Synthesis of Polyester Dendrimers

by

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Submitted for the Degree of

Doctor of Philosophy

Department of Chemistry

University of Warwick

September 1998

Dedicated to John and Mark

Contents

Acknowledgements

I would initially like to thank my supervisors Dr Paul Taylor, Prof. Dave Haddleton and Dr Steve Yeates for all their help, advice and encouragement during the last three years. Thanks also go to the University of Warwick and Zeneca Resins for their contributions to my funding.

Thanks are also due to Dr Adam Clarke for advice concerning NMR spectra, Ms Sue Cannan and Mr Paul Moore for the elemental analyses, Mr Inder Katyal for mass spectra and Dr Thomas Straw for help with the work concerning the iminium salts.

I would also like to thank all my friends and colleagues. This includes everyone from labs C420 and C421 past and present especially Steve, Nick, Pete, Joanne, Karen, Stuart, Tom, Hardeep and Ismail. Thanks for all listening to the aeroplane story and for keeping me in the insane state of mind that I have become accustomed to. Thanks go to the gang from Nuneaton who proved that you don't have to be a Chemist to be a nutter - though it does help. I am deeply indebted to my parents and Shelagh. My final thanks go to two very special people. Firstly to Mark, thanks for all the brilliant times, it is hard to imagine that someone can be missed so very much by so many people. Last but certainly not least, I would like to thank John for all his love, support and patience. It all goes back to that camping trip, who would have thought that romance could be found in Cromer.

Declaration

The work described in this thesis is the original work of the author, except where acknowledgement has been made to results and ideas previously published. The work was carried out at the Department of Chemistry, University of Warwick, between October 1st 1994 and September 30th 1997 and has not been previously submitted for a degree at any institution.

Abstract

Dendrimers are a fairly new class of macromolecule. They have many potential uses including use in surface coatings and as host molecules. There are two main methods available for constructing dendrimers, the convergent approach and the divergent approach. In this thesis dendrimers were synthesised using the divergent approach. In chapter one our original aim was to synthesise dendrimers based on bicine, but there were complications involved in synthesis and storage of the monomer. However, it was possible to make a iminium salt using bicine as the starting material, which was reacted with various nucleophiles. With 2,2-bishydroxymethylpropionic acid it was possible to produce a generation one protected dendrimer, but deprotection could not be achieved.

In the third chapter the syntheses of dendrimers based on 4,4-bis(4-hydroxyphenyl)valeric acid are described. Dendrimers were successfully synthesised up to and including generation two. These were made using various esterification methods.

Chapter four describes the synthesis of functionalised dendrimers. Generation one deprotected dendrimers were reacted with a variety of reagents to produce pent-4-enoyl, urethane and lineoyl functionalised dendrimers.

Chapter five describes the analysis of dendrimers using MALDI-MS. For every dendrimer synthesis molecular weights were obtained well within the

boundaries of experimental error. It was also shown how preparation time and laser power can affect the spectra obtained

Abbreviations

Ar	Aryl
Bn	Benzyl
bp	Boiling Point
br	Broad
CI	Chemical ionization
d	Doublet
dd	Doublet of doublets
DCC	N,N-Dicyclohexylcarbodiimide
DHB	2,5-Dihydroxybenzoic acid
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DPTS	4-(Dimethylamino)pyridinium toluene-*p*-sulfonate
DCU	Dicyclohexylurea
E_a	Energy of Activation
EI	Electron Impact
equiv.	Equivalent
ESI-MS	Electrospray ionization mass spectrometry
Et	Ethyl
EtOH	Ethanol
FAB	Fast atom bombardment
GPC	Gel Permeation Chromatography
HA	Haemagglutinin

HPLC	High performance liquid chromatography
hr	Hour
hrs	Hours
Hz	Hertz
IR	Infra-red
J	Coupling constant
LD	Laser-desorption
m	Multiplet
MALDI-MS	Matrix assisted laser desorption-ionization mass spectrometry
Me	Methyl
MeOH	Methanol
mins	Minutes
M_n	Number average molecular weight
mol	Mole
mp	Melting point
MS	Mass spectrum
M_w	Weight average molecular weight
MW	Molecular weight
NMR	Nuclear Magnetic Resonance
PAMAM	polyamidoamine
PDi	Polydispersity
Ph	Phenyl
ppm	Parts per million

psi	Pounds per square inch
p-TSA	*p*-Toluenesulfonic acid
R	Alkyl
s	Singlet
SEC	Size exclusion chromatography
t	Triplet
TBAF	Tetra-n-butylammonium flouride
TBDMS	*tert*butyldimethyl silyl
TEA	Triethylamine
TGA	Thermogravimetric analysis
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TMSCl	Chlorotrimethylsilane
TOF	Time of flight
wt %	Percent by weight

CHAPTER 1

Introduction

1.1 Introduction to Dendrimers

Dendrimer is the name given to a fairly new class of oligomers. The word 'dendrimer' is a combination of the Greek word for tree, dendron, and the word polymer. A less common name used to refer to dendrimers is arborol, from the Latin word for tree. Dendrimers are highly branched moieties, this results in high numbers of terminal functional groups in each molecule.

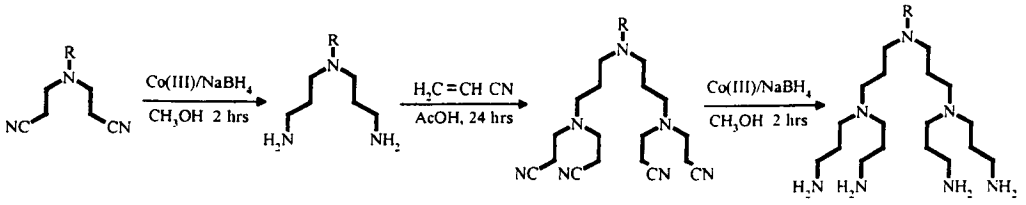
1.1.1 Historical Background

Dendritic polymer chemistry is based on two well-established fields of chemistry, polymer chemistry and traditional synthetic organic chemistry. 'Classical' polymers are synthesized by reacting monomer units with one another. These monomer units usually have the ability to link with only two other monomer units resulting in the formation of a linear polymer. Generally this results in polymers being synthesised with a distribution of molecular weights and non-discrete topologies. However, due to the formation of dendrimers being based on an

iterative strategy, precise control is exerted over both physical and architectural properties during the construction of the dendrimer.

In 1952 Flory proposed that highly branched molecules could be constructed by using a trifunctional monomer possessing two different functional groups, A and B, where A and B can react with one another.[1] However, it was not until nearly forty years later, in 1978, that Vogtle reported one of the first examples of molecules made by a protection – deprotection scheme; he referred to these compounds as 'cascade – like' molecules.[2] These molecules were built up by alternating between Michael addition reactions and reduction of the nitrile group to an amino group **(scheme 1.1)**.

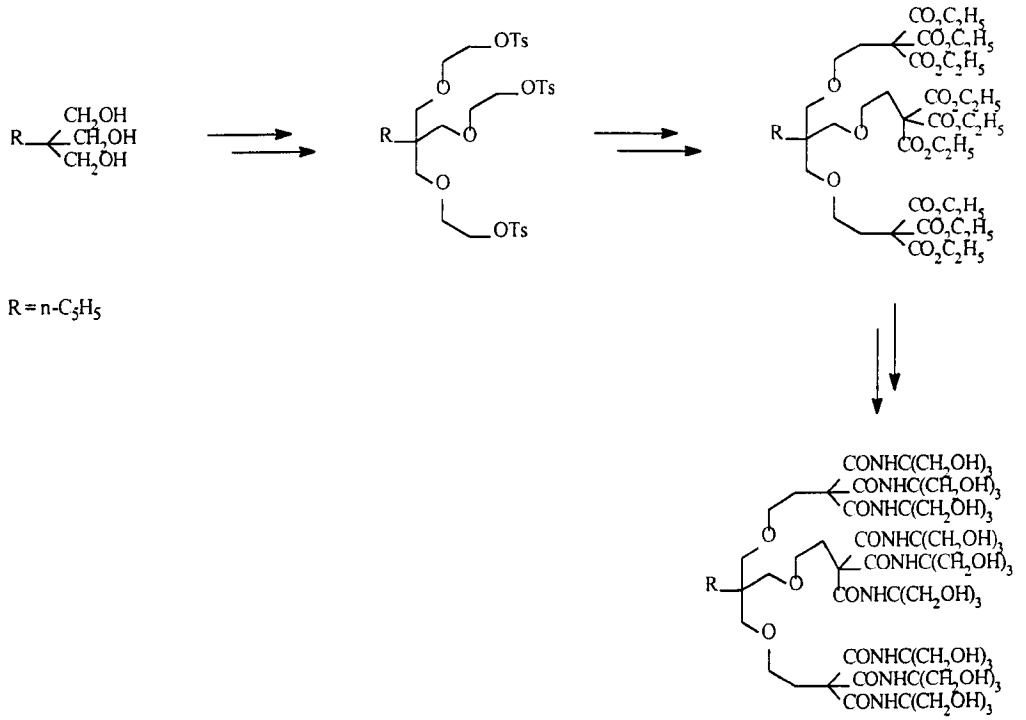
Scheme 1.1



In 1985 two groups reported independently their contributions towards cascade syntheses. Tomalia published worked involving the synthesis of poly(amidoamine) (PAMAM) Starburst* dendrimers.[3] The PAMAM dendrimers were obtained by repetition of two consecutive reactions. The first reaction was a Michael addition of an amine followed by amidation of the ester with an excess of diamine. In the same year Newkome published work on his arborols **(scheme 1.2)**.[4]

- Starburst is a registered trademark of The Dow Chemical Company

Scheme 1.2

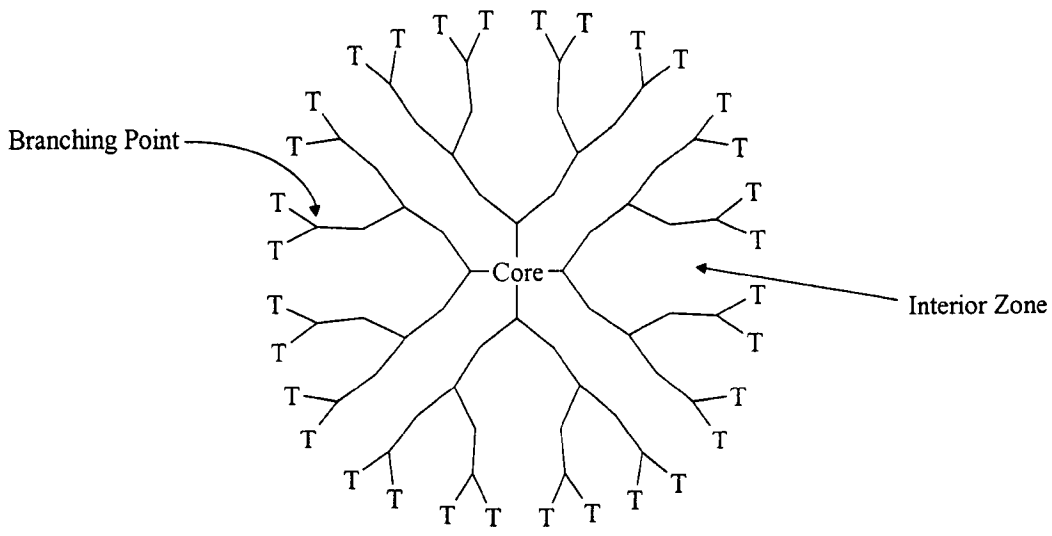


The pioneering work of these two groups led to interest in the synthesis, properties and applications of dendrimers. They demonstrated that polymers could be constructed possessing discrete sizes, shapes and molecular weights. Therefore it is unsurprising that since the middle of the 1980s there have been numerous reviews on the subject of dendrimers.[5-9]

1.1.2 Structure

Dendrimers have three main structural features **(figure 1.1)**:

Figure 1.1 Main Structural Features of a Dendrimer



(i) Initiator core – this can be any atom or molecule, as long as it possesses at least two reactive sites. This is situated in the middle of the dendrimer and is used to anchor dendrons, resulting in exponential growth.

(ii) Interior region – this region contains the branched, repeating sub-units which are attached to the initiator core. These branches are lengthened by a step-by-step addition involving protection and deprotection approaches.

(iii) Exterior region – this region contains the branch termini. As these lie either on the surface of the dendrimer or very near to it, the nature of the functional groups in this region has a significant effect on the physical properties of the dendrimer.

Another aspect of a dendrimer which should be considered is the size to which it can grow. Calculations predict that a starburst dendrimer will reach a size known as a starburst limited generation. Beyond this generation branching will no longer occur in an ideal fashion.[10]

1.1.3 Dendrimer Models

There are two main theoretical models which represent the structure of dendritic macromolecules. The most recent theory was proposed by Lescanec and Muthukumar.[11] They predicted that a density maximum would exist at the centre of a dendrimer. The evidence for this model was obtained by kinetically grown structures as opposed to equilibrium ones. This model takes into account inward folding of branch units and, as well as predicting a maximum density at the centre, also suggests that the terminal groups are distributed throughout the dendrimer.

The second model, proposed by de Gennes and Hervet, predicts that a density minimum exists at the centre of a dendrimer rather than a density maximum.[10] The

density maximum was predicted to be located at the surface of a dendrimer. The flaw in this proposal is that it does not take into consideration the occurrence of back folding which could be experienced by flexible dendrimers.

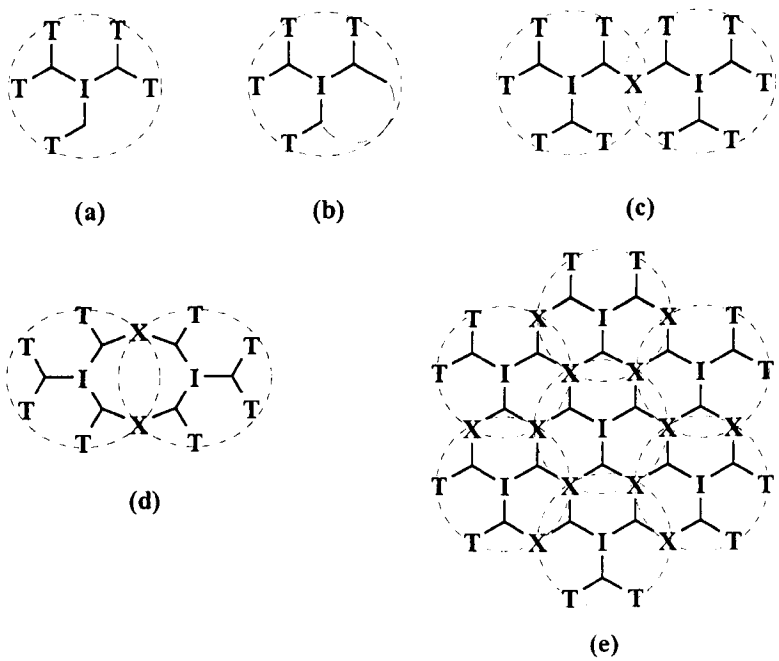
Using the de Gennes model it can be predicted that as the functional groups are found at the periphery, the more functional groups there are, the higher the probability of steric congestion. Therefore, as the generation of a dendrimer increases, the probability of all terminal groups reacting decreases. De Gennes used mathematical calculations to predict when the growth of a Starburst dendrimer could no longer occur in an ideal fashion. He termed this limit the Starburst limited generation. When this point is reached, the area on the surface per terminal group approaches the van der Waals diameter of each terminal group, resulting in incomplete growth of a dendrimer.

Starburst dense packing is a term used to describe the point when a dendrimer begins to grow and exist in a three dimensional manner.[12] This does not occur initially but only after a couple of generations are achieved. This occurs so that as the number of terminal groups are increased as the generation of a dendrimer is increased, the terminal groups can still be located at the periphery.

1.1.4 Defects

The defects that can occur during the synthesis of a dendrimer fall into two categories, those which result from intra-dendrimer events and those due to inter-dendrimer bridging or looping.[6] Defects caused by intra-dendrimer events result in non-ideality in the branching of a dendrimer. Inter-dendrimer events lead to more polydisperse systems.

Figure 1.2 Defects in Dendrimers



I = initiator core; T = terminal functions; X = inter-dendrimer bridging defect.

Defects as shown in **a** and **b** (**figure 1.2**) lead to a decrease in the number of terminal functions; this in turn results in a reduction in the number of points from which the branches can grow. Branch defects are caused by a number of factors: -

(1) Fragmentation of branches;

(2) Steric problems leading to prevention of branch growth;

(3) Development of abnormal branches;

(4) Incomplete reactions, either not all the protecting groups are not removed or branch growth is incomplete.

All of the above defects may affect the symmetry and ultimately the properties of a dendrimer.

Defects as shown in **c**, **d** and **e** (**figure 1.2**) are examples of intermolecular events; they illustrate bridged and looped structures which ultimately lead to increased polydispersity.

1.1.5 Nomenclature

Standard nomenclature, such as *Chemical Abstracts*, results in long names when identifying dendrimers. These names usually do not give information on either the number of terminal groups or the initiator core in the dendrimer. Newkome has

devised a system whereby the name given to a dendrimer can reflect the initiator core, branch units and terminal groups.[13] Also, this system of nomenclature manages to take into consideration dendrimers which are made from differing branch units or dendrimers which consist of unsymmetrical branch units such as Denkewalter's polylysine dendrimers.[14] Today the problem of naming dendrimers still exists. In this work dendrimers are named at the author's discretion. In this naming system the generation of dendrimer is indicated along with the initiator core. This is then followed by the number of terminal groups and the nature of the terminal groups.

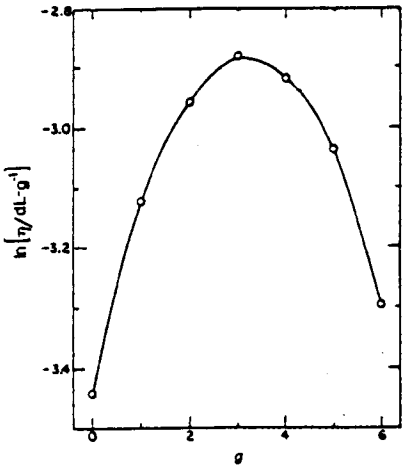
1.1.6 Properties

Dendrimers have many distinguishing features which make them worthy of investigation. Unlike traditional polymers, which are composed of long chains of repeating units leading to linear compounds, high molecular weight dendrimers are globular, three-dimensional globular spheres. Due to their unusual architecture, new exciting physical properties are expected to emerge. As a dendrimer can have many terminal groups on its surface, especially in the higher generation dendrimers, it will be these groups that will dictate the physical properties of a dendrimer.[8] Therefore, if these terminal groups are polar then the dendrimer will only be soluble in polar solvents; the converse is also true. This ultimately means

that the terminal groups can be deliberately modified to make them compatible with a whole range of solvents.

Frechet has shown that dendrimers display unique intrinsic viscosity behavior when compared with linear polymers.[15] As the molecular weight of a linear polymer is increased, the intrinsic viscosity of that polymer will increase in a linear fashion. However, Frechet found that this relationship did not apply to his polyether dendrimers. He found that intrinsic viscosity increased in his polyether dendrimers as their molecular weight increased. However, this was only true up to generation three, after which any increase in molecular weight led to a decrease in intrinsic viscosity (**figure 1.3**).

Figure 1.3 Viscosity versus Generation of Dendrimer

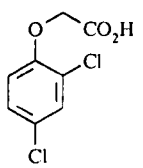


This data suggests that at low generations dendrimers probably exist as barrel-like species. The maximum viscosity probably represents the point at which the dendrimers change from disk-like structures into spheroids.

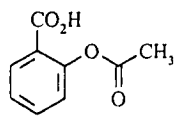
1.1.6.1 Host-Guest Properties

In 1982 Maciejewski suggested the use of dendrimers as hosts to guest molecules.[6, 16] Initially the only examples of guest encapsulation were limited to the dissolving of organic guests inside a dendrimer. Tomalia has demonstrated, using NMR relaxation measurements, that 2,4-dichlorophenoxyacetic acid 1 and aspirin **2** (**figure 1.4**) can penetrate into PAMAM dendrimers.[17] Frechet has been successful in the inclusion of pyrene in water in a water-soluble dendrimer.[18] However, both of these cases of inclusion can be readily explained using dynamic processes, as the guests can easily diffuse in or out of the host dendrimer depending on the equilibrium conditions. Therefore, little control was exerted over the inclusion or non-inclusion of these and other instances of inclusion of guest molecules.[19-21]

Figure 1.4 Structures 1 and 2



1



2

In 1996 Meijer reported that he was able to encapsulate a guest molecule inside a dendrimer.[22] The difference between this example of encapsulation and the two mentioned above was that Meijer was able to exert full control over the release of the guest molecule. The guest molecule used was a dye, Bengal Rose. He also called the dendrimer host a 'dendritic box'. The key feature involved in trapping the guests was that they were encapsulated during the construction of the dendrimer. One drawback to this work was that although the Bengal Rose molecules were easily locked in the host dendrimer, exhaustive dialysis was required to remove the guest molecules.

1.2 Synthesis

Many different types of dendrimers have been successfully synthesized including polyesters,[23-25] polyamidoamines,[3, 12, 26, 27] polyamines,[28-32] polyorganometallics[33-36] and even chiral dendrimers.[37-44] There exist two main strategies for the construction of dendrimers: -

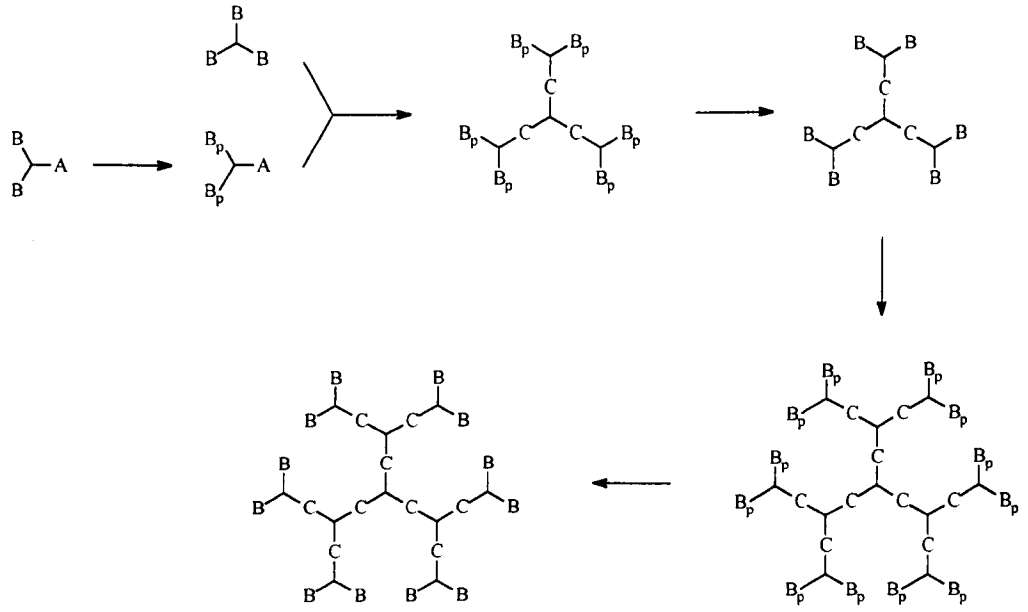
(i) Divergent Method – growth is from nucleus to terminal groups.

(ii) Convergent Method – growth from terminal groups to nucleus.

1.2.1 Divergent Method

This method was developed independently by the groups of Tomalia[13] and of Newkome,[45] and was the original strategy utilised to synthesise dendrimers. During a divergent synthesis a dendrimer is built up radially from an initiator core by iterative addition of branch units followed by a deprotection step (**scheme 1.3**).

Scheme 1.3

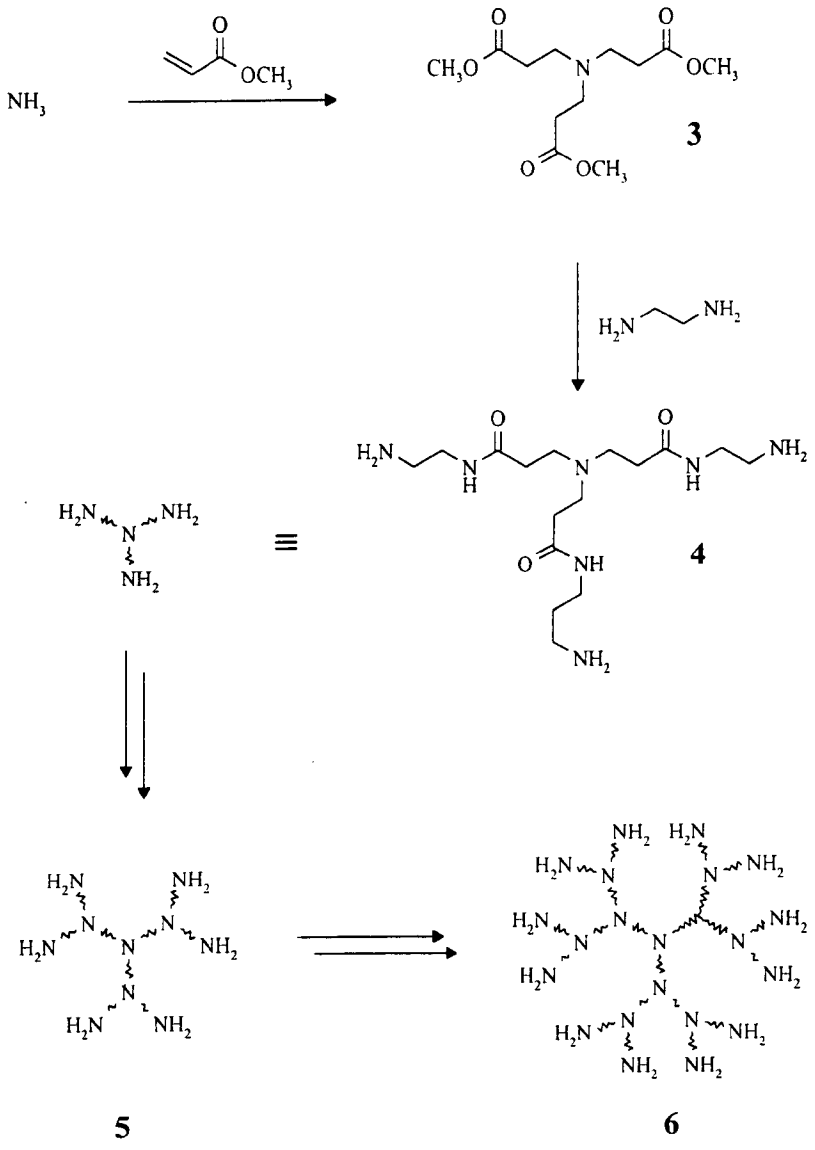


A, B = Functional Groups; A_p, B_p = Protected Functional Groups; C = A + B linkage

Tomalia achieved a 10th generation polyamidoamine (PAMAM) starburst dendrimer using this method.[17] The initiator core, ammonia, was reacted with

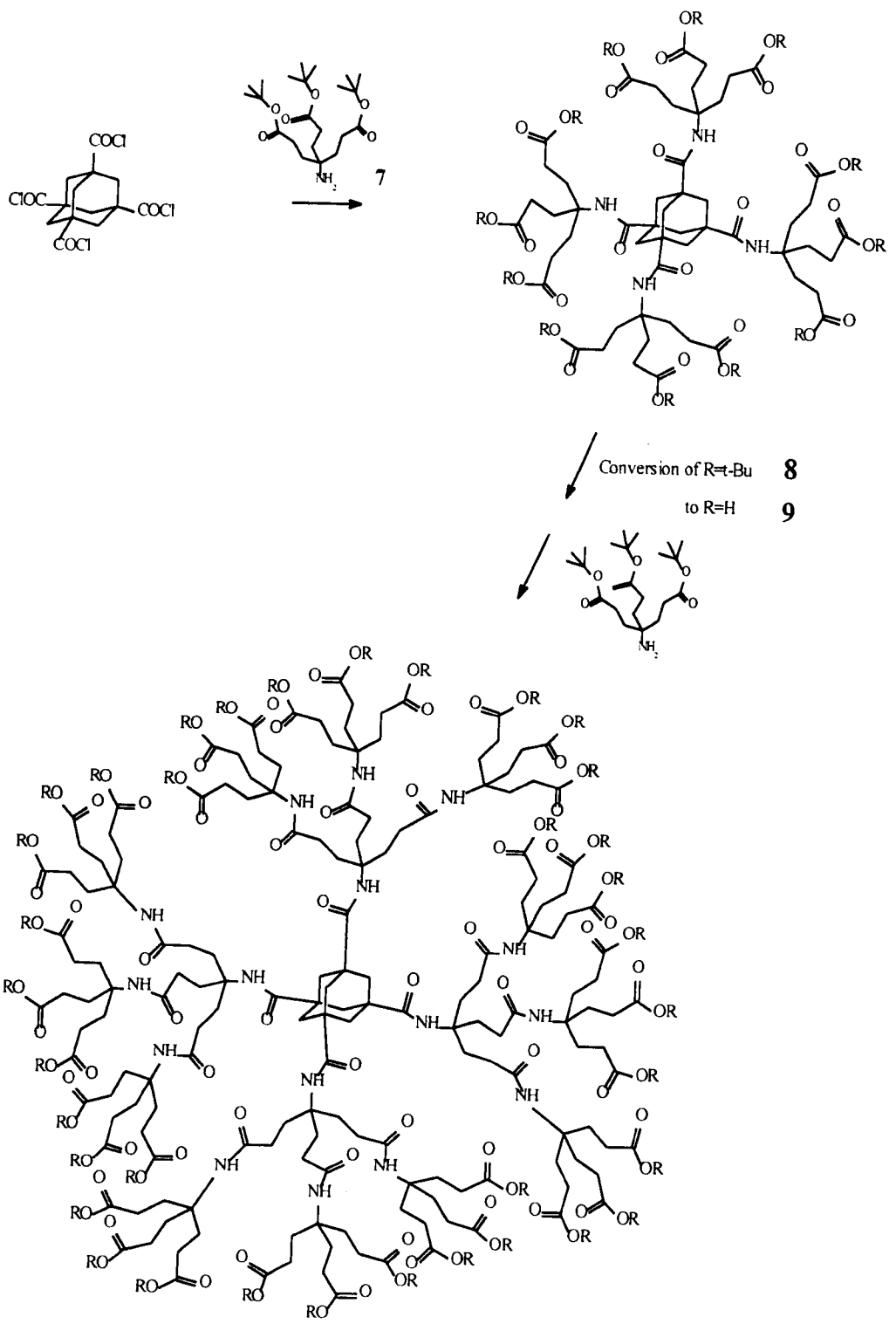
methyl acrylate in a Michael addition to give **3** (**scheme 1.4**). This was then followed by reaction with excess ethylene diamine to give the generation one dendrimer **4**. These two steps were repeated to yield the dendrimers **5** and **6** (**scheme 1.4**).

Scheme 1.4



As mentioned earlier, Newkome also successfully synthesized dendrimers using the divergent approach. One of the first dendrimers he synthesized was based on an adamatane core (**scheme 1.5**).[45, 46] Compound **7** was reacted with the core in an acylation process to give the first generation **8**. Formic acid was then used to induce hydrolysis of the ester moieties to give terminal acid groups, **9**. Compound **9** was then exposed to the same reaction conditions to give the second generation dendrimer **10**. It can easily be observed that the thirty-six terminal groups are causing congestion at the periphery of **10**. Therefore, it is no surprise that Newkome was unable to synthesize the next generation.

Scheme 1.5



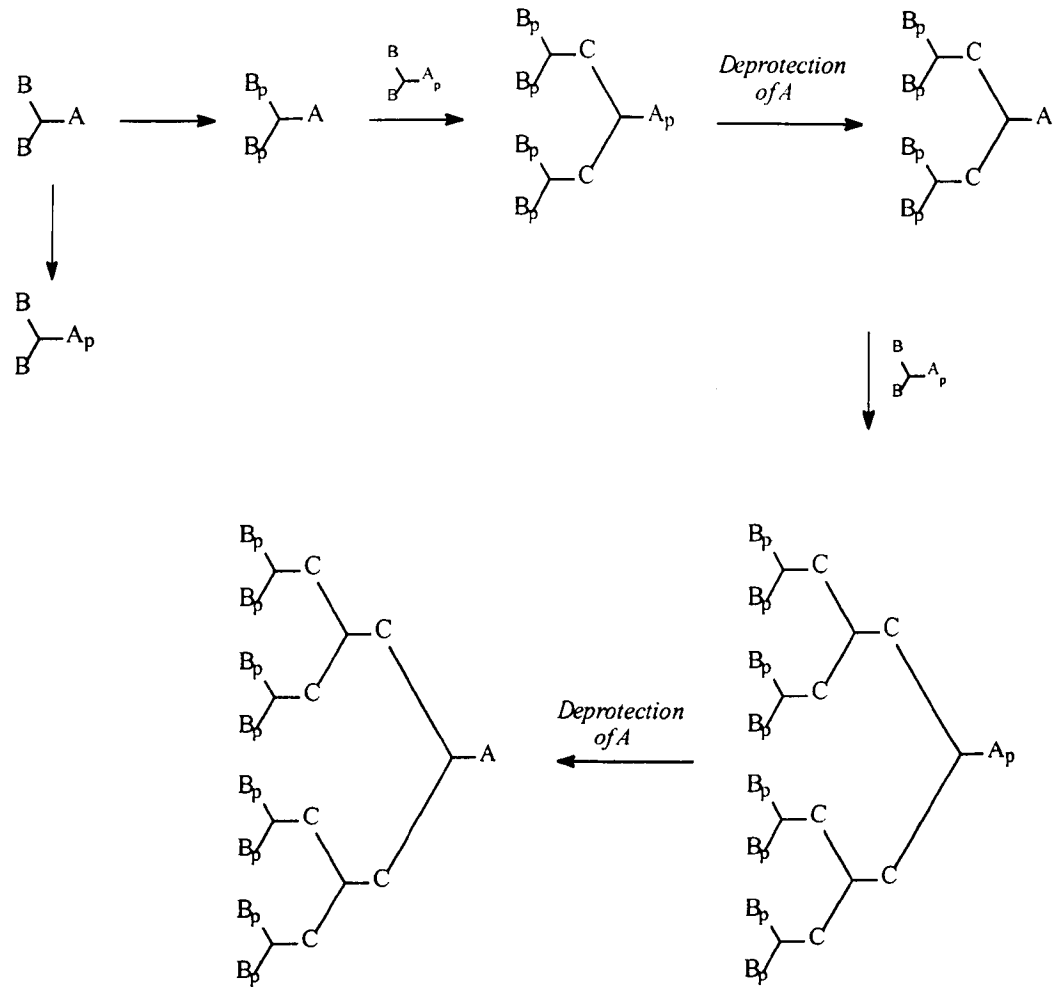
10

The advantage of this approach is that a dendrimer can be quickly grown with rapid increases in number of terminal groups without too much steric hindrance in early generations. The downside is that at higher generations the terminal groups become heavily congested, leading to branch defects as the peripheral groups become inaccessible.

1.2.2 Convergent Method

Like the divergent method, the convergent method was reported independently by two groups, those of Frechet[47-49] and of Neenan and Miller.[50] With this method, growth of the dendrimer begins from the periphery with growth inwards towards the eventual focal point. This forms a dendron which can be tethered, via its focal point, to a core along with other dendrons (**scheme 1.6**).

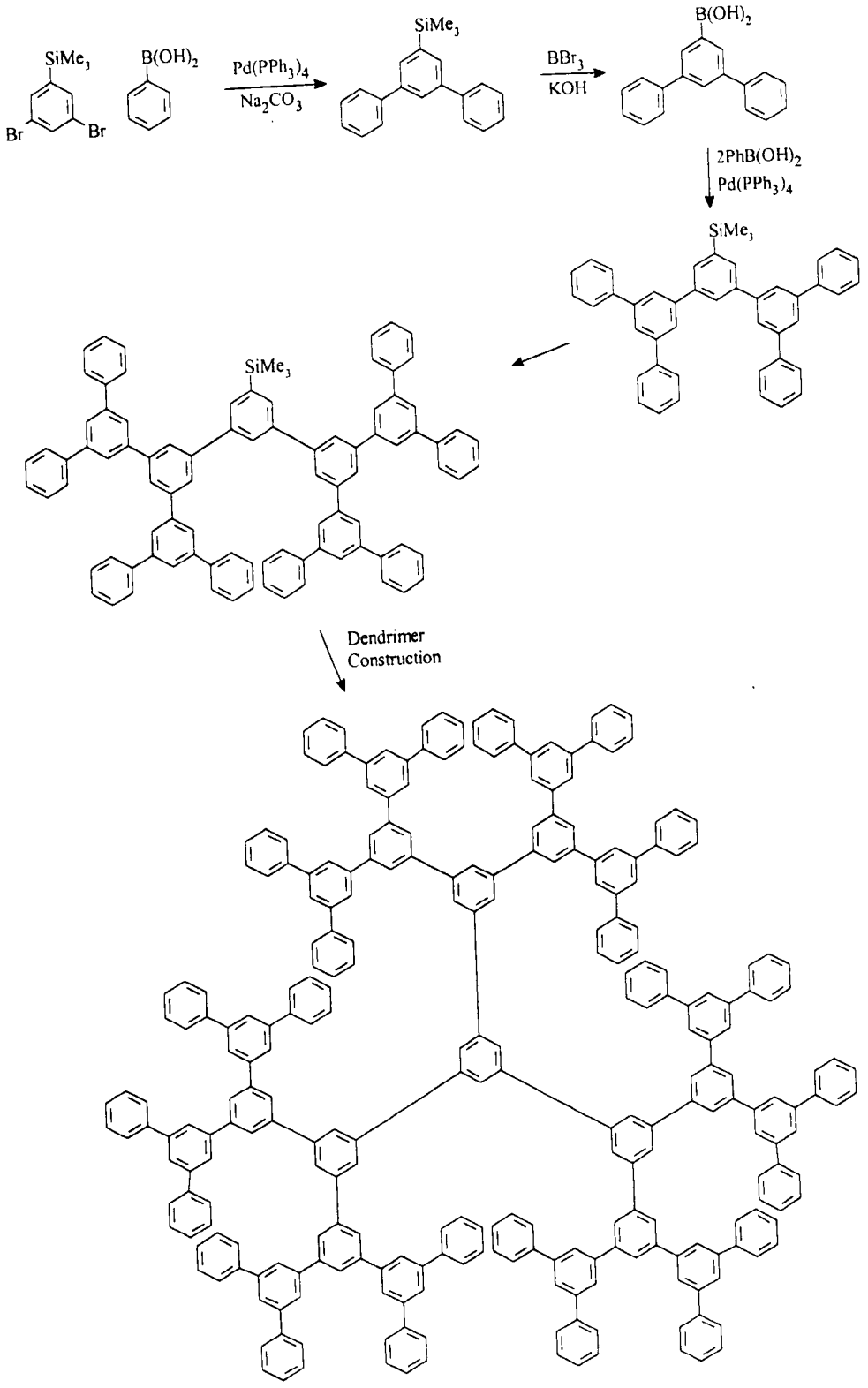
Scheme 1.6



A, B = Functional Groups; A_p, B_p = Protected Functional Groups; C = A + B linkage.

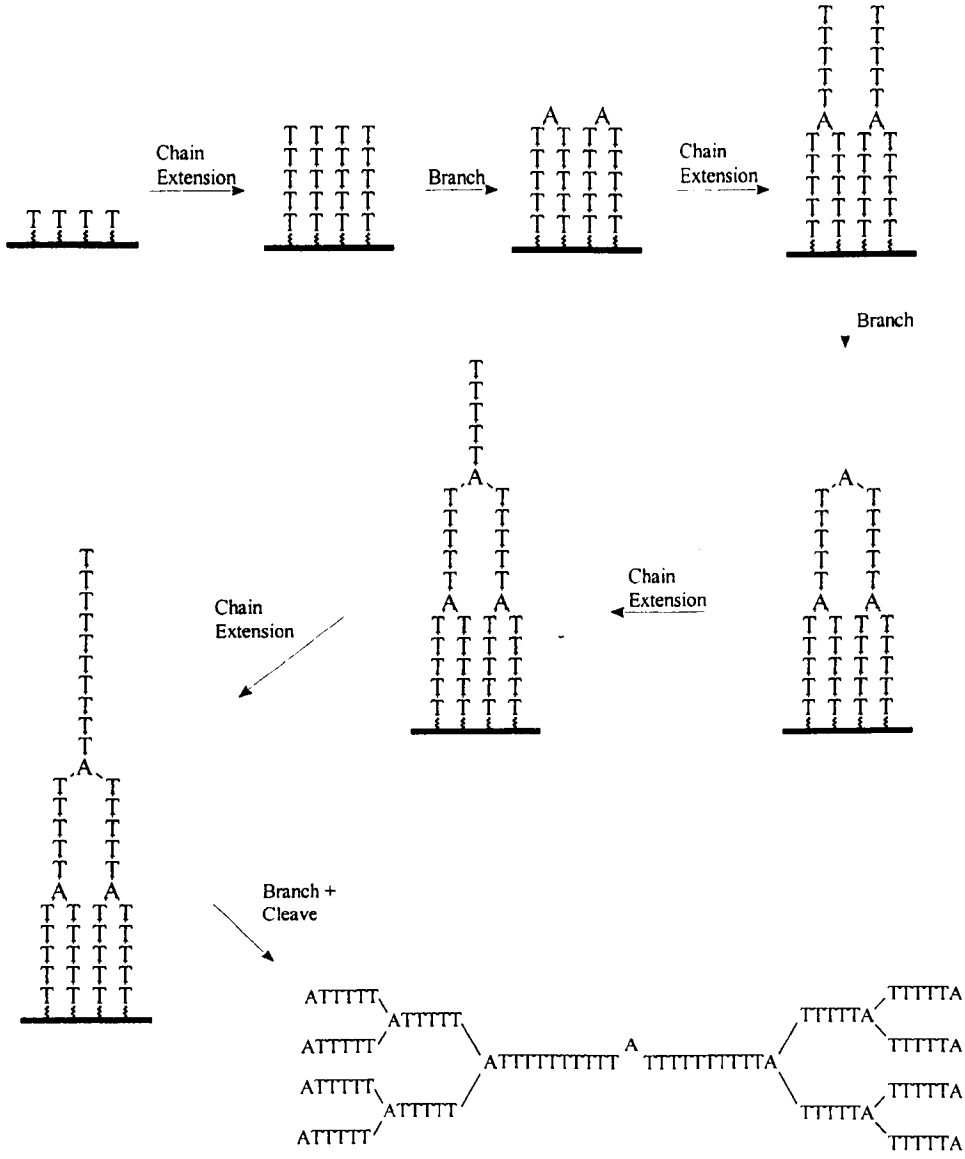
An example of this type of synthesis is a fourth generation dendrimer constructed by Neenan and Miller (**scheme 1.7**).[51] The dendrons were constructed and then finally coupled to an initiator core using Suzuki coupling.

Scheme 1.7


SiMe3
B(OH)2
Br
Br
Pd(PPh3)4
Na2CO3
SiMe3
BBr3
KOH
B(OH)2
2PhB(OH)2
Pd(PPh3)4
SiMe3
SiMe3
Dendrimer
Construction

The convergent method was also used to synthesize nucleic acid analogues. This work was carried out by Hudson and Damha who managed to obtain a second generation dendrimer (**scheme 1.8**).[52]

Scheme 1.8



When this synthesis was originally carried out, a chain extension was not used, resulting in only a first generation dendrimer being produced. When the chain extension was used, a generation two dendrimer was obtained. This illustrates a disadvantage of the convergent method, that as the size of the dendron increases, the focal point becomes more sterically hindered, leading to problems when either increasing the generation of the dendron or when trying to tether it to an initiator core.

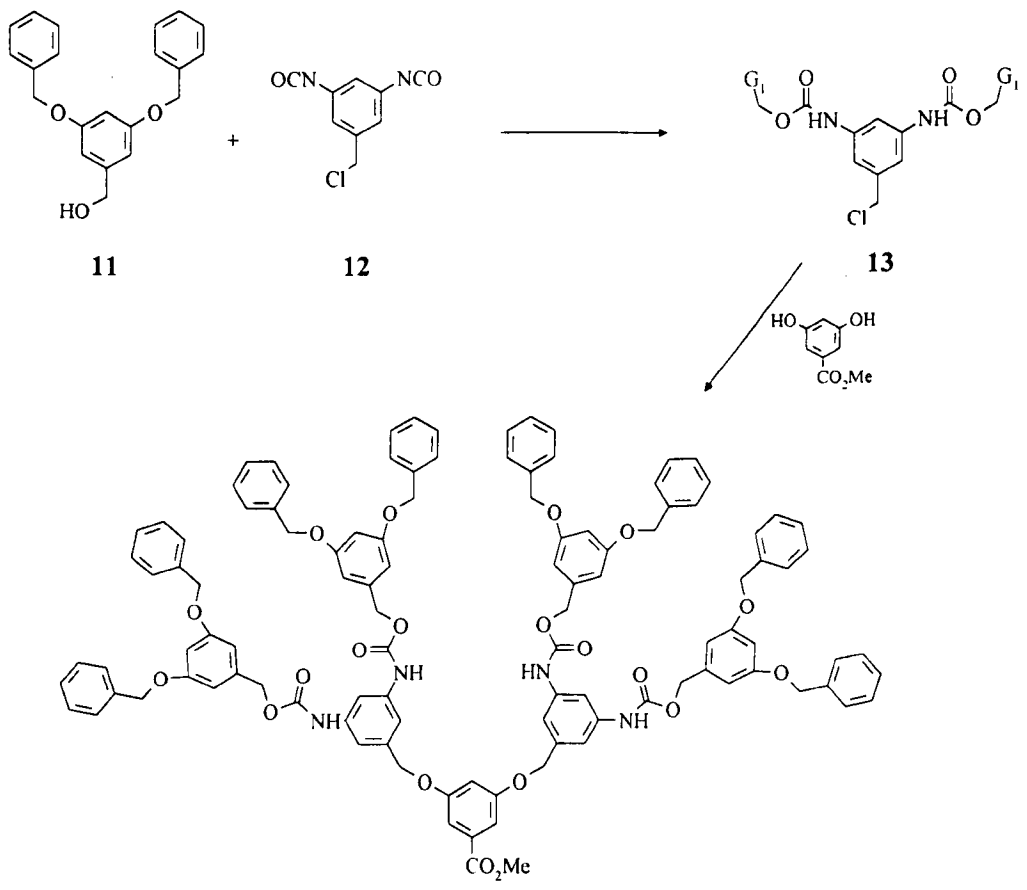
One advantage of the convergent approach is the low number of reactive sites for each generation growth. The number of sites is usually three and because of this low number the probability of obtaining monodisperse products is increased. Another advantage is that different types of dendron can be attached to the same initiator core to give differentiated sectors with differentiated surfaces.[53]

1.2.2.1 Two Step Approach

The synthesis of dendrimers is a long, drawn out task. For just one generation growth of dendrimer the reactive groups have to be activated, which usually involves some kind of deprotection process. The activated dendrimer is purified and then coupled with a monomer. This second generation dendrimer then needs to be purified. However, this process is necessary as it ensures complete control over every aspect of synthesis of a dendrimer.

Frechet developed an approach that allowed the accelerated growth of dendrimers by growth of not one but two generations in a single step (**scheme 1.9**).[54] This method meant that a deprotection step followed by a purification process was not necessary. Frechet synthesized the generation one dendrimer, **13**, by reacting a slight excess of dihydroxybenzyl alcohol **11** with 3,5-diisocyanatobenzyl chloride **12**. To yield the generation three dendrimer **14**, **13** was reacted with methyl 3,5-dihydroxybenzoate.

Scheme 1.9



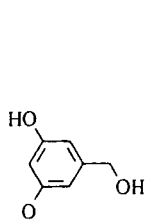
11 **12** **13** **14**

The advantage is that a generation three dendrimer can be synthesized via a 'one-pot' process from a generation one dendrimer with the need for only one purification step. Unfortunately this process is limited to monomers that can only react pairwise as a result of their addition in sequential fashion. Another stipulation is the absence of any side reactions and that the terminal groups must be stable to the overall reaction conditions.

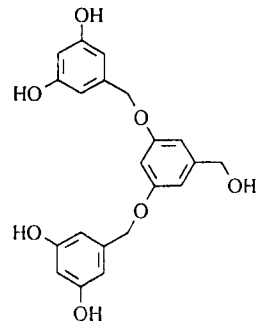
1.2.2.2 'Branched Monomer' Approach

This approach, like the previous one, was also developed by Frechet.[55] In this process the repeating unit/monomer is replaced with a larger fractal component of the next generation. For example, instead of using **15** which is an AB_2 monomer, **16**, an AB_4 monomer, is used instead (**figure 1.5**). The consequence of this is that the generation of a dendrimer can be increased by two generations at a time.

Figure 1.5 Structures 15 and 16



15

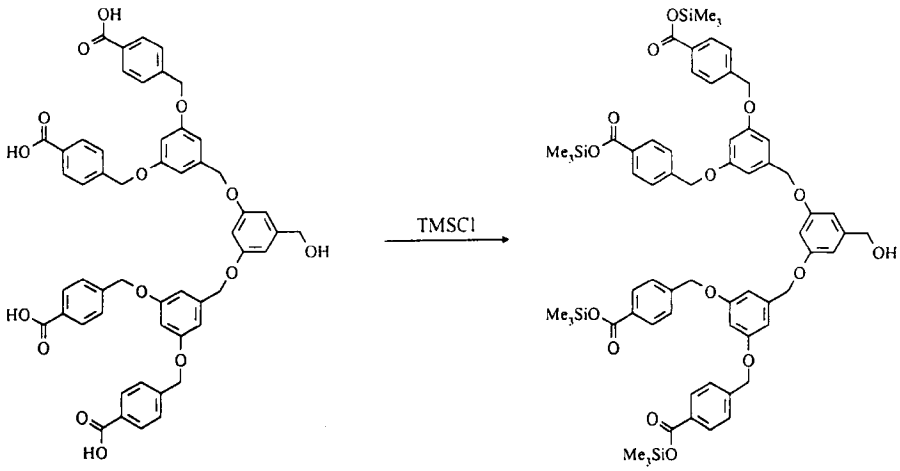


16

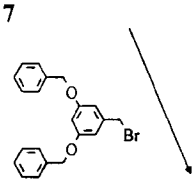
Unfortunately problems were encountered with the synthesis of **16** in high yields. In view of this **17** was used as the AB_4 monomer. Compound **17** was converted to the trimethylsilyl ester **18** and as well as the benzyl ether **19** (**scheme 1.10**).

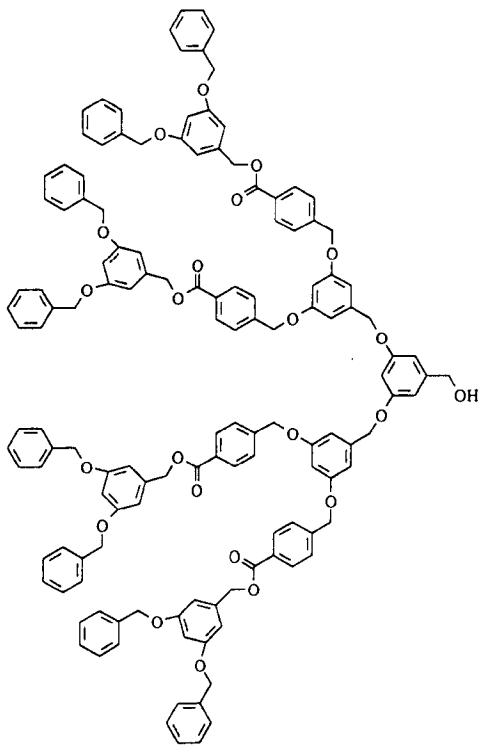
The benzyl alcohol in **19** was activated as benzyl bromide to give **20**. The third generation dendron **20** was then transformed to the fifth generation dendrimer **21** by reacting it with **18** (**scheme 1.11**). Overall this illustrates how a generation five dendrimer can be synthesized in only three steps. If **21** was synthesized in a conventional way it would take seven steps.

Scheme 1.10



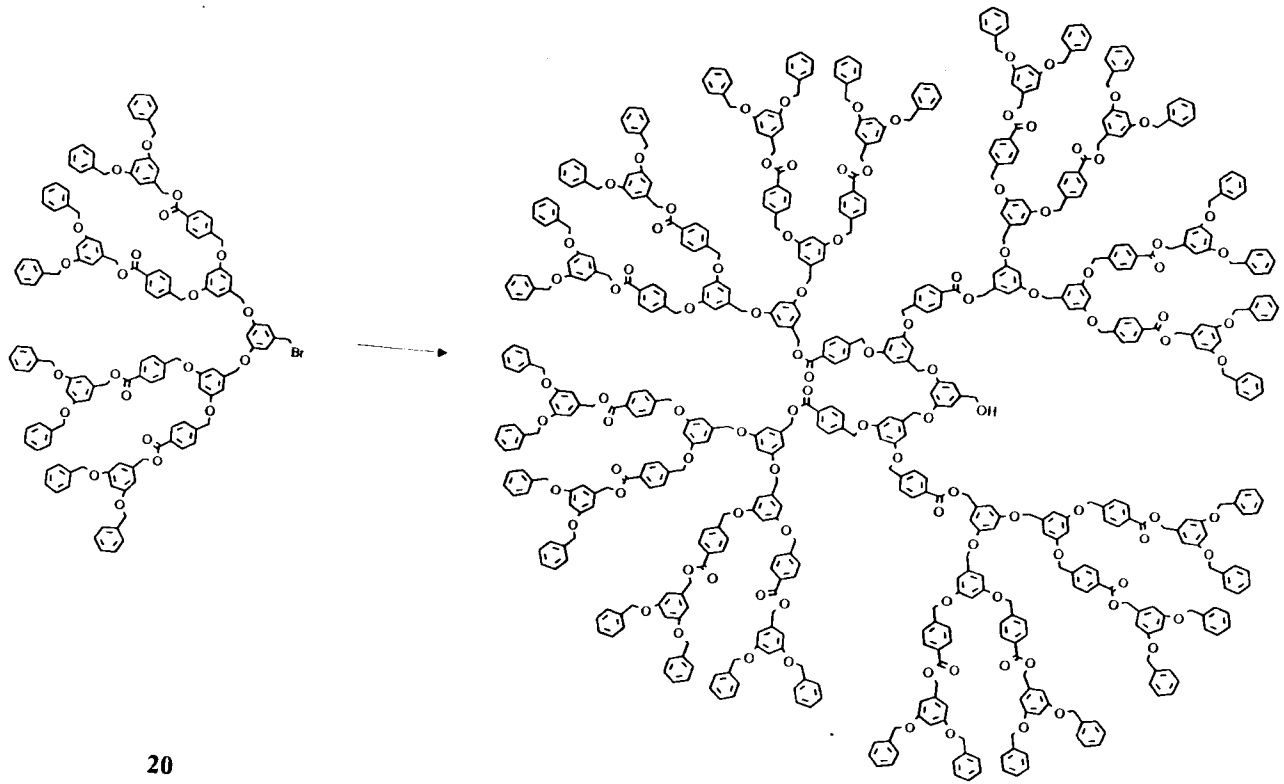
17 **18**





19

Scheme 1.11



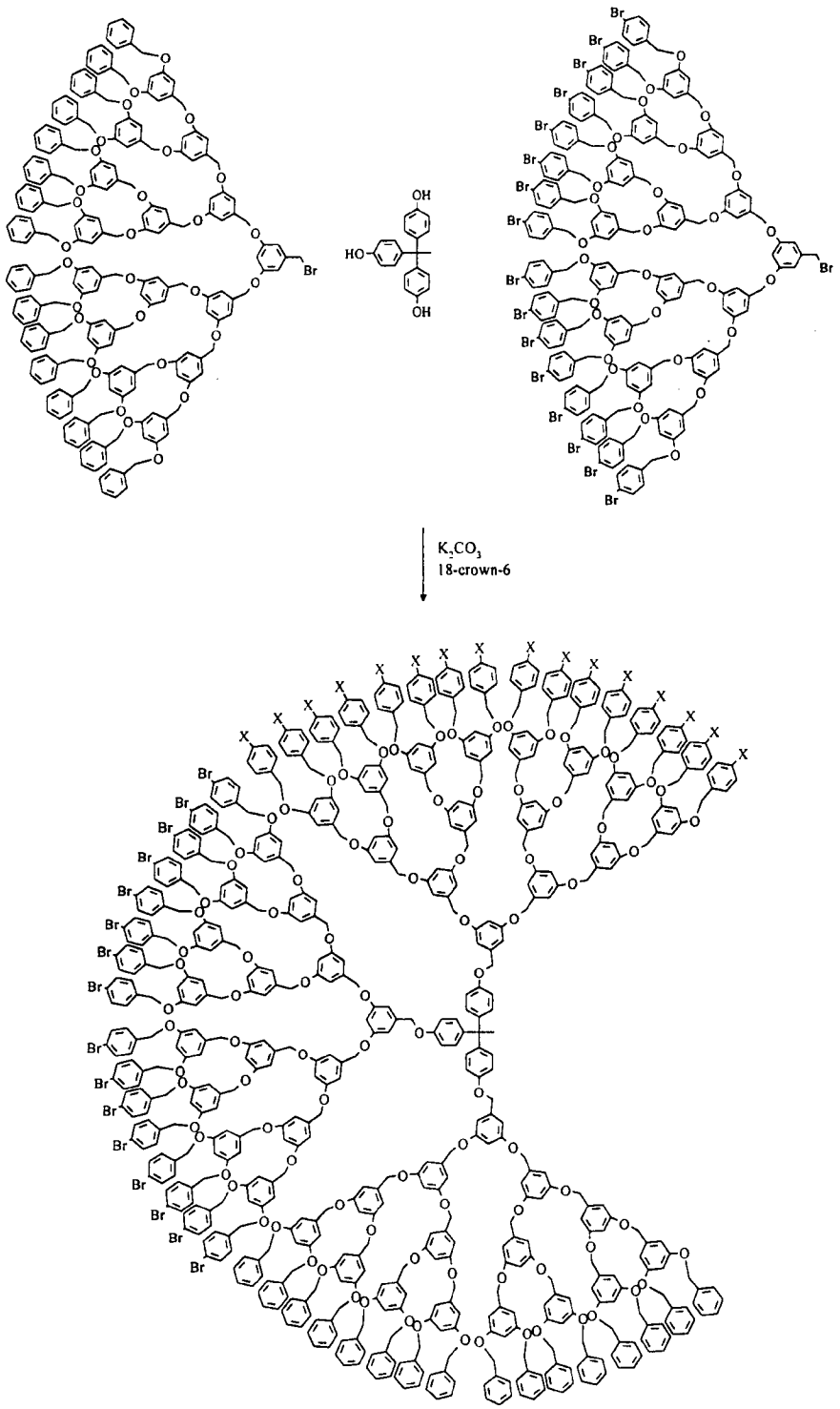
20 **21**

1.2.2.3 Differing Dendrons

As mentioned earlier, one of the advantages of the convergent method is that the branches do not have to be identical. Frechet managed to construct an unsymmetrical dendrimer using the convergent approach.[53] The dendrons were made by stepwise alkylation of a monomer unit with unsubstituted and substituted benzylic bromides. The differing dendrons were then attached to a core molecule to give a dendrimer with different groups on its periphery (**scheme 1.12**). It can be observed that the dendrimer can have either sixteen or thirty-two bromine atoms on its periphery.

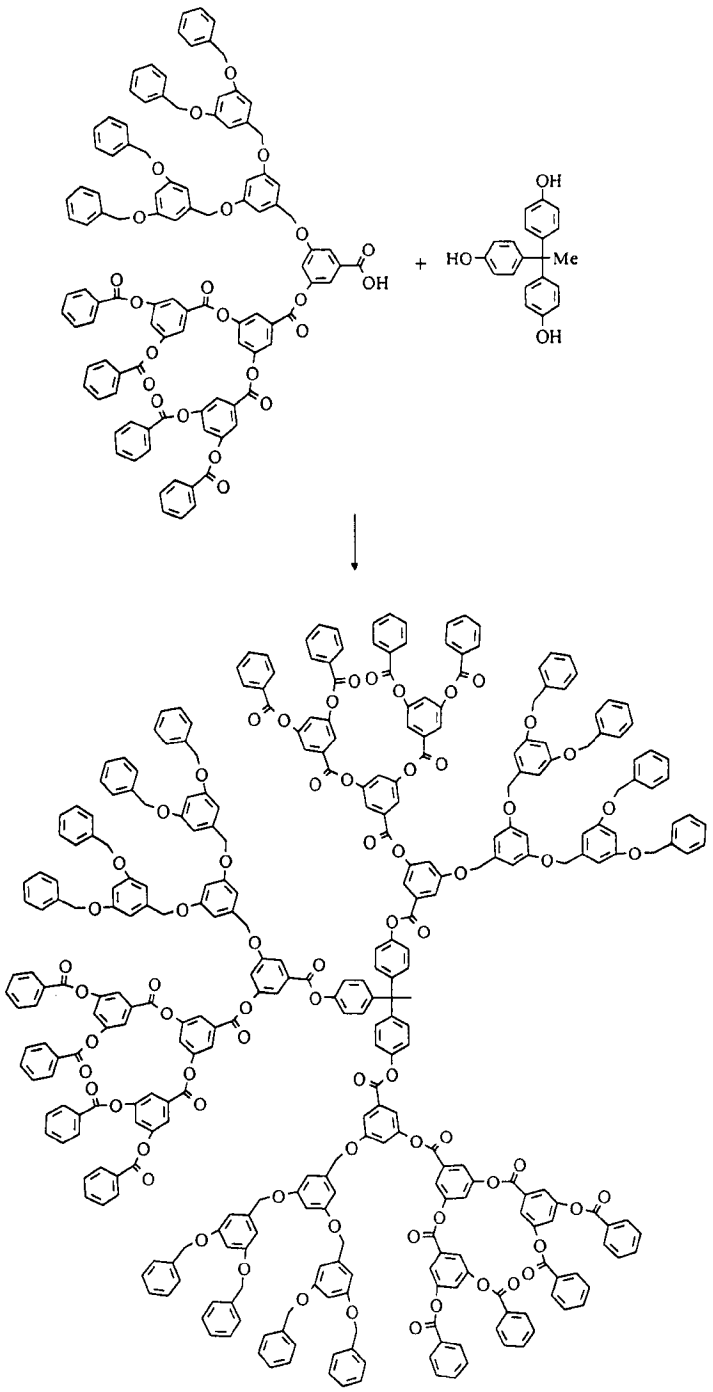
Frechet adapted this method to construct dendrimers with different branches in the dendrons.[53] **Scheme 1.13** shows how Frechet constructed a dendrimer with ester and ether monomer units.

Scheme 1.12



X = H or Br

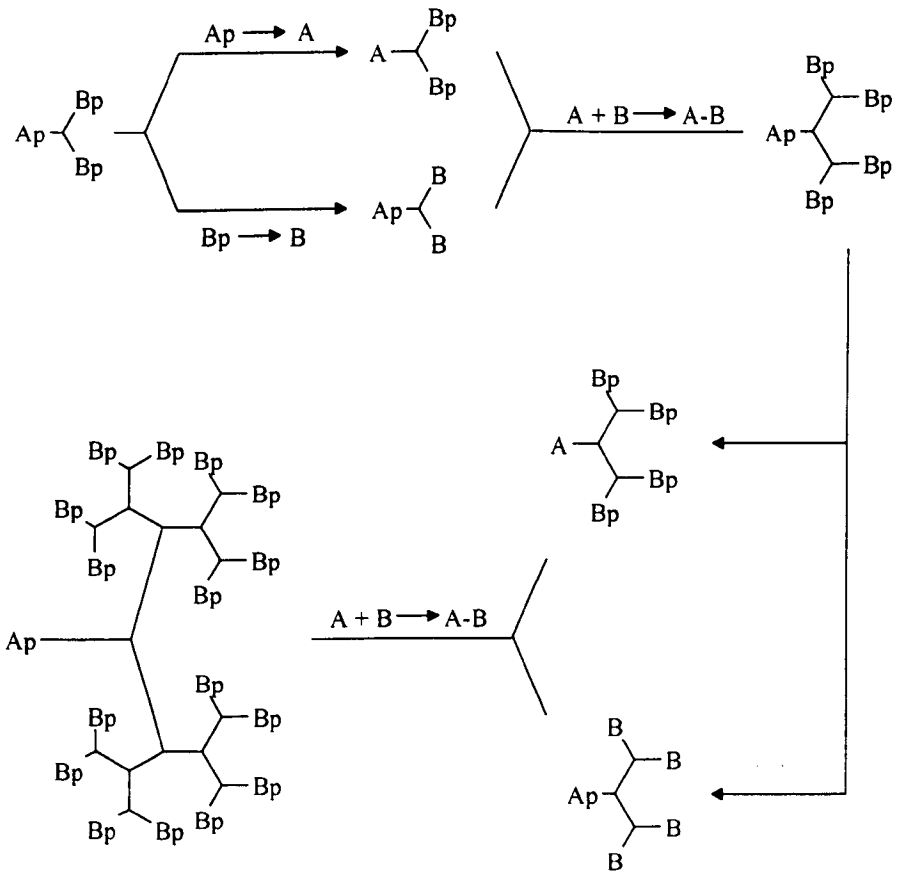
Scheme 1.13



1.2.2.4 Double Exponential Growth

Moore devised a method of accelerated convergent growth of a dendrimer.[56, 57] He achieved this by using a trifunctional monomer of the type $A_p(B_p)_2$. The important aspect of this process is that it must be possible to remove the protecting groups on A and B selectively. After deprotection of A and B, coupling produces a single large dendron (**scheme 1.14**). Similar steps are repeated to increase the size of the dendron.

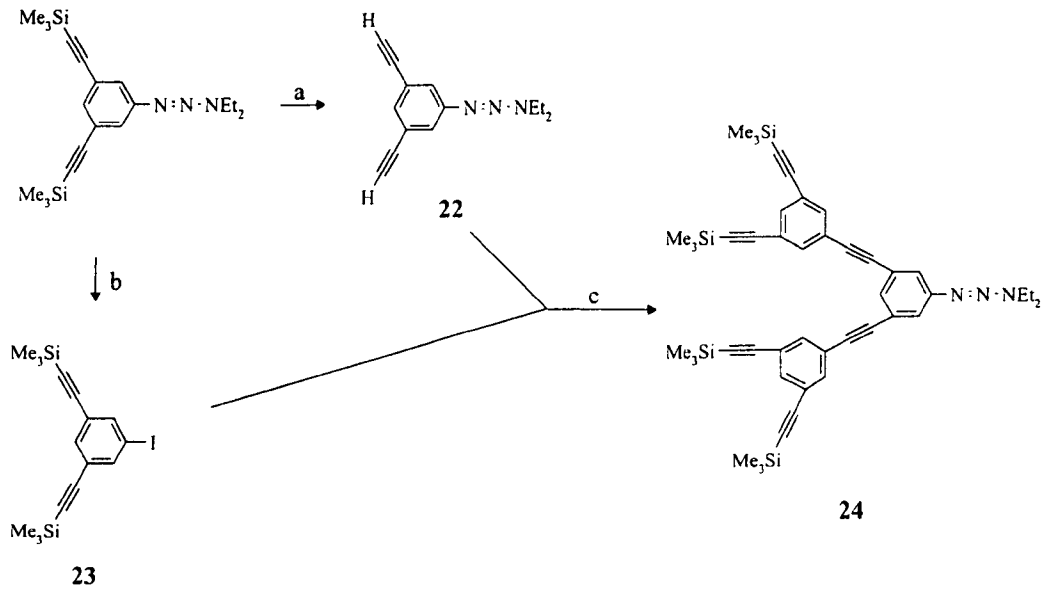
Scheme 1.14



A,B = Functional Groups; Ap, Bp = Protected Functional Groups

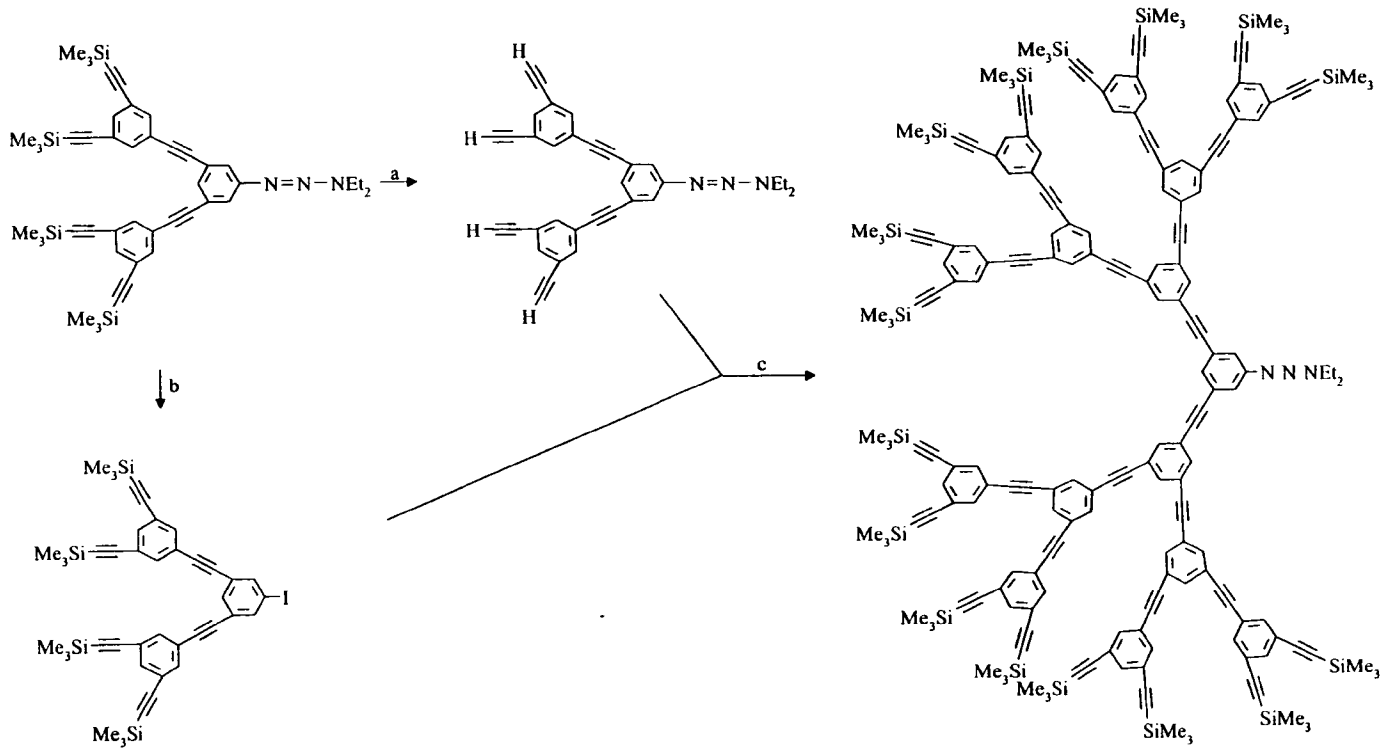
Moore synthesized phenylacetylene dendrimers using three different approaches; the convergent, divergent and double-stage convergent method.[57-59] He found that the divergent method was the least useful method with these types of dendrimers as he encountered major problems with solubility. However, with both the convergent and double-stage convergent method he found that he was able to construct dendrimers up to the fourth generation. In this case the double-stage synthesis is the most convenient method to use as it required the least amount of steps; it only needed six steps to synthesize a fourth generation dendrimer. Moore achieved this by coupling together **22** and **23** to give the second generation dendron **24** (**scheme 1.15**). This process was then repeated to give the fourth generation dendrimer **25** (**scheme 1.16**).

Scheme 1.15



a = K_2CO_3 / MeOH; b = MeI, 90-110 °C; c = $[Pd(dba)_2]$ /CuI /PPh_3 / TEA / 46-65 °C

Scheme 1.16



25

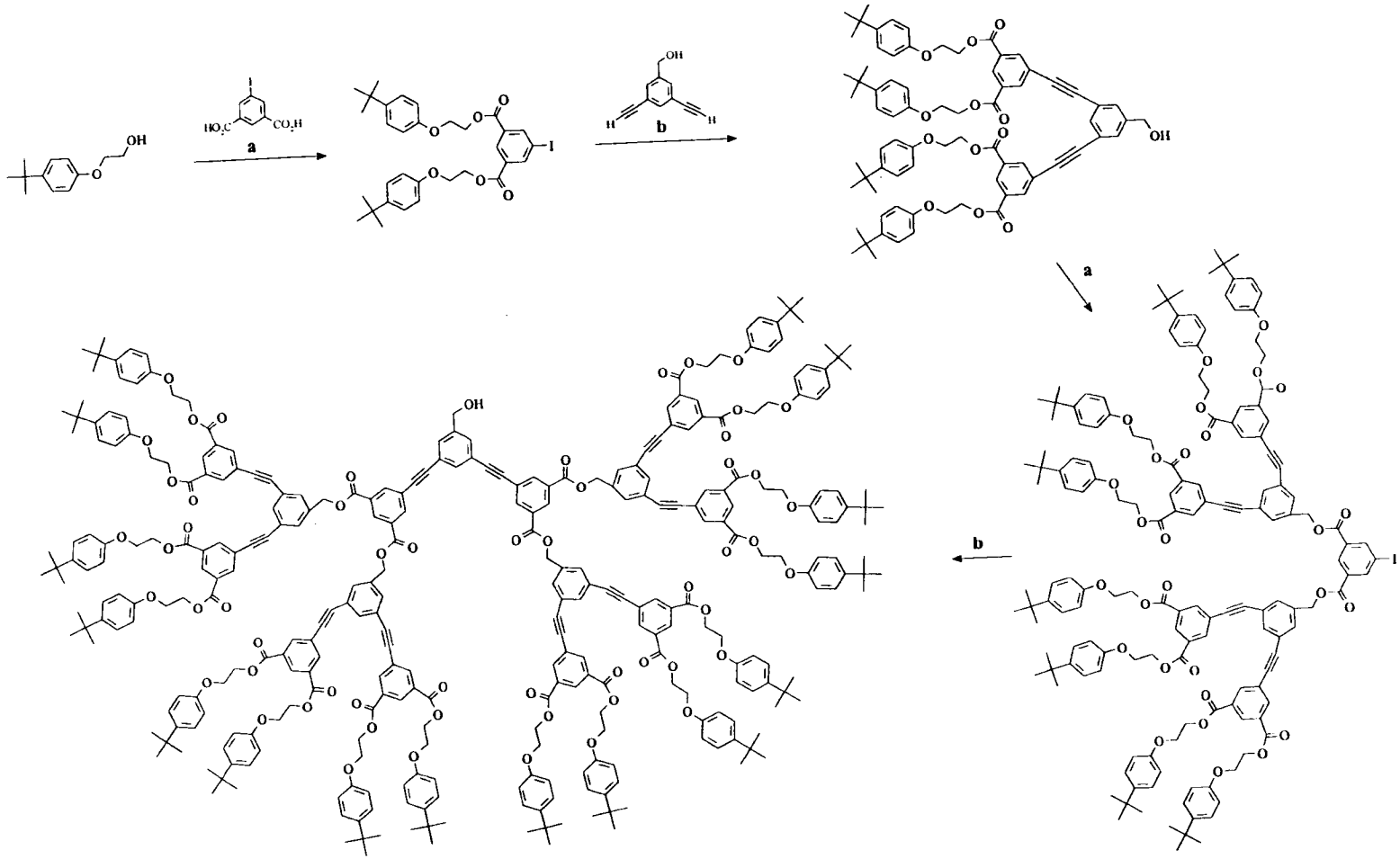
1.2.3 Orthogonal Coupling Strategy

In 1977 Baranay and Merrifield stated that an orthogonal system is 'a set of completely independent classes of protection groups, such that each class can be removed in any order and in the presence of all other classe's.[60] The essence of this approach is that, as Merrifield stated, the need for protecting groups is eliminated due to the fact that the two monomers require different reaction conditions. However, under the conditions needed to couple, each monomer needs to be inert to the functional groups on the other monomer. This paved the way for the synthesis of dendrimers without the need for any protection-deprotection strategies.

Zimmerman applied this technique to synthesize dendrimers.[61] By using monomer units that could undergo either an esterification reaction or a Sonogashira reaction of a terminal acetylene with an aryl iodide, he was able to synthesize dendrimers up to a sixth generation (**scheme 1.17**).

The efficiency of this strategy was increased when this method was applied to Frechet's branched monomer approach. This meant that the two monomers that Zimmerman used were actually both second generation dendrons. This allowed the synthesis of a generation six dendrimer in four steps.

Scheme 1.17



1.3 Hyperbranched Polymers

1.3.1 Introduction to Hyperbranched Polymers

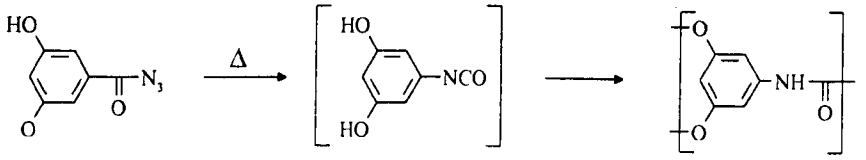
Although dendrimers and their properties have created a great deal of interest, the fact remains that their synthesis is tedious. This reduces their commercial viability. Hyperbranched compounds have the advantage over dendrimers as they have extensive branched geometry but can be prepared in one single polymerization step, as there is no longer a need for protection or deprotection steps. The disadvantages of hyperbranched polymers are that complete control cannot be exerted over molecular weight and broader polydispersities are obtained.

1.3.2 Synthesis

Many hyperbranched polymers have been prepared by direct polymerization of an AB_2 type monomer including polyesters,[62-66] polyurethanes [67-69] and polyamides.[70]

An example of a hyperbranched compound is the polymers made by Ramakrishnan *et al.*[67] These were prepared by initially thermally decomposing 3,5-dihydroxybenzoyl azide **26**; the product isocyanate **27** then polymerizes directly to give the hyperbranched polymer **28** (**scheme 1.18**).

Scheme 1.18



26 **27** **28**

1.4 Characterization

Many methods are needed for the unequivocal characterization of dendrimers due to the various structural subtleties.

1.4.1 Molar Mass

The two most widely used techniques that can be used to measure the molar mass of a compound are gel permeation chromatography (GPC) and mass spectrometry. Unfortunately obtaining the molar mass of a dendrimer is not straightforward and neither of these methods can be relied upon to obtain accurate mass measurements.

The molecular mass of even the lowest generation of most dendrimers is still too high for most conventional mass spectrometers. This is mainly due to the low

volatility and thermal sensitivity of polymers. However, this problem has been overcome by the use of laser techniques giving rise to soft ionization processes. The use of matrix-assisted laser desorption ionization mass spectrometry (MALDI-MS)[71-72] has meant that the accurate molar mass of molecules with a mass as high as 200,000 Da can be obtained. The tendency of a large molecule to fragment is also reduced with both MALDI-MS and electrospray ionization mass spectrometry (ESI-MS).[73-75] While fragmentation is useful in the study of some polymers to determine their structure, it can give ambiguous results when only the mass of the polymer is required as in the case of monodisperse dendrimers.

Probably the most popular technique for measuring the mass of a polymer is by GPC. However, one problem with GPC is that the resolution is a great deal less than MALDI MS, resulting in less precise molecular masses. Another problem is that the mass values of a polymer are determined by comparing the elution time of the polymer with a standard calibrant. Dendrimers do not have comparable calibration standards and thus do not interact in the same fashion as the standards available. This means that GPC cannot be relied upon to give accurate information about the molar masses of dendrimers. The use of dendrimers as standards has been tried,[76] however, this is not an appropriate solution as different dendrimers have different viscosity characteristics and are thus incomparable. The difference in vicosities between dendrimers may be due to differing length and flexibility of branches.

1.4.2 Elemental Analysis

The elemental composition of dendrimers can be ascertained by C, H, N analyses and by studying spectrometric fragmentation patterns. However, these studies on their own are not conclusive as defects in the structure of a dendrimer may pass undetected by elemental analyses as they may not affect the percentage ratios of the elements contained in a dendrimer.

1.4.3 Polydispersity

The best method for obtaining the polydispersity of a dendrimer is by GPC; this technique can also be coupled with low angle light scattering (LALLS). Branch defects giving rise to varying polydispersities can be studied using HPLC fractionation. These branch defects can also be identified using high field ^{13}C NMR.[8] The major contributor to high polydispersities in dendrimers is the failure to remove propagating reagents.

1.4.4 Structures

^{1}H and ^{13}C NMR spectra can be used to clarify the structure of a dendrimer. In some cases it may be necessary to use more complicated NMR techniques such as

COSY. Electro-spray mass spectrometry and computer-assisted molecular simulations are also useful tools in structure evaluation.

1.4.5 Interior and End Groups

Functional groups can easily be identified using IR spectroscopy. Titration is a useful tool for the identification of end groups. However, the surface of a dendrimer can become very congested which may lead to inaccurate titration values due to the inaccessibility of the terminal groups. ^{15}N, ^{13}C, ^{31}P, ^{29}Si, and ^{1}H NMR are other techniques which can be utilized for end group determination.

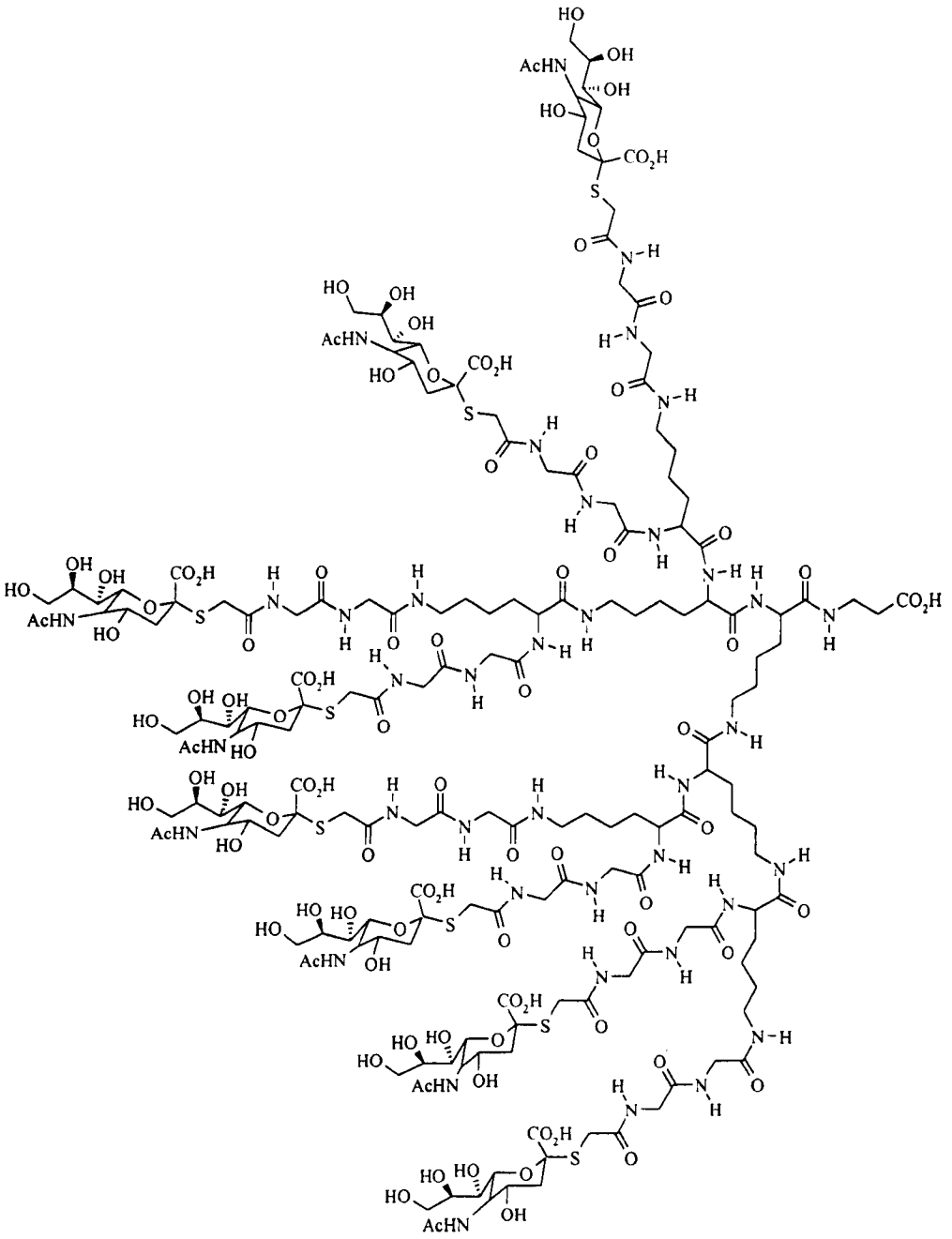
1.5 Uses and Applications

Due to the unique architecture of dendrimers there has been much interest in their properties and their potential applications. A lot of interest has been shown in using dendrimers as guest molecules following Meijer's discovery involving the encapsulation of Bengal Rose inside his dendritic boxes.[22] However, the only dendrimers which are commercially available are Tomalia's PAMAM dendrimers and Meijer's poly(propylene imine) dendrimers.

Tanaka *et al* used the PAMAM dendrimers to separate uncharged aromatic compounds under electrophoretic conditions.[77] Water-methanol mixtures were used as it was found that by changing the methanol concentration the binding of aromatic compounds was affected. An advantage of using dendrimers as carriers in electrokinetic chromatography is that, when compared with micellar systems, increased stability and selectivity were obtained.

An example of a biological use of dendrimers is their use as inhibitors of influenza A virus haemagglutinin.[78] Influenza viruses infect cells by recognizing and binding to α-sialosides which are present on the surface of a cell. It was discovered that although the virus has only a weak affinity for monomeric α-sialosides, the use of clusters of α-sialosides causes a hundred fold increase in the affinity of adhesion.[79] Using this information Roy *et al* synthesized dendrimers containing α-sialoside units (**scheme 1.19**). These dendrimers have exhibited excellent inhibitory capabilities, giving up to 10^6 times better inhibition than monomeric α-sialosides.

Scheme 1.19 α-Sialoside units Tethered to a Dendrimer



1.5.1 Surface Coatings

Surface coatings do not just serve a cosmetic role, they are actually very versatile. Many have a protective role such as coatings on metallic food containers which prevent contamination of the contents of the tin.

The majority of coatings are applied as a solution. This solution comprises of an organic linear polymer dissolved in an organic solvent. As most of the linear polymers used are of high molecular weight, it therefore follows that the polymers will have high viscosities. This in turn means that the volume of solvent required to make the coating the correct consistency/viscosity will be relatively high. After application, the coating dries and the organic solvent evaporates into the atmosphere. This is an undesirable quality of coatings as the presence of organic solvents in the atmosphere is detrimental to the environment. This has caused an interest in the development of coatings which are 'environmentally friendly'.

One way to make coatings environmentally friendly is to reduce the amount of solvents used in paints. It is thought that dendrimers and hyperbranched polymers may hold the answer to this problem. As mentioned earlier it has been noted that the viscosity of dendrimers can be much lower than their linear polymer counterparts.[6, 15, 80] Therefore, less solvent would be required to give a coating containing dendritic polymers the desired viscosity needed by a surface coating.

CHAPTER 2

Synthesis of Aliphatic Polyester Dendrimers

2.1 Synthetic Strategy

Due to the interesting viscosity properties of dendrimers it was decided to investigate their use as surface coatings. Previously work by Sahota *et al* has shown that aromatic polyester dendrimers can be synthesised relatively easily in quite high yields.[81] However, their usefulness as surface coatings is doubtful due to their glass transition temperatures (Tgs) being too high. The reason for this is that these dendrimers are too rigid. It was decided that more flexible dendrimers would probably display the type of Tgs necessary for a good surface coating. It therefore followed that the next logical step would be to try to synthesise aliphatic dendrimers. These could then be compared with the aromatic polyester dendrimers previously made by our group at Warwick.

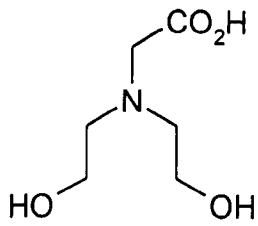
As mentioned earlier, one disadvantage of the convergent method is that as the size of the dendron increases, the focal point becomes more sterically hindered leading to problems when either increasing the generation of the dendron or when trying to tether it to an initiator core. Because small cores were to be used it was decided that the best approach would be a divergent one to eliminate problems of tethering branches to an initiator core at the end of the synthesis.

2.2 Attempted Synthesis of Benzyl Protected Bicine

Due to the success of using benzyl groups as the protecting group in the synthesis of the aromatic dendrimers it was decided that this would probably be the best strategy to use.

Bicine **29** was chosen to be the repeating monomer unit as it was readily available and cheap (**figure 2.1**).

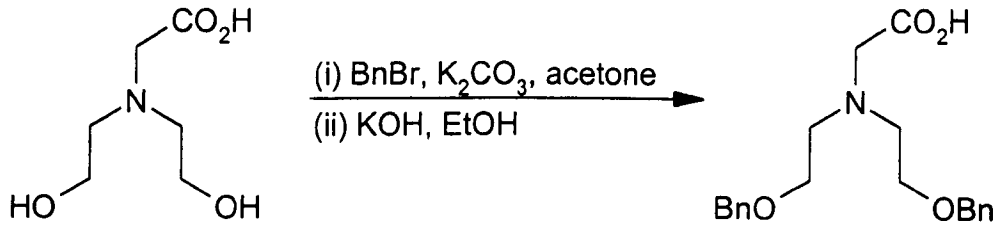
Figure 2.1 Structure 29



29

Using an adaptation of literature methods the aim was to protect the two hydroxyl groups and acid moiety with benzyl (Bn) groups and then selectively remove the protecting group from the carboxyl group to leave a free acid (**scheme 2.1**).[62, 82]

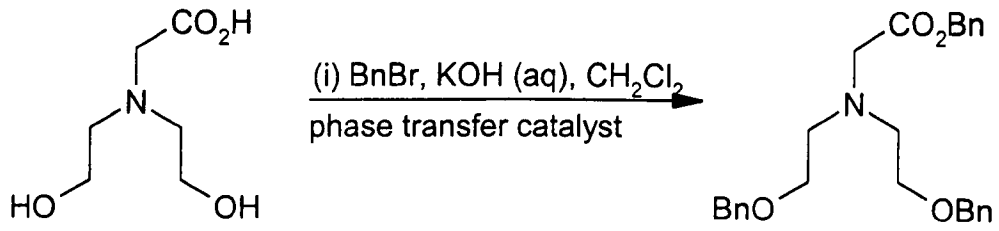
Scheme 2.1



Unfortunately the experiment was not successful, there were no benzyl peaks present in the ^{1}H NMR between 4.0 and 5.5 ppm. Instead unidentifiable products were synthesised. The lack of success was initially thought to be due to the low solubility of bicine in acetone. For this reason the experiment was repeated under the same conditions but with dimethylformamide (DMF). However, this did not change the outcome.

In case the problem of solubility was the cause for the low yields another solution was proposed. The solution was to use a phase transfer catalyst. Bicine was placed in a baffle flask with a phase transfer catalyst, benzyltriethyl ammonium chloride, a protecting group, benzyl bromide, and potassium hydroxide (**scheme 2.2**).

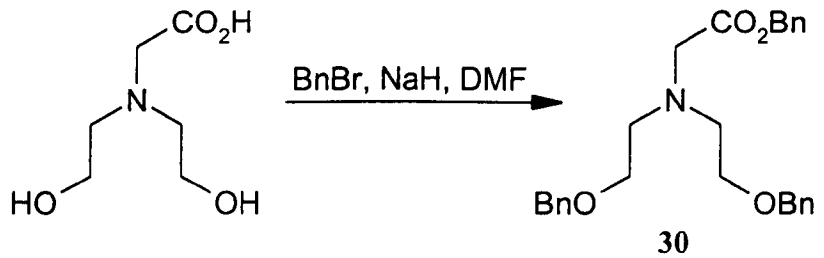
Scheme 2.2



Unfortunately at the end of the experiment the only compounds present by ^{1}H NMR were the unreacted starting materials benzyl bromide and bicine.

The next approach used was to change the base used in the deprotection step. We reasoned that a stronger base might be helpful. Sodium hydride was selected and the protection of bicine was attempted on a 1 g scale using an adaptation of the literature method (**scheme 2.3**).[83]

Scheme 2.3



30

This reaction had limited success. The bicine was successfully protected but only in a 15% yield. Compound **30** was characterised by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry.

The reaction conditions were varied with the aim of improving the yield but this approach did not prove successful. Therefore we decided to scale the reaction up so that enough of **30** could be synthesised so that the next step, deprotection of the acid moiety, could be attempted. This plan was thwarted by the fact that as the reaction was scaled up, the yield of **30** decreased (**table 2.1**).

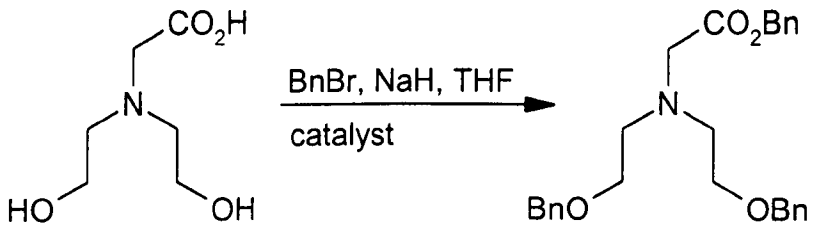
Table 2.1 Effect of Changing Scale of Experiment on Yield of 30

Mass of bicine	Mol of bicine	Yield of **30**
1 g	6.1 mmol	15%
2 g	12.3 mmol	1.25%
5 g	30.7 mmol	0%

The optimum conditions for the reaction were found to be when the base and benzyl bromide were added at the same time and the reaction was refluxed for several days. These conditions afforded a maximum yield of 15%.

To try to improve the yield it was decided to use a catalyst which was mentioned in the literature (**scheme 2.4**).[84] The catalyst, tetrabutylammonium iodide, was shown to have no influence on the reaction as it produced similar yields when compared with experiments carried out without the catalyst.

Scheme 2.4



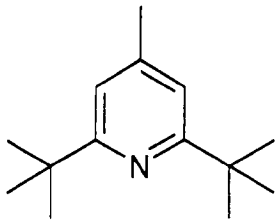
A variety of other bases were used instead of sodium hydride, such as lithium hydroxide, potassium hydroxide and silver oxide; however, these were all to no avail.

2.2.1 Failed Protection of Bicine

It was initially postulated that the failed protection was due to the effect of the metallic base on bicine. It was proposed that the metal was able to co-ordinate to the monomer and thus make it very difficult for any groups to react further.

One way to test this theory was to use an organic hindered base instead of sodium hydride. The reason for this was that there would be no chance of co-ordination on **29** once it had been deprotonated, increasing the probability of **29** being successfully protected. The choice of base used was 2,6-di-tert-butyl-4-methylpyridine, **31** (**figure 2.2**).

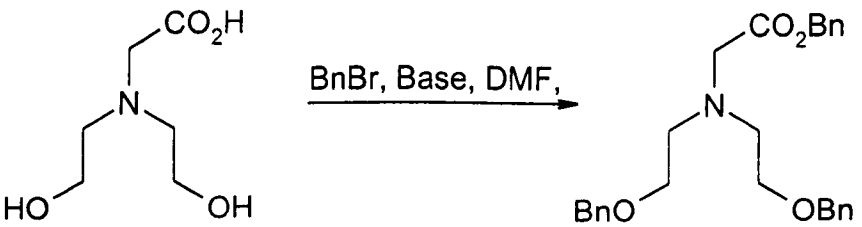
Figure 2.2



31

The experiment was carried out with 5 equivalents of base and the reactants were left refluxing overnight (**scheme 2.5**)

Scheme 2.5



The crude mixture was analysed by ^{1}H NMR. Unfortunately no singlets were present between 4.5-5.5 ppm, indicating that the reaction had not been successful. This may mean that our previous hypothesis was incorrect. However, no other explanation can be offered.

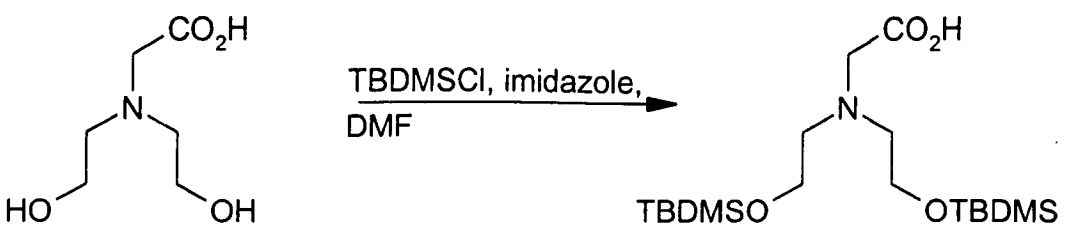
2.3 Synthesis of Silyl Protected Bicine

After exhausting many possibilities it was decided that the use of a different protecting group should be attempted.

It was decided that a silyl protecting group should be used as it could fulfil the criteria that were required, that is to protect the two hydroxyl groups and acid moiety and then selectively remove the protecting group on the carboxyl group to leave a free acid. Trimethylsilyl (TMS) was an obvious choice; however, this group was unsuitable since acid conditions are required for the esterification step which would undoubtedly cause all the protecting groups to be removed. We thus selected *tert*butyldimethyl silyl (TBDMS). This protecting group is much more stable to acidic conditions.

Using an adaptation of a literature procedure, the protection of bicine was attempted (**scheme 2.6**).[85]

Scheme 2.6



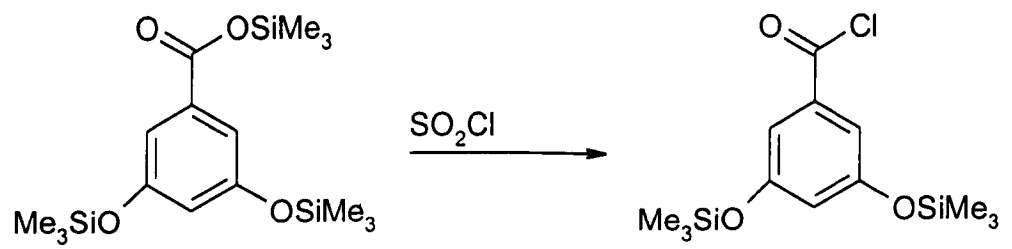
32

From the ^{1}H NMR spectrum of the crude product it could be ascertained that the reaction had been successful. Peaks were present at 0.03 and 0.85 ppm. It was found that the reaction had gone better than expected as no peaks were present for the silyl ester group. This meant that there was no need for a deprotection step.

Unfortunately things then took a turn for the worse since it became apparent that **32** was not stable to storage and purification. It was postulated that the reason for this was that the diprotected bicine, **32**, was reacting with itself. This in turn meant that **32** could be used as a monomer in the synthesis of hyperbranched polymers.

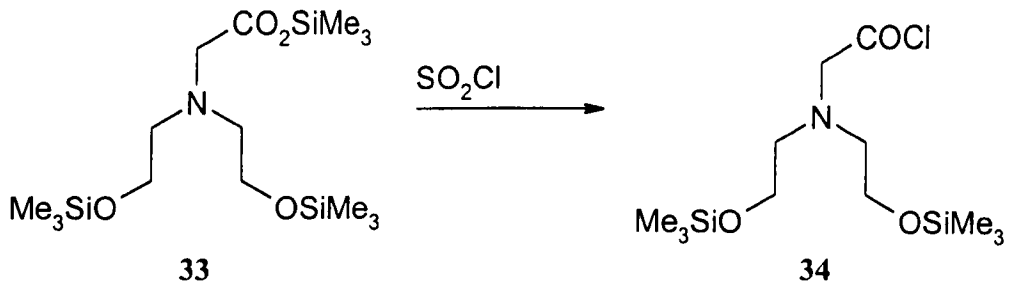
Frechet's work involved the conversion of a silyl ester into an acid chloride in order to prepare a monomer that could be used in the preparation of hyperbranched compounds (**scheme 2.7**).[62]

Scheme 2.7



It was decided that the bicine derivative **34** would be prepared from the corresponding trimethylsilyl ester **33** using an analogy with Frechet's work (**scheme 2.8**).

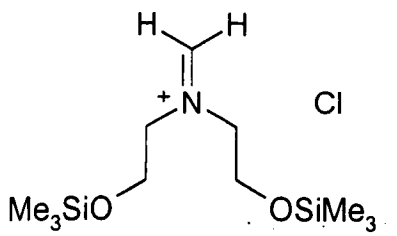
Scheme 2.8



33 **34**

However, when the reaction was carried out ^{1}H and ^{13}C NMR data confirmed that the iminium salt **35** had been formed in a quantitative yield (**figure 2.3**).

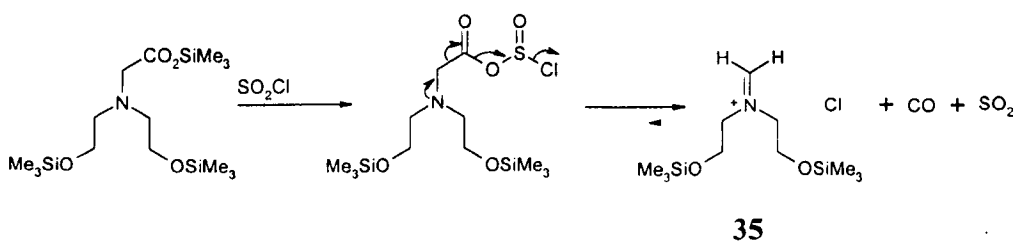
Figure 2.3 Structure of 35



35

A mechanism for the formation of **35** is shown in **scheme 2.9**.

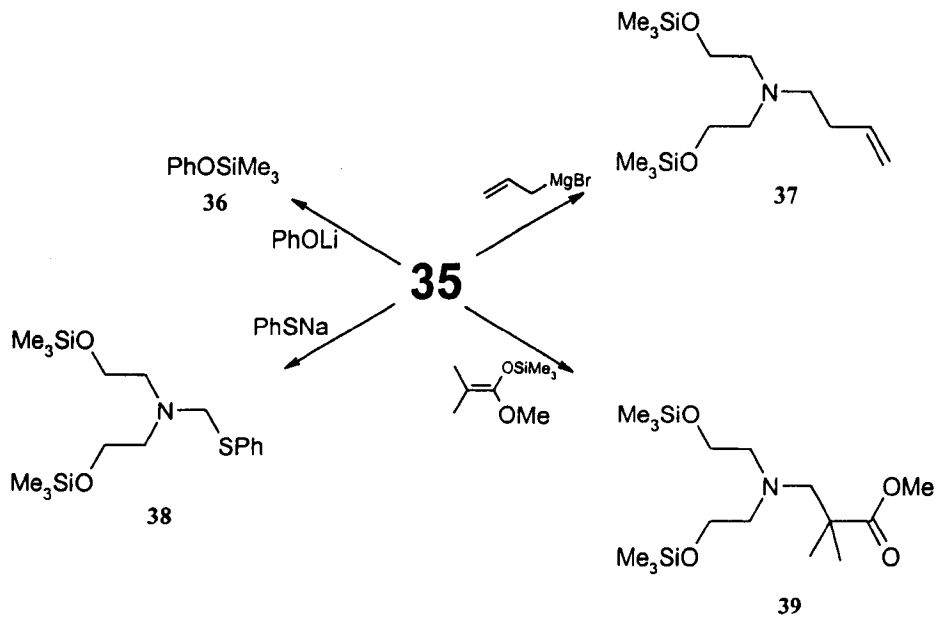
Scheme 2.9



35

The reactivity of **35** was investigated using a variety of reagents (**scheme 2.10**). The products were characterised by ^{1}H and ^{13}C NMR alone.

Scheme 2.10



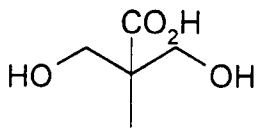
It was found that **35** had a preference for soft nucleophiles. For example, when **35** was reacted with PhSNa the desired product was obtained, but, desilylation occurred when reacted with PhOLi. Salt **35** was also reacted with both allyl magnesium bromide and with a silyl ketene acetal to investigate the ability of **35** to undergo carbon-carbon bond formation. Product **39** is a homologous bicine monomer.

Iminium salts are used in Mannich-type reactions in which they are superior to imines which lead to troublesome by-products.[86-88] To our knowledge, **35** is the first example of a stable branched iminium salt which thus has potential in dendrimer synthesis.

2.4 The Use of 2,2-Bishydroxymethylpropionic acid As A Branch Unit

Encouraged by the near success of the silyl bicine approach it was decided to build a dendrimer using another aliphatic monomer; 2,2-bishydroxymethylpropionic acid, **40**, (**figure 2.4**) was chosen as it was readily available and cheap.

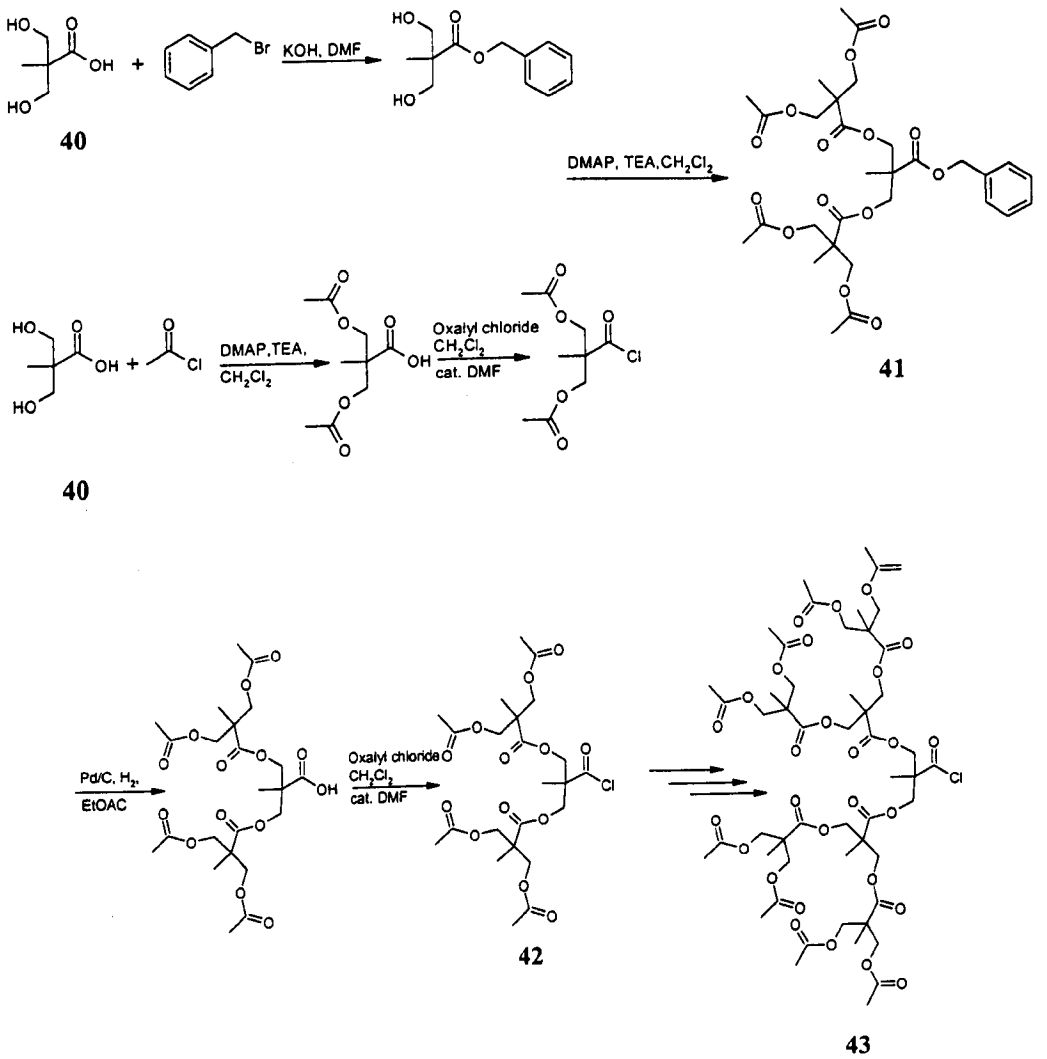
Figure 2.4 Structure of 36



40

Work has already been carried out by Hult *et al* using **40**.[89] However Hult prepared his dendritic aliphatic polyesters using the convergent approach (**scheme 2.11**). The drawback with the Hult approach is that the acetate groups used to protect the terminal alcohols cannot readily be removed to yield deprotected dendrimer. Our aim was to prepare polyester dendrimers using the divergent approach.

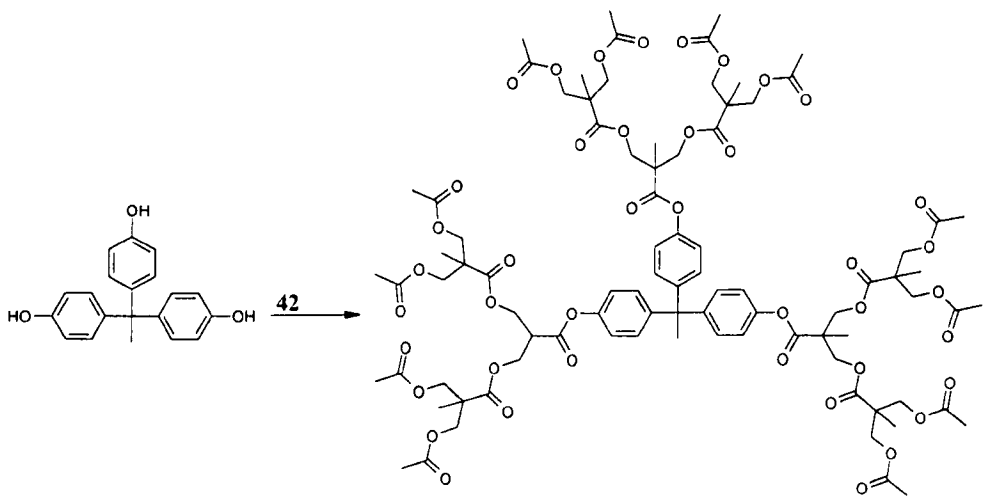
Scheme 2.11



40 **41** **40** **42** **43**

In Hult's work compound **40** was used as the branch molecule. Initially the carboxylic acid group was protected using benzyl bromide. The hydroxyl groups on **40** were protected by conversion into the corresponding acetate esters. This was achieved by reacting **40** with acetyl chloride, triethylamine (TEA) and 4-(dimethylamino)pyridine (DMAP). This compound was then converted to the corresponding acid chloride using an excess of oxalyl chloride with a catalytic amount of DMF. These steps were repeated with to give **41**. The protecting benzyl group was then removed by carrying out hydrogenolysis at atmospheric pressure using Pd/C (10%) as catalyst. This compound was then converted to the acid chloride **42** by using oxalyl chloride. The dendron was then built up by repetition of steps to give **42**. Either compound **42** or **43** could then be tethered to the core molecule to give a dendrimer, for example **42** tethered to the core produces a generation two dendrimer (**scheme 2.12**).

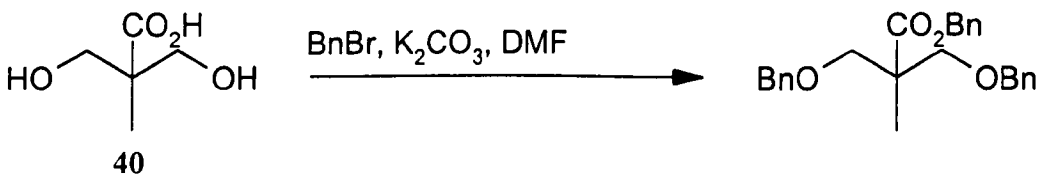
Scheme 2.12



2.5 Attempted Synthesis of Benzyl Protected 2,2-bis(hydroxymethyl)propionic acid

The first protection attempted involved trying to protect **40** using benzyl groups as was initially attempted with bicine (**scheme 2.13**).[62]

Scheme 2.13

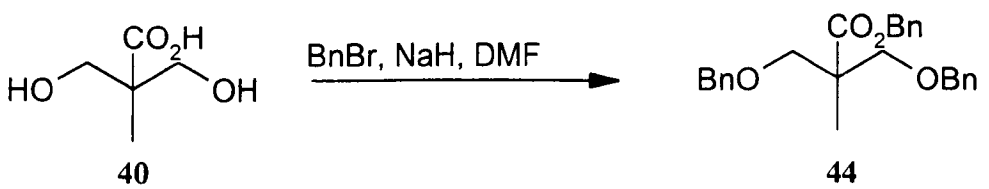


40

To confirm our fears the ^1H NMR spectrum of the product showed no benzyl peaks between 4.0 and 5.5 ppm.

Again a stronger base, sodium hydride, was used to see, if as with bicine, it would give any success (**scheme 2.14**).[83]

Scheme 2.14



40 **44**

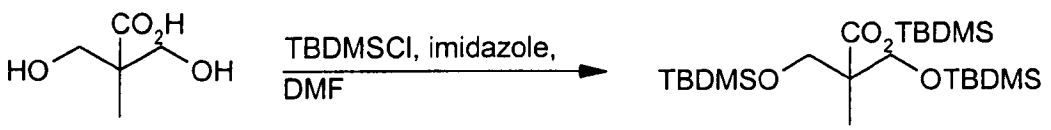
The reaction was carried out on a 0.5 g scale and left for five days. After work up, a ^1H NMR spectrum was run of the product yellow oil which showed that the reaction had been successful. However, the isolated yield was only 5%, rendering this approach futile.

2.6 Synthesis of Silyl Protected 2,2-bis(hydroxymethyl)propionic acid

As mentioned previously it was decided that the most appropriate silyl protecting group was TBDMS. It is stable to acidic conditions, but at the same time should be quite easily removed from both alcohol and carboxylic acid groups.

Compound **40** was reacted with 10 equivalents of imidazole and 5 equivalents of TBDMSCl to give **45** with a yield of 86 % (**scheme 2.15**).[85]

Scheme 2.15

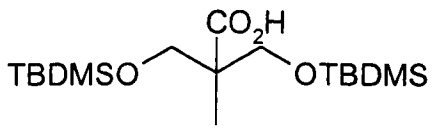


40 **45**

Now that **45** had been successfully protected, all that was needed to obtain our target monomer was to remove the protecting group on the carboxylic acid.

During purification of **45** on silica it was noticed that if left too long the product would begin to decompose to give **46** our target monomer (**figure 2.5**).

Figure 2.5 Structure of Target Monomer 46

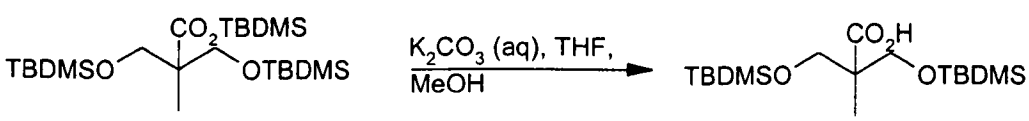


46

This meant that a natural starting point for the removal of the protecting group would be to leave **46** stirring over silica. This was done overnight and the product was analysed by ^{1}H NMR. Unfortunately the spectrum was identical to the starting material, meaning that no deprotection had taken place.

Using an adaptation from the literature another attempt was made to prepare our target monomer.[85] This time a base, potassium carbonate, was used to initiate the hydrolysis (**scheme 2.16**).

Scheme 2.16



45 **46**

The crude product was analysed by ^{1}H NMR. From the spectrum it was noticed that there were an absence of peaks at 0.92 ppm and 0.24 ppm which correlated to the hydrogens on the silyl ester. This confirmed that **46** had been successfully prepared in a yield of 68%.

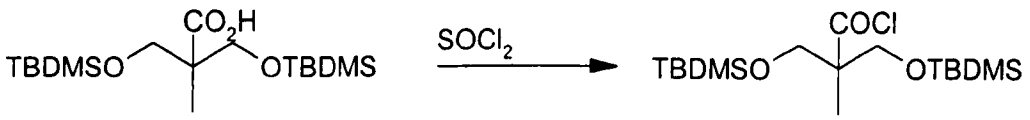
2.7 Synthesis of the Acid Chloride Derivative

Once the protected monomer, **46**, had been synthesised, there were two routes available. Compound **46** could be reacted with a core directly to give a generation one protected dendrimer. However, an alternative route was that the carboxylic acid could be converted into an acid chloride which could then be attached to a suitable core. By using both routes the best route could be realised and used in the overall synthesis of the dendrimers.

To be able to compare both methods for the preparation of aliphatic polyester dendrimers, the acid chloride derivative of **46** had to be synthesised.

Our initial attempt to convert the carboxylic acid to an acid chloride involved using an excess of thionyl chloride (**scheme 2.17**).

Scheme 2.17

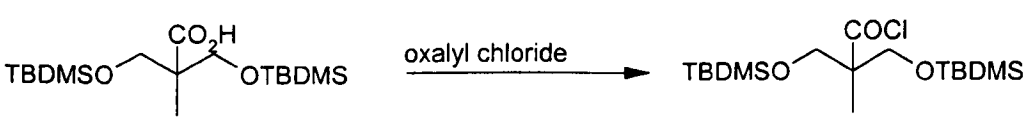


Unfortunately the approach proved unsuccessful. After an hour of refluxing the ^{13}C NMR spectrum showed the presence of both acid and acid chloride. However, the ^{1}H NMR spectrum showed a number of peaks between 0.0 ppm and 1.0 ppm, suggesting a certain amount of deprotection of silyl protecting groups.

This evidence meant that thionyl chloride may give us an acid chloride derivative but would have a detrimental effect on the protecting groups. One solution was to use a milder reagent which would give the acid chloride without adversely affecting the protecting groups. Thus oxalyl chloride was selected.

An excess of oxalyl chloride was refluxed with **46** for 1 hour (**scheme 2.18**). If the reaction was left for longer then deprotection would occur.

Scheme 2.18



46 **47**

After one hour the excess oxalyl chloride was removed to give a clear oil. On analysis of the oil, by ^{13}C NMR, it was shown the acid chloride, **47**, had been successfully prepared in a quantitative yield.

2.8 Nomenclature

The dendrimers in this thesis are given a name using a code very similar to one utilised by Frechet. This code comprises of four parts: -

1. The first part correlates to the generation number of the dendrimer: G_1 refers to generation one.

2. The second part describes the branch unit: Aro for the aromatic branch unit, Ali for the aliphatic one.

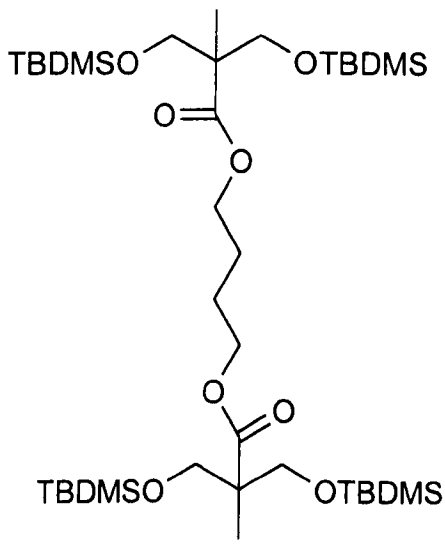
3. The third part refers to the core itself: B for 1,4-butanediol and H for hydroquinone.

4. The fourth part relates to the total number of functional groups at the end of the branch units: four groups would be represented by [4].

5. The fifth and final part refers to the type of functional group at the branch termini: OH for deprotected dendrimers and OBn or OTBDMS for protected ones.

An example of naming a dendrimer using this nomenclature is G_1Ali-B-[4]-OTBDMS which refers to a generation one dendrimer with aliphatic branch units, 1.4-butanediol as the core and silyl terminating groups (**figure 2.6**).

Figure 2.6 Structure of G_1Ali-B-[4]-OTBDMS

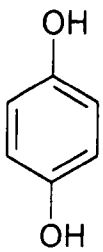


2.9 Synthesis of Aliphatic Branched Dendrimers

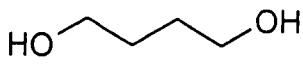
2.9.1 Choice of Cores

Two initiator cores were chosen, both being bi-functional. It was thought that if tri-functional or more were used this could cause steric problems with the latter generations. The cores used were hydroquinone **48** and 1,4-butanediol **49** (**figure 2. 7**).

Figure 2. 7 Structures 48 and 49



48



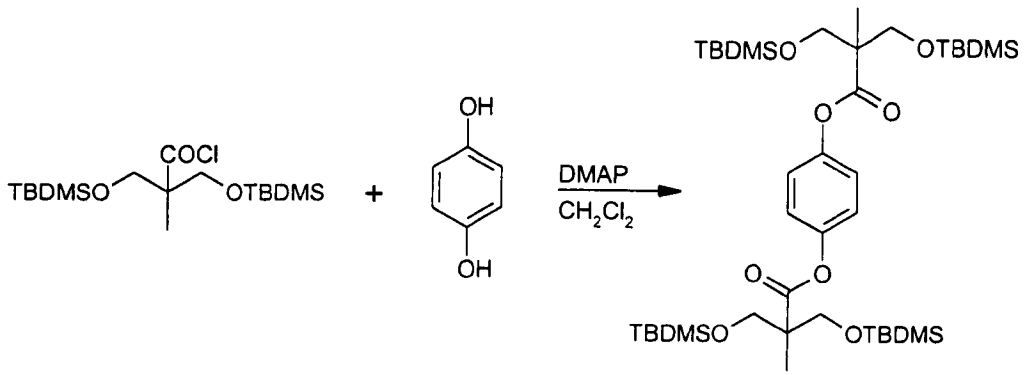
49

These cores were chosen to see if different types of core, aliphatic or aromatic, would affect the physical properties of the dendrimers.

2.9.2 Hydroquinone Core Based Dendrimers

Initially G_1Ali-H-[4]- OTBDMS was prepared using the acid chloride monomer **47**. An excess of **47** was reacted with **48** in the presence of the base DMAP. The reactants were stirred in anhydrous dichloromethane at room temperature (**scheme 2.19**). The reaction was monitored by GPC.

Scheme 2.19

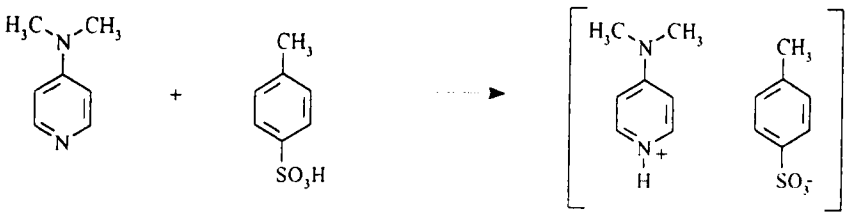


47 **48** **50**

The generation one dendrimer **50** was prepared in a 92% yield. The dendrimer was characterised using ^{1}H NMR, ^{13}C NMR, GPC, elemental analysis and MALDI-MS. The low polydispersity value, 1.006, proved that the dendrimer was monodisperse. The molecular weight of the dendrimer, obtained using MALDI-MS, corresponded with the value that had been calculated for $M+Na^{+}$ with the experimental value of *m/z* being 822 and the calculated value being 822.

An attempt was then made to prepare **50** using the original protected monomer **46**. An excess of **46** was reacted with **48** in the presence of the esterification agent 1,3-dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridinium *p*-toluenesulfonate (DPTS) acting as a catalyst.[90] DPTS, **51**, is a salt and is prepared from DMAP, **52**, and *p*-toluenesulfonic acid (*p*-TSA) **53** (**scheme 2.20**).[91]

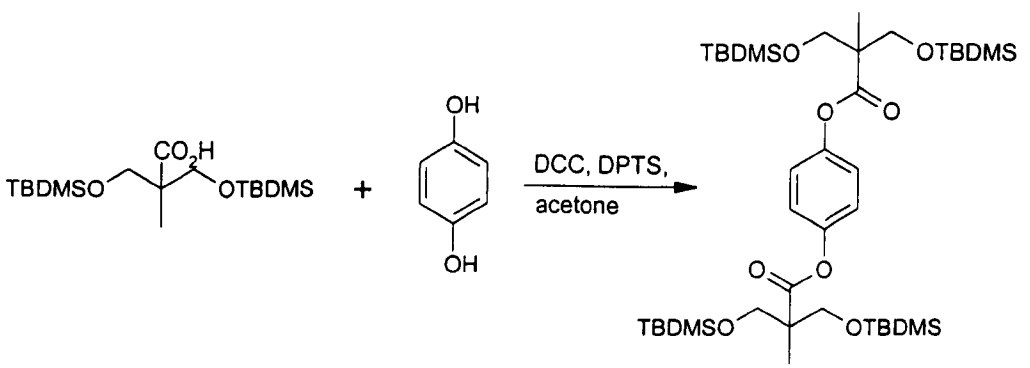
Scheme 2.20



52 **53** **51**

DPTS, DCC, **48** and **46** were stirred in anhydrous acetone under nitrogen for 4 days (**scheme 2.21**).

Scheme 2.21



46 **48** **50**

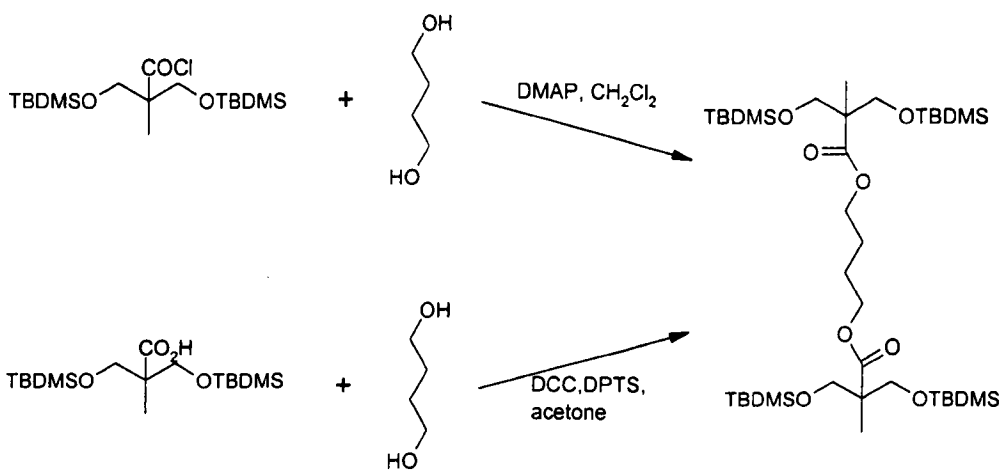
As in the previous approach **50** was successfully prepared, however, this time with a decrease in yield from 92% to 68%. Again the generation one dendrimer **50** had a low polydispersity value indicating that the product was monodisperse.

2.9.3 1,4-Butanediol Core Based Dendrimer

By using an aliphatic core such as **49** it was possible to synthesise a wholly aliphatic dendrimer.

The two approaches used previously with hydroquinone, **48**, were used again (**scheme 2.22**).

Scheme 2.22



54

Both methods were successful. With the free acid a yield of 80% was obtained. Alternatively with the acid chloride derivative a better yield of 91% was achieved. Analysis confirmed that G_1Ali-B-[4]-OTBDMS, **54**, had been prepared. GPC showed that the product was monodisperse (M_n 1059, PDi 1.013). The experimental value, 802 (m/z calculated for [M+Na+]), from MALDI-MS correlated exactly with the calculated value of 802.

2.9.4 Attempted Deprotection of Generation One Protected Dendrimers

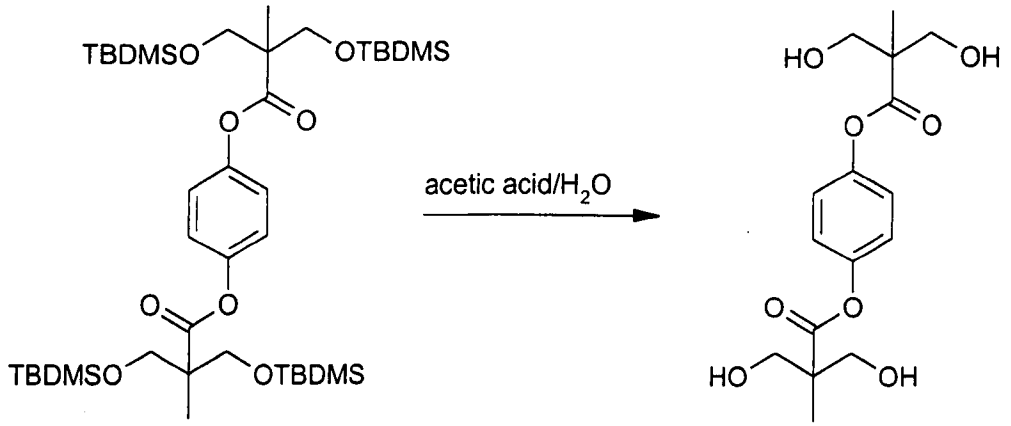
To prepare the next generation of dendrimers, generation two, it was necessary to deprotect dendrimers **50** and **54**. As there are many methods of removing TBDMS groups in the literature, this step was not expected to be problematic.

The most popular method in the literature is one involving tetra-n-butylammonium fluoride (TBAF).[92] The protected generation one dendrimer was stirred with TBAF, 1.8 equiv. per protecting group, overnight. This procedure was attempted with both generation one dendrimers **50** and **54**. Unfortunately the procedure was unsuccessful for both of these dendrimers.

In both cases the results were exactly the same. After work up a black oil was obtained. When these oils were analysed by ^{1}H and ^{13}C NMR they showed unidentifiable peaks. MALDI-MS was also inconclusive as many peaks were obtained but no peaks were present at the desired values of either 822 or 802, which corresponded to the *m/z* value of $[M+Na^{+}]$ for G_1Ali-H-[4]-OH and G_1Ali-B-[4]-OH respectively.

The next approach used to remove the silyl protecting groups involved the use of aqueous acetic acid. The reaction involved adding **50** to an acetic acid/water mixture (1:4) (**scheme 2.23**).[93]

Scheme 2.23



50

After being refluxed for 3 hours the solution went clear. This was a hopeful sign as this now meant that the dendrimer, which had originally been insoluble in water, was now soluble which hinted that perhaps the silyl groups had been removed to leave free hydroxyl groups. However, on inspection of ^{1}H and ^{13}C NMR spectra of the product yellow oil it was discovered that as well as unidentifiable by-products there was still a high proportion of starting material.

Due to the results obtained, the experiment was repeated again but with a higher proportion of acetic acid (acetic acid: water, 8:2). However, again this method proved futile.

Using an adaptation of a literature procedure it was decided to use hydrofluoric acid to try and remove the protecting groups.[94] Again one of our protected dendrimers was stirred in a solution of 5% aqueous hydrofluoric acid and 95%

acetonitrile. After the solution had been stirred for 4 hours at room temperature the crude oil was analysed by ^{1}H NMR. The results from this showed that only starting materials were present, hence the reaction had not worked.

2.10 Conclusion

It soon became clear that only limited success could be obtained when the aliphatic monomers **29** and **36** were protected with any protecting group that required a metallic base to deprotonate the target groups, for example, benzyl groups could not be used as they require a base such as potassium carbonate or sodium hydride for deprotonation.

It was postulated that this phenomenon was due to co-ordination of the monomer to the metal, making it very difficult for any groups to participate in protection. However, it was not possible to prove this hypothesis and no explanation can currently be given for this phenomenon.

Monomers **29** and **36** can, however, be successfully protected with silyl protecting groups as they are used in conjunction with an organic base such as imidazole. Problems occur on storage.

Bicine can be readily converted to a branched iminium salt which displays useful reactivity and may which have applications in dendrimer synthesis

Compound **45** can be successfully deprotected to give **46** which was one of the initial target monomers. Compound **46** could also easily be converted to the acid chloride derivative, **47**.

50 and **54** were successfully synthesised. However, the method involving **47** and DMAP proved much more successful than reacting **46** and a core in the presence of DCC and DPTS. We currently have no explanation for this phenomenon.

Deprotection of the silyl ethers proved a major problem. Many reagents were tried but none were successful.

CHAPTER 3

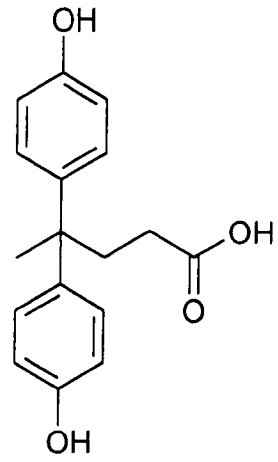
Synthesis of Dendrimers

3.1 Synthetic Strategy

The original idea was to incorporate more flexible units into the dendrimers which would lower the Tgs. However, the protecting group strategies were unsuccessful with the aliphatic monomers. Therefore it was decided that a monomer would be used that had some but not too much flexibility.

Bearing these criteria in mind it was decided that the starting material for our monomer would be 4,4-bis(4-hydroxyphenyl)valeric acid, **55** (**figure 3.1**). Once the protected monomer had been prepared, it could then be used to build dendrimers using a divergent strategy.

Figure 3.1 Structure 55



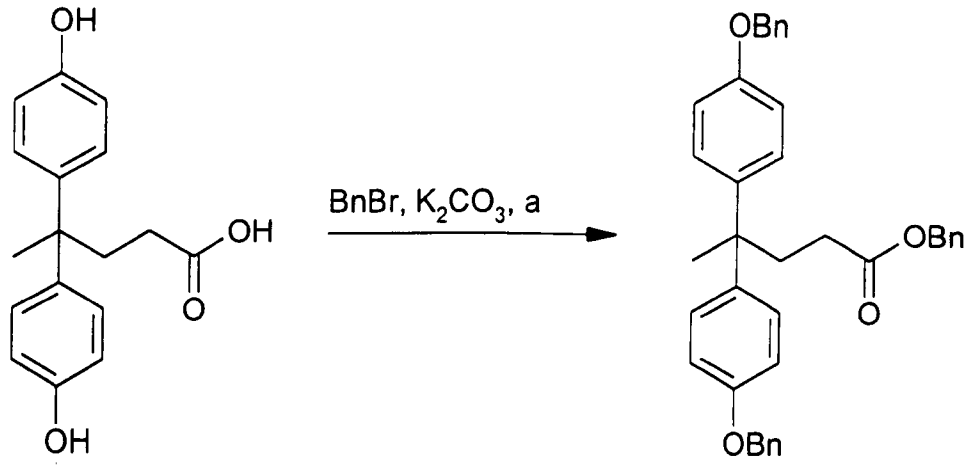
55

The cores **48** and **49**, used in the previous chapter, were again the choice of cores with our new monomer. These were used for exactly the same reasons, to see if the nature of the core, aliphatic or aromatic, would have an effect on the physical properties of the final dendrimers.

3.2 Synthesis of Benzyl Protected Monomer

Due to the presence of rigid components it was thought that it would be much more likely that benzyl groups could be used to protect **55**. The aim was to protect the two hydroxyl groups and carboxylic acid with benzyl groups to give **56 (scheme 3.1)**.[62]

Scheme 3.1



55 **56**

a = acetone or methyl ethyl ketone

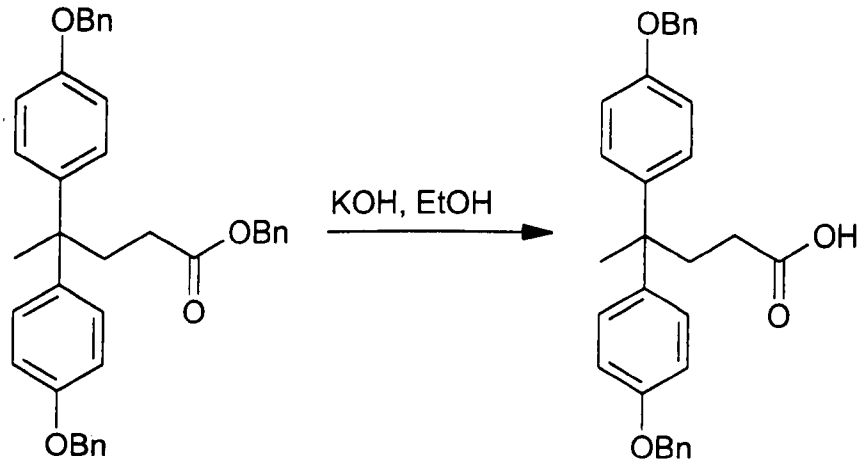
Originally the reaction was carried out in acetone and left overnight. The crude mixture was then analysed by ^{1}H NMR; the spectrum obtained showed clearly that the reaction had been successful. However, when **56** was isolated it was quite disappointing as the yield obtained was quite low, 46%. The reaction was repeated but no increase in yield was obtained.

To improve the yield it was decided that changing the solvent might hold the answer. Methyl ethyl ketone was used instead of acetone as it has a higher boiling point. This would mean that higher temperatures could be reached which would in turn increase the rate of reaction leading to an increase in yield.

When **scheme 3.1** was repeated with methylethyl ketone there was an improvement in yield from 46% to 85%.

Now that **56** had been successfully been synthesised all that was needed was to remove the benzyl ester. The hydrolysis of the ester linkage was achieved by using potassium hydroxide and refluxing the mixture overnight (**scheme 3.2**).[82] Compound **57** was isolated in 90% yield by precipitation with dichloromethane.

Scheme 3.2

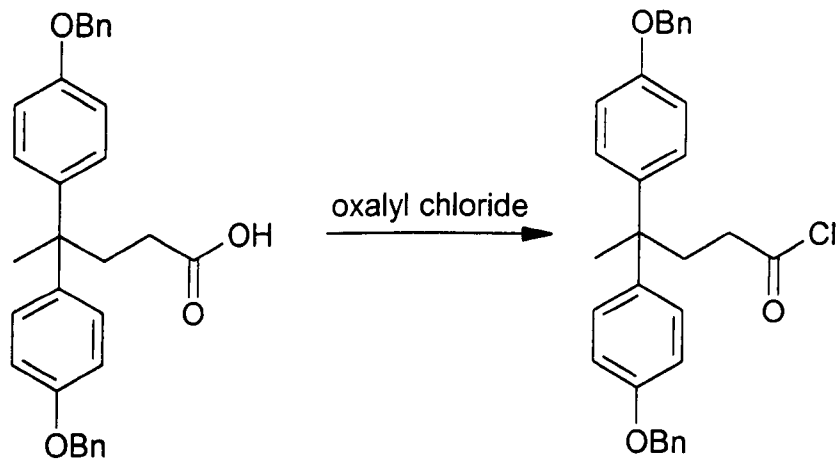


56 **57**

As with **46** there were now two different routes that could be followed. The acid chloride derivative could be synthesised and coupled with a core to give a generation one dendrimer or alternatively the monomer **57** could be coupled, without any modification, to a core to give a first generation dendrimer.

Initially the first route was attempted. Compound **57** was refluxed for an hour in an excess of oxalyl chloride to give **58** in a quantitative yield (**scheme 3.3**).

Scheme 3.3



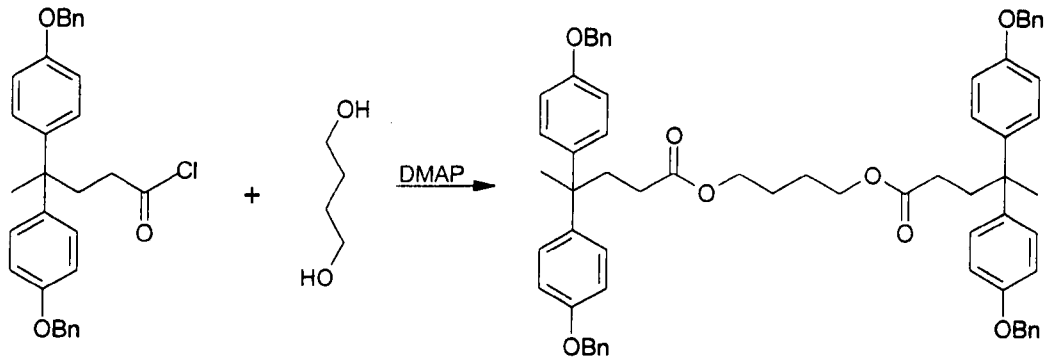
57 58

3.3 Synthesis of Dendrimers Using Branch Units based on 4,4-Bis(4-hydroxyphenyl)valeric acid

3.3.1 Synthesis of Generation One Dendrimers

Using the same method as described previously generation one dendrimer G_1Aro-B-[4]-OBn, **59**, was synthesised. This was achieved by reacting an excess of **58** with **49** in the presence of DMAP (**scheme 3.4**).

Scheme 3.4

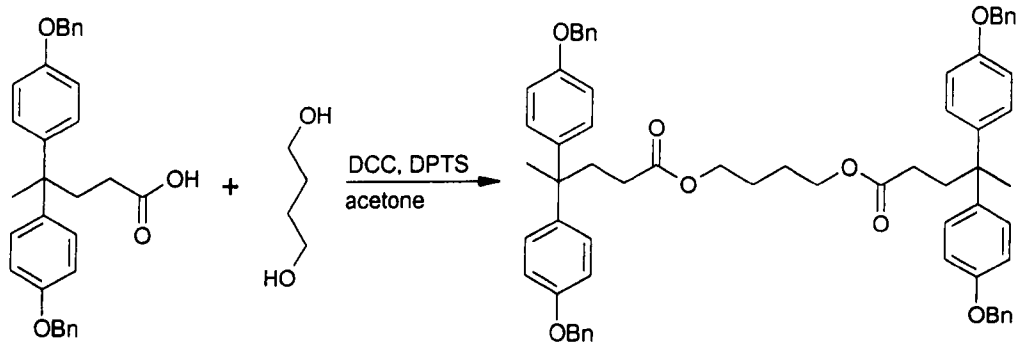


59

The reaction was monitored by GPC. The DMAP was precipitated using diethyl ether to give white crystals. The clear filtrate was then reduced to give white crystals that were purified using column chromatography, to give a yield of 86%. The pure white crystals were analysed by MALDI-MS. The molecular weight obtained corresponded with the calculated value ([M+Na^+] at *m/z* 1010 – calculated 1010). Analysis by GPC showed that the dendrimer was monodisperse (M_n 1212, PDi 1.014).

Compound **59** was also prepared using the alternative method. Again an excess of **57** was reacted with **49** but this time in the presence of the esterification agents DCC and DPTS (**scheme 3.5**).[90]

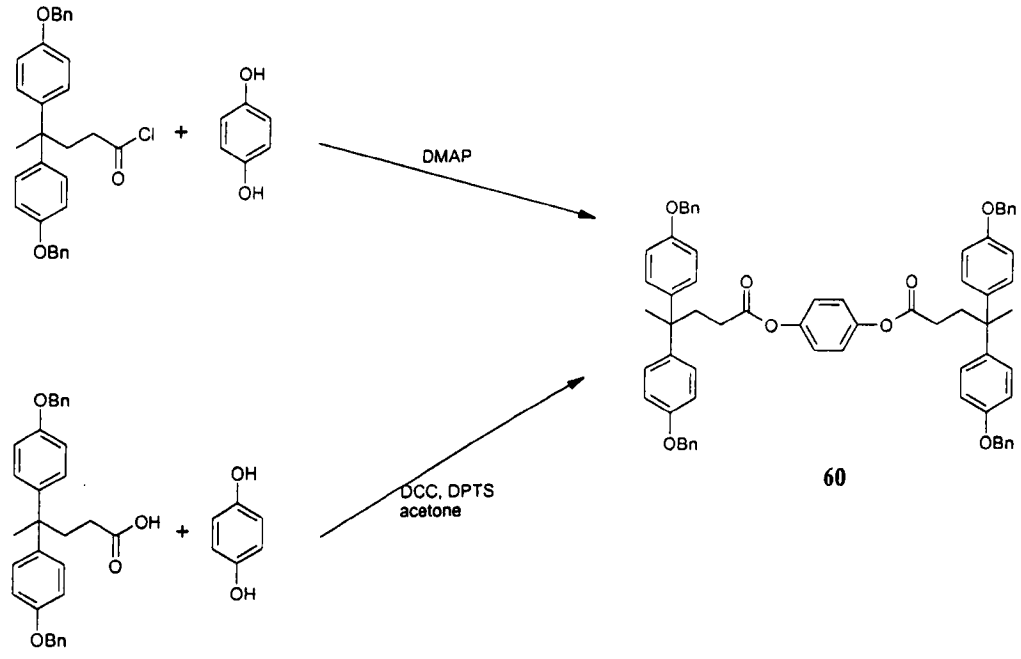
Scheme 3.5



59

Again analysis by GPC and MALDI-MS confirmed that **59** had been made successfully using this alternative approach. However, the yield obtained, 61%, was much lower than the previous method. Both of these approaches were then repeated with the aromatic core, **48** (**scheme 3.6**).

Scheme 3.6



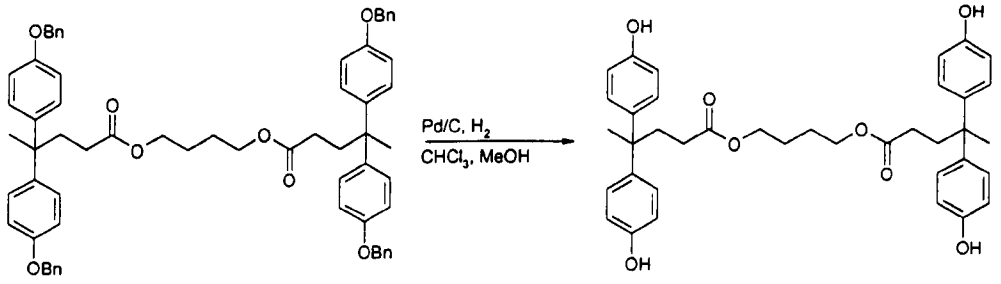
Both reactions were monitored by GPC to check the polydispersity of the reaction mixtures.

The method involving the esterification agent DCC and DPTS was the least successful again. Although GPC showed that **60** was monodisperse, (M_n 1329, PDi 1.030), and MALDI-MS confirmed that the desired product had been obtained, the yield of 59% was disappointing. However, once again the method involving DMAP proved to be the most successful as the dendrimer was made in a yield of 91%.

Hydrogenation was the method used to remove the benzyl protecting groups.[95] This process was catalysed by using 10% palladium on carbon. The hydrogen

pressure was between 25-45 psi. Compound **59** was hydrogenated for 2 days with the reaction being monitored by TLC and GPC (**scheme 3.7**). G_1Aro-B-[4]-OH, **61**, was produced as a white crystalline solid in a yield of 89%. The ^{1}H NMR spectrum confirmed that the compound had been successfully hydrogenated as it clearly showed the absence of any CH_2 benzyl signals at 5.09 ppm. MALDI-MS also confirmed that the dendrimer synthesis had been successful as the molecular weight obtained corresponded with the calculated value ([M+Na$^+$] at *m/z* 649 – calculated 650). GPC measurements showed that the product was monodisperse (M_n 1329, PDi 1.030).

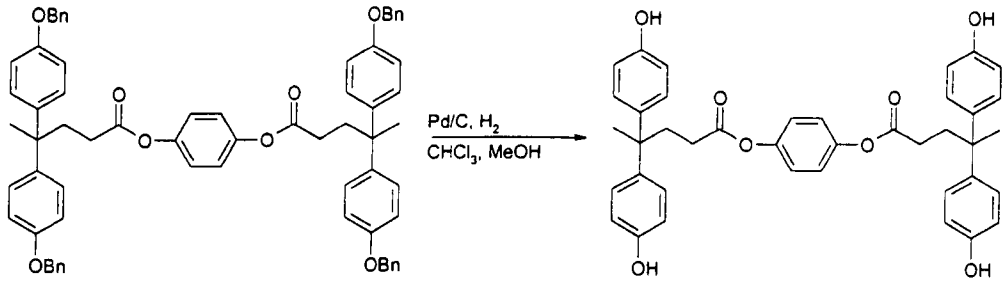
Scheme 3.7



59 **61**

The reaction was then repeated for **60** with a similar amount of success. G_1Aro-H-[4]-OH, **62**, was produced in a yield of 92% (**scheme 3.8**). The pure white crystals were analysed by MALDI-MS. The molecular weight obtained corresponded with the calculated value ([M+Na$^+$] at *m/z* 670 – calculated 670). Analysis by GPC showed that the dendrimer was monodisperse (M_n 1044, PDi 1.080).

Scheme 3.8



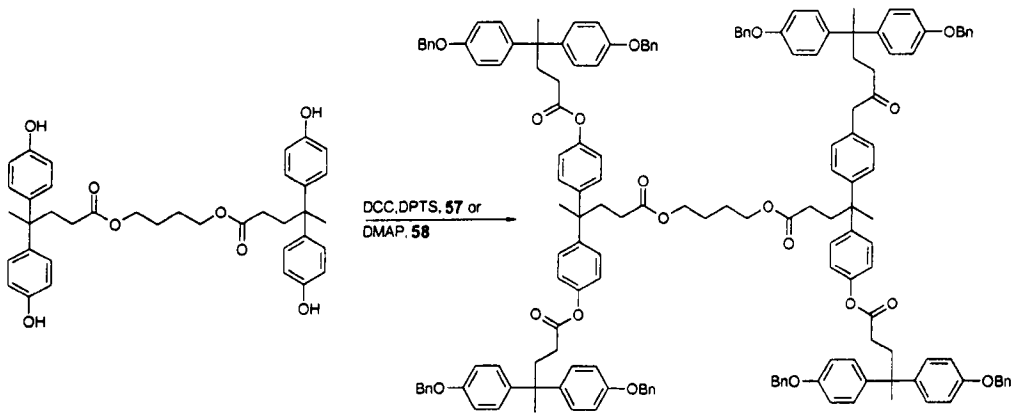
60 **62**

Due to the benzyl groups being removed during hydrogenolysis, the dendrimer became increasingly less soluble in chloroform due to the change in polarity of the molecule. To combat this a polar solvent, methanol, was added to the reaction vessel during the reaction.

3.3.2 Synthesis of Generation Two Dendrimers

G_1Aro-B-[4]-OH was separately reacted with **57** and **58** to make G_2Aro-B-[8]-OBn, **63** (**scheme 3.9**). This time it was noted that the most successful method was the one involving DCC and DPTS. GPC analysis confirmed that our product was monodisperse as the polydispersity value obtained was 1.006. MALDI-MS also confirmed that the reactions were successful as the *m/z* value calculated for [M+Na+] was 2444 and the one obtained was 2444.

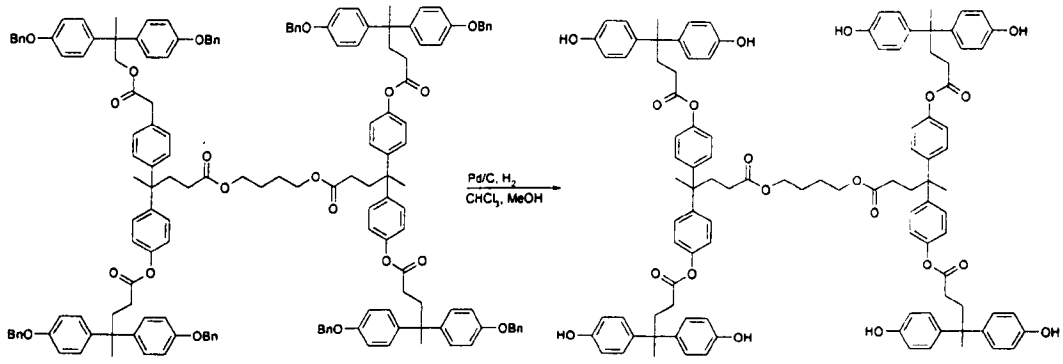
Scheme 3.9



63

Using catalytic hydrogenation G_2Aro-B-[8]-OBn was converted to G_2Aro-B-[8]-OH, **64**, in a yield of 83% (**scheme 3.10**). Analysis by GPC confirmed that a single species was present (M_n 2276 and PDi 1.008). The molecular weight of the product, using MALDI-MS, gave good agreement with the calculated value ([M+Na+] at *m/z* 1723 – calculated 1724).

Scheme 3.10



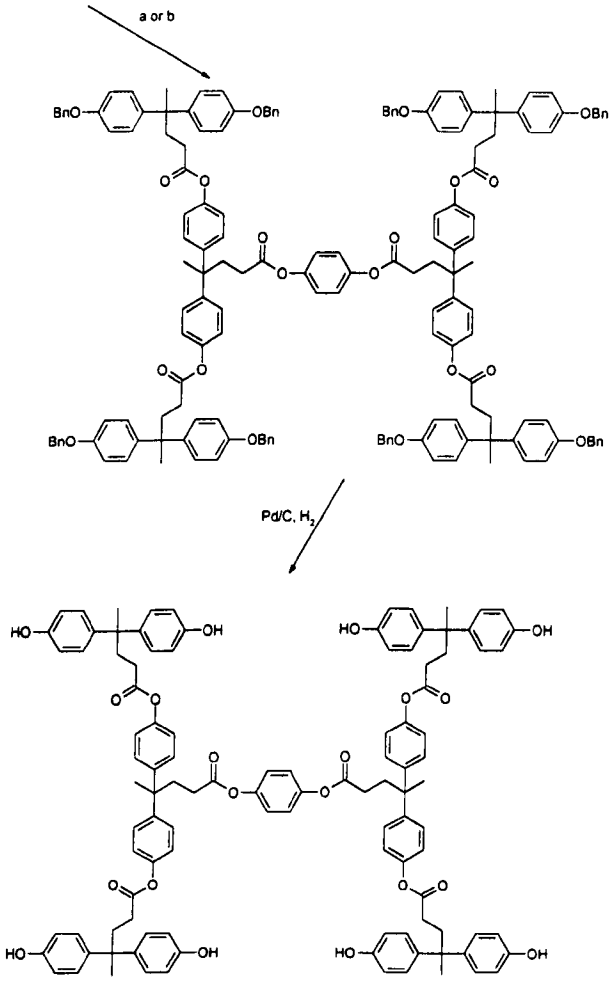
63 **64**

Again these processes were then repeated with G_1Aro-H-[4]-OH (**scheme 3.11**). Both the DCC-DPTS and the DMAP methods were successful giving yields of 87% and 80% respectively. GPC confirmed that a single product had been produced (M_n 2292 and PDi 1.007) and MALDI-MS verified the molecular weight of the product (*m/z* calculated [M+Na+] 2464, obtained 2464).

This was then followed by catalytic hydrogenation of G_2Aro-H-[8]-OBn, **65** to give G_2Aro-H-[8]-OH, **66** (**scheme 3.11**). This was produced in a yield of 92%. The homogeneity of the product was determined by GPC (M_n 2285 and PDi 1.007) which indicated that the product was monodisperse. The molecular weight was verified by MALDI-MS (calculated m/z for [M+Na^+] = 1743, obtained = 1744).

Scheme 3.11

G_1Aro-H-[4]-OH



66

Synthesis of further generations proved unsuccessful. Both methods were utilised; the DCC-DPTS and DMAP ones, to produce generation three dendrimers but all attempts were fruitless. When these products were analysed by GPC they were shown to be polydisperse with all the PDi values being greater than 1.5.

3.4 Characterisation of Dendrimers

3.4.1 ^{1}H and ^{13}C NMR

Initially when a dendrimer was prepared, the success of the reaction was judged by both ^{1}H and ^{13}C NMR. At first glance of a dendrimer it would seem that the NMR spectra would be very complicated. However, on closer examination it can be observed that the dendrimers synthesised are symmetrical, and therefore the spectra obtained are fairly straightforward.

^{13}C NMR spectroscopy is just as useful as ^{1}H NMR spectroscopy. The purity of a dendrimer can be confirmed by the presence of a single resonance at approximately 70 ppm which corresponds to the benzyl carbons. Again, due to the symmetrical nature of the dendrimers the ^{13}C NMR spectra are not over complicated.

3.4.2 Elemental Analysis

Obtaining adequate elemental analysis data was unproblematic. However, better results were obtained with the benzyl terminated dendrimers than the hydroxyl terminated ones. This phenomena was put down to the fact that the hydroxyl terminated dendrimers are hygroscopic. The problem was overcome by thorough drying of the hydroxy dendrimers.

3.4.3 GPC

GPC is an excellent tool for characterising traditional polymers. Unfortunately, for dendrimers GPC is less helpful. Although GPC is good for measuring whether a dendrimer is monodisperse or not, a problem arises when the molecular weight of a dendrimer needs to be obtained. Problems arise due to GPC being calibrated using linear polymer standards such as polymethylmethacrylate. This results in this method being appropriate to be used as a standard for similar macromolecules. Dendrimers are not in the same class as linear polymers as they exist as globular molecules. Therefore, values of molecular weights for standard linear polymers are not comparable to the molecular weights obtained for dendrimers.

Table 3.1 is a summary of some of the results obtained using GPC of a variety of dendrimers.

Table 3.1 GPC Data of a Variety of Dendrimers

Dendrimer	M_n	Calculated MW	PDi
G_1Aro-H-[4]-OBn	1329	1007	1.030
G_1Aro-H-[4]-OH	1044	647	1.080
G_1Aro-B-[4]-OBn	1212	987	1.014
G_1Aro-B-[4]-OH	956	627	1.053

When the observed values of Mn are compared to the calculated values there are discrepancies. Errors greater than 35% occur. A trend has been noticed, that is that the hydroxyl terminated dendrimers have nearly twice as high percentage error as the benzyl terminated dendrimers. This could be due to interactions occurring between the hydroxyl groups and the polystyrene packing material of the column.

The polydispersity values indicate that all the dendrimers are monodisperse in nature. On closer examination the PDi values for the hydroxyl terminated dendrimers were found to be higher than the ones obtained for the benzyl terminated dendrimers. This phenomenon is not just restricted to our group but has also been observed by others.[63] Turner et al observed higher PDi values with his phenol terminated hyperbranched polymers. It is thought that this effect is again due to interactions occurring between the hydroxyl groups on the dendrimers and the polystyrene packing material of the column.

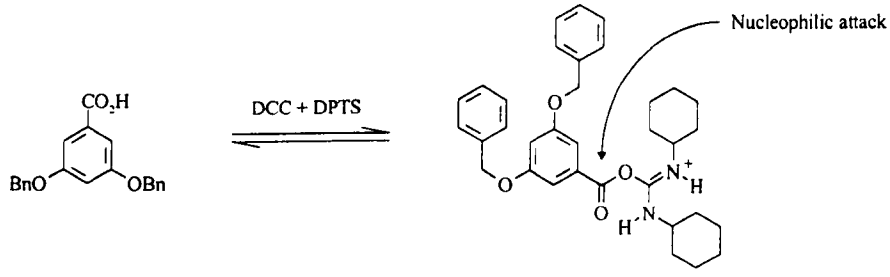
Some groups have noticed that impurities are present in their GPC traces. Attempts were made to remove these impurities using a variety of purification techniques, all of which failed. Sahota *et al* found that these impurities were twice the molecular weight of the corresponding dendrimer. They postulated that these impurities were actually the result of dendrimers being entangled.[71]

3.4.4 Failed Synthesis of Generation Three

Unfortunately only two generations of dendrimers were made successfully. There are a few explanations as to why this was so.

One obvious explanation, as shown with the first generation dendrimers, is that the success of the reaction is dependent on type of synthesis utilised. If the mechanism of the DCC/DPTS reaction is considered it becomes apparent that a problem may exist. During the esterification procedure the acid and the DCC form a complex. The next step is the nucleophilic attack by the alcohol at the carbonyl carbon. This is followed by the loss of dicyclohexylurea (DCU) (**scheme 3.12**).

Scheme 3.12



From **scheme 3.12** it can easily be seen that the DCC-acid intermediate is sterically demanding and may restrict the access of the dendritic alcohols. However the DMAP acid chloride route which involves less bulky intermediates also proved unsuccessful.

3.5 Conclusion

The dendrimers were made using two different methods. One involved the use of an acid chloride and DMAP, the other DCC and DPTS. The yields for the reaction with each method varied and are given in **table 3.2**.

Table 3.2 Comparison of Yields of Dendrimers Using 2 Different Methods

Dendrimer	% Yield Using DMAP Method	% Yield Using DCC-DPTS Method
G_1Aro-B-[4]-OBn	86	61
G_1Aro-H-[4]-OBn	91	59
G_2Aro-B-[8]-OBn	81	85
G_2Aro-H-[8]-OBn	80	87

From the **table 3.2** it can be observed that the method involving DMAP was the most successful for generation one. However, for dendrimers higher than this generation DCC-DPTS was the preferred method. Other groups have also found the same to be true.[81] At the moment there is no explanation for this phenomenon.

Hydrogenolysis of the dendrimers was fairly non-problematic, with all the yields obtained being over 85%. There were two points to watch. One was the solubility of the dendrimers. This meant the addition of an amount of methanol to the reaction vessel which was just enough not to cause precipitation of the

protected dendrimer. The other was that the maximum amount of dendrimer that could be hydrogenated at a time was 8 g. Any more than this and the yields were reduced considerably.

The most probable reason for failure to reach generation 3 was steric factors.

CHAPTER 4

Functionalisation of Dendrimers

4.1 Introduction

As mentioned in chapter 1, dendrimers possess a number of terminal groups, which lie on or very near the surface. Because of their positioning on the surface they are thought to contribute greatly towards the physical properties of the dendrimer.[96, 97]

Roy *et al* synthesised dendrimers with α-sialoside units. These could then act as inhibitors of the influenza A virus haemagglutinin (HA) by binding to the virus (see chapter 1).[78] This and many other examples can be found in the literature of functionalising dendrimers with the purpose of altering their physical properties.

We wished to develop methodology for functionalisation of our dendrimers, using generation one dendrimers as models.

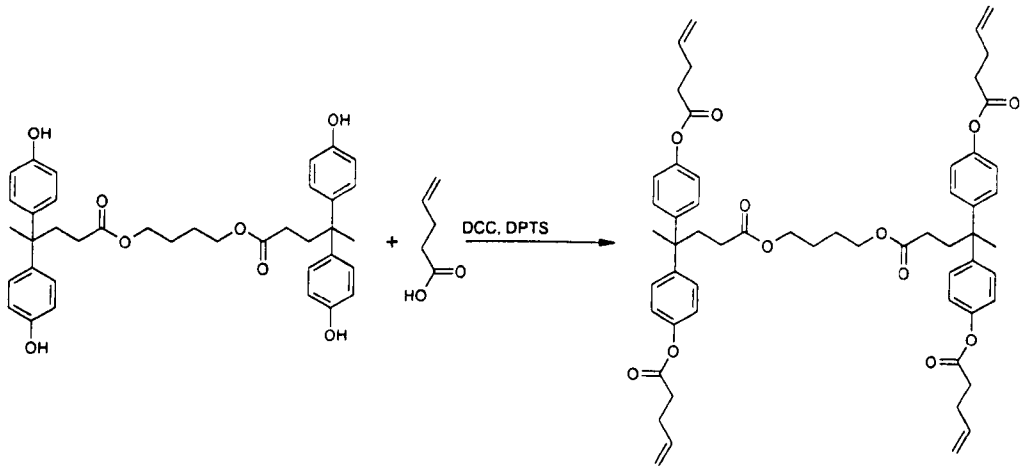
4.2 Alkene Terminated Dendrimers

The first modification that was attempted was the conversion of the hydroxyl terminated dendrimers into alkene terminated ones. Alkene functional groups are very useful in organic synthesis as once they are introduced into a compound they can easily be converted into a variety of other functional groups such as alcohols, epoxides and halides.

4.2.1 Pent-4-enoyl Terminated Dendrimers

To introduce an alkene end group onto a dendrimer, pent-4-enoic acid **67** was chosen. The acid was reacted with G_1Aro-B-[4]-OH in the presence of the esterification agents DCC and DPTS to give G_1Aro-B-[4]-O-pent-4-enoyl **68** (**scheme 4.1**). The crude yellow oil was purified using flash chromatography to give a clear oil in a 47% yield. GPC confirmed that the product was monodisperse (Mn 1425, PDi 1.004). The molecular weight was obtained using MALDI-MS analysis and gave good agreement with the calculated value ([M+Na^+] at *m/z* 978 – calculated 978).

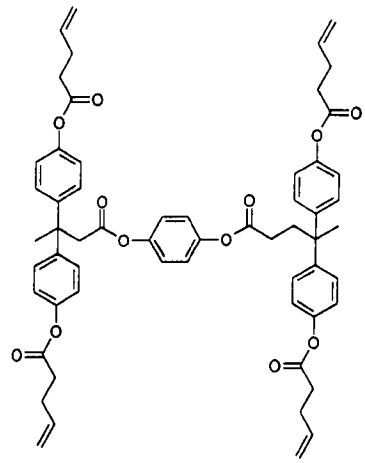
Scheme 4.1



67 **68**

The experiment was repeated with G_1Aro-H-[4]-OH to give **69** (**figure 4.1**). The reaction was monitored by GPC. The crude oil was purified by column chromatography to give a clear oil in a 56% yield. GPC confirmed that the product was monodisperse (Mn 1585, PDi 1.003). The molecular weight was obtained using MALDI-MS analysis and gave good agreement with the calculated value ([M+Na^+] at *m/z* 998 – calculated 998).

Figure 4.1 Structure of 69



69

4.3 Urethane Terminated Dendrimers

4.3.1 Introduction to Polyurethanes

Bayer discovered the polyurethane class of polymers that is one of the most widely used polymers in the world today. In the US alone, over a billion pounds are spent every year on polyurethanes. Polyurethane products include coatings, adhesives, plastics and foams.

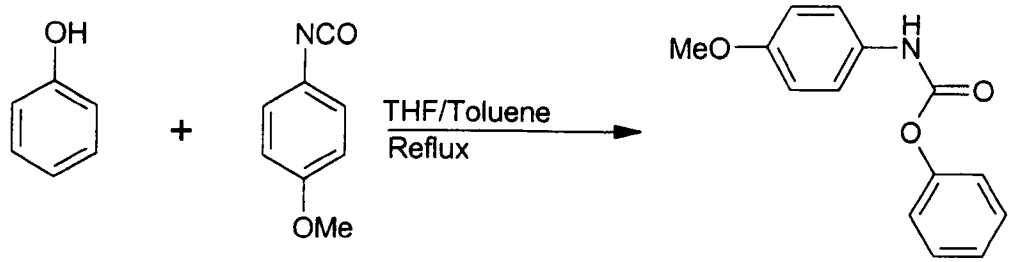
4.3.2 Synthesis of Methoxy Phenyl Urethane Terminated Dendrimers

It was decided that the first approach to be used would be to convert a hydroxyl terminated dendrimer to a urethane with the use of copper(I) chloride as catalyst.[98] G_1Aro-H-[4]-OH was stirred with 4 equivalents of copper(I) chloride and 4.8 equivalents of methoxy phenyl isocyanate. The reaction was unsuccessful as at the end of the reaction the only materials recovered were starting materials.

Further work on preparing urethanes was carried out initially on a model compound, phenol.

Two approaches were used simultaneously. One approach involved refluxing phenol with methoxy phenyl isocyanate in THF, the other was exactly the same except that toluene was used instead of THF (**scheme 4.2**).[99]

Scheme 4.2

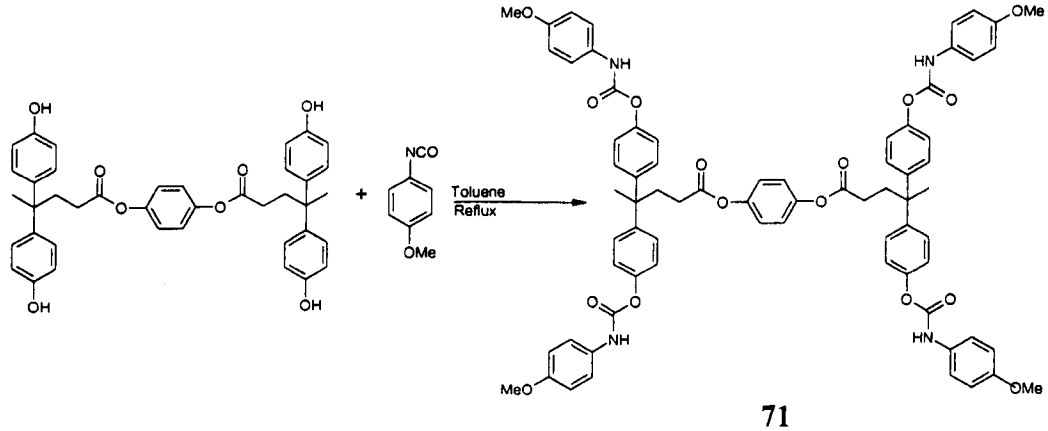


70

Both of the experiments successfully produced **70**. With THF as solvent a yield of 87% was obtained, however, with toluene the percentage yield was even higher, 92%. Taking these figures into consideration and the ease of each preparation it was decided that the approach that would be continued with was the one involving toluene as solvent.

This approach was then extended to use with hydroxyl terminated dendrimers. Initially G_1Aro-H-[4]-OH (1 equiv.) was refluxed with methoxy phenyl isocyanate (4.8 equiv.) in toluene for 24 hours to give **71** (**scheme 4.3**). The reaction was monitored by GPC.

Scheme 4.3

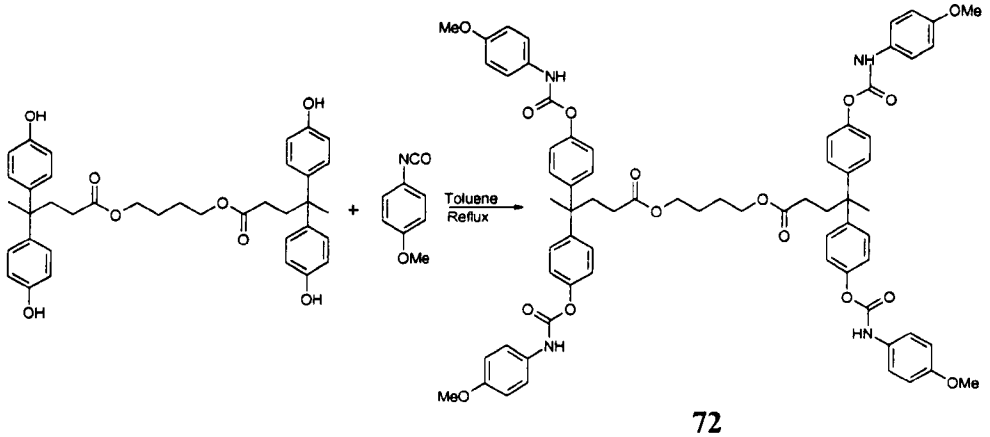


71

GPC confirmed that the product was monodisperse (M_n 1992, PDi 1.000). The molecular weight was obtained using MALDI-MS analysis and gave good agreement with the calculated value ([M+Na^+] at *m/z* 1266 – calculated 1266). The overall yield was 46%.

The reaction was repeated again with G_1Aro-B-[4]-OH (**scheme 4.4**). G_1Aro-B-[4]-O-carbamic acid methoxy phenyl ester **72** was produced as a colourless glue in a yield of 41%. The molecular weight was obtained using MALDI-MS analysis and gave good agreement with the calculated value ([M+Na^+] at *m/z* 1246 – calculated 1245). GPC confirmed that the product was monodisperse (M_n 1472, PDi 1.000).

Scheme 4.4



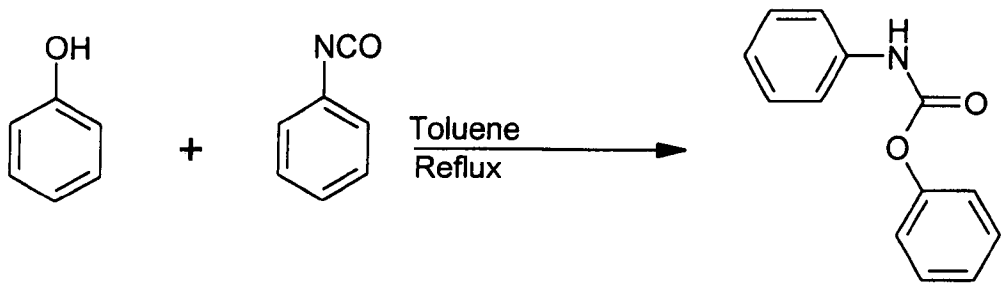
72

4.3.3 Synthesis of Phenyl Urethane Terminated Dendrimers

Due to the success of the synthesis of the methoxy phenyl urethane dendrimers it was decided that another type of isocyanate would be used to synthesise some different types of urethanes.

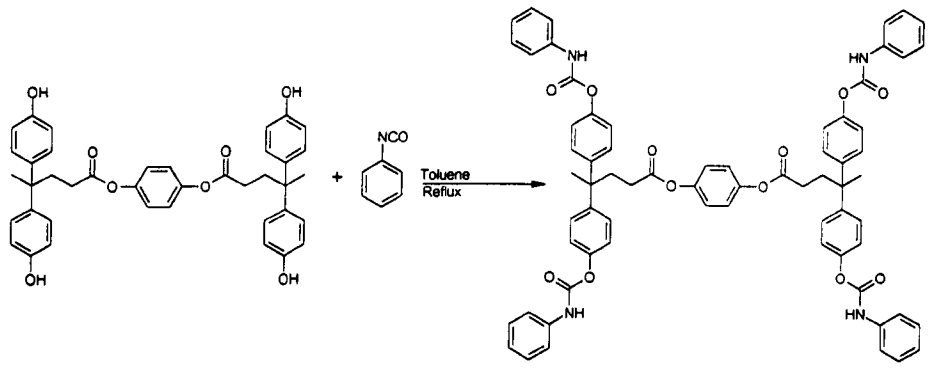
The second isocyanate used was phenyl isocyanate. This was reacted with phenol, as a model compound, in toluene (**scheme 4.5**). This synthesis was successful with **73** being synthesised in 96% yield. This approach was then applied to G_1Aro-H-[4]-OH (**scheme 4.6**).

Scheme 4.5



73

Scheme 4.6

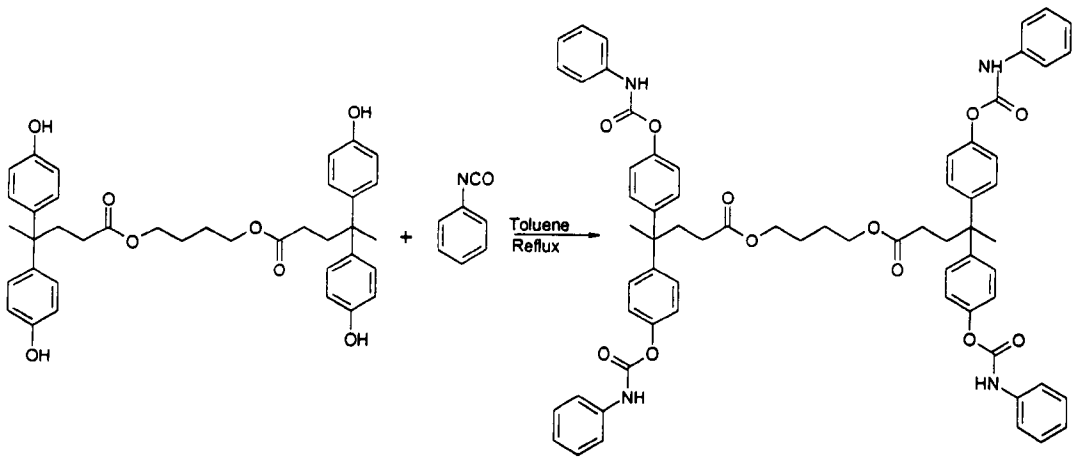


74

The reaction was monitored by GPC. The crude cream product **74** was purified by column chromatography to give a monodisperse product, Mn 1786, PDi 1.008. The molecular weight was obtained using MALDI-MS analysis and gave good agreement with the calculated value ([M+Na^+] at *m/z* 1146 – calculated 1146).

The reaction was repeated again with G_1Aro-B-[4]-OH (**scheme 4.7**). G_1Aro-B-[4]-O-carbamic acid phenyl ester **75** was produced as a white solid in a yield of 40%. GPC confirmed that the product was monodisperse (M_n 1871, PDi 1.005).

Scheme 4.7



75

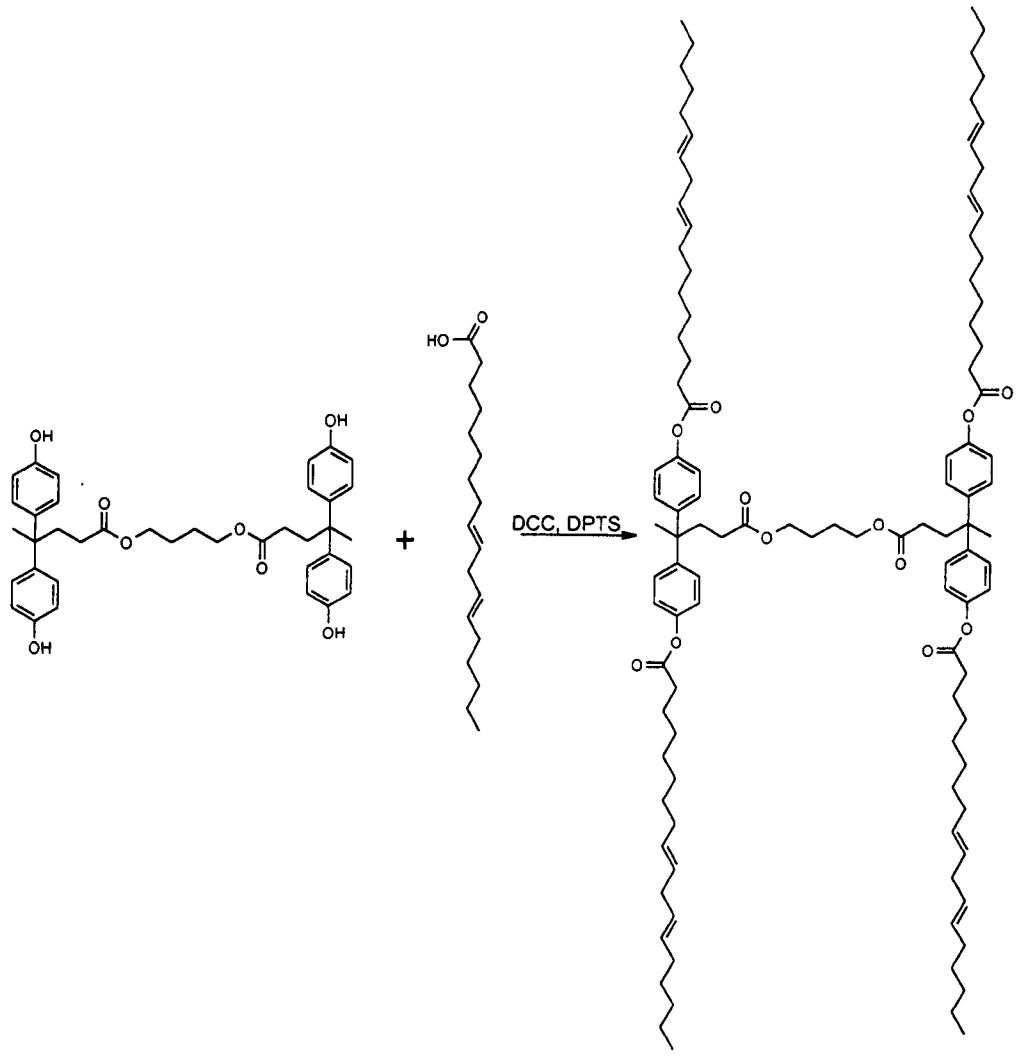
4.4 Fatty Acid Terminated Dendrimers

Linseed oil is obtained from flaxseed and is one of the most common drying oils used. A drying oil is used as a coating because when it is exposed to air it will dry to form a solid film. It is the double bonds in the drying oil that undergo aerial oxidation and then polymerisation to give a solid film. This is not new as this type of coating technique dates back to Roman times when linseed oil was used to help make paints. Today drying oils are used in many applications such as printing inks and putty.[100] Linseed oil comprises of oleic acid 22%, linoleic acid 16% and linolenic acid 52%.

4.4.1 Synthesis of A Fatty Acid Terminated Dendrimer

A fatty acid terminated dendrimer was synthesised by using the DCC-DPTS method of esterification. G_1Aro-B-[4]-OH was reacted with linoleic acid in the presence of the esterification agents to give G_1Aro-B-[4]-O-lineoyl **76** in a yield of 83% (**scheme 4.8**). Analysis using GPC confirmed that the product was monodisperse (Mn 2098, PDi 1.012). Previously when our group had attempted to analyse fatty acid dendrimers using MALDI-MS they had always been unsuccessful. However, with **76** the molecular weight was successfully confirmed with MALDI-MS (*m/z* calculated for $[M+K^+]$ 1715, obtained 1718).

Scheme 4.8



76

4.5 Conclusion

Pent-4-enoyl, urethane and lineoyl terminated dendrimers were all made successfully. All the dendrimers were fully analysed and shown to be monodisperse. The fatty acid terminated dendrimer was found to be much

harder to handle than the other functionalised dendrimers. However, a lineoyl functionalised dendrimer was successfully analysed by MALDI-MS to verify the molecular weight of the dendrimer.

CHAPTER 5

MALDI Mass Spectrometry of Dendrimers

5.1 Introduction

Mass spectrometry is a very useful tool for the analysis of many compounds. However, the usefulness of this analysis technique cannot be applied to all classes of molecules as this technique of ionisation can only be used on molecules which already exist in a gaseous form. Techniques have been developed to counteract part of this problem. Methods such as fast atom bombardment and laser desorption were developed so that the ionisation of thermally labile molecules could be achieved.

5.2 MALDI MS

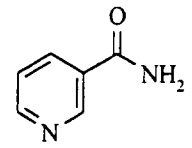
However, even these ionisation techniques are limited in their usage. Problems occur with high molecular mass molecules. Both fast atom bombardment and laser desorption have an upper working reliability limit. In the case of laser desorption the upper working limit is approximately 9000 Da due to the heating effect of the laser.[101] If analysis is attempted above these limits then fragmentation occurs. Fragmentation manifests itself by generating multi-lined spectra.

It was not until the middle of the 1980s that a solution was developed to overcome the problems mentioned above. A technique was developed independently by the groups of Karas[102] and Tanaka[103]. This new technique was named matrix assisted laser desorption-ionisation MS and is a soft ionisation technique, ideal for the analysis of non-volatile, high molecular mass molecules. It meant that analysis could be carried out without the process of fragmentation occurring.

The analyte is mixed with a suitable matrix. The mixture of analyte and matrix is then irradiated. The matrix seems to protect the analyte by absorbing most of the energy. Little is known about this mechanism, however, it has been postulated that the matrix protects the analyte as mentioned and then transfers energy to the analyte in a way that allows desorption and ionisation to occur but reduces the risk of occurrence of fragmentation.

The choice of matrix is determined by the fact that the matrix must strongly absorb light at the laser wavelength. The most common lasers used are carbon dioxide and nitrogen lasers (337 nm). To complement the lasers used, nicotinic acid **77**, cinnamic acid **78**, 2,5-dihydroxybenzoic acid **79** (DHB), 9-nitroanthracene **80**, α-cyano-4-hydroxycinnamic acid **81** and sinapinic acid **82** are all commonly used matrices (**figure 5.1**).

Figure 5.1 Structures of Common Matrices



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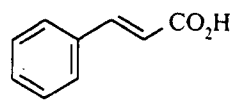

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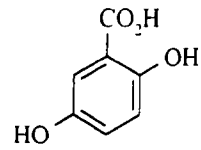
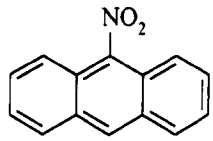
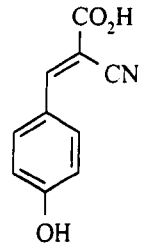


79



80



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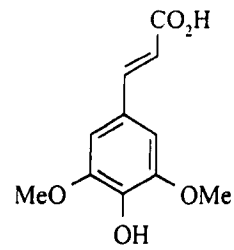


82

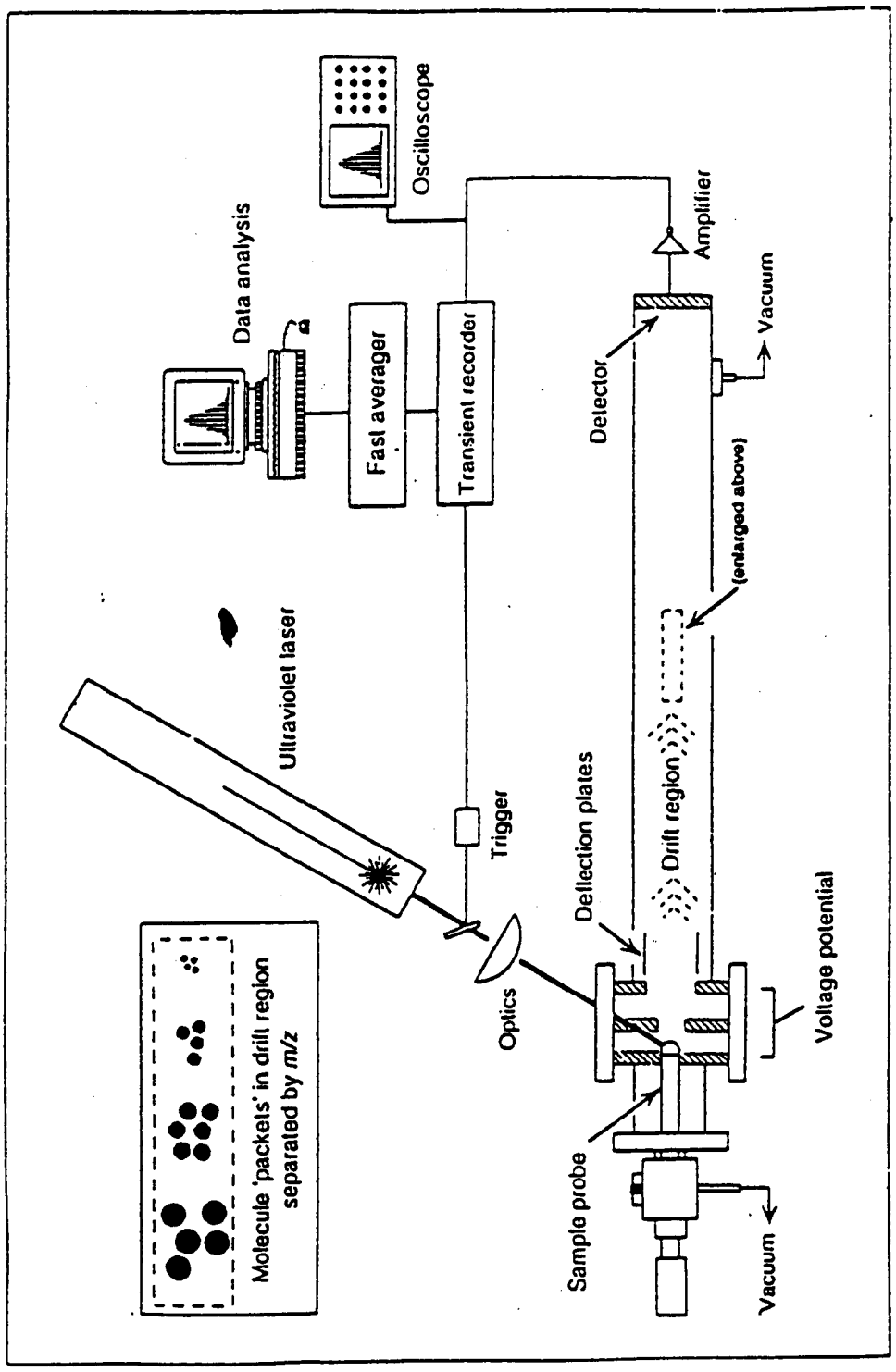
Once the analyte has been ionised, the ions, which form packets, can be analysed. Time of flight (TOF) is an obvious choice of analyser as TOF works best with pulsed ion sources. Initially TOF uses an electric potential to accelerate the packets of ions so that they all possess the same amount of kinetic energy. The ions then pass through a field-free region known as a drift tube. It is here that the ions begin to separate. They do this according to their velocity as each individual velocity is characteristic to that ion's mass. The velocity of an ion is dependent on $(m_i/z_i)^{-1/2}$ where m_i is the mass of the ion and z_i is the corresponding charge. Molecules with low molecular weights will travel faster than molecules with higher molecular weights for a given amount of energy.

Figure 5.2 is a diagrammatic representation of an MALDI-TOF instrument. This is the simplest type of machine. It consists of a linear path for the ions to

travel down whilst in the drift tube. A resolution of 500 Da is obtainable with this device. If increased resolution is required then a reflectron model can be used. With this model a resolution of up to 6000 Da can be achieved. Unlike the linear mode when the ions travel in a straight line down one tube, the ions in the case of a reflectron model travel down two tubes. An ion mirror is used to reflect the ions down the second tube and thus increase the path length. The mirror also has a secondary role in that it decelerates the ions. This results in ions with a higher kinetic energy spending more time in the mirror than ions with lower kinetic energy. The benefit of this is that ions of the same molecular weight but of differing energies are collated back together. This causes the resolution to be much higher. An instrument such as this is referred to as a reflectron TOF MS.

There are several problems with MALDI-MS, one is reproducibility. This is due to the preparation of the sample before analysis. The analyte is either laid on the slide after the matrix or both analyte and matrix are mixed together and then laid onto the slide. Either way poor shot to shot reproducibility is obtained. It is thought that this is due to crystal inhomogeneity of the sample.

Figure 5.2 MALDI-TOF Mass Spectrometer



H. S. Creel, *Trends in Polymer Science*, 1993, 1 (11), 336.

5.3 Analysis of Dendrimers

Walker et al and Sahota et al reported independently and simultaneously the use of MALDI-MS for the analysis of dendrimers.[104, 71] Walker's work involved the analysis of Moore's phenylacetylene dendrimers.[58, 59] Since these studies, the analysis of dendrimers using MALDI-MS has become routine.

Due to dendrimers being monodisperse, only one signal should be observed in a MALDI-MS spectrum. However, this is not always the case. Fragmentation of a dendrimer or defects present in its structure will lead to a multi-lined spectrum.

All of the MALDI-MS spectra reported in this thesis were obtained using a Kratos Kompact III MALDI-TOF MS which was equipped with a nitrogen laser irradiating at 337 nm. The hydroxyl terminated dendrimers were prepared in a water-acetone mixture (50:50). The benzyl and silyl terminated dendrimers were prepared in chloroform unless stated otherwise. All solutions were prepared at 1 x 10^{-4} M concentrations.

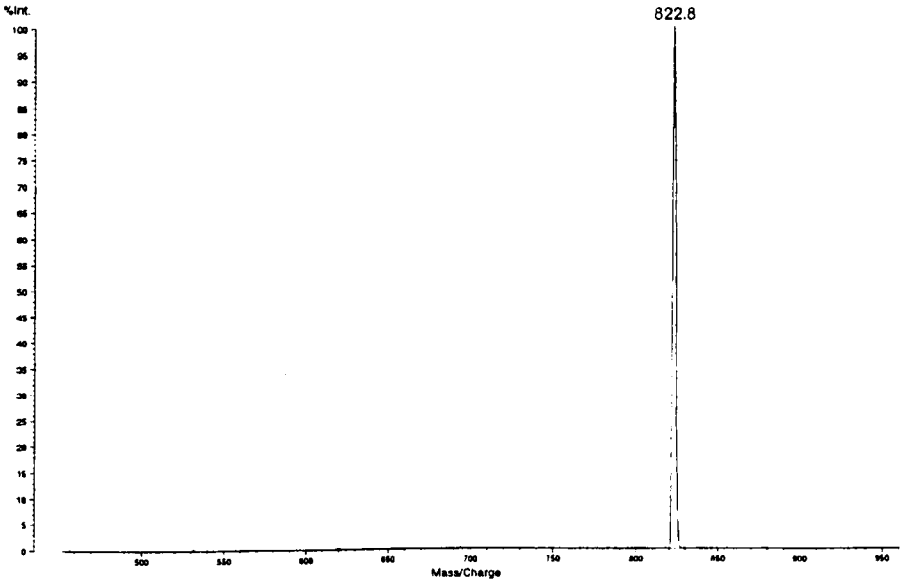
5.3.1 Dendrimers based On the Aliphatic Branch Unit

Both the dendrimers made using the aliphatic branch unit, G_1Ali-H-[4]-OTBDMS and G_1Ali-B-[4]-OTBDMS, were analysed by MALDI-MS. In both cases the signal obtained for the dendrimer species represented the cation

species, that is the dendrimer plus sodium. Therefore the signal obtained was M + 23. Only one signal was observed for each dendrimer indicating that both dendrimers were monodisperse.

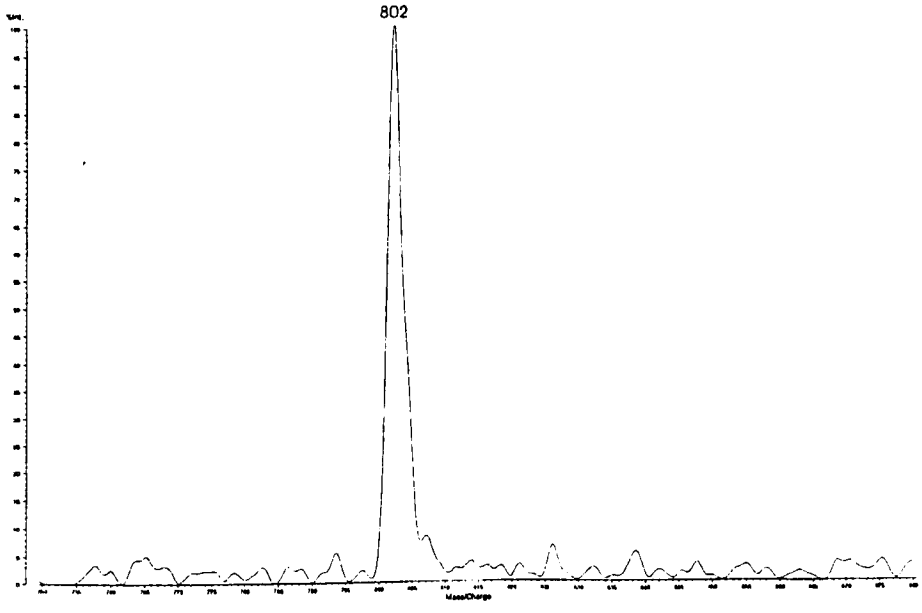
Figure 5.3 is the MALDI-MS spectrum for G_1Ali-H-[4]-OTBDMS (799 Da). The signal is at 823 Da which corresponds to dendrimer plus sodium. This indicated that the reaction had been successful..

Figure 5.3 MALDI-MS of G_1Ali-H-[4]-OTBDMS



Successful results were also obtained with G_1Ali-B-[4]-OTBDMS (779 Da). Again a single signal was observed, this time at 802 Da, which corresponds to the dendrimer coupled with sodium (**figure 5.4**).

Figure 5.4 MALDI-MS of G_1Ali-B-[4]-OTBDMS



As well as being useful for analysis, MALDI-MS proved a useful tool for determining the end point of reactions. MALDI-MS was used to monitor the deprotection attempts; samples were taken from the reaction mixtures and analysed. The results confirmed our fears that none of the deprotection attempts were successful, in fact for many of the reactions only starting materials were present.

5.3.2 Dendrimers based On the Branch Unit 4,4-bis(4-hydroxyphenyl)valeric acid

All the dendrimers synthesised with this branch unit were analysed using MALDI-MS.

Table 5.1 shows the results of analysis obtained using the dendrimers based on the aliphatic core. **Figure 5.5** is an example of one of the MALDI-MS spectra obtained. It shows the signals obtained for G_1Aro-B-[4]-OH. The calculated mass of G_1Aro-B-[4]-OH is 626 Da and the two signals observed at 649 and 665 Da correspond to G_1Aro-B-[4]-OH plus sodium and G_1Aro-B-[4]-OH and potassium respectively. Unlike the MALDI-MS spectra for the aliphatic dendrimers, a signal corresponding to the complex involving potassium can be observed.

Table 5.1 MALDI-MS Data for Dendrimers Based on the Aliphatic Core

Dendrimer	Calculated MW + Na^+	MW Determined by MALDI-MS + Na^+
G_1Aro-B-[4]-OBn	1010	1010
G_1Aro-B-[4]-OH	650	649
G_2Aro-B-[8]-OBn	2444	2444
G_2Aro-B-[8]-OH	1723	1724

Figure 5.5 MALDI-MS Spectrum for G_1Aro-B-[4]-OH

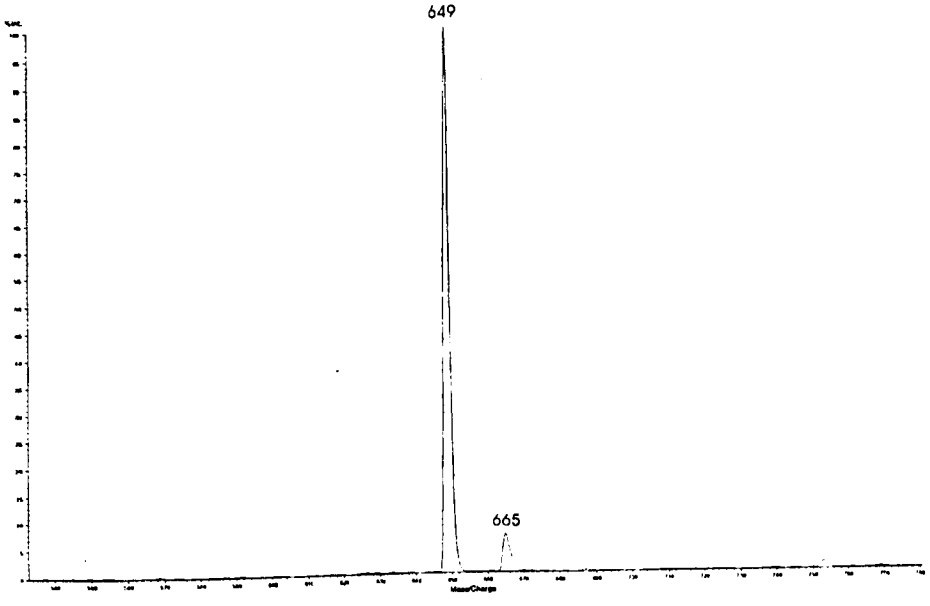


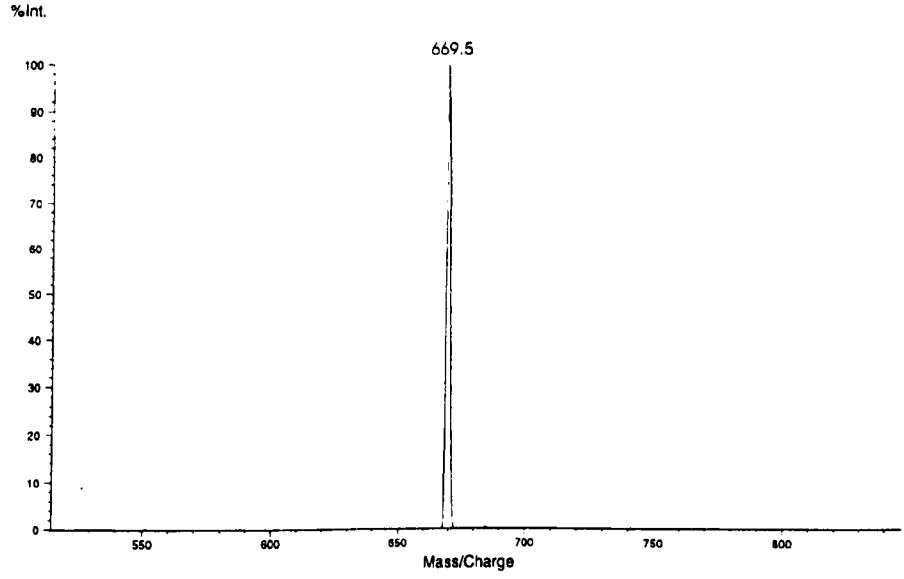
Table 5.2 is a summary of the MALDI-MS results obtained from the dendrimers based on the aromatic core. Again there was no problem with this method of analysis, all the dendrimers were analysed successfully

Table 5.2 MALDI-MS Data for Dendrimers Based on the Aliphatic Core

Dendrimer	Calculated MW + Na^+	MW Determined by MALDI-MS + Na^+
G_1Aro-H-[4]-OBn	1030	1030
G_1Aro-H-[4]-OH	670	670
G_2Aro-H-[8]-OBn	2464	2464
G_2Aro-H-[8]-OH	1743	1744

Figure 5.6 is the MALDI-MS spectrum for G_1Aro-H-[4]-OH. The molecular weight of this dendrimer is 647 Da, the signal obtained is 670 Da which corresponds to the complex of dendrimer with sodium.

Figure 5.6 MALDI-MS Spectrum for G_1Aro-H-[4]-OH



5.4 Fragmentation in MALDI-MS Spectra

There are numerous ways in which multiple lines can occur in a MALDI-MS spectrum. These include fragmentation in the mass spectrometer and the presence of impurities arising from the synthesis of the compound or decomposition on storage.

5.4.1 Multiple Lines Due to Sample Preparation

Due to the MALDI-MS samples being prepared in an aqueous acetone solution, there was a risk of hydrolysis occurring, hence causing the appearance of lower molecular mass species in the MALDI-MS spectra.

To investigate this phenomenon further a sample of G_1Ali-H-[4]-OTBDMS was prepared in a solution of acetone and water (1:1) doped with potassium. A MALDI-MS spectrum was recorded immediately. This showed a peak at 837 Da which corresponded to $M+K^+$ (**figure 5.7**). The solution was then left to stand for a week. The sample was then reanalysed by MALDI-MS and another spectrum was obtained (**figure 5.8**). When these two spectra were compared no differences could be observed between them. There was no presence of a peak around 493 Da which would indicate that hydrolysis had occurred. Neither were there any peaks around 170 which would correspond to the loss of any of the silyl protecting groups. This showed that for the dendrimers based on an aliphatic core, speed of analysis was not an important factor. At the same time it also confirms that the silyl groups are very stable to hydrolysis conditions, hence the reason why problems were encountered in trying to deprotect the protected dendrimers G_1Ali-H-[4]-OTBDMS and G_1Ali-B-[4]-OTBDMS.

Figure 5.7 MALDI-MS Spectrum for G_1Ali-H-[4]-OTBDMS After 10 Minutes

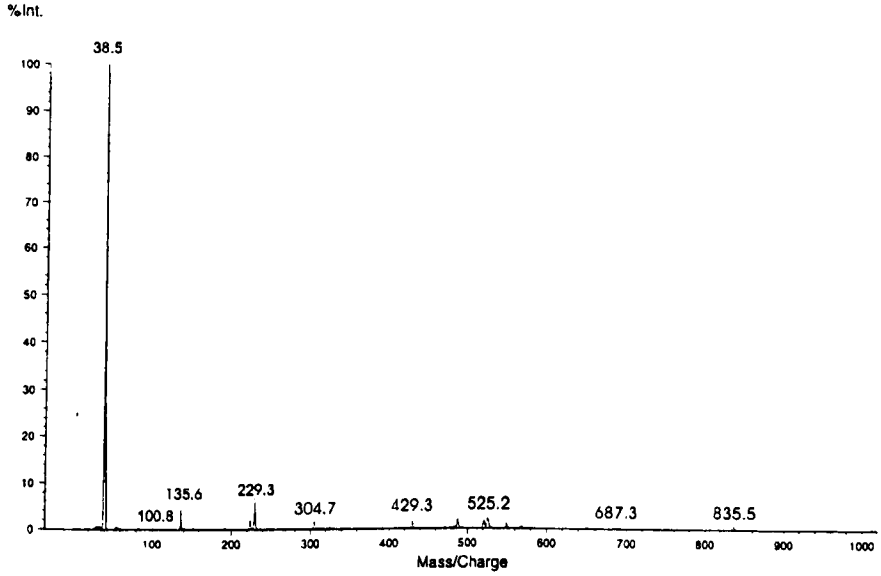
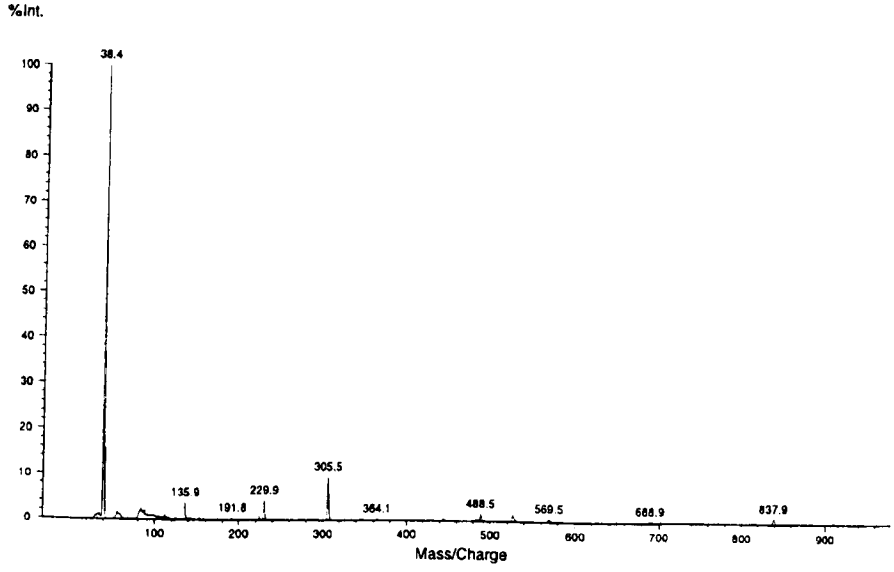
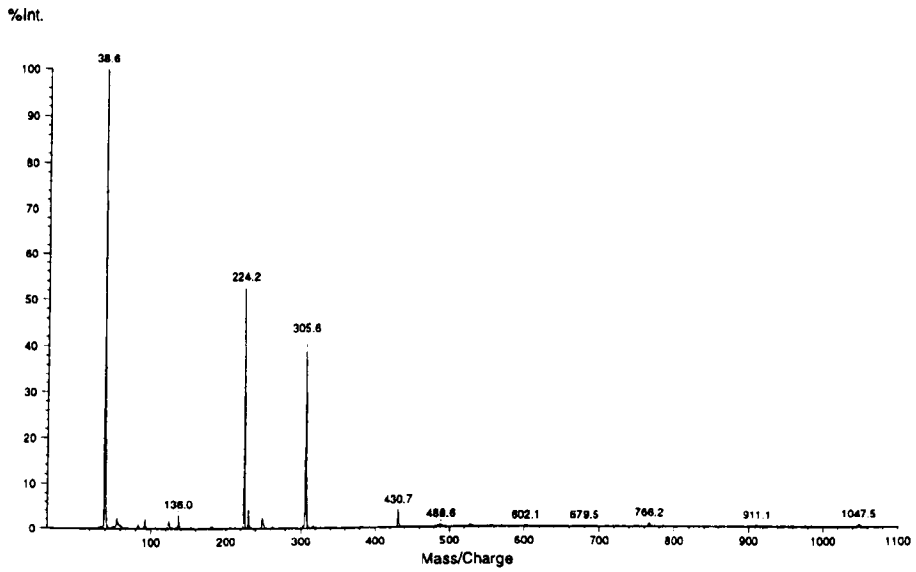


Figure 5.8 MALDI-MS Spectrum for G_1Ali-H-[4]-OTBDMS After 7 Days



Completely different results were obtained with the dendrimers based on the aromatic monomer. G_1Aro-H-[4]-OBn showed no signs of hydrolysis after 10 minutes. However, after being left standing for 7 days signs of hydrolysis could be easily observed in the spectrum (**figure 5.9**). The peak at 488 Da corresponds to hydrolysis occurring to the ester linkage.

Figure 5.9 MALDI-MS Spectrum for G_1Aro-H-[4]-OBn After 7 Days



5.4.2 Multiple Lines Due to Laser Power

The way a compound is analysed can also have an effect on fragmentation. One parameter, which can increase the amount of lower molecular mass species observed in a spectrum, is laser power. It was hypothesised that as laser power

increased so would the number of lower molecular mass species. To test this theory a MALDI-MS spectrum was recorded of G_1Aro-B-[4]-O-pent-4-enoyl (**figure 5.10**). The peaks at 994 and 978 Da correspond to the sample complexed with potassium and sodium respectively. The sample was irradiated with a laser at power 100 averaged over 200 shots. The experiment was then repeated, however, this time the laser power was 180 (**figure 5.11**). As in the previous spectrum peaks at 994 and 978 Da can be observed. However, in figure **5.11** four peaks can be seen which do not exist in **figure 5.10**. These peaks at 911, 826, 747 and 609 correspond to the loss of 1, 2, 3, and 4 pentenoyl groups respectively.

From these observations we can conclude that increasing laser power will cause fragmentation of our dendritic samples.

Figure 5.10 MALDI-MS Spectrum for G_1Aro-B-[4]-O-pent-4-enoyl At Power 100

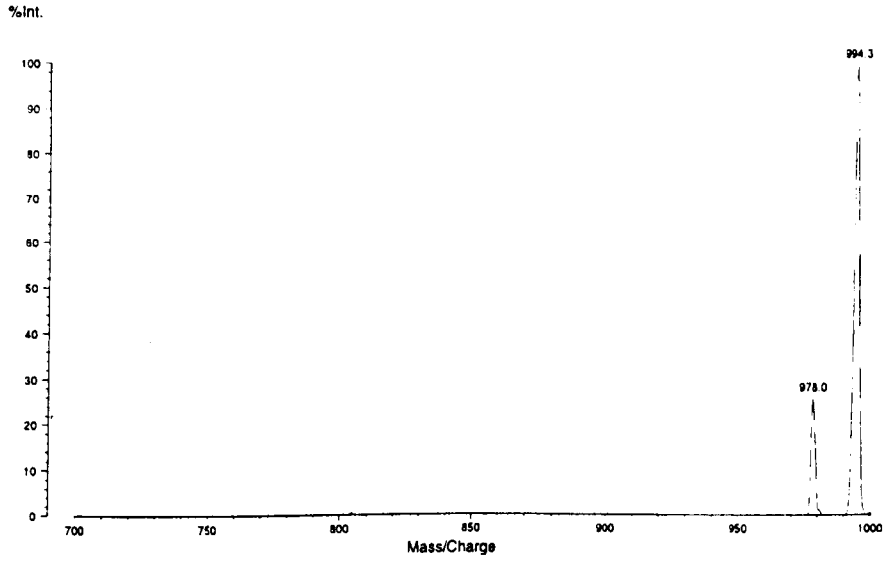
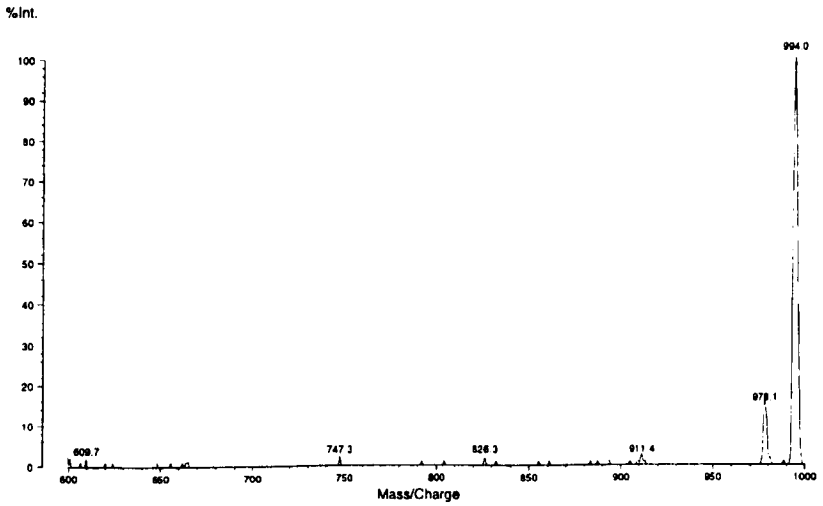


Figure 5.11 MALDI-MS Spectrum for G_1Aro-B-[4]-O-pent-4-enoyl At Power 180



5.5 Analysis of Functionalised Dendrimers

There was no problem in recording spectra of our functionalised dendrimers. Again DHB was used as the matrix. The results are shown in**Table 5.3**.

Table 5.3 MALDI-MS Data for Functionalised Dendrimers

Dendrimer	Calculated MW + Na^+	MW Determined by MALDI-MS + Na^+
G_1Aro-B-[4]-O-pent-4-enoyl	978	978
G_1Aro-H-[4]-O-pent-4-enoyl	998	998
G_1Aro-H-[4]-O-carbamic acid methoxy phenyl ester	1266	1266
G_1Aro-B-[4]-O-carbamic acid methoxy phenyl ester	1246	1245
G_1Aro-H-[4]-O-carbamic acid phenyl ester	1146	1146

5.6 Conclusion

MALDI-MS TOF is an excellent tool for the characterisation of dendrimers. When calculated molecular masses were compared with the observed ones the

values were correct within the bounds of experimental error. The MW values obtained were much more accurate that values obtained using GPC.

For the dendrimers made from the aliphatic monomer rapidity of analysis of the samples is not an issue. Even when left standing in acetone:water (1:1) for 7 days no hydrolysis could be observed in the MALDI-MS spectrum

However, for the dendrimers made from the aromatic monomer a considerable amount of hydrolysis occurred after G_1Aro-H-[4]-OBn had been left standing in acetone:water (1:1) for 7 days.

It has also been shown that increasing the laser power of irradiation can cause the sample to fragment resulting in the appearance of lower molecular mass species in the MALDI-MS spectrum.

CHAPTER 6

Experimental

6.1 General Experimental

Melting points and glass transition points were obtained using a Stuart Scientific SMP1 melting point apparatus (uncorrected). Microanalyses were performed at the University of Warwick. Infra red spectra were recorded using sodium chloride plates either as a neat solution or with nujol mull on a Perkin - Elmer 1720X fourier transform infra red spectrophotometer. Selected absorbencies (ν_{max}) are reported. ^{1}H NMR spectra were recorded in $CDCl_3$ or [$^{2}H_6$]-acetone solution either at 250 MHz or 400 MHz on a Bruker ACF250 or a Bruker ACP400 instrument respectively. The solvent deuterium signal was used as an internal standard with chemical shifts (δ) being quoted in parts per million (ppm). ^{13}C NMR spectra were recorded in $CDCl_3$ or [$^{2}H_6$]-acetone solution either at 62.9 MHz or 100.6 MHz on a Bruker ACF250 or a Bruker ACP400 instrument respectively. Chemical shifts (δ) are quoted in ppm using solvent deuterium signal as internal standard. Chemicals were purchased from Aldrich, Avocado, Fluka or Johnsen Mathey at the highest possible grade. All solvents were purchased from Fisons Scientific Equipment at SLR grade and purified, when required, using methods from the literature. Solvents were dried using the following procedures: acetone, distilled from calcium sulfate under

nitrogen; dichloromethane, distilled form calcium hydride under nitrogen; DMF, distilled from calcium hydride under nitrogen; THF, distilled from sodium benzophenone ketal under nitrogen and toluene, distilled from sodium under nitrogen. Analytical TLC was carried out on aluminium backed commercial plates pre-coated with silica gel 60 F254 (0.2 mm thick) which were developed using one or more of the following agents: UV fluorescence (254 nm), potassium permanganate solution and phosphomolybdic acid reagent. Flash chromatography was performed using Merck Kieselgel 60 (230-400 mesh).. Hydrogenolyses were carried out at pressures of 25-50 pounds per square inch (psi) on a Parr hydrogenation apparatus. Accurate mass spectra and electron ionisation mass spectra were recorded on a Kratos MS 90 spectrometer with (M^+), major peaks being reported. All mass spectra of dendrimers were obtained using matrix assisted laser desorption-ionization mass spectrometry (MALDI-MS) on a Kratos KOMPACT. Irradiation was at 357 nm from a nitrogen laser source using 2,5-dihydroxybenzoic acid as matrix unless stated otherwise. In most instances the matrix was loaded first followed by the analyte. The dendrimers were loaded using an acetone-water mixture. For GPC analysis a Polymer Laboratories™ modular system was used. This utilises a 3 μm, 15 cm mixed-E column with PL Caliber™ GPC software (version 5.1) with THF eluent at 1 ml min^{-1} and DRI detection. Calibration was with Polymer Laboratories polystyrene narrow molecular weight standards.

6.2 Experimental for Chapter 2

6.2.1 Attempted Synthesis of N,N-bis(2-benzyloxyethyl)glycine benzyl ester 30

Using an adaptation of a literature method,[62] bicine (1.0 g, 6.13 mmol), benzyl bromide (2.63 ml, 22.1 mmol) and potassium carbonate (3.38 g, 24.5 mmol) were refluxed overnight in either dry acetone (30 ml) or dry DMF (30 ml) under nitrogen. The mixture was allowed to cool. The cooled white slurry was filtered and the filtrate was evaporated to dryness. The resultant oil was then dissolved in dichloromethane (25 ml) and washed with water (3 x 15 ml). The organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The ^{1}H NMR spectrum of the crude product showed that the reaction had not been successful with either solvent.

6.2.2 Attempted Synthesis of N,N-bis(2-benzyloxyethyl)glycine benzyl ester 30

Bicine (1 g, 6.13 mmol) was placed in a baffle flask with dichloromethane (50 ml), benzyl bromide (2.92 ml, 24.52 mmol) and benzyltriethylammonium chloride (0.5 g). Aqueous 4M potassium hydroxide (50 ml) was added and the solution was refluxed for 5 days. The cooled mixture was washed with water (2

x 30 ml). The organic layers were combined, dried over anhydrous magnesium sulfate and evaporated to dryness. Unreacted starting material was recovered.

6.2.3 N,N-Bis(2-benzyloxyethyl)glycine benzyl ester 30

Reactions were carried out on a 1-5 g scale at either room temperature or at 80 ^{0}C using an adaptation of a literature method.[83] Bicine (1.0 g, 6.13 mmol) was added to a stirred solution of sodium hydride (0.74 g, 30.65 mmol) in dry DMF (20 ml). The mixture was stirred at room temperature under nitrogen overnight. Benzyl bromide (2.92 ml, 24.52 mmol) was added to the stirred solution which was refluxed for 4 days. Ethyl acetate (20 ml) and water (20 ml) were added to the cooled solution. The organic layer was washed with water (3 x 15 ml). The organic phases were combined, dried over anhydrous magnesium sulfate and reduced *in vacuo*. The residue was purified using flash chromatography eluting with ethyl acetate-petroleum ether (3:7) to give the product as a yellow oil (0.32 g, 12%) (Found: C, 74.9; H, 7.3; N, 3.3. Calc. for $C_{27}H_{31}NO_4$: C, 74.9; H, 7.2; N, 3.2%); ν_{max}/cm^{-1} 1731 (C=O) and 1650 (C=C); δ_H($CDCl_3$, 250) 3.05 (4H, t, *J* 5.5, $NC\underline{H}_2CH_2$), 3.60 (4H, t, *J* 5.5, $NCH_2C\underline{H}_2$), 3.69 (2H, s, NCH_2C=O), 4.64 (4H, s, $CH_2OC\underline{H}_2Ph$), 5.02 (2H, s, $CO_2C\underline{H}_2Ph$) and 7.28-7.34 (15H, m, ArH); δ_C($CDCl_3$, 62.9) 54.1 ($N\underline{C}H_2CH_2$), 55.9 ($N\underline{C}H_2$), 65.7 ($NCH_2\underline{C}H_2$), 67.0 (OCH_2Ph), 73.2 ($CO_2\underline{C}H_2Ph$), 126.9 (Ar), 128.1 (Ar), 128.4 (Ar), 135.8 (Ar), 138.4 (Ar) and 171.3 (carbonyl).

6.2.4 N,N-Bis(2-benzyloxyethyl)glycine benzyl ester 30[84]

Reaction **6.2.3** was repeated. However, a catalytic amount of tetrabutylammonium iodide was added to the reaction mixture, which was then left stirring for overnight. Work up was identical to reaction **6.2.3**. The product was isolated in 12% yield. Spectral data were as for **6.2.3**.

6.2.5 Attempted Synthesis of N,N-bis(2-benzyloxyethyl)glycine benzyl ester 30

Bicine (0.5 g, 3.1 mmol) was stirred in a Schlenk tube with potassium hydroxide (2.08 g, 37.2 mmol) in dry DMF (30 ml) under nitrogen. After 1 hour benzyl bromide (1.47 ml, 12.4 mmol) was added dropwise, the solution was stirred for 5 days under nitrogen. Ethyl acetate (30 ml) was added and the solution was washed with water (3 x 20 ml). The aqueous phase was then extracted with diethyl ether (2 x 15 ml). The combined organic phases were dried with anhydrous magnesium sulfate and evaporated to dryness under reduced pressure. The ^{1}H NMR spectrum proved that the resultant yellow oil did not contain the desired product.

6.2.6 Attempted Synthesis of N,N-bis(2-benzyloxyethyl)glycine benzyl ester 30

Bicine (0.5 g, 3.1 mmol) was stirred in a Schlenk tube with lithium hydroxide (0.89 g, 37.2 mmol) in dry DMF (30 ml) under nitrogen. After 1 hour benzyl bromide (1.47 ml, 12.4 mmol) was added. The solution was stirred for a further 7 days under nitrogen. Work up procedure was the same as for reaction **6.2.5**. The ^{1}H NMR spectrum proved that the resultant yellow oil did not contain the desired product.

6.2.7 Attempted Synthesis of N,N-bis(2-benzyloxyethyl)glycine benzyl ester 30

Bicine (0.5 g, 3.1 mmol) was added to a solution of silver oxide (1.0 g, 4.31 mmol) in dry DMF (20 ml). Benzyl bromide (1.47 ml, 12.4 mmol) was added dropwise and the solution was then stirred for 8 days at room temperature under nitrogen. Work up procedure the same as for reaction **6.2.5**. The ^{1}H NMR spectrum proved that the resultant yellow oil did not contain the desired product.

6.2.8 Attempted Synthesis of N,N-bis(2-benzyloxyethyl)glycine benzyl ester 30

Bicine (0.1 g, 0.613 mmol), benzyl bromide (0.26 ml, 2.21 mmol) and 2,6-di-tert-butyl-4-methylpyridine (0.6 g, 3.07 mmol) were refluxed overnight in dry DMF (30 ml) under nitrogen. Work up was as for **6.2.1**. The ^{1}H NMR spectrum proved that the resultant colourless oil did not contain the desired product.

6.2.9 N,N-Bis[(*tert*butyldimethylsiloxy)ethyl]glycine 32

Using an adaptation of a literature procedure,[85] bicine (5.0 g, 30.7 mmol), imidazole (20.88 g, 0.307 mol) and TBDMSCl (13.87 g, 92.0 mmol) were stirred in dry DMF in a Schlenk tube under nitrogen for 3 days. The reaction was monitored by TLC. The reaction was quenched with water (20 ml). Work up was the same as **6.2.5**. The combined organic phases were dried *in vacuo* to give a yellow oil (8.4 g, 70%); δ_H($CDCl_3$, 250) –0.03 (12 H, s, $SiCH_3$), 0.85 (18 H, s, $SiCCH_3$), 2.97 (4 H, t, NCH_2), 3.50 (2 H, s, CH_2CO_2H) and 3.74 (4 H, t, $CH_2OTBDMS$); δ_C($CDCl_3$, 62.9) –5.5 ($SiCH_3$), 18.2 ($C\underline{C}H_3$), 25.9 ($\underline{C}CH_3$), 56.8 (CH_2), 58.2 (CH_2), 60.5 (CH_2) and 172.0 (carbonyl).

6.2.10 Bis[2-(trimethylsiloxy)ethyl)](methylene)ammonium chloride 35

Bicine (60 mmol) and hexamethyldisilazane (120 mmol) were stirred in dichloromethane (25 ml) at 40 °C for 48 hrs. The crude solution was reduced under pressure. The residue was distilled (130 °C at 0.1 mm Hg) to give **33** in a 90% yield. Compound **33** (7 mmol) was added to dichloromethane (10 ml). Thionyl chloride (7 mmol) was added to this solution which was left to stand until the evolution of gases had subsided. The solution was evaporated under reduced pressure to give a brown solid in a quantitative yield; $\delta_H(CDCl_3, 250)$ 0.07 (18H, s, CH_3), 3.95 (4H, m,$NC\underline{H}_2CH_2$), 4.14 (4H, m, $NC\underline{H}_2CH_2$) and 8.53 (2H, s, CH_2=N); $\delta_C(CDCl_3, 62.9)$ −1.5 ($SiCH_3$), 58.0 (CH_2), 61.1 (CH_2) and 166.8($N=CH_2$).

6.2.11 General procedure for reaction of 35 with nucleophiles

Compound **35** (7 mmol) was added to THF (10 ml) and to this solution was added a nucleophile (8mmol, PhSLi added in 5 ml THF, allyl magnesium bromide added as a 1 M solution in ether) which was then stirred at room temperature. The reaction was monitored by tlc. The solution was filtered and

evaporated under reduced pressure to give a residue. This was distilled at 0.1 mm Hg to give yields of the desired product between 60-90%.

6.2.12 Trimethylphenoxy silane 36

$\delta_H(CDCl_3, 250)$ 0.26 (18 H, s, CH_3) and 6.82-7.26 (5 H, m, ArH).

6.2.13 Di[2-(trimethyl-silanoxy)-ethyl]-phenylsulfanyl methyl-amine 38

$\delta_H(CDCl_3, 250)$ 0.06 (18 H, s, $OSiCH_3$), 2.77 (4 H, t, $NC\underline{H}_2CH_2$), 3.57 (4 H, t, $NCH_2C\underline{H}_2$), 4.57 (2 H, s, NCH_2S) and 7.14-7.45 (5 H, m, ArH); $\delta_C(CDCl_3, 62.9)$ –0.7 (CH_3), 55.3 ($N\underline{C}H_2CH_2$), 60.9 ($NCH_2\underline{C}H_2$), 66.2 (NCH_2S), 126.2 (Ar), 128.6 (Ar), 132.0 (Ar) and 137.4 (Ar).

6.2.14 But-3-enyl-di[2-(trimethyl-silanoxy)-ethyl]-amine 37

δ_H($CDCl_3$, 250) -0.05 (18 H, s, $OSiCH_3$), 2.05 (2 H, m, $NC\underline{H}_2CH_2O$, 2.51 (6 H, m, $NCH_2C\underline{H}_2O$ and NCH_2), 3.47 (4 H, t, CH_2O), 4.91 (2 H, m, $CH=C\underline{H}_2$) and 5.62 (1 H, m, $C\underline{H}=CH_2$); δ_C($CDCl_3$, 62.9) –0.8 ($SiCH_3$), 31.4 ($\underline{C}H_2CH=CH_2$), 54.9 ($\underline{C}H_2CH_2CH=CH_2$), 56.6 ($N\underline{C}H_2CH_2O$), 60.8 ($NCH_2\underline{C}H_2O$), 115.2 ($CH=\underline{C}H_2$) and 136.2 ($\underline{C}H=CH_2$).

6.2.15 Di[2-(trimethyl-silanoxy)-ethyl]-amino-2,2-dimethyl-propionic acid methyl ester 39

δ_H($CDCl_3$, 250) 0.01 (18 H, s, $SiCH_3$), 1.04 (6 H, s, CCH_3), 2.57 (4 H, t, $NC\underline{H}_2CH_2O$), 2.63 (2 H, s, $NC\underline{H}_2CCH_3$), 3.48 (4 H, t, $NCH_2C\underline{H}_2O$) and 3.55 (3 H, s, OCH_3); δ_C($CDCl_3$, 62.9) –0.64 ($SiCH_3$), 23.4 ($C\underline{C}H_3$), 44.3 ($\underline{C}CH_3$), 51.4 (CH_2), 58.4 (CH_2), 60.8 (CH_2), 65.8 (OCH_3) and 177.7 (C=O).

6.2.16 Attempted Synthesis of 2,2-bis(benzyloxymethyl)propionic acid benzyl ester 44

Using an adaptation of a literature procedure,[62] 2,2-bis(hydroxymethyl)propionic acid (1.0 g, 7.5 mmol) and potassium carbonate (4.12 g, 29.9 mmol) were stirred in dry DMF (30 ml). To this solution benzyl bromide (3.2 ml, 26.9 mmol) was added dropwise. The mixture was stirred at 80 °C under nitrogen overnight. Work up was as for **6.2.5**. The ^{1}H NMR spectrum showed that the experiment had been unsuccessful.

6.2.17 2,2-Bis(benzyloxymethyl)propionic acid benzyl ester 44

Using an adaptation of a literature procedure,[83] 2,2-bis(hydroxymethyl)propionic acid (0.50 g, 3.75 mmol) was added to a solution of sodium hydride (0.45 g, 18.75 mmol) in dry DMF (20 ml). Benzyl bromide (1.78 ml, 15 mmol) was added dropwise to the solution which was stirred at room temperature under nitrogen for 7 days. Ethyl acetate (20 ml) and water (20 ml) were added. The organic layer was washed with water (2 x 20 ml). The aqueous layers were extracted with diethyl ether (2 x 20 ml). The combined organic layers were dried over anhydrous magnesium sulfate and dried *in vacuo*. The resultant crude yellow oil was purified using flash chromatography and eluting with ethyl acetate-petroleum ether (2:3) to yield the product as a yellow oil (0.08 g, 5%) (Found: C, 77.4; H, 7.0. Calc. for $C_{26}H_{28}O_4$: C, 77.2; H, 7.0%);

ν_{max}/cm^{-1} 1681 (C=O) and 1632 (C=C); $\delta_H(CDCl_3, 250)$ 1.09 (3H, s, CH_3), 3.64 (4H, AB, *J* 9.6 and 18, CH_2), 4.91 (4H, s, OCH_2Ph), 5.04 (2H, s, CO_2CH_2Ph) and 7.25-7.34 (15H, m, ArH); $\delta_C(CDCl_3, 62.9)$ 16.9 (CH_3), 50.7 ($\underline{C}CH_2$), 63.9 (CH_2), 73.3 (OCH_2Ph), 69.8 (CO_2CH_2Ph), 127.0 (Ar), 128.2 (Ar), 128.6 (Ar), 137.0 (Ar), 137.2 (Ar) and 172.1 (C=O).

6.2.18 2,2-bis[(*tert*butyldimethylsiloxy)methyl]propionic acid silyl *tert*butyldimethylsilyl ester 45

Using an adaptation of a literature procedure,[85] reactions were carried out on a 1-20 g scale. 2,2-Bis(hydroxymethyl)propionic acid (1.0 g, 7.46 mmol), imidazole (5.08 g, 74.6 mmol) and TBDMSCl (5.62 g, 37.3 mmol) were stirred in dry DMF in a Schlenk tube under nitrogen for 4 days. The reaction was monitored by TLC. The reaction was quenched with water (20 ml). Work up was as for **6.2.5**. The resultant yellow oil was subjected to flash chromatography with ethyl acetate-petroleum ether (1:9) as the eluent to yield the desired product as a colourless solid (3.02 g, 86%), mp 39°C (Found: C, 57.9; H, 11.0. Calc. for $C_{23}H_{52}O_4Si_3$: C, 58.0; H, 11.0%); ν_{max}/cm^{-1} 3168-2957 (CH), 1719 (C=O); $\delta_H(CDCl_3, 250)$ –0.03 (12 H, s, $OSiCH_3$), 0.18 (6 H, s, CO_2SiCH_3), 0.81 (18 H, s, $OSiCCH_3$) 0.87 (9 H, s, CO_2SiCCH_3), 1.01 (3 H, s, CH_3) and 3.62 (4 H, AB, *J* 9.6 and 18, CH_2); $\delta_C(CDCl_3, 62.9)$ –5.4 ($SiCH_3$), -5.3 ($SiCH_3$), 17.0 9.6 and 18, 17.4 ($Si\underline{C}CH_3$), 18.0 ($SiC\underline{C}H_3$), 25.4 (CH_3) , 25. 7 (CH_3), 50.7 ($\underline{C}CO_2$), 64.0 (CH_2) and 175.0 (C=O).

6.2.19 Attempted Synthesis of 2,2-bis[(*tert*butyldimethylsiloxy)methyl]propionic acid 46

Compound **45** (0.25 g, 0.52 mmol) was added to a stirred solution of silica [Merck Kieselgel 60 (230-400 mesh)] (1 g) in methanol (2 ml). The solution was stirred overnight at room temperature. The silica was removed by filtration and the filtrate was reduced under pressure. The ^{1}H NMR spectrum showed that only starting material was present.

6.2.20 2,2-Bis[(*tert*butyldimethylsiloxy)methyl]propionic acid 46[85]

Reaction was carried out on a 0.25 g-20 g scale. Compound **45** (0.25 g, 0.52 mmol) was dissolved in THF (2 ml) and methanol (6 ml). To this stirred solution potassium carbonate (0.2 g) in water (2 ml) was added. The solution was stirred at room temperature for 36 hours. The solution was then concentrated down to a quarter of its volume under reduced pressure. Brine (6 ml) was added to the clear solution. The aqueous mixture was then adjusted to pH 4-5 at 0 °C with 1M potassium bisulfate then extracted with diethyl ether (2 x 10 ml). The organic phases were combined and washed with brine (2 x 10 ml), dried over anhydrous magnesium sulfate and reduced *in vacuo* to give a colourless, viscous oil. This oil was purified by flash chromatography eluting with ethyl acetate-petroleum ether (2:8) to yield a clear, colourless viscous oil

(0.13 g, 68 %) (Found: C, 56.3; H, 10.5. Calc. for $C_{17}H_{38}O_4Si_2$: C, 56.3; H, 10.6%); ν_{max} /cm^{-1} 3583 br (OH) and 1666 (C=O); δ_H($CDCl_3$, 250) 0.05 (12 H, s, $OSiCH_3$), 0.9 (18 H, s, CCH_3), 1.13 (3 H, s, CH_3) and 3.7 (4 H, AB, *J* 9.6 and 18, CH_2); δ_C($CDCl_3$, 62.9) –5.73 ($SiCH_3$), 16.94 (CH_3), 18.08 ($\underline{C}(CH_3)_3$), 25.67 ($C(\underline{C}H_3)_3$), 49.6, 64.22 (CH_2) and 179.57 (C=O).

6.2.21 Attempted Synthesis of 2,2-bis[(*tert*butyldimethylsiloxy)methyl]propyl chloride 47

Compound **46** (0.5 g, 1.38 mmol) was refluxed with an excess of freshly distilled thionyl chloride (5 ml) for 1 hour. The solution was distilled under reduced pressure to remove excess thionyl chloride. The ^{1}H NMR spectrum of the crude product showed that the reaction had been unsuccessful.

6.2.22 2,2-bis[(*tert*butyldimethylsiloxy)methyl]propyl chloride 47

Compound **46** (0.34 g, 0.937 mmol) was refluxed with an excess of oxalyl chloride (5 ml) for 1 hour. The excess oxalyl chloride was removed under reduced pressure to yield a colourless oil. The crude product could then be used without any further purification; (0.33 g, 92%) (Found: C, 53.7; H, 9.8. Calc. for $C_{17}H_{37}O_3ClSi_2$: C, 53.6; H, 9.8%); ν_{max} /cm^{-1} 3117-2956 (CH) and 1827

(C=O); δ_H($CDCl_3$, 250) 0.07 (12 H, s, $OSiCH_3$), 0.89 (18 H, s, CCH_3) 1.23 (3 H, s, CH_3) and 3.75 (4 H, AB, *J* 9.6 and 18, CH_2); δ_C($CDCl_3$, 62.9) –5.8 ($\underline{Si}CH_3$), 16.9 (CH_3), 18.0 ($C\underline{C}H_3$), 25.6 ($C\underline{C}H_3$), 60.5 ($\underline{C}CH_2$), 64.0 (CH_2) and 176.1 (C=O).

6.2.23 4-(Dimethylamino)pyridinium *p*-toluenesulfonate (DPTS) 51[91]

Monohydrated *p*-toluenesulfonic acid (4.99 g, 26.2 mmol) was dried by azeotropic distillation in benzene (80 ml) using a Dean-Stark trap. 4-(Dimethylamino)pyridine (3.2 g, 26.2 mmol) in benzene (70 ml) was added to the warm anhydrous solution with stirring. The mixture was stirred thoroughly and allowed to cool to room temperature. The resulting white precipitate was isolated by filtration. The crude product was found to be pure enough not to need any further purification; (7.21 g, 94%) mp 165-167°C (lit. 165°C), δ_H($CDCl_3$, 62.9); 2.25 (3 H, s, $ArCH_3$), 3.07 (6 H, s, $N(CH_3)$), 3.22 (1 H, br m, NH), 6.67 (2 H, AA'BB', *J* 7.0, PyH,) 7.06 (2 H, AA'BB', *J* 8.0, PhH), 7.71 (2 H, AA'BB', J 8.0, PhH) and 8.03 (2 H, m, PyH); δ_c($CDCl_3$, 250) 21.2, 40.0, 106.8, 125.8, 128.6, 139.2, 139.7, 142.7 and 157.1.

6.2.24 G_1Ali-H-[4]-OTBDMS 50

This compound was prepared using an adaptation of a literature procedure.[90] Reactions were carried out on 0.5-10 g scale. Compound **46** (5 g, 13.8 mmol) and hydroquinone (0.63 g, 5.74 mmol) were stirred in a Schlenk tube under nitrogen with dry acetone (50 ml). DCC (2.84 g, 13.8 mmol) and DPTS (0.68 g, 2.3 mmol) were added to the solution which was stirred for a further 4 days during which time a heavy white precipitate formed. The reaction was monitored by GPC. The white precipitate was filtered off and the filtrate was evaporated under reduced pressure. The resultant white solid was dissolved in dichloromethane (10 ml) and washed with water (3 x 10 ml). The organic phase was dried over anhydrous magnesium sulfate and evaporated to dryness. The crude white product was purified using flash chromatography eluting with ethyl acetate-petroleum ether (1:4) to give a white solid; (3.9 g, 85%), mp 68 °C (Found: C, 60.3; H, 9.9. Calc. for $C_{40}H_{78}O_8Si_4$: C, 60.1; H, 9.8%); ν_{max} /cm^{-1} 1757 (C=O); δ_H($CDCl_3$, 250) 0.06 (24 H, s, $OSiCH_3$), 0.90 (36 H, s, CCH_3) 1.26 (6 H, s, CH_3) 3.81 (8 H, AB, *J* 9.6 and 18, CH_2) and 7.04 (4 H, s, ArH); δ_C($CDCl_3$, 62.9) –5.7 ($SiCH_3$), 17.0 (CH_3), 18.1 ($\underline{C}CH_3$), 25.7 ($\underline{C}CH_3$), 50.9 ($\underline{C}CH_2$), 64.2 (CH_2), 122.1 (Ar), 148.1 (Ar) and 173.4 (carbonyl); GPC: M_n 1151, PDi 1006; *m/z* 822 ($M+Na^+$ requires 822).

6.2.25 G_1Ali-B-[4]-OTBDMS 54

This compound was prepared using an adaptation of a literature procedure.[90] Reactions were carried out on 0.5-10 g scale. Compound **46** (0.5 g, 1.38 mmol) and 1,4-butanediol (52 mg, 0.57 mmol) were stirred in a Schlenk tube under nitrogen with dry acetone (10 ml). DCC (0.28 g, 1.38 mmol) and DPTS (68 mg, 0.23 mmol) were added to the solution which was then stirred for a further 3 days during which time a heavy white precipitate formed. The reaction was monitored by GPC. The work up was the same as for **6.2.17**. The crude white product was purified using flash chromatography eluting with ethyl acetate-petroleum ether (1:9) to give a white solid (0.46 g, 80%), mp 43 °C (Found: C, 58.6; H, 10.8. Calc. for $C_{38}H_{82}O_8Si_4$: C, 58.9; H, 10.6%); ν_{max} /cm^{-1} 2855-3010 (CH), 1735 (C=O); δ_H($CDCl_3$, 250) 0.00 (24 H, s, $OSiCH_3$), 0.84 (36 H, s, $SCCH_3$) 1.08 (6 H, s, CH_3) 1.67 (4 H, m, $OCH_2C\underline{H}_2$), 3.66 (8 H, AB, *J* 9.6 and 18, CH_2) and 4.05 (4 H, t, CO_2CH_2); δ_C($CDCl_3$, 62.9) –5.6 ($\underline{Si}CH_3$), 17.1 ($\underline{C}CH_3$), 18.2 (CH_3), 25.4 ($\underline{C}CH_3$), 25.8 (CH_3), 50.3 (CH_2), 63.6 (CH_2), 64.2 (CH_2) and 175.0 (C=O); GPC: M_n 1059, PDi 1013; *m/z* 802 ($M+Na^+$ requires 802).

6.2.26 G_1Ali-H-[4]-OTBDMS 50

This compound was prepared using an adaptation of a literature procedure.[105] Reactions were carried out on 0.5-10 g scale. Compound **47** (0.94 g, 2.46 mmol), hydroquinone (113 mg, 1 mmol) and DMAP (0.25g, 2.05 mmol) were stirred under nitrogen in dry dichloromethane (10 ml) for 5 days. The solvent was removed from the reaction vessel in *vacuo*. Petroleum ether (20 ml) was added to the white solid to give a white solution. Any solids were removed by suction filtration to yield a clear solution. This solution was then evaporated to dryness and the crude product was purified using flash chromatography eluting with dichloromethane to give a white solid (0.73 g, 92%). Spectral data were identical to those from **6.2.17.**

6.2.27 G_1Ali-B-[4]-OTBDMS 54

This compound was prepared using an adaptation of a literature procedure.[105] Reactions were carried out on 0.5-10 g scale. Compound **47** (0.94 g, 2.46 mmol), 1,4-butanediol (92.3 mg, 1 mmol) and DMAP (0.25g, 2.05 mmol) were stirred under nitrogen in dry dichloromethane (10 ml) for 5 days. Work up was as for **6.2.19**. The crude product was purified using flash chromatography eluting with dichloromethane to give a white solid (0.71 g, 91%). Spectral data were identical to those from **6.2.18**.

6.2.28 Attempted Synthesis Of G_1Ali-H-[4]-OH

Using an adaptation of a literature procedure,[92] Compound **50** (0.23 g, 0.288 mmol) was placed in a round bottom flask with dry THF (5 ml). The solution was degassed and flushed with nitrogen three times. The solution was cooled using an ice bath and TBAF in THF(1M solution) (2.08 ml, 2.08 mmol) was added dropwise. The solution was then stirred at 5 °C overnight. The dark solution was diluted with brine (10 ml) and extracted with ethyl acetate (2 x 20 ml). The combined organic extracts were washed with brine (2 x 20 ml), dried with magnesium sulfate and concentrated in *vacuo*. The resultant black solid was taken up in chloroform to give a viscous black solution. This was then filtered using suction filtration. The filtrate and solution were both analysed by ^{1}H NMR. The product showed no NMR resonances which were consistent with the desired product.

6.2.29 Attempted Synthesis Of G_1Ali-H-[4]-OH

Using an adaptation of a literature procedure,[93] G_1Ali-H-[4]-OTBDMS (0.30 g, 0.375 mmol) was placed in a round bottom flask with aqueous acetic acid (acetic acid:water, 1:4) (10 ml). The reaction mixture was refluxed for 3 hours.. The clear solution was evaporated to dryness with the use of toluene to remove any excess acetic acid. The resultant yellow solid was dissolved in acetone, dried over magnesium sulfate and evaporated to dryness. ^{1}H and ^{13}C NMR

spectra of the product yellow oil showed only starting material and other unidentified by products.

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6.2.30 Attempted Synthesis Of G_1Ali-H-[4]-OH

The previous reaction was repeated but with a higher proportion of acetic acid (acetic acid:water, 4:1). The work up was also the same, however, the crude product was purified using flash chromatography eluting with ethyl acetate and petroleum ether (3:2). The ^{1}H NMR spectrum revealed starting material was present (0.28g, 94%).

6.2.31 Attempted Synthesis Of G_1Ali-H-[4]-OH

Using an adaptation of a literature procedure,[94] G_1Ali-H-[4]-OTBDMS (0.211 g, 0.264 mmol) was placed in a round bottom flask with 5% aqueous hydrofluoric acid and 95% acetonitrile and stirred for four hours at room temperature. The crude reaction mixture was analysed using ^{1}H NMR which showed that only starting materials were present. The reaction was then left for longer, however, the starting material remained unchanged.

6.3 Experimental for Chapter 3

6.3.1 4,4-Bis-(4-benzyloxyphenyl)valeric acid benzyl ester 56[62]

4,4-bis(4-hydroxyphenyl)valeric acid (5.0 g, 17.5 mmol) was refluxed with benzyl bromide (7.5 ml, 63 mmol) and potassium carbonate (9.66 g, 70 mmol) in methyl ethyl ketone (60 ml) for 4 days under nitrogen. The reaction was monitored by TLC. The heavy white solid was removed by filtration, the filtrate was reduced under pressure to give a white solid. Diethyl ether (60 ml) was added and the solution was filtered again. The white solid was then recrystallised from diethyl ether to give a white solid (8.32 g, 85%) mp 83 °C, (Found: C, 81.8; H, 6.5. Calc. for $C_{38}H_{36}O_4$: C, 81.9; H, 6.5%); ν_{max} /cm^{-1} 1732 (C=O); δ_H($CDCl_3$, 250) 1.60 (3 H, s, CH_3), 2.19 (2 H, m, $C\underline{H}_2CH_2CO_2$), 2.46 (2 H, m, $CH_2C\underline{H}_2CO_2$), 5.05 (4 H, s, OCH_2Ph), 5.08 (2 H, s, CO_2CH_2Ph), 6.90 (4 H, AA'BB', *J* 9.0, ArH), 7.14 (4 H, AA'BB', *J* 9.0, ArH) and 7.31-7.48 (15 H, m, $PhCH_2$); δ_C($CDCl_3$, 62.9) 27.8 (CH_3), 30.3 ($\underline{C}H_2CH_2CO_2$), 36.5 ($CH_2\underline{C}H_2CO_2$), 44.5 ($\underline{C}CH_3$), 66.2 ($CO_2\underline{C}H_2Ph$), 69.9 ($O\underline{C}H_2Ph$), 114.2 (Ar), 127.5 (Ar), 127.9 (Ar), 128.2 (Ar), 128.5 (Ar), 135.9 (Ar), 137.0 (Ar), 141.2 (Ar), 156.8 (Ar) and 173.8 (C=O).

6.3.2 4,4-Bis-(4-benzyloxyphenyl)valeric acid 57

The synthesis of this compound was attempted using an adaptation of a literature method,[82] reactions were carried out on a 1-50 g scale. Compound **56** (5.0 g, 9.0 mmol) was dissolved in ethanol (50 ml). To this solution 40% aqueous potassium hydroxide (100 ml) was added and the resultant solution was refluxed for 20 hours. The cooled solution was poured into water (150 ml) and adjusted to pH 5 with hydrochloric acid. The resulting yellow precipitate was removed by filtration and dissolved in dichloromethane (150 ml). The organic phase was dried with anhydrous magnesium sulfate and evaporated to dryness under reduced pressure to give a pale yellow solid (3.77 g, 90%) mp 86 °C, (Found: C, 79.8; H, 6.5. Calc. for $C_{31}H_{30}O_4$: C, 79.8; H, 6.5%); ν_{max} /cm^{-1} 3110-3405 (OH) and 1690 (C=O); δ_H($CDCl_3$, 250) 1.58 (3 H, s, CH_3), 2.16 (2 H, m, $C\underline{H}_2CH_2CO_2$), 2.42 (2 H, m, $CH_2C\underline{H}_2CO_2$), 5.03 (4 H, s, OCH_2Ph), 6.88 (4 H, AA'BB', *J* 9.0, ArH), 7.11 (4 H, AA'BB', *J* 9.0, ArH) and 7.30-7.46 (10 H, m, $PhCH_2$); δ_C($CDCl_3$, 62.9) 27.7 (CH_3), 30.1 ($\underline{C}H_2CH_2CO_2$), 36.3 ($CH_2\underline{C}H_2CO_2$), 44.4 ($\underline{C}CH_3$), 69.9 ($O\underline{C}H_2Ph$), 114.3 (Ar), 127.5 (Ar), 127.9 (Ar), 128.2 (Ar), 128.5 (Ar), 137.0 (Ar), 141.0 (Ar), 156.8 (Ar) and 180.3 (C=O); M^+, 466.2143. M^+ requires 466.2141.

6.3.3 4,4-Bis-(4-benzyloxyphenyl)valeryl chloride 58

Compound **57** (0.50 g, 1.15 mmol) was refluxed with an excess of oxalyl chloride (8 ml) for 1 hour. The excess oxalyl chloride was removed under reduced pressure to yield a colourless oil. The crude product could then be used without any further purification; (0.54 g, 97%) (Found: C, 76.9; H, 6.2. Calc. for $C_{31}H_{29}O_3Cl$: C, 76.8; H, 6.0%); ν_{max} /cm^{-1} 1714 (C=O) and 1581 (C=C) ring; δ_H($CDCl_3$, 250) 1.64 (3 H, s, CH_3), 2.53 (2 H, m, $C\underline{H}_2CH_2COCl$), 2.75 (2 H, m, $CH_2C\underline{H}_2COCl$), 5.09 (4 H, s, OCH_2Ph), 6.96 (4 H, AA'BB', *J* 8.4, ArH), 7.15 (4 H, AA'BB', *J* 8.4, ArH) and 7.37-7.51 (10 H, m, $PhCH_2$); δ_C($CDCl_3$, 62.9) 27.8 (CH_3), 36.5 ($\underline{C}H_2CH_2CO_2$), 43.6 ($CH_2\underline{C}H_2CO_2$), 44.3 ($\underline{C}CH_3$), 70.0 ($O\underline{C}H_2Ph$), 114.3 (Ar), 127.5 (Ar), 128.0 (Ar), 128.1 (Ar), 128.6 (Ar), 137.0 (Ar), 140.4 (Ar), 157.0 (Ar) and 174.1 (C=O).

6.3.4 G_1Aro-B-[4]-OBn 59

This compound was prepared using an adaptation of a literature procedure.[105] Reactions were carried out on 0.5-10 g scale. Compound **58** (0.42 g, 0.93 mmol), 1,4-butanediol (35.0 mg, 0.39 mmol) and DMAP (94 mg, 0.77 mmol) were stirred under nitrogen in dry dichloromethane (10 ml) for 5 days. Work up was as for **6.2.19**. The crude product was purified using flash chromatography eluting with dichloromethane to give a white solid (0.33 g, 86%), mp 93 °C,

(Found: C, 80.5; H, 6.9. Calc. for $C_{66}H_{66}O_8$: C, 80.3; H, 6.7%); ν_{max} /cm^{-1} 1698 (C=O); δ_H($CDCl_3$, 250) 1.67 (6 H, s, CH_3), 1.72 (4 H, m, $C\underline{H}_2CH_2O$), 2.20 (4 H, m, $C\underline{H}_2CH_2CO_2$), 2.52 (4 H, m, $CH_2C\underline{H}_2CO_2$), 4.12 (4 H, t, $CH_2C\underline{H}_2O$), 5.09 (8 H, s, $OC\underline{H}_2Ph$), 6.97 (8 H, AA'BB', *J* 7.5, ArH), 7.15 (8 H, AA'BB', *J* 7.5, ArH) and 7.35-7.41 (20 H, m, $PhCH_2$); δ_C($CDCl_3$, 62.9) 25.2 (CH_3), 27.8 ($\underline{C}H_2CH_2CO_2$), 30.3 ($\underline{C}H_2CH_2O$), 36.6 ($CH_2\underline{C}H_2CO_2$), 44.5 ($\underline{C}CH_3$), 63.9 ($CH_2\underline{C}H_2O$), 70.0 ($O\underline{C}H_2Ph$), 114.3 (Ar), 127.5 (Ar), 128.0 (Ar), 128.3 (Ar), 128.6 (Ar), 137.1 (Ar), 141.2 (Ar), 156.7 (Ar) and 173.9 (C=O); GPC: M_n 1212, PDi 1014; *m/z* 1010 ($M+Na^+$ requires 1010).

6.3.5 G_1Aro-B-[4]-OBn 59

This compound was prepared using an adaptation of a literature procedure.[90] Reactions were carried out on 0.5-10 g scale. Compound **57** (0.5 g, 1.15 mmol) and 1,4-butanediol (47.0 mg, 0.52 mmol) were stirred in a Schlenk tube under nitrogen with dry acetone (10 ml). DCC (0.26 g, 1.26 mmol) and DPTS (62 mg, 0.21 mmol) were added to the solution which was then stirred for a further 3 days during which time a heavy white precipitate formed. The reaction was monitored by GPC. The work up was the same as for **6.2.17**. The crude white product was purified using flash chromatography eluting with dichloromethane to give a white solid (0.31 g, 61%). Spectral data were as for **6.3.4**.

6.3.6 G_1Aro-H-[4]-OBn 60

This compound was prepared using an adaptation of a literature procedure.[105] Reactions were carried out on 0.5-10 g scale. Compound **58** (1.0 g, 2.06 mmol), hydroquinone (94 mg, 0.86 mmol) and DMAP (0.21 g, 1.72 mmol) were stirred under nitrogen in dry dichloromethane (10 ml) for 5 days. Work up was as for **6.2.19**. The crude product was purified using flash chromatography eluting with dichloromethane to give a white solid (0.79 g, 91%), mp 73 °C, (Found: C, 81.2; H, 6.2. Calc. for $C_{68}H_{62}O_8$: C, 81.1; H, 6.2%); ν_{max} /cm^{-1} 1751 (C=O); δ_H($CDCl_3$, 250) 1.70 (6 H, s, CH_3), 2.42 (4 H, m, $C\underline{H}_2CH_2CO_2$), 2.59 (4 H, m, $CH_2C\underline{H}_2CO_2$), 5.09 (8 H, s, $OC\underline{H}_2Ph$), 6.97 (8 H, AA'BB', *J* 7.5, ArH), 7.10 (4 H, s, Ar), 7.21 (8 H, AA'BB', *J* 7.5, ArH) and 7.37-7.52 (20 H, m, $PhCH_2$); δ_C($CDCl_3$, 62.9) 27.9 (CH_3), 30.4 ($\underline{C}H_2CH_2CO_2$), 36.4 ($CH_2\underline{C}H_2CO_2$), 44.6 ($\underline{C}CH_3$), 70.0 ($O\underline{C}H_2Ph$), 114.3 (Ar), 122.3 (Ar), 127.5 (Ar), 127.9 (Ar), 128.3 (Ar), 128.6 (Ar), 137.1 (Ar), 141.0 (Ar), 147.9 (Ar), 156.9 (Ar) and 172.2(C=O); GPC: M_n 1329, PDi 1.030; *m/z* 1030 ($M+Na^+$ requires 1030).

6.3.7 G_1Aro-H-[4]-OBn 60

This compound was prepared using an adaptation of a literature procedure.[90] Reactions were carried out on 0.5-10 g scale. Compound **57** (5.0 g, 10.7 mmol) and hydroquinone (0.49 mg, 4.47 mmol) were stirred in a Schlenk tube under

nitrogen with dry acetone (10 ml). DCC (2.21 g, 10.7 mmol) and DPTS (0.53 g, 1.80 mmol) were added to the solution which was then stirred for a further 3 days during which time a heavy white precipitate formed. The reaction was monitored by GPC. The work up was the same as for **6.2.17**. The crude white product was purified using flash chromatography eluting with dichloromethane to give a white solid (2.48 g, 59%). Spectral data were as for **6.3.6**.

6.3.8 G_1Aro-B-[4]-OH 61

This compound was prepared using an adaptation of a literature procedure.[95] Reactions were carried out on 0.5-8 g scale. G_1Aro-B-[4]-OBn (5.41 g, 5.48 mmol) was placed in a hydrogenation flask. Chloroform was added until the dendrimer had dissolved. Methanol was added slowly until a precipitate could be seen. This precipitate was then redissolved by the addition of more chloroform. To the flask 10% Pd/C (0.54 g) was added. This value was always 10% by weight of the dendrimer. The flask and its contents were shaken under an atmosphere of hydrogen (25-45 psi) for 2 days. The reaction was monitored by TLC and GPC. The crude solution was filtered through celite and then evaporated to dryness. The crude product was purified using flash chromatography eluting with dichloromethane to give a white solid (3.06 g, 89%), mp 189 °C, (Found: C, 73.0; H, 6.7. Calc. for $C_{38}H_{42}O_8$: C, 72.8; H, 6.8%); ν_{max} /cm^{-1} 3222-3402 (OH) and 1698 (C=O); δ_H([$^2H_6$]-acetone, 250) 1.47 (6 H, s, CH_3), 1.55 (4 H, m, C<u>H</u>$_2$CH$_2$O), 2.01 (4 H, m, C<u>H</u>$_2$CH$_2$CO$_2$), 2.29 (4 H,

m, $CH_2C\underline{H}_2CO_2$), 3.95 (4 H, t, $CH_2C\underline{H}_2O$), 6.68 (8 H, AA'BB', *J* 8.5, ArH) and 6.96 (8 H, AA'BB', *J* 8.5, ArH); δ_C([$^2H_6$]-acetone, 62.9) 26.3 (CH_3), 28.4 ($\underline{C}H_2CH_2CO_2$), 30.3 ($\underline{C}H_2CH_2O$), 37.8 ($CH_2\underline{C}H_2CO_2$), 45.3 ($\underline{C}CH_3$), 64.6 ($CH_2\underline{C}H_2O$), 115.9 (Ar), 129.3 (Ar), 141.2 (Ar), 156.4 (Ar) and 174.4 (C=O); GPC: M_n 956, PDi 1.003; *m/z* 649 ($M+Na^+$ requires 650).

6.3.9 G_1Aro-H-[4]-OH 62

This compound was prepared using an adaptation of a literature procedure.[95] Reactions were carried out on 0.5-8 g scale. G_1Aro-H-[4]-OBn (0.49 g, 0.49 mmol) was placed in a hydrogenation flask with 10%Pd/C see **6.3.8** for method and work up. The crude product was purified using flash chromatography eluting with dichloromethane to give a white solid (0.29 g, 92%), mp 118 °C, (Found: C, 73.6; H, 6.2. Calc. for $C_{40}H_{38}O_8$: C, 74.3; H, 5.9%); ν_{max} /cm^{-1} 3050-3510 (OH) and 1734 (C=O); δ_H([$^2H_6$]-acetone, 250) 1.54 (6 H, s, CH_3), 2.38 (4 H, m, $C\underline{H}_2CH_2CO_2$), 2.46 (4 H, m, $CH_2C\underline{H}_2CO_2$), 6.76 (8 H, AA'BB', *J* 7.5, ArH) and 7.07 (8 H, AA'BB', *J* 7.5, ArH); δ_C([$^2H_6$]-acetone, 250) 28.1 (CH_3), 30.4 ($\underline{C}H_2CH_2CO_2$), 37.3 ($CH_2\underline{C}H_2CO_2$), 45.1 ($\underline{C}CH_3$), 115.6 (Ar), 123.3 (Ar), 129.0 (Ar), 140.8 (Ar), 149.1 (Ar), 156.2 (Ar) and 172.7 (C=O); GPC: M_n 1044, PDi 1.080; *m/z* 670 ($M+Na^+$ requires 670).

6.3.10 G_2Aro-B-[8]-OBn 63[105]

Reactions were carried out on 0.5-2 g scale. Compound **61** (0.68 g, 1.08 mmol), 58 (2.53 g, 5.21 mmol) and DMAP (0.53 g, 4.34 mmol) were stirred under nitrogen in dry dichloromethane (7 ml) for 5 days. Work up was as for **6.2.19**. The crude product was purified using flash chromatography eluting with dichloromethane to give a white solid (2.12 g, 81%), mp 143 °C, (Found: C, 80.7; H, 6.5. Calc. for $C_{162}H_{154}O_{20}$: C, 80.4; H, 6.4%); ν_{max} /cm^{-1} 1720 (C=O); δ_H($CDCl_3$, 250) 1.69 (18 H, s, CH_3), 1.75 (4 H, m, $C\underline{H}_2CH_2O$), 2.31 (12 H, m, $C\underline{H}_2CH_2CO_2$), 2.53 (12 H, m, $CH_2C\underline{H}_2CO_2$), 4.08 (4 H, t, $CH_2C\underline{H}_2O$), 5.09 (16 H, s, $OC\underline{H}_2Ph$) and 6.94-7.44 (88 H, m, Ar); GPC: M_n 2289, PDi 1.006; *m/z* 2444 ($M+Na^+$ requires 2444).

6.3.11 G_2Aro-B-[8]-OBn 63

This compound was prepared using an adaptation of a literature procedure.[90] Reactions were carried out on 0.5-2 g scale. Compound **61** (0.51 g, 0.81 mmol) and **57** (1.82 g, 3.91 mmol) were stirred in a Schlenk tube under nitrogen with dry acetone (7 ml). DCC (0.81 g, 3.91 mmol) and DPTS (0.19 g, 0.65 mmol) were added to the solution which was then stirred for a further 7 days during which time a heavy white precipitate formed. The reaction was monitored by GPC. The work up was the same as for **6.2.17**. The crude white product was

purified using flash chromatography eluting with dichloromethane to give a white solid (1.67 g, 85%). Spectral data were as for **6.3.10**.

6.3.12 G_2Aro-H-[8]-OBn 65[105]

Reactions were carried out on 0.5-2 g scale. Compound **62** (0.76 g, 1.18 mmol), **58** (2.74 g, 5.64 mmol) and DMAP (0.57 g, 4.70 mmol) were stirred under nitrogen in dry dichloromethane (7 ml) for 5 days. Work up was as for **6.2.19**. The crude product was purified using flash chromatography eluting with dichloromethane to give a white solid (2.29 g, 80%), mp 168 °C, (Found: C, 80.9; H, 6.2. Calc. for $C_{164}H_{150}O_{20}$: C, 80.7; H, 6.2%); ν_{max} /cm^{-1} 1731 (C=O); δ_H($CDCl_3$, 250) 1.64 (18 H, s, CH_3), 2.38 (12 H, m, $C\underline{H}_2CH_2CO_2$), 2.51 (12 H, m, $CH_2C\underline{H}_2CO_2$), 5.04 (16 H, s, $OC\underline{H}_2Ph$) and 6.90-7.55 (92 H, m, Ar); GPC: M_n 2292, PDi 1.007; *m/z* 2464 ($M+Na^+$ requires 2464).

6.3.13 G_2Aro-H-[8]-OBn 65

This compound was prepared using an adaptation of a literature procedure.[90] Reactions were carried out on 0.5-3 g scale. Compound **62** (0.95 g, 14.7 mmol) and **57** (3.29 g, 7.05 mmol) were stirred in a Schlenk tube under nitrogen with dry acetone (10 ml). DCC (1.45 g, 7.05 mmol) and DPTS (0.36 g, 1.18 mmol) were added to the solution which was then stirred for a further 3 days during

which time a heavy white precipitate formed. The reaction was monitored by GPC. The work up was the same as for **6.2.17**. The crude white product was purified using flash chromatography eluting with dichloromethane to give a white solid (3.12 g, 87%). Spectral data were as for **6.3.12**.

6.3.14 G_2Aro-B-[8]-OH 64

This compound was prepared using an adaptation of a literature procedure.[95] Reactions were carried out on 0.5-2 g scale. G_2Aro-B-[8]-OBn (0.59 g, 0.24 mmol) was placed in a hydrogenation flask with 10% Pd/C see **6.3.8** for method and work up. The crude product was purified using flash chromatography eluting with dichloromethane to give a white solid (0.34 g, 83%), mp 217 °C, (Found: C, 75.2; H, 6.3. Calc. for $C_{106}H_{106}O_{20}$: C, 74.9; H, 6.3%); ν_{max} /cm^{-1} 3116-3510 (OH) and 1698 (C=O); δ_H([$^2H_6$]-acetone, 250) . 1.63 (18 H, s, CH_3), 1.71 (4 H, m, C$\underline{H}_2$CH$_2$O), 2.281 (12 H, m, C$\underline{H}_2$CH$_2$CO$_2$), 2.49 (12 H, m, CH$_2$C$\underline{H}_2$CO$_2$), 4.01 (4 H, t, CH$_2$C$\underline{H}_2$O) and 7.03-7.38 (48 H, m, Ar); GPC: M_n 2276, PDi 1.008; *m/z* 1724 (M+Na$^+$ requires 1723).

6.3.15 G_2Aro-H-[8]-OH 65

This compound was prepared using an adaptation of a literature procedure.[95] Reactions were carried out on 0.5-2 g scale. G_2Aro-H-[4]-OBn (0.49 g, 0.49 mmol) was placed in a hydrogenation flask with 10% Pd/C see **6.3.8** for method and work up. The crude product was purified using flash chromatography eluting with dichloromethane to give a white solid (0.29 g, 92%), mp 217 °C, (Found: C, 74.9; H, 6.2. Calc. for $C_{108}H_{102}O_{20}$: C, 74.4; H, 6.0%); ν_{max} /cm^{-1} 3116-3510 (OH) and 1698 (C=O); δ_H([$^2H_6$]-acetone, 250) 1.64 (18 H, s, CH_3), 2.31 (12 H, m, $C\underline{H}_2CH_2CO_2$), 2.47 (12 H, m, $CH_2C\underline{H}_2CO_2$) and 7.05-7.35 (52 H, m, Ar); GPC: M_n 2285, PDi 1.007; *m/z* 1744 (M+Na$^+$ requires 1743).

6.4 Experimental for Chapter 4

6.4.1 G_1Aro-B-[4]-O-pent-4-enoyl 68

Using an adaptation of a literature procedure,[90] G_1Aro-B-[4]-OH (0.64 g, 1.02 mmol), pent-4-enoic acid (0.49 g, 4.90 mmol), DCC (1.01 g, 4.90 mmol) and DPTS (0.24 g, 0.82 mmol) were stirred in dry acetone (20 ml) under nitrogen for 4 days. The reaction was monitored by GPC. The solution was filtered and reduced under pressure. The product crude oil was dissolved in dichloromethane (20 ml) and washed with water (3 x 15 ml). The organic layer was dried over magnesium sulfate and concentrated *in vacuo*. The product oil was purified by flash chromatography eluting with dichloromethane-hexane (4:1) to give a clear, colourless oil (0.46 g, 47%), (Found: C, 72.6; H, 6.8. Calc. for $C_{58}H_{66}O_{12}$: C, 72.9; H, 7.0%); ν_{max}/cm^{-1} 1757 (C=O) and 1505 (C=C); δ_H($CDCl_3$, 250) 1.61 (10 H, m, $C\underline{H}_2CH_2O$ and CH_3), 2.09 (4 H, m, $C\underline{H}_2CH_2CO_2$), 2.44 (12 H, m, $CH_2C\underline{H}_2CO_2$ and $C\underline{H}_2CH{=}CH_2$), 2.64 (8 H, m, $C\underline{H}_2CH_2CH{=}CH_2$), 4.02 (4 H, t, $CH_2C\underline{H}_2O$), 5.05 (8 H, m, $CH{=}C\underline{H}_2$), 5.88 (4 H, m, $C\underline{H}{=}CH_2$), 6.97 (8 H, AA'BB', *J* 7.5, Ar H) and 7.17 (8 H, AA'BB', *J* 7.5, ArH); δ_C($CDCl_3$, 62.9) 25.1 (CH_3), 27.7 (CH_2), 28.8 (CH_2), 30.0 (CH_2), 33.5 (CH_2), 36.3 (CH_2), 45.2 ($\underline{C}CH_3$), 63.9 (OCH_2), 115.9 ($CH{=}\underline{C}H_2$), 121.0 (Ar), 128.2 (Ar), 136.22 ($\underline{C}H{=}CH_2$), 145.7 (Ar), 148.7 (Ar), 171.44 (C=O) and 173.5 (C=O); GPC: M_n 1425, PDi 1.004; *m/z* 978 ($M+Na^+$ requires 978).

6.4.2 G_1Aro-H-[4]-O-pent-4-enoyl 69[90]

Synthesis of this compound was the same as for **6.4.1**. G_1Aro-H-[4]-OH (1.00 g, 1.55 mmol), pent-4-enoic acid (0.74 g, 7.42 mmol), DCC (1.53 g, 7.42 mmol) and DPTS (0.36 g, 1.24 mmol) were stirred in dry acetone (20 ml) under nitrogen for 4 days. Work up was as for **6.4.1**. Flash chromatography afforded a clear, colourless oil (0.85 g, 56%) (Found: C, 73.5; H, 6.7. Calc. for $C_{60}H_{62}O_{12}$: C, 73.9; H, 6.4%); ν_{max}/cm^{-1} 1747 (C=O) and 1650 (C=C); δ_H($CDCl_3$, 250) 1.66 (6 H, s, CH_3), 2.36 (4 H, m, $C\underline{H}_2CH_2CO_2$), 2.52 (12 H, m, $CH_2C\underline{H}_2CO_2$ and $C\underline{H}_2CH=CH_2$), 2.68 (8 H, m, $C\underline{H}_2CH_2CH=CH_2$), 5.10 (8 H, m, $CH=C\underline{H}_2$), 5.89 (4 H, m, $C\underline{H}=CH_2$), 7.00 (12 H, AA'BB', *J* 7.5, Ar H) and 7.17 (8 H, AA'BB', *J* 7.5, ArH); δ_C($CDCl_3$, 62.9) 27.7 (CH_3), 28.9 (CH_2), 29.2 (CH_2), 33.5 (CH_2), 36.1 (CH_2), 45.2 ($\underline{C}CH_3$), 115.8 ($CH=\underline{C}H_2$),, 121.1 (Ar), 122.2 (Ar), 128.2 (Ar), 136.2 ($\underline{C}H=CH_2$),, 145.5 (Ar), 147.7 (Ar), 148.8 (Ar), 171.4 (C=O) and 171.9 (C=O); GPC: M_n 1585, PDi 1.003; *m/z* 998 ($M+Na^+$ requires 998).

6.4.3 Attempted Synthesis G_1Aro-H-[4]-O-carbamic acid methoxyphenyl ester 71

Synthesis of this compound was attempted using an adaptation of a literature procedure.[98]. To a stirred solution of G_1Aro-H-[4]-OH (0.15 g, 0.23 mmol) in dry THF (10ml) methoxy phenyl isocyanate (0.166 g, 1.11 mmol) followed by copper(I) chloride (91.8 mg, 0.93 mmol) were added. The green solution was

stirred under nitrogen for 2 days. The mixture was filtered through a pad of celite to remove the insoluble copper species and the filtrate was evaporated to dryness under reduced pressure. The resulting oil was dissolved in dichloromethane (20 ml) and washed with water (3 x 10 ml). The organic layer was dried over anhydrous magnesium sulfate and evaporated to dryness. The resultant oil was purified by flash chromatography eluting with dichloromethane increasing to acetone-dichloromethane (1:9). Like fractions were analysed by ^{1}H NMR, the only product formed that was identified was dendritic starting material (0.07 g, 47%).

6.4.4 (4-Methoxyphenyl)carbamic acid phenyl ester 70[99]

Methoxyphenyl isocyanate (0.95 g, 6.4 mmol) was added to a solution of phenol (0.50 g, 5.3 mmol) dissolved in dry THF (20 ml). The solution was refluxed under nitrogen for 24 hours. The reaction was monitored by TLC. The solution was allowed to cool to room temperature, filtered and then the filtrate was reduced *in vacuo*. The resultant oil was dissolved in dichloromethane (20 ml) and washed with water (3 x 15 ml). The organic layer was dried over anhydrous magnesium sulfate and evaporated to dryness. The crude solution was purified using flash chromatography eluting first with dichloromethane and then acetone-dichloromethane (1:9) to give the product as a white solid (1.14 g, 87%) mp 153 °C (Found: C; 68.9, H; 5.4, N; 5.6. Calc. for $C_{14}H_{13}NO_3$: C, 69.1; H; 5.4; N; 5.8%); ν_{max}/cm^{-1} 3337 (NH) and 1709 (C=O); δ_H($CDCl_3$, 250) 3.79 (3

H, s, CH_3) and 6.86-7.42 (10 H, m, ArH and NH); δ_C($CDCl_3$, 100.6) 55.5 (OCH_3), 114.4 (Ar), 120.7 (Ar), 121.7 (Ar), 125.6 (Ar), 129.4 (Ar), 130.5(Ar), 150.7 (CCO), 152.0 (C=O) and 156.3 ($COCH_3$).

6.4.5 (4-Methoxyphenyl)carbamic acid phenyl ester 70[99]

Methoxyphenyl isocyanate (0.95 g, 6.4 mmol) was added to a solution of phenol (0.50 g, 5.3 mmol) dissolved in dry toluene (20 ml). The mixture was refluxed under nitrogen for 24 hours. The reaction was monitored by TLC. The solution was allowed to cool to room temperature and the resulting white crystals were collected by filtration and dried on a freeze drier. It was found that the white solid required no further purification; (1.19g, 92%). Spectral data were as for **6.4.4**.

6.4.6 G_1Aro-H-[4]-O-carbamic acid methoxyphenyl ester 71[99]

To a solution of G_1Aro-H-[4]-OH (0.5 g, 0.773 mmol) in dry toluene (20 ml) methoxyphenyl isocyanate (0.55g, 3.7 mmol) was added. The mixture was then refluxed for 24 hours under nitrogen. The reaction was monitored by GPC. The solution was then evaporated to dryness. The resultant oil was dissolved in dichloromethane (20 ml) and washed with water (3 x 15 ml). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. To

yield a pink solid (0.44 g, 46%) mp 125 °C, (Found: C, 69.8; H, 5.4; N, 4.5. Calc. for $C_{72}H_{66}N_4O_{16}$: C, 69.6; H, 5.4; N, 4.5%); ν_{max}/cm^{-1} 3359 (NH) and 1737 (C=O); $\delta_H(CDCl_3, 250)$ 1.72 (6 H, s, CH_3), 2.44 (4 H, m, $C\underline{H}_2CH_2CO_2$), 2.59 (4 H, m, $CH_2C\underline{H}_2$ CO_2), 4.15 (12 H, s, OCH_3) and 6.76-7.38 (40 H, m, ArH and NH); GPC: M_n 1992, PDi 1.00; *m/z* 1266 ($M+Na^+$ requires 1266).

6.4.7 G_1Aro-B-[4]-O-carbamic acid methoxyphenyl ester 72[99]

To a solution of G_1Aro-B-[4]-OH (0.31 g, 0.49 mmol) in dry toluene (20 ml) methoxyphenyl isocyanate (0.35 g, 2.37 mmol) was added. The mixture was refluxed for 24 hours under nitrogen. The reaction was monitored by GPC. The mixture was filtered to yield a tan product. Work up was as for **6.4.6**. The resultant brown crystals were purified using flash column chromatography eluting first with dichloromethane then increasing to acetone-dichloromethane (1: 19) to give cream crystals (0.25 g, 41%) mp 115 °C, (Found: C, 68.9; H, 5.8; N, 4.7. Calc. for $C_{70}H_{70}N_4O_{16}$: C, 68.7; H, 5.8; N, 4.6%); ν_{max}/cm^{-1} 3357 (NH) and 1738 (C=O); $\delta_H(CDCl_3, 250)$ 1.56 (6 H, s, CH_3), 1.66 (4 H, m, $C\underline{H}_2CH_2O$), 2.13 (4 H, m, $C\underline{H}_2CH_2CO_2$), 2.43 (4 H, m, $CH_2C\underline{H}_2CH_2$), 3.77 (12 H, s, OCH_3), 4.00 (4 H, t, $CH_2C\underline{H}_2O$) and 6.83-7.39 (36 H, m, ArH and NH); GPC: M_n 1472, PDi 1.000; *m/z* 1245 ($M+Na^+$ requires 1246).

6.4.8 Phenyl carbamic acid phenyl ester 73

This compound was prepared using an adaptation of a literature method.[99] To a solution of phenol (0.5 g, 5.3 mmol) in dry toluene (20 ml) phenyl isocyanate (0.76g, 6.4 mmol) was added. The mixture was refluxed under nitrogen for 24 hours. The reaction was monitored by TLC. The solution was allowed to cool down to room temperature and then evaporated to dryness. Work up the same as for **6.4.4**. The organic layer was then dried over anhydrous magnesium sulfate and evaporated to dryness to yield white crystals (1.09 g, 96%) mp 121 °C, (Found: C, 72.9; H, 5.2; N, 6.6. Calc. for $C_{13}H_{11}NO_2$: C, 73.2; H, 5.2; N, 6.6%); ν_{max}/cm^{-1} 3315 (NH) and 1712 (C=O); $\delta_H(CDCl_3, 62.9)$ 7.01 (1 H, br s, NH) and 7.20 (10 H, m, ArH); $\delta_C(CDCl_3, 62.9)$ 118.8 (Ar), 121.6 (Ar), 123.8 (Ar), 125.6 (Ar), 129.0 (Ar), 129.3 (Ar), 137.3 (Ar), 150.49 (CO) and 151.7 (C=O); M^+, 213.0787. M^+ requires 213.0790.

6.4.9 G_1Aro-H-[4]-O-carbamic acid phenyl ester 74[99]

To a solution of G_1Aro-H-[4]-OH (0.5 g, 0.773 mmol) in dry toluene (20 ml) phenyl isocyanate (0.44 g, 3.7 mmol) was added. The mixture was refluxed under nitrogen for 24 hours. The reaction was monitored by GPC. The solution was allowed to cool down to room temperature and then dried *in vacuo*. The resultant oil was purified using flash chromatography eluting first with dichloromethane then increasing to acetone-dichloromethane (2:8) to give a

white solid (0.48 g, 55%) mp 115 °C, (Found: C, 73.1; H, 5.2; N, 5.1. Calc. for $C_{68}H_{58}N_4O_{12}$: C, 72.7; H, 5.2; N, 5.0%); ν_{max}/cm^{-1} 3410 (NH) and 1714 (C=O); $\delta_H(CDCl_3, 250)$ 1.66 (6 H, s, CH_3), 2.43 (4 H, m, $C\underline{H}_2CH_2CO_2$), 2.53 (4 H, m, $CH_2C\underline{H}_2CO_2$) and 7.01-7.48 (44 H, m, ArH and NH); $\delta_C(CDCl_3, 250)$ 27.9 (CH_3), 30.3 ($\underline{C}H_2CH_2CO_2$), 36.2 ($CH_2\underline{C}H_2CO_2$), 45.3 ($\underline{C}CH_3$), 118.9 (Ar), 121.3 (Ar), 122.2 (Ar), 124.0 (Ar), 128.3 (Ar), 129.1 (Ar), 137.3 (Ar), 145.5 (Ar), 148.0 (Ar), 148.7 (Ar), 151.6 (C=O) and 172.1 (C=O); GPC: M_n 1786, PDi 1.008; *m/z* 1146 ($M+Na^+$ requires 1146).

6.4.10 G_1Aro-B-[4]-O-carbamic acid phenyl ester 75[99]

To a solution of G_1Aro-B-[4]-OH (0.37 g, 0.59 mmol) in dry toluene (20 ml) phenyl isocyanate (0.34 g, 2.8 mmol) was added. The solution was refluxed for 36 hours. The reaction was monitored by GPC. The mixture was evaporated to dryness. The resultant oil was purified using flash chromatography eluting with dichloromethane-acetone (9:1) to give a white solid (0.26 g, 40%) mp 131 °C, (Found: C, 72.0; H, 5.7; N, 5.1. Calc. for $C_{66}H_{62}N_4O_{12}$: C, 71.9; H, 5.7; N, 5.1%); ν_{max}/cm^{-1} 3352 (NH) and 1731 (C=O); $\delta_H(CDCl_3, 250)$ 1.57 (6 H, s, CH_3), 1.69 (4 H, m, $C\underline{H}_2CH_2CO$), 2.14 (4 H, m, $C\underline{H}_2CH_2CO_2$), 2.44 (4 H, m, $CH_2C\underline{H}_2CO_2$), 4.01 (4 H, t, $CH_2C\underline{H}_2O$) and 7.03-7.51 (40 H, m, ArH and NH); GPC: M_n 1871, PDi 1.005; *m/z* 1126 ($M+Na^+$ requires 1126).

6.4.11 G_1Aro-B-[4]-O-linoleoyl 76[90]

Synthesis of this compound was the same as **6.4.1**. G_1Aro-B-[4]-OH (0.26 g, 0.45 mmol), linoleic acid (0.60 g, 2.14 mmol), DCC (0.44 g, 2.14 mmol) and DPTS (0.11 g, 0.36 mmol) were stirred in dry acetone (20 ml) under nitrogen for 4 days. Work up the same as **6.4.1**. Flash chromatography afforded a clear, colourless oil (0.62 g, 85%) (Found: C, 79.2; H, 9.9. Calc. for $C_{110}H_{162}O_{12}$: C, 78.8; H, 9.7%); ν_{max}/cm^{-1} 1769 (C=O) and 1592 (C=C); δ_H($CDCl_3$, 250) 0.89 (12 H, br t, $(CH_2)_4C\underline{H}_3$), 1.28 (56 H, m, CH_2), 1.62 (18 H, m, CH_2 and CH_3), 2.04 (20 H, m, CH_2), 2.34 (4 H, m, CH_2), 2.49 (8 H, m, CH_2), 2.76 (8 H, m, CH_2), 4.00 (4 H, m, CH_2), 5.32 (16 H, m, CH_2), 6.95 (8 H, AA'BB', *J* 9.0, Ar H) and 7.21 (8 H, AA'BB', *J* 9.0, ArH); GPC: M_n 2098, PDi 1.012; *m/z* 1718 ($M+K^+$ requires 1715).

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