

Review

## Polyester Dendrimers

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**Abstract:** Polyester dendrimers have been comprehensively reviewed starting from their first synthesis in the early 1990s by Hawker and Fréchet. Polyester dendrimers have attracted and continue to attract extensive interest because they are comparatively easy to make and because, whenever they have been tested, they have been found to be non-toxic. A number of different strategies for their synthesis have been examined and the methods employed for formation of the ester bond during dendrimer assembly have been summarized. The newest approaches, including the use of bifunctional orthogonally reacting dendrons and accelerated synthesis have been surveyed.

**Keywords:** dendrimers; dendrons; hyperbranched polymers; polyester dendrimers; alternating dendrimers

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### Abbreviations:

ADH	alcohol dehydrogenase
ADH-LB	alcohol dehydrogenase from <i>Lactobacillus brevis</i>
ADH-T	alcohol dehydrogenase from <i>Thermoanaerobacter sp.</i>
ATRP	atom transfer radical polymerization
bis-HMPA	2,2-bis(hydroxymethyl)propanoic acid
BOP	benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate
CCS	core cross-linked star

COMU	1-[(1-(cyano-2-ethoxy-2-oxoethylideneaminoxy)dimethylaminomorpholinomethylene)] methanaminium hexafluorophosphate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMPA	2,2-dimethoxy-1,2-diphenylacetophenone
DPPA	diphenylphosphoryl azide
DPTS	4-(dimethylamino)pyridinium <i>p</i> -toluenesulfonate
EDCI	<i>N</i> -(3-dimethylaminopropyl)- <i>N'</i> -ethylcarbodiimide hydrochloride
FDLCP	ferroelectric dendritic liquid crystalline polymer
FLCPs	ferroelectric liquid crystalline polymers
HBTU	2-(1 <i>H</i> -benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HOBT	1-hydroxybenzotriazole
LCPs	linear crystalline polymers
MTBD	7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
MOMCl	methoxymethyl chloride
NADPH	nicotinamide adenine dinucleotide phosphate
PAMAM	polyamidoamine
PEO-NH <sub>2</sub>	amine functionalized polyethylene oxide
PTP	proton-transfer polymerization
ROP	ring opening polymerization
SCROP	self-condensing ring-opening polymerization
SCVP	self-condensing vinyl polymerization
SEC	size exclusion chromatography
SET-LRP	single electron transfer living radical polymerization
SPECT	single photon emission computed tomography
TATU	2-(1 <i>H</i> -7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TBAF	tetrabutylammonium fluoride
TBDMSCl	<i>tert</i> -butyldimethylsilyl chloride
TBTU	2-(1 <i>H</i> -benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TEA	triethylamine
TPP	triphenylphosphine
TPPH <sub>2</sub>	tetraphenylporphyrin
TPPZn	zinc-cored tetraphenylporphyrin
TsEt	2- <i>p</i> -toluenesulfonyl ethyl

## 1. Introduction

The first description of molecules that have come to be known as dendrimers appeared in 1978. Vögtle and coworkers made highly branched molecules by exhaustively performing Michael-type reactions of acrylonitrile with an amine followed by the reduction of nitrile groups to primary amines [1]. When this first generation polyamine was treated with acrylonitrile followed by reduction in the same way, a second generation dendrimer was produced. Further repetition produced higher generation highly branched amines with defined structures [1]. The field developed slowly through the 1980s. In 1981, Denkwalter *et al.* at Allied Corporation described dendritic polylysine [2]. A few years later, Tomalia *et al.* reported the synthesis and characterization of the first dendritic family [3,4], now commercialized as PAMAM dendrimers. In 1985, Newkome *et al.* reported initial results about the synthesis of tribranched dendritic amides [5]. Further developments occurred in the late 1980s but the review by Tomalia *et al.* [6] sparked an explosion of research that has continued to the present, including the first syntheses of polyester dendrimers [7,8], the subject of this review. This interest has prompted the publication of at least 3 books [9–11] and many review articles, including one in 2000 on polyester dendrimers [12]. Some of the other recent reviews of dendrimer synthesis, properties, and applications are listed in the bibliography [13–37].

A major incentive for the use of polyester dendrimers as frameworks for biological applications is that whenever they have been tested, they have been found to have low toxicity [38–40], unlike many other dendrimers [33].

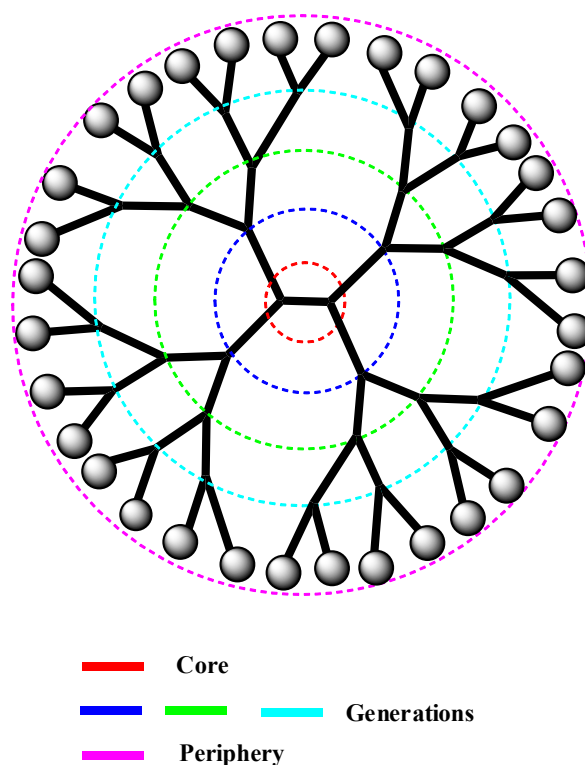
Hyperbranched polymers are branched molecules synthesized under conditions where the resulting structures cannot be precisely defined. Polymers of this type have been known since Berzelius condensed tartaric acid ( $A_2B_2$  monomer) and glycerol ( $B_3$  monomer) in the 1800s [41] followed by Watson Smith [42] and Kienle *et al.* [41,43–45] using phthalic anhydride or phthalic acid (both  $A_2$  monomers) with glycerol. Baekeland developed the first commercial plastics through polymerization of formaldehyde (latent  $A_2$  monomer) and phenol (latent  $B_3$  monomer) [46,47]. Hyperbranched polymers from single branched monomers came later. Flory [48–50] and Stockmayer [51] developed theory relating molecular size distributions to the degree of branching in the monomer and in 1952 Flory predicted molecular size distributions if they were made from  $AB_x$ -type monomers [52] and provided initial examples [53]. The first synthesis of a hyperbranched polyester from a single monomer was only reported in 1991, when Hawker and Fréchet reported the one-step thermal self-condensation of 3,5-bis(trimethylsilyloxy)benzoyl chloride [54]. A few years later, Malmström and coworkers presented a hyperbranched aliphatic system based on 2,2-bis(hydroxymethyl)propanoic acid (**1**) as the building block, and 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (**2**) as the core moiety [55], commercialized as Boltorn™ dendritic polymers by Perstop. The topic of hyperbranched polymers is very extensive and includes many types of structures including dendronized polymers [56–60], dendrigrafts [61,62] and other types of structures [63]. At least one book [63] and numerous reviews have appeared on this topic [24,55,64–74], including two recent reviews on hyperbranched polyesters based on 2,2-bis(hydroxymethyl)propanoic acid [72,74] and one on hyperbranched aromatic polyesters [70]. This review will examine polyester dendrimers. Hyperbranched polyesters are closely related and will be discussed briefly but they are adequately described by the recent reviews [70,72,74].

## 2. Structure and Synthetic Strategies

### 2.1. Dendrimers

A dendrimer is a polymeric molecule composed of multiple perfectly branched monomers that elongate radially from a central core, similar to branches of some trees. The dendritic architecture can be divided into three different regions: the core, the interior, and the periphery or end groups (Figure 1). The number of branch points encountered upon moving outward from the core to its periphery defines its generation (G1, G2, G3, *etc.*). These macromolecules are prepared in a stepwise fashion [4,75–77] and therefore, the products are theoretically monodisperse in size. A monodisperse product is extremely desirable not only for synthetic reproducibility, but also for reducing experimental and therapeutic variability [78,79]. Vögtle and coworkers have termed perfectly monodisperse dendrimers, cascades [11].

**Figure 1.** The architecture of a dendrimer.

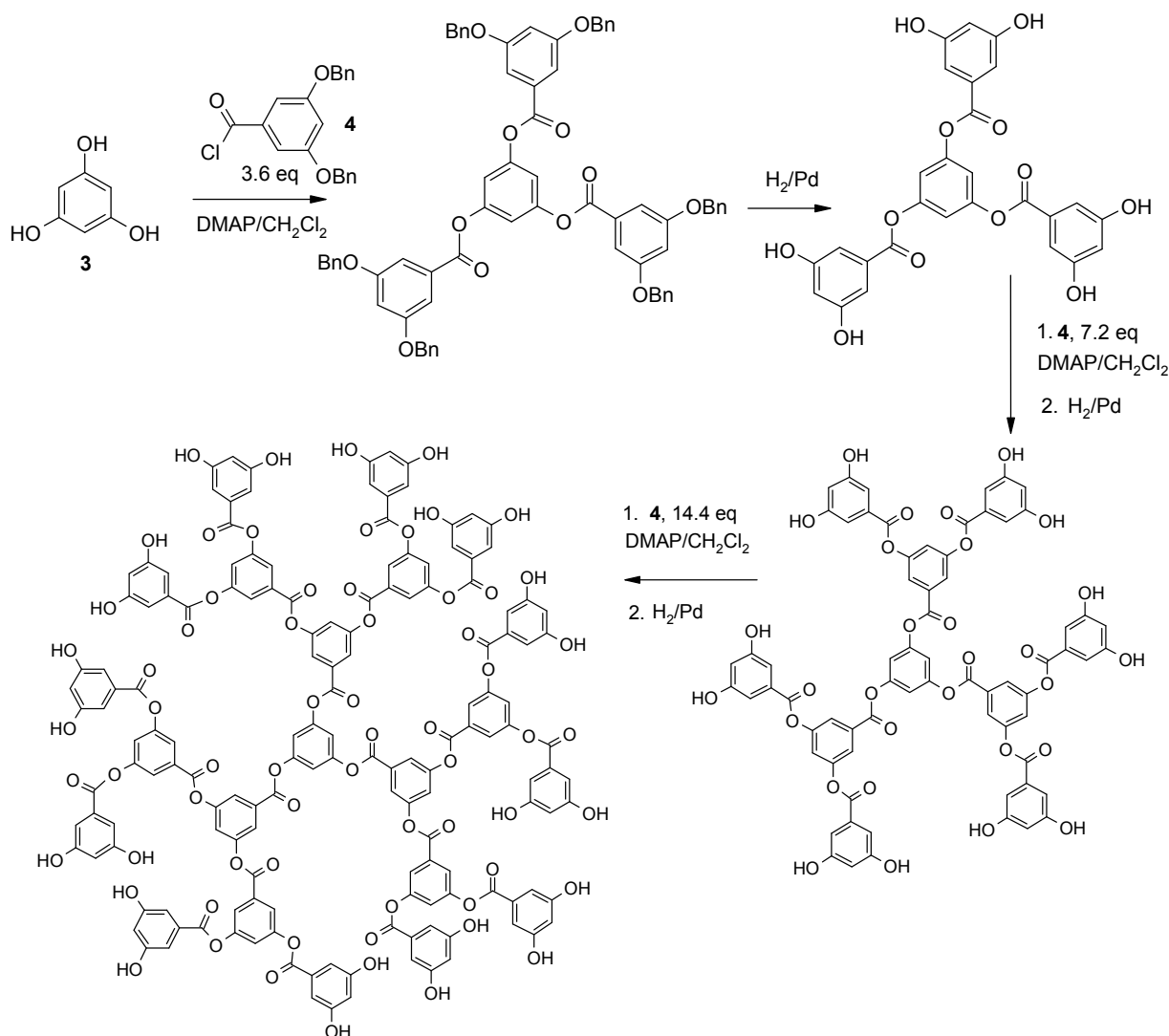


A dendrimer may be based on practically any type of chemistry, the nature of which can determine its solubility, degradability and biological activity if any.

Two strategies have been formulated for dendrimer synthesis. The divergent approach is more obvious and was used by most of the early workers in the area [1,3–5]. In this method, dendrimers grow outwards from a multifunctional core molecule. The core molecule reacts with monomeric molecules containing one reactive and various dormant groups giving the first generation dendrimer. Then the new periphery of the molecule is activated for reactions with more monomers. The process is repeated several times and a dendrimer is built layer after layer. See Scheme 1 for the first example of polyester dendrimer synthesis using this approach [80]. The number of functional groups in the

outermost layer increases exponentially with the generation number. The synthesis is elaborate and the conversion of the functional groups has to be perfect at each stage in order to guarantee a defect-free product. To prevent side reactions and to force the reaction to completion, excess reagents may be required, which causes problems in the purification of the final product. In addition, steric hindrance increases as the generation level increases so that defects and hence polydispersity increases with generation level.

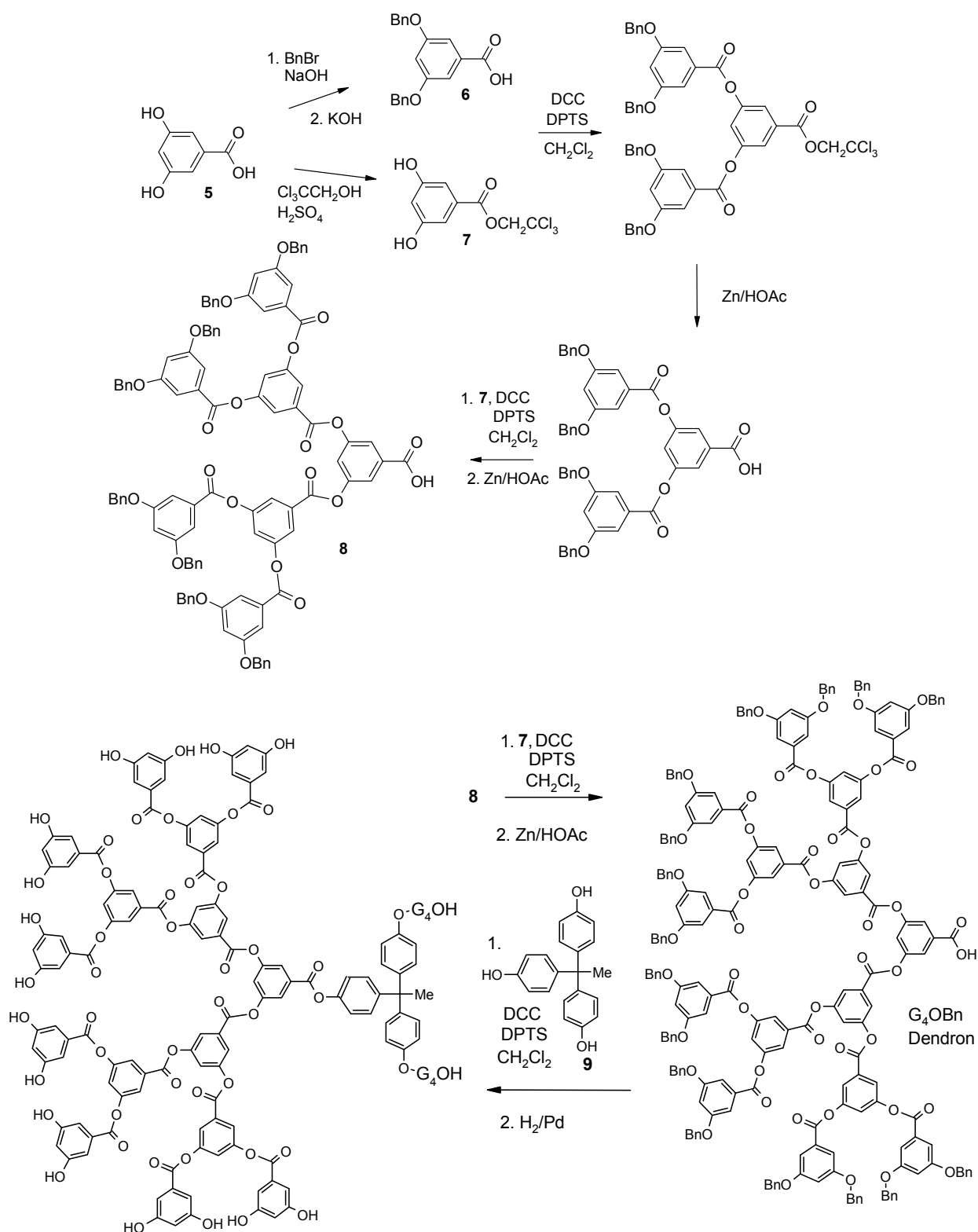
**Scheme 1.** The first example of the divergent growth approach to polyester dendrimers [80].

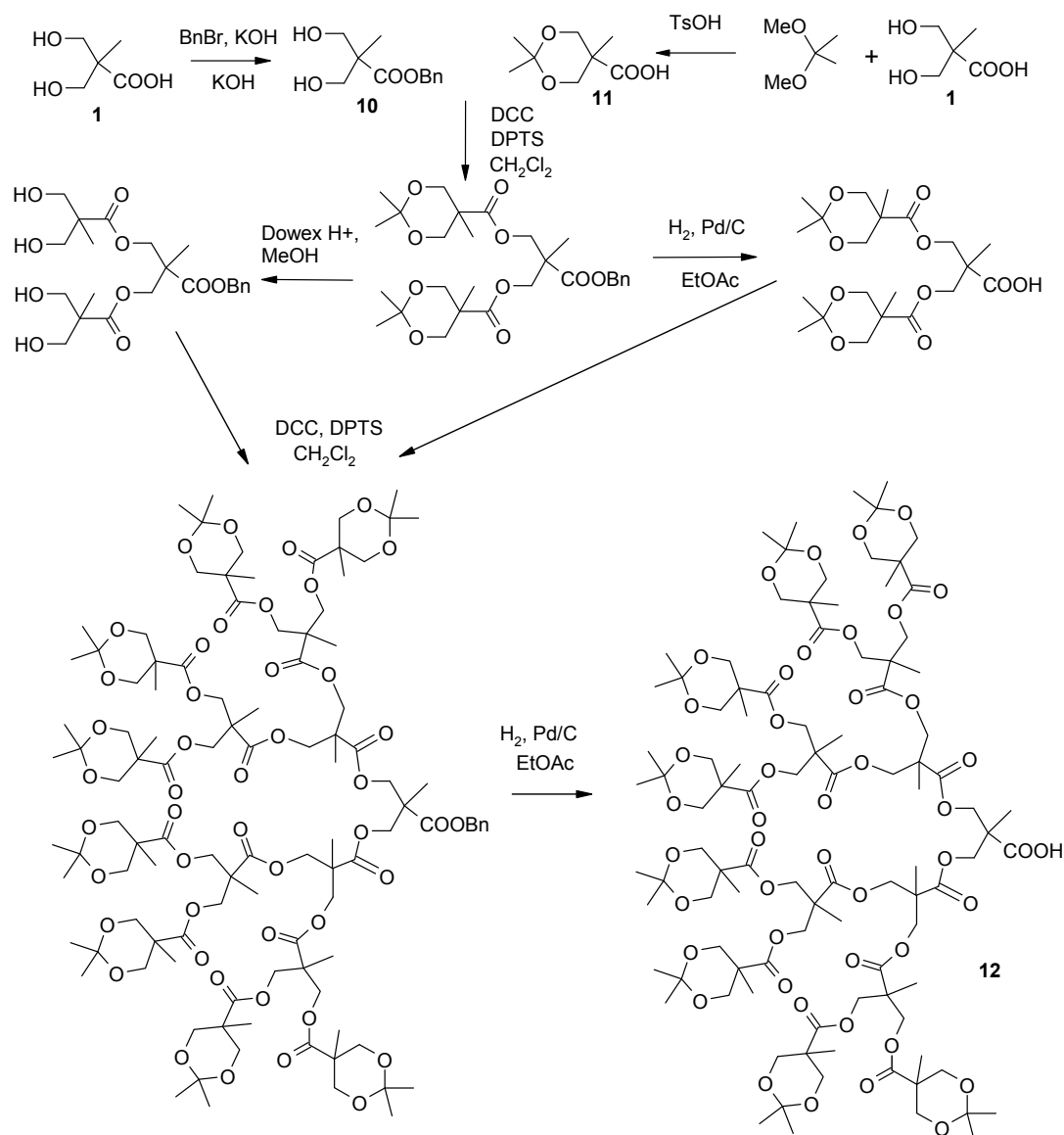


The second method, the convergent route was developed by Hawker and Fréchet [77]. In this approach, the units that will be attached to the core, the dendrons, are constructed first. When the growing dendrons have reached the desired size, they are attached to the multifunctional core molecule. This method has several advantages. It is relatively easy to purify the final product and the occurrence of defects in the final structure is minimised. The convergent route provides better structural control since intermediates are purified better at successive stages of the synthesis. However, this method may not allow the formation of high generations, because steric problems may occur in the reactions of the dendrons with the core molecule. Scheme 2.2 illustrates this approach [8]. Reduction in the number of both synthetic and purification steps in convergent dendrimer synthesis can be achieved if a convergent

approach is taken to dendron synthesis rather than the strictly divergent synthesis of the dendron illustrated in Scheme 2. This approach, termed double exponential growth [81–83], is illustrated for polyester dendrimers in Scheme 3 [84]. In this methodology, both components for formation of the higher generation structure, the polyol and the carboxylic acid for polyester dendrimers, are prepared using a single starting material.

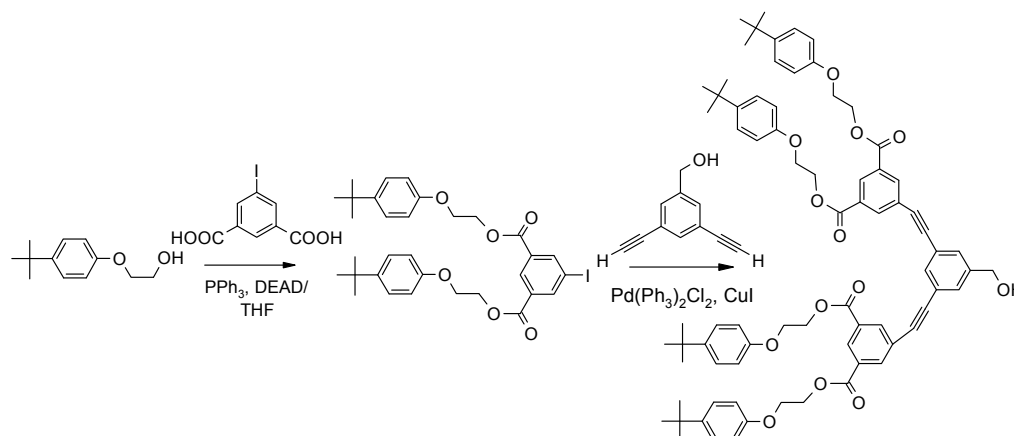
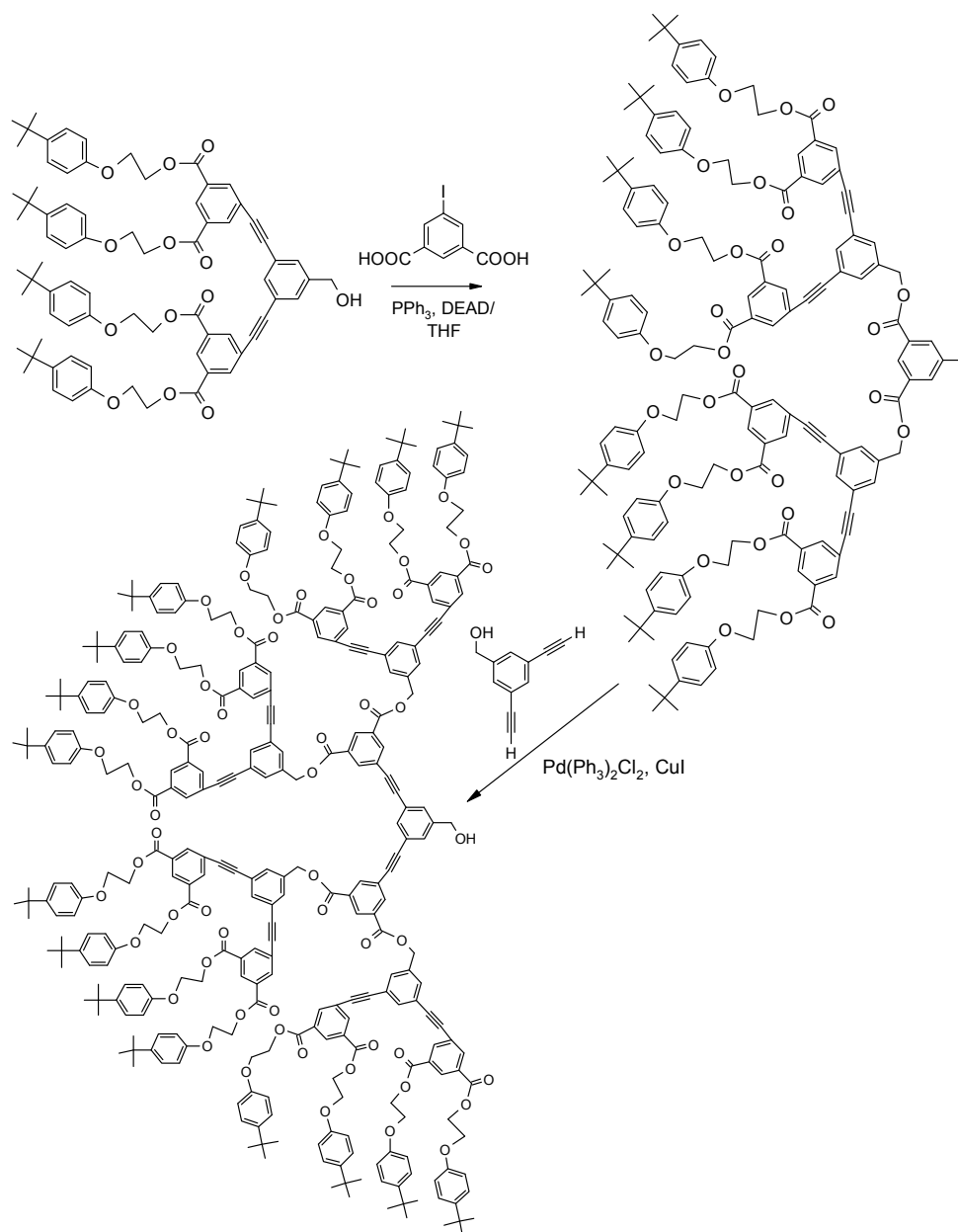
**Scheme 2.** The first convergent synthesis of a deprotected polyester dendrimer [8].



**Scheme 3.** Double exponential dendron growth [84].

Different types of dendrimers, called alternating dendrimers here, can be produced if orthogonal coupling methods are used in alternation to produce dendrimers with different functional groups joining alternate dendrons [40,73,85–101]. The first example of this strategy incorporating ester units, shown in Schemes 4 and 5, used the Mitsunobu reaction to form esters [102] and Sonagashira coupling as its orthogonal partner [102]. More recent examples of orthogonal coupling in which ester formation is one of the two coupling reactions include the following: ester formation and click reactions [103], ester formation and thiol-ene reactions [104,105], thiol displacement of  $\alpha$ -ketohalides and ester formation [95], ester and amide formation [106], and thiol-yne reaction and ester formation [107] (see Section 4.4).

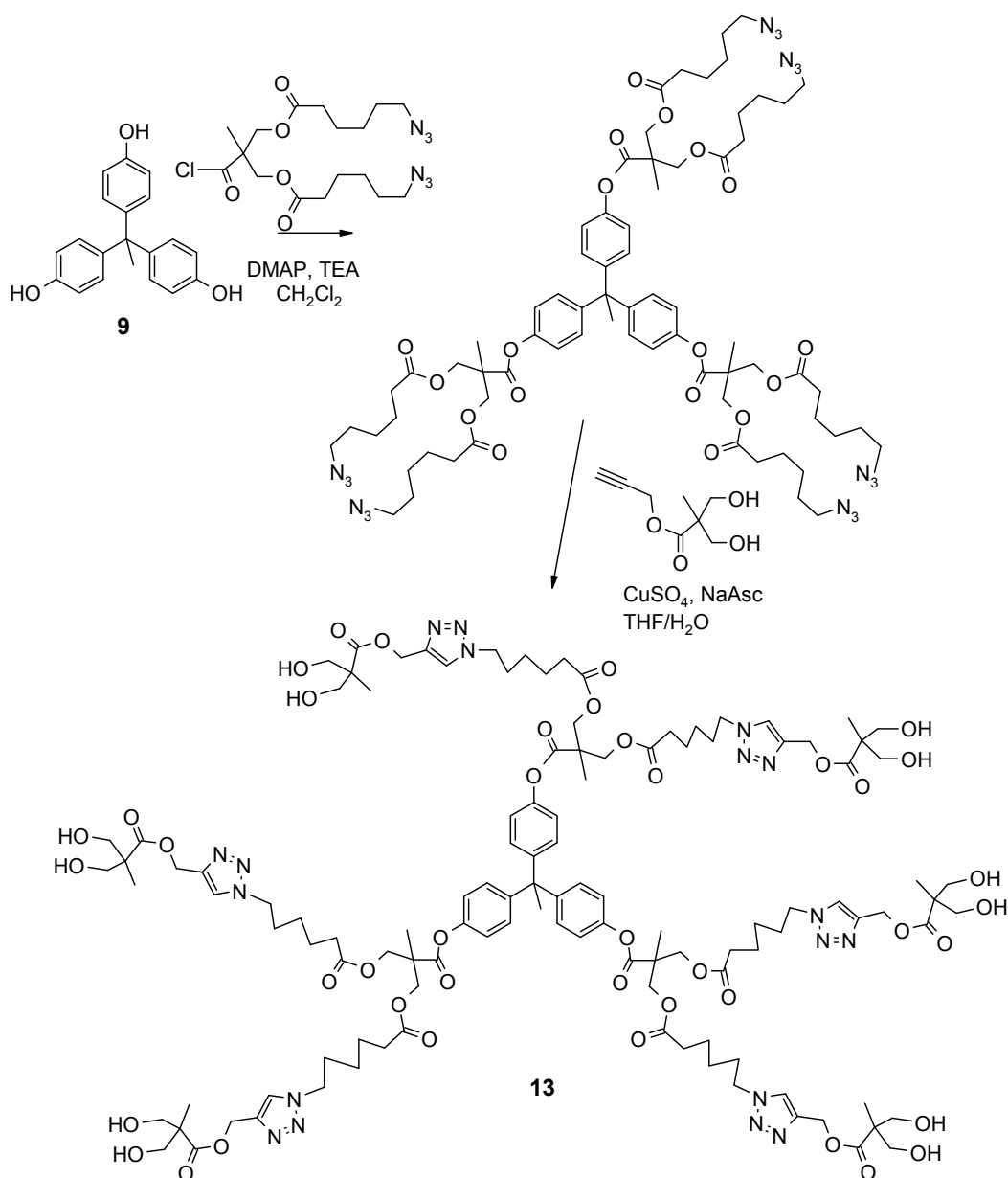
A variant of this approach can yield dendrimers with a greater number of functional groups on the periphery with fewer synthetic steps if the two orthogonal reactions both employ branched dendrons [93,98,103,104,108–110]. Majoral and coworkers have termed this approach LEGO chemistry [98]; Antoni *et al.* called this strategy accelerated synthesis [103]. An example involving ester formation is shown in Scheme 6 [103].

**Scheme 4.** Formation of the dendron for an alternating polyester dendrimer [102].**Scheme 5.** Formation of an alternating polyester dendrimer [102].

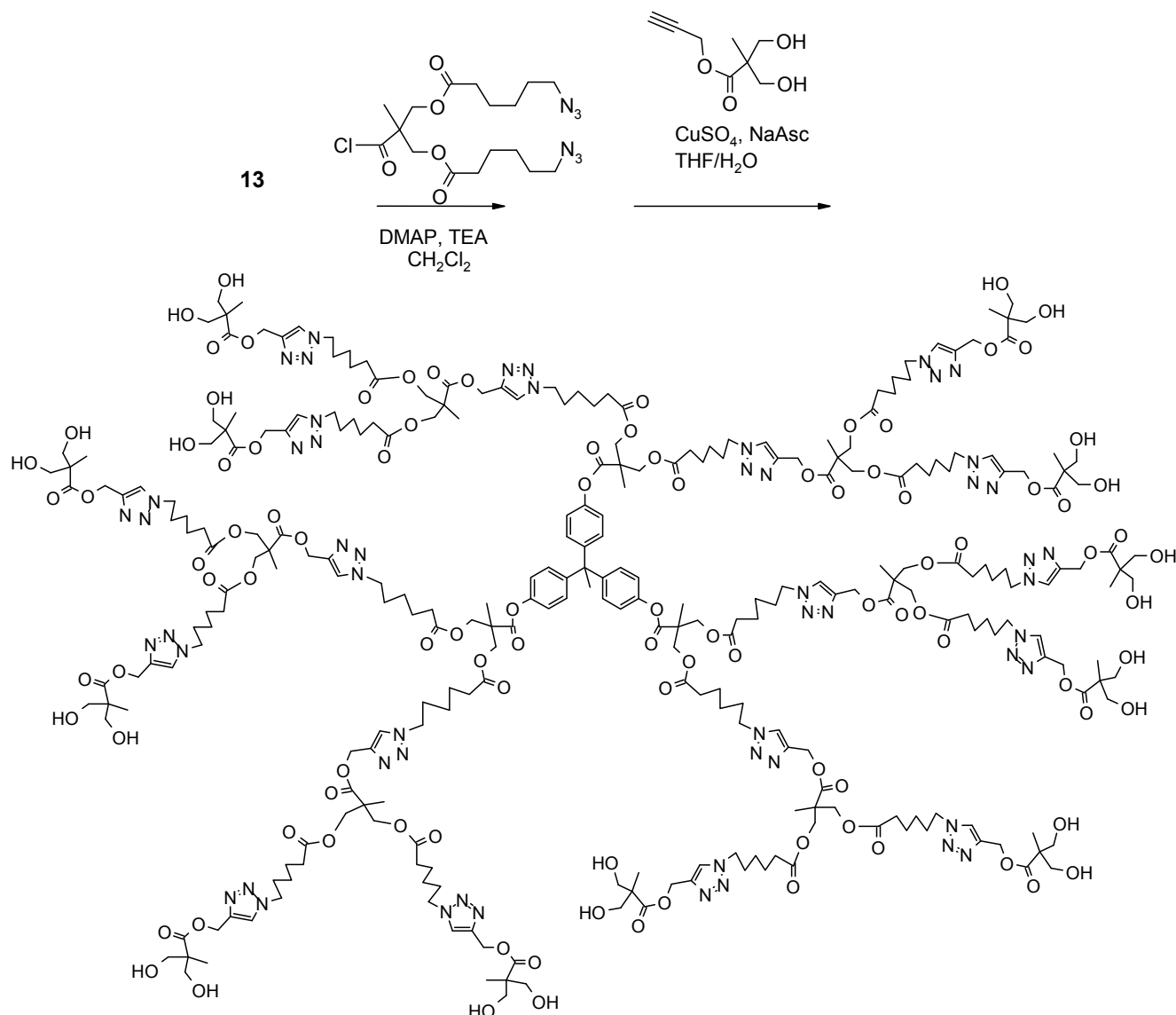


The highly congested branching that occurs in the bulk of the dendrimer interior can have interesting effects on the dendrimer's conformation. Because dendrimer diameters increase linearly while the number of surface groups increase exponentially with generation number, the space between groups decreases with generation [111]. For example, at low generations, a dendrimer typically has a floppy, flat structure, but at higher generations (usually > G-4), the polymer adopts a more globular or even spherical conformation [112] and rigidity increases with generation [113]. The behaviour of these compounds is complex with backfolding being significant [114–116].

**Scheme 6.** Accelerated synthesis of a G4 polyester dendrimer in four steps by using two different AB<sub>2</sub> dendrons [103].



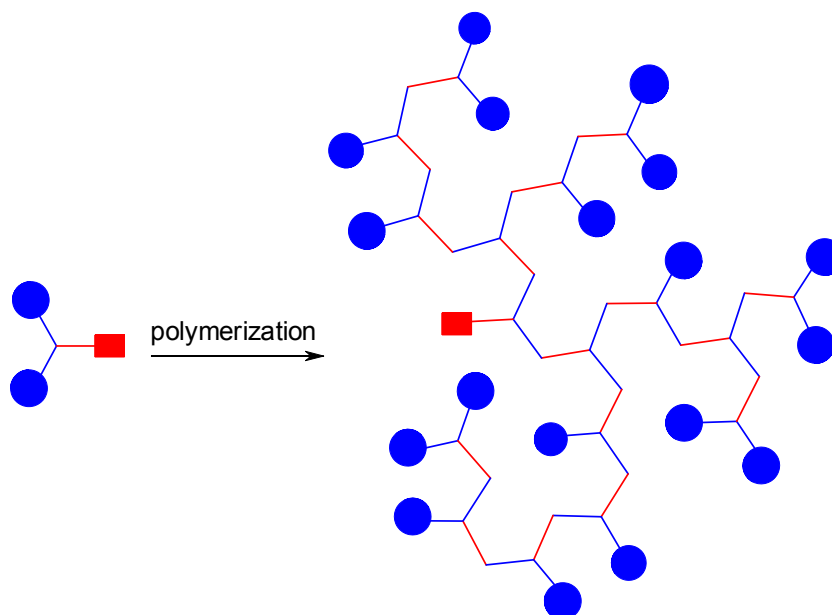
Scheme 6. Cont.



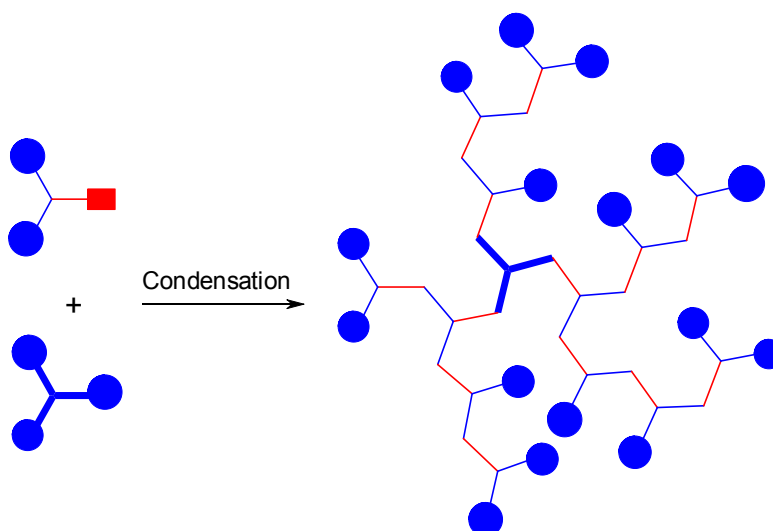
## 2.2. Hyperbranched Polymers

Hyperbranched polymers are usually the product of random or non-controlled synthetic procedures. They exhibit an irregular architecture with many defects throughout the structure as a result of incompletely reacted functional groups. Even though they lack the advantages of having well defined structures and molecular weight, hyperbranched polymers are often easily synthesized on a large scale which brings down their cost and makes them important for large-scale and industrial applications.

If dendronized polymers and dendrigrafts are excluded, two broad types of hyperbranched polymers can be defined. One type is obtained using polymerization of a single monomer unit. Many methods have been used for polymerization, including proton-transfer polymerization (PTP) [117], self-condensing vinyl polymerization (SCVP) [118], self-condensing ring-opening polymerization (SCROP) [119], and condensation [120]. Many of the hyperbranched polyesters reported in the literature have been prepared using a one-pot polycondensation of  $\text{A}_x\text{B}$  monomers.

**Scheme 7.** An  $A_2B$  monomer polycondensation.

In this approach toward hyperbranched polymers [54,121], monomers containing  $A$  functional groups with similar reactivity react with functional group  $B$  as shown in Scheme 7. The final mixture usually contains highly branched polymers having a similar focal point  $B$  but with varying molecular weights and varying degree of branching. The use of  $A_xB$  monomers where  $x$  is  $> 2$  has also been exploited. As the number of  $A$  functionalities in a monomer increases, the degree of branching tends to reduce for steric reasons. Examples include those of Mathias [122], Hunter [123], and Yoon [124] for the use of  $A_3B$  monomers and the work of Miravet and Fréchet for the use of both  $A_4B$  and  $A_6B$  monomers [125]. This approach can be used without adding core molecules or with added core molecules.

**Scheme 8.** Polycondensation of  $A_2B$  and  $A_3$  monomers with excess  $A_2B$  monomer.

A second type of hyperbranched polymers is formed by polymerization of two different types of monomers of which, at least one must be branched. Many different combinations are possible

including  $A_2B_2 + B_3$  of Berzelius' first hyperbranched polymers [41] and  $A_2B + A_3$  of the commercial Boltorn hyperbranched polyesters [55]. In the case of the Boltorn polyesters [55], the monomers with two functional groups,  $A_2B$  in this case, are used in a large excess so that the next layer of reactive centers can only come from such a monomer. Scheme 8 below illustrates a schematic representation for the polycondensation of  $A_2B$  and  $A_3$  monomers.

Hyperbranched polymers have continued to be the backbone of many industrial processes and over the years, new methodologies for their synthesis have continued to be developed.

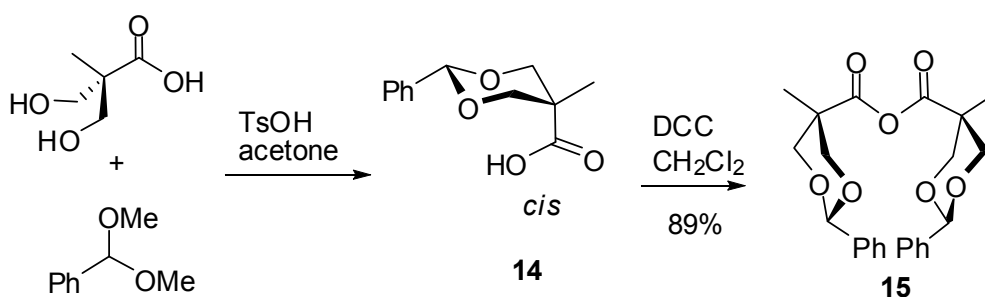
### 3. Methods Used for Ester Bond Formation

The method chosen for ester bond formation during the synthesis of polyester dendrons and dendrimers must not result in cleavage of other functional groups or in transesterification reactions.

The first method used for ester bond formation in dendrimer synthesis involved the reaction of the carboxylic acid and the alcohol activated by dicyclohexylcarbodiimide (DCC) under mild acid catalysis (Scheme 2) [8] and this procedure has been used often. Formation of acid chlorides followed by reaction with the alcohol under mild base activation was also used early (Scheme 1) [80] but has only been used occasionally [103,126] because the dendron must survive the vigorous conditions used to make the acid chloride.

One of the methods used most often is to convert the alcohol-protected carboxylic acid into the anhydride (Scheme 9), then react the anhydride with the alcohol in the presence of DMAP or other mildly basic promoters [127]. The anhydrides of acetal-protected 2,2-bis-(hydroxymethyl)propanoic acid have been used often [127,128]. Restricting the mobility of the alcohol-terminated chains through formation of a cyclic acetal decreases steric hindrance during ester formation, allowing facile access to high generation dendrimers [129]. Using NMR parameters, we have recently established that the configuration of the *O*-benzylidene derivative of 2,2'-bis(hydroxymethyl)propanoic acid is *cis* [130].

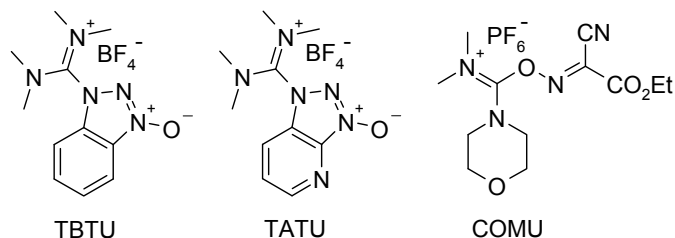
**Scheme 9.** Formation of the anhydride of benzylidene-protected 2,2-bis-(hydroxymethyl)propanoic acid (**14**) [127].



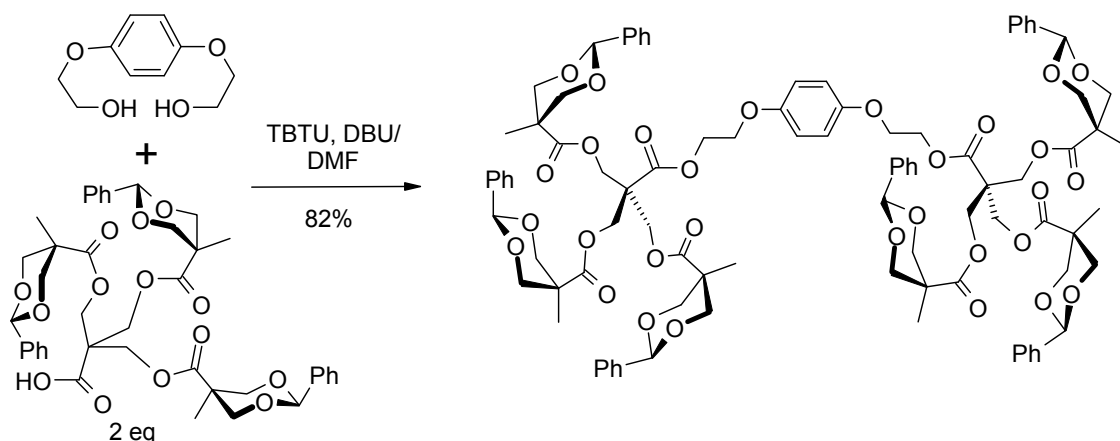
Two alternatives have been proposed recently. We used the uronium-based coupling agents, TBTU [131], TATU [132], and COMU [133] (See Figure 2 for structures), to promote ester formation [134]. An example is shown in Scheme 10. This method has the advantage that primary hydroxyls can be selected over secondary by choosing to use TATU or TBTU with a trialkylamine as base. Secondary alcohols react with carboxylic acids using all three uronium-based agents if the stronger base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), is used. Tertiary alcohols form esters only

when the promoter is COMU and a still stronger base, 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), is used [134].

**Figure 2.** Structures of uronium-based compounds used to promote ester formation [134].

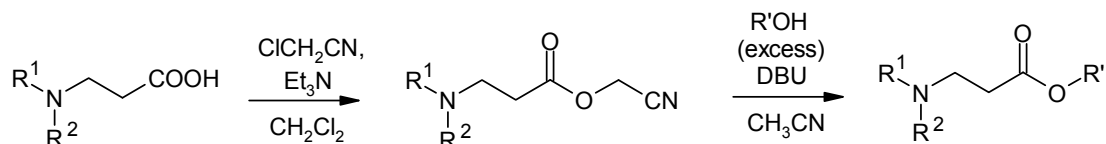


**Scheme 10.** Use of an uronium-based promoter for ester bond formation in assembly of a second generation dendrimer [134].



Bouillon *et al.* have synthesized amine-containing polyester dendrimers by activating the carboxylic acids as cyanomethyl ester intermediates (Scheme 11) [135,136]. This method has been used previously for acylation of ribonucleotide derivatives with *N*-protected amino acids [137].

**Scheme 11.** Ester formation from carboxylic acids containing tertiary amines [135].



As shown in Schemes 4 and 5, Zeng and Zimmerman used a Mitsunobu reaction with an aromatic bicarboxylic acid as the nucleophile to form alternating polyester dendrimers [102].

#### 4. Advances in the Synthesis of Polyester Dendrons and Dendrimers

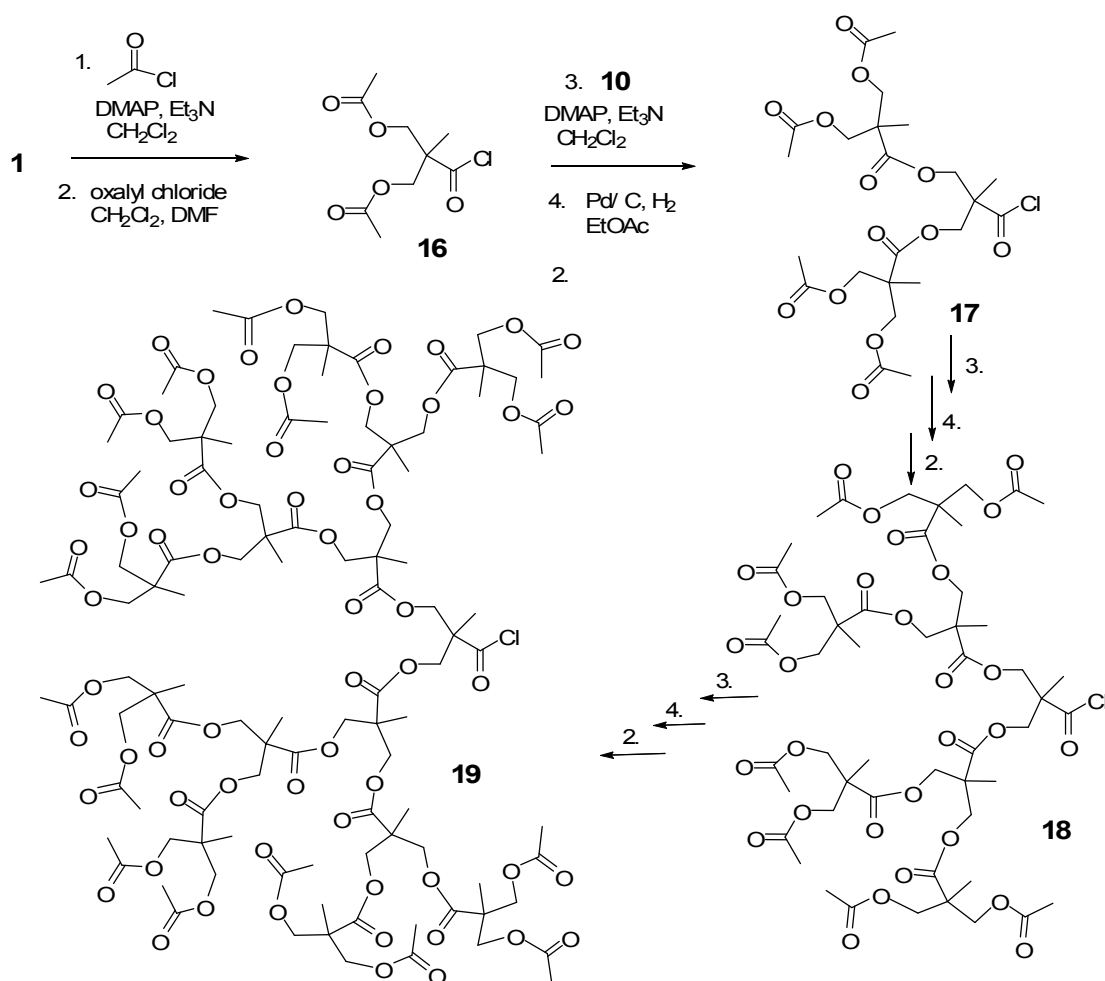
##### 4.1. The Use of 2,2-Bis(Hydroxymethyl)Propanoic Acid-Derived Dendrons

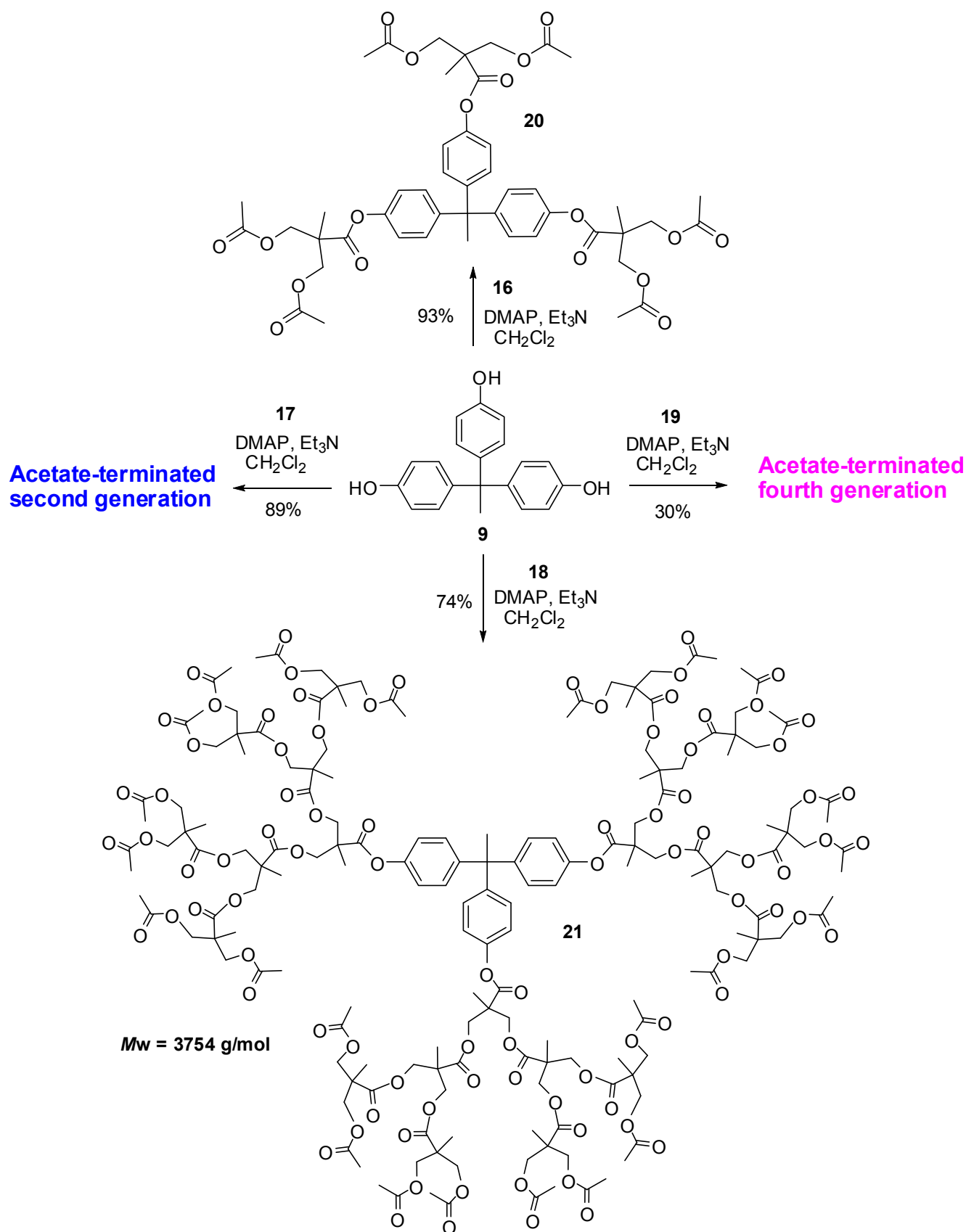
Ever since its first use for dendrimer formation [126], one aliphatic building block has been and continues to be the dendron of choice. 2,2-Bis(hydroxymethyl)propanoic acid (**1**) (bis-HMPA) is commercially available at a low cost, and most importantly, the resulting polyester dendrimers are

non-toxic and biodegradable [38], which makes them attractive for biological and drug delivery applications.

The first report on the synthesis of aliphatic polyester dendrimers based on **1** was by Ihre, Hult, and Söderlind [126]. First to fourth generation dendrons were synthesized from **1** by protecting the carboxylic acid as a benzyl ester group and the hydroxyls as acetate esters (Scheme 12). Esterifications were performed by conversion of the acid into the corresponding acid chloride with oxalyl chloride followed by reaction of the acid chloride with the hydroxyl groups in the presence of triethylamine (TEA) and 4-(dimethylamino)pyridine (DMAP). Deprotection by hydrogenolysis allowed repetition. Acetate-terminated polyester dendrimers with 1,1,1-tris(*p*-hydroxyphenyl)ethane (**9**) as a core were synthesized from generation one to four ( $M_w$ : 906, 1,856, 3,754, and 7,549 g/mol) by adding the above dendrons in a convergent growth approach (Scheme 13). The simplicity of the  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra and elemental analyses suggest that pure and monodisperse dendrimers were obtained. However, attempts to selectively remove the acetate groups in order to obtain the corresponding hydroxyl-terminated dendrimers for further chemical surface modification were not successful due to the lack of selectivity in the hydrolysis of the acetate and ester groups. In addition, lower yields were obtained in the final coupling step of the fourth generation dendrons to the core molecule when compared to the coupling steps used to prepare lower generation dendrimers.

**Scheme 12.** Synthetic route to first to fourth generation dendrons [126].

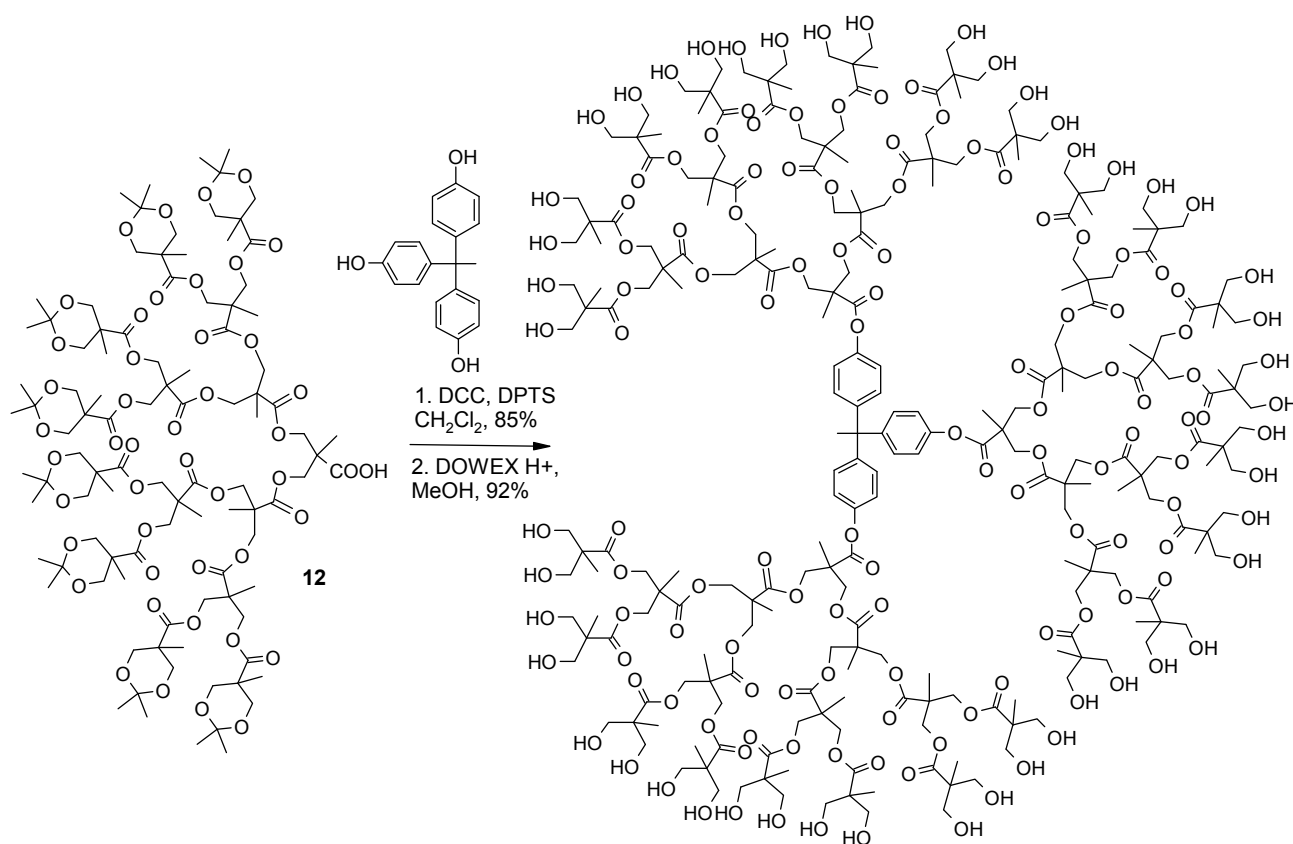


**Scheme 13.** Synthesis of first to fourth generation acetate-terminated dendrimers [126].

The problems accompanying acetate protection was remedied two years later by using isopropylidene acetals for protection of the 1,3-propanediol in **1** (see Scheme 3) [84]. The six-membered ring acetal is

very easily hydrolyzed in acid allowing deprotection in the presence of benzyl esters. A further improvement was the use of DCC and 4-(dimethylamino)pyridinium *p*-toluenesulfonate (DPTS) to promote ester formation directly from the hydroxyl and carboxylic acid groups rather than activate the carboxylic acid as the acid chloride. As shown in Scheme 14, reacting the fourth generation dendron (**12**) with **9** gave a fourth generation polyester dendrimer in good yield. The periphery of the hydroxyl-terminated polyester dendrimer was then functionalized using reactions of its hydroxyl groups with various acid chlorides (benzoyl, octanoyl, and palmitoyl chloride) in the presence of TEA and DMAP in  $\text{CH}_2\text{Cl}_2$  to give high yields of monodisperse dendrimers, according to  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra, size exclusion chromatography, and elemental analyses of the products.

**Scheme 14.** Synthesis of fourth generation dendrimer [84].

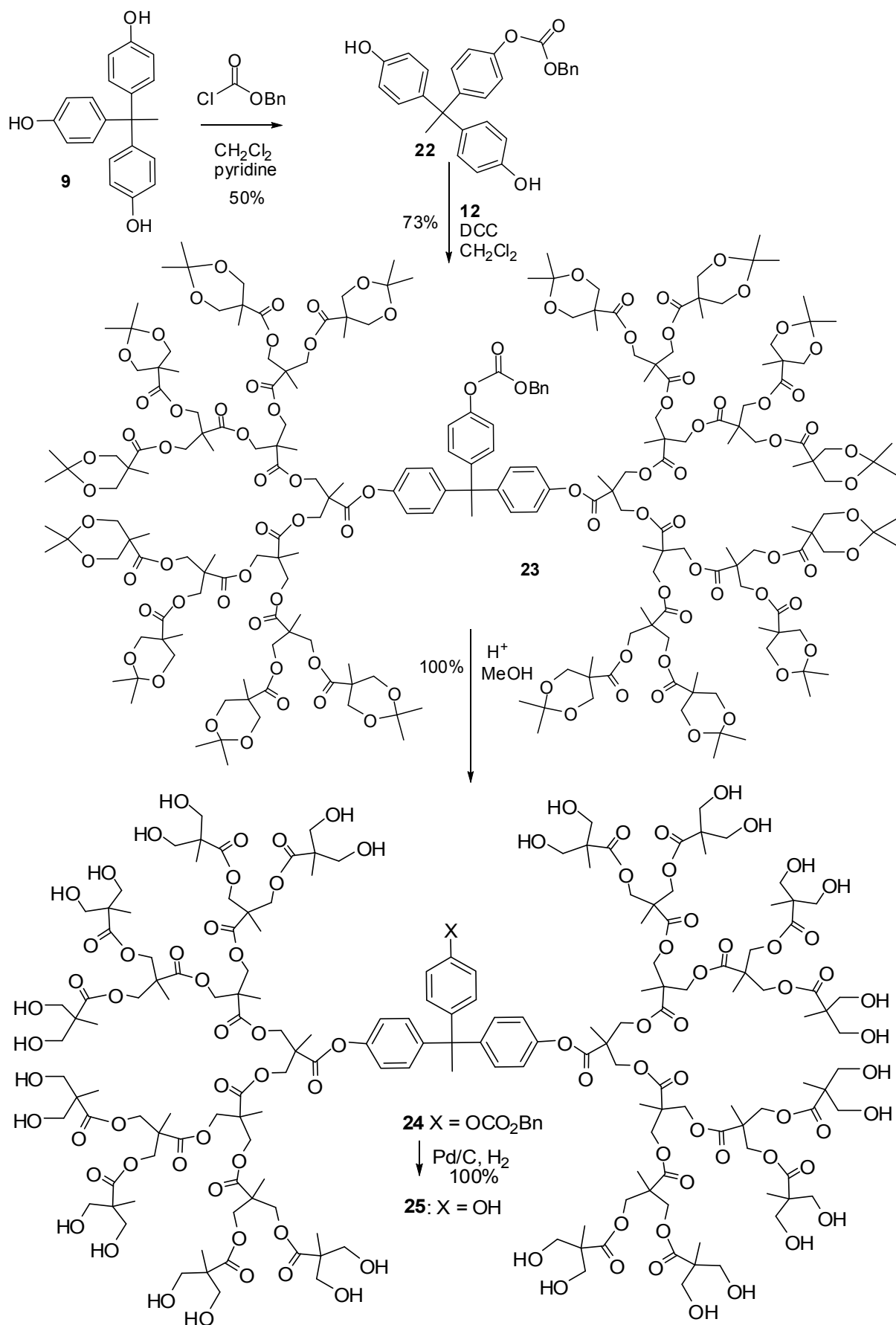


In order to evaluate this type of non-toxic dendrimer for drug delivery applications, a modified core moiety was prepared by reacting an excess amount of 1,1,1-tris(*p*-hydroxyphenyl)ethane (**9**) with benzyl chloroformate, affording a monoprotected trisphenolic in 50% yield after purification [138] (Scheme 15). Reacting this divalent core with two equivalents of the [G-4]-COOH dendron (**12**—Scheme 3) in the presence of DCC followed by the cleavage of the acetonide groups under mild acidic conditions produced a water soluble system containing 32 free hydroxyl groups on the surface. Finally, the benzyl carbonate group was cleaved by hydrogenolysis to provide the free phenol.

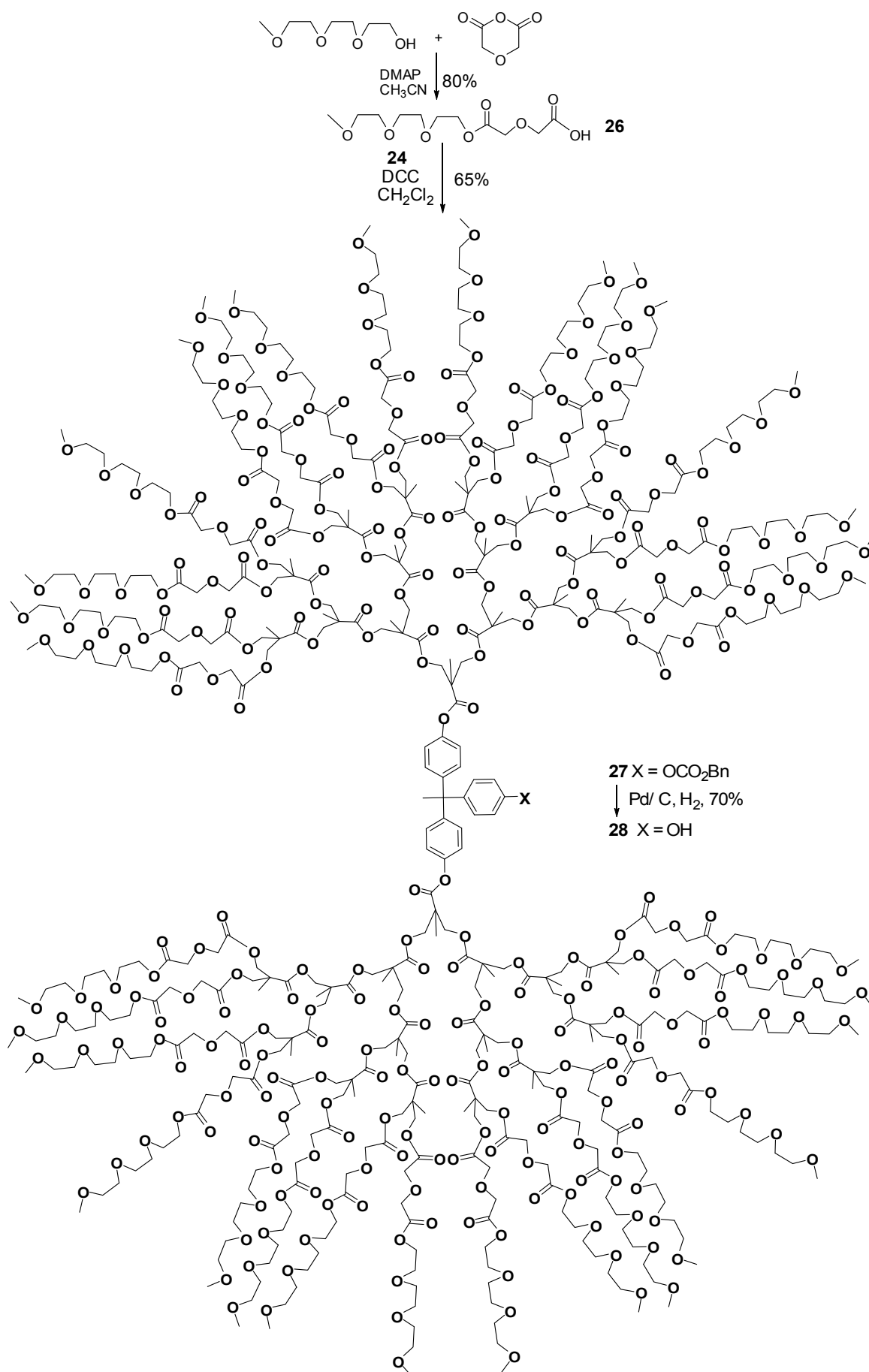
To evaluate the effect of increasing the mass of the dendritic system, a second dendritic model compound was prepared. The preparation involved the surface functionalization of dendrimers **24/25**.



**Scheme 15.** Preparation of a divalent fourth generation polyester dendrimer (first section) and its surface functionalization (second section) [138].



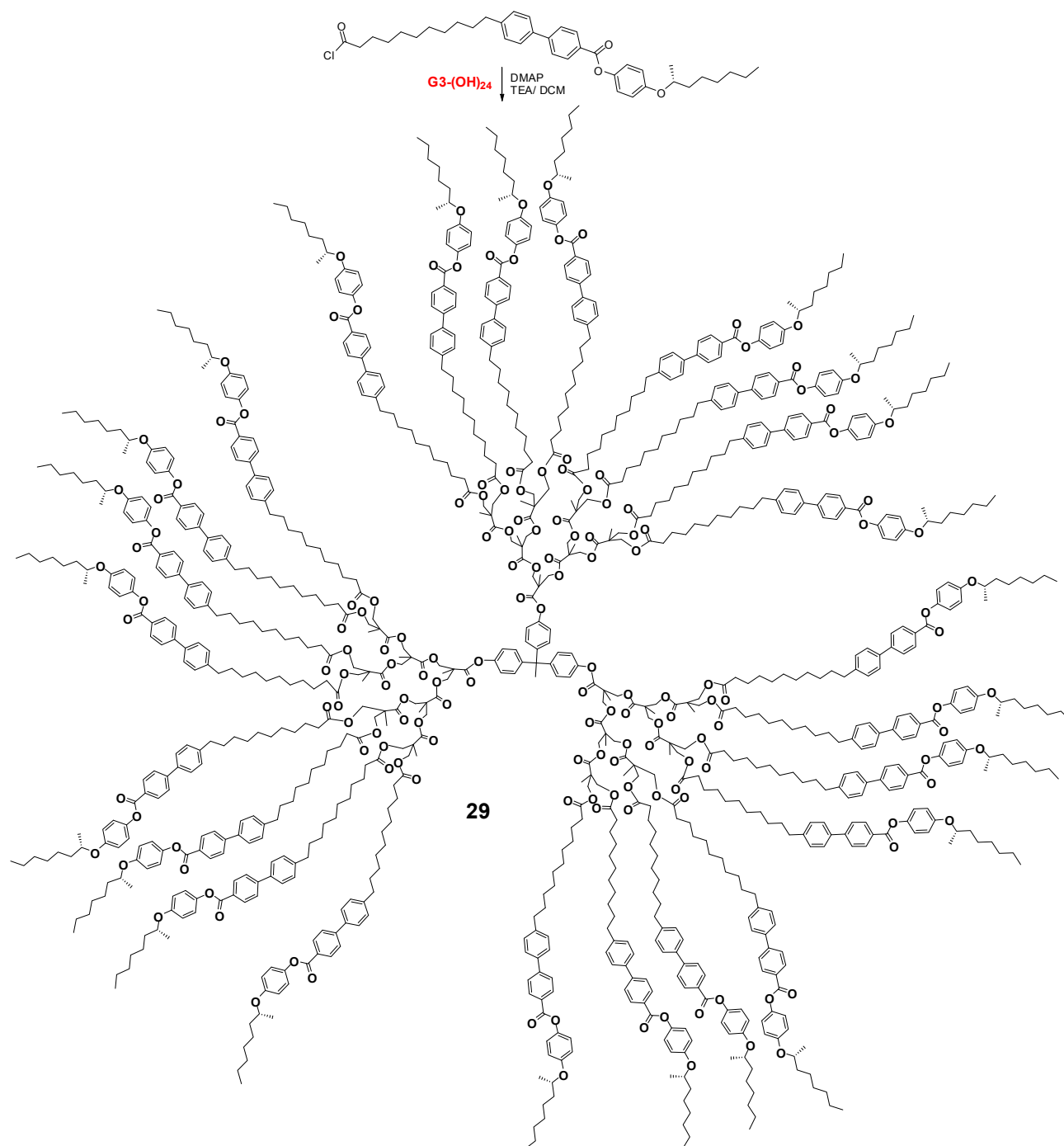
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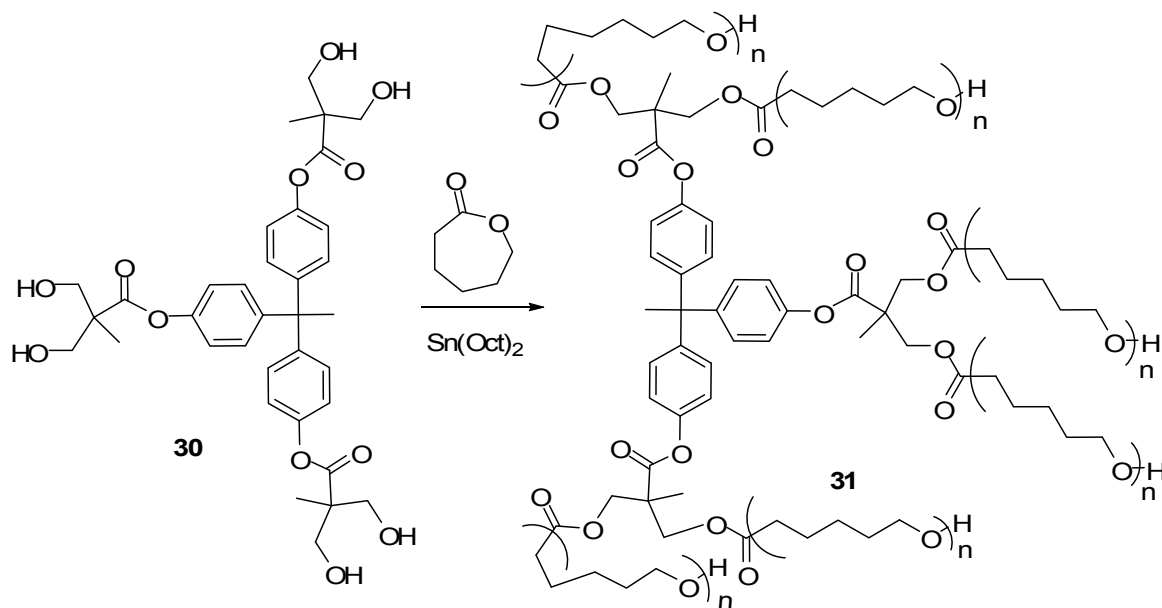
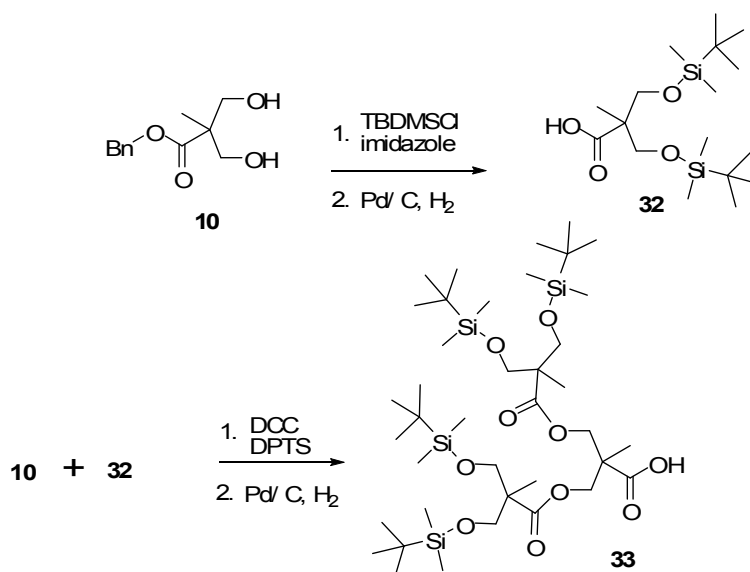


For the preparation of these higher molecular mass dendrimers (**27** and **28**), a capping agent **26** consisting of monomethyl ether tri(ethylene glycol) was used, because poly(ethylene glycol) and its derivatives have advantages for biological applications due to their high water solubility and biocompatibility properties [139]. To couple this moiety to the periphery of the hydroxyl-terminated dendrimer **24**, an acid derivative of the monomethyl ether of tri(ethylene glycol) was prepared by reaction with diglycolic anhydride in the presence of DMAP as the catalyst. An excess of the acid capping agent **26** was then reacted with the polyhydroxylated surface of **24** using DCC as the coupling agent to afford **27**. As earlier, the phenolic protecting group located at the core was removed using hydrogenolysis to give **28** with an exposed free phenol for radio labelling purposes.

When conventional mesogenic groups in linear crystalline polymers (LCPs) are replaced by chiral mesogens, ferroelectric liquid crystalline polymers (FLCPs) are obtained [140–142]. FLCPs are regarded as important species for optical switching and electrooptical applications [143,144]. Because of chain entanglements however, their viscosity is often high which leads to slow switching thereby narrowing the field of their potential practical applications. Knowing that using dendritic structures may result in monodisperse FLCPs and therefore low viscosity and less chain entanglements, Busson *et al.* synthesized and characterized the first ferroelectric dendritic liquid crystalline polymer (FDLCP). In this work [145], a third generation aliphatic polyester dendrimer, bearing 24 hydroxyl groups on its surface, was functionalized using a ferroelectric mesogen. The mesogenic group, 4'-((*R*)-1-methylheptyloxy)phenyl 4-(4'-(10-(hydroxycarbonyl)decyloxy)-phenyl)benzoate, responsible for realization of the liquid crystalline state, was coupled to the dendritic matrix via an acid chloride reaction as shown in Scheme 16. The purity and hence the monodispersity of the final compound was established using  $^1\text{H}$  NMR spectroscopy and size exclusion chromatography (SEC) measurements.

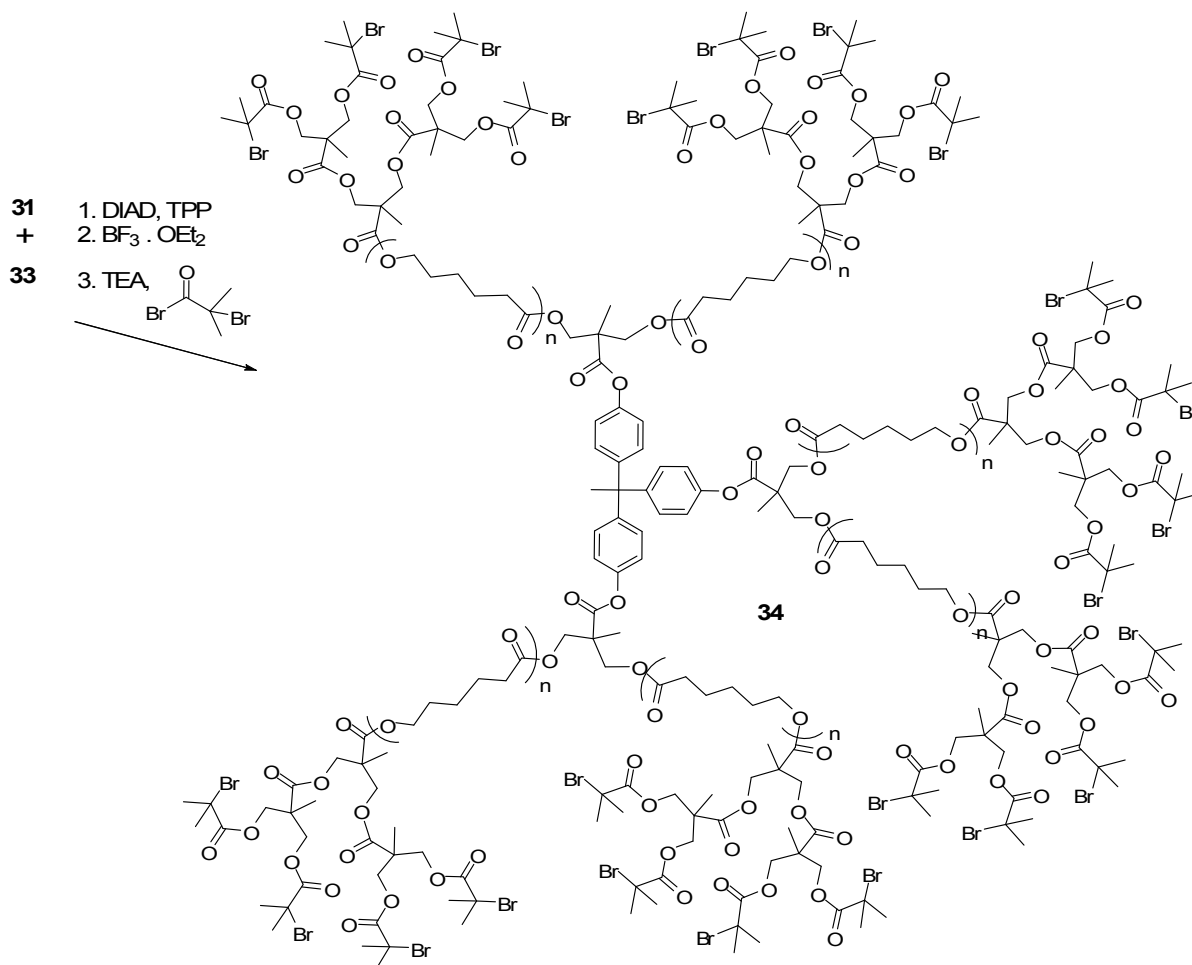
In 1998, another new type of polyester dendrimer was prepared using a novel approach [146]. The goal here was to extend the possibilities of dual living polymerizations (either consecutive or concurrent) to encompass new and complex molecular architectures, ultimately leading to structures that may mimic unimolecular polymeric micelles. The type of dendrimers reported in this paper, denoted as dendrimer-like star block copolymers, are described by a radial geometry where the different generations or layers are comprised of high molecular weight polymer emanating from a central core. For their synthesis, 1,1,1-tris(*p*-hydroxyphenyl)ethane (**9**) and **1** were reacted to produce a hexahydroxyl-terminated first generation dendrimer (**30**) which became the functional initiator for the “living” ring opening polymerization (ROP) of  $\epsilon$ -caprolactone producing a hydroxyl terminated six-arm star polymer with controlled molecular weight (**31**) as shown in Scheme 17. The arms ends were then capped with dendrons containing activated bromide moieties to furnish “macro-initiators” for atom transfer radical polymerization (ATRP) [147,148]. Schemes 18 and 19 illustrate the synthesis of one of the “micro-initiators”. Methyl methacrylate was polymerized from these macro-initiators in the presence of an organometallic promoter to produce dendrimer-like star polymers with high molecular weights and low polydispersity ( $<1.2$ ). In addition, amphiphilic character could be introduced by designing different generations as either hydrophobic or hydrophilic.

**Scheme 16.** Synthesis of the first ferroelectric dendritic liquid crystalline polymer [145].

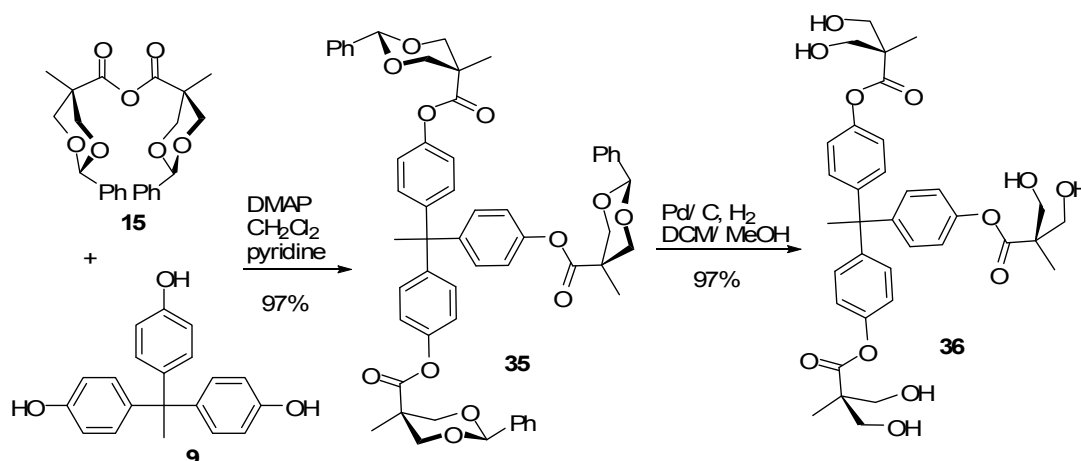
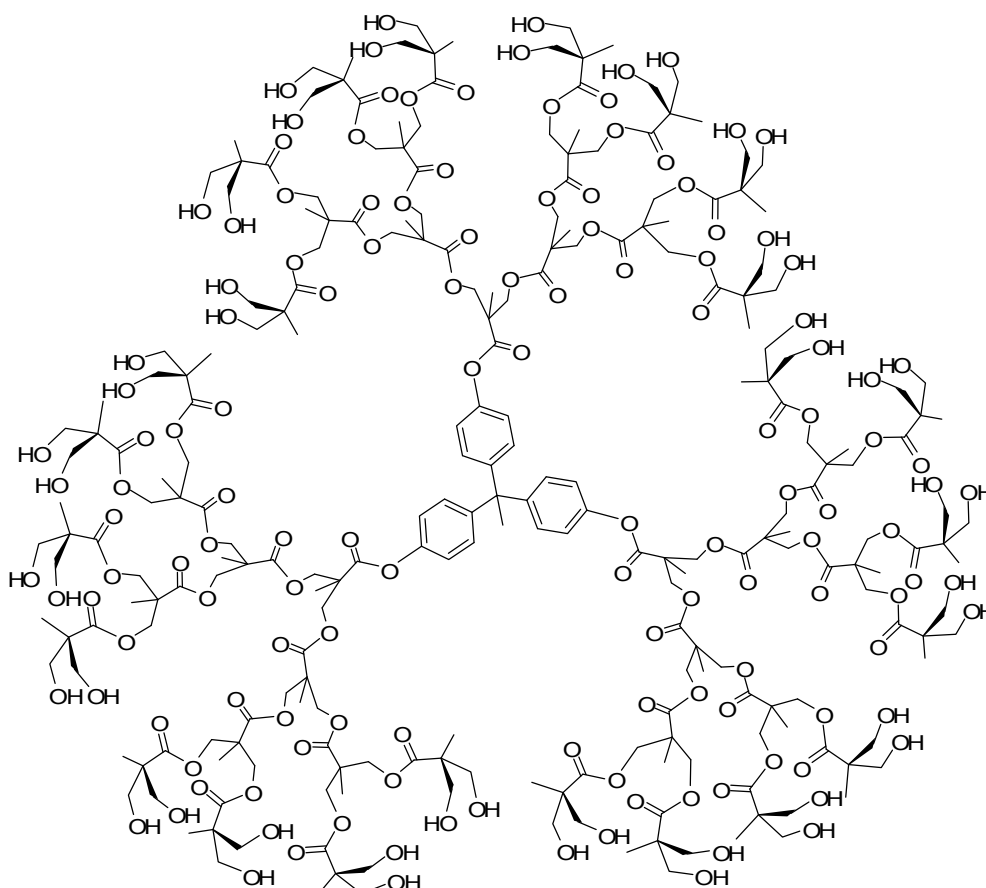
**Scheme 17.** Ring opening polymerization of  $\epsilon$ -caprolactone [146].**Scheme 18.** Convergent synthesis of the  $\text{AB}_4$  dendron [146].

While exploring various routes to dendrimers, Annby *et al.* demonstrated that benzylidene-protected bis-HMPA (**14**) was a versatile reagent for the formation of polyester dendrimers [149]. Polyester dendrimers were prepared up to the fourth generation using even sterically congested cores like pentaerythritol in good yields using DMAP and DCC to promote ester formation. Since then, a number of research groups have utilized the benzylidene-protected bis-HMPA as a convenient building block [127,129,130,146,150–153].

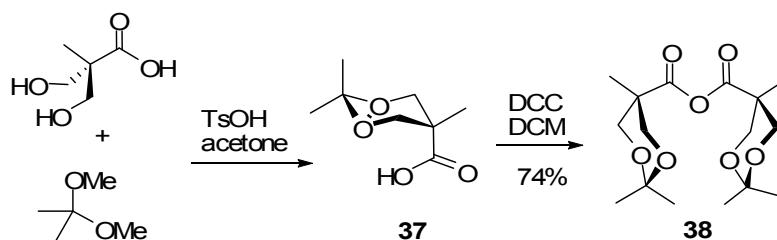
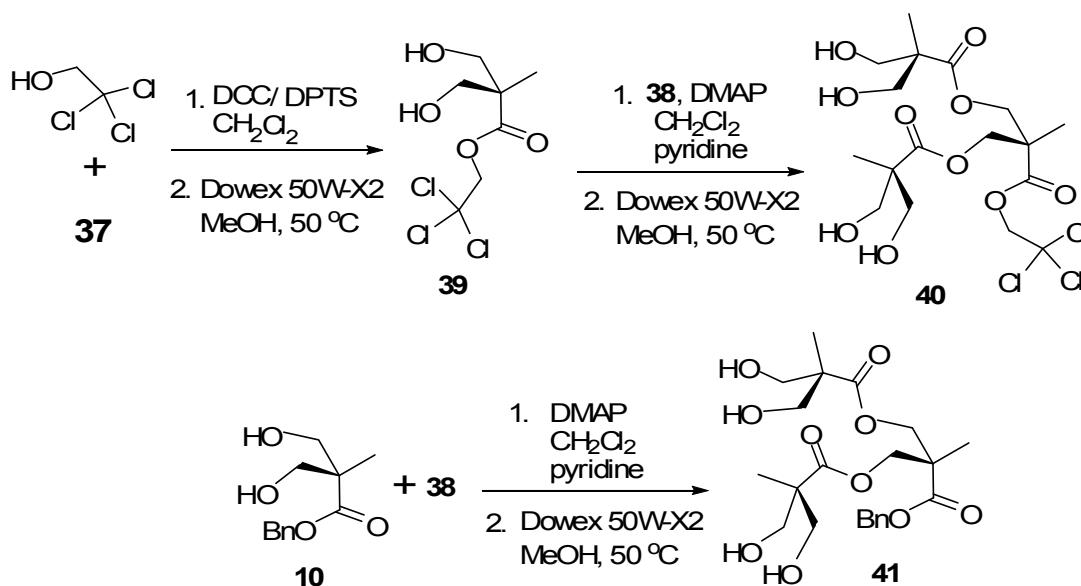
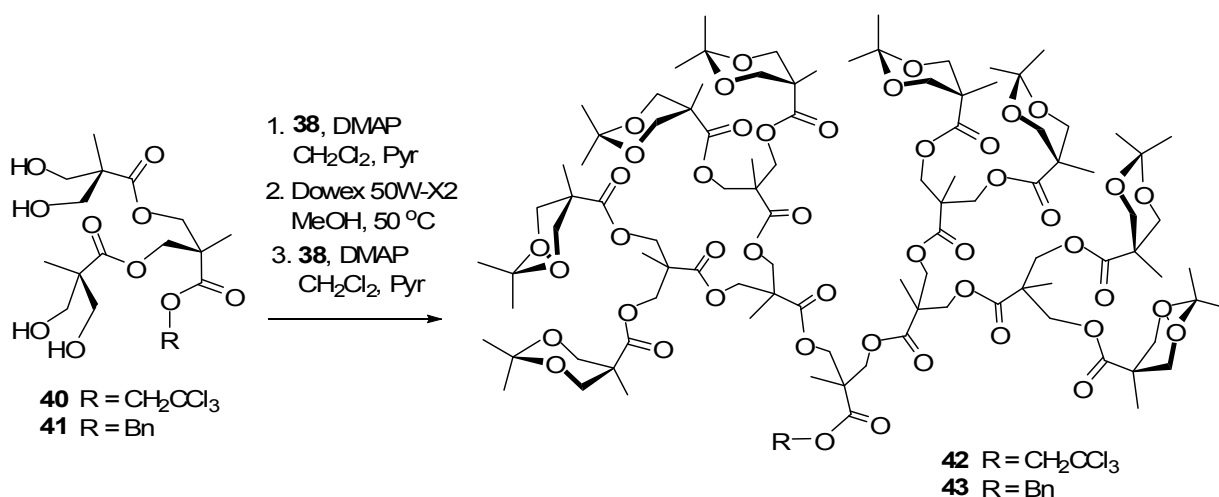
**Scheme 19.** Synthesis of a dendritic macro-initiator for atom transfer radical polymerization [146].



A significant advance in dendrimer synthesis using **1** occurred when it was discovered that the anhydride of **14** (**15**) could be formed readily by dehydration of the carboxylic acid using DCC [127]. Its preparation and utilization in the formation of a first generation dendrimer using 1,1,1-tris(*p*-hydroxyphenyl)ethane (**9**) as the core is shown in Scheme 20 [127]. Repetition of the ester formation and deprotection steps gave up to the sixth generation dendrimer in good yield using this divergent approach (Figure 3) [127]. In the divergent approach, structural uniformity is usually difficult to maintain, because the number of reactions that must be completed at each step of growth increases exponentially, thus requiring large excesses of reagents. The anhydride method however, unlike others, required only a small excess of reagent to achieve quantitative growth, and only simple solvent extraction or precipitation was sufficient purification to obtain monodisperse dendritic structures up to the sixth generation. The amount of anhydride used was only 1.25 equiv per hydroxyl group. Further evidence of the effectiveness of this route was obtained by Parrott *et al.* who prepared up to eighth generation dendrons using this method achieving yields of >90% at every stage without altering reaction conditions [129].

**Scheme 20.** Preparation of first generation dendrimers using benzylidene-protected **1** (**14**) [127].**Figure 3.** Hydroxyl-terminated fourth generation polyester dendrimer [127].

In efforts to establish a large library comprised of dendritic compounds based on bis-HMPA, Malkoch *et al.* made use of the efficiency of the above anhydride chemistry [128]. To complement the benzylidene-protected anhydride esterification strategy reported by Fréchet and coworkers [127], acetonide-protected bis-HMPA anhydride was introduced to combine anhydride chemistry with the use of a benzyl and 2,2,2-trichloroethyl ester-protected focal points (see Schemes 22 and 22) [128]. In the same year, Gillies and Fréchet described the use of the acetonide-protected bis-HMPA anhydride in their synthesis of “bow-tie dendrimers” (see below) [154].

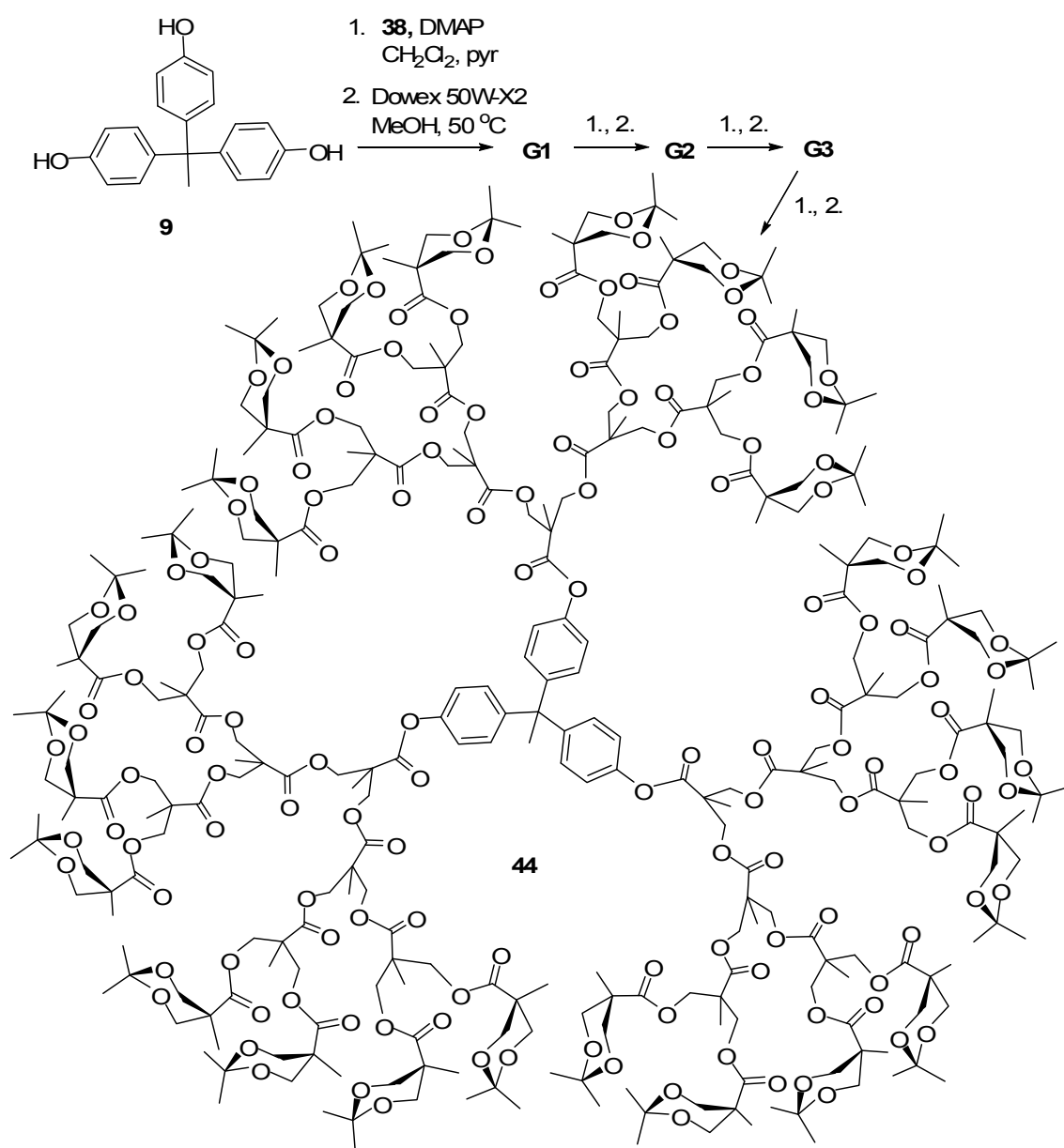
**Scheme 21.** Preparation of the acetonide-protected bis-HMPA anhydride [128].**Scheme 22.** Preparation of 2,2,2-tris(chloroethyl) ester and benzyl ester protected dendrons [128].**Scheme 23.** Preparation of protected fourth generation dendrons [128].

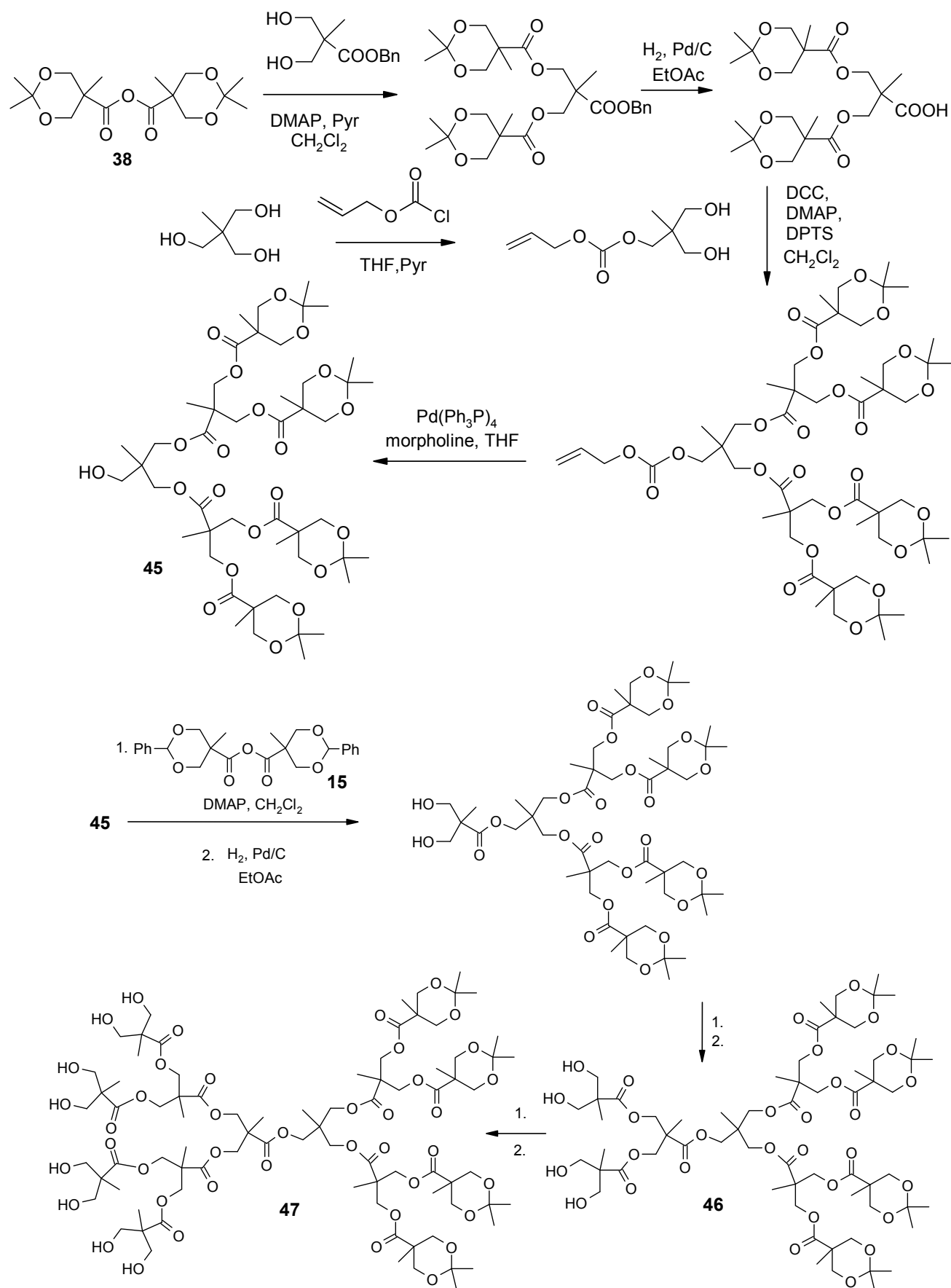
Three different monodisperse fourth generation acetonide-protected dendrons based on 2,2,2-tris(chloroethyl) ester **47** and benzyl ester **48** as focal points were divergently synthesized in high yields (Scheme 23) [128]. In order to demonstrate the versatility of the anhydride chemistry, a fourth generation acetonide-protected polyester dendrimer **52** was also divergently constructed as illustrated in Scheme 24 [128].

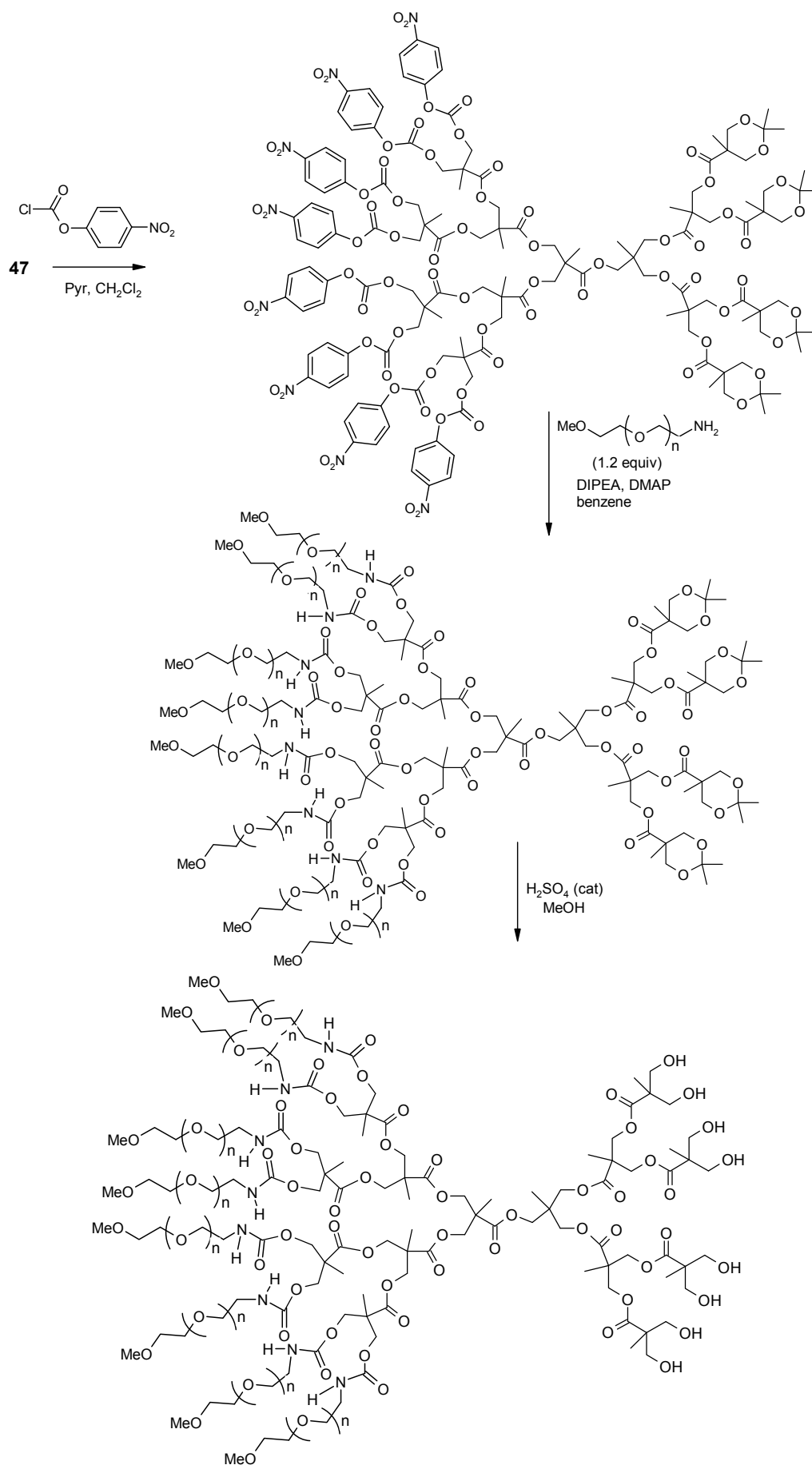


Gillies and Fréchet described dendrimers with two dendrons orthogonally protected and covalently attached as “bow-tie” dendrons and synthesized the first examples using acetonide-protected bis-HMPA anhydride for synthesis of one-half of the growing dendrimer and benzylidene-protected bis-HMPA for synthesis of the other half (Scheme 25) [154]. These authors then attached amine functionalized polyethylene oxide (PEO-NH<sub>2</sub>) to the deprotected half of the dendrimer via reaction with p-nitrophenylcarbonates to form carbamate linkages and cleaved the protecting acetonides to create potential water soluble drug carriers (Scheme 26) [154]. Reaction of four PEO-NH<sub>2</sub> samples with molecular weights of 5 to 20 kDa with p-nitrophenylcarbonates derived from **45** and **46** yielded a library of eight compounds with molecular weights of 22 to ~150 kDa [154].

**Scheme 24.** Divergently-grown acetonide-protected fourth generation dendrimer [128].

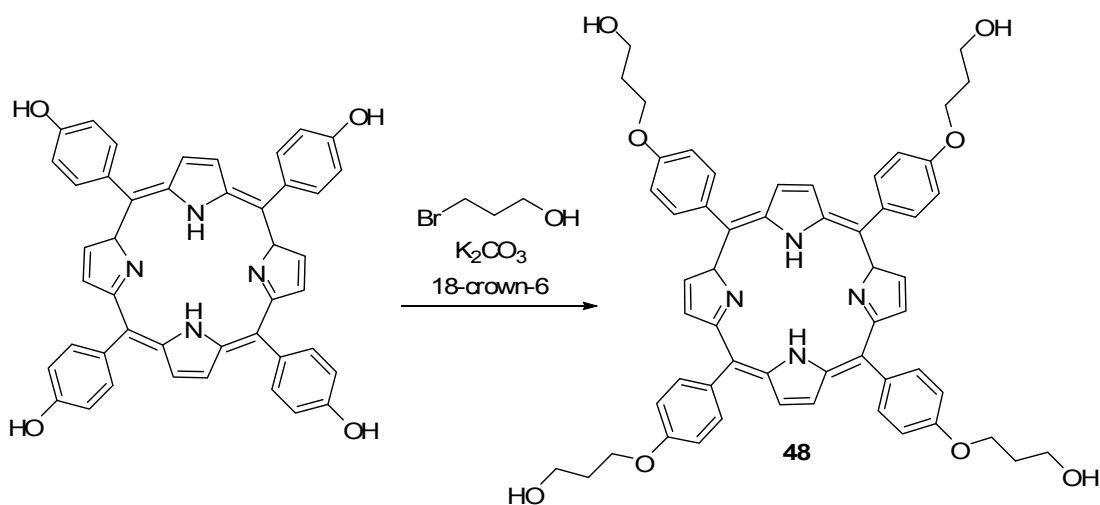


**Scheme 25.** Synthesis of “bow-tie” dendrimers [154].

**Scheme 26.** Addition of PEG chains to “bow-tie” dendrimers [154].

Two years later, Malmström, Hult and coworkers reported the synthesis and characterization of dendron-coated porphyrins up to the fifth generation [155]. Here, both free base and zinc-cored tetraphenylporphyrin (TPPH<sub>2</sub> and TPPZn) were used, from which the dendrons were divergently grown using **38**. Porphyrins were selected as core molecules because of their potential applications in many areas [156–159]. Reports dealing with porphyrins decorated with dendrimers had previously appeared [112,160–168]. After investigating three different synthetic strategies for this study, it was concluded that a spacer was required to be attached to the porphyrin to increase the hydrolytic stability and allow synthesis of higher generations. Normally, acidic DOWEX-50-X2 resin is used for the deprotection of the acetonide groups, but here the porphyrin core attached irreversibly to the DOWEX-50-X2 resin. A number of various dilute acids were explored for this deprotection but the results from these acidic deprotections showed that the porphyrin phenolic ester linkage also hydrolyzes, hence the need for a spacer. The spacer was added through the reaction of the porphyrin with 1,3-bromopropanol to afford **48** (Scheme 27). The dendrimers were then grown by subsequent addition of acetonide-protected bis-HMPA followed by deprotection with 2M H<sub>2</sub>SO<sub>4</sub> in tetrahydrofuran. The preparation of a fourth generation free base porphyrin-cored polyester dendrimer of this type is shown in Scheme 28.

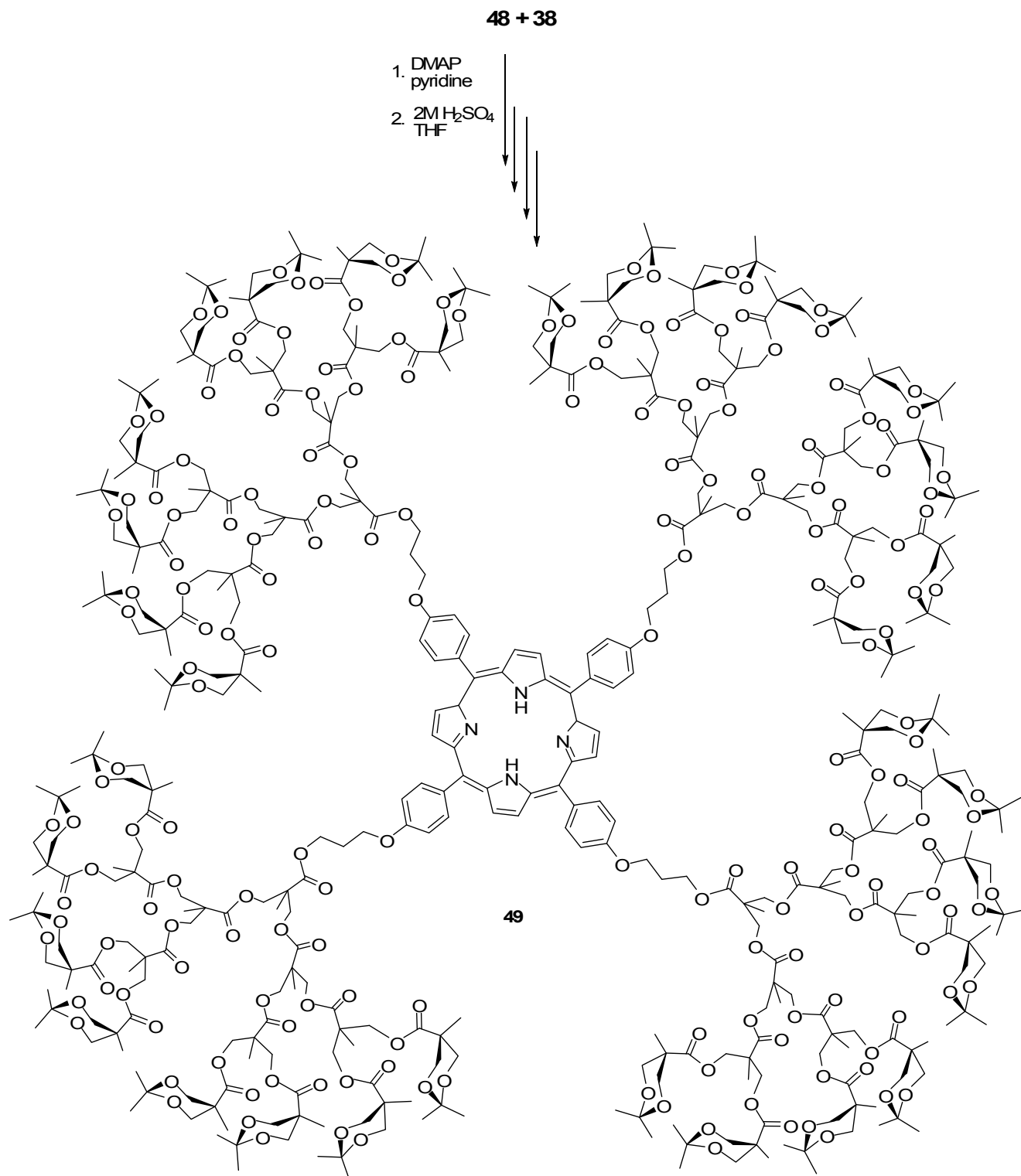
**Scheme 27.** Spacer addition to the porphyrin core [155].

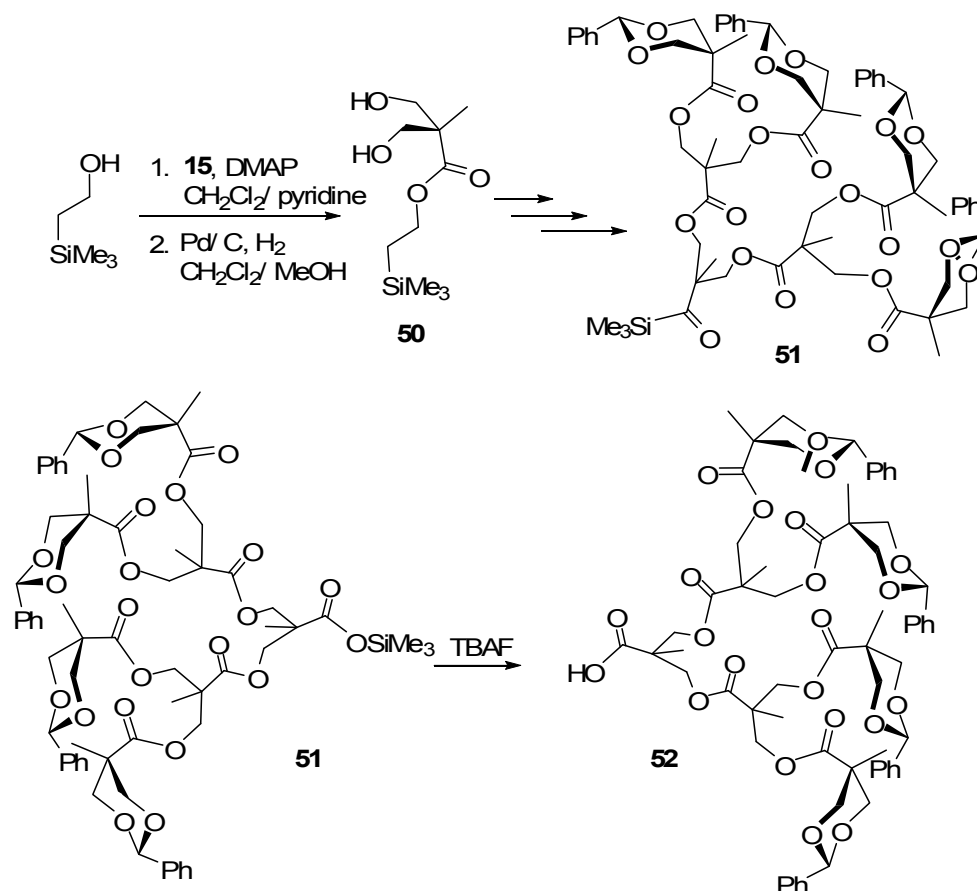
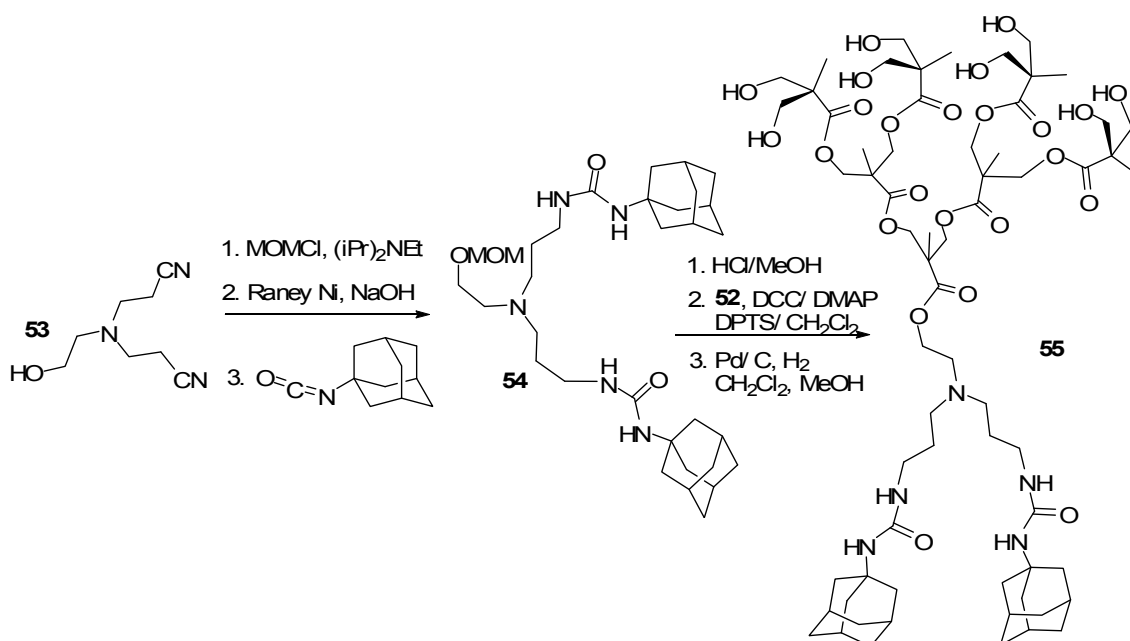


Dendritic species based on bis-HMPA containing carboranes were reported by both Adronov [153] and Zharov [169]. These compounds are of interest because of their potential use for boron neutron capture therapy in the treatment of diseases such as cancer.

The noncovalent synthesis of polyester dendritic bow-ties based on anhydrides **15** and **38** using the complementary bis-(adamantylurea)-glycinyurea system [170,171] at the focal point of the bow-tie was reported by Gillies and Fréchet (Schemes 29 and 30) [172]. The system allows the possibility of bringing together two orthogonally functionalized dendrons since it is not self-complementary. Self-assembled polyester dendritic bow-ties with various peripheral groups were prepared, and their association constants were measured by <sup>1</sup>H NMR spectroscopy in CDCl<sub>3</sub>.

**Scheme 28.** Divergent construction of a fourth generation (acetone-protected) free base porphyrin-cored polyester dendrimer [155].



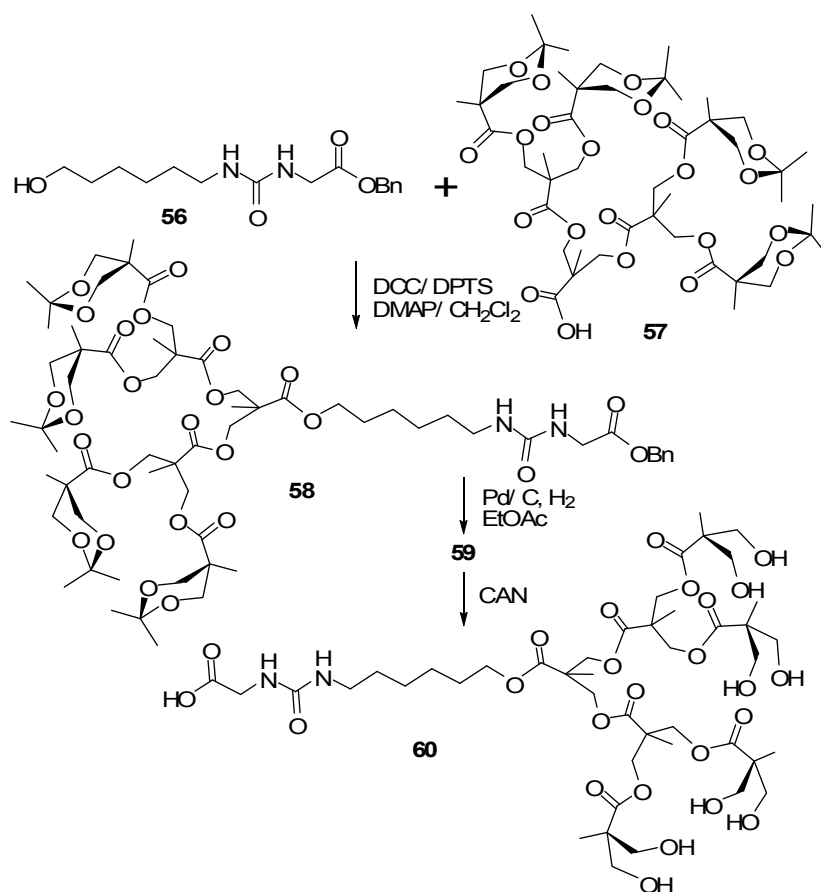
**Scheme 29.** Divergent growth of a third generation dendron [172].**Scheme 30.** Preparation of a bow-tie polyester dendron **55** [172].

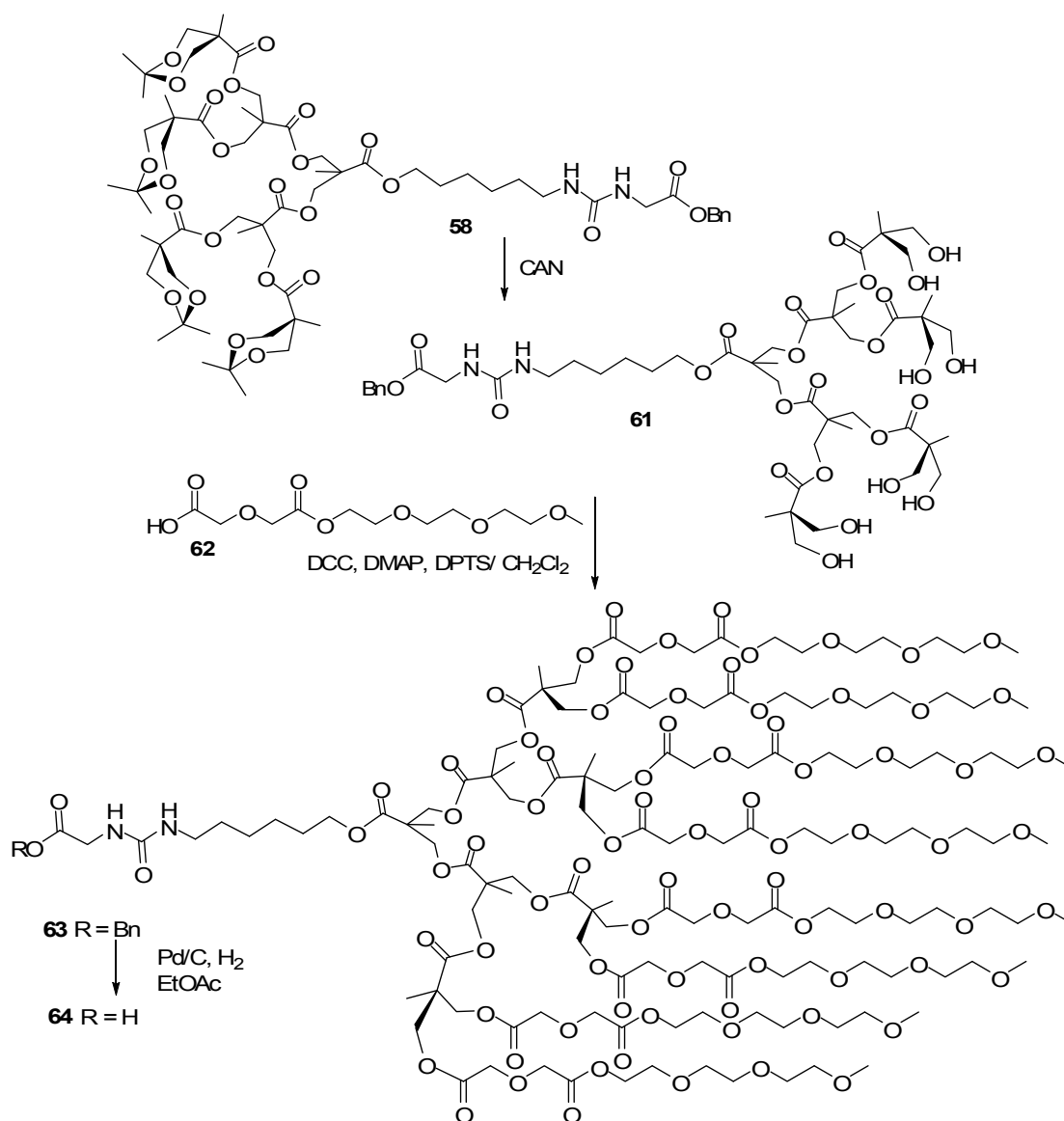
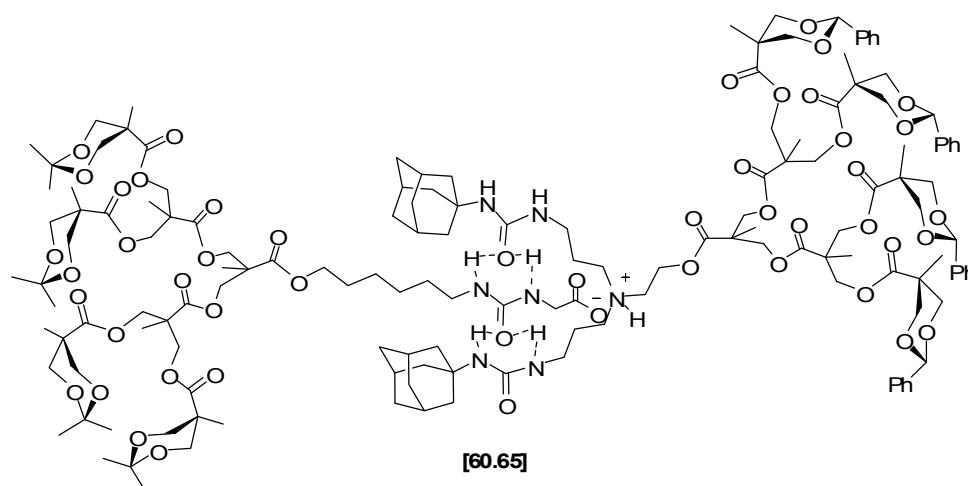
Initially, a trimethylsilylethyl ester was used as the protecting group for the acid focal point by coupling trimethylsilylethanol with **15**. The removal of the benzylidene acetal protecting group using hydrogenolysis provided **50**. Coupling and deprotection procedures were repeated until dendron **51**

was obtained. The trimethylsilylethyl ester protecting group was removed using tetrabutylammonium fluoride (TBAF), yielding acid **52** with four peripheral benzylidene acetals. To synthesize the adamantylurea moiety, the dinitrile **53** [173] was protected as the MOM ether as shown in Scheme 30, and then the nitrile groups were reduced to amines using Raney nickel under basic conditions. The amine groups were reacted with adamantyl isocyanate to form bis(adamantylurea) **54**. The MOM protecting group was then removed under acidic conditions and the product was coupled to **52** to provide dendron **55** after deprotection.

Schemes 30 and 31 illustrate the chemistry used for further protection of the acid focal point. In addition, oligo(ethylene oxide) units were introduced to the periphery of dendrons such as **61** (Scheme 32 to yield acid **64** after removal of the benzyl ester at the focal point. When equimolar amounts of **60** and the benzylidene-protected version of **55** (**65** not previously drawn) were dissolved in  $\text{CDCl}_3$ , the orthogonally-protected parent dendrimer complex [**65**·**60**] shown in Figure 4 was formed and its structure was confirmed using NMR spectroscopy.

**Scheme 31.** Synthesis of dendron **60** [172].

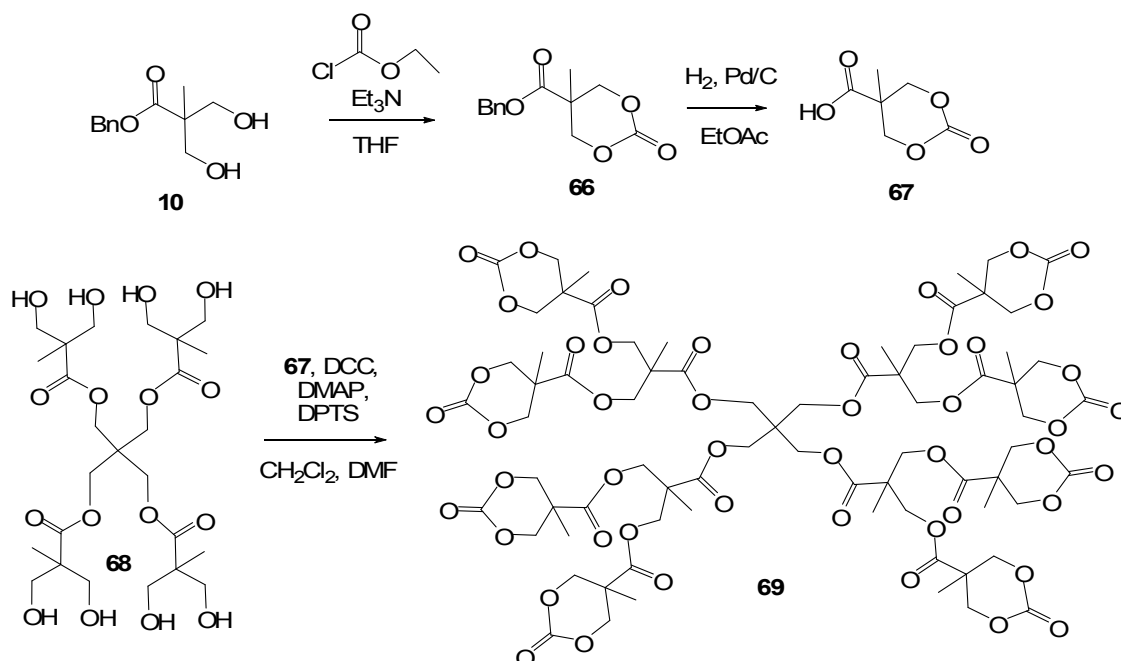


**Scheme 32.** Dendron functionalization using oligo(ethylene oxide) units [172].**Figure 4.** Orthogonally-protected parent dendrimer complex [172].

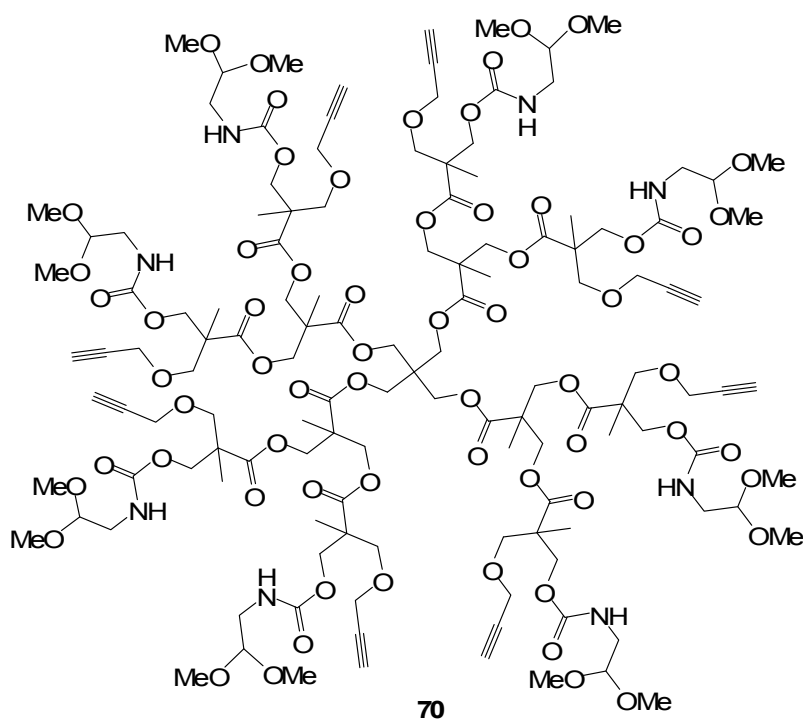


Another novel development was the use of cyclic carbonates on the periphery of polyester dendrimers [174]. This functional group reacts with amines [175], even in water with quantitative yields [176], to yield bifunctional products. In the reaction, the amine opens the carbonate ring to form a carbamate with liberation of an alcohol that may then be used for a subsequent functionalization step.

**Scheme 33.** Synthesis of [G-2] bis-HMPA dendrimer with a cyclic carbonate periphery [174].



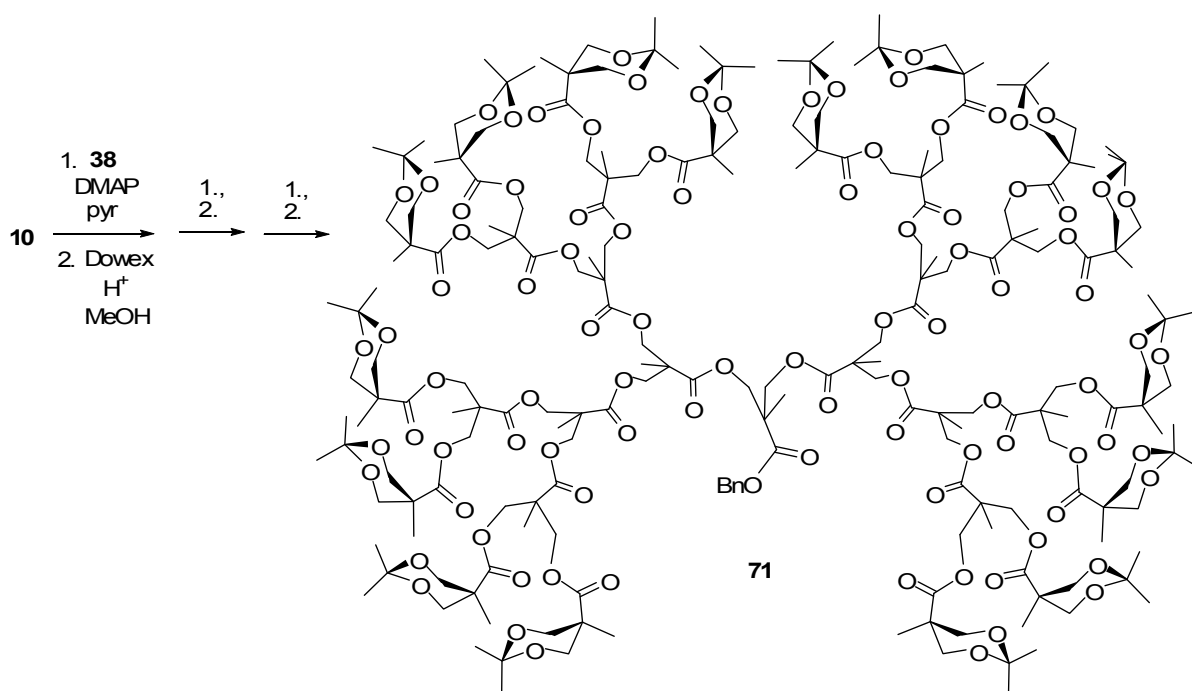
**Figure 5.** Second generation dendrimer having a bifunctionalized periphery [174].



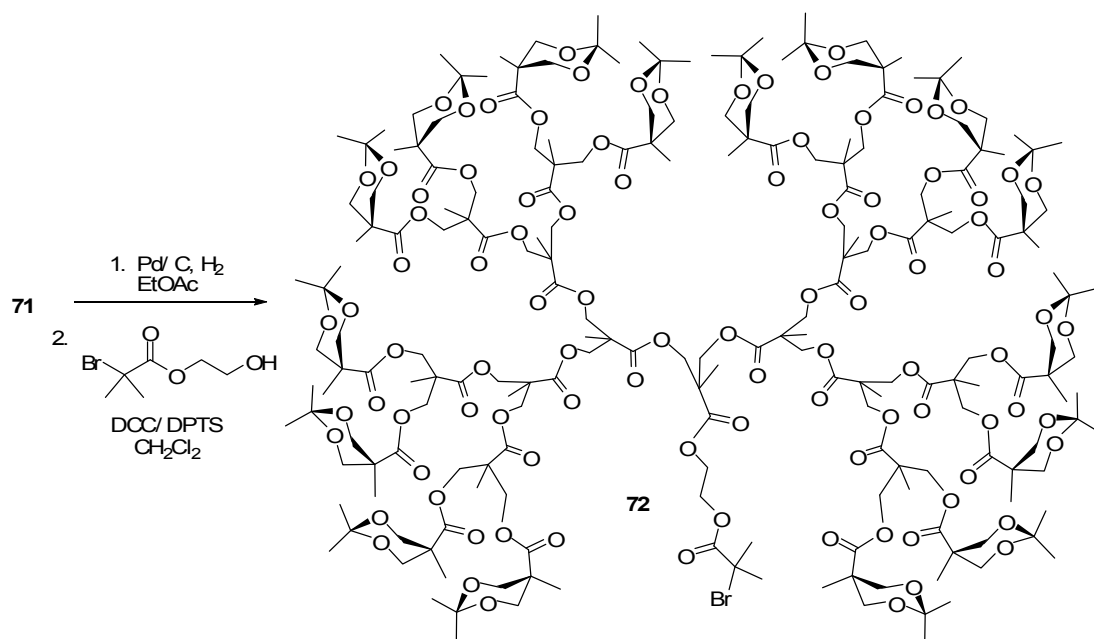
Two different moieties may be added in immediate succession without any deprotection steps or functional group conversions. To provide a model platform for testing the reaction, dendrimer **68** with eight hydroxyl groups was prepared from pentaerythritol (Scheme 33). DCC-promoted coupling of **67** and **68** furnished carbonate-bearing dendrimer **69**. Finally, reacting **69** with  $(\text{MeOH})_2\text{CHCH}_2\text{NH}_2$  and then propargyl bromide afforded dendrimer **70** (Figure 5). This is an example of how dendrimers can be precisely designed and functionalized to impart desired properties.

The coupling of preformed dendrons with bifunctional monomers to form core cross-linked star (CCS) polymers is a versatile strategy which has been widely used [177–184]. In order to explore this approach, the so-called “arm first” synthetic strategy, Hawker and coworkers prepared dendrons as functional initiators capable of initiating polymerization by atom transfer radical polymerization (Schemes 34 to 37) [185]. The synthesis of polyester dendrons up to the fifth generation by the divergent route using **38** is described. Dendrons were then functionalized at the focal point using a single 2-hydroxyethyl 2-bromo-2-methylpropanoate moiety to form dendron functional macroinitiators. A library of highly branched, 3-dimensional, dendron functional CCS polymers were prepared from these macroinitiators by varying generation number and polystyrene chain length, followed by reaction with divinyl benzene, utilizing the “arm first” approach.

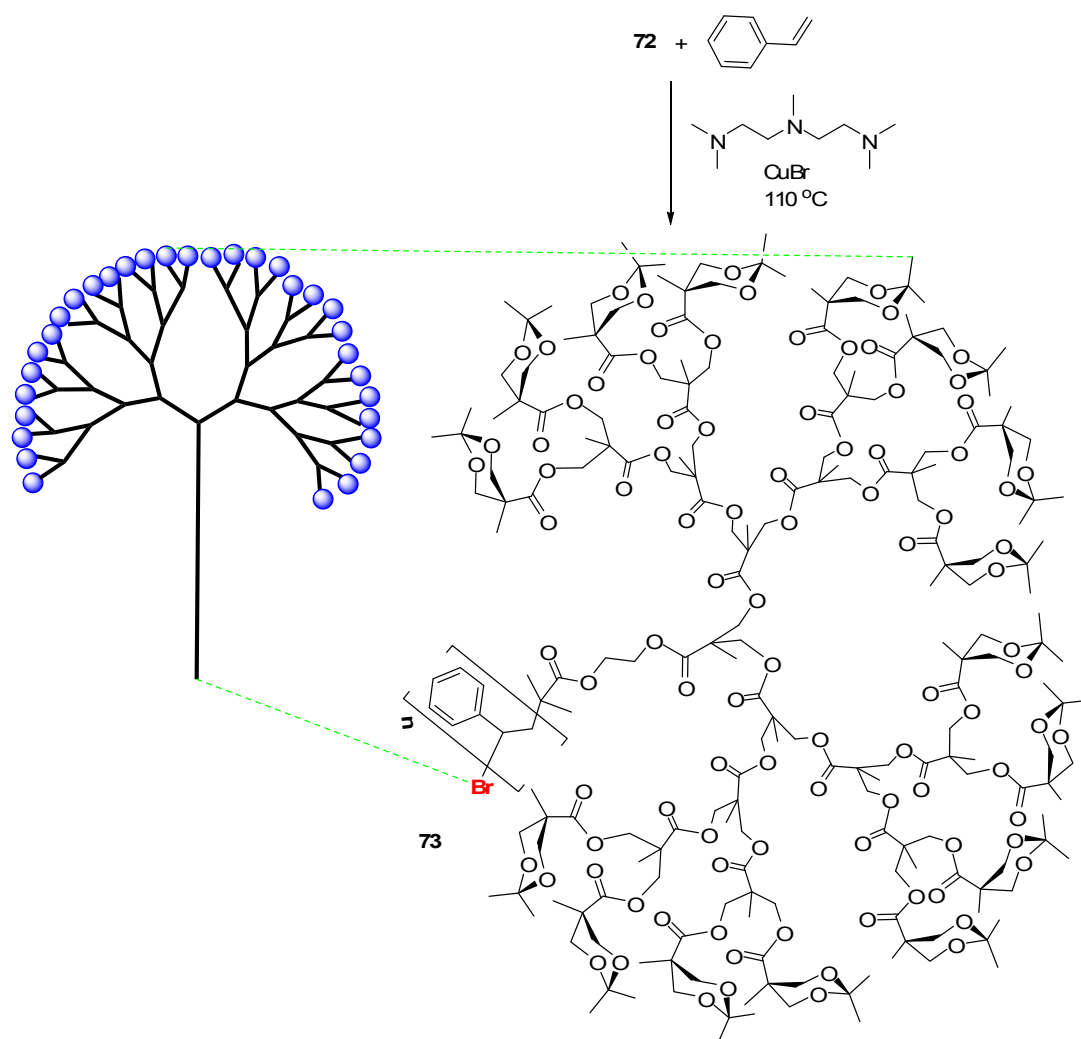
**Scheme 34.** Divergent growth of acetonide-protected fifth generation polyester dendron [185].



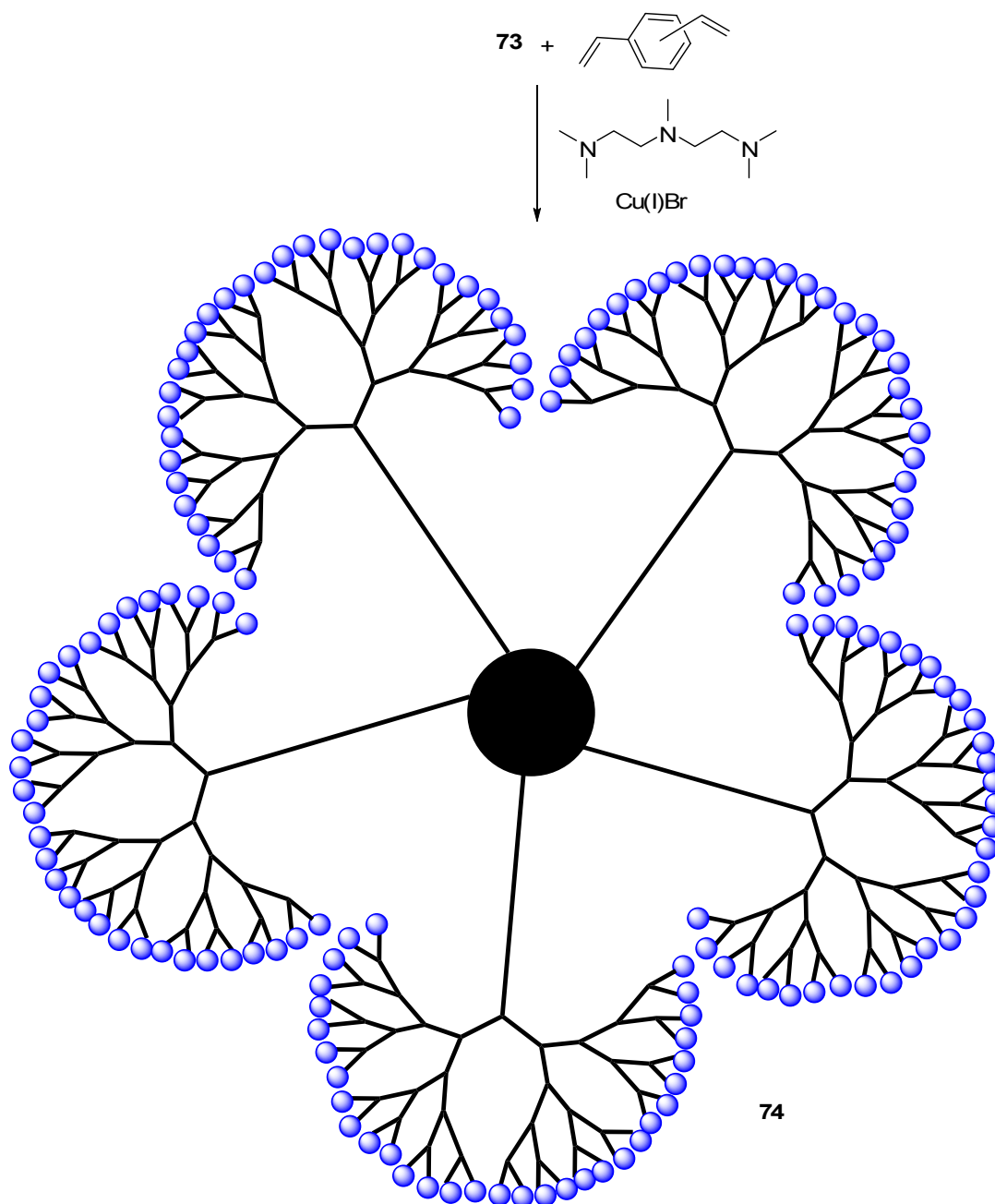
**Scheme 35.** Synthesis of fifth generation dendron with initiating moiety for atom transfer radical polymerization at the focal point [185].



**Scheme 36.** Focal point functionalization using atom transfer radical polymerization [185].



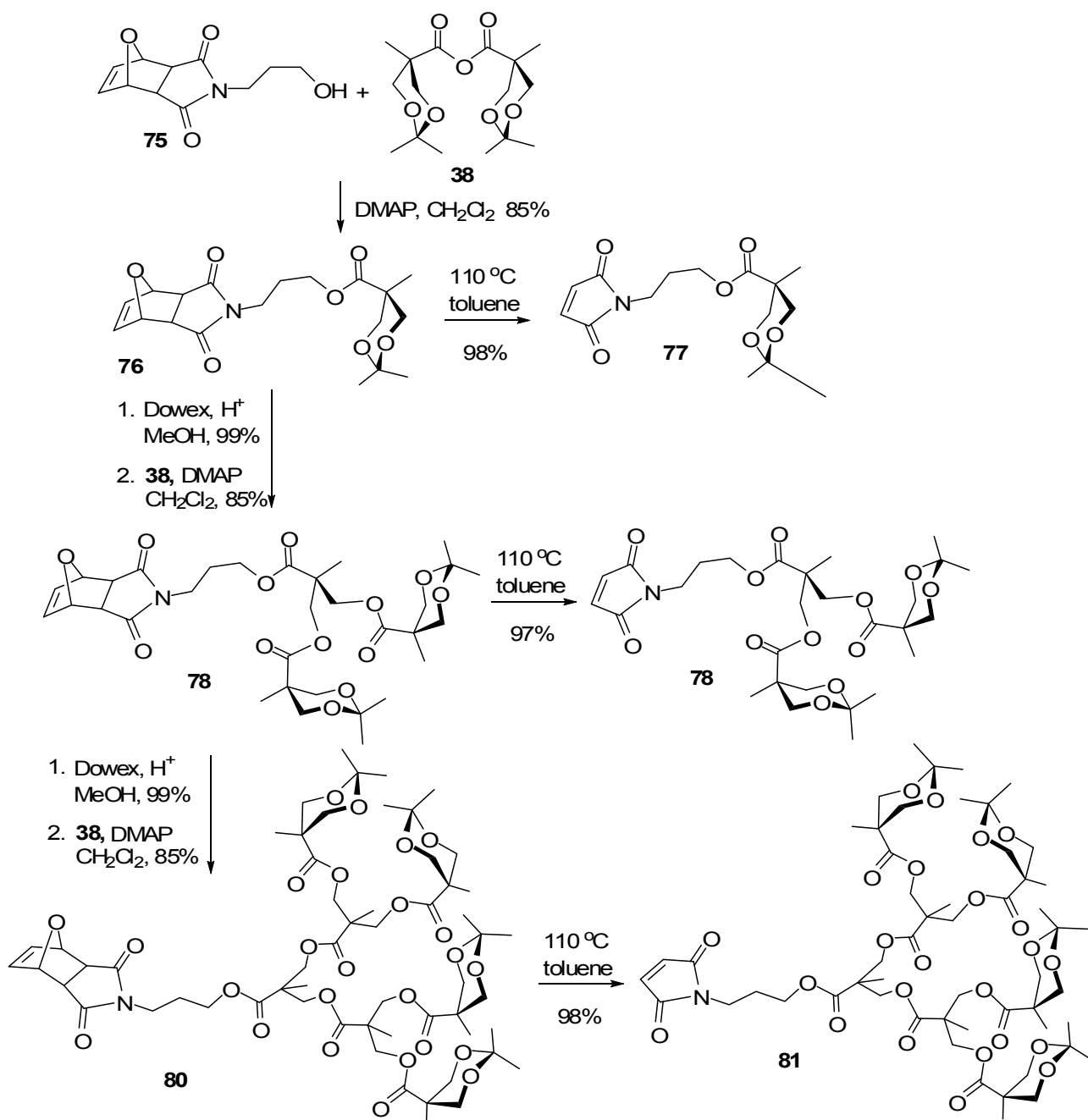
**Scheme 37.** Preparation of a fifth generation functionalized core cross-linked star (CCS) polymers via the “Arm First” approach [185].

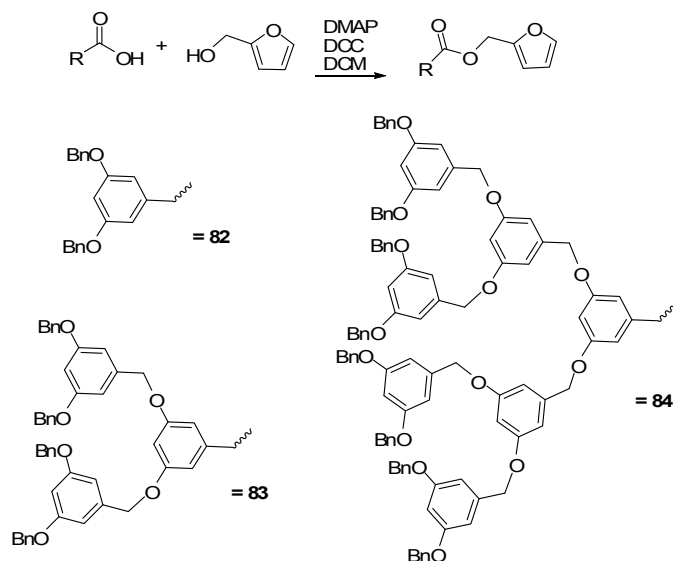


Until the work of Sanyal and coworkers was published in 2008 [186], few reports describing dendrimer synthesis using the Diels-Alder reaction had appeared. However, these reports described the combination of identical dendrons to furnish symmetrical dendrimers [187,188]. Sanyal's work was the first example of the synthesis of segment block dendrimers using the Diels-Alder-based synthetic strategy toward the synthesis of unsymmetrical dendrimers. Here, three generations of furan functionalized polyaryl ether dendrons were reacted with maleimide functionalized polyester dendrons of the same generation to obtain segment block dendrimers in good yields. The thermoreversible nature of these macromolecules was investigated by subjecting them to elevated temperatures in the presence of anthracene as a scavenger diene. Acetonide-protected polyester dendrons were prepared

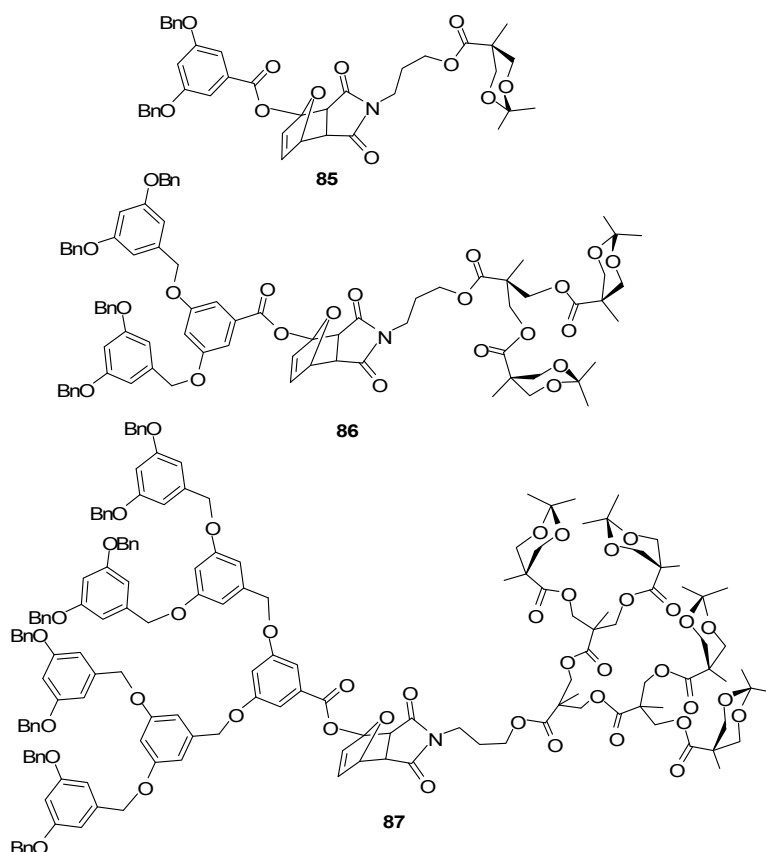
divergently starting from a furan-protected *N*-hydroxypropylmaleimide **74**. Reacting **74** with anhydride **43** in the presence of DMAP produced **75**, which was refluxed in toluene at 110 °C to yield second generation dendron **76** containing the reactive dienophile maleimide group at the focal point. The removal of acetonide-protecting group of compound **75** followed by another coupling step with anhydride **43** furnished **77**, which was also refluxed in toluene to yield **78**, a second generation dienophile. Another round of the three steps from **77** gave a third generation dienophile **80** as shown in Scheme 38. To prepare the Diels-Alder coupling partners, the acid-functionalized Fréchet dendrons [189,190] were coupled with furfuryl alcohol in the presence of DMAP and DCC to yield three generations of furan-functionalized polyaryl ether dendrons in 88%, 90%, and 58% yields, respectively (Scheme 39).

**Scheme 38.** Divergent syntheses of maleimide-functionalized dendrons [186].



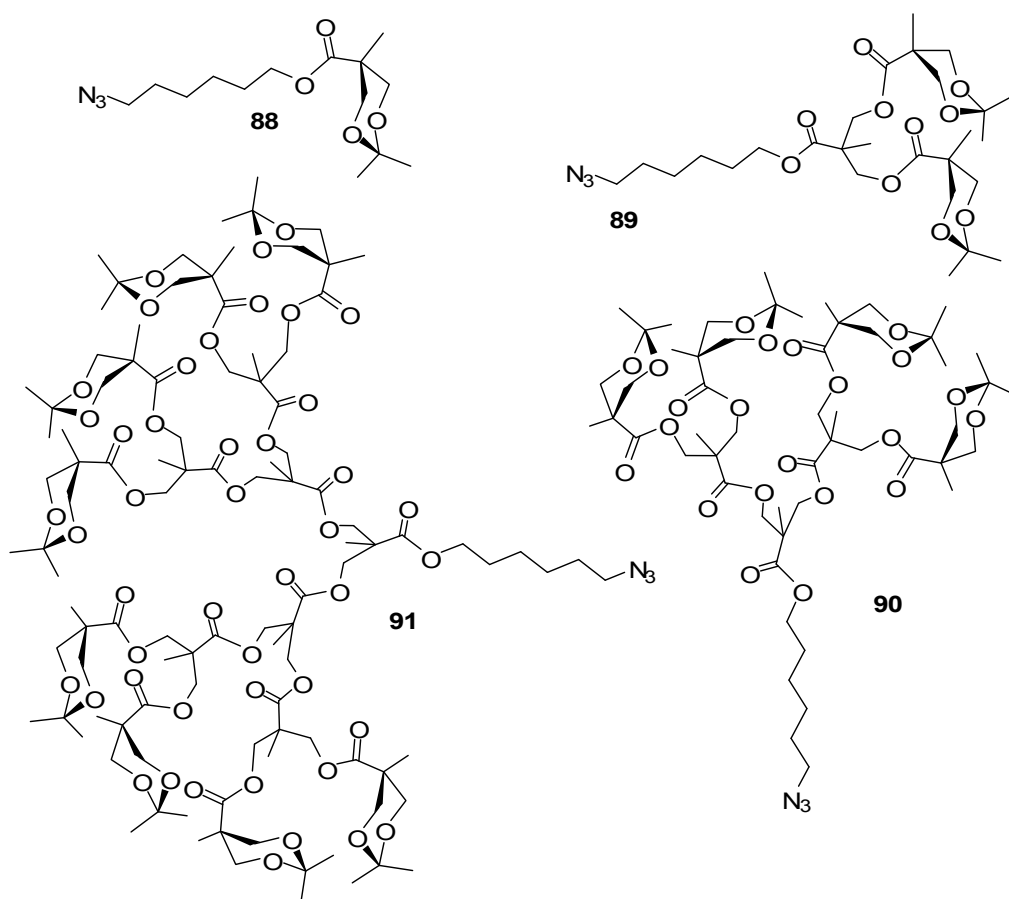
**Scheme 39.** Preparation of diene partners [186].

The reaction of furan-functionalized dienes **82–84** with dienophiles **77**, **79**, and **81** in benzene at 85 °C for 24 h afforded the three generations of unsymmetrical dendrimers **85–87** in 98%, 76%, and 79% yields, respectively (see Figure 6). This reagent free Diels-Alder cycloaddition is attractive as the resulting dendrimers are free of impurities such as metals which are usually toxic and therefore problematic in biological applications.

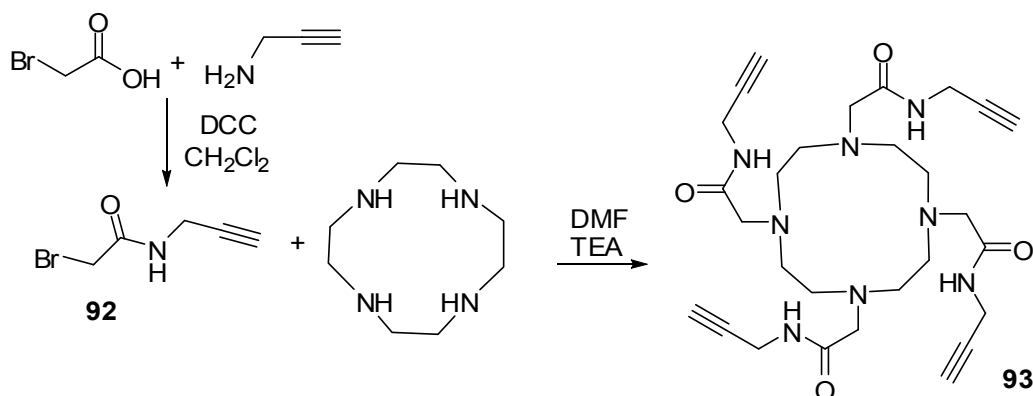
**Figure 6.** Unsymmetrical dendrimers [186].

Antoni *et al.* prepared azide-terminated bis-HMPA-based polyester dendrons (see Figure 7) up to the fourth generation in order to perform photophysical studies on their products with alkynes [191]. New dendrimer architectures were produced by the “click reaction” [192,193] of these dendrons with a tetravalent alkyne functionalized cyclen core [191]. The preparation of tetravalent alkyne functional cyclen core is shown in Scheme 40.

**Figure 7.** Azide-functionalized polyester dendrons [191].



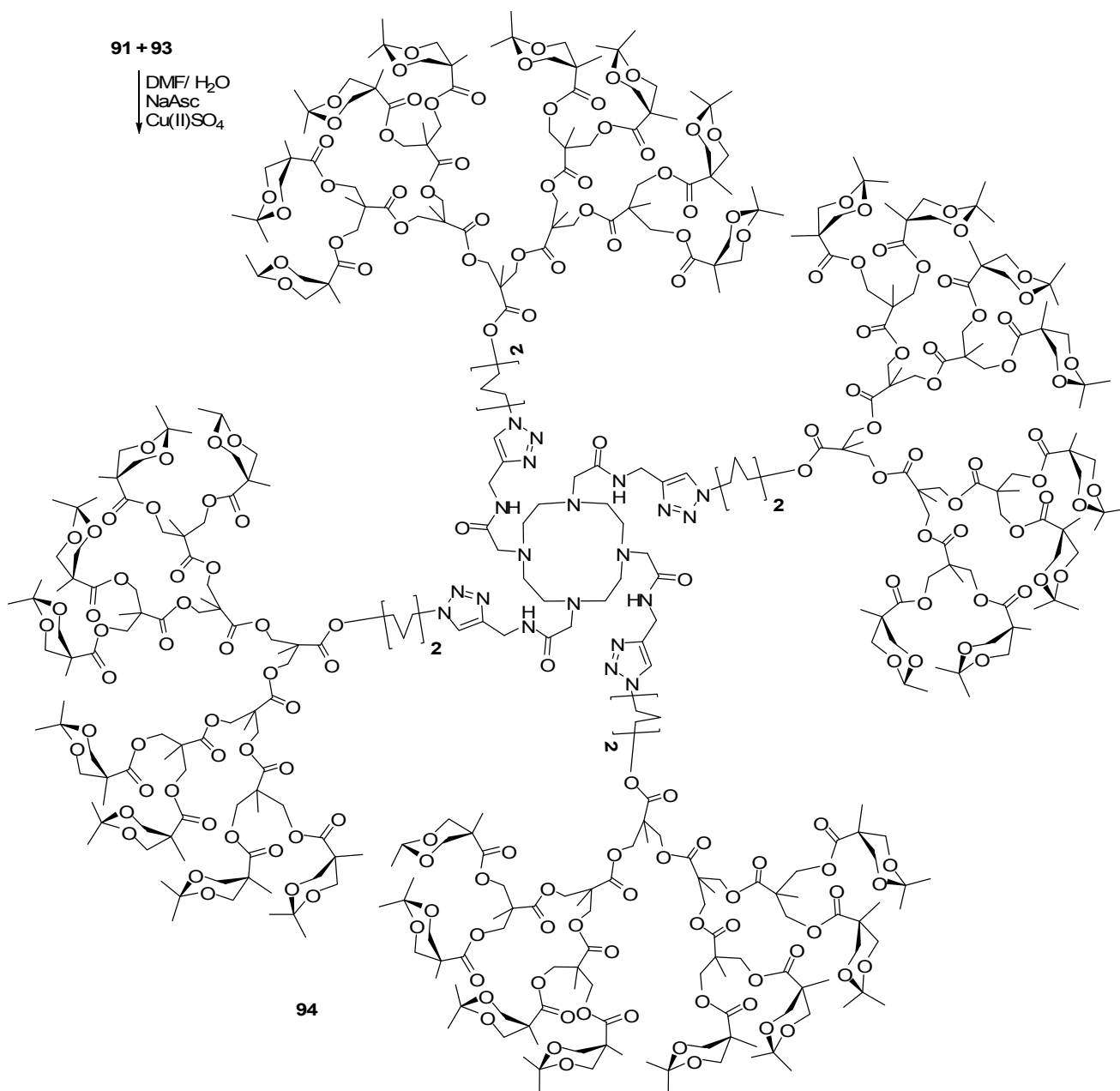
**Scheme 40.** Synthesis of a tetravalent alkyne-functionalized cyclen core [191].



The preparation of the fourth generation polyester dendrimer is shown in Scheme 41. These dendrimers are interesting because triazole groups were shown to be stable, intra-locked between the cyclen and dendron wedges. The incorporation of a lanthanide metal ion, europium, into the interior of

all cyclen dendrimers was monitored by FT-IR and the photophysical results showed that the proximate triazole acts as both a stable linker and sensitizer, transferring its singlet-singlet excitation in the ultraviolet region (270–290 nm) to the partially filled luminescent lanthanide 4f shell [191].

**Scheme 41.** Assembly of a fourth generation polyester dendrimer using a click reaction [191].

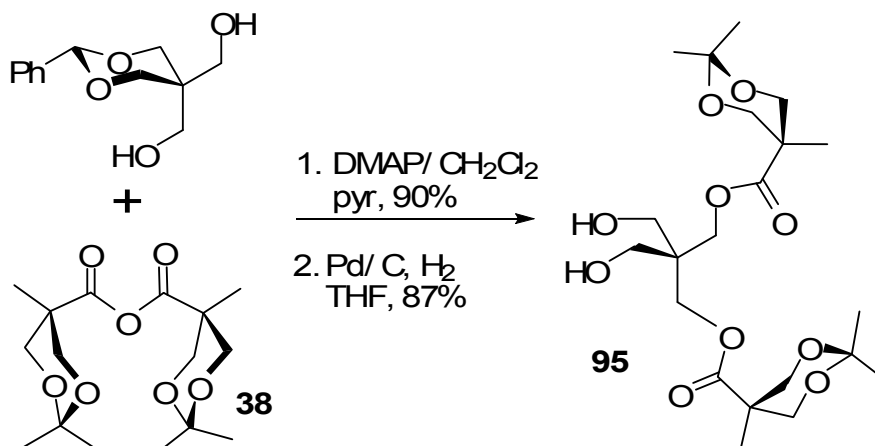


Azobenzene-containing dendrimers [194] have continued to draw interest because of their optical properties [195–202]. Rissanen's group has shown interest in the synthesis of Janus-type dendrimers having possible non-linear optical properties arising from the non-centrosymmetric structure of chiral azobenzene conjugates. One report describes the synthesis of bisfunctionalized Janus-type polyester dendrimers, which consist of a polar hydroxyl functionalized end, and a photoactive end constructed from donor–acceptor azobenzenes and chiral naproxen units [203]. An aliphatic polyester skeleton was constructed by reacting monobenzylidene pentaerythritol with the anhydride of acetonide-protected

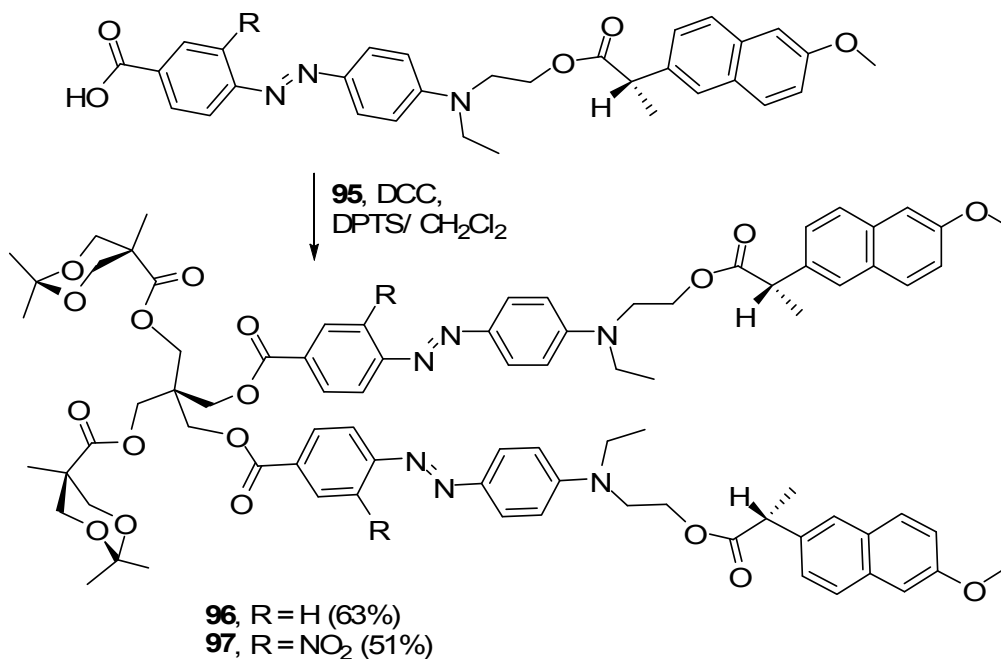


bis-HMPA. Azobenzene moieties, previously reported by the same research group [204], were chosen to be incorporated as electron donor–acceptor chromophores, since they possess non-linear optical properties [205]. Shown in Schemes 42 and 43 are the syntheses of the first and second generations for this type of unsymmetrical dendrimers.

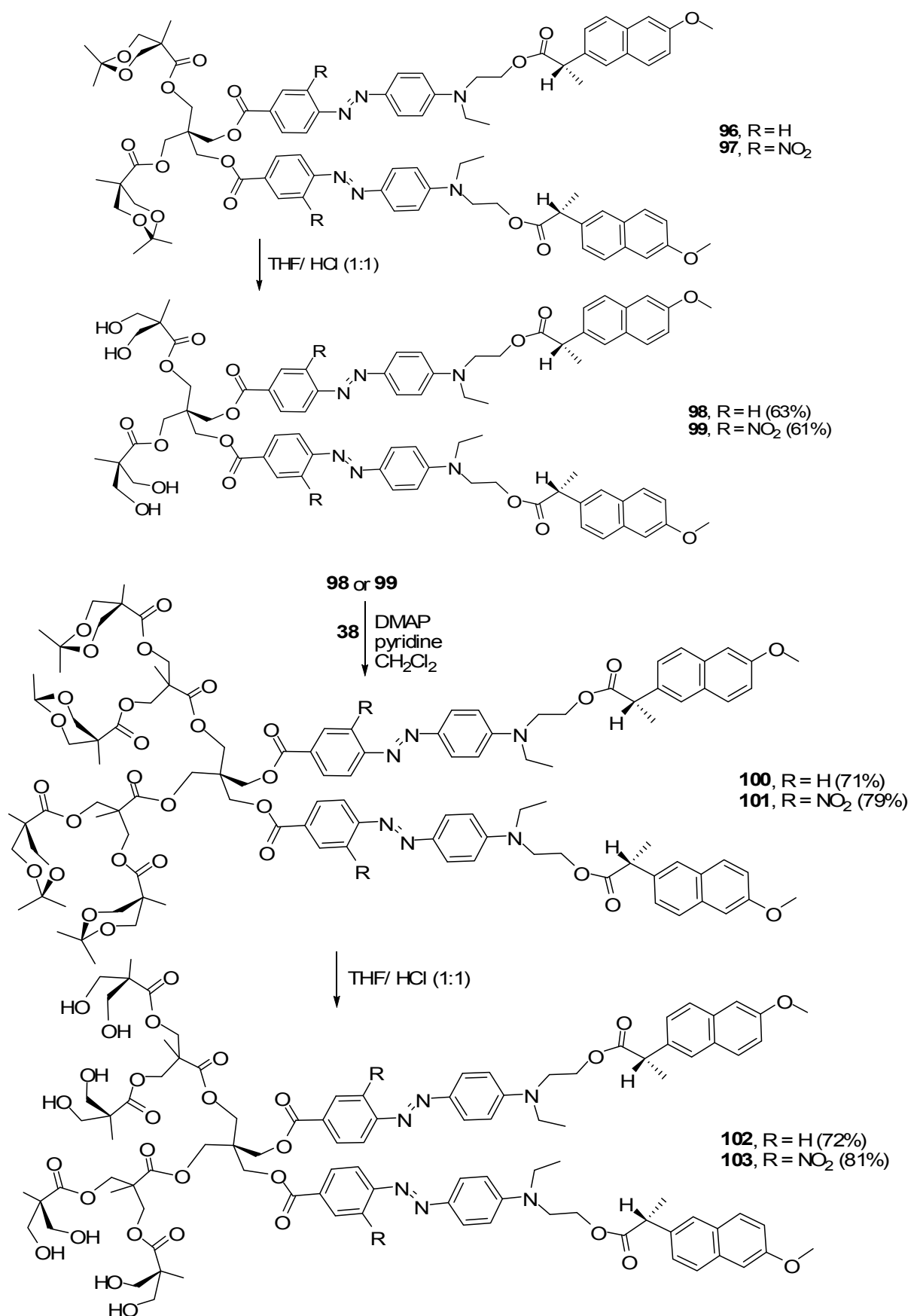
**Scheme 42.** Synthesis of acetonide-protected first generation dendrimer (**95**) [203].



**Scheme 43.** Synthesis of second generation unsymmetrical polyester dendrimer [203].

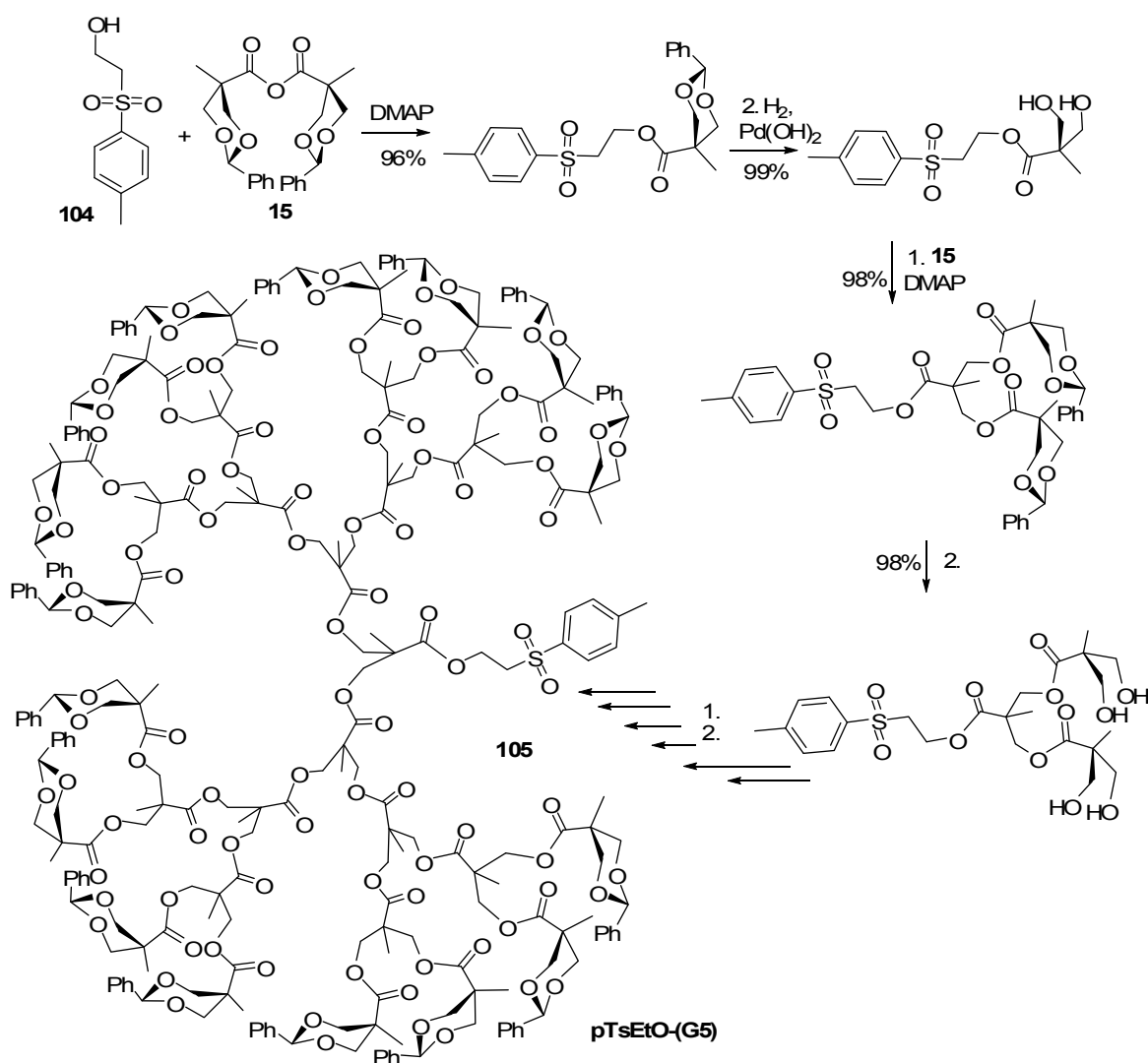


## Scheme 43. Cont.



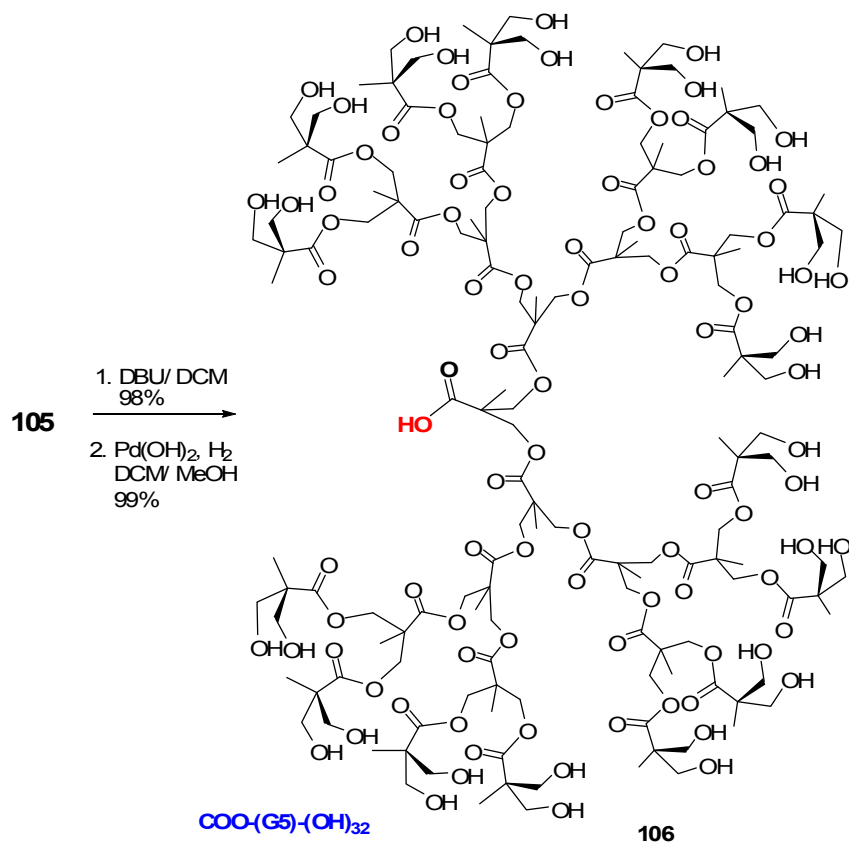
Parrott *et al.* recently introduced a new carboxylic acid protecting group for the synthesis of polyester dendrons based on bis-HMPA [129], the 2-*p*-toluenesulfonyl ethyl group [129]. Dendrons up to the eighth generation were prepared in excellent yields using benzylidene-protected bis-HMPA as the unit being added as shown in Scheme 44 [129]. The protecting group was removed under mild conditions with the non-nucleophilic base DBU in dichloromethane (Scheme 45).

**Scheme 44.** Divergently-grown fifth generation dendron **105** [129].

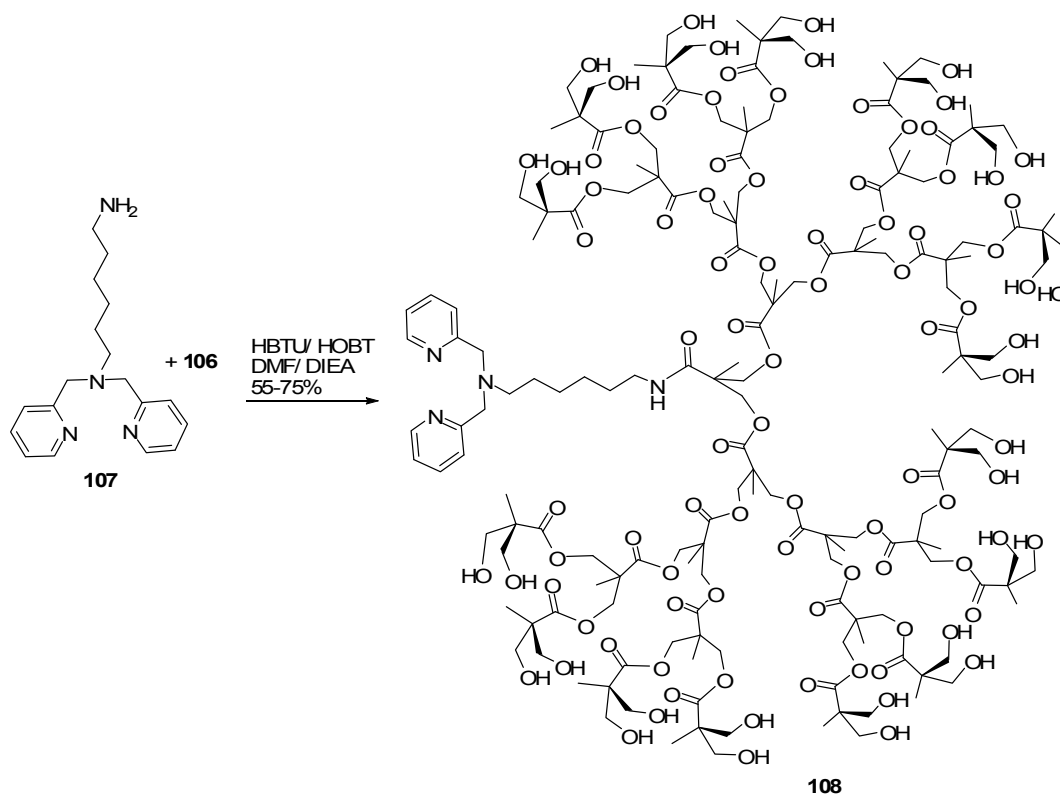


This group was interested in the preparation of high generations of well-defined and robust  $^{99m}\text{Tc}$ -labeled dendrimers suitable for single photon emission computed tomography (SPECT) imaging. The  $\gamma$ -emitting  $^{99m}\text{Tc}$  is the most commonly used medical isotope in diagnostic medicine due to its ideal half-life (6 h) and  $\gamma$ -energy (140 keV), low dose burden to patients, and the universal availability of low cost  $^{99}\text{Mo}/^{99m}\text{Tc}$ -generators [206]. A single high-affinity Tc ligand at the core of the dendrimer was desired to ensure that radiolabeling occurs in a well-defined, site-specific manner and at only a single point within the dendrimer skeleton. In addition, the incorporation of the radionuclide was not to significantly affect the overall size, shape, polarity, and mode of interaction of the dendrimer periphery with its external environment so as not to alter the biodistribution of the non-radiolabeled dendrimer.

**Scheme 45.** Deprotection of the periphery and focal point of the 2-*p*-toluenesulfonylethyl protected dendron [129].

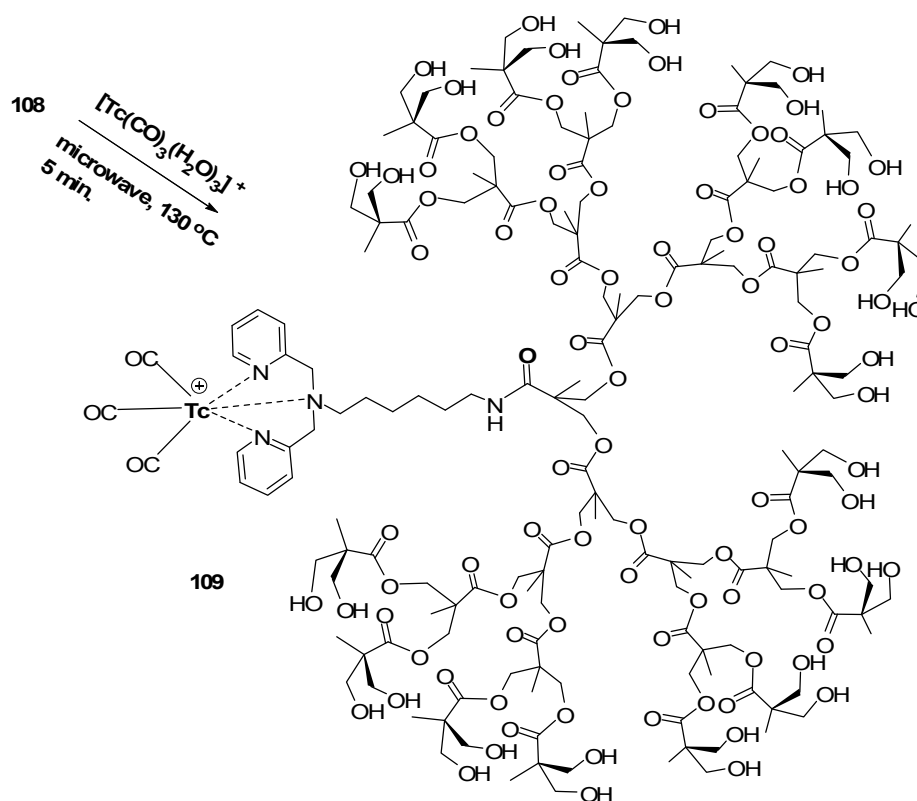


**Scheme 46.** Amidation of the focal point using aminohexyl-functionalized bis(pyridyl)amine ligand [129].



Amidation of the deprotected core with an aminoalkyl-functionalized bis(pyridyl)amine ligand allowed the introduction of an extremely efficient single-site chelator **108** for  $^{99m}\text{Tc}$ . Dendron labelling was then accomplished by first converting sodium pertechnetate ( $\text{Na}^{99m}\text{TcO}_4$ ) from the  $^{99}\text{Mo}/^{99m}\text{Tc}$ -generator to  $[\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3]^+$ . Microwave irradiation of amidated dendrons in the presence of the aqua species at 130 °C gave the desired radiolabelled dendrons within 5 min (Scheme 47).

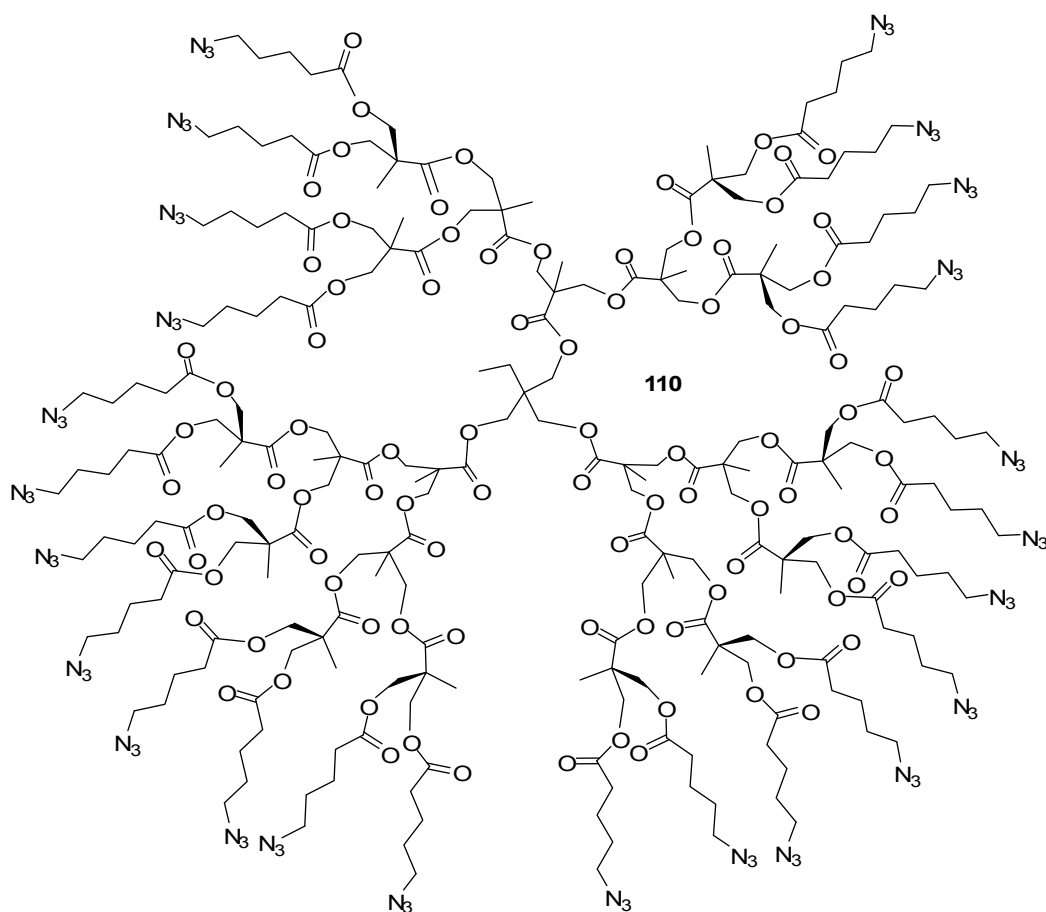
**Scheme 47.** Direct radiolabelling of dendrons using the tris-aqua species  $[\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3]^+$  [129].



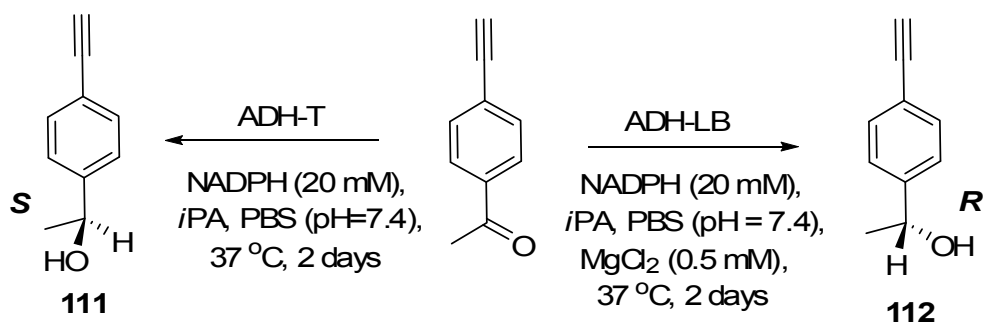
The process by which information from a source is converted into symbols to be communicated or information encoding is an important field owing to its potential applications [207–209]. While exploring chirality for the development of encodeable macromolecules, which can be read out by simple optical rotation measurements or by enantioselective bioresponse, Heise and coworkers reported the synthesis of encoded dendrimers with defined chiral composition via ‘click’ reactions of enantiopure building blocks [210]. Heise and coworkers had previously reported the synthesis of copolymers from the enantiomerically pure monomers of (*R*) and (*S*)-*p*-vinylphenylethanol [211] but copolymers have a disadvantage in that there is uncertainty about the distribution of chiral units along the polymer skeleton. A viable approach was to use dendrimers of well-defined architectures in which orthogonal functionalization encodes a defined optical rotation into the dendrimer by the use of enantiomerically pure (*R*) and (*S*) building blocks. Here, an azide-terminated dendrimer (Figure 8) based on bis-HMPA was divergently constructed as previously described [212] and functionalized using 1,3-dipolar cycloadditions (click reactions) with different ratios of the matching alkyne functional enantiopure building blocks (Scheme 49). Scheme 48 shows the selective alcohol dehydrogenase

(ADH) reduction of 1-(4-ethynylphenyl)ethanone to give the desired chiral building blocks. When measurements of the optical rotation were taken, it was found that the specific optical rotation of the dendrimers increased linearly with increasing percentage of (*R*) end-groups in the dendrimer, indicating that both (*R*) and (*S*) building blocks had been incorporated into the dendrimer in agreement with the enantiomeric feed ratio.

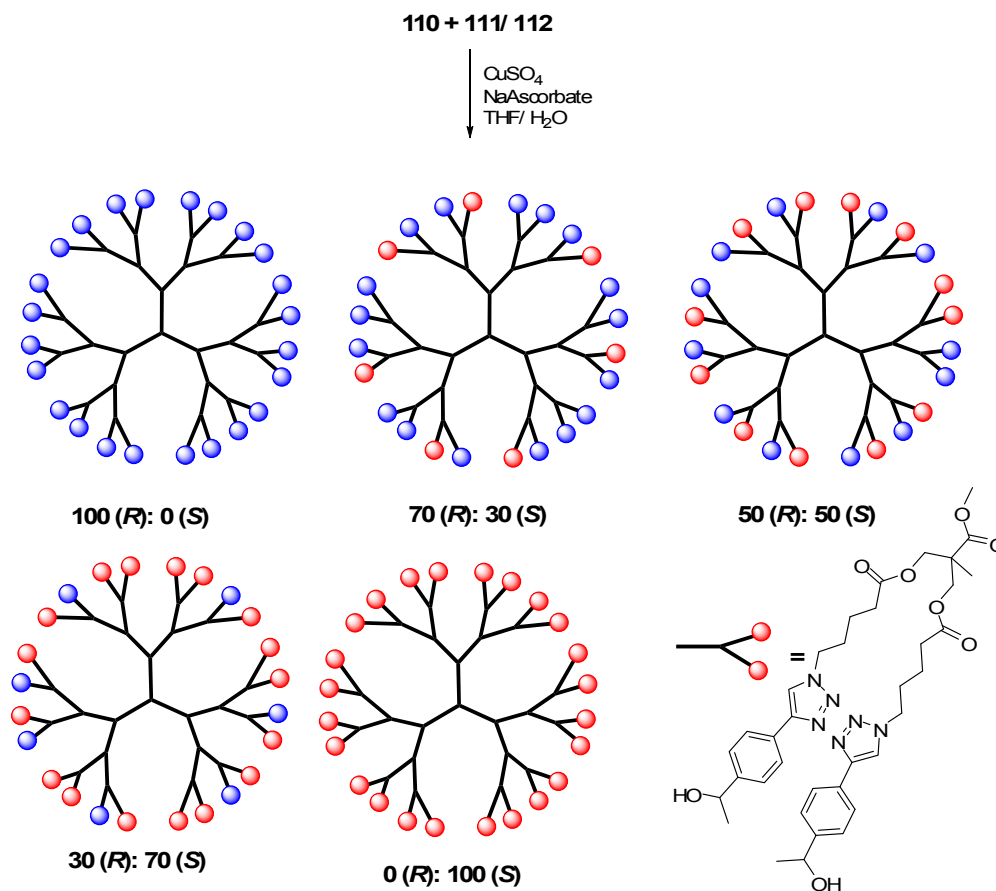
**Figure 8.** Azide-terminated third generation dendrimer [212].



**Scheme 48.** Enzymatic preparation of enantiopure building blocks [211].

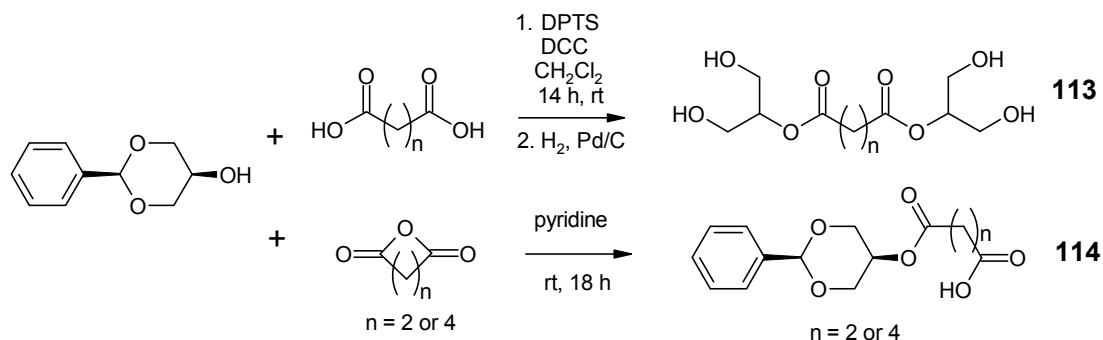
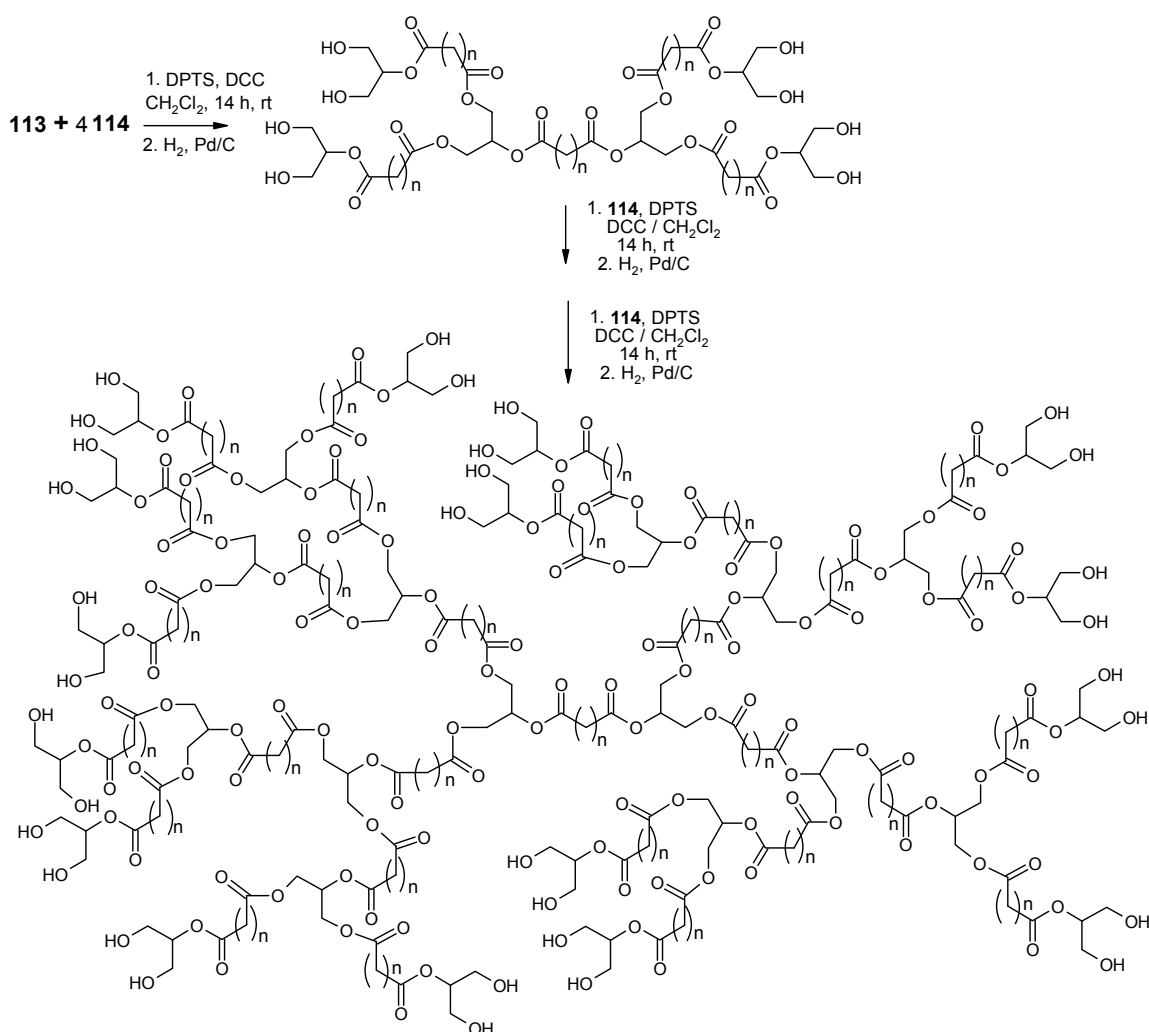


**Scheme 49.** Modification of azide functional dendrimers using different ratios of enantiomers [210].



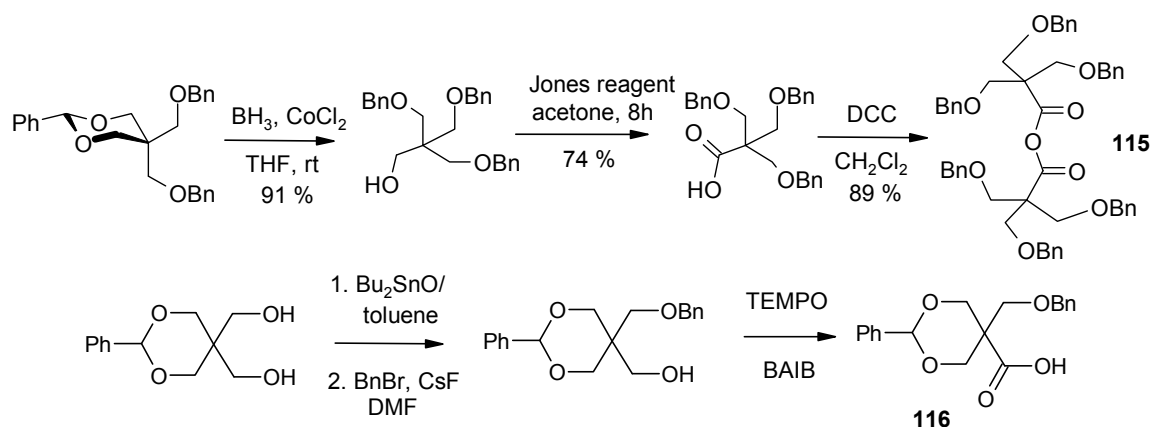
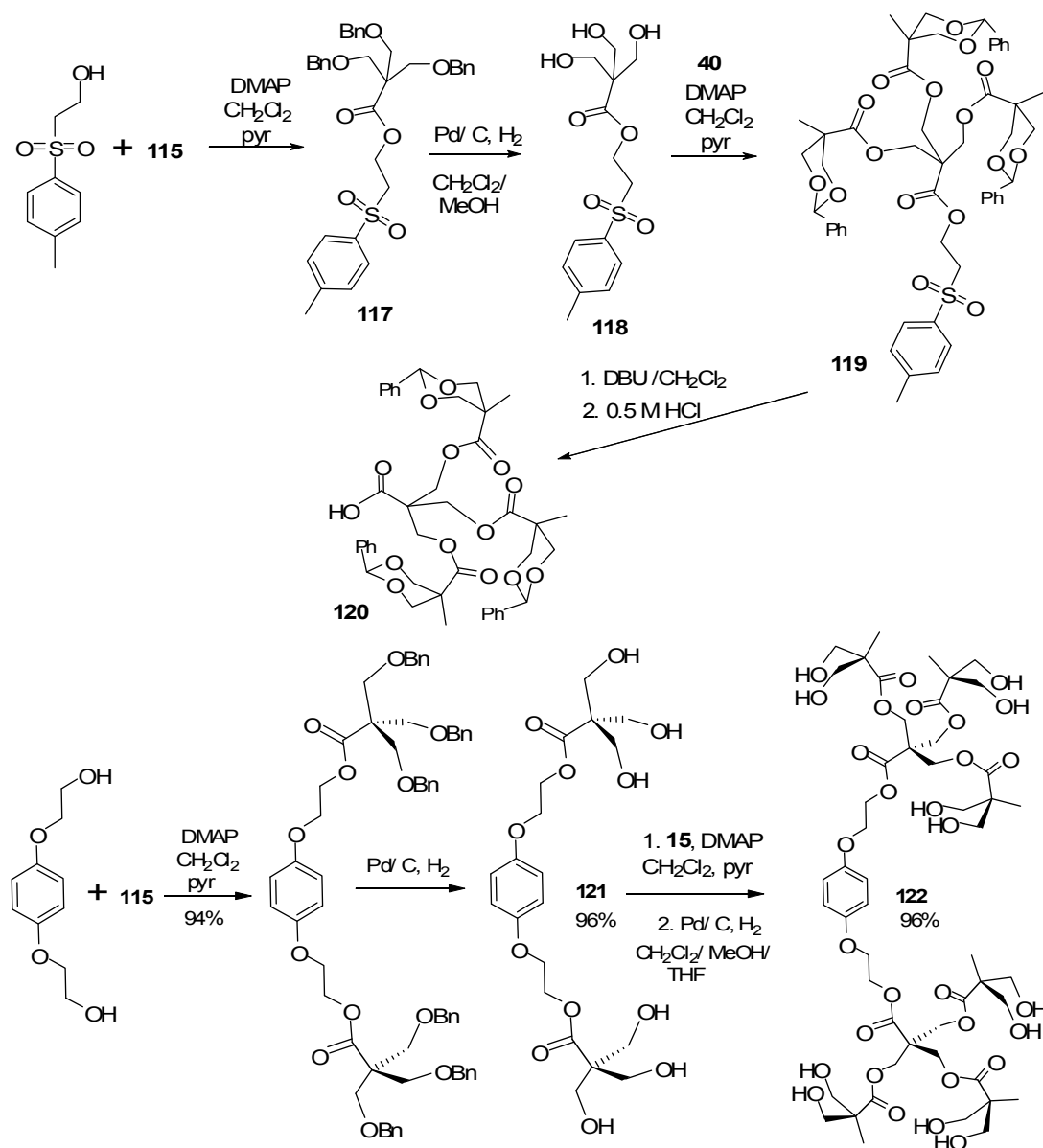
#### 4.2. The Use of Other Aliphatic Dendrons

Other aliphatic dendrons have been used less often than bis-HMPA. Carnahan and Grinstaff developed tetraol dendrons **113** by esterification of the hydroxyl group of *cis*-5-hydroxy-2-phenyl-1,3-dioxane with succinic or adipic anhydride as shown in Scheme 50 [213,214]. Up to fourth generation dendrimers were prepared by DCC-promoted esterification of tetraols **113** with the benzylidene-protected monocarboxylic acid **114**, then deprotection of the latent hydroxyls (Scheme 51) [213]. It should be noted that these materials will be diastereomeric mixtures because the plane of symmetry present in the starting material, *cis*-5-hydroxy-2-phenyl-1,3-dioxane, is not present in the dendritic products. Dendrimers were prepared containing only succinic acid, only adipic acid, and mixtures of the two [214]. The properties of the latter dendrimers rely heavily on the composition of the outer generation layer [214]. By esterifying the dendrimers with succinic acid monomethylallyl ether, and photochemically polymerizing the alkenes, soft gels were produced [213]. These materials are used as corneal adhesives [215,216] and for cartilage repair [217,218].

**Scheme 50.** Preparation of tetraol dendrons [213,214].**Scheme 51.** Synthesis of a third generation dendrimer [213,214].

We have synthesized tribranched dendrons in order to prepare dendrimers that have denser layers than those derived from bis-HMPA (Scheme 52) [130,219]. Polyester dendrimers with denser layers are likely to be longer lived under physiological conditions. As shown in Scheme 53, we have recently used the TsEt protecting group in the synthesis of a second generation acid dendron [134]. A tri-branched acid anhydride dendron **115** [130] was reacted with TsEtOH in the presence of DMAP to give benzyl-protected first generation **117**. Hydrogenolysis then gave **118** in good yield.

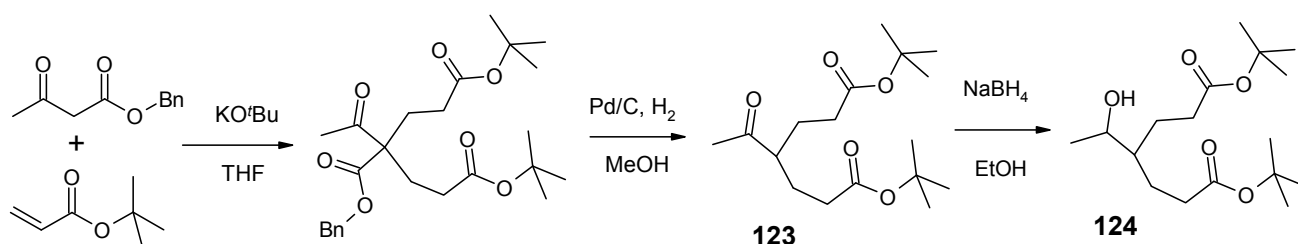


**Scheme 52.** Synthesis of tribranched dendrons [130].**Scheme 53.** Divergent syntheses of a second generation tribranched dendron and a second generation dendrimer incorporating a tribranched dendron [130].

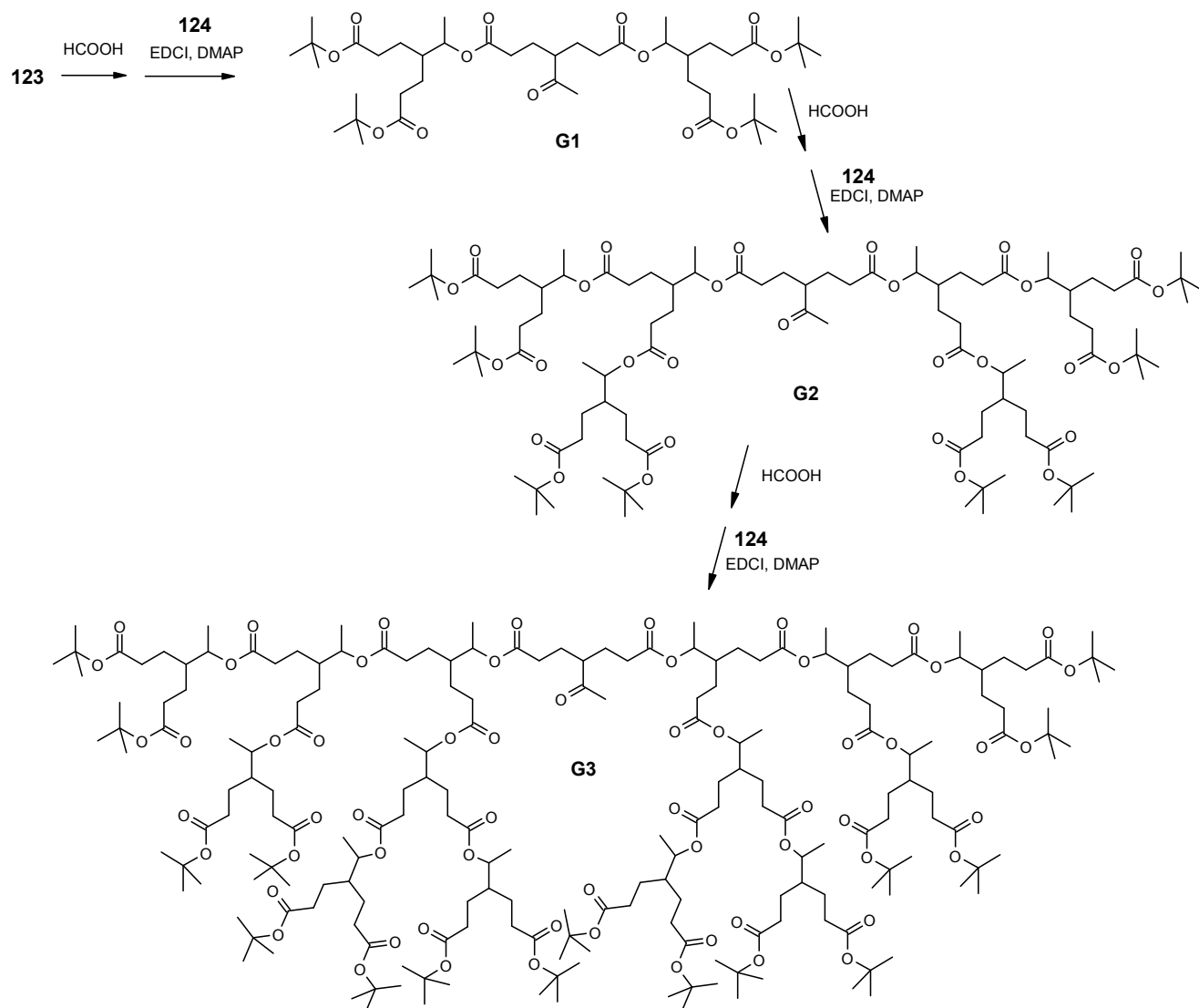
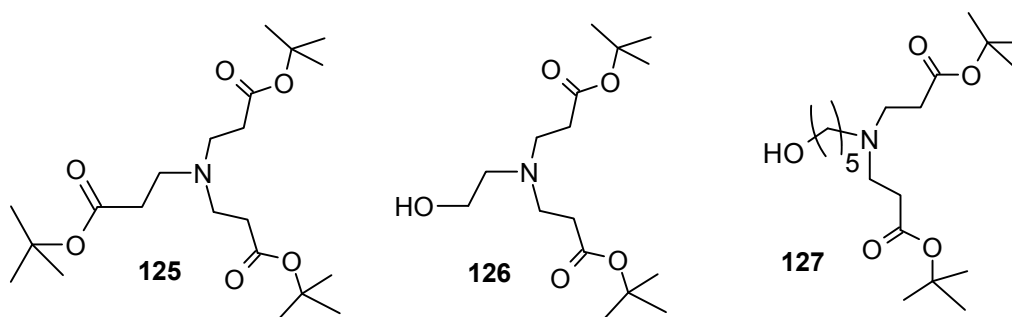
Reacting **117** with benzylidene-protected anhydride **15** followed by deprotection of the focal point using DBU gave the desired acid dendron **120** (Scheme 53). Using coupling agent 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) [130] in the presence of an organic base, ester formation between **120** and various alcohols was achieved in good yield [134]. Scheme 53 also illustrates the preparation of a second generation dendrimer using this approach. Core moiety **121** have also been used to prepare other polyester dendrimers [130] and compound **122** has also been prepared using a divergent approach.

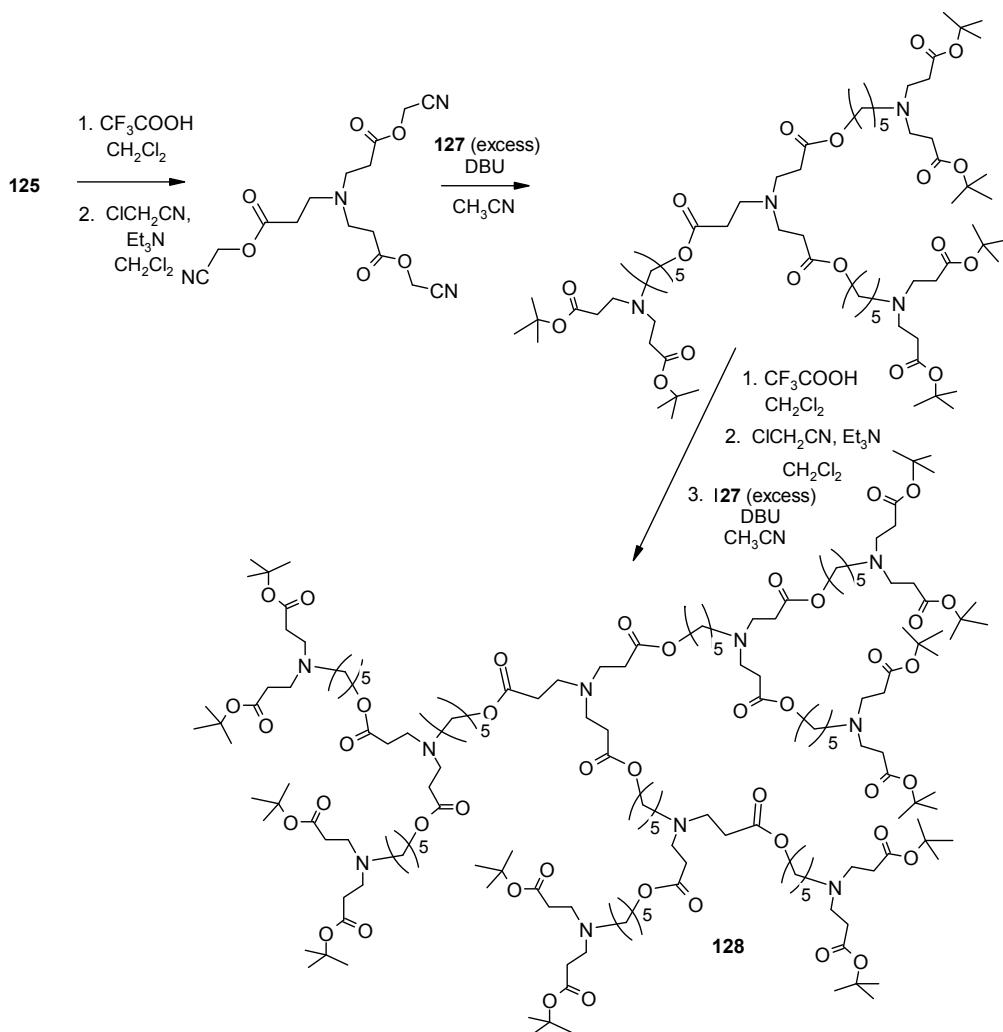
Hirayama *et al.* devised a synthesis of polyester dendrimers using benzyl acetoacetate and tert-butyl acrylate or 3-hydroxyacetophenone as starting materials [220,221]. Shown in Scheme 54 is the preparation of the AB<sub>2</sub> dendron from the Michael addition of benzyl acetoacetate to two equivalents of tert-butyl acrylate followed by hydrogenolysis of the benzyl group, spontaneous decarboxylation, and reduction of the ketone. Scheme 55 shows the assembly of the dendrimer, which used **123** as bivalent core. Up to the fourth generation dendrimer was prepared with all steps being performed in good yield [221]. Similar dendrimers were prepared where 3-hydroxyacetophenone and its *tert*-butyldimethylsilyl ether served as the Michael nucleophile [220]. These compounds were designed as drug delivery systems.

**Scheme 54.** Synthesis of an AB<sub>2</sub> dendron [221].



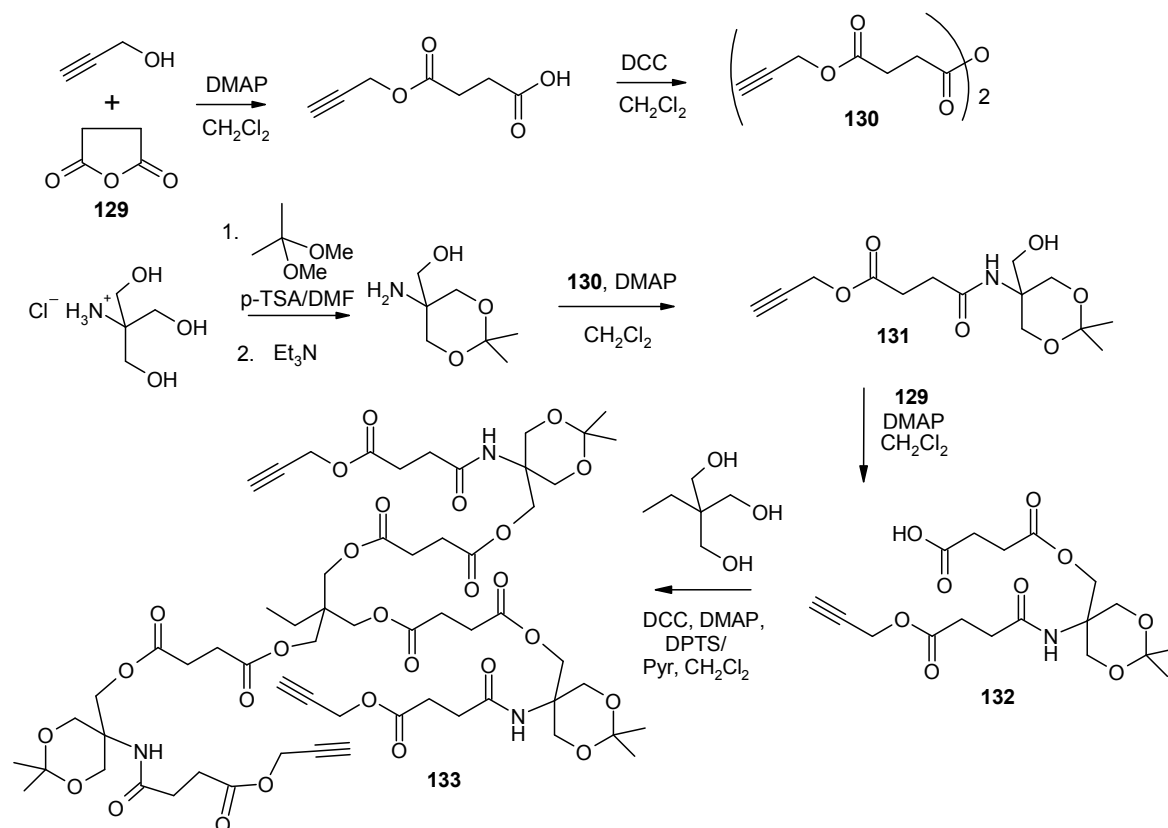
Bouillon prepared a series of tertiary amine-containing polyester dendrimers [136] from the starting materials shown in Figure 9, where **125** is the core and **126** and **127** are the dendrons. The ester bonds were formed by making cyanomethyl esters that react with excess alcohol (the dendron) in the presence of DBU as shown in Scheme 56. Excess alcohol was removed by reaction with benzoic anhydride after each ester bond forming step (not shown in Scheme 56) [136]. Poly(amino)ester dendrimers are particularly attractive as drug delivery systems because the amine functionalities present in the dendrimers can serve as buffers to neutralize the acids generated from ester hydrolysis during dendrimer degradation.

**Scheme 55.** Synthesis of an acetoacetate *tert*-butyl acrylate derived dendrimer [221].**Figure 9.** Starting materials for amine-containing polyester dendrimers [136].

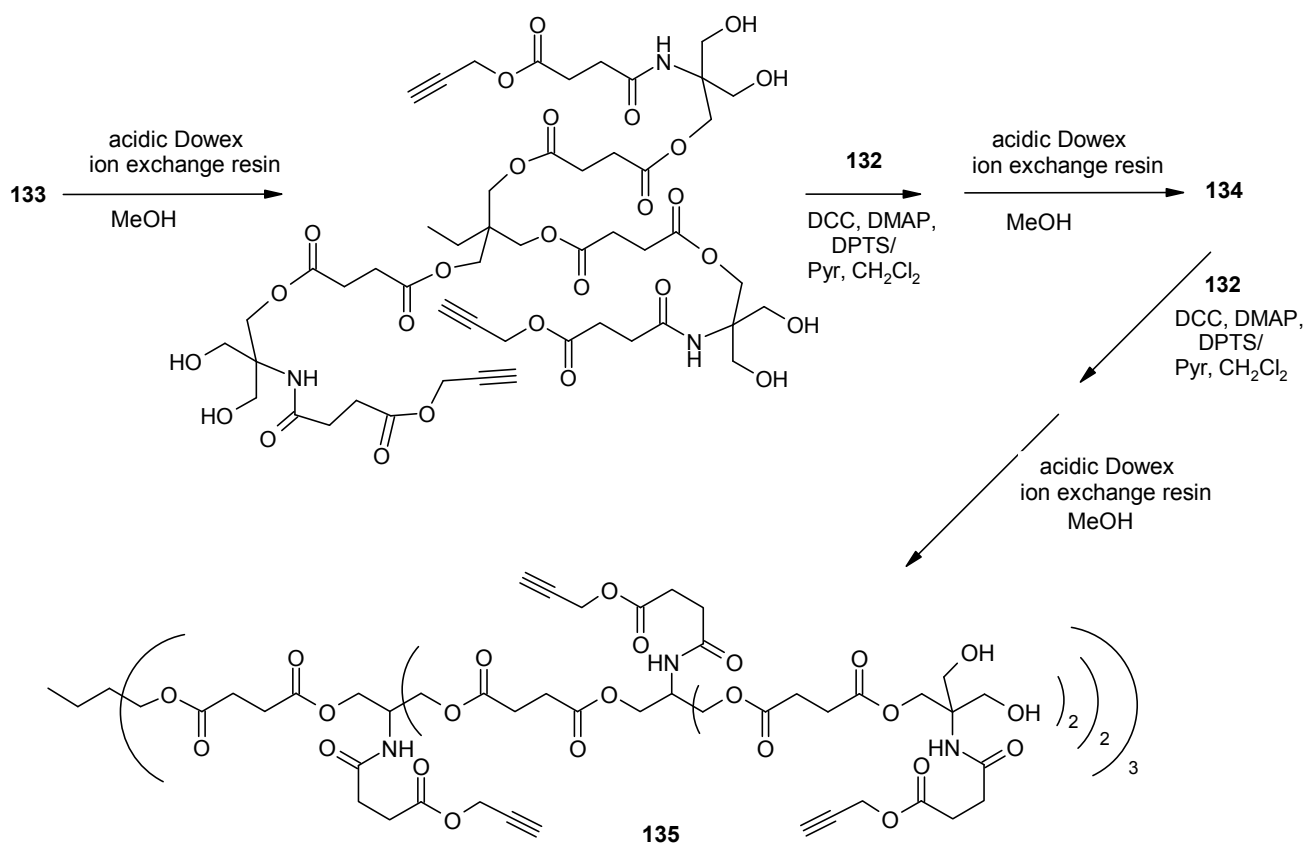
**Scheme 56.** Synthesis of a second generation amine-containing dendrimer [136].

Another interesting development was the synthesis of polyester dendrimers bearing functional groups capable of orthogonal reactions, that is, bifunctional dendrimers [40]. A complex carboxylic acid bearing a latent diol and an alkyne, an  $\text{AB}_2\text{C}$  dendron (**132**), was prepared and then esterified with a triol to give a first generation dendrimer bearing three alkyne units and six latent hydroxyls (**133**) (Scheme 57). The latent hydroxyls were exposed by hydrolysis of the acid-labile six-membered isopropylidene ring with an acidic ion exchange resin, and then the process was repeated twice more with added **132** to give the bifunctional product **135** bearing 21 alkyne groups and 24 hydroxyl groups as shown in Scheme 58 [40]. The second generation dendrimer **134** was tested for cytotoxicity on a MG-63 osteoblast cell line and found to have no or low toxicity at the concentrations tested. Second and third generation intermediates on the route to **135** were reacted with alkyl azides in click reactions as shown in Scheme 59. Compound **137**, a candidate for atom transfer radical polymerization (ATRP) was obtained in 77% yield and the second generation analog of **135** was also reacted with an azide derivative of  $\text{PEG}_{8000}$  to yield a hydrogel in good yield. A bifunctional dendrimer having azide and alcohol functionality was also synthesized as outlined in Scheme 60 [40].

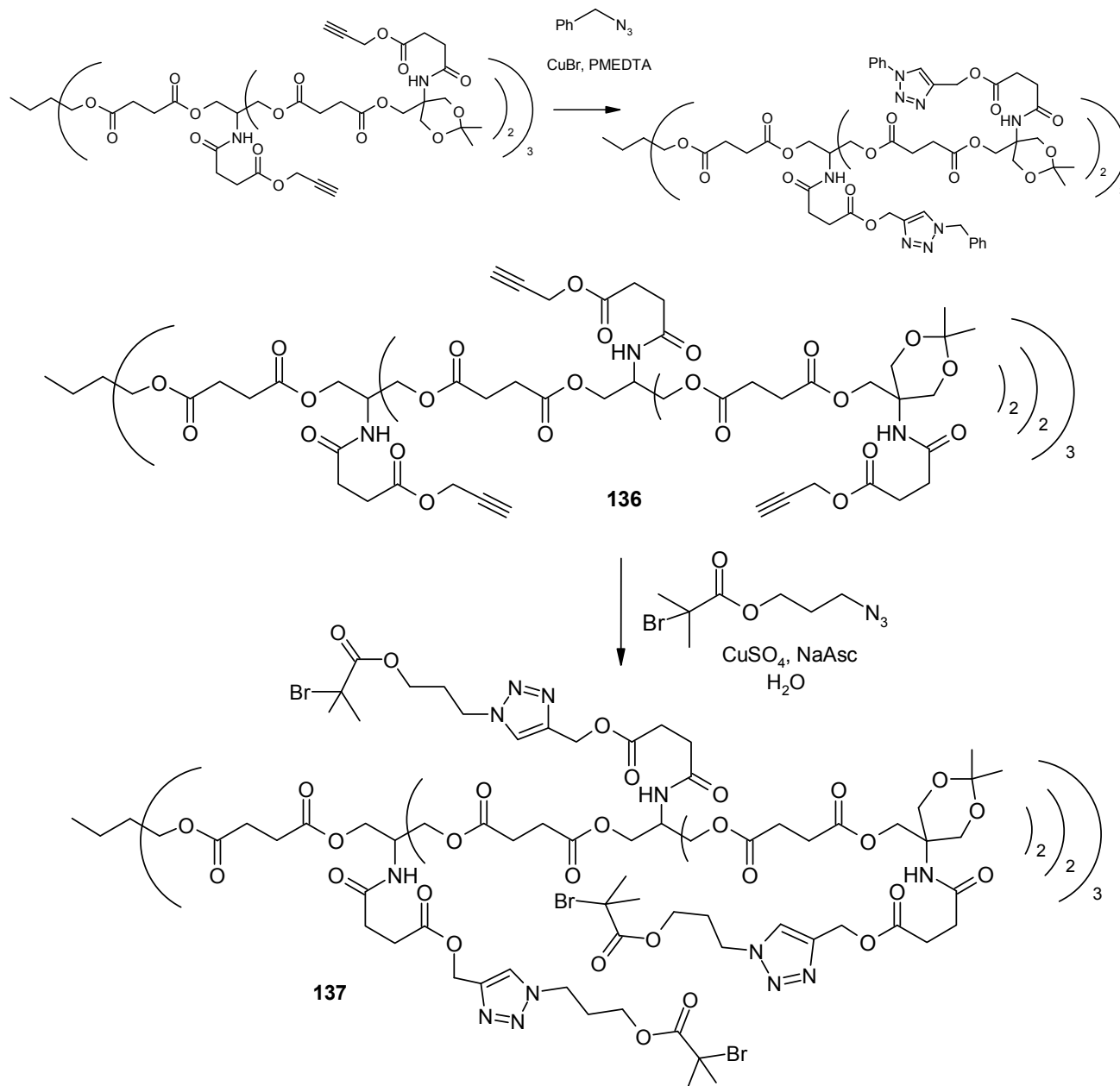
**Scheme 57.** Synthesis of an AB<sub>2</sub>C dendron (**132**) and a first generation dendrimer bearing three alkyne groups and six latent hydroxyls [40].

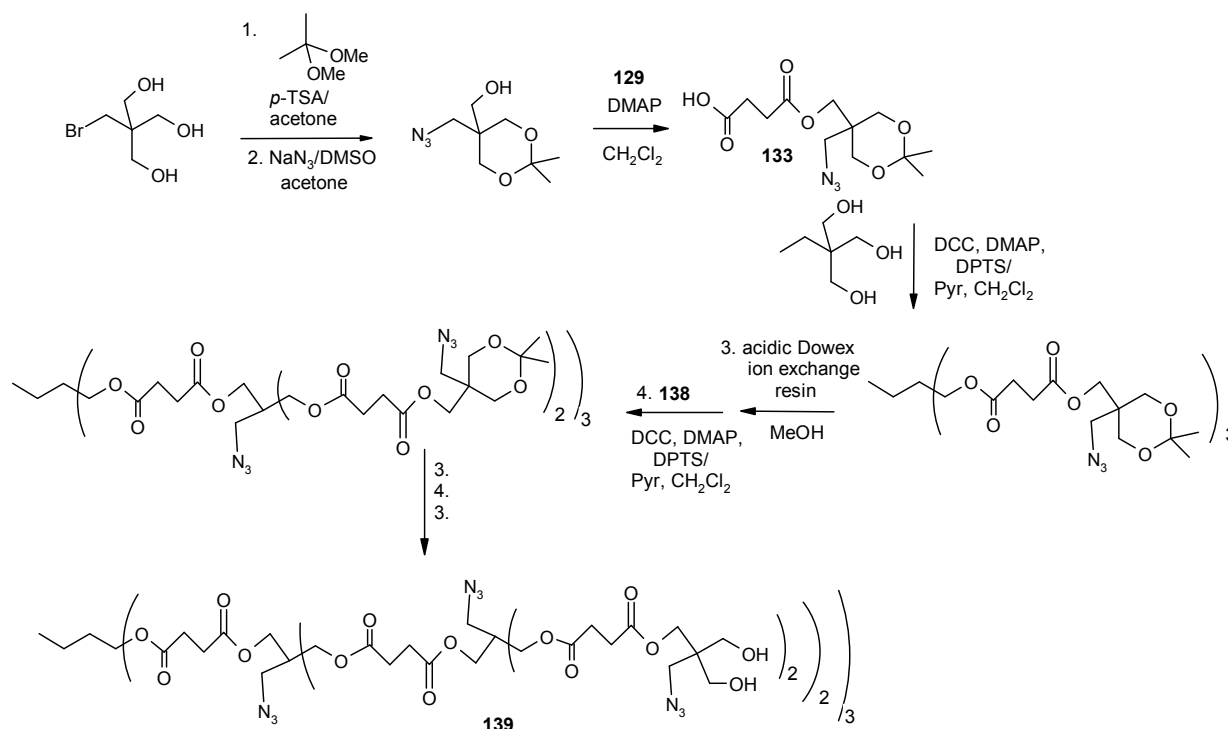


**Scheme 58.** Synthesis of the third generation bifunctional dendrimer [40].



**Scheme 59.** Click reactions of azide-terminated molecules with the bifunctional dendrimers [40].



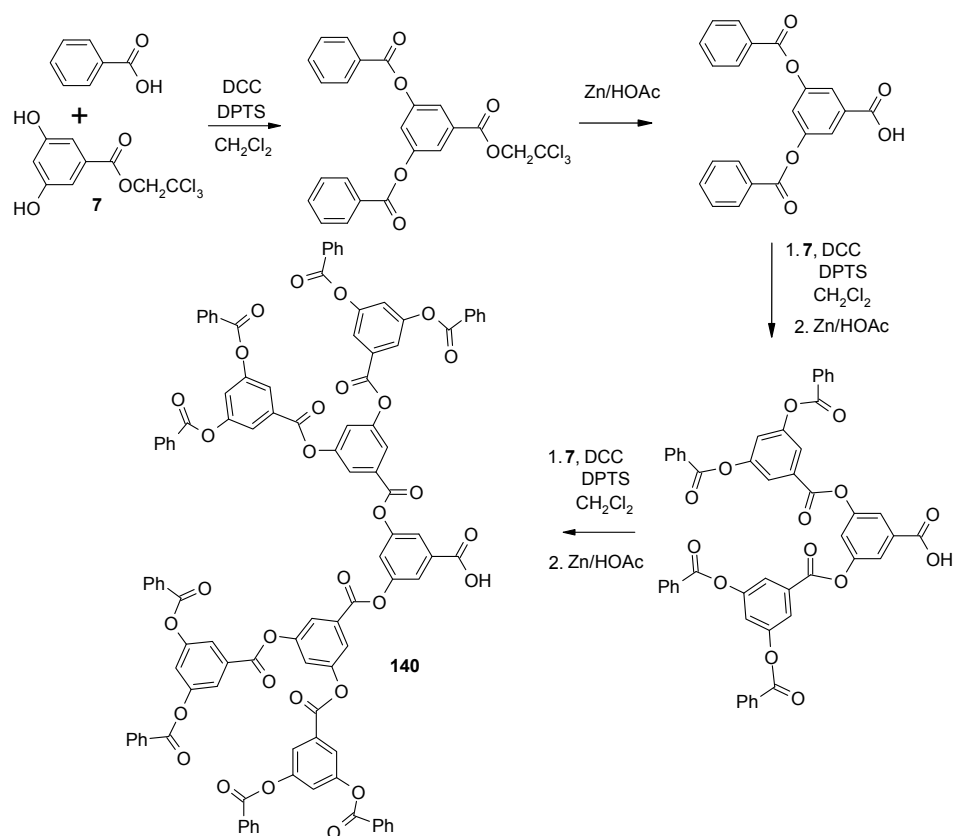
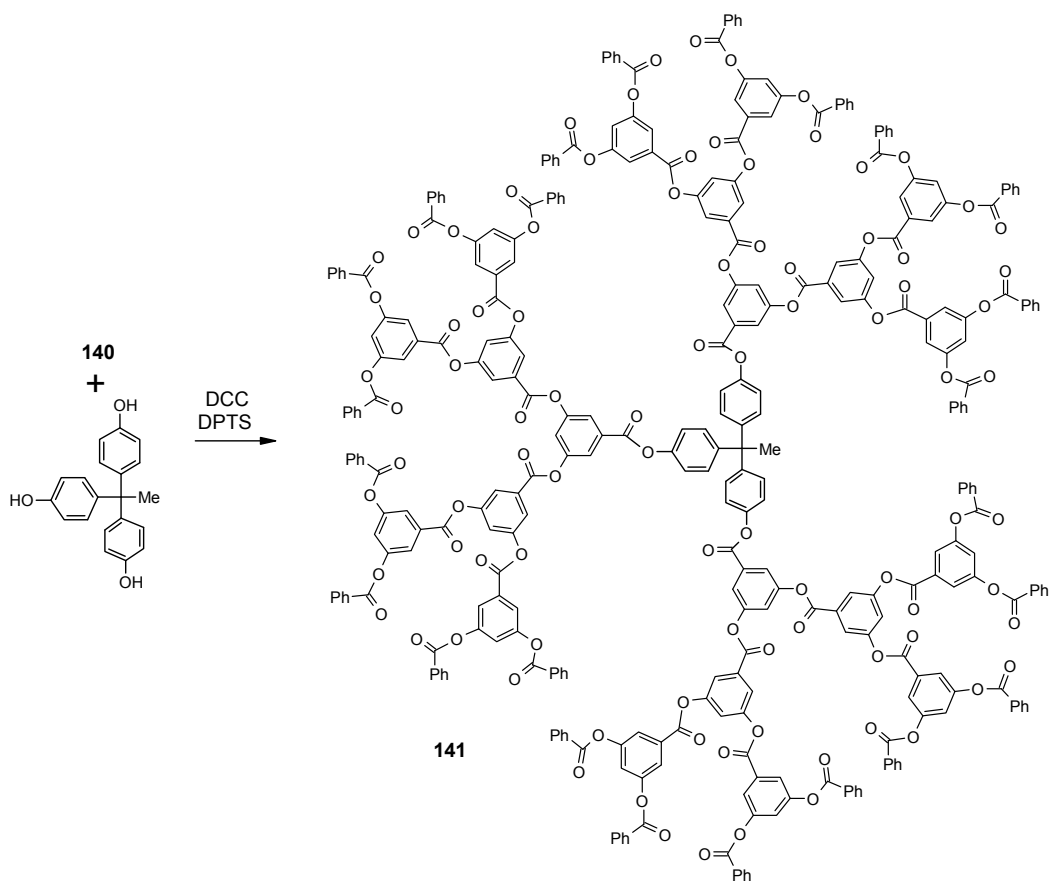
**Scheme 60.** Preparation of bifunctional dendrimers bearing azide and alcohol groups [40].

#### 4.3. The Use of Aromatic Dendrons

Aromatic polyester dendrimers were the first polyester dendrimers to be made [8] and the synthetic route of Hawker and Frechét introduced the convergent approach (Scheme 2). A similar approach was published by the same authors at about the same time (Schemes 61 and 62) [7].

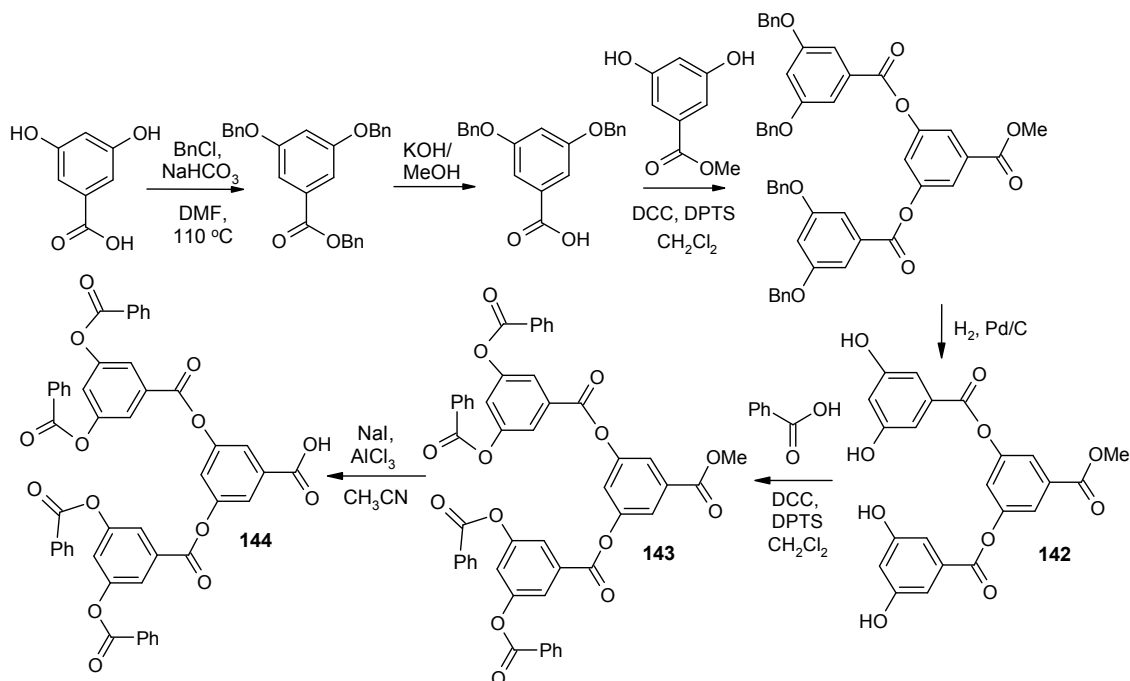
The first divergent approach to polyester dendrimers also used aromatic carboxylic acids (see Scheme 1) [80].

Bo *et al.* used methyl 3,5-dihydroxybenzoate to produce an  $\text{AB}_4$  dendron (**142**) for the synthesis of aromatic polyester dendrimers as illustrated in Scheme 63 [222]. They were unable to use benzyl groups for hydroxyl protection when the focal carboxylic acid was protected as a methyl ester because the deprotection conditions for the latter ( $\text{NaI}$  and  $\text{AlCl}_3$  in acetonitrile) also removed the benzyl ethers. They were able to use **142** to make up to fourth generation protected dendrons (Scheme 64) and, using 1,4-dihydroxybenzene and 1,3,5-trihydroxybenzene as cores, up to third generation dendrimers (Scheme 65) [222]. The same group prepared a dendron with a carboxylic acid focal point linked through alkyl ether linkers to carbazole units. Attachment of this dendron to polyester dendrimers terminated in phenolic groups produced dendrimers of interest for their electro-optical properties (Scheme 66) [223].

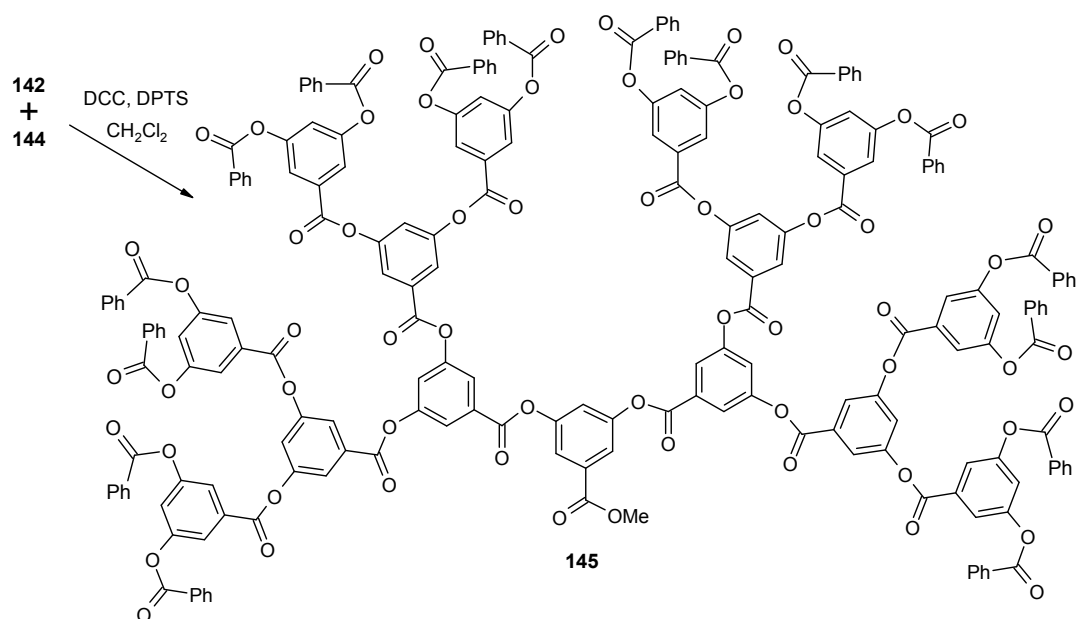
**Scheme 61.** Synthesis of a third generation aromatic polyester dendron [7].**Scheme 62.** Synthesis of a third generation aromatic polyester dendrimer [7].



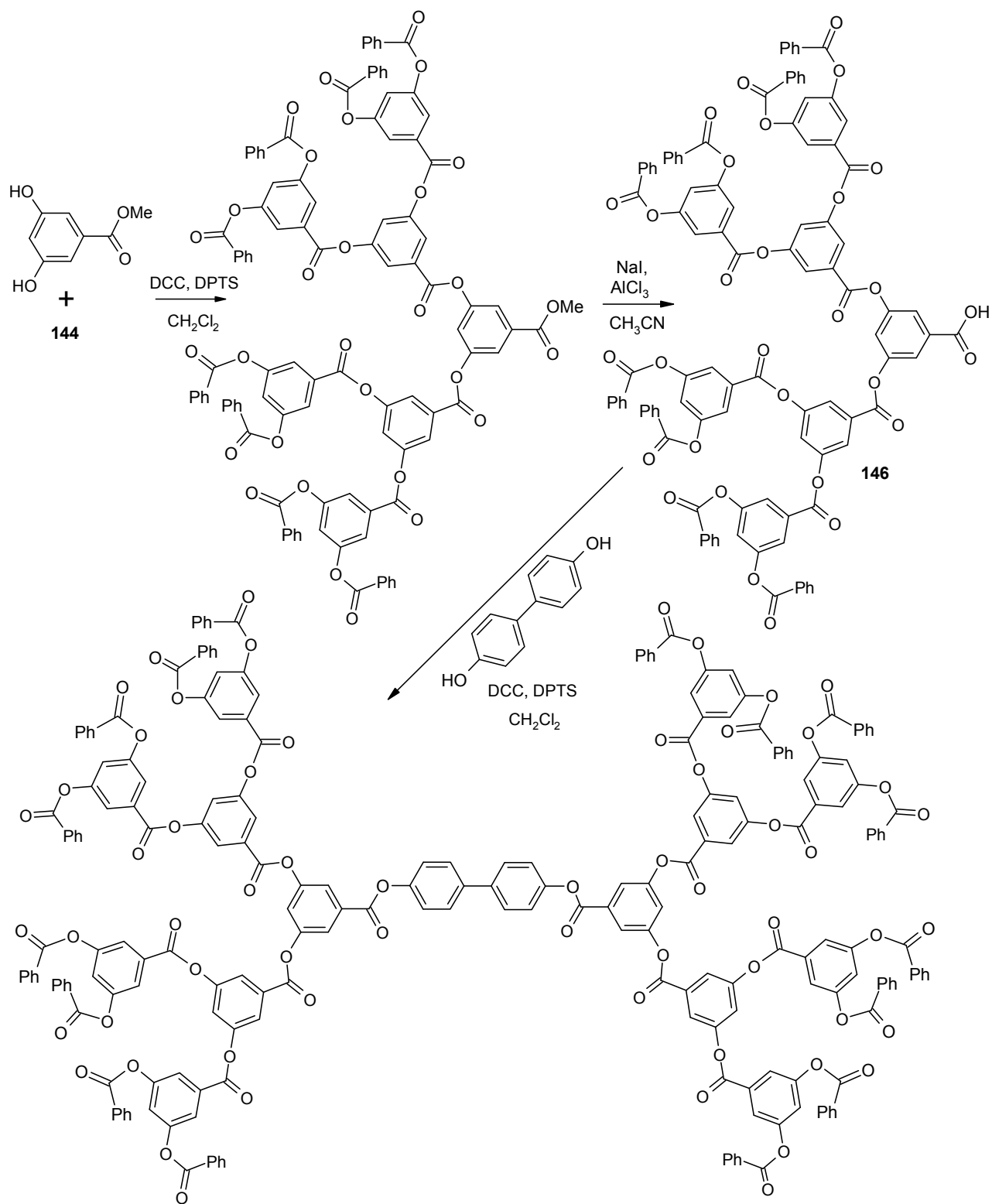
**Scheme 63.** Synthesis of an AB<sub>4</sub> dendron, its protection as the perbenzoate, and deprotection of the focal point [222].



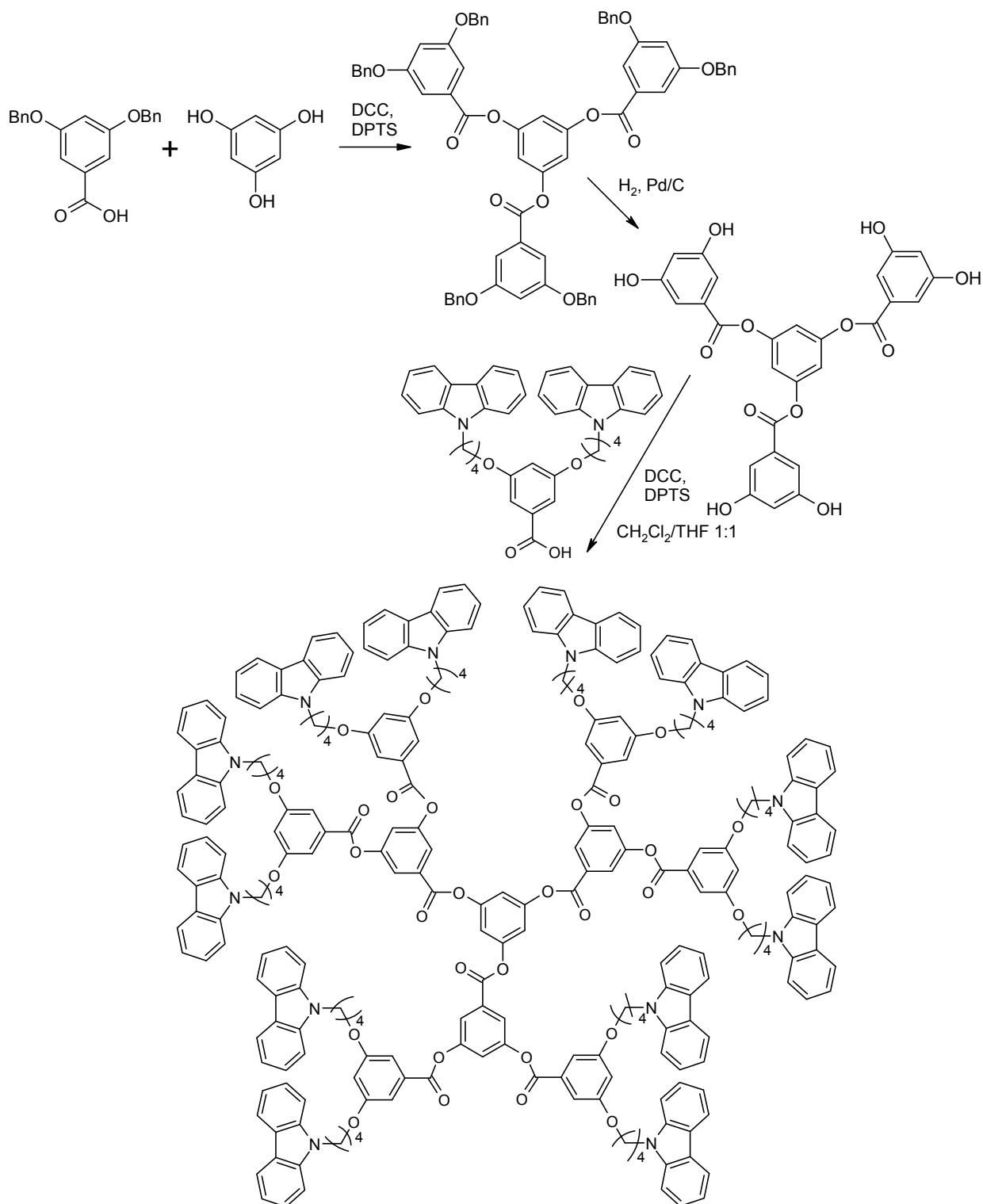
**Scheme 64.** Synthesis of a fourth generation protected dendron [222].



**Scheme 65.** Synthesis of a third generation dendrimer with 4,4'-dihydroxybiphenyl as the core [222].



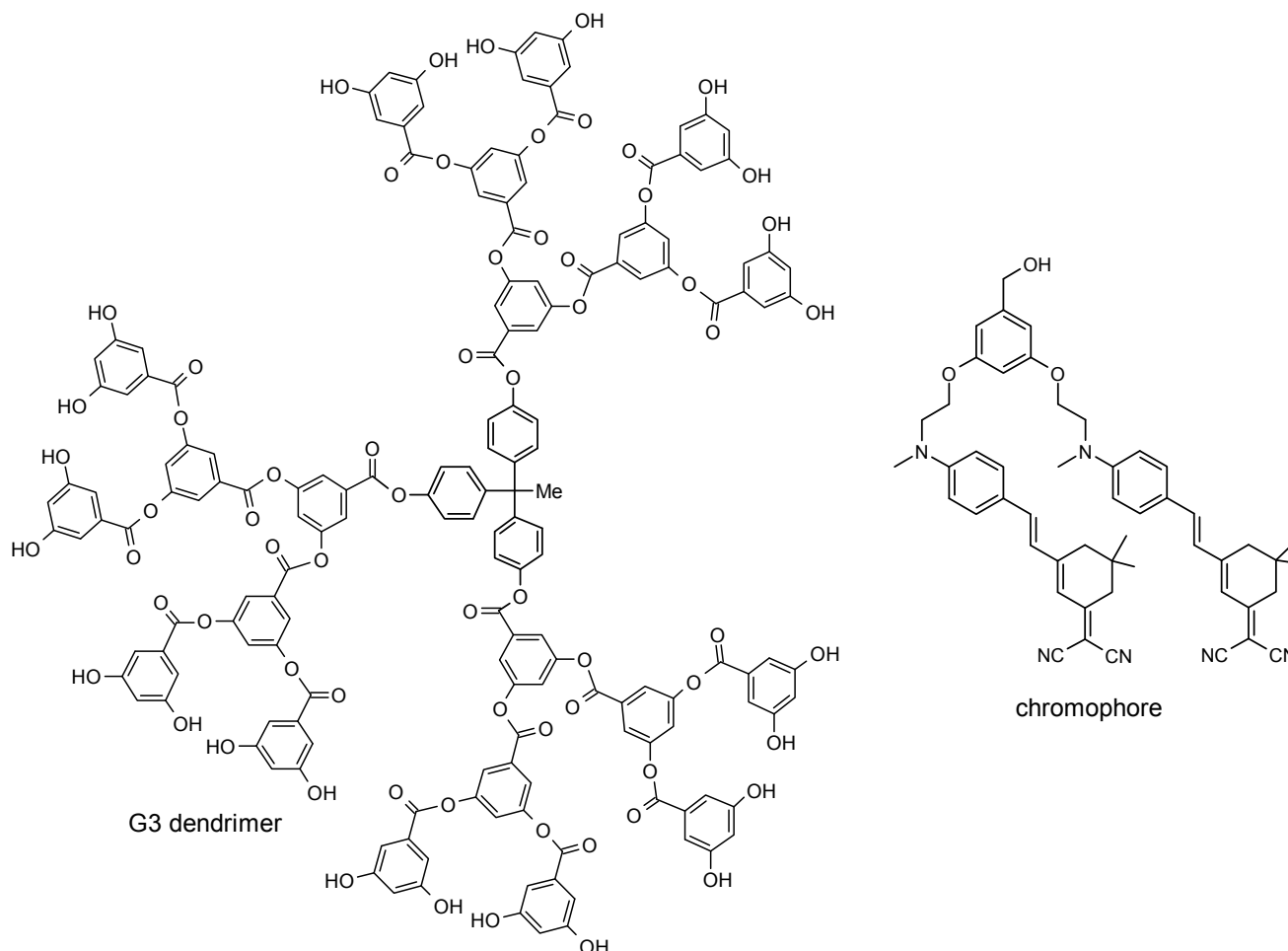
**Scheme 66.** Synthesis of a second generation aromatic polyester dendrimer bearing carbazole groups on the periphery [223].



Do *et al.* also prepared polyester dendrimers of interest for their optical properties [224,225]. They made polyester dendrimers of the type prepared by Hawker and Freché<sup>t</sup> [8] (see Figure 10), then added chromophores through Mitsunobu reactions on benzylic alcohols bearing chromophores using the phenolic groups of the dendrimers as nucleophiles. Generation zero to generation three materials were

prepared and tested for their optical properties [224,225]. The generation one compound showed the best optical non-linearity of the four optical dendrimers.

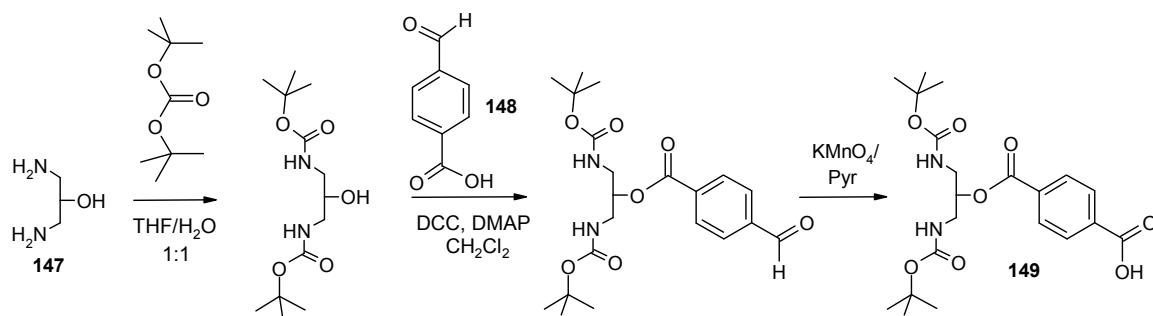
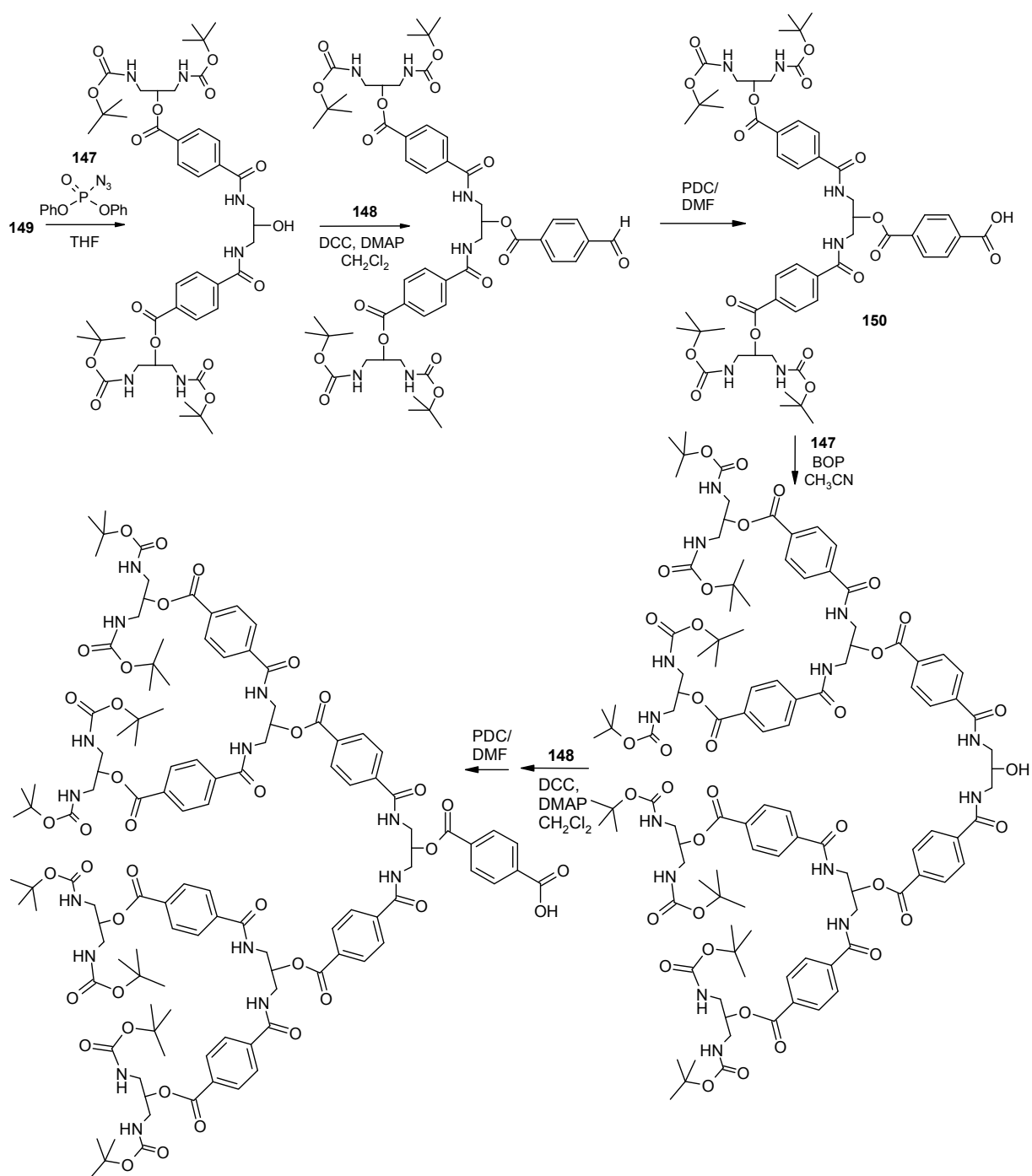
**Figure 10.** Optical dendrimers were prepared by using the G0 to G3 (shown on left) polyester dendrimers as nucleophiles in multiple substitutions of the benzylic hydroxyl of the chromophore on the right [224,225].

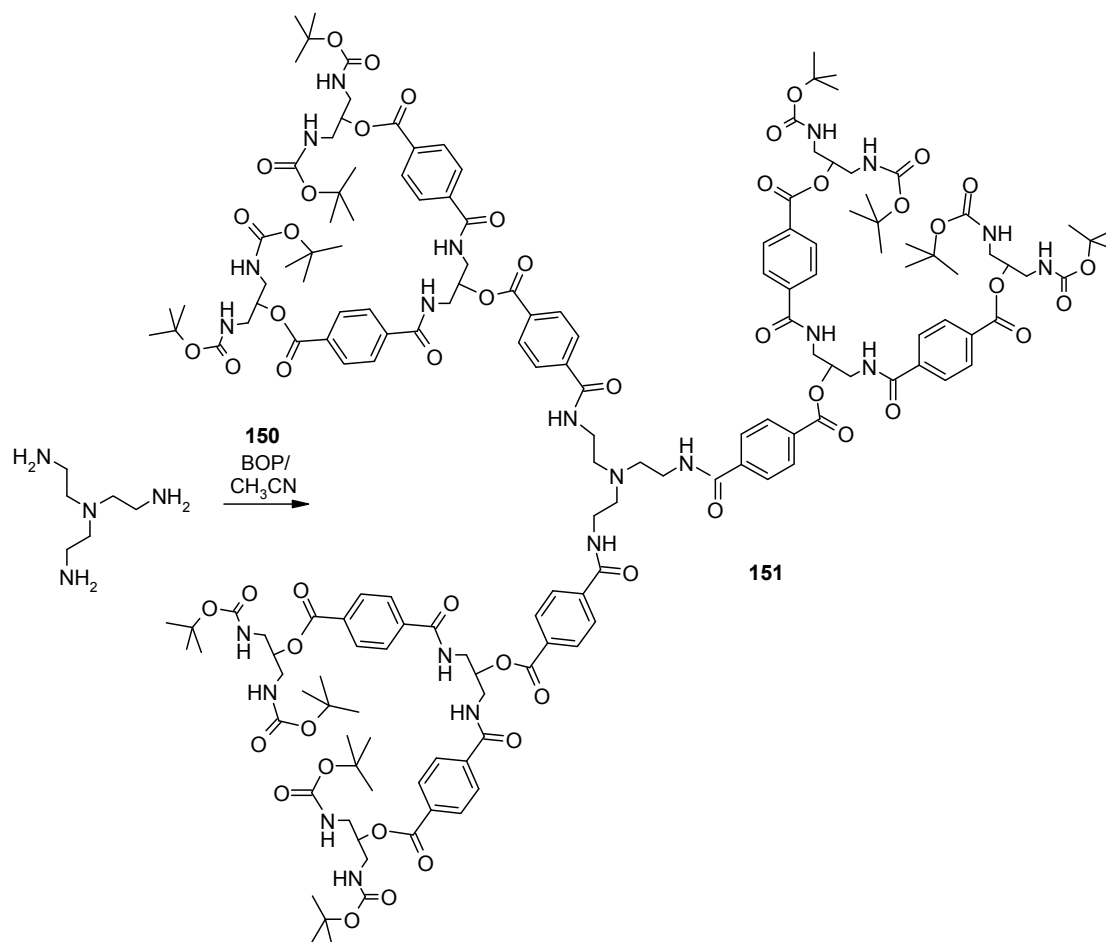
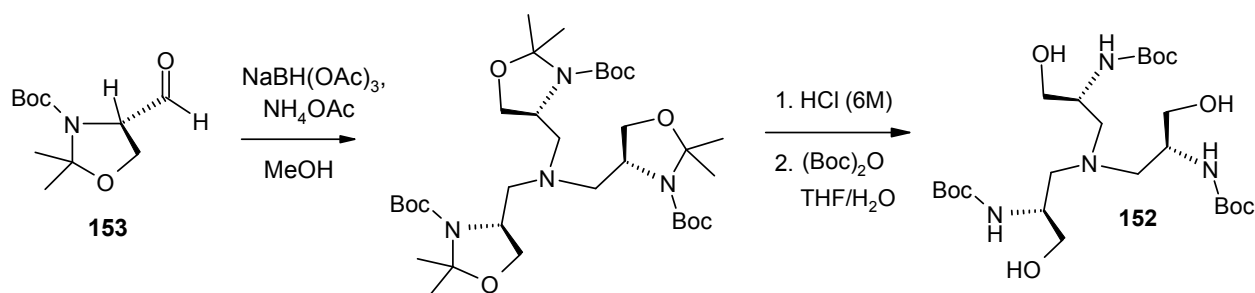


#### 4.4. Alternating Polyester Dendrimers

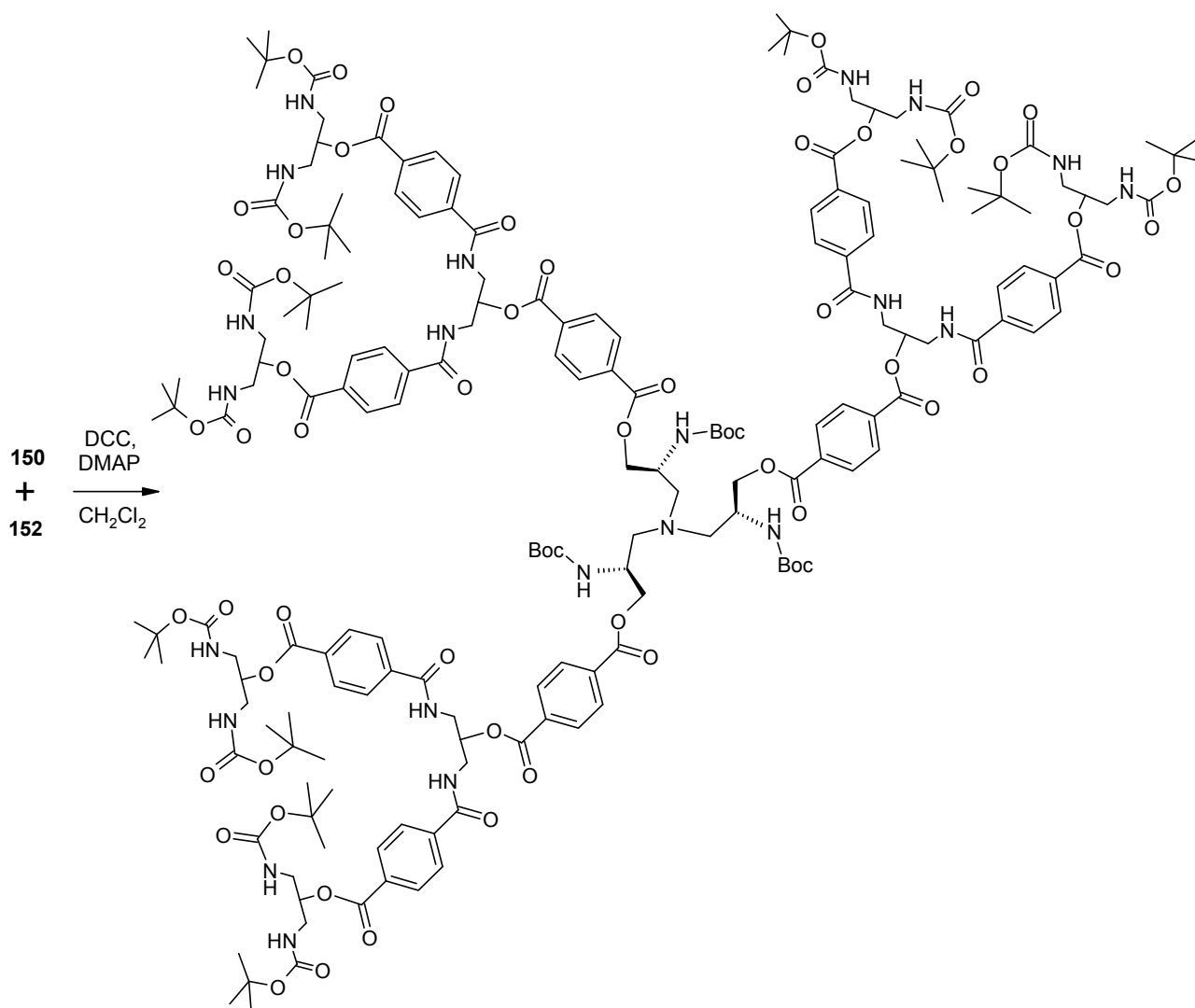
A number of polyester dendrimers have been synthesized where the ester linkages alternate with other types of linkages, the orthogonal coupling strategy, since the first example prepared by Zeng and Zimmerman (Scheme 4) [102].

Romagnoli *et al.* prepared ester-amide dendrimers as outlined in Schemes 67 to 70 using 1,3-diamino-2-propanol (**147**) and 4-carboxybenzaldehyde (**148**) as starting materials [106]. They evaluated a number of coupling agents for the amide bond forming steps and found that DPPA was best for the initial coupling of the dendron **149** with **147** (Scheme 67) but BOP was best for the subsequent coupling reactions (Schemes 68 and 69). Most yields in the synthetic sequences were good but the yields in the oxidation of aldehyde to carboxylic acid were moderate with the larger dendrons (Schemes 68 and 69).

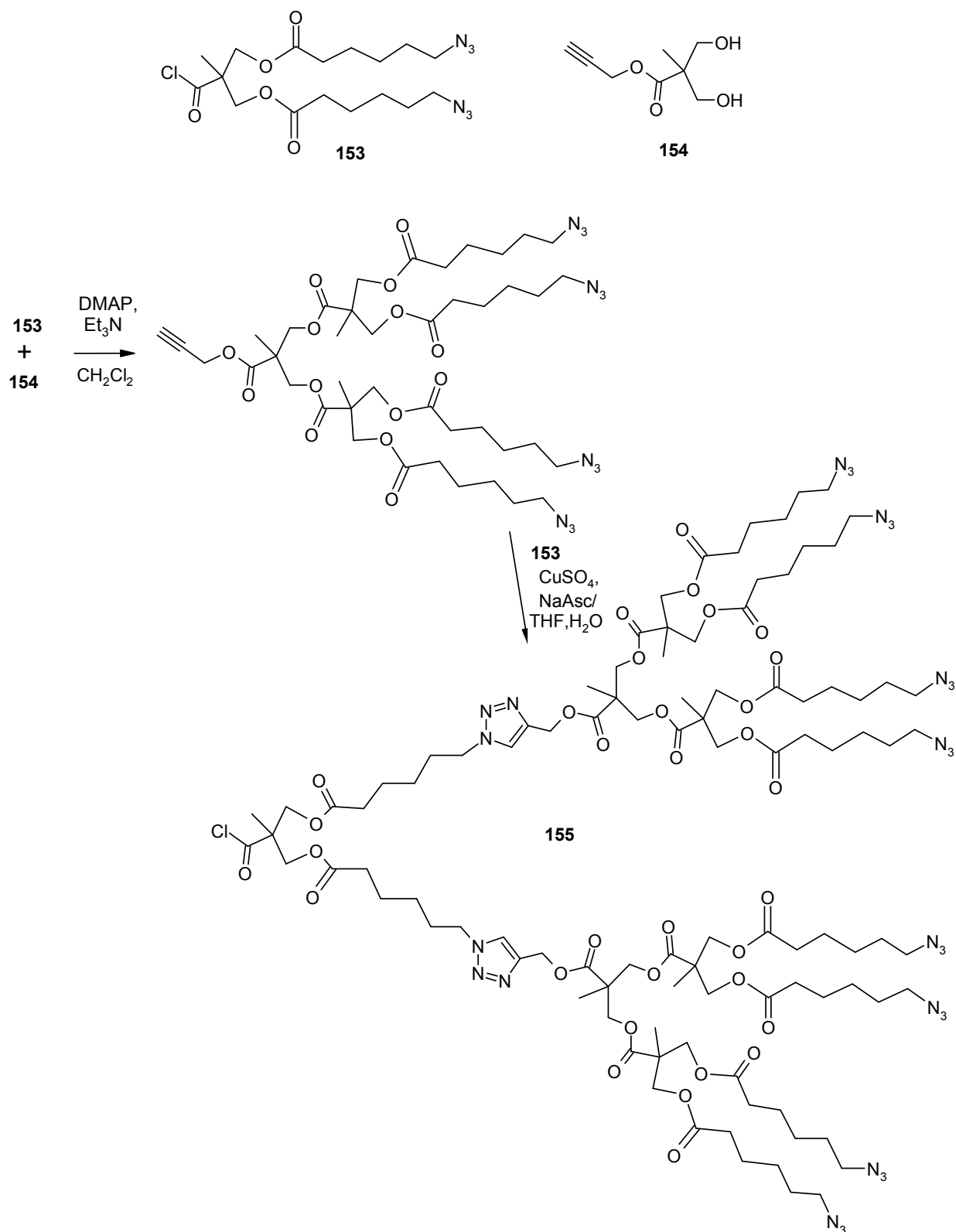
**Scheme 67.** Preparation of the AB<sub>2</sub> dendron [106].**Scheme 68.** Synthesis of the G2 to G3 dendrons [106].

**Scheme 69.** Preparation of the G2 dendrimer [106].**Scheme 70.** Synthesis of a chiral core [226].

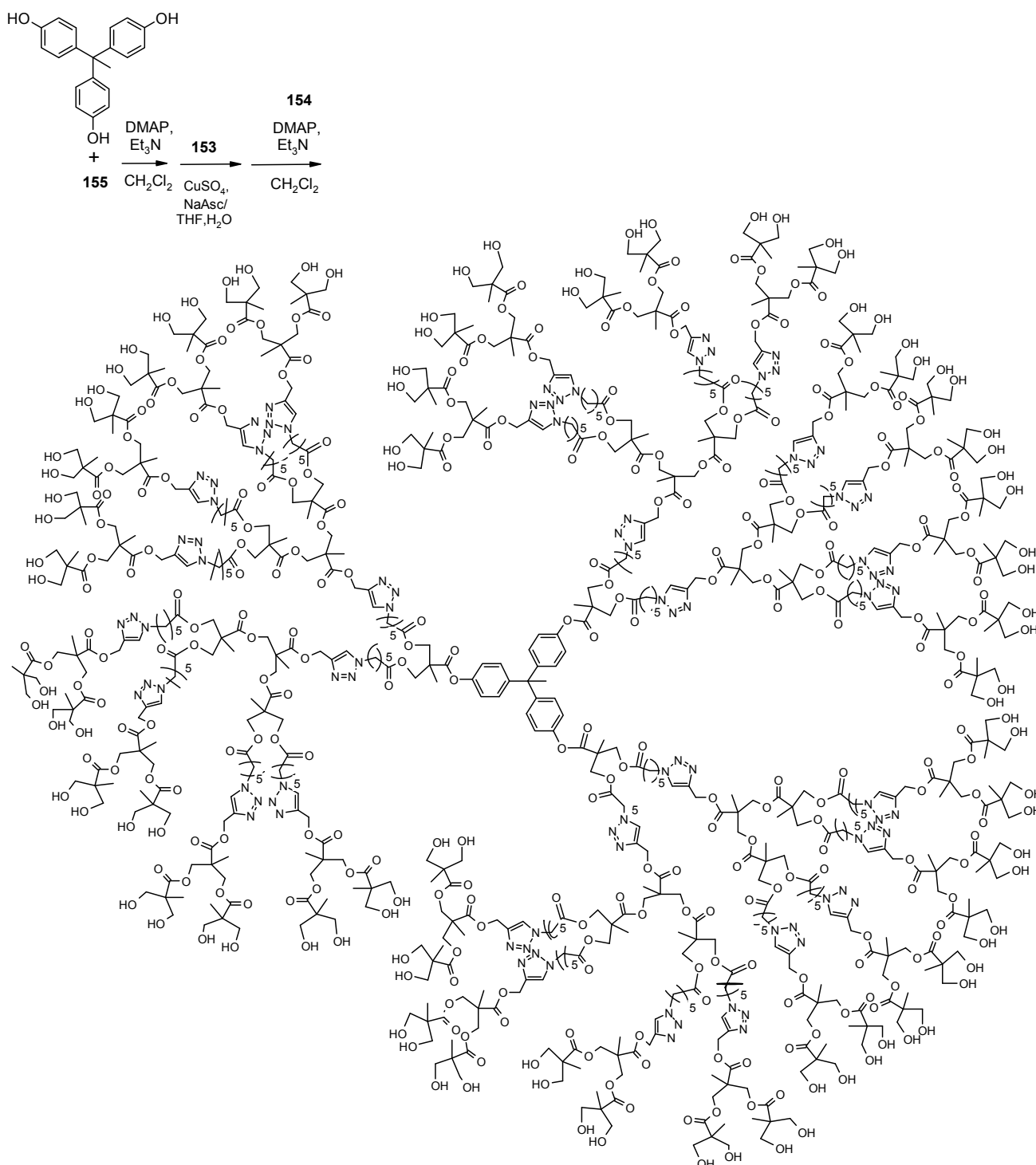
The same group utilized some of the above dendrons to synthesize chiral dendrimers by replacing the achiral tetraamine core of **151** with a chiral triol (**152**) [226], synthesized as in Scheme 70 from L-Garner aldehyde (**153**), itself synthesized from serine using the method of Taylor and coworkers [227]. Scheme 71 shows the reaction with the G2 dendron; dendrimers bearing G1 and G2 dendrons were synthesized by reaction with core 152 and its enantiomer [226].

**Scheme 71.** Synthesis of a chiral amide-ester dendrimer [226].

Antoni *et al.* alternated ester formation with click reactions using two different AB<sub>2</sub> dendrons, **153** and **154**, for the accelerated synthesis of dendrimers as shown in Scheme 72 [103]. Because these orthogonal reactions did not require any activation or deprotection steps, the preparation of a quite large dendrimer was accomplished very rapidly. Only five steps yielded the fourth generation dendrimer (see Scheme 73) [103]. It is surprising that the acid chloride functional group of **153** survived the aqueous THF solution used for the click reaction but other conditions (e.g., DCC) could have been used for the esterification step.

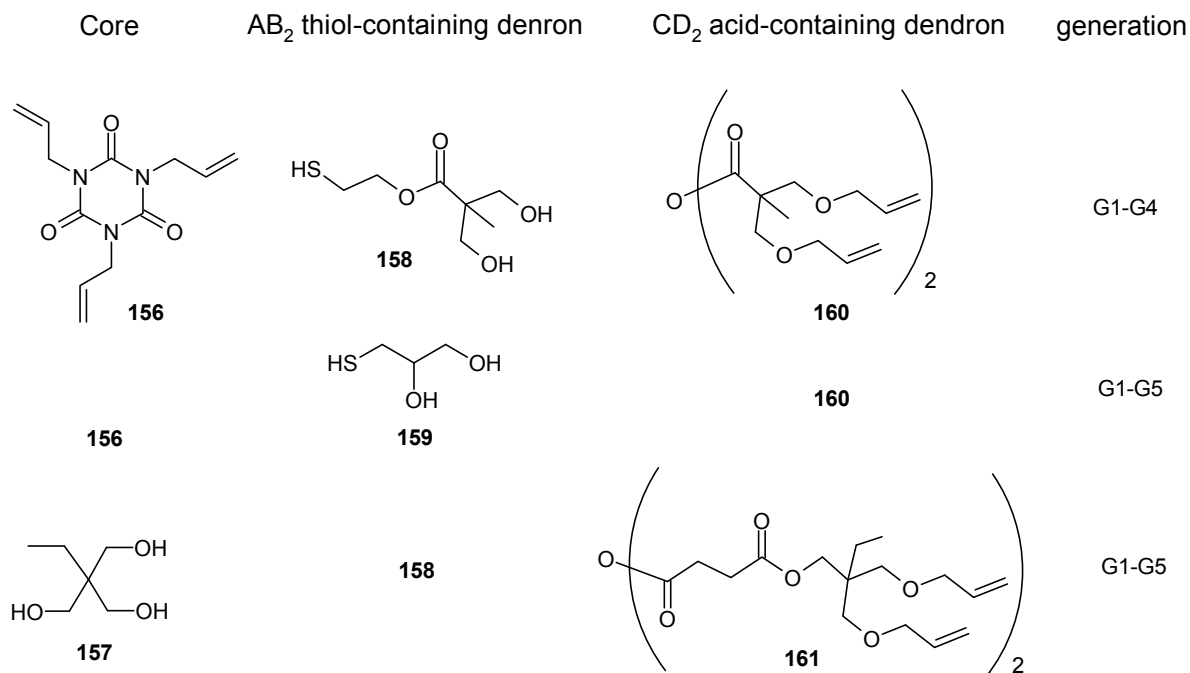
**Scheme 72.** The starting materials and second generation dendron for accelerated synthesis [103].



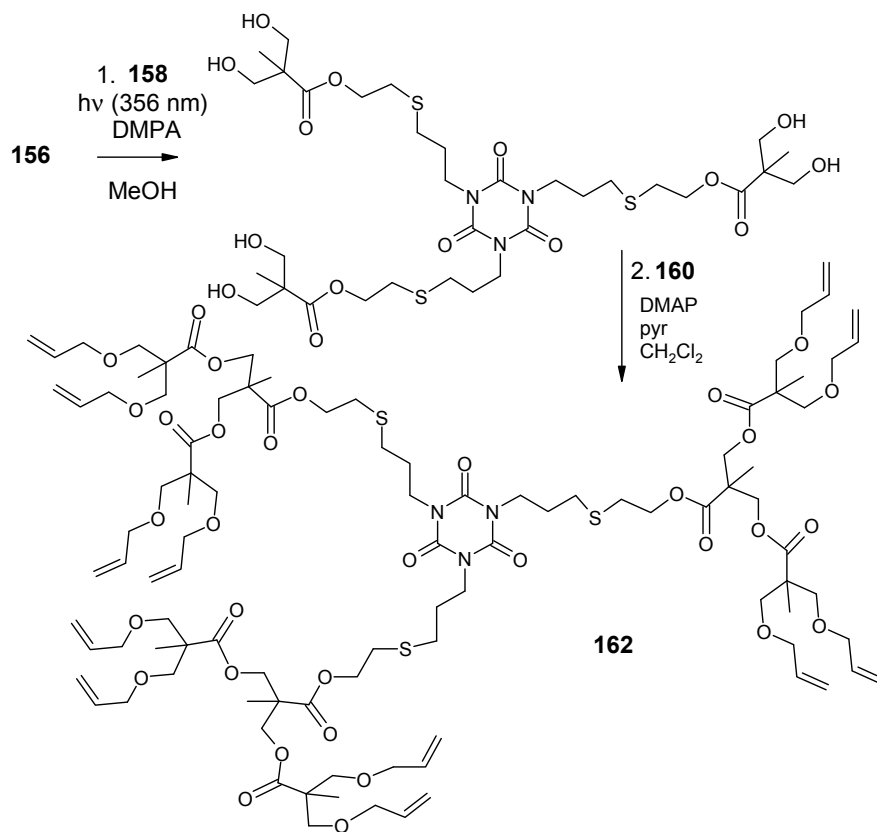
**Scheme 73.** A fourth generation dendrimer resulting from accelerated synthesis [103].

Montañez utilized AB<sub>2</sub> dendrons that combined ester formation with thiol-ene reactions to provide another approach for the accelerated synthesis of dendrimers [104]. These authors combined the dendrons shown in Figure 11 as shown in Scheme 74. The thiol-ene reactions were conducted by irradiation with 356 nm light in the presence of the photoinitiator, 2,2-dimethoxy-1,2-diphenylacetophenone (DMPA).

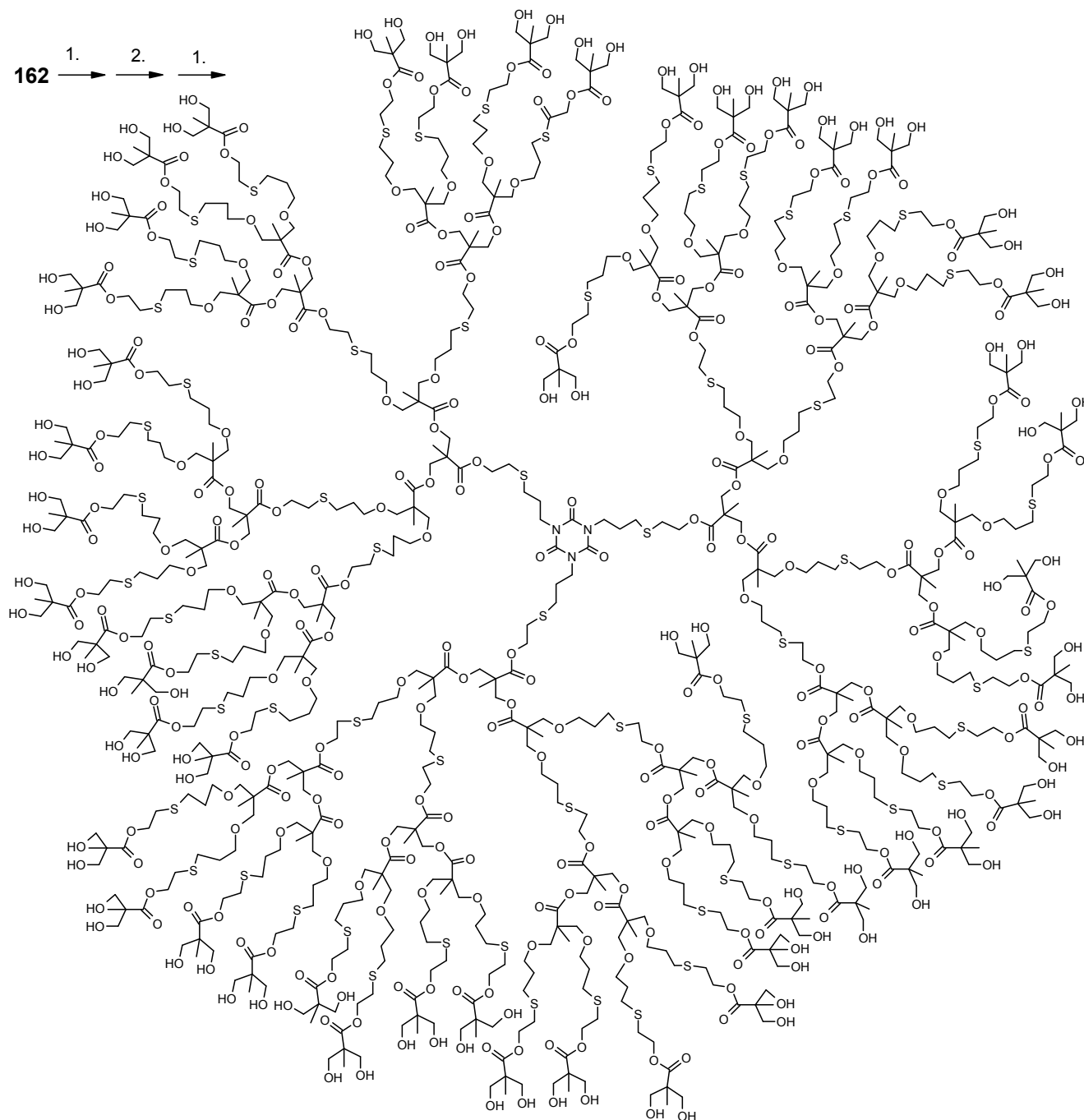
**Figure 11.** Monomers and cores employed for the synthesis of dendrimers using thiol-ene and esterification reactions [104].



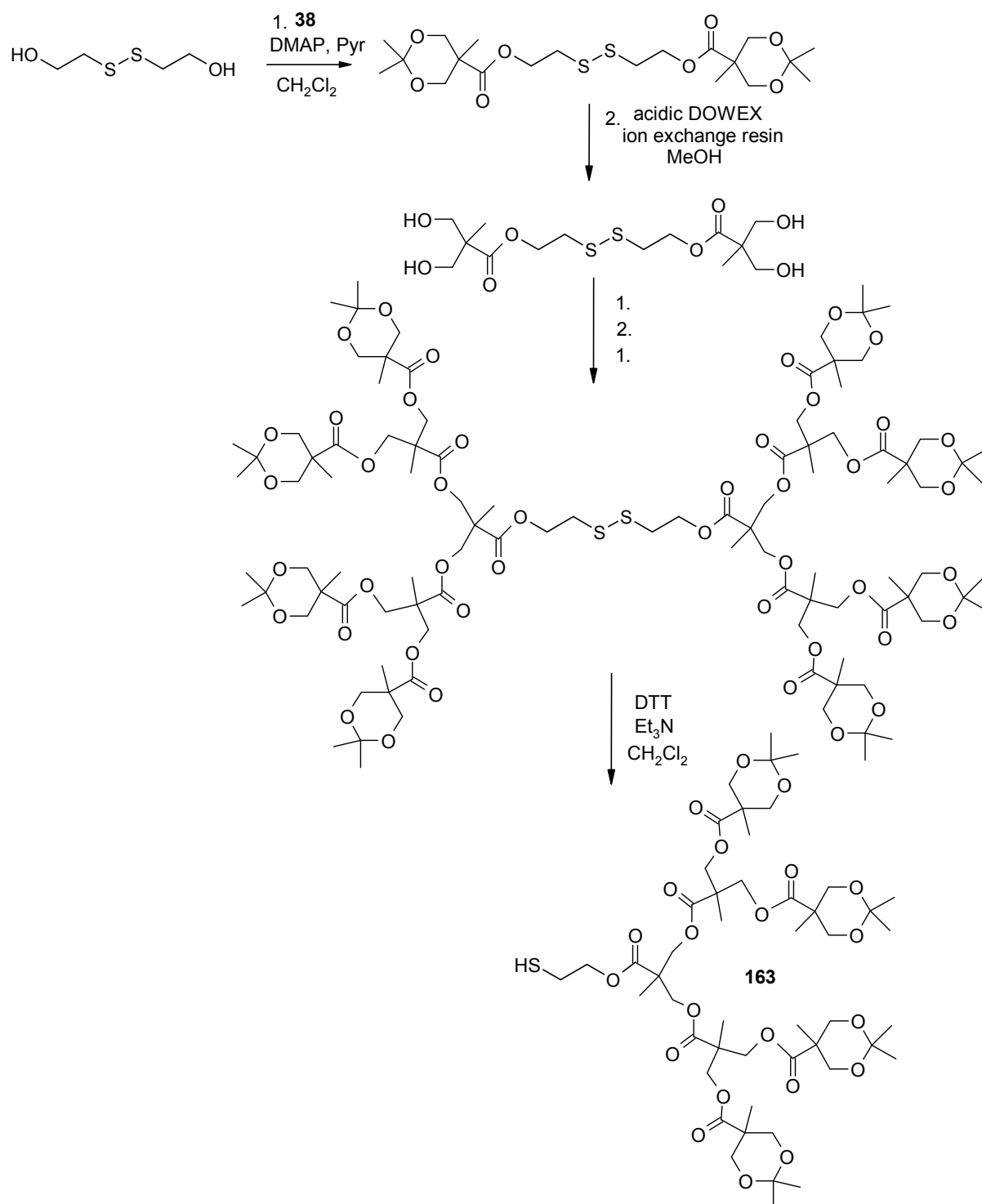
**Scheme 74.** Synthesis of a second generation dendrimer using thiol-ene and esterification reactions [104].

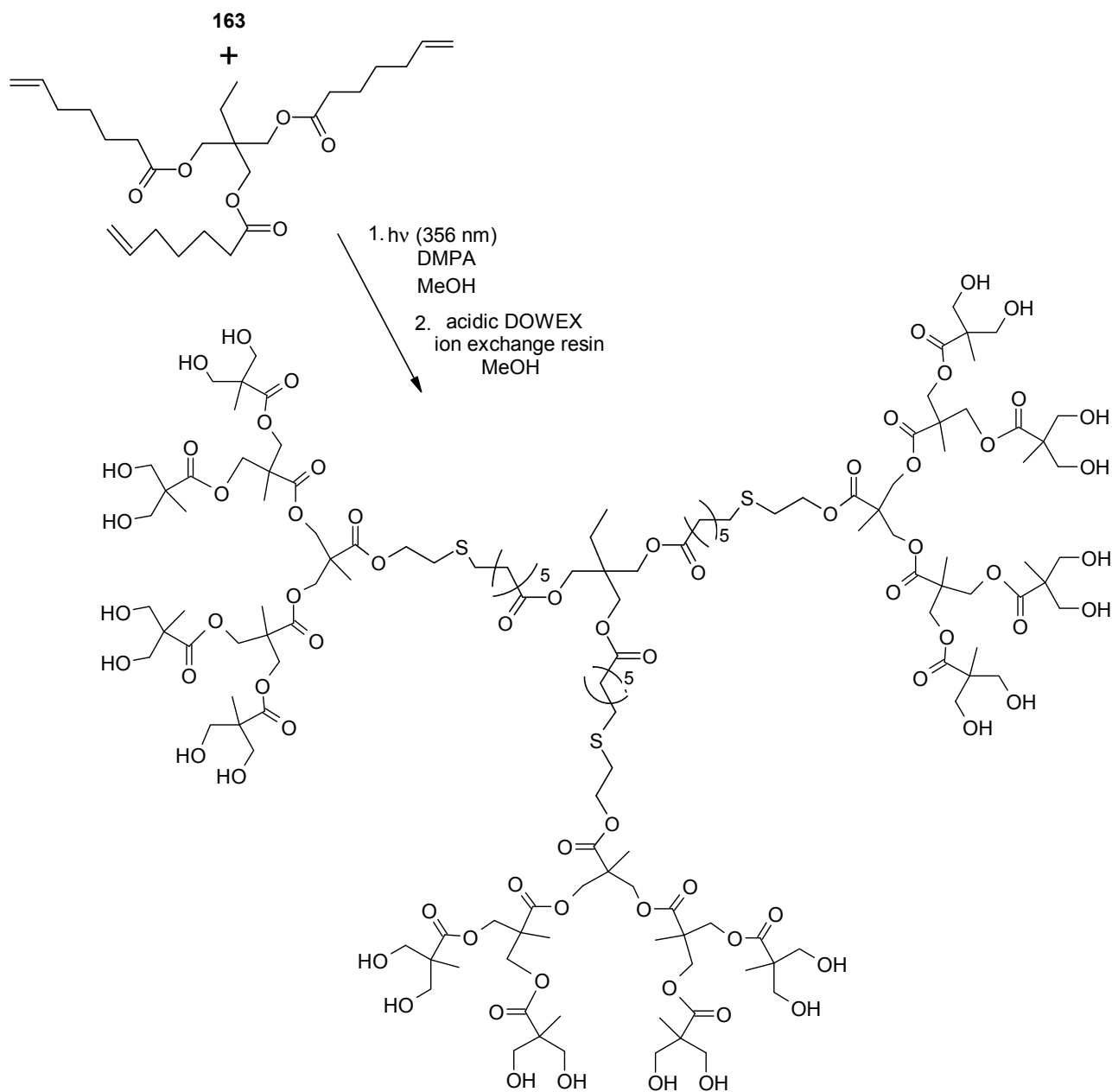


**Scheme 75.** Synthesis of a fourth generation dendrimers using thiol-ene and esterification reactions [104].



Walter *et al.* developed this theme further by creating a series of macrothiols bearing latent hydroxyls through reduction of dendronized disulfides (see Scheme 76 for one example) [105]. Dendrimers were obtained through the light-promoted addition of these thiols to core molecules terminating in alkenes. Deprotection of the latent hydroxyls gave a hydroxyl-terminated dendrimer, as shown in Scheme 77 [105]. These dendrimers can then be reacted further to give products with desired properties.

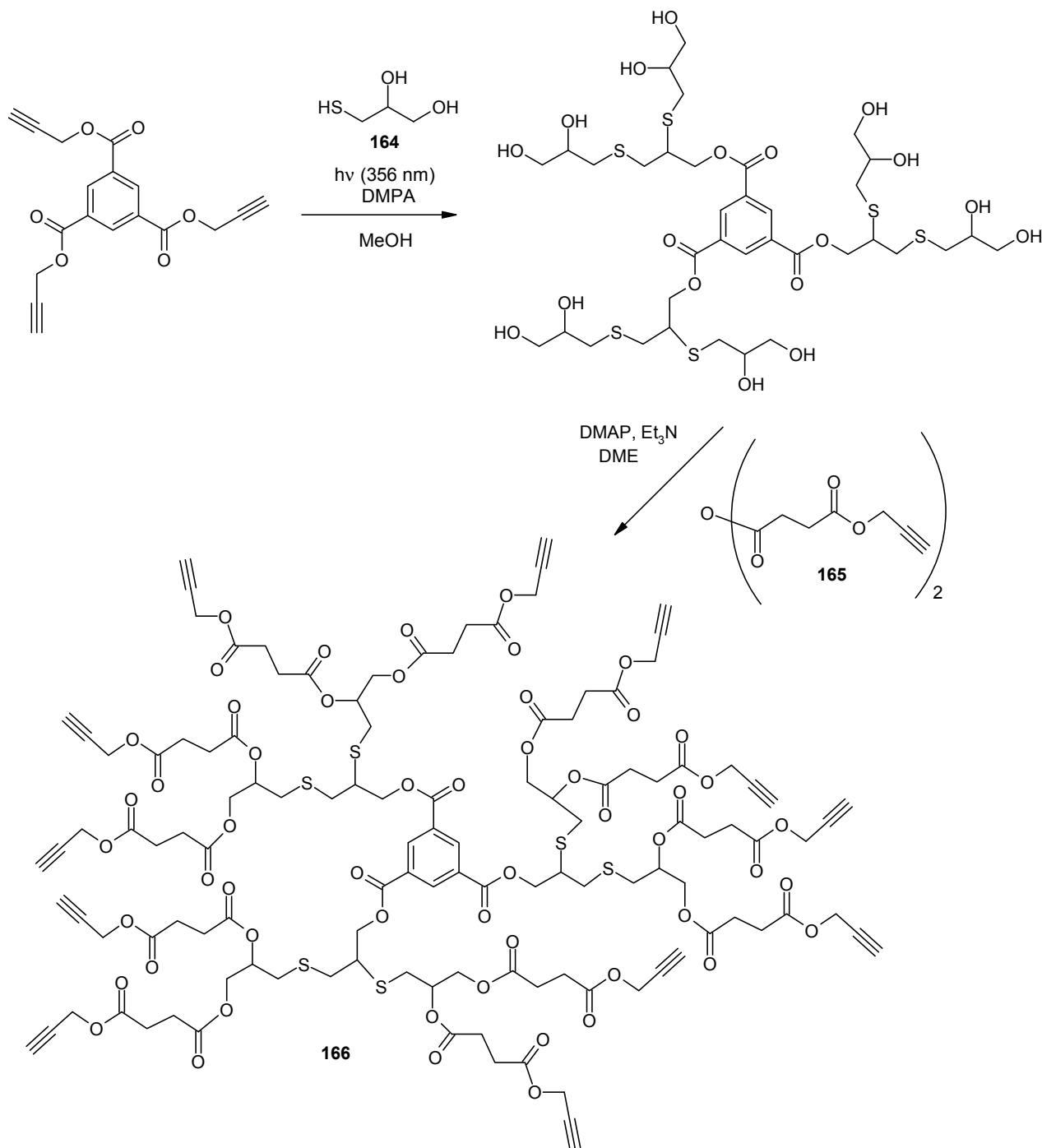
**Scheme 76.** Synthesis of a macrothiol [105].

**Scheme 77.** Thiol-ene reaction of the macrothiol [105].

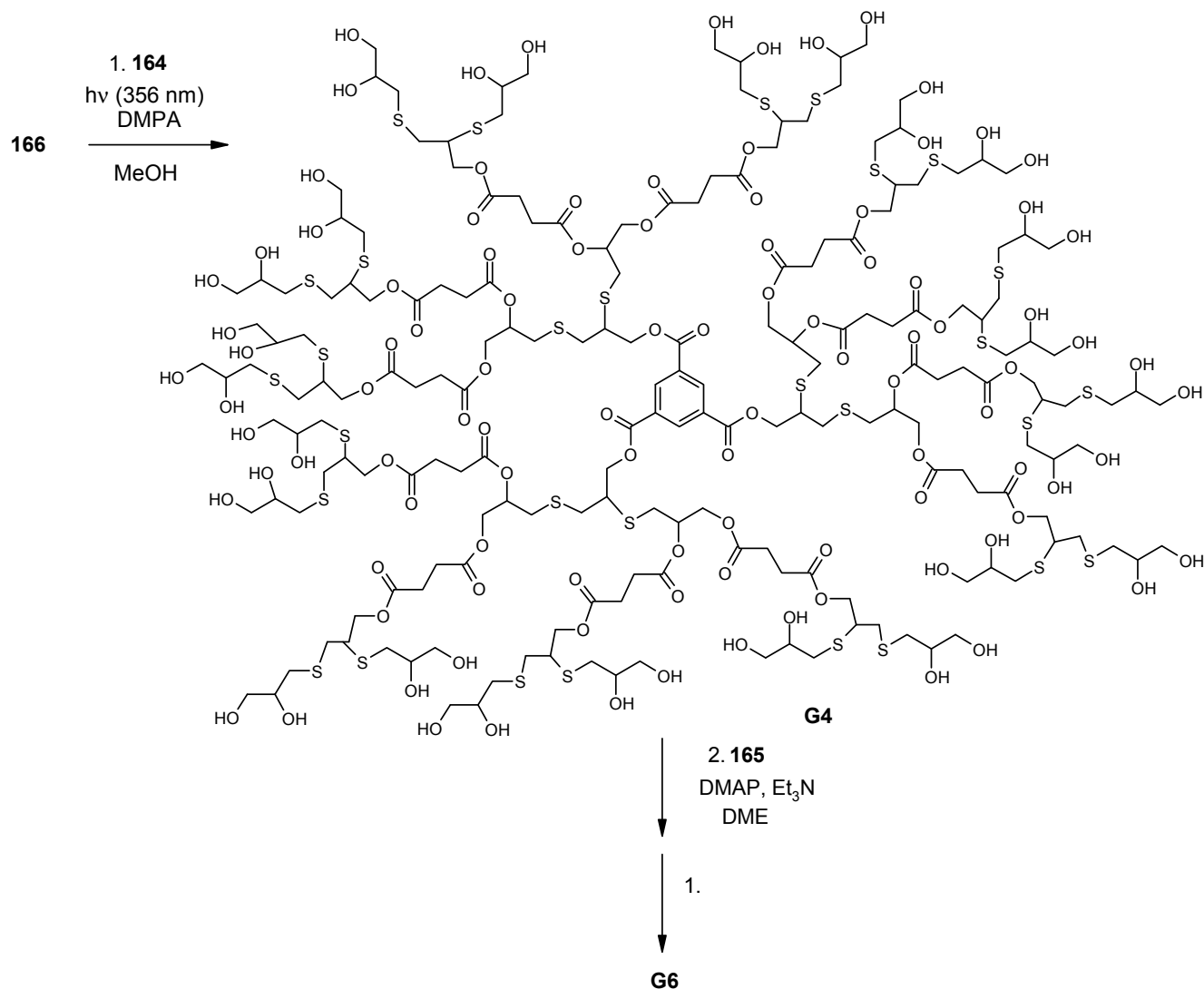
Chen *et al.* described a very efficient alternating convergent dendrimer synthesis where the reaction complementing esterification was photochemically induced addition of a thiol to an alkyne (see Schemes 78 and 79) [107]. Tris-3-propynyl 1,3,5-benzenetricarboxylate served as the starting material and provided a trivalent core. Photochemically-aided addition of 1-thioglycerol (**164**) gave the first generation dendrimer that was esterified with anhydride **165**, terminated by an alkyne. Repetition of these two steps twice gave a dendrimer termed by Chen *et al.*, the third generation dendrimer, although most workers in the area of alternating dendrimers call the product of each addition the next generation. Following this latter convention, we have named the product the sixth generation dendrimer in the title of Scheme 79 and G6 in the Scheme. The thiol-yne addition is very efficient because each step is a double addition, in this case raising the number of peripheral groups by four. Because the 1-thioglycerol used as the thiol was racemic, the resulting dendrimer was a mixture of diastereomers, a

disadvantage for characterization. Chen *et al.* went on to add 1-thioglycolic acid to **166**, yielding a dendrimer bearing 24 peripheral carboxylic acid groups [107]. This compound was shown to bind the anti-cancer drug, cis-dichlorodiammineplatinum(II), effectively.

**Scheme 78.** Convergent synthesis of a second generation dendrimer by alternating thiol-yne reactions with esterification [107].

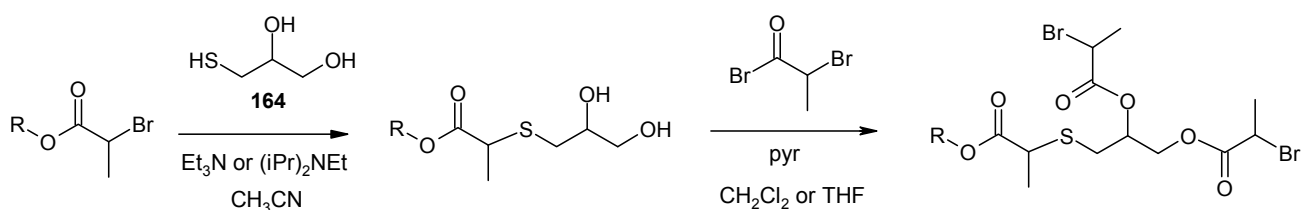


**Scheme 79.** Convergent synthesis of a sixth generation dendrimer by alternating thiol-yne reactions with esterification [107].

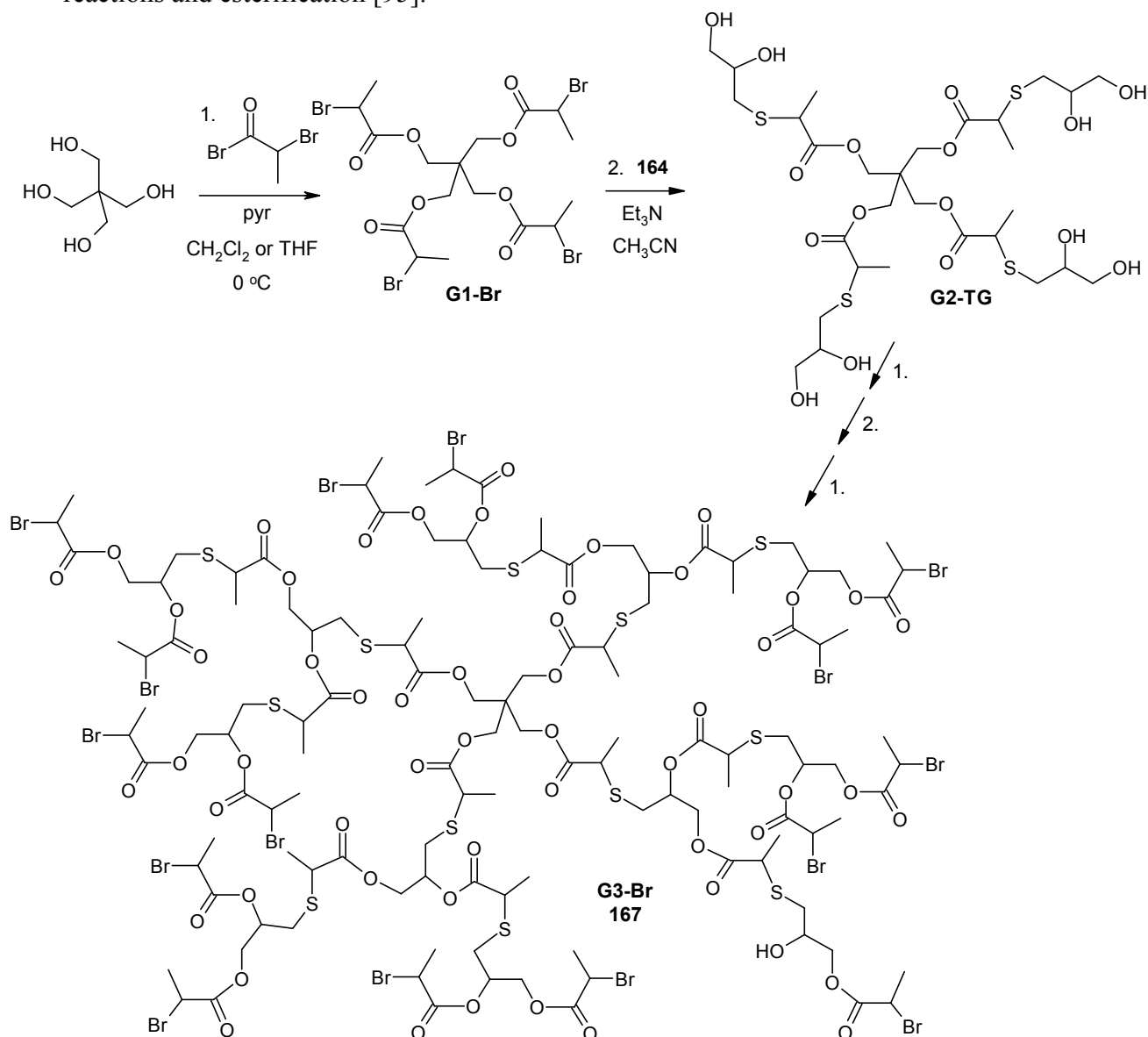


Another approach that yields alternating polyester dendrimers was described by Rosen *et al.* [95,228]. The two reactions involved are the displacement of bromide from  $\alpha$ -bromo esters by thiols that are also alcohols and esterification of the alcohols by  $\alpha$ -bromoacyl bromides (see Scheme 80).

**Scheme 80.** Synthesis of alternating polyester dendrimers by thiol- $\alpha$ -bromo ester reactions and esterification [95].



**Scheme 81.** Synthesis of a G3 alternating polyester dendrimer by thiol- $\alpha$ -bromo ester reactions and esterification [95].



Yields for the two-step sequence are good, on the order of 85% and up to the G4-Br dendrimer has been produced (see Scheme 81). These products are also mixtures of diastereomers. Compounds containing  $\alpha$ -bromo esters are candidates for single electron transfer living radical polymerization (SET-LRP) and Rosen *et al.* have demonstrated that compounds similar to **167** are effective substrates [228]. They polymerized low generation dendrimers with methyl acrylate to produce star polymers. Because the termination step of the polymerization is reaction of an acrylate-derived radical with an  $\alpha$ -bromoester, the dendritic polymers have dendrimer units at the centre and on the periphery. This three step sequence has been termed a “branch and grow” strategy [228].

## 5. Conclusions

Although many types of structures have been synthesized, the enormous structural diversity of both organic and inorganic chemistry guarantees that there are a huge number of potential novel types of



polyester dendrimers yet to be synthesized. The efficient synthesis of dendrimers through orthogonal reactions is just beginning to be studied. Consequently, properties and new potential applications are still essentially unexplored.

## Acknowledgments

We thank NSERC for support.

## References

1. Buhleier, E.; Wehner, W.; Vögtle, F. “Cascade”- and “nonskid-chain-like” syntheses of molecular cavity topologies. *Synthesis* **1978**, *1978*, 155–158.
2. Denkwalter, R.G.; Kolc, J.; Kukasavage, W.J. Macromolecular highly branched homogeneous compound based on lysine units. U.S. Patent 4289872, 15 September 1981.
3. Tomalia, D.A.; Dewald, J.R.; Hall, M.R.; Martin, S.J.; Smith, P.B. In *1st International Polymer Conference*, Kyoto, Japan, August 1984; Society of Polymer Science of Japan; p. 65.
4. Tomalia, D.A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. A new class of polymers: Starburst-dendritic macromolecules. *Polym. J.* **1985**, *17*, 117–132.
5. Newkome, G.R.; Yao, Z.Q.; Baker, G.R.; Gupta, V.K. Micelles. 1. Cascade molecules—A new approach to micelles—A [27]-arborol. *J. Org. Chem.* **1985**, *50*, 2003–2004.
6. Tomalia, D.A.; Naylor, A.M.; Goddard, W.A. Starburst dendrimers—Molecular-level control of size, shape, surface chemistry, topology, and flexibility from atoms to macroscopic matter. *Angew. Chem. Int. Ed.* **1990**, *29*, 138–175.
7. Hawker, C.J.; Fréchet, J.M.J. Unusual macromolecular architectures—The convergent growth approach to dendritic polyesters and novel block copolymers. *J. Am. Chem. Soc.* **1992**, *114*, 8405–8413.
8. Hawker, C.J.; Fréchet, J.M.J. Monodispersed dendritic polyesters with removable chain ends—A versatile approach to globular macromolecules with chemically reversible polarities. *J. Chem. Soc. Perkin Trans. I* **1992**, 2459–2469.
9. Fréchet, J.M.J.; Tomalia, D.A. *Dendrimers and Other Dendritic Polymers*; Wiley: Hoboken, NJ, USA, 2001; p. 647.
10. Newkome, G.R.; Morefield, C.N.; Vögtle, F. *Dendritic Molecules: Concepts, Synthesis, Perspectives*; Wiley-VCH: New York, NY, USA and Weinheim, Germany, 2001; p. 261.
11. Vögtle, F.; Richardt, G.; Werner, N. *Dendrimer Chemistry: Concepts, Syntheses, Properties, Applications*; Wiley-VCH: Weinheim, Germany, 2009; p. 342.
12. Nummelin, S.; Skrifvars, M.; Rissanen, K. Polyester and ester functionalized dendrimers. *Topics Curr. Chem.* **2000**, *210*, 1–67.
13. Newkome, G.R.; Shreiner, C. Dendrimers derived from 1 to 3 branching motifs. *Chem. Rev.* **2010**, *110*, 6338–6442.
14. Astruc, D.; Boisselier, E.; Ornelas, C. Dendrimers designed for functions: From physical, photophysical, and supramolecular properties to applications in sensing, catalysis, molecular electronics, photonics, and nanomedicine. *Chem. Rev.* **2010**, *110*, 1857–1959.

15. Boas, U.; Heegaard, P.M.H. Dendrimers in drug research. *Chem. Soc. Rev.* **2004**, *33*, 43–63.
16. Heegaard, P.M.H.; Boas, U.; Sorensen, N.S. Dendrimers for vaccine and immunostimulatory uses. A review. *Bioconjugate Chem.* **2010**, *21*, 405–418.
17. Fréchet, J.M.J. Dendrimers and other dendritic macromolecules: From building blocks to functional assemblies in nanoscience and nanotechnology. *J. Polym. Sci. Part A* **2003**, *41*, 3713–3725.
18. Grayson, S.M.; Fréchet, J.M.J. Convergent dendrons and dendrimers: From synthesis to applications. *Chem. Rev.* **2001**, *101*, 3819–3867.
19. Menjoge, A.R.; Kannan, R.M.; Tomalia, D.A. Dendrimer-based drug and imaging conjugates: Design considerations for nanomedical applications. *Drug Discov. Today* **2010**, *15*, 171–185.
20. Tomalia, D.A. Birth of a new macromolecular architecture: Dendrimers as quantized building blocks for nanoscale synthetic polymer chemistry. *Prog. Polym. Sci.* **2005**, *30*, 294–324.
21. Medina, S.H.; El-Sayed, M.E.H. Dendrimers as carriers for delivery of chemotherapeutic agents. *Chem. Rev.* **2009**, *109*, 3141–3157.
22. Jang, W.D.; Selim, K.M.K.; Lee, C.H.; Kang, I.K. Bioinspired application of dendrimers: From bio-mimicry to biomedical applications. *Prog. Polym. Sci.* **2009**, *34*, 1–23.
23. Cameron, D.J.A.; Shaver, M.P. Aliphatic polyester polymer stars: Synthesis, properties and applications in biomedicine and nanotechnology. *Chem. Soc. Rev.* **2011**, *40*, 1761–1776.
24. Scholl, M.; Kadlecova, Z.; Klok, H.A. Dendritic and hyperbranched polyamides. *Prog. Polym. Sci.* **2009**, *34*, 24–61.
25. Satija, J.; Sai, V.V.R.; Mukherji, S. Dendrimers in biosensors: Concept and applications. *J. Mater. Chem.* **2011**, *21*, 14367–14386.
26. Lin, Q.M.; Jiang, G.H.; Tong, K.K. Dendrimers in drug-delivery applications. *Des. Monomers Polym.* **2010**, *13*, 301–324.
27. Hourani, R.; Kakkar, A. Advances in the elegance of chemistry in designing dendrimers. *Macromol. Rapid Commun.* **2010**, *31*, 947–974.
28. Villalonga-Barber, C.; Micha-Screttas, M.; Steele, B.R.; Georgopoulos, A.; Demetzos, C. Dendrimers as biopharmaceuticals: Synthesis and properties. *Curr. Top. Med. Chem.* **2008**, *8*, 1294–1309.
29. Cheng, Y.Y.; Zhao, L.B.; Li, Y.W.; Xu, T.W. Design of biocompatible dendrimers for cancer diagnosis and therapy: Current status and future perspectives. *Chem. Soc. Rev.* **2011**, *40*, 2673–2703.
30. Soliman, G.M.; Sharma, A.; Maysinger, D.; Kakkar, A. Dendrimers and miktoarm polymers based multivalent nanocarriers for efficient and targeted drug delivery. *Chem. Commun.* **2011**, *47*, 9572–9587.
31. Wolinsky, J.B.; Grinstaff, M.W. Therapeutic and diagnostic applications of dendrimers for cancer treatment. *Adv. Drug Deliv. Rev.* **2008**, *60*, 1037–1055.
32. Newkome, G.R.; Shreiner, C.D. Poly(amidoamine), polypropylenimine, and related dendrimers and dendrons possessing different 1 → 2 branching motifs: An overview of the divergent procedures. *Polymer* **2008**, *49*, 1–173.
33. Jain, K.; Kesharwani, P.; Gupta, U.; Jain, N.K. Dendrimer toxicity: Let's meet the challenge. *Int. J. Pharm.* **2010**, *394*, 122–142.

34. Nanjwade, B.K.; Bechra, H.M.; Derkar, G.K.; Manvi, F.V.; Nanjwade, V.K. Dendrimers: Emerging polymers for drug-delivery systems. *Eur. J. Pharm. Sci.* **2009**, *38*, 185–196.
35. Simanek, E.E.; Abdou, H.; Lalwani, S.; Lim, J.; Mintzer, M.; Venditto, V.J.; Vittur, B. The 8 year thicket of triazine dendrimers: Strategies, targets and applications. *Proc. R. Soc. A* **2010**, *466*, 1445–1468.
36. Konkolewicz, D.; Monteiro, M.J.; Perrier, S. Dendritic and hyperbranched polymers from macromolecular units: Elegant approaches to the synthesis of functional polymers. *Macromolecules* **2011**, *44*, 7067–7087.
37. Harvison, M.A.; Lowe, A.B. Combining RAFT radical polymerization and click/highly efficient coupling chemistries: A powerful strategy for the preparation of novel materials. *Macromol. Rapid Commun.* **2011**, *32*, 779–800.
38. Gillies, E.R.; Dy, E.; Fréchet, J.M.J.; Szoka, F.C. Biological evaluation of polyester dendrimer: Poly(ethylene oxide) “Bow-Tie” hybrids with tunable molecular weight and architecture. *Mol. Pharm.* **2005**, *2*, 129–138.
39. Morgan, M.T.; Carnahan, M.A.; Immoos, C.E.; Ribeiro, A.A.; Finkelstein, S.; Lee, S.J.; Grinstaff, M.W. Dendritic molecular capsules for hydrophobic compounds. *J. Am. Chem. Soc.* **2003**, *125*, 15485–15489.
40. Antoni, P.; Hed, Y.; Nordberg, A.; Nyström, D.; von Holst, H.; Hult, A.; Malkoch, M. Bifunctional dendrimers: From robust synthesis and accelerated one-pot postfunctionalization strategy to potential applications. *Angew. Chem. Int. Ed.* **2009**, *48*, 2126–2130.
41. Kienle, R.H.; Hovey, A.G. The polyhydric alcohol-polybasic acid reaction I Glycerol-phthalic anhydride. *J. Am. Chem. Soc.* **1929**, *51*, 509–519.
42. Smith, W. A new glyceride: Glycerine phthalate. *J. Soc. Chem. Ind.* **1901**, *20*, 1075–1076.
43. Kienle, R.H.; van der Meulen, P.A.; Petke, F.E. Polyhydric alcohol-polybasic acid reaction. III. Further studies of the glycerol-phthalic anhydride reaction. *J. Am. Chem. Soc.* **1939**, *61*, 2258–2268.
44. Kienle, R.H.; van der Meulen, P.A.; Petke, F.E. Polyhydric alcohol-polybasic acid reaction. IV. Glyceryl phthalate from phthalic acid. *J. Am. Chem. Soc.* **1939**, *61*, 2268–2271.
45. Kienle, R.H.; Petke, F.E. The polyhydric alcohol-polybasic acid reaction. V. The glyceryl succinate and glyceryl maleate polyesters. *J. Am. Chem. Soc.* **1940**, *62*, 1053–1056.
46. Baekeland, L.H. The synthesis, constitution, and uses of bakelite. *Ind. Eng. Chem.* **1909**, *1*, 149–161.
47. Baekeland, L.H.; Bender, H.L. Phenol resins and resinoids. *Ind. Eng. Chem.* **1925**, *17*, 225–237.
48. Flory, P.J. Molecular size distribution in three dimensional polymers. I. Gelation. *J. Am. Chem. Soc.* **1941**, *63*, 3083–3090.
49. Flory, P.J. Molecular size distribution in three dimensional polymers. II. Trifunctional branching units. *J. Am. Chem. Soc.* **1941**, *63*, 3091–3096.
50. Flory, P.J. Molecular size distribution in three dimensional polymers. III. Tetrafunctional branching units. *J. Am. Chem. Soc.* **1941**, *63*, 3096–3100.
51. Stockmayer, W.H. Theory of molecular size distribution and gel formation in branched-chain polymers. *J. Chem. Phys.* **1943**, *11*, 45–55.

52. Flory, P.J. Molecular size distribution in three dimensional polymers. VI. Branched polymers containing A-R-B<sub>f-1</sub> type units. *J. Am. Chem. Soc.* **1952**, *74*, 2718–2723.
53. Schaefgen, J.R.; Flory, P.J. Synthesis of multichain polymers and investigation of their viscosities. *J. Am. Chem. Soc.* **1948**, *70*, 2709–2718.
54. Hawker, C.J.; Lee, R.; Fréchet, J.M.J. One-step synthesis of hyperbranched dendritic polyesters. *J. Am. Chem. Soc.* **1991**, *113*, 4583–4588.
55. Malmström, E.; Johansson, M.; Hult, A. Hyperbranched aliphatic polyesters. *Macromolecules* **1995**, *28*, 1698–1703.
56. Schlüter, A.D.; Rabe, J.P. Dendronized polymers: Synthesis, characterization, assembly at interfaces, and manipulation. *Angew. Chem. Int. Ed.* **2000**, *39*, 864–883.
57. Zhang, A.; Shu, L.; Bo, Z.; Schlüter, A.D. Dendronized polymers: Recent progress in synthesis. *Macromol. Chem. Phys.* **2003**, *204*, 328–339.
58. Frauenrath, H. Dendronized polymers—Building a new bridge from molecules to nanoscopic objects. *Prog. Polym. Sci.* **2005**, *30*, 325–384.
59. Zhang, A. Synthesis, characterization and applications of dendronized polymers. *Prog. Chem.* **2005**, *17*, 157–171.
60. Carlmark, A.; Hawker, C.J.; Hult, A.; Malkoch, M. New methodologies in the construction of dendritic materials. *Chem. Soc. Rev.* **2009**, *38*, 352–362.
61. Gauthier, M. Arborescent polymers and other dendrigraft polymers: A journey into structural diversity. *J. Polym. Sci. Part A* **2007**, *45*, 3803–3810.
62. Wurm, F.; Frey, H. Linear-dendritic block copolymers: The state of the art and exciting perspectives. *Prog. Polym. Sci.* **2011**, *36*, 1–52.
63. Yan, D.; Gao, C.; Frey, H. *Hyperbranched Polymers: Synthesis, Properties and Applications*; John Wiley & Sons: New York, NY, USA, 2011; p. 480.
64. Hult, A.; Johansson, M.; Malmström, E. Hyperbranched polymers. *Adv. Polym. Sci.* **1999**, *143*, 1–34.
65. Gao, C.; Yan, D. Hyperbranched polymers: From synthesis to applications. *Prog. Polym. Sci.* **2004**, *29*, 183–275.
66. Voit, B. Hyperbranched polymers—All problems solved after 15 years of research? *J. Polym. Sci. Part A* **2005**, *43*, 2679–2699.
67. Yates, C.R.; Hayes, W. Synthesis and applications of hyperbranched polymers. *Eur. Polym. J.* **2004**, *40*, 1257–1281.
68. McKee, M.G.; Unal, S.; Wilkes, G.L.; Long, T.E. Branched polyesters: Recent advances in synthesis and performance. *Prog. Polym. Sci.* **2005**, *30*, 507–539.
69. Voit, B.I.; Lederer, A. Hyperbranched and highly branched polymer architectures-synthetic strategies and major characterization aspects. *Chem. Rev.* **2009**, *109*, 5924–5973.
70. Zhang, X. Hyperbranched aromatic polyesters: From synthesis to applications. *Prog. Org. Coat.* **2010**, *69*, 295–309.
71. Calderón, M.; Quadir, M.A.; Strumia, M.; Haag, R. Functional dendritic polymer architectures as stimuli-responsive nanocarriers. *Biochimie* **2010**, *92*, 1242–1251.
72. Žagar, E.; Žigon, M. Aliphatic hyperbranched polyesters based on 2,2-bis(methylol)propionic acid-Determination of structure, solution and bulk properties. *Prog. Polym. Sci.* **2011**, *36*, 53–88.

73. Binauld, S.; Damiron, D.; Connal, L.A.; Hawker, C.J.; Drockenmuller, E. Precise synthesis of molecularly defined oligomers and polymers by orthogonal iterative divergent/convergent approaches. *Macromol. Rapid Commun.* **2011**, *32*, 147–168.
74. Zhang, X. Modifications and applications of hyperbranched aliphatic polyesters based on dimethylolpropionic acid. *Polym. Int.* **2011**, *60*, 153–166.
75. Newkome, G.R.; Nayak, A.; Behera, R.K.; Moorefield, C.N.; Baker, G.R. Chemistry of micelles series. 22. Cascade polymers—synthesis and characterization of 4-directional spherical dendritic macromolecules based on adamantane. *J. Org. Chem.* **1992**, *57*, 358–362.
76. De Brabander-van den Berg, E.M.M.; Meijer, E.W. Poly(propylene imine) dendrimers: Large-scale synthesis by heterogeneously catalyzed hydrogenations. *Angew. Chem. Int. Ed.* **1993**, *32*, 1308–1311.
77. Hawker, C.J.; Fréchet, J.M.J. Preparation of polymers with controlled molecular architecture—A new convergent approach to dendritic macromolecules. *J. Am. Chem. Soc.* **1990**, *112*, 7638–7647.
78. Gillies, E.R.; Fréchet, J.M.J. Dendrimers and dendritic polymers in drug delivery. *Drug Discov. Today* **2005**, *10*, 35–43.
79. Lee, C.C.; Gillies, E.R.; Fox, M.E.; Guillaudeu, S.J.; Fréchet, J.M.J.; Dy, E.E.; Szoka, F.C. A single dose of doxorubicin-functionalized bow-tie dendrimer cures mice bearing C-26 colon carcinomas. *Proc. Nat. Acad. Sci. USA* **2006**, *103*, 16649–16654.
80. Haddleton, D.M.; Sahota, H.S.; Taylor, P.C.; Yeates, S.G. Synthesis of polyester dendrimers. *J. Chem. Soc. Perkin Trans. 1* **1996**, 649–656.
81. Kawaguchi, T.; Walker, K.L.; Wilkins, C.L.; Moore, J.S. Double exponential dendrimer growth. *J. Am. Chem. Soc.* **1995**, *117*, 2159–2165.
82. Klopsch, R.; Franke, P.; Schlüter, A.-D. Repetitive strategy for exponential growth of hydroxy-functionalized dendrons. *Chem. Eur. J.* **1996**, *2*, 1330–1334.
83. Ashton, P.R.; Hounsell, E.F.; Jayaraman, N.; Nilsen, T.M.; Spencer, N.; Stoddart, J.F.; Young, M. Synthesis and biological evaluation of  $\alpha$ -D-mannopyranoside-containing dendrimers. *J. Org. Chem.* **1998**, *63*, 3429–3437.
84. Ihre, H.; Hult, A.; Fréchet, J.M.J.; Gitsov, I. Double-stage convergent approach for the synthesis of functionalized dendritic aliphatic polyesters based on 2,2-bis(hydroxymethyl)propionic acid. *Macromolecules* **1998**, *31*, 4061–4068.
85. Spindler, R.; Fréchet, J.M.J. 2-Step approach towards the accelerated synthesis of dendritic macromolecules. *J. Chem. Soc. Perkin Trans. 1* **1993**, 913–918.
86. Xu, Z.F.; Moore, J.S. Stiff dendritic macromolecules. 3. Rapid construction of large-size phenylacetylene dendrimers up to 12.5 nonometers in molecular diameter. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1354–1357.
87. Zeng, F.W.; Zimmerman, S.C. Rapid synthesis of dendrimers by an orthogonal coupling strategy. *J. Am. Chem. Soc.* **1996**, *118*, 5326–5327.
88. Deb, S.K.; Maddux, T.M.; Yu, L.P. A simple orthogonal approach to poly(phenylenevinylene) dendrimers. *J. Am. Chem. Soc.* **1997**, *119*, 9079–9080.
89. Klopsch, R.; Koch, S.; Schlüter, A.-D. Amino-functionalized, second-generation dendritic building blocks. *Eur. J. Org. Chem.* **1998**, 1275–1283.

90. Ingerl, A.; Neubert, I.; Klopsch, R.; Schlüter, A.D. Hydroxy-functionalized dendritic building blocks. *Eur. J. Org. Chem.* **1998**, 2551–2556.
91. Ishida, Y.; Jikei, M.; Kakimoto, M.A. Rapid synthesis of aromatic polyamide dendrimers by an orthogonal and a double-stage convergent approach. *Macromolecules* **2000**, *33*, 3202–3211.
92. Burai, R.; Chatwichien, J.; McNaughton, B.R. A programmable “build-couple” approach to the synthesis of heterofunctionalized polyvalent molecules. *Org. Biomol. Chem.* **2011**, *9*, 5056–5058.
93. Antoni, P.; Robb, M.J.; Campos, L.; Montanez, M.; Hult, A.; Malmström, E.; Malkoch, M.; Hawker, C.J. Pushing the limits for thiol-ene and CuAAC reactions: Synthesis of a 6th generation dendrimer in a single day. *Macromolecules* **2010**, *43*, 6625–6631.
94. Ma, X.; Tang, J.; Shen, Y.; Fan, M.; Tang, H.; Radosz, M. Facile synthesis of polyester dendrimers from sequential click coupling of asymmetrical monomers. *J. Am. Chem. Soc.* **2009**, *131*, 14795–14803.
95. Rosen, B.M.; Lligadas, G.; Hahn, C.; Percec, V. Synthesis of dendrimers through divergent iterative thio-bromo “click” chemistry. *J. Polym. Sci. Part A* **2009**, *47*, 3931–3939.
96. In, I.; Kim, S.Y. Orthogonal synthesis of poly(aryl ether amide) dendrons. *Macromolecules* **2005**, *38*, 9399–9401.
97. Kozaki, M.; Okada, K. Snowflake-like dendrimers via site-selective synthesis of dendrons. *Org. Lett.* **2004**, *6*, 485–488.
98. Maraval, V.; Pyzowski, J.; Caminade, A.M.; Majoral, J.P. “Lego” chemistry for the straightforward synthesis of dendrimers. *J. Org. Chem.* **2003**, *68*, 6043–6046.
99. Zhang, W.; Nowlan, D.T.; Thomson, L.M.; Lackowski, W.M.; Simanek, E.E. Orthogonal, convergent syntheses of dendrimers based on melamine with one or two unique surface sites for manipulation. *J. Am. Chem. Soc.* **2001**, *123*, 8914–8922.
100. Leu, C.M.; Shu, C.F.; Teng, C.F.; Shiea, J. Dendritic poly(ether-imide)s: Synthesis, characterization, and modification. *Polymer* **2001**, *42*, 2339–2348.
101. Wong, E.H.H.; Altintas, O.; Stenzel, M.H.; Barner-Kowollik, C.; Junkers, T. Nitron-mediated radical coupling reactions: A new synthetic tool exemplified on dendrimer synthesis. *Chem. Commun.* **2011**, *47*, 5491–5493.
102. Zeng, F.; Zimmerman, S.C. Rapid synthesis of dendrimers by an orthogonal coupling strategy. *J. Am. Chem. Soc.* **1996**, *118*, 5326–5327.
103. Antoni, P.; Nyström, D.; Hawker, C.J.; Hult, A.; Malkoch, M. A chemoselective approach for the accelerated synthesis of well-defined dendritic architectures. *Chem. Commun.* **2007**, 2249–2251.
104. Montañez, M.I.; Campos, L.M.; Antoni, P.; Hed, Y.; Walter, M.V.; Krull, B.T.; Khan, A.; Hult, A.; Hawker, C.J.; Malkoch, M. Accelerated growth of dendrimers via thiol-ene and esterification reactions. *Macromolecules* **2010**, *43*, 6004–6013.
105. Walter, M.V.; Lundberg, P.; Hult, A.; Malkoch, M. Novel macrothiols for the synthesis of a structurally comprehensive dendritic library using thiol-ene click chemistry. *J. Polym. Sci. Part A* **2011**, *49*, 2990–2995.
106. Romagnoli, B.; Ashton, P.R.; Harwood, L.M.; Philp, D.; Price, D.W.; Smith, M.H.; Hayes, W. Synthesis and properties of polyaromatic dendrimers possessing a repetitive amide-ester coupling sequence. *Tetrahedron* **2003**, *59*, 3975–3988.

107. Chen, G.J.; Kumar, J.; Gregory, A.; Stenzel, M.H. Efficient synthesis of dendrimers via a thiol-yne and esterification process and their potential application in the delivery of platinum anti-cancer drugs. *Chem. Commun.* **2009**, 6291–6293.
108. Maraval, V.; Caminade, A.M.; Majoral, J.P.; Blais, J.C. Dendrimer design: How to circumvent the dilemma of a reduction of steps or an increase of function multiplicity? *Angew. Chem. Int. Ed.* **2003**, *42*, 1822–1826.
109. Servin, P.; Rebout, C.; Laurent, R.; Peruzzini, M.; Caminade, A.M.; Majoral, J.P. Reduced number of steps for the synthesis of dense and highly functionalized dendrimers. *Tetrahedron Lett.* **2007**, *48*, 579–583.
110. Maraval, V.; Laurent, R.; Marchand, P.; Caminade, A.M.; Majoral, J.P. Accelerated methods of synthesis of phosphorus-containing dendrimers. *J. Organomet. Chem.* **2005**, *690*, 2458–2471.
111. De Gennes, P.G.; Hervet, H. Statistics of starburst polymers. *J. Phys. Lett.* **1983**, *44*, L351–L360.
112. Hecht, S.; Fréchet, J.M.J. Dendritic encapsulation of function: Applying nature's site isolation principle from biomimetics to materials science. *Angew. Chem. Int. Ed.* **2001**, *40*, 74–91.
113. Bosman, A.W.; Janssen, H.M.; Meijer, E.W. About dendrimers: Structure, physical properties, and applications. *Chem. Rev.* **1999**, *99*, 1665–1688.
114. Moreno, K.X.; Simanek, E.E. Conformational analysis of triazine dendrimers: Using NMR spectroscopy to probe the choreography of a dendrimer's dance. *Macromolecules* **2008**, *41*, 4108–4114.
115. Tanis, I.; Karatasos, K. Local dynamics and hydrogen bonding in hyperbranched aliphatic polyesters. *Macromolecules* **2009**, *42*, 9581–9591.
116. Tanis, I.; Karatasos, K.; Assimopoulou, A.N.; Papageorgiou, V.P. Modeling of hyperbranched polyesters as hosts for the multifunctional bioactive agent shikonin. *Phys. Chem. Chem. Phys.* **2011**, *13*, 10808–10817.
117. Chang, H.T.; Fréchet, J.M.J. Proton-transfer polymerization: A new approach to hyperbranched polymers. *J. Am. Chem. Soc.* **1999**, *121*, 2313–2314.
118. Fréchet, J.M.J.; Henmi, M.; Gitsov, I.; Aoshima, S.; Leduc, M.R.; Grubbs, R.B. Self-condensing vinyl polymerization: An approach to dendritic materials. *Science* **1995**, *269*, 1080–1083.
119. Suzuki, M.; Ii, A.; Saegusa, T. Multibranching polymerization: Palladium-catalyzed ring-opening polymerization of cyclic carbamate to produce hyperbranched dendritic polyamine. *Macromolecules* **1992**, *25*, 7071–7072.
120. Flory, P.J. Kinetics of condensation polymerization: The reaction of ethylene glycol with succinic acid. *J. Am. Chem. Soc.* **1937**, *59*, 466–470.
121. Flory, P.J. Molecular size distribution in three dimensional polymers. 6 branched polymers containing A-R-BF-1 type units. *J. Am. Chem. Soc.* **1952**, *74*, 2718–2723.
122. Mathias, L.J.; Carothers, T.W. Hyperbranched poly(siloxysilanes). *J. Am. Chem. Soc.* **1991**, *113*, 4043–4044.
123. Hunter, W.H.; Woollett, G.H. A catalytic decomposition of certain phenol silver salts. IV. The constitution of the amorphous oxides. *J. Am. Chem. Soc.* **1921**, *43*, 135–151.
124. Yoon, K.; Son, D.Y. Syntheses of hyperbranched poly(carbosilarylenes). *Macromolecules* **1999**, *32*, 5210–5216.

125. Miravet, J.F.; Fréchet, J.M.J. New hyperbranched poly(siloxysilanes): Variation of the branching pattern and end-functionalization. *Macromolecules* **1998**, *31*, 3461–3468.
126. Ihre, H.; Hult, A.; Söderlind, E. Synthesis, characterization, and H-1 NMR self-diffusion studies of dendritic aliphatic polyesters based on 2,2-bis(hydroxymethyl)propionic acid and 1,1,1-tris(hydroxyphenyl)ethane. *J. Am. Chem. Soc.* **1996**, *118*, 6388–6395.
127. Ihre, H.; Padilla De Jesús, O.L.; Fréchet, J.M.J. Fast and convenient divergent synthesis of aliphatic ester dendrimers by anhydride coupling. *J. Am. Chem. Soc.* **2001**, *123*, 5908–5917.
128. Malkoch, M.; Malmström, E.; Hult, A. Rapid and efficient synthesis of aliphatic ester dendrons and dendrimers. *Macromolecules* **2002**, *35*, 8307–8314.
129. Parrott, M.C.; Benhabbour, S.R.; Saab, C.; Lemon, J.A.; Parker, S.; Valliant, J.F.; Adronov, A. Synthesis, radiolabeling, and bio-imaging of high-generation polyester dendrimers. *J. Am. Chem. Soc.* **2009**, *131*, 2906–2916.
130. Twibanire, J.K.; Al-Mughaid, H.; Grindley, T.B. Synthesis of new cores and their use in the preparation of polyester dendrimers. *Tetrahedron* **2010**, *66*, 9602–9609.
131. Knorr, R.; Trzeciak, A.; Bannwarth, W.; Gillessen, D. New coupling reagents in peptide chemistry. *Tetrahedron Lett.* **1989**, *30*, 1927–1930.
132. Carpino, L.A. 1-Hydroxy-7-azabenzotriazole—An efficient peptide coupling additive. *J. Am. Chem. Soc.* **1993**, *115*, 4397–4398.
133. El-Faham, A.; Subirós-Funosas, R.; Prohens, R.; Albericio, F. Comu: A safer and more effective replacement for benzotriazole-based uronium coupling reagents. *Chem. Eur. J.* **2009**, *15*, 9404–9416.
134. Twibanire, J.K.; Grindley, T.B. Efficient and controllably selective preparation of esters using uronium-based coupling agents. *Org. Lett.* **2011**, *13*, 2988–2991.
135. Bouillon, C.; Quelever, G.; Peng, L. Efficient synthesis of esters containing tertiary amine functionalities via active cyanomethyl ester intermediates. *Tetrahedron Lett.* **2009**, *50*, 4346–4349.
136. Bouillon, C.; Tintaru, A.; Monnier, V.; Charles, L.; Quelever, G.; Peng, L. Synthesis of poly(amino)ester dendrimers via active cyanomethyl ester intermediates. *J. Org. Chem.* **2010**, *75*, 8685–8688.
137. Robertson, S.A.; Ellman, J.A.; Schultz, P.G. A general and efficient route for chemical aminoacylation of transfer-RNAs. *J. Am. Chem. Soc.* **1991**, *113*, 2722–2729.
138. Ihre, H.R.; Padilla De Jesús, O.L.; Szoka, F.C.; Fréchet, J.M.J. Polyester dendritic systems for drug delivery applications: Design, synthesis, and characterization. *Bioconjugate Chem.* **2002**, *13*, 443–452.
139. Greenwald, R.B.; Conover, C.D.; Choe, Y.H. Poly(ethylene glycol) conjugated drugs and prodrugs: A comprehensive review. *Crit. Rev. Ther. Drug Carr. Syst.* **2000**, *17*, 101–161.
140. Kapitza, H.; Zentel, R.; Twieg, R.J.; Nguyen, C.; Vallerien, S.U.; Kremer, F.; Willson, C.G. Ferroelectric liquid-crystalline polysiloxanes with high spontaneous polarization and possible applications in nonlinear optics. *Adv. Mater.* **1990**, *2*, 539–543.
141. Keller, P.; Shao, R.F.; Walba, D.M.; Brunet, M. The first high polarization ferroelectric main-chain liquid-crystalline polymers. *Liq. Cryst.* **1995**, *18*, 915–918.



142. Walba, D.M.; Keller, P.; Shao, R.F.; Clark, N.A.; Hillmyer, M.; Grubbs, R.H. Main-chain ferroelectric liquid crystal oligomers by acyclic diene metathesis polymerization. *J. Am. Chem. Soc.* **1996**, *118*, 2740–2741.
143. Hermann, D.S.; Hult, A.; Komitov, L.; Lagerwall, S.T.; Lindgren, M. Pyroelectric polymers for nonlinear optics. *Ferroelectrics* **1998**, *213*, 405–415.
144. Hermann, D.S.; Hult, A.; Komitov, L.; Lagerwall, S.T.; Sahlen, F.; Trollsås, M. The influence of chiral strength on the spontaneous polarization and the second-order nonlinear optical susceptibility in ferroelectric liquid crystals. *Ferroelectrics* **1998**, *213*, 417–427.
145. Busson, P.; Ihre, H.; Hult, A. Synthesis of a novel dendritic liquid crystalline polymer showing a ferroelectric SmC\* phase. *J. Am. Chem. Soc.* **1998**, *120*, 9070–9071.
146. Hedrick, J.L.; Trollsås, M.; Hawker, C.J.; Atthoff, B.; Claesson, H.; Heise, A.; Miller, R.D.; Mecerreyes, D.; Jérôme, R.; Dubois, P. Dendrimer-like star block and amphiphilic copolymers by combination of ring opening and atom transfer radical polymerization. *Macromolecules* **1998**, *31*, 8691–8705.
147. Kato, M.; Kamigaito, M.; Sawamoto, M.; Higashimura, T. Polymerization of methyl-methacrylate with the carbon-tetrachloride dichlorotris(triphenylphosphine) ruthenium(II) methylaluminum bis(2,6-di-tert-butylphenoxide) initiating system—Possibility of living radical polymerization. *Macromolecules* **1995**, *28*, 1721–1723.
148. Wang, J.S.; Matyjaszewski, K. Controlled living radical polymerization—Atom-transfer radical polymerization in the presence of transition-metal complexes. *J. Am. Chem. Soc.* **1995**, *117*, 5614–5615.
149. Annby, U.; Malmberg, M.; Pettersson, B.; Rehnberg, N. Benzyldiene protected bis-MPA—A convenient dendrimer building block. *Tetrahedron Lett.* **1998**, *39*, 3217–3220.
150. Trollsås, M.; Atthoff, B.; Claesson, H.; Hedrick, J.L. Hyperbranched poly(epsilon-caprolactone)s. *Macromolecules* **1998**, *31*, 3439–3445.
151. Hao, X.J.; Nilsson, C.; Jesberger, M.; Stenzel, M.H.; Malmström, E.; Davis, T.P.; Östmark, E.; Barner-Kowollik, C. Dendrimers as scaffolds for multifunctional reversible addition-fragmentation chain transfer agents: Syntheses and polymerization. *J. Polym. Sci. Part A* **2004**, *42*, 5877–5890.
152. Wang, L.L.; Meng, Z.L.; Yu, Y.L.; Meng, Q.W.; Chen, D.Z. Synthesis of hybrid linear-dendritic block copolymers with carboxylic functional groups for the biomimetic mineralization of calcium carbonate. *Polymer* **2008**, *49*, 1199–1210.
153. Parrott, M.C.; Marchington, E.B.; Valliant, J.F.; Adronov, A. Synthesis and properties of carborane-functionalized aliphatic polyester dendrimers. *J. Am. Chem. Soc.* **2005**, *127*, 12081–12089.
154. Gillies, E.R.; Fréchet, J.M.J. Designing macromolecules for therapeutic applications: Polyester dendrimer-poly(ethylene oxide) “bow-tie” hybrids with tunable molecular weight and architecture. *J. Am. Chem. Soc.* **2002**, *124*, 14137–14146.
155. Vestberg, R.; Nystrom, A.; Lindgren, M.; Malmström, E.; Hult, A. Porphyrin-cored 2,2-bis(methylol)propionic acid dendrimers. *Chem. Mater.* **2004**, *16*, 2794–2804.
156. Nishiyama, N.; Stapert, H.R.; Zhang, G.D.; Takasu, D.; Jiang, D.L.; Nagano, T.; Aida, T.; Kataoka, K. Light-harvesting ionic dendrimer porphyrins as new photosensitizers for photodynamic therapy. *Bioconjugate Chem.* **2003**, *14*, 58–66.

157. Armstrong, N.R. Phthalocyanines and porphyrins as materials. *J. Porphyrins Phthalocyanines* **2000**, *4*, 414–417.
158. Krivokapic, A.; Anderson, H.L.; Bourhill, G.; Ives, R.; Clark, S.; McEwan, K.J. Meso-tetra-alkynyl porphyrins for optical limiting—A survey of group III and IV metal complexes. *Adv. Mater.* **2001**, *13*, 652–656.
159. Finikova, O.; Galkin, A.; Rozhkov, V.; Cordero, M.; Hagerhall, C.; Vinogradov, S. Porphyrin and tetrabenzoporphyrin dendrimers: Tunable membrane-impermeable fluorescent pH nanosensors. *J. Am. Chem. Soc.* **2003**, *125*, 4882–4893.
160. Pollak, K.W.; Sanford, E.M.; Fréchet, J.M.J. Comparison of two convergent routes for the preparation of metalloporphyrin-core dendrimers: Direct condensation vs. chemical modification. *J. Mater. Chem.* **1998**, *8*, 519–527.
161. Pollak, K.W.; Leon, J.W.; Fréchet, J.M.J.; Maskus, M.; Abruna, H.D. Effects of dendrimer generation on site isolation of core moieties: Electrochemical and fluorescence quenching studies with metalloporphyrin core dendrimers. *Chem. Mater.* **1998**, *10*, 30–38.
162. Maes, W.; Amabilino, D.B.; Dehaen, W. Synthesis of novel dendrimers containing pyrimidine units. *Tetrahedron* **2003**, *59*, 3937–3943.
163. Capitosti, G.J.; Guerrero, C.D.; Binkley, D.E.; Rajesh, C.S.; Modarelli, D.A. Efficient synthesis of porphyrin-containing, benzoquinone-terminated, rigid polyphenylene dendrimers. *J. Org. Chem.* **2003**, *68*, 247–261.
164. Yeow, E.K.L.; Ghiggino, K.P.; Reek, J.N.H.; Crossley, M.J.; Bosman, A.W.; Schenning, A.; Meijer, E.W. The dynamics of electronic energy transfer in novel multiporphyrin functionalized dendrimers: A time-resolved fluorescence anisotropy. *J. Phys. Chem. B* **2000**, *104*, 2596–2606.
165. Rajesh, C.S.; Capitosti, G.J.; Cramer, S.J.; Modarelli, D.A. Photoinduced electron-transfer within free base and zinc porphyrin containing poly(amide) dendrimers. *J. Phys. Chem. B* **2001**, *105*, 10175–10188.
166. Jiang, D.L.; Aida, T. Morphology-dependent photochemical events in aryl ether dendrimer porphyrins: Cooperation of dendron subunits for singlet energy transduction. *J. Am. Chem. Soc.* **1998**, *120*, 10895–10901.
167. Matos, M.S.; Hofkens, J.; Verheijen, W.; De Schryver, F.C.; Hecht, S.; Pollak, K.W.; Fréchet, J.M.J.; Forier, B.; Dehaen, W. Effect of core structure on photophysical and hydrodynamic properties of porphyrin dendrimers. *Macromolecules* **2000**, *33*, 2967–2973.
168. Kimura, M.; Shiba, T.; Yamazaki, M.; Hanabusa, K.; Shirai, H.; Kobayashi, N. Construction of regulated nanospace around a porphyrin core. *J. Am. Chem. Soc.* **2001**, *123*, 5636–5642.
169. Galie, K.M.; Mollard, A.; Zharov, I. Polyester-based carborane-containing dendrons. *Inorg. Chem.* **2006**, *45*, 7815–7820.
170. Baars, M.; Meijer, E.W. Host-guest chemistry of dendritic molecules. *Dendrimers II* **2000**, *210*, 131–182.
171. Baars, M.; Karlsson, A.J.; Sorokin, V.; de Waal, B.F.W.; Meijer, E.W. Supramolecular modification of the periphery of dendrimers resulting in rigidity and functionality. *Angew. Chem. Int. Ed.* **2000**, *39*, 4262–4265.
172. Gillies, E.R.; Fréchet, J.M.J. Synthesis and self-assembly of supramolecular dendritic “Bow-Ties”: Effect of peripheral functionality on association constants. *J. Org. Chem.* **2004**, *69*, 46–53.

173. Bell, J.A.; Kenworthy, C. Cyanoethylation of some alkanolamines. *Synthesis* **1971**, 650–652.
174. Goodwin, A.P.; Lam, S.S.; Fréchet, J.M.J. Rapid, efficient synthesis of heterobifunctional biodegradable dendrimers. *J. Am. Chem. Soc.* **2007**, *129*, 6994–6995.
175. Burgel, T.; Fedtke, M.; Franzke, M. Reaction of cyclic carbonates with amines—Linear telechelic oligomers. *Polym. Bull.* **1993**, *30*, 155–162.
176. Ochiai, B.; Satoh, Y.; Endo, T. Nucleophilic polyaddition in water based on chemo-selective reaction of cyclic carbonate with amine. *Green Chem.* **2005**, *7*, 765–767.
177. Gurr, P.A.; Qiao, G.G.; Solomon, D.H.; Harton, S.E.; Spontak, R.J. Synthesis, characterization, and direct observation of star microgels. *Macromolecules* **2003**, *36*, 5650–5654.
178. Bosman, A.W.; Vestberg, R.; Heumann, A.; Fréchet, J.M.J.; Hawker, C.J. A modular approach toward functionalized three-dimensional macromolecules: From synthetic concepts to practical applications. *J. Am. Chem. Soc.* **2003**, *125*, 715–728.
179. Lord, H.T.; Quinn, J.F.; Angus, S.D.; Whittaker, M.R.; Stenzel, M.H.; Davis, T.P. Microgel stars via reversible addition fragmentation chain transfer (RAFT) polymerisation—A facile route to macroporous membranes, honeycomb patterned thin films and inverse opal substrates. *J. Mater. Chem.* **2003**, *13*, 2819–2824.
180. Wiltshire, J.T.; Qiao, G.G. Synthesis of core cross-linked star polymers with adjustable coronal properties. *Macromolecules* **2008**, *41*, 623–631.
181. Wiltshire, J.T.; Qiao, G.G. Selectively degradable core cross-linked star polymers. *Macromolecules* **2006**, *39*, 9018–9027.
182. Hawker, C.J.; Wooley, K.L. The convergence of synthetic organic and polymer chemistries. *Science* **2005**, *309*, 1200–1205.
183. Abrol, S.; Kambouris, P.A.; Looney, M.G.; Solomon, D.H. Studies on microgels. 3. Synthesis using living free radical polymerization. *Macromol. Rapid Commun.* **1997**, *18*, 755–760.
184. Baek, K.Y.; Kamigaito, M.; Sawamoto, M. Star-shaped polymers by metal-catalyzed living radical polymerization. 1. Design of Ru(II)-based systems and divinyl linking agents. *Macromolecules* **2001**, *34*, 215–221.
185. Connal, L.A.; Vestberg, R.; Hawker, C.J.; Qiao, G.G. Synthesis of dendron functionalized core cross-linked star polymers. *Macromolecules* **2007**, *40*, 7855–7863.
186. Kose, M.M.; Yesilbag, G.; Sanyal, A. Segment block dendrimers via Diels-Alder cycloaddition. *Org. Lett.* **2008**, *10*, 2353–2356.
187. McElhanon, J.R.; Wheeler, D.R. Thermally responsive dendrons and dendrimers based on reversible furan-maleimide Diels-Alder adducts. *Org. Lett.* **2001**, *3*, 2681–2683.
188. Szalai, M.L.; McGrath, D.V.; Wheeler, D.R.; Zifer, T.; McElhanon, J.R. Dendrimers based on thermally reversible furan-maleimide Diels-Alder adducts. *Macromolecules* **2007**, *40*, 818–823.
189. Kawa, M.; Fréchet, J.M.J. Enhanced luminescence of lanthanide within lanthanide-cored dendrimer complexes. *Thin Solid Films* **1998**, *331*, 259–263.
190. Kawa, M.; Fréchet, J.M.J. Self-assembled lanthanide-cored dendrimer complexes: Enhancement of the luminescence properties of lanthanide ions through site-isolation and antenna effects. *Chem. Mater.* **1998**, *10*, 286–296.

191. Antoni, P.; Malkoch, M.; Vamvounis, G.; Nyström, D.; Nyström, A.; Lindgren, M.; Hult, A. Europium confined cyclen dendrimers with photophysically active triazoles. *J. Mater. Chem.* **2008**, *18*, 2545–2554.
192. Tornøe, C.W.; Christensen, C.; Meldal, M. Peptidotriazoles on solid phase: [1,2,3]-triazoles by regiospecific copper(I)-catalyzed 1,3-dipolar cycloadditions of terminal alkynes to azides. *J. Org. Chem.* **2002**, *67*, 3057–3064.
193. Kolb, H.C.; Finn, M.G.; Sharpless, K.B. Click chemistry: Diverse chemical function from a few good reactions. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021.
194. Mekelburger, H.B.; Rissanen, K.; Vögtle, F. Repetitive synthesis of bulky dendrimers—A reversibly photoactive dendrimer with six azobenzene side-chains. *Chem. Berichte* **1993**, *126*, 1161–1169.
195. Momotake, A.; Arai, T. Photochemistry and photophysics of stilbene dendrimers and related compounds. *J. Photochem. Photobiol. C* **2004**, *5*, 1–25.
196. Liao, L.X.; Stellacci, F.; McGrath, D.V. Photoswitchable flexible and shape-persistent dendrimers: Comparison of the interplay between a photochromic azobenzene core and dendrimer structure. *J. Am. Chem. Soc.* **2004**, *126*, 2181–2185.
197. Puntoriero, F.; Ceroni, P.; Balzani, V.; Bergamini, G.; Vögtle, F. Photoswitchable dendritic hosts: A dendrimer with peripheral azobenzene groups. *J. Am. Chem. Soc.* **2007**, *129*, 10714–10719.
198. Gabriel, C.J.; Parquette, J.R. Expanding dendrons. The photoisomerism of folded azobenzene dendrons. *J. Am. Chem. Soc.* **2006**, *128*, 13708–13709.
199. Kumar, G.S.; Neckers, D.C. Photochemistry of azobenzene-containing polymers. *Chem. Rev.* **1989**, *89*, 1915–1925.
200. Yagai, S.; Karatsu, T.; Kitamura, A. Photocontrollable self-assembly. *Chem. Eur. J.* **2005**, *11*, 4054–4063.
201. Barrett, C.J.; Mamiya, J.I.; Yager, K.G.; Ikeda, T. Photo-mechanical effects in azobenzene-containing soft materials. *Soft Matter* **2007**, *3*, 1249–1261.
202. Yager, K.G.; Barrett, C.J. Photomechanical surface patterning in azo-polymer materials. *Macromolecules* **2006**, *39*, 9320–9326.
203. Tuuttila, T.; Lipsonen, J.; Lahtinen, M.; Huuskonen, J.; Rissanen, K. Synthesis and characterization of chiral azobenzene dye functionalized Janus dendrimers. *Tetrahedron* **2008**, *64*, 10590–10597.
204. Tuuttila, T.; Lipsonen, J.; Huuskonen, J.; Rissanen, K. Synthesis and characterization of polyene chromophores with hydroxyl functionalization. *Dyes Pigment.* **2008**, *77*, 357–362.
205. Yokoyama, S.; Nakahama, T.; Otomo, A.; Mashiko, S. Intermolecular coupling enhancement of the molecular hyperpolarizability in multichromophoric dipolar dendrons. *J. Am. Chem. Soc.* **2000**, *122*, 3174–3181.
206. Abram, U.; Alberto, R. Technetium and rhenium—Coordination chemistry and nuclear medical applications. *J. Braz. Chem. Soc.* **2006**, *17*, 1486–1500.
207. Kim, S.K.; Lee, S.B. Highly encoded one-dimensional nanostructures for rapid sensing. *J. Mater. Chem.* **2009**, *19*, 1381–1389.
208. Finkel, N.H.; Lou, X.H.; Wang, C.Y.; He, L. Barcoding the microworld. *Anal. Chem.* **2004**, *76*, 353A–359A.

209. White, K.A.; Chengelis, D.A.; Gogick, K.A.; Stehman, J.; Rosi, N.L.; Petoud, S. Near-infrared luminescent lanthanide MOF barcodes. *J. Am. Chem. Soc.* **2009**, *131*, 18069–18071.
210. Yenziad, B.; Naik, H.; Amir, R.J.; Koning, C.E.; Hawker, C.J.; Heise, A. Encoded dendrimers with defined chiral composition via ‘click’ reaction of enantiopure building blocks. *Chem. Commun.* **2011**, *47*, 9870–9872.
211. Duxbury, C.J.; Hilker, I.; de Wildeman, S.M.A.; Heise, A. Enzyme-responsive materials: Chirality to program polymer reactivity. *Angew. Chem. Int. Ed.* **2007**, *46*, 8452–8454.
212. Vestberg, R.; Malkoch, M.; Kade, M.; Wu, P.; Fokin, V.V.; Sharpless, K.B.; Drockenmuller, E.; Hawker, C.J. Role of architecture and molecular weight in the formation of tailor-made ultrathin multilayers using dendritic macromolecules and click chemistry. *J. Polym. Sci. Part A* **2007**, *45*, 2835–2846.
213. Carnahan, M.A.; Grinstaff, M.W. Synthesis and characterization of poly(glycerol-succinic acid) dendrimers. *Macromolecules* **2001**, *34*, 7648–7655.
214. Carnahan, M.A.; Grinstaff, M.W. Synthesis of generational polyester dendrimers derived from glycerol and succinic or adipic acid. *Macromolecules* **2006**, *39*, 609–616.
215. Oelker, A.M.; Grinstaff, M.W. Ophthalmic adhesives: A materials chemistry perspective. *J. Mater. Chem.* **2008**, *18*, 2521–2536.
216. Oelker, A.M.; Berlin, J.A.; Wathier, M.; Grinstaff, M.W. Synthesis and characterization of dendron cross-linked PEG hydrogels as corneal adhesives. *Biomacromolecules* **2011**, *12*, 1658–1665.
217. Söntjens, S.H.M.; Nettles, D.L.; Carnahan, M.A.; Setton, L.A.; Grinstaff, M.W. Biodendrimer-based hydrogel scaffolds for cartilage tissue repair. *Biomacromolecules* **2006**, *7*, 310–316.
218. Berdahl, J.P.; Johnson, C.S.; Proia, A.D.; Grinstaff, M.W.; Kim, T. Comparison of sutures and dendritic polymer adhesives for corneal laceration repair in an *in vivo* chicken model. *Arch. Ophthalmol.* **2009**, *127*, 442–447.
219. Twibanire, J.K.; Al-Mughaid, H.; MacIsaac, E.; Huesis, M.; Grindley, T.B. Unpublished results.
220. Hirayama, Y.; Sakamoto, Y.; Yamaguchi, K.; Sakamoto, S.; Iwamura, M. Synthesis of polyester dendrimers and dendrons starting from Michael reaction of acrylates with 3-hydroxyacetophenone. *Tetrahedron Lett.* **2005**, *46*, 1027–1030.
221. Hirayama, Y.; Nakamura, T.; Uehara, S.; Sakamoto, Y.; Yamaguchi, K.; Sei, Y.; Iwamura, M. Synthesis and characterization of polyester dendrimers from acetoacetate and acrylate. *Org. Lett.* **2005**, *7*, 525–528.
222. Bo, Z.S.; Zhang, X.; Zhang, C.M.; Wang, Z.Q.; Yang, M.L.; Shen, J.C.; Ji, Y.P. Rapid synthesis of polyester dendrimers. *J. Chem. Soc. Perkin Trans. 1* **1997**, 2931–2935.
223. Bo, Z.S.; Zhang, W.K.; Zhang, X.; Zhang, C.M.; Shen, J.C. Synthesis and properties of polyester dendrimers bearing carbazole groups in their periphery. *Macromol. Chem. Phys.* **1998**, *199*, 1323–1327.
224. Do, J.Y.; Park, S.K.; Ju, J.J.; Park, S.; Lee, M.H. Electro-optic materials: Hyperbranched chromophores attached linear polyimide and dendritic polyesters. *Polym. Adv. Technol.* **2005**, *16*, 221–226.
225. Do, J.Y.; Jung, J.J. Polyester dendrimers carrying NLO chromophores: Synthesis and optical characterization. *Macromol. Chem. Phys.* **2005**, *206*, 1326–1331.

226. Romagnoli, B.; van Baal, I.; Price, D.W.; Harwood, L.M.; Hayes, W. Chiral poly(aromatic amide ester) dendrimers bearing an amino acid derived C-3-symmetric core—Synthesis and properties. *Eur. J. Org. Chem.* **2004**, 4148–4157.
227. Campbell, A.D.; Raynham, T.M.; Taylor, R.J.K. A simplified route to the (*R*)-Garner aldehyde and (*S*)-vinyl glycinol. *Synthesis* **1998**, 1707–1709.
228. Rosen, B.M.; Lligadas, G.; Hahn, C.; Percec, V. Synthesis of dendritic macromolecules through divergent iterative thio-bromo “click” chemistry and SET-LRP. *J. Polym. Sci. Part A* **2009**, *47*, 3940–3948.

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