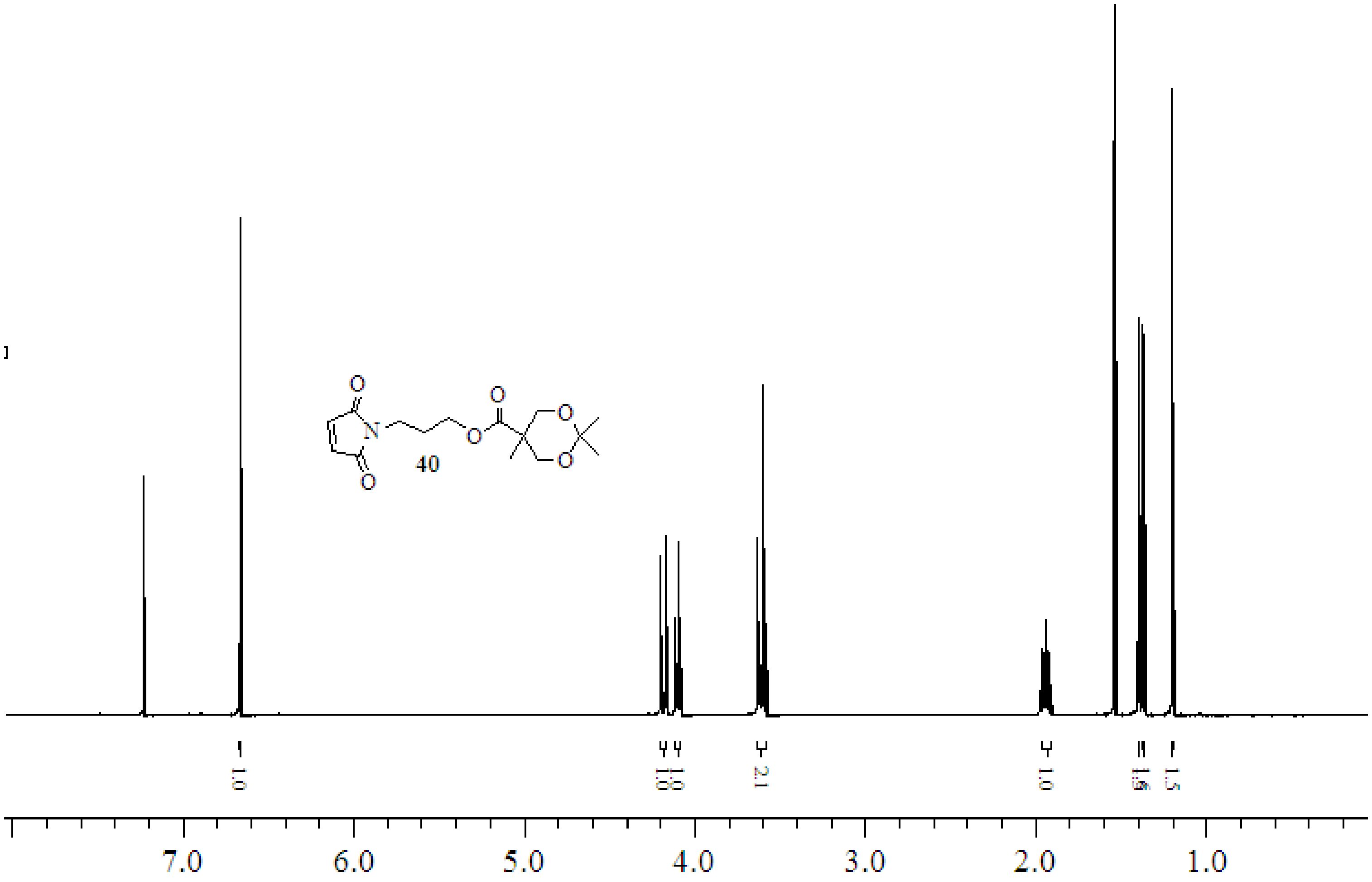


Figure A.7. ^{1}H NMR spectrum of 1st generation maleimide functionalized dendron **40**

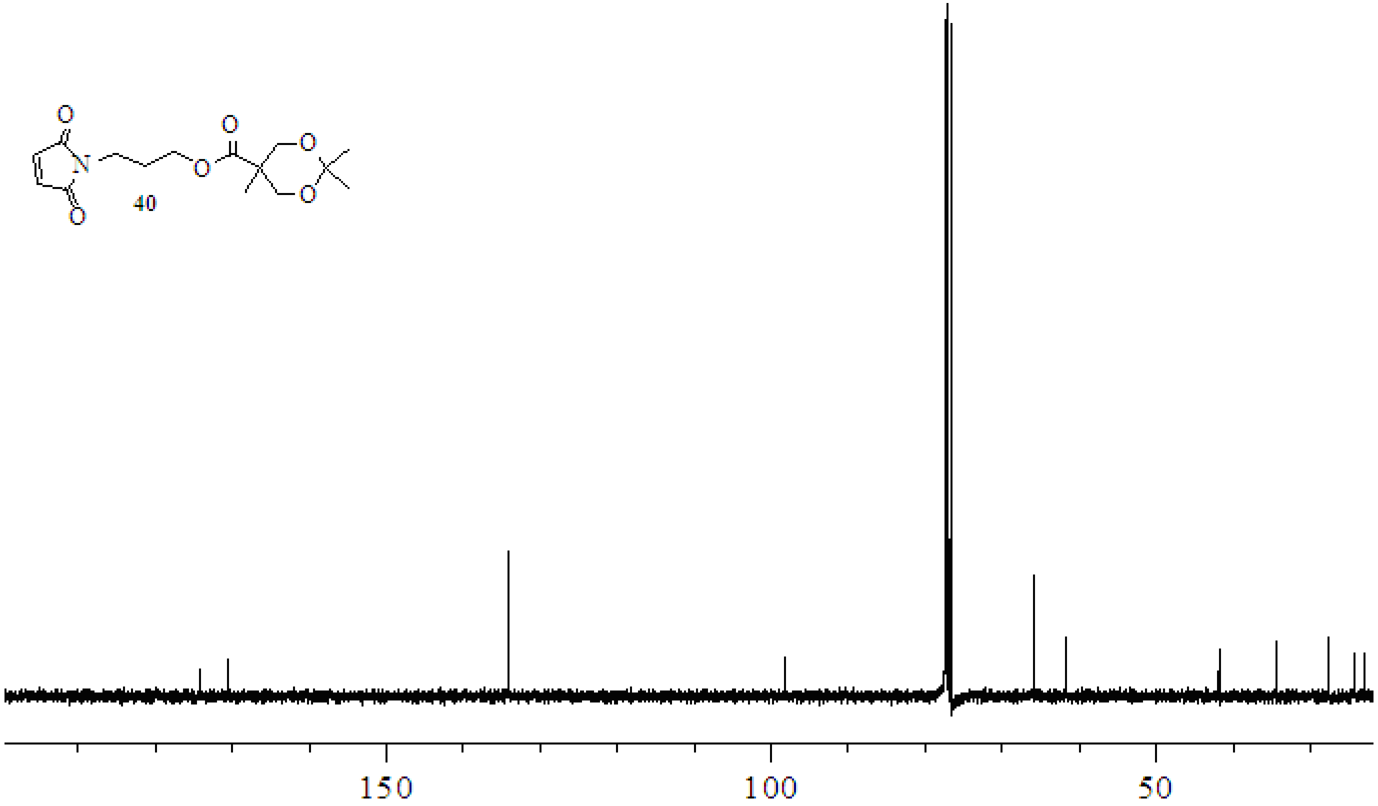


Figure A.8. ^{13}C NMR spectrum of 1st generation maleimide functionalized dendron **40**

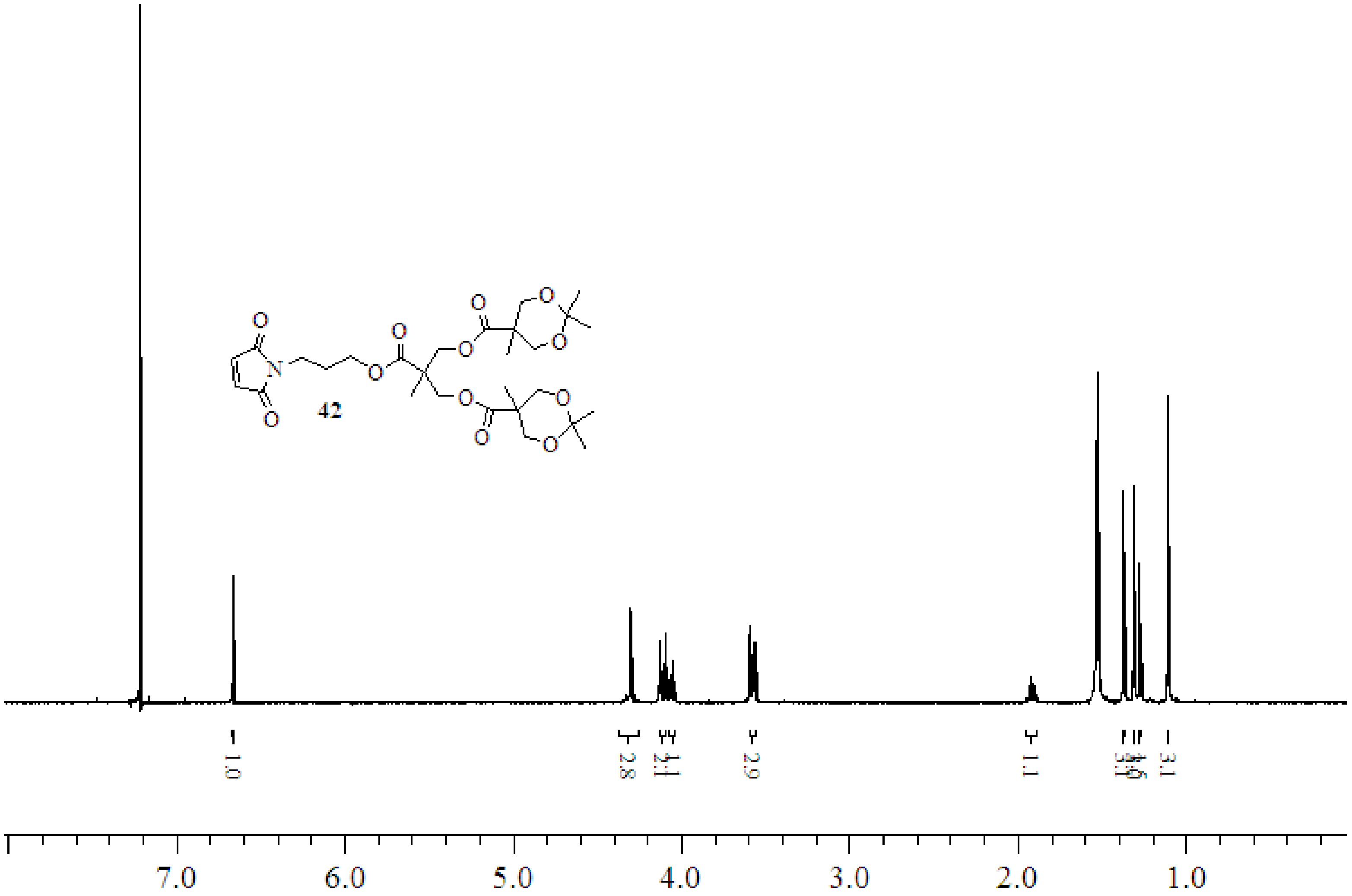


Figure A.9. ^{1}H NMR spectrum of 2nd generation maleimide functionalized dendron **42**

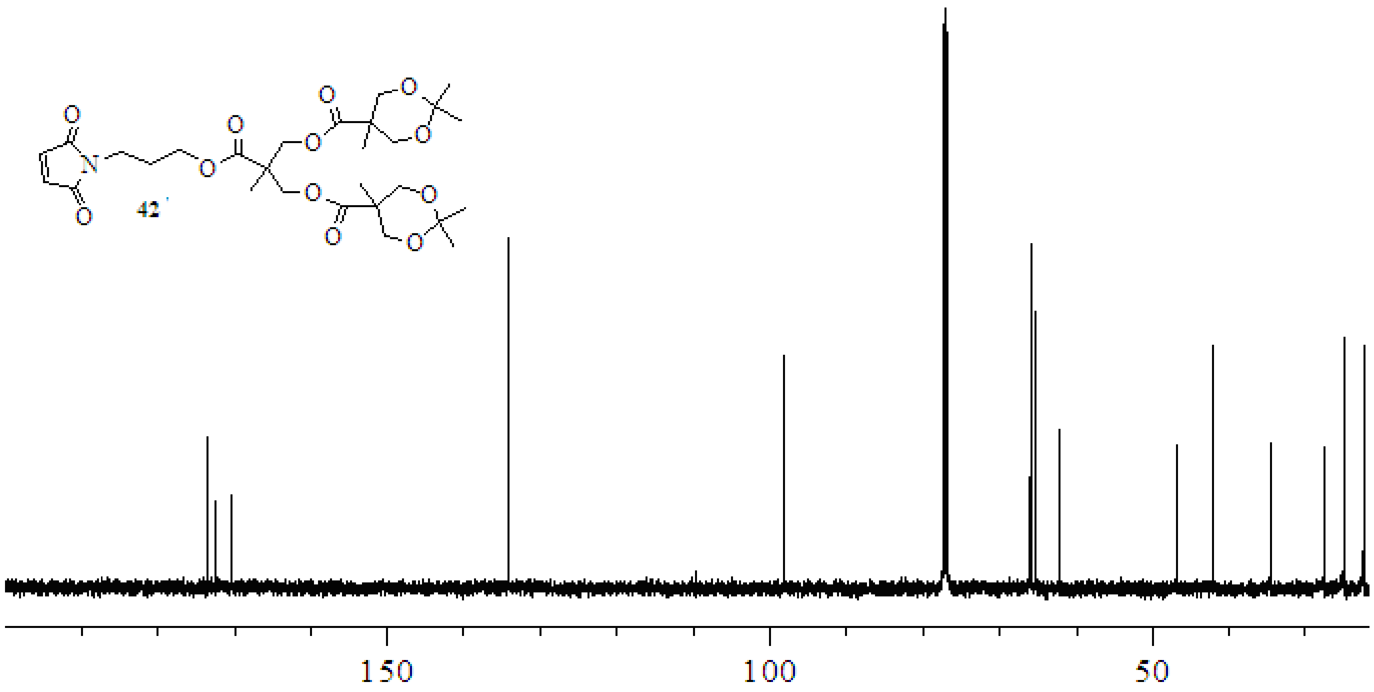


Figure A.10. ^{13}C NMR spectrum of 2nd generation maleimide functionalized dendron **42**

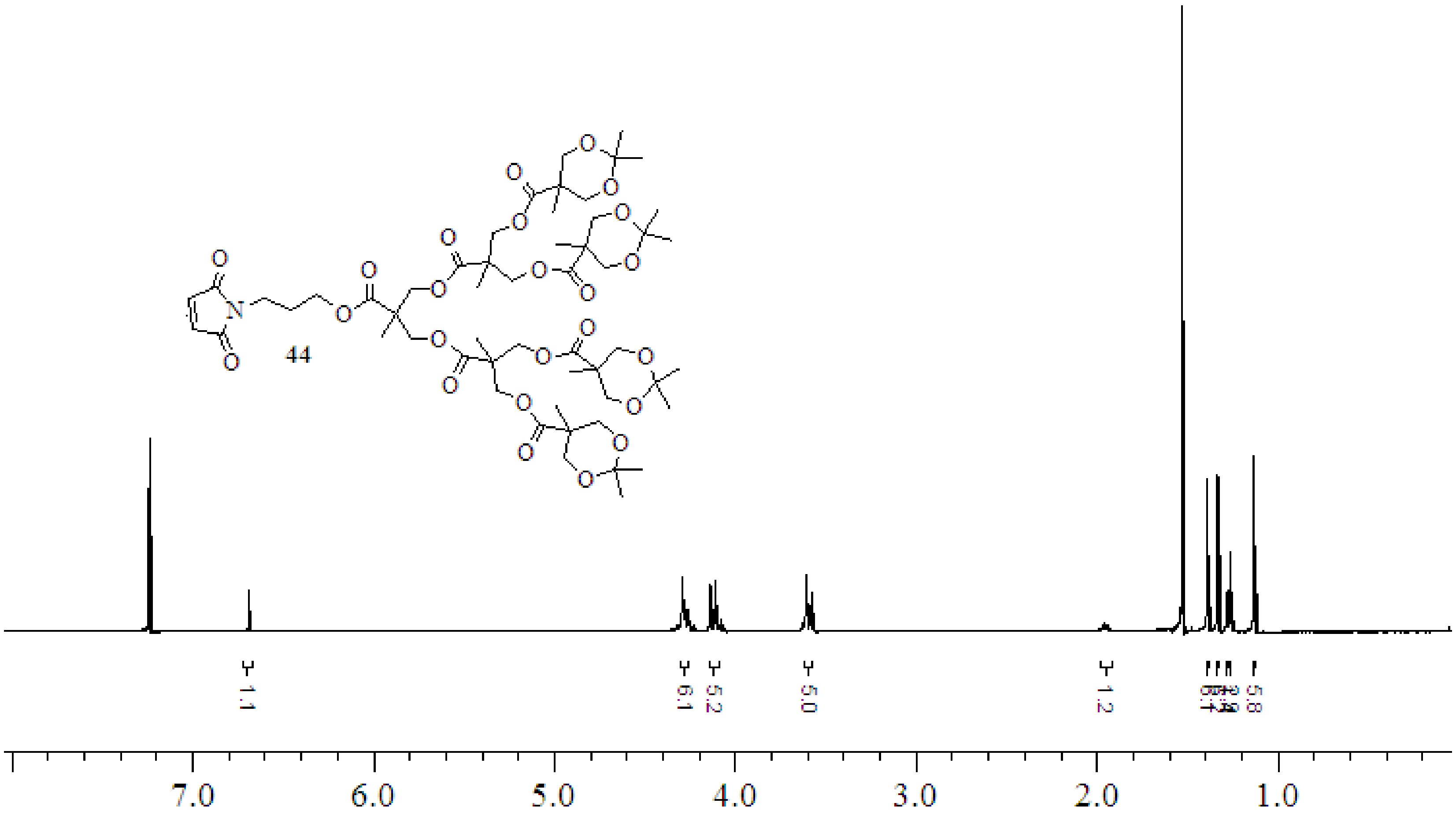


Figure A.11. ^{1}H NMR spectrum of 3rd generation maleimide functionalized dendron **44**

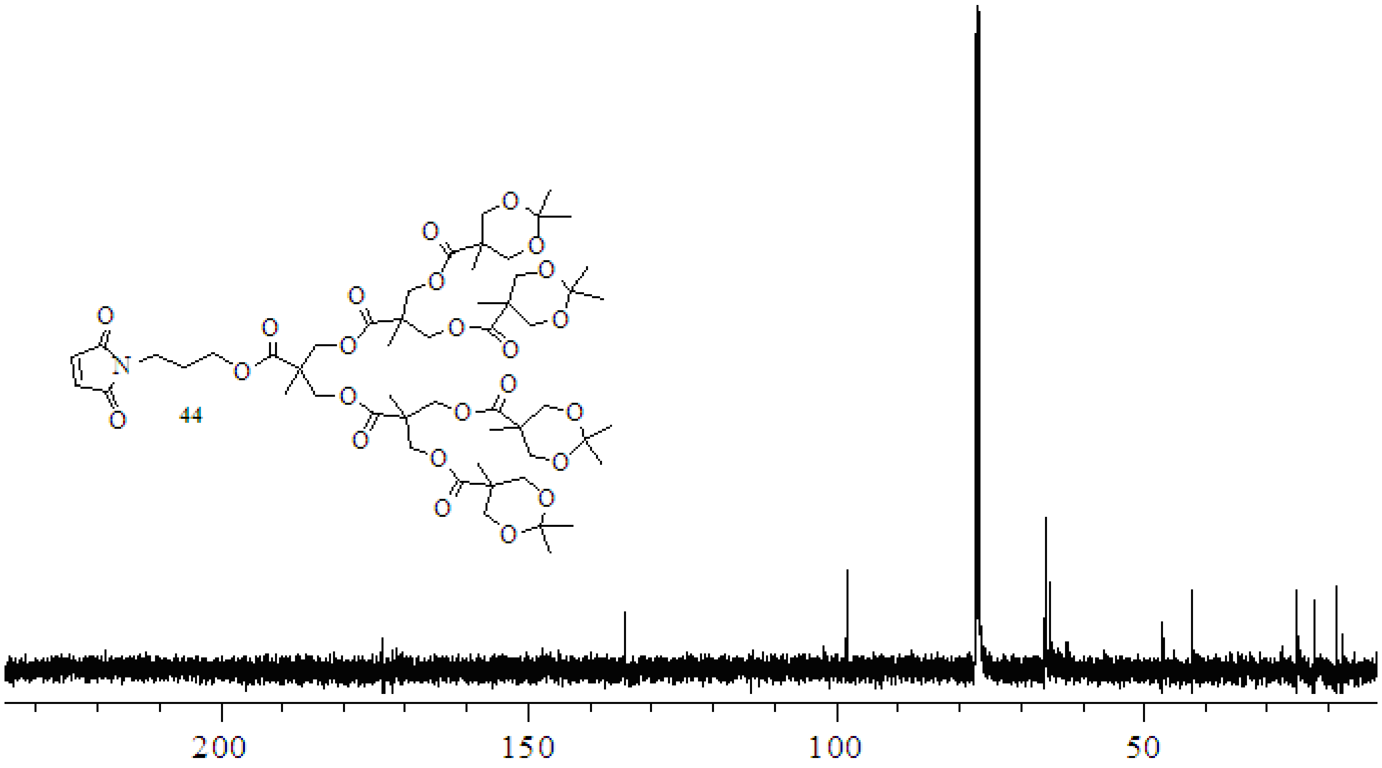


Figure A.12. ^{13}C NMR spectrum of 3rd generation maleimide functionalized dendron **44**

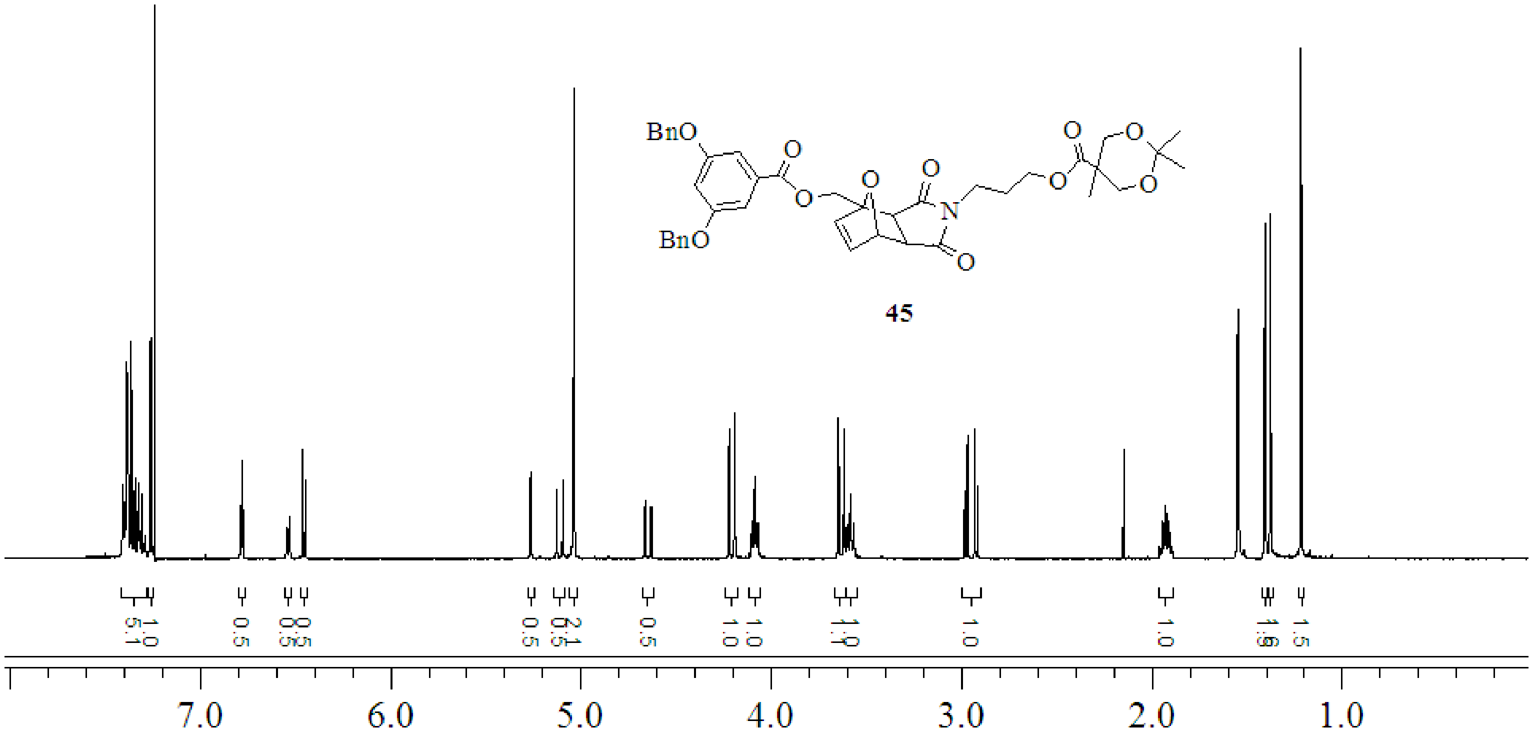


Figure A.13. ^{1}H NMR spectrum of 1st generation dendrimer **45**

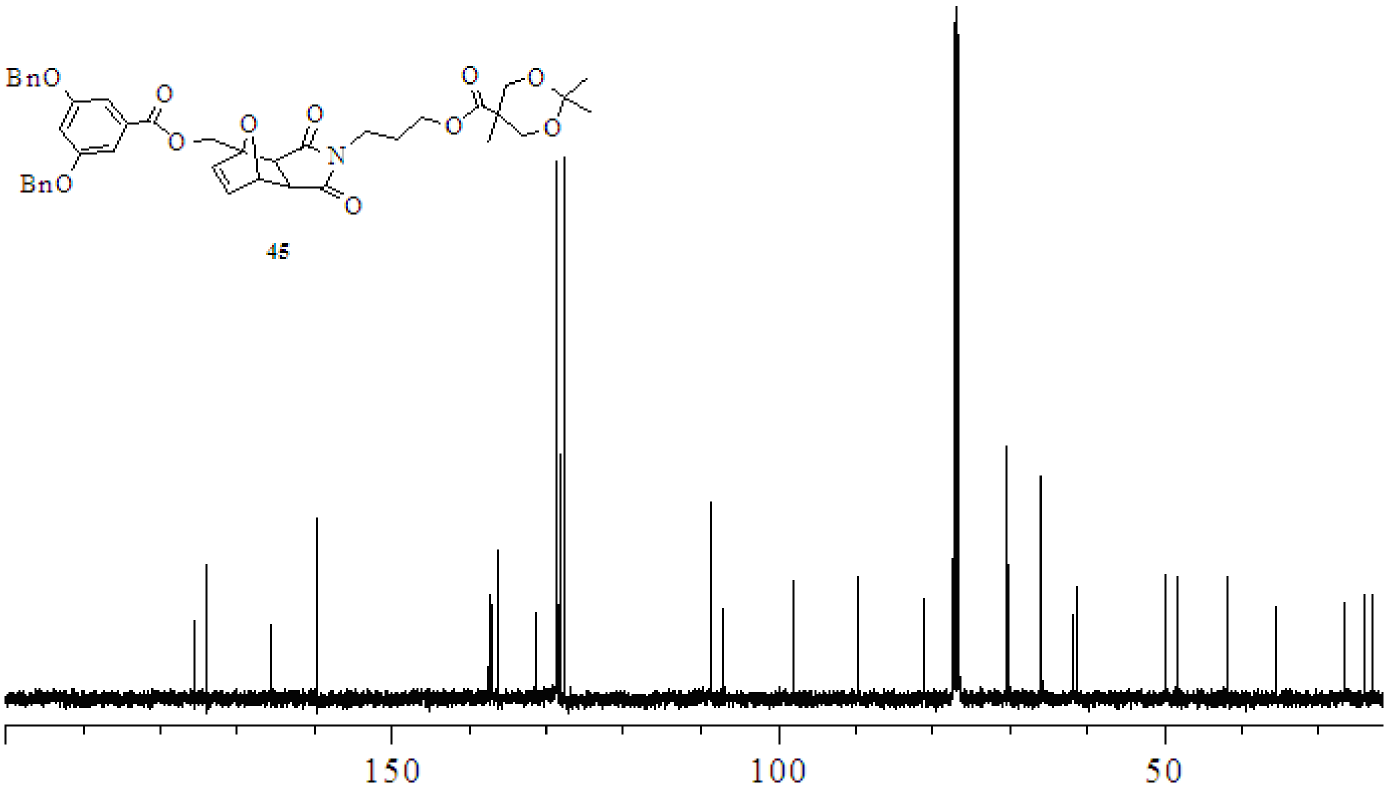


Figure A.14. ^{13}C NMR spectrum of 1st generation dendrimer **45**

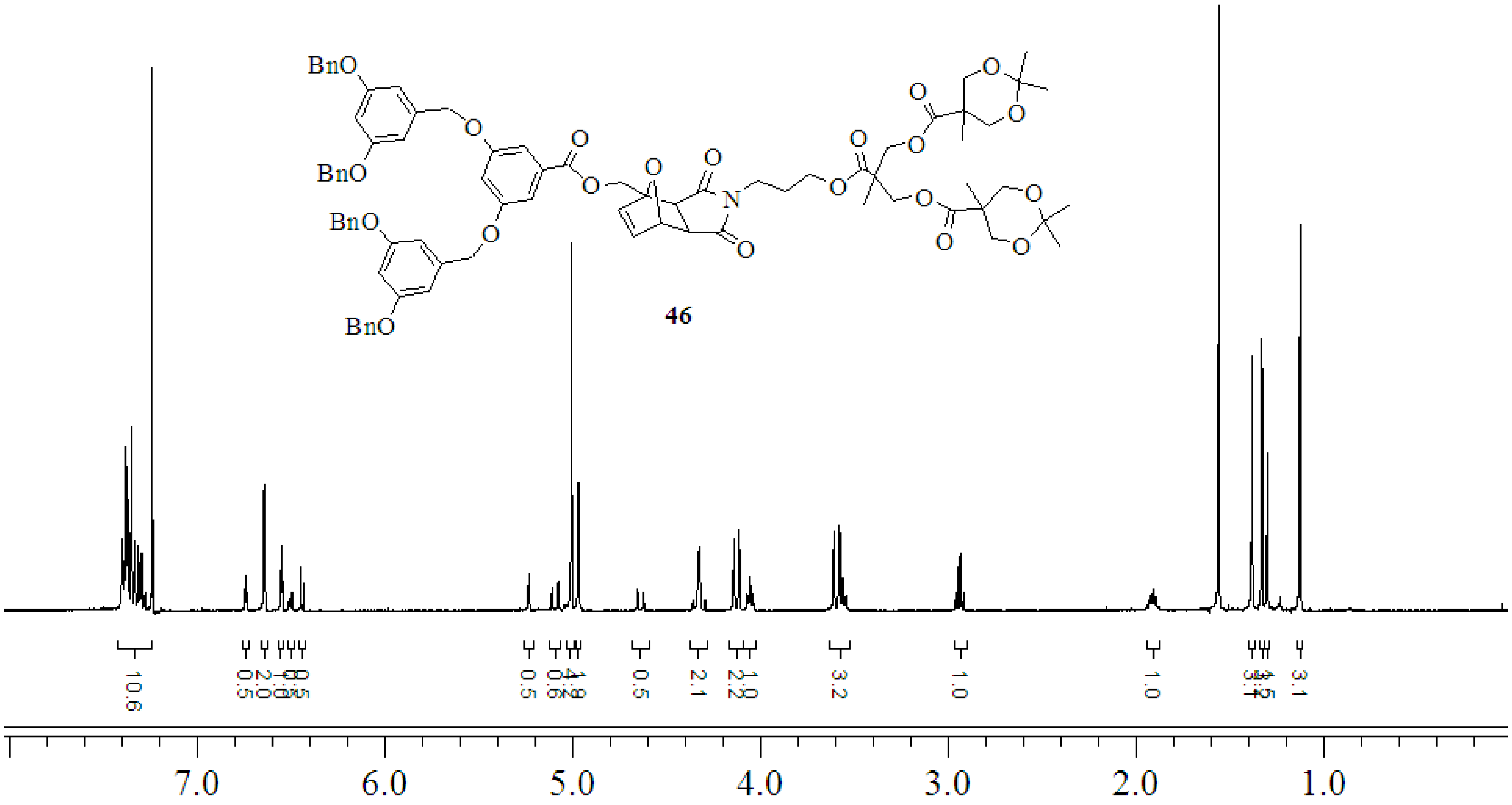


Figure A.15. ^{1}H NMR spectrum of 2nd generation dendrimer **46**

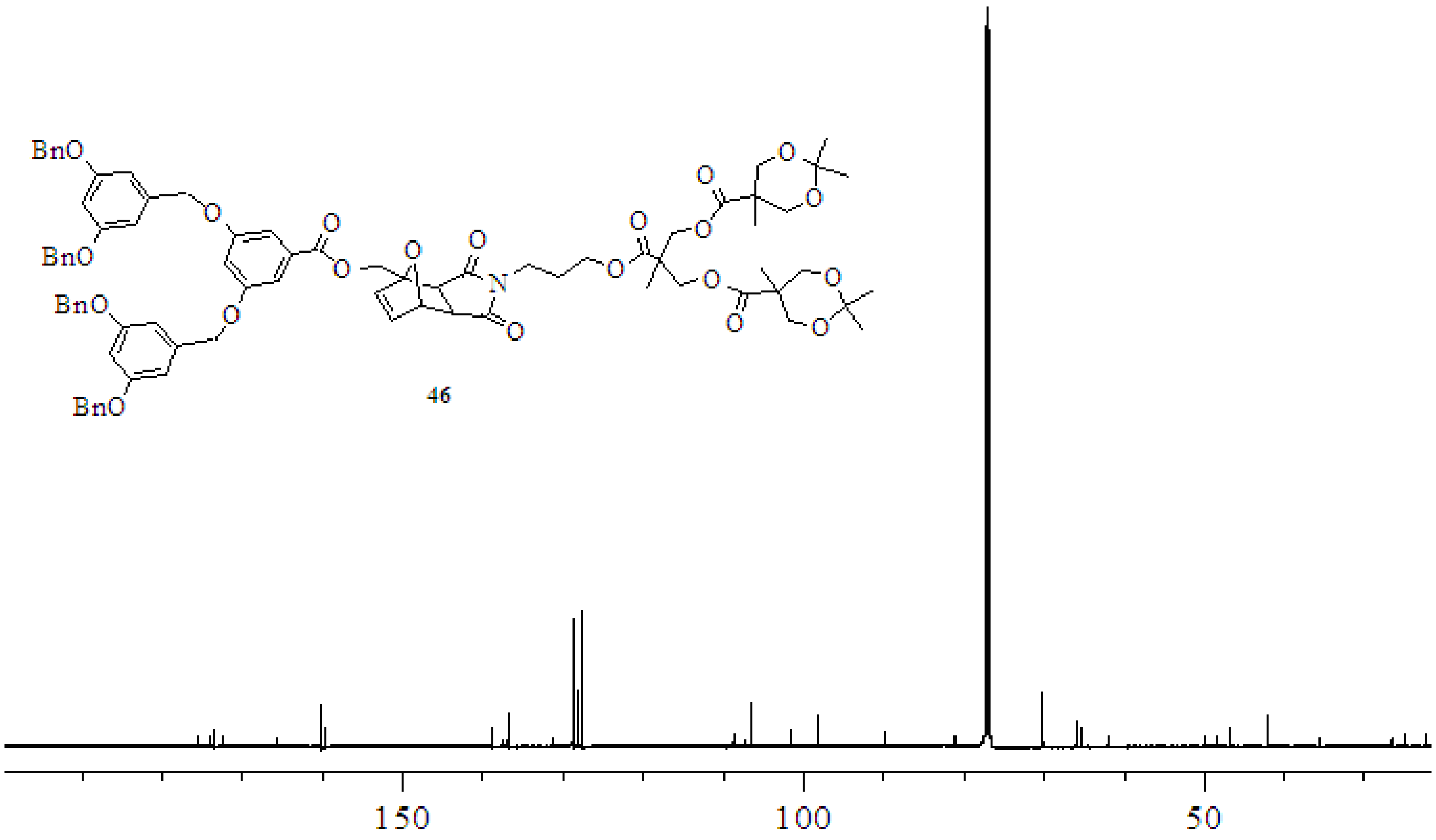


Figure A.16. ^{13}C NMR spectrum of 2nd generation dendrimer **46**

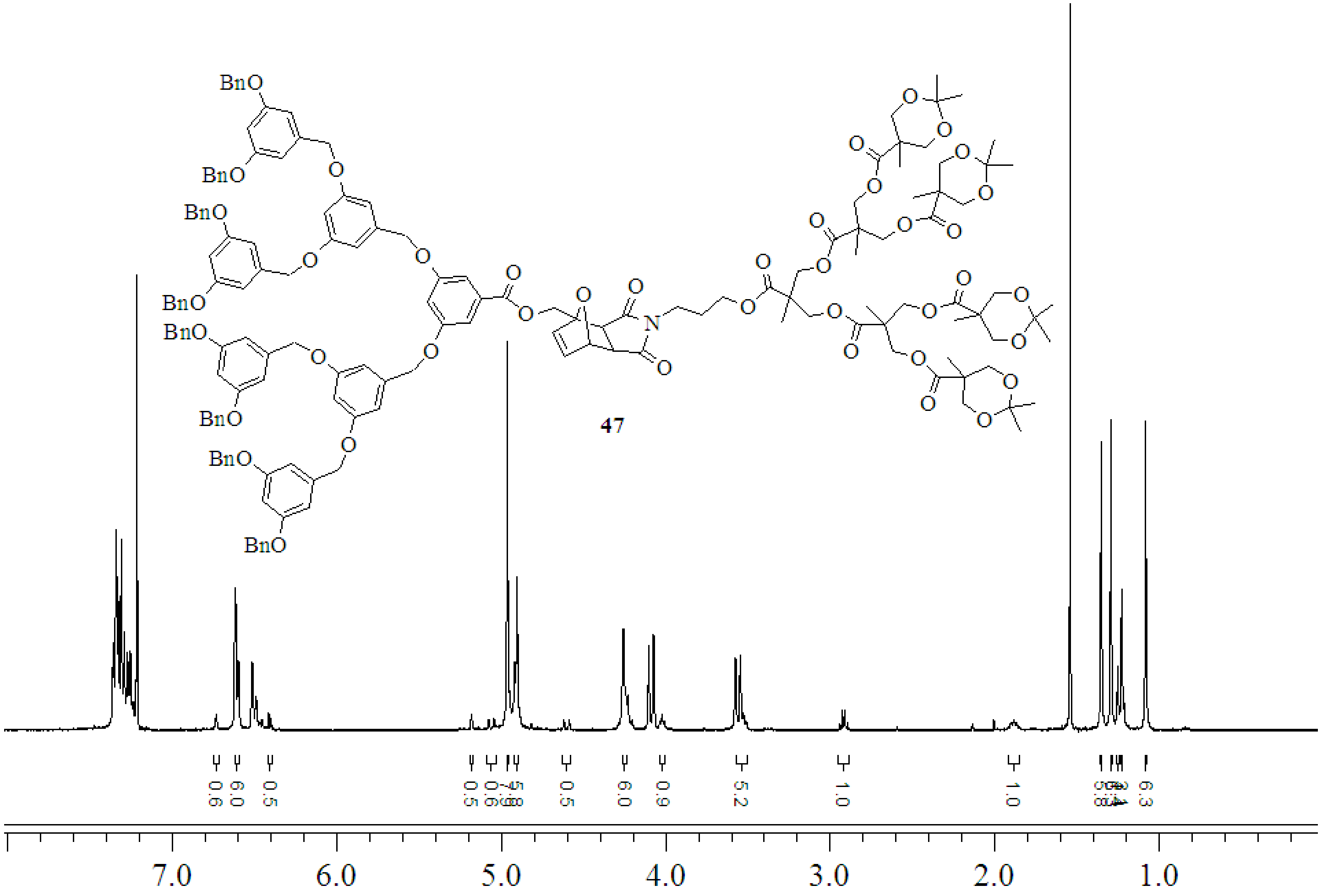


Figure A.17. ^{1}H NMR spectrum of 3rd generation dendrimer **47**

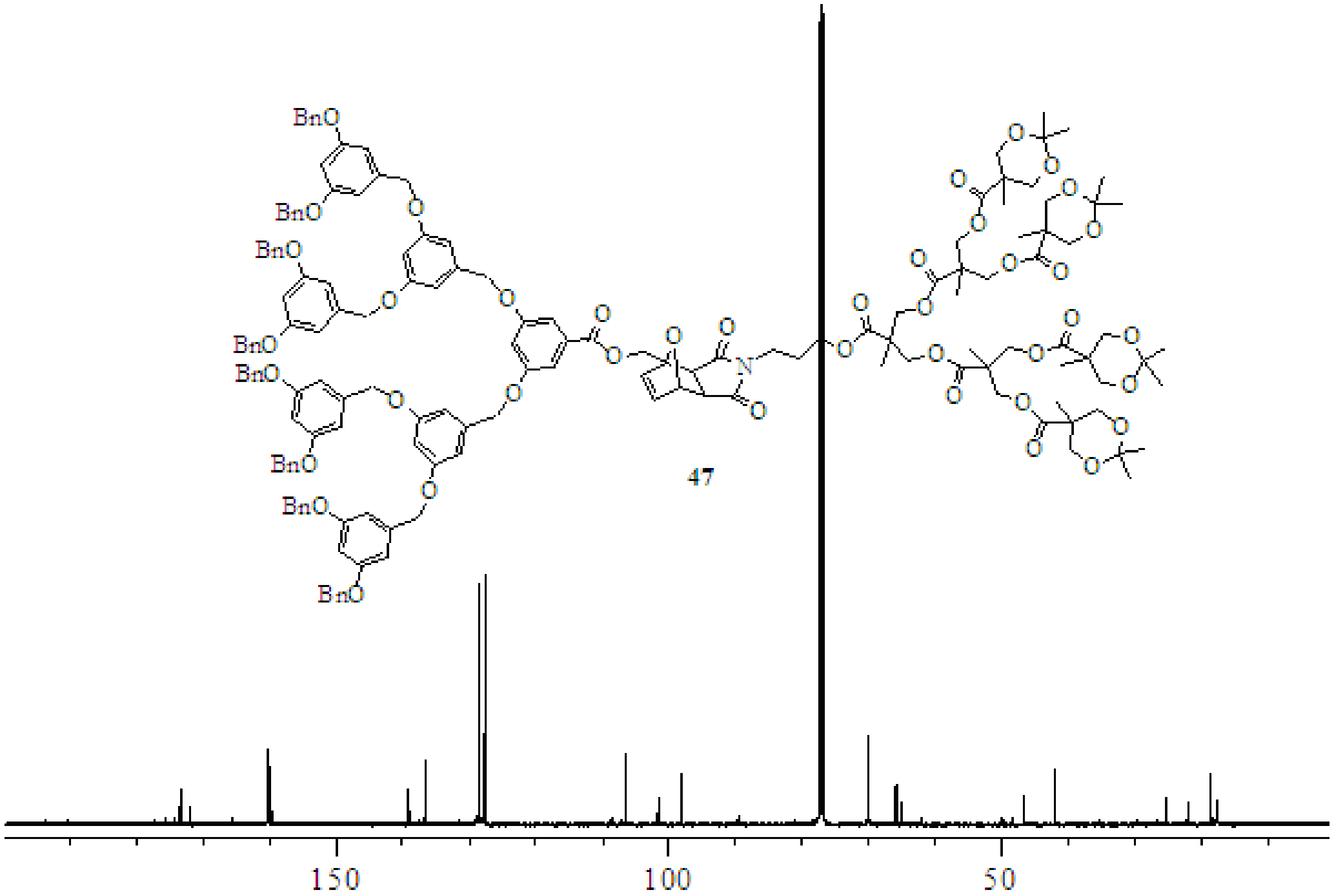


Figure A.18. ^{13}C NMR spectrum of 3rd generation dendrimer **47**

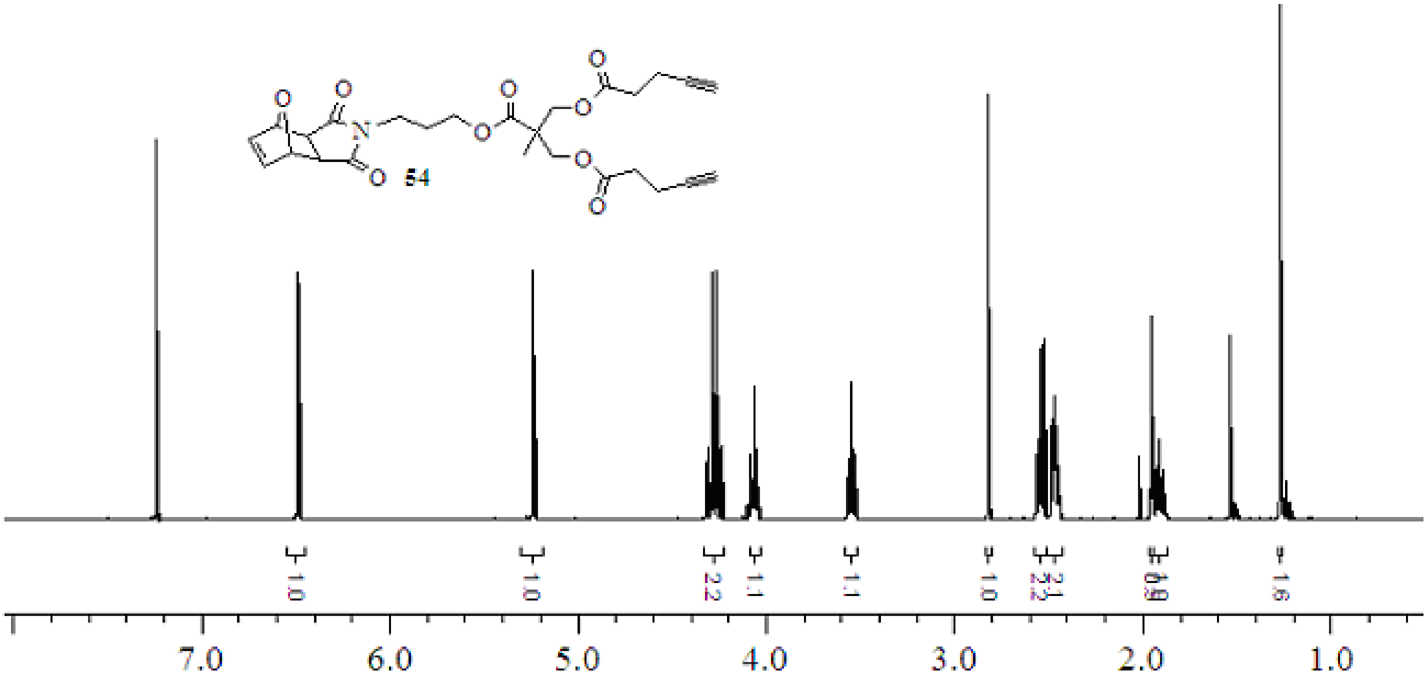


Figure A.19. ^{1}H NMR spectrum of dendron **54**

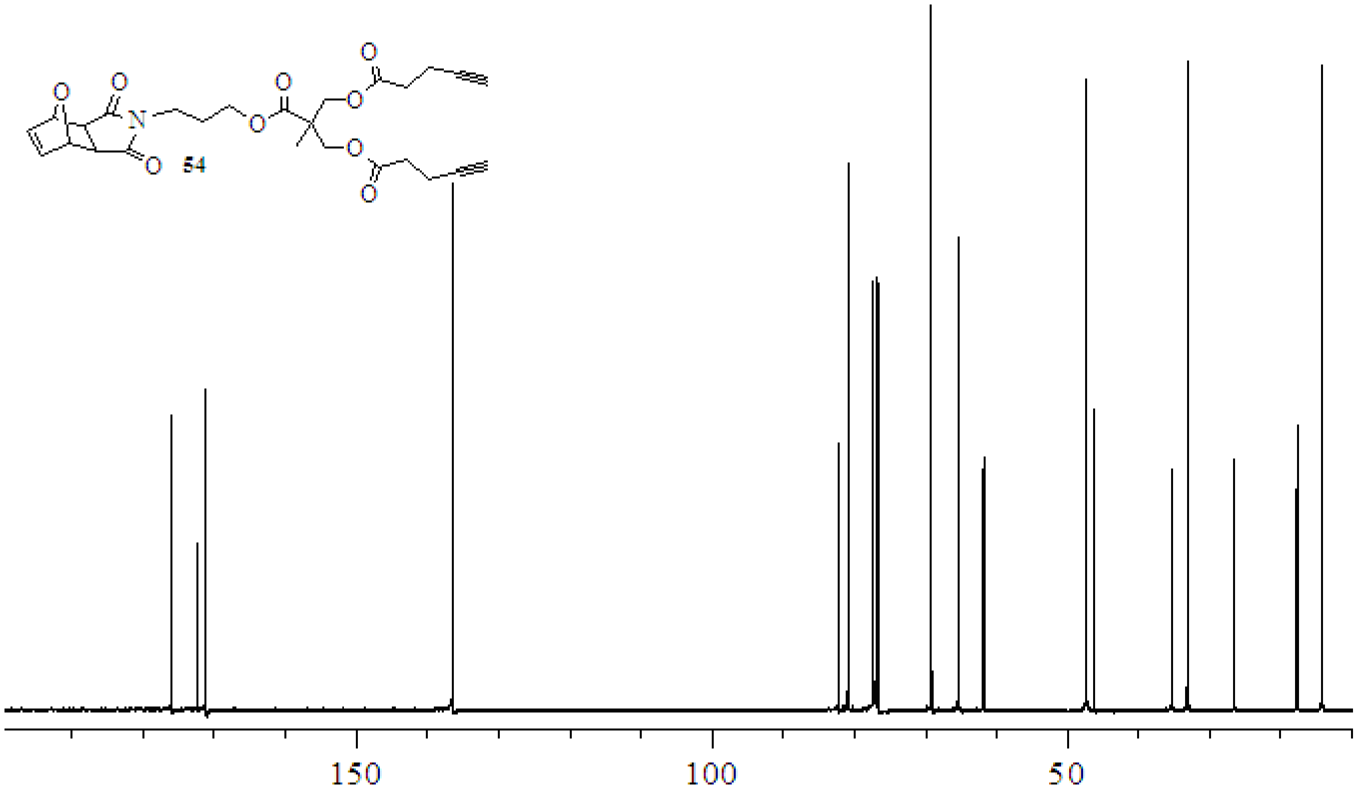


Figure A.20. ^{13}C NMR spectrum of dendron **54**

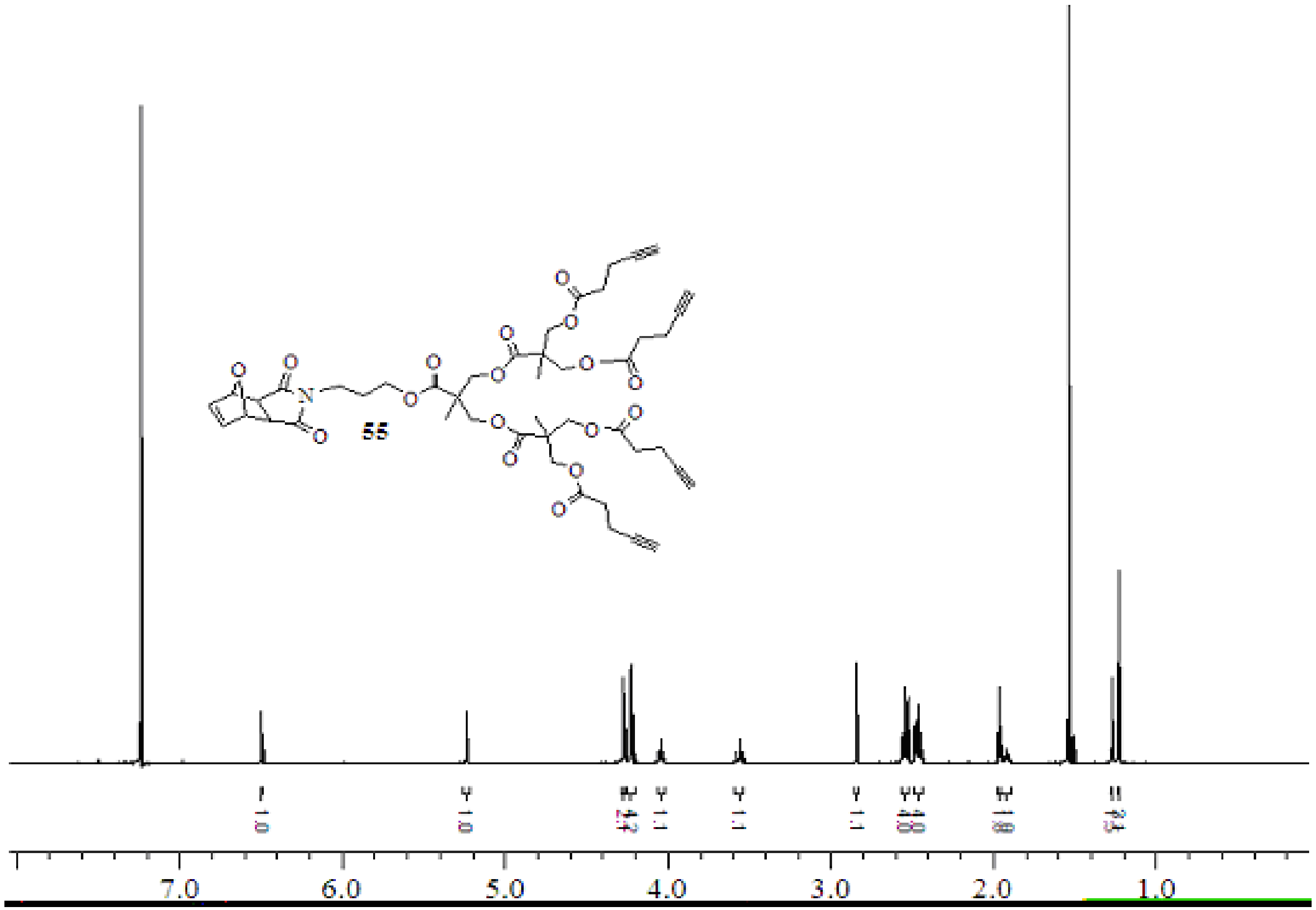


Figure A.21. ^{1}H NMR spectrum of dendron **55**

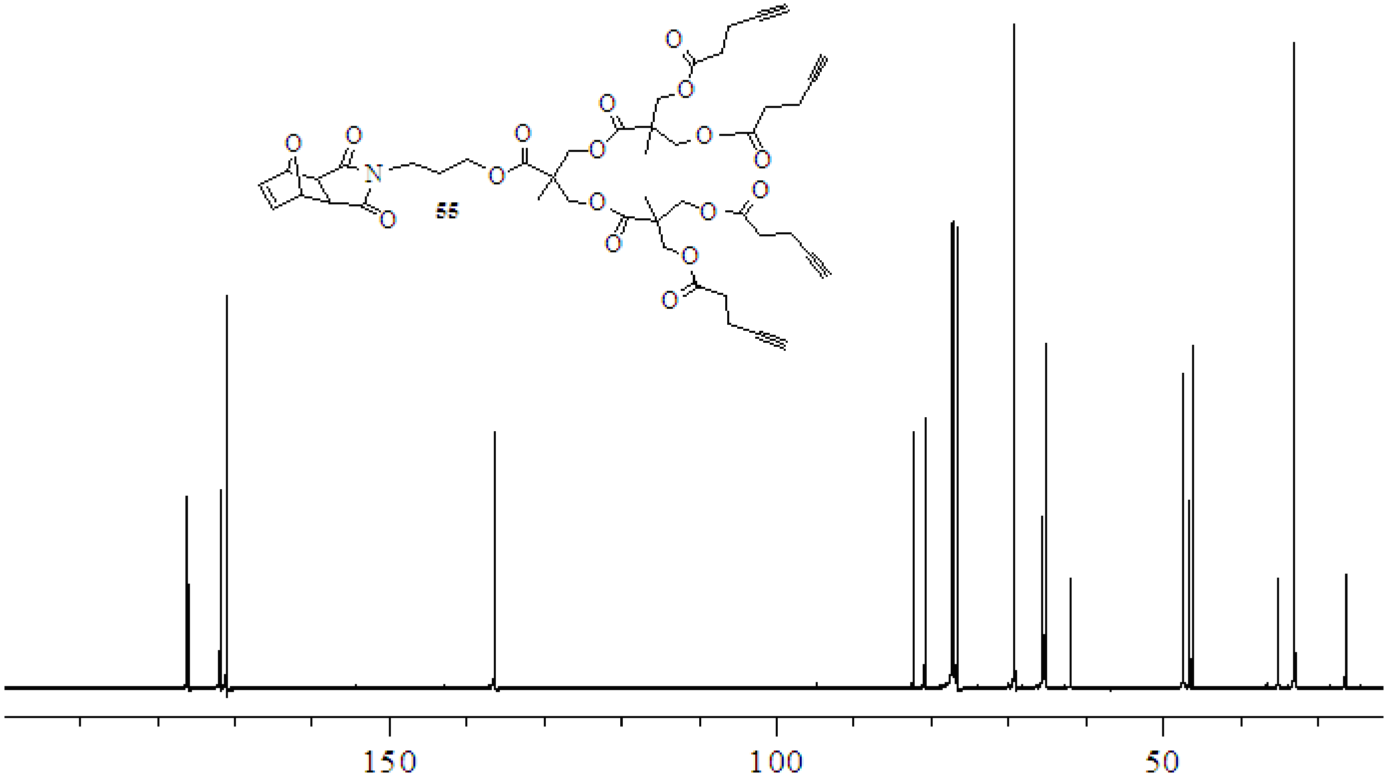


Figure A.22. ^{13}C NMR spectrum of dendron **55**

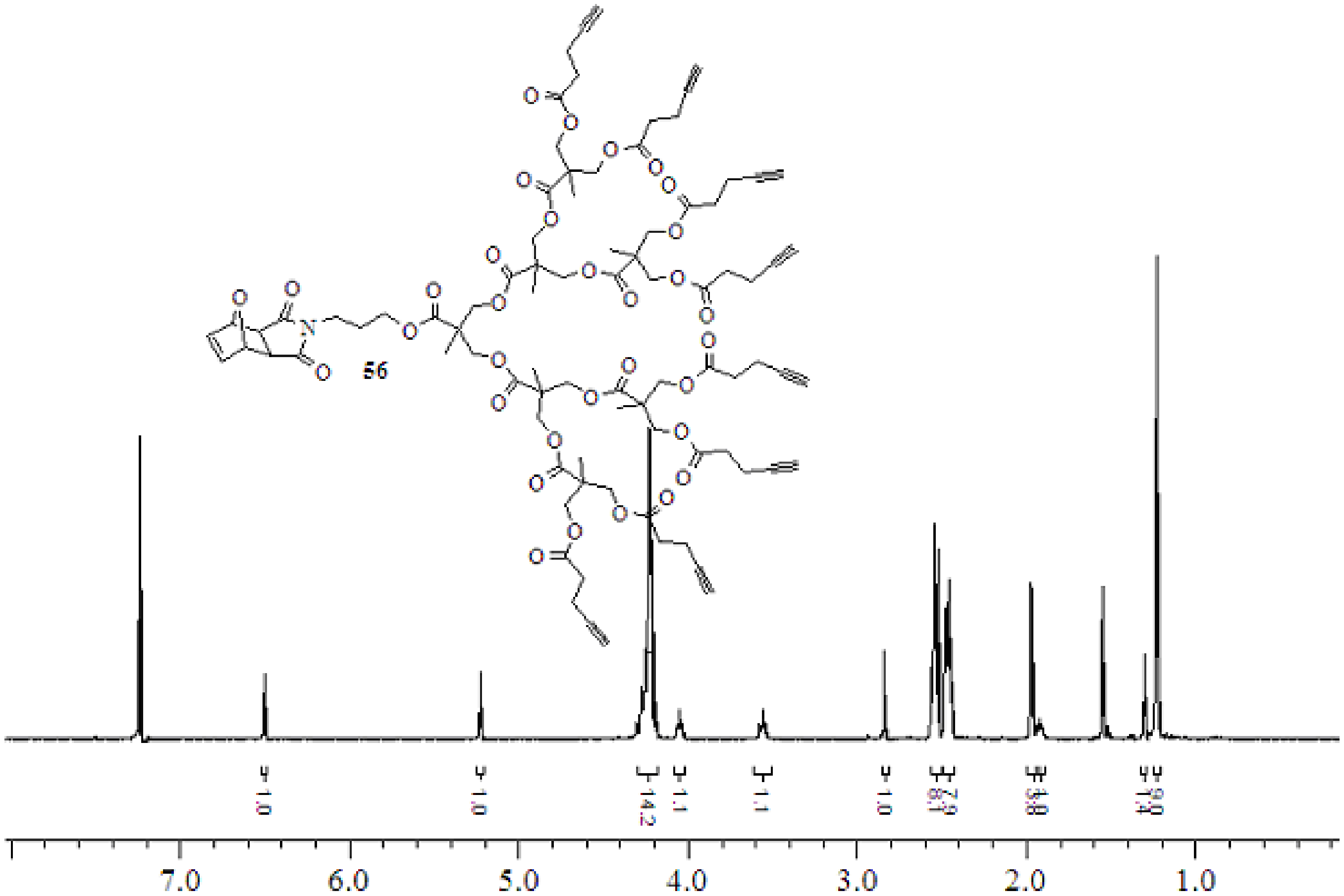


Figure A.23. ^{1}H NMR spectrum of dendron **56**

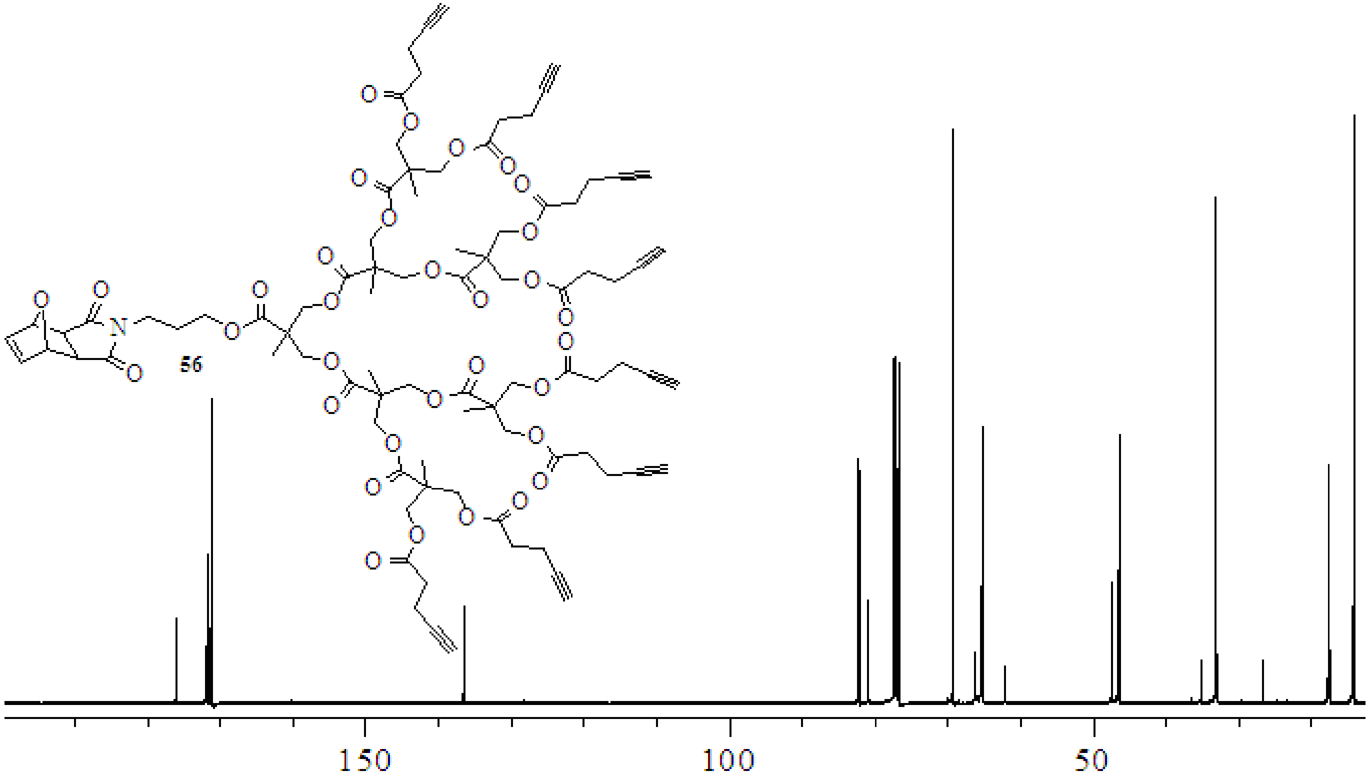


Figure A.24. ^{13}C NMR spectrum of dendron **56**

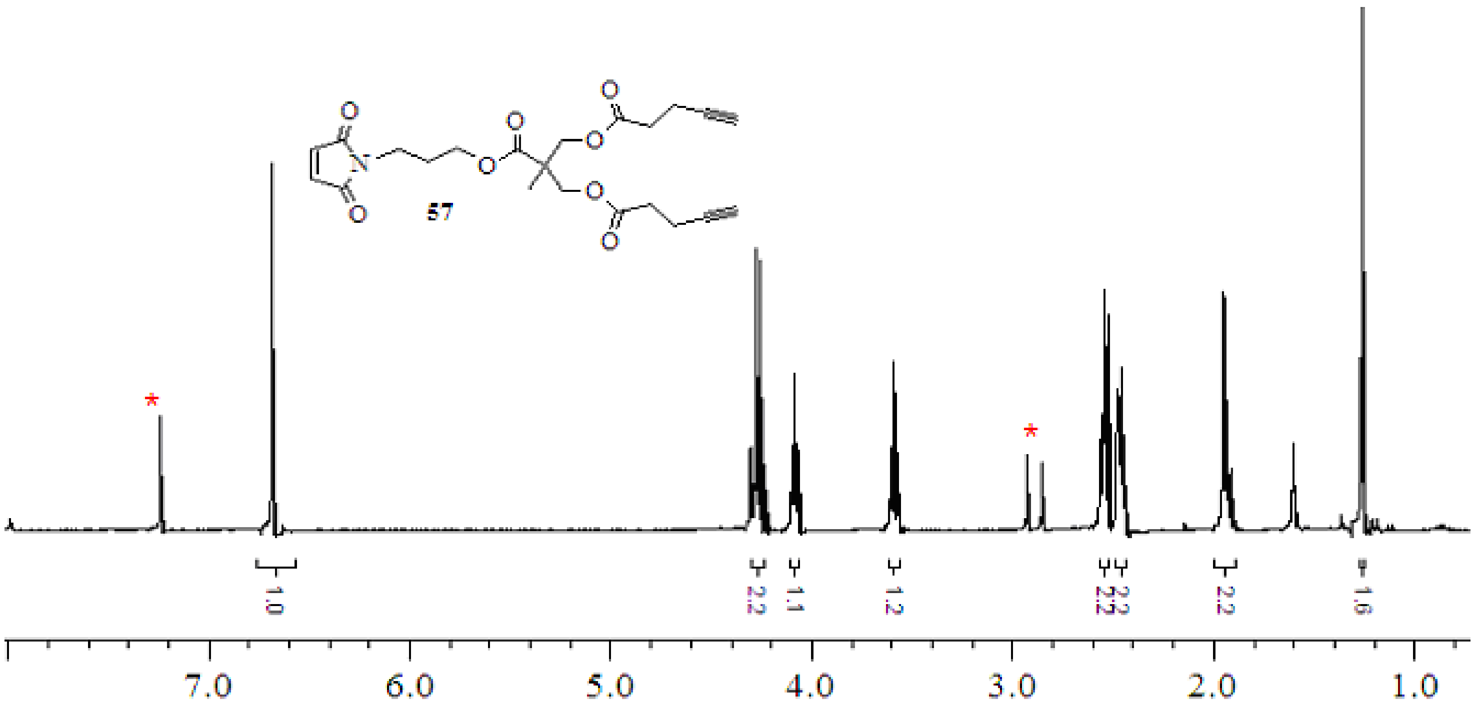


Figure A.25. ^{1}H NMR spectrum of dendron **57**

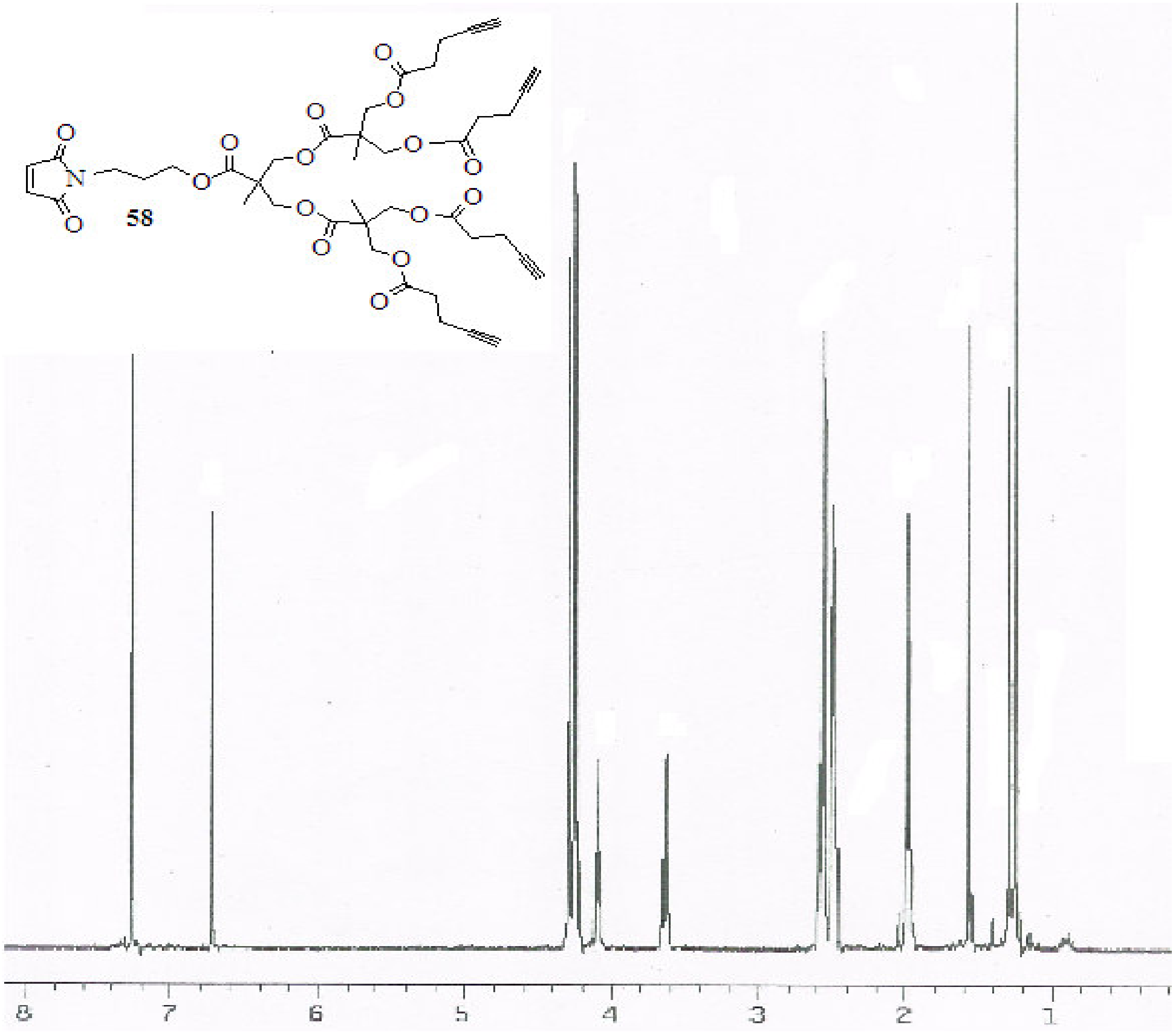


Figure A.26. ^{1}H NMR spectrum of dendron **58**

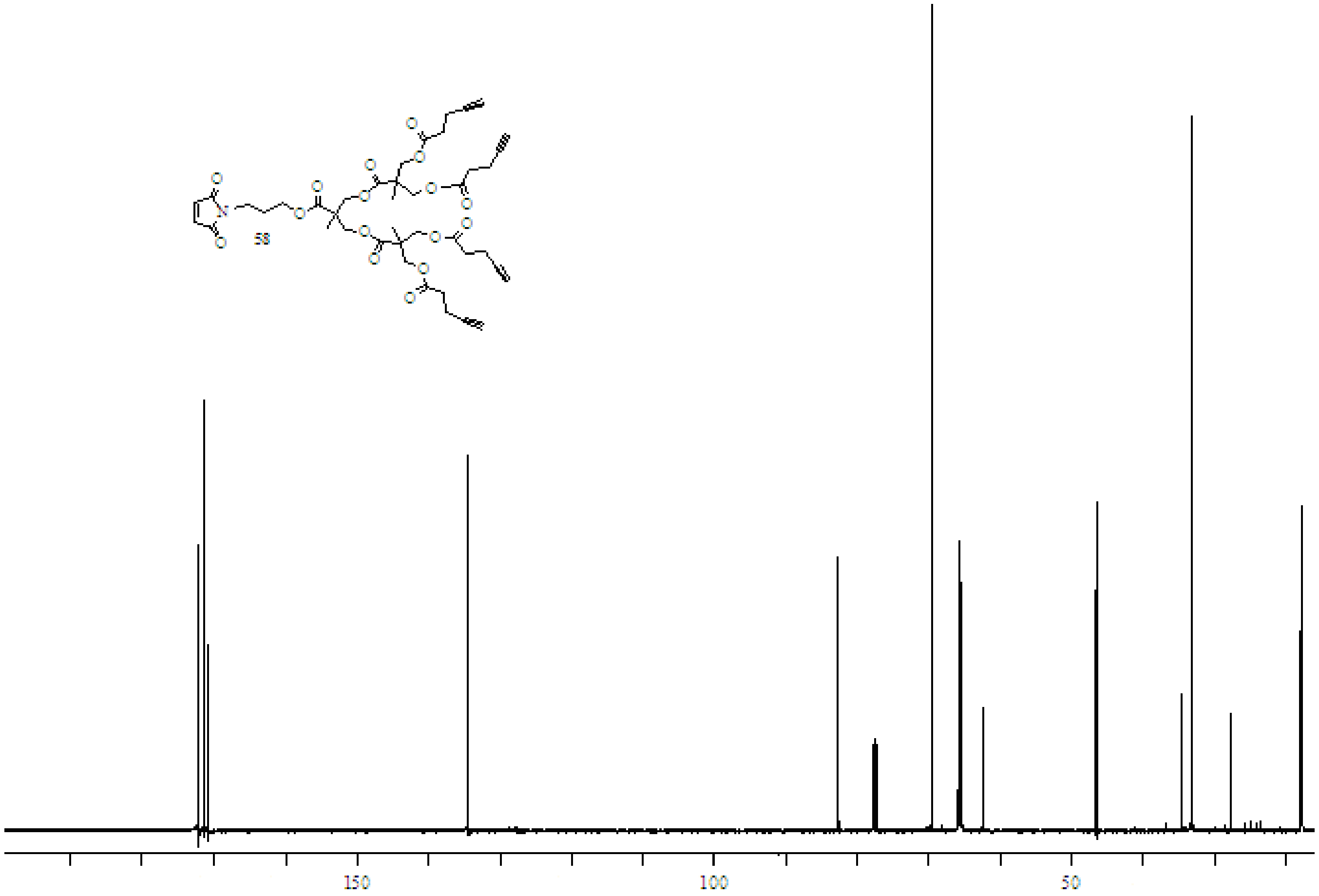


Figure A.27. ^{13}C NMR spectrum of dendron **58**

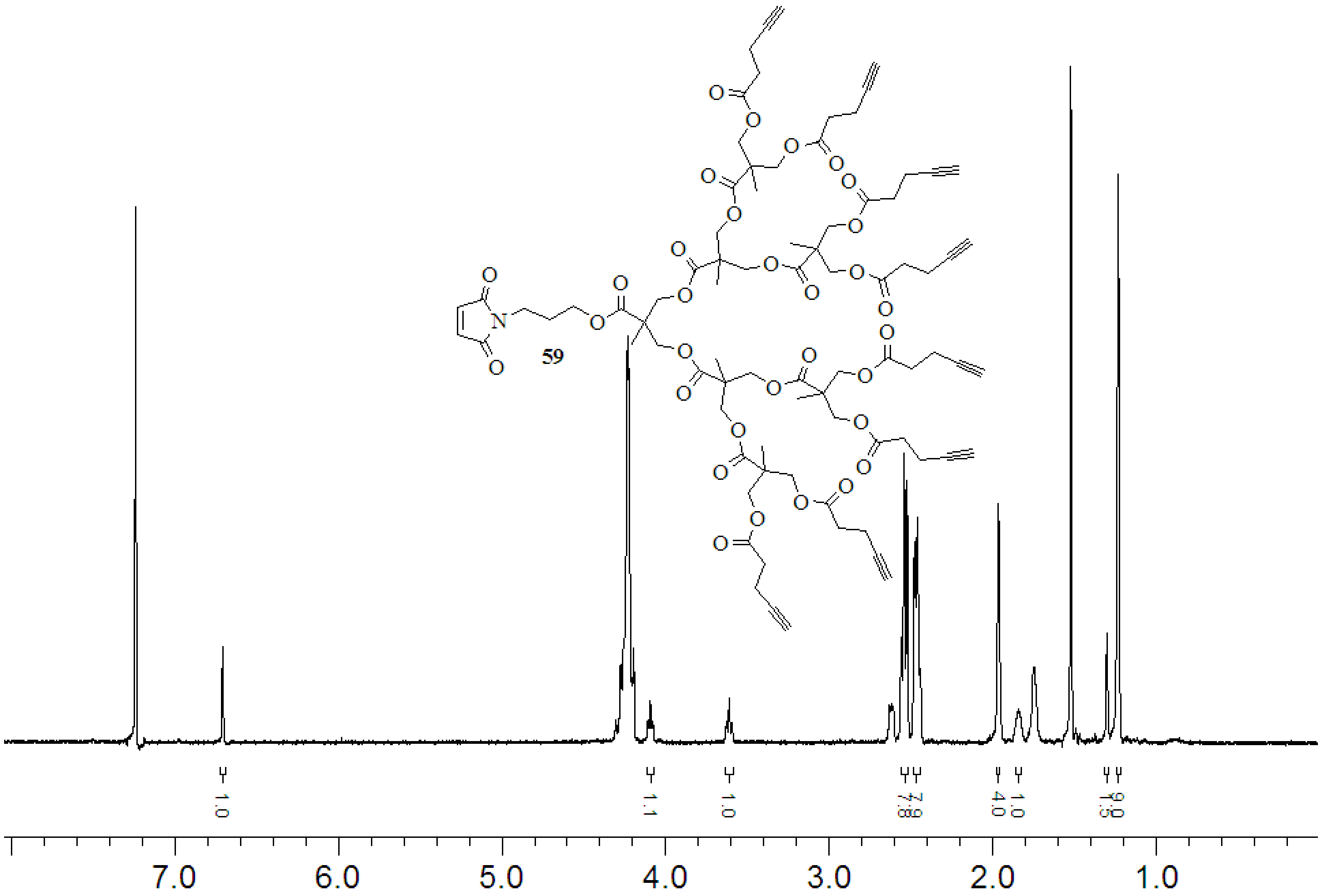


Figure A.28. ^{1}H NMR spectrum of dendron **59**

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