Synthesis of Some Novel Chiral Dendrimers 1,1-Binaphthyl Derivatives

A dissertation submitted to The University of Manchester for the degree of Master of Science in the Faculty of Engineering and Physical Sciences.

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SCHEME:

ABSTRACT:

Despite a number of reports on synthetic methods for 1,1'- binaphthyl molecules with a substitution in certain positions, to the best of our knowledge neither the synthesis of binaphthyl-based chiral dendrimers by 1,3-cycloaddition reactions, "Click" chemistry, or attempts to achieve the substitution in multiple potential positions on binaphthyl cores has been studied yet. Previously reported optically active binaphthyl-based dendrimers have shown application in a number of applications, such as in asymmetric catalysts, enantioselective fluorescent sensors and chiral molecular recognition. Therefore, this project will focus on the synthesis of some novel chiral multiply functionalized 1,1'-binaphthyl molecules, including those that contain suitable groups to enable "Click" reactions and to facilitate the synthesis of some symmetric and asymmetric chiral dendrimers.

Declaration:

I declare that no portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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ACKNOWLEDGEMENTS:

In the name of ALLAH whom we thank and praise, God's blessing and peace are upon Prophet Mohammad and all Prophets. I would like to express my sincere thanks and great gratitude to my supervisor, Dr. John M. Gardiner, Senior Lecturer of Organic Chemistry in the School of Chemistry at The University of Manchester, for giving me the opportunity to study under his supervision and his continuous support, valuable guidance and helpful advice in beginning and completing my research. Also, I offer my sincere thanks to all of my colleagues in the Gardiner's groups for their kind helping and to all of my friends for their support. Special thanks to the Government of Saudi Arabia which is represented by the Ministry of Higher Education and to the Saudi Cultural Bureau in the United Kingdom for their support.

Finally and always, I send my warm wishes and sincere thanks to my loving and merciful father, mother, sisters and brothers who supported me with deep, tender feelings all throughout my life. And of course, all my love for my wife and daughter Shadn.

Chapter One

1. Introduction:

1.1 Historical Background:

Since the formation of the world, the environment has been, and will continue to be, a prime and steady source of inspiration to scientists. In the late 1970s, a random growth of tall, big-branched trees in central Michigan was a source of inspiration for Donald Tomalia, who used the structures as a model for the synthesis of huge-branched macromolecules now well-known as dendrimers.[1] The idea of repetitive branching increase was first reported in 1978 by Vögtle,[2] who applied it to the building of low molecular weight amines (Figure 1), and this was followed by the analogous and independent synthesis of true dendrimers by Tomalia´s group.[3]

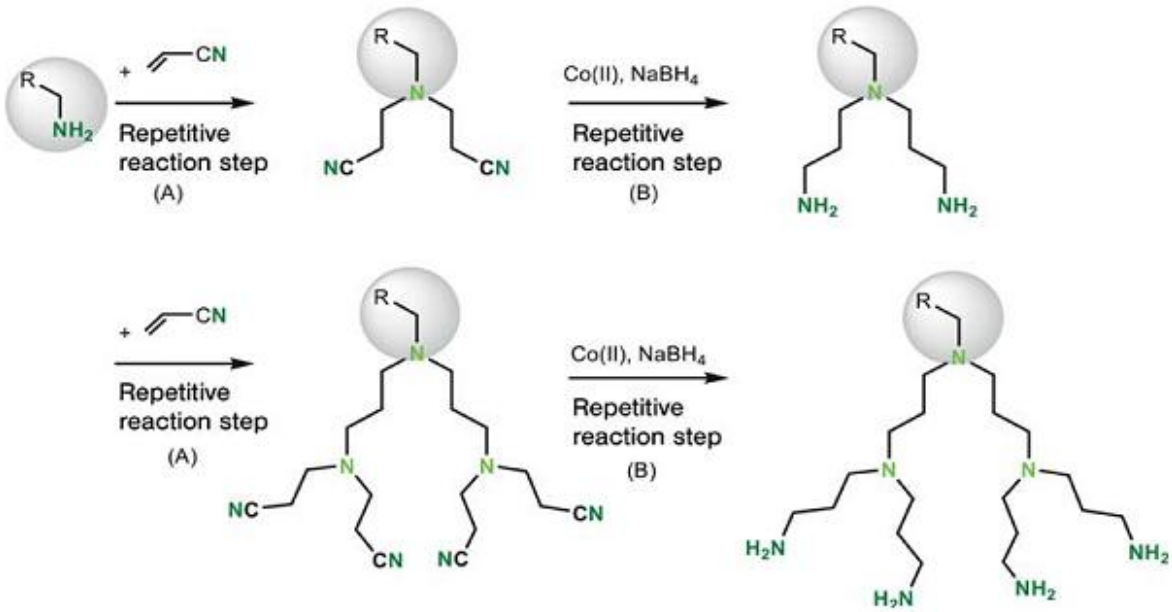


Figure 1: First synthesis of cascade molecules (according to Vögtle et al.).[4]

Although dendrimer synthesis was achieved by Tomalia's group in 1979,[3,4] the first full paper and public presentation on dendrimers was given by Tomalia at the Winter Polymer Gordon Conference in 1983. The preparation of poly(amidoamine) dendrimers appeared in this paper and was followed by several patents between 1985-1989.[3,5,6] Much scholarly attention was paid to dendritic polymer architecture, which continues to this day, but most of the major scientific journals were hesitant to accept research results for publication at the time.[7,8]

However, the amount of published materials has drastically increased since that first seminal paper in 1983.[3] (Figure 2)

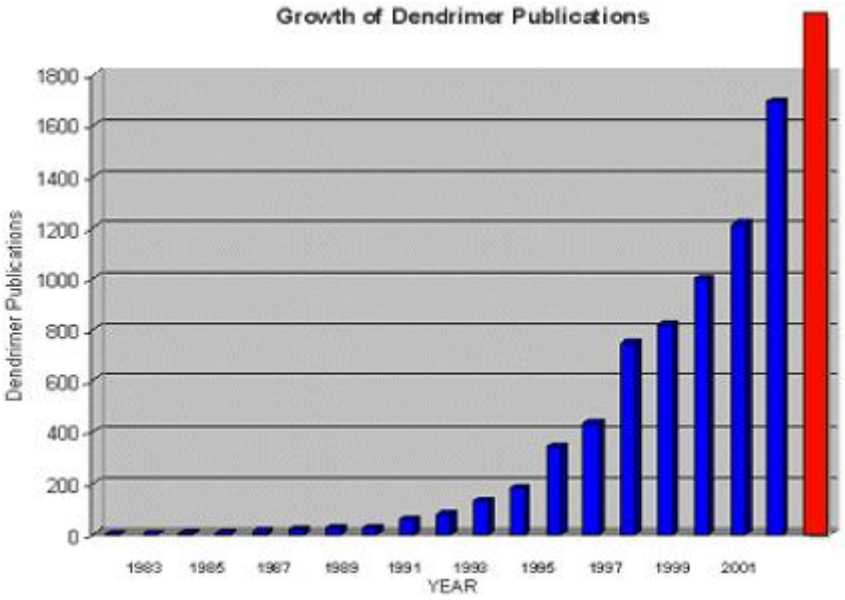


Figure 2: Growth of dendrimer publications

1.2 Definition of dendrimers:

The name "dendrimer" is derived from the Greek (*dendron* = tree and *meros* = part), and dendritic macromolecules are hugely branched structures consisting of a central core linked to a large number of chain ends, which are three-dimensional polymers with a tree-like structure.[9] The dendritically branched molecule was described as a cascade molecule and could be synthesised divergently via a cascade synthesis[10]. It has been described as Cascade,[2] Starburst,[3] Arborols,[11] Silvanols,[12] and Fractal structures[13], which are essentially a type of polymer.[14] The dendrimer macromolecule differentiates itself from normal polymers in two ways. Firstly, the dendrimer is constructed from $(AB)_n$ monomers (n is usually 2 or 3); in contrast, normal (AB) polymers contain a hyper-branched structure and produce linear polymers.[15]Secondly, dendrimers are synthesized in an iterative fashion.[16] These constructs come together gradually in a non-linear, synthetic growth in which the number of monomer cores included in each iteration are (AB_2), or (AB_3) in the previous generation.[17] Dendrimers are a new type of polymer, with a clearly molecular structure, and are produced via linking together branched monomers.[18]

1.3 Components of Dendrimers:

Dendrimers consist of three basic components: a core unit, generations and a surface region (Terminal functional group). (Figure 3)

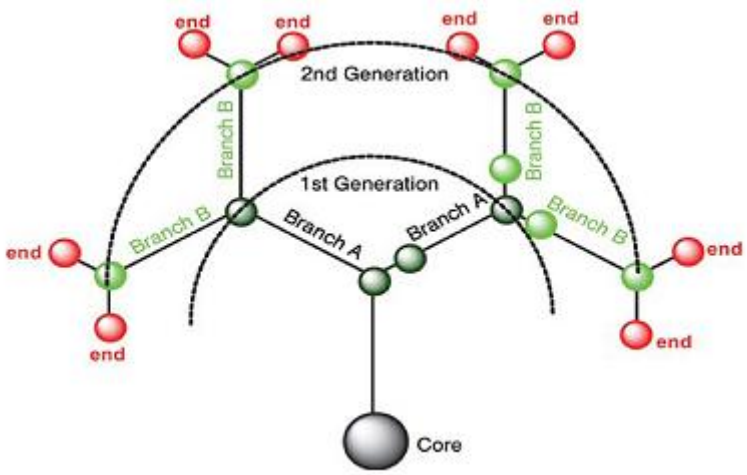


Figure 3: components of dendrimer.[4]

1.3.1 Core unit:

The core unit is the main unit to which the dendron is attached or grows by convergent [20]or divergent[2] methods. The core unit is the first component in the preparation of the dendron. In addition, during the synthesis and selection of the core unit it should consider the size, shape, and molecular centre from which the covalent connectivity are expressed to the generations that will affect the dendrimer construction.[20] The functional group at the core signals a position reaction to growing dendrimers,[21] for example a starting monomer (core unit) grows with two position reactions like 1, or with three position reactions like 2, or with three position reactions like 3; the many core units have developed as shown in (Figure 4) compounds 1, 2 and 3.[23]

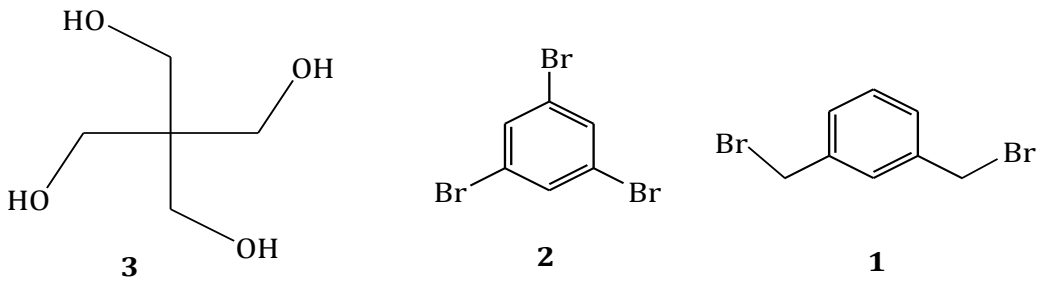


Figure 4: Examples of core unit

The steric crowding in the monomers can be overcome via the insertion of spacer groups to each arm of the core. The tetra bromide compound **6** reported by Newkome *et al*[24] is an example of this strategy that includes this improvement. This was adopted to raise the reactivity to compound **4** and its homologue compounds **5** and **6** (Figure 5).

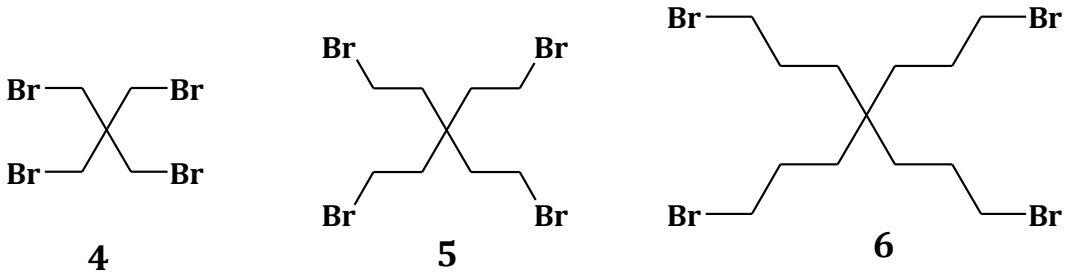


Figure 5: Examples of core unit developed to reduce steric factor on the core.

1.3.2 Generations:

The second essential component in dendrimer molecules is the generation; Lehn (1988) said,[25] "Molecules are to dendrimers what atoms are to molecules." This clarifies how essential the dendrimers' fragments. The generations are supplied to characterise the size of molecule within a given type of dendrimer. They are possibly linked by the surface region as the dendrimer grows and could also be linked with many various units. [26]

1.3.3 Terminal functional group (surface region):

The third and final essential components in dendrimer molecules are the terminal functional groups, which consist of either inactive or active terminal groups that are the external part of the dendrimer structure. The physical properties of the dendrimer are dependent upon the core units. Surface groups may be aliphatic or aromatic inactive groups such as ester, nitro, and benzyl groups, or active groups such as halogens, amines and acids. [26]

1.4 Synthetic methods of dendrimer:

There are three methods of dendrimer synthesis: divergent[2,3] synthesis, convergent [20,23] synthesis and click chemistry. The convergent method has been reasonably successful, so a

considerable amount of effort has been put in to improve its speed and synthetic efficiency. These attempts lead to increasingly new ways to make the convergent method faster (Figure 6).

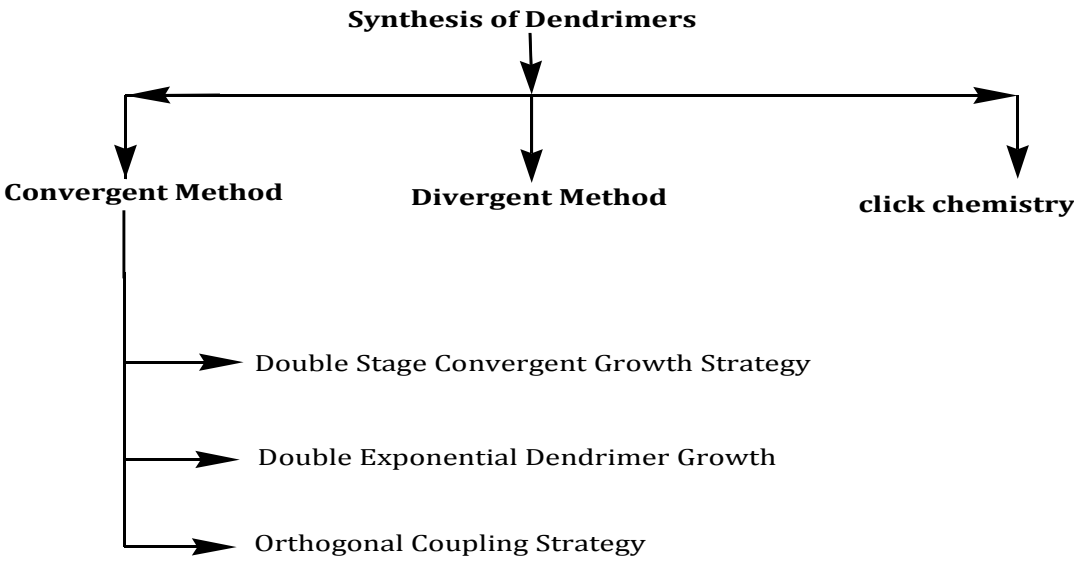
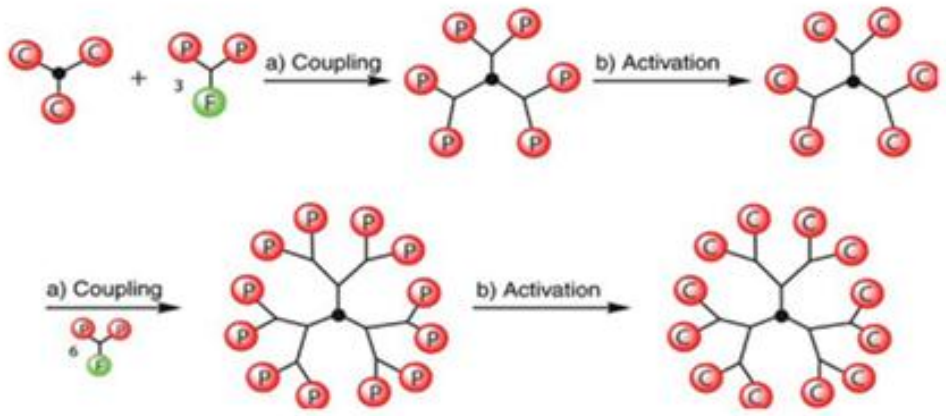


Figure 6: Methods of dendrimers synthesis

1.4.1 Divergent synthesis:

The first known syntheses of dendritic molecules, used by the research groups of Vögtle, Denkewalter, Tomalia, and Newkome, were divergent. The divergent method was used for early dendrimer synthesis; the name comes from the method in which the dendrimers grow around the core, diverging into space[2,3] while at the same time involving the growth of various dendron around a core unit. Adding these through several generations results in an increase to a wider three-dimensional when the final core of the dendrimer is synthesized [2,3] (Figure 7).



C = coupling points; ***F*** = active, unprotected functional group;
P = protected, inactive (protective group) functionality
Steps:
a) Coupling and; **b**) activation stand for a repetitive pair of steps for construction of the next generation.[4]

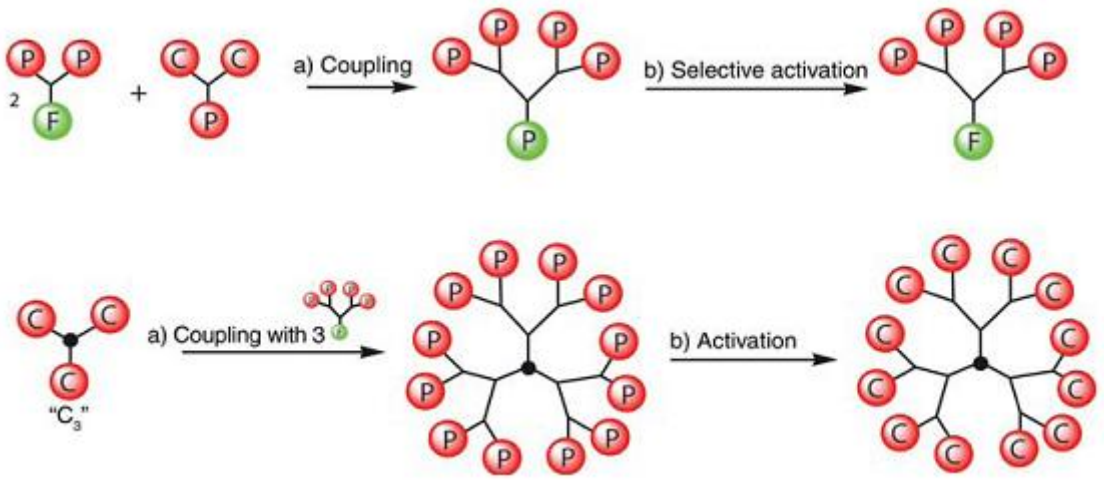
Figure 7: Divergent synthesis.

The divergent methods process starts from a multi-functionalised core building block. The first reaction step is the reactive coupling between site C and terminal functional F. Throughout the reaction, other functional groups of the branching unit are protected, as indicated by the letter P. After this step, the activation of the protection functional group P becomes a convenient place for a new active site to react with new branched units to increase generation in dendrimer molecules (Figure 7).[27]

1.4.2 Convergent synthesis:

The other major strategy for dendrimer synthesis is the convergent method; this methodology came about as a response to the limitations of divergent strategies. The convergent growth starts at what will end up being the surface of the dendrimer molecule.[20] It operates inwardly by gradually linking surface units together with more core units, *i.e.* the branched polymeric arms are grown from the 'outside-in'. The convergent method was first explained by Fréchet, Hawker, Miller and Neenan in 1989-1990.[20] In this method, the formation starts with what will become the external surface of the dendrimer. The huge dendrimer arms

are synthesized by a small number - usually two or three - of smaller arms linking together to a dendrimer molecule (zero generation), such as one from a protected group that could be easy to reactivate and two from active groups. The activation and deactivation procedures are tried again throughout the formation until a high number of generations have been achieved. Finally, by this procedures method and by using appropriate chemistry, the completed dendrons are joined to a functional group, a core unit that includes a small number - usually three - to synthesise the final dendrimers compound (Figure 8).[27]

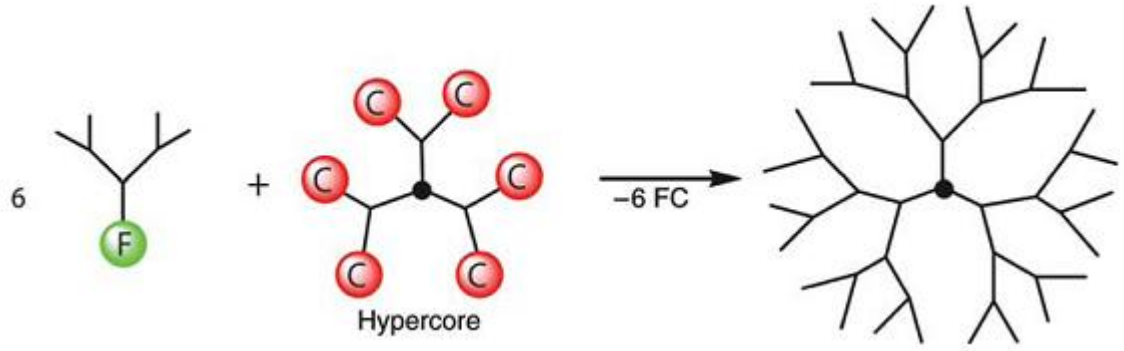


C = coupling group; F=functional group; P=protective group

Figure 8: Convergent synthesis.[4]

1.4.2.1 Double stage convergent dendrimer method:

The double stage convergent method was reported by Wooley *et al*,[23] and a new alternative of it is a combination of the convergent and the divergent method. This method contributed significantly to the synthesis of huge molecular weight dendrimers. The intention of this method was to reduce the number of synthetic steps and time required to synthesise huge dendrimers by saving and raising the yield. [20] There have been many researchers interested in the formation of big monomeric building blocks: AB_4 synthons called branched monomers or hypermonomers. (Figure 4).[27]



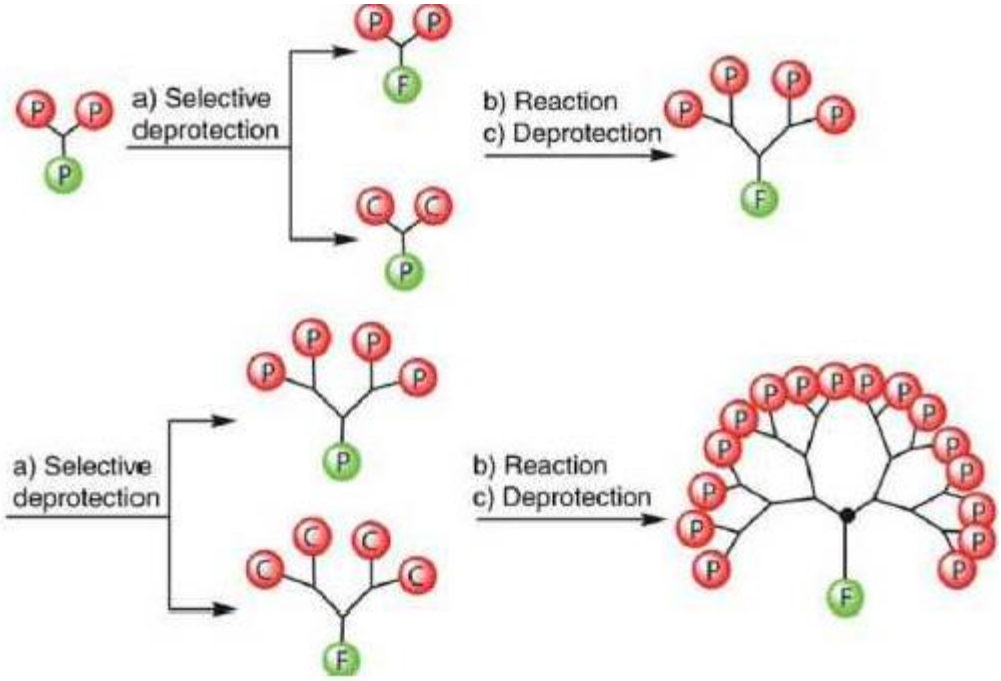
C=coupling group, ***F***=functional group

Figure 9: Double stage convergent method.[4]

This method's important step consists of linking an active functional group F with a small dendron, formed by convergent method, to a low generation functionalities dendrimer with the peripheral functionalities of the sites C, the hypercore, formed by divergent method.[27]

1.4.2.2 Double exponential dendrimer method:

The double exponential dendrimer method[28] begins with a protected brunching core and includes two protected linking places C and a protected functionality F. Selective deprotection is performed; for example, the functional group F was activated in one of the two activated linkage units and one of the branching units was in the other. As a result, a second generation dendron has been synthesized by allowing two branching units in active groups F (green color in Figure 10) to react with a group of two linkage places C (red color in Figure 10) and to reach to a higher generation dendron via repetition of the synthesis. The high molecular weight dendrimers double synthesised over just three to four steps. [27]

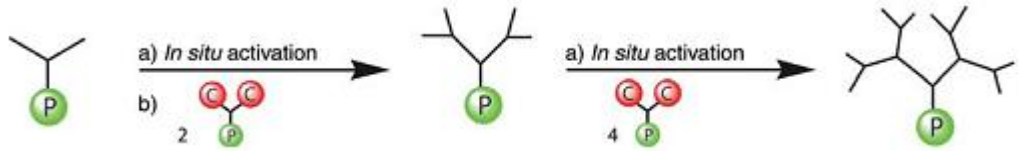


C=coupling group, ***F***=functional group; **P**=protected group

Figure 10: Double-exponential method.[4]

1.4.2.3 Orthogonal coupling dendrimer method:

The double exponential dendrimer method [28] and double stage convergent method[23] have been successful in dendrimer syntheses. However, the synthesis of dendrimers in both of them has needed to protect the peripheral groups, which lead to a few difficulties.[20] Consequently, the idea of the orthogonal coupling dendrimer method (figure11) was developed in order to overcome the difficulties involved with the double exponential dendrimer and double stage convergent methodology.[28] In this methodology no activation step is required. Two different branching units with complementary coupling functions are alternated, and the linkage product can be activated in place of the needed following reaction or linking but it must be inert towards the following reaction conditions (Figure 11).[27] The orthogonal coupling dendrimer method has found great success in the rapid synthesis of high generation numbers of dendrimers, but it has not been used very widely because the structural blocks have to meet very stringent requirements. [20]



C=coupling group; ***P***=protected group.

Figure 11: Orthogonal synthesis.[4]

The first application of the orthogonal coupling dendrimer method was reported by Zimmerman and Zeng,[29] where the synthesis of higher-generation dendrimers-dendrons up to generation six-based on the use of alternating Sonogashira reactions and Mitsunobu esterifications produced heterogeneous dendrimers possessing an alkynes and ester coupling in an alternating sequence.[27]

1.5 Comparison between Convergent Method and Divergent Method:

Both the convergent and divergent method are capable of forming hyper-molecular weight dendrimers, and indeed dendrons. Making use of either a convergent or divergent method or any other previous methods could aid the synthesis of the target dendrimers. The convergent method has certain advantages over the divergent method, although both of them give the same final properties and structure (Figure 12).

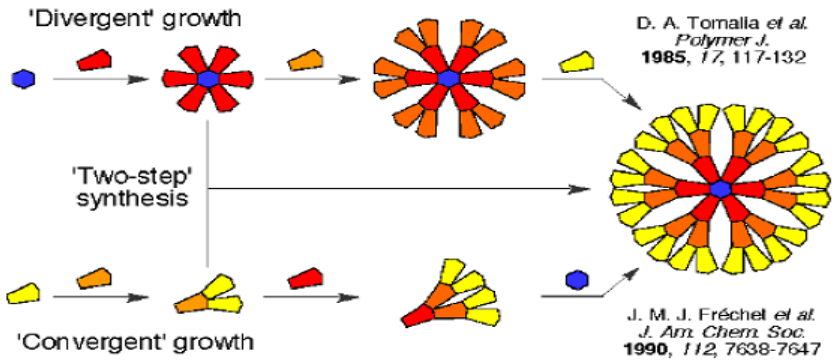


Figure 12: Comparison between Convergent Method and Divergent Method.[30]

1.5.1 Advantage and disadvantages of the divergent method:

The advantage of the divergent method is its capability for building hyper-generation dendrimers, as the amount of construction blocks that can be added is dependent upon the available reactive places on the surface of the dendrimer. This can lead to an exponential rise in

the amount of generations. [2,20] The disadvantage of the divergent approach is the fact that a big amount of monomer cores are needed to react both successfully and simultaneously with the growing dendrimer. A complete reaction is obtained easily at first, but with bigger generations there is a delay to react for each group on the surface.[24] In the previous generation, side or defective synthesized products can be allowed (ending in the final dendritic structure), but some defects result in a discontinuation in the production. In the divergent method, excess numbers of equivalents of reagent are required to ensure adequate reactions. Throughout the formation of the hyper-generation, dendrimers are vitally needed to remove excess reagents after every cycle. In the divergent method it is difficult to produce different dendrimers as those needed through the deprotection - protection scheme.[2,20]

1.5.2 Advantage and disadvantages of the Convergent method:

The advantages of the convergent method were that a limited amount of growth reaction for every sequence is needed to lead the properties to carefully control molecular weights, and to produce material having functionalities, positions and amounts within these material, and to prevent the construction of side products known as one of the major problems consuming cost and time. In the convergent method it is possible to put different types of dendrons into one dendrimer.[20] The disadvantages of the convergent method are that an active location for putting together the dendron to the monomer units in order to obtain a bigger dendron becomes extremely crowded by the increasing amount of generations. These results in incomplete linkage reactions, and for the same reason the attachment of the dendron to the core in order to get the dendrimer formed becomes difficult to reach because of factors caused by the dendron's arms, which at a bigger generation around the active position on the dendron impedes a complete reaction with the core's active positions. A convergent method depletes time and uses expensive materials, as purification is needed at every step of synthesis.[20,30]

1.6 Characterization of Dendrimers:

Dendrimers are classified by the procedures usually coupled with organic chemistry, namely ^{1}H, ^{13}C NMR, IR, mass spectroscopy and chromatography.[31] The crucial evidence of the

molecular structure is achieved by the determination of a crystal structure.[32] However, this procedure is of little use. The polymeric nature of dendrimers generally leaves their solid-state structure without any long-range order. Even when some degree of structure is present, for example in the case of extremely crowded surface dendrimers, there is such a large degree of disorder in the inside generations that a crystal structure cannot be obtained.[31] However, there are examples reported[33,34] for crystalline dendrimers, single crystal X-ray studies and powder of dendrimers, but these are confined to low generation and rigid, inhibited molecules, like the one shown in (Figure 13).[35]

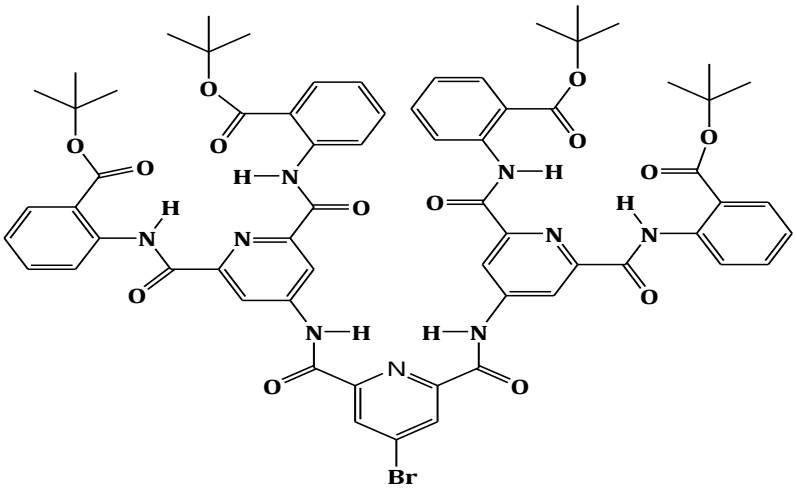


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Figure 13: Formation of crystals are limited to rigid dendrimers.

Mass spectroscopy and Nuclear Magnetic Resonance (NMR) spectroscopy are both crucial procedures that are usually used in the classification of dendrimers. In fact, the ^{1}H and ^{13}C NMR spectra of dendrimers have the ability to be surprisingly simple, and these spectra are able to give information about any impurities in dendrimer compounds.[20,31] The mass spectrometry analysis of dendrimers has been widely used and helpful from the soft ionisation procedures originally developed for cases such as the study of large bio-molecules. Many results have been achieved by the mass spectrometric, Electro Spray (ES) processes and IR spectroscopy for interior and end groups. In addition, Electron microscopy has been utilized in

the idea of dendrimers and their collection, and Gel Permeation Chromatography (GPC) has been utilized for the calculation of radii of gyration, hydrodynamic radii and polydispersities.[31]

1.7 Nomenclature of Dendrimers:

Like other known polymers, (macro) dendritic molecules are able to be named by IUPAC nomenclature rules. However, they are not always all-inclusive to be able to be adequately and clearly named; for example, in the case of complex structures dendritic molecules. Using either IUPAC or chemical nomenclature was not possible for researchers to use for retrieval purposes because they needed long names.[11,26,27] In 1992 Newkome suggested[36] a new nomenclature system for the nomenclature dendrimer on the basis of the cascade molecules. This modular naming system for dendritic molecules starts with the number of outside terminal groups. After the class designation 'cascade', the individual branches are enumerated and the individual generations separated by punctuation starting from the core. The terminal groups are then characterised. Compounds named using this system have the general form: [27,36]

Z cascade: core building block, [N_{core}]: (branching unit) ^{G} : end groups.

Z: number of terminal groups, N_{core}: core multiplicity

G: number of generations with branching building blocks

1.8 Applications of Dendrimer Compounds:

Since the introduction of low cascade molecules by Vögtle,[2] the quick development of dendrimers has led to their adoption and application in an interesting, still growing, range of research areas.[31,37] Dendrimers can be formed for possible applications in a wide multiplicity of different areas. The different characteristics of big dendrimers compared to their classic polymeric correlation creates fascinating compounds for further study in these molecules in catalysis,[38,39] biomedical anti-adhesion agents,[40] host-guest chemistry,[41]drug delivery agents, ,[43] gene transfer vectors,[43] dyes,[44]chromatography,[8]and many other fields.

1.8.1 Dendrimers as catalysts:

One of the essential applications for dendrimer compounds has been in the area of catalysis.[38,39] Heterogeneous catalysts are insoluble in reaction solvents, thus the reactions take place at the interface between two phases. This catalysis can result in a negative impact on efficiency. However, homogeneous catalysts are soluble in the reaction media and can be very capable but recovering these catalysts is difficult and costly. On the other hand, heterogeneous catalysts can be recovered which is essential with regard to costly catalysts. A homogeneous catalyst that can be recovered by less costly procedures like filtration is required to obtain the desired. In attempting to address these problems and to obtain superior catalysts, chemists turned their attention to dendrimers. [38,39]Homogeneous and heterogeneous catalysts both easily become greatly influential[103] as a result of their large size when compared to the product and because they can be removed from the reaction medium via a membrane and/or ultra-filtration procedure. However, catalytic sites can be included within the dendritic structure in a number of ways: peripheral functionalised dendrimers,[45] central or focal point functionalised and dendritic catalysts featuring catalytic site at a branched point. [38,39] (Figure 13).

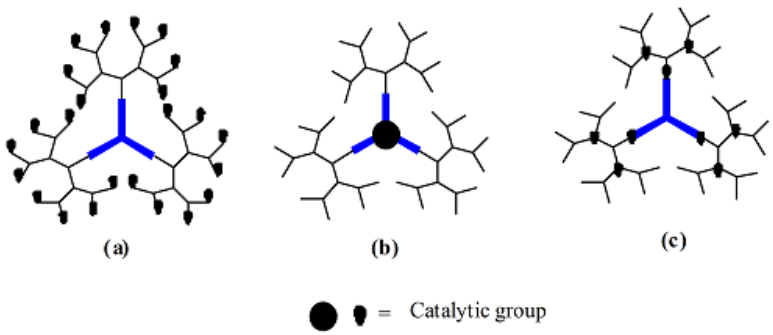


Figure 14: The regions within a dendrimer where catalytic groups can be attached (a) Periphery (b) core (c) interior.[46]

To be "chiral" means it cannot be superimposed upon its mirror image; chirality can occur in the three-dimensional structure of molecules. Both the symmetry and asymmetry present in a molecule's objects has attracted the interest of chemists. Three-dimensional symmetry in macromolecules or nanosize structure is encountered within the domain of

dendrimers and hyper-branched polymers.[46] Many studies have described the production and analysis of chiroptical characteristics of dendrimers aimed at comprehending the fundamental relationships between molecular and macroscopic chirality aimed at reaching new materials whose makeup and performances depend on the chirality at a macromolecular level.[47] The addition of chirality to dendrimers' molecules has been an important of research. Asymmetry within these highly "symmetrical" dendrimers, a contradiction in terms, is indeed introduced.[16] Incorporating chirality can alter the physical makeup of the dendrimer, like refractive index and optical rotation, which can cause reasonable effects that may be useful for applications in medicine and drugs synthesis. Of course, chirality can be brought into different positions within a dendrimer compound. The first to classify the different possibilities of inserting chirality within the dendrimer compounds was Seebach *et.al*.[48] However, the chiral dendrimers described so far in the literature can be classified to one of the following groups accordingly:

1.8.1 Dendrimers with a chiral core and achiral branches:

Dendrimers having a chiral core and achiral branches were first reported by Seebach *et al*. [48] They studied and synthesised chiral dendrimers up to the third generation based on a tris(hydroxymethyl)methane core unit 8 linked to aromatic polyether dendrons (Fréchet type)[20] 9 (i-ii) with aromatic spacers 10 (i-iii) and with aliphatic spacers 11 (i-iii), as shown in (Figure 15).

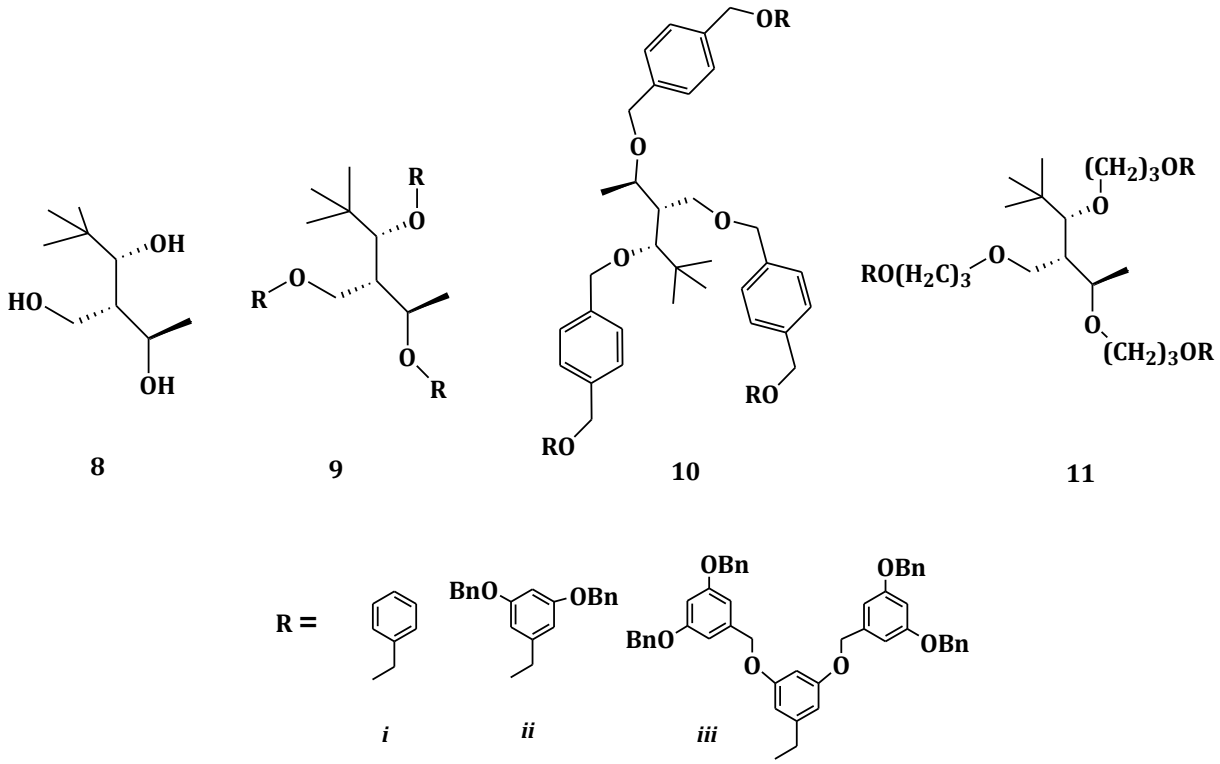


Figure 15: Chiral dendrimers based on a tris(hydroxymethyl)methane core unit and aromatic polyether dendrons (Fréchet type).

Studies of the chiroptical makeup revealed that in the case of the branched system featuring an aliphatic spacer 11 (i-iii) between the achiral dendrons and the chiral core unit, both molar and optical rotations were minimal for every generation because the loss of chiral information was a dilution effect that has been predicted to happen when achiral branches are anchored to a chiral core[49] and the increased flexibility of the dendrons are induced by the aliphatic spacer linker. When the same chiral core unit that was coupled to the aromatic polyether dendrons directly 9 (i-iii) or *via* a rigid aromatic space moiety 10 (i-iii) a different chiroptical makeup is measured in case 10 (i-iii) the molar rotation values were virtually constant as the generation number increased from the first to third. This trend indicates that the chirality of the core unit is maintained but does not induce chiral substructures within the hyperbranched macromolecules. In the same study, when the dendrons were coupled directly to the chiral core unit 9 (i-iii) (*e.g* neither aliphatic nor aromatic spacer were involved), the molar rotation decreased slightly from the first generation 9 (i) to 2nd generation 10 (ii)

dendrimers, but then almost doubled upon progression to the third generation 10 (iii). Seebach also described the chiroptical properties of related dendrimers that have the same chiral tris(hydroxymethyl)-methane core unit 8 but were instead coupled to rigid polyamide aromatic dendrons 12 (i-iii) **(**Figure 16). However, many studies have demonstrated that these observed anomalies in the optical activity of dendrimers possess a chiral core that cannot always be attributed to induced conformational order with the dendritic architecture. Several structural and conformational factors have to be considered when interpreting the chiroptical makeup.[50]

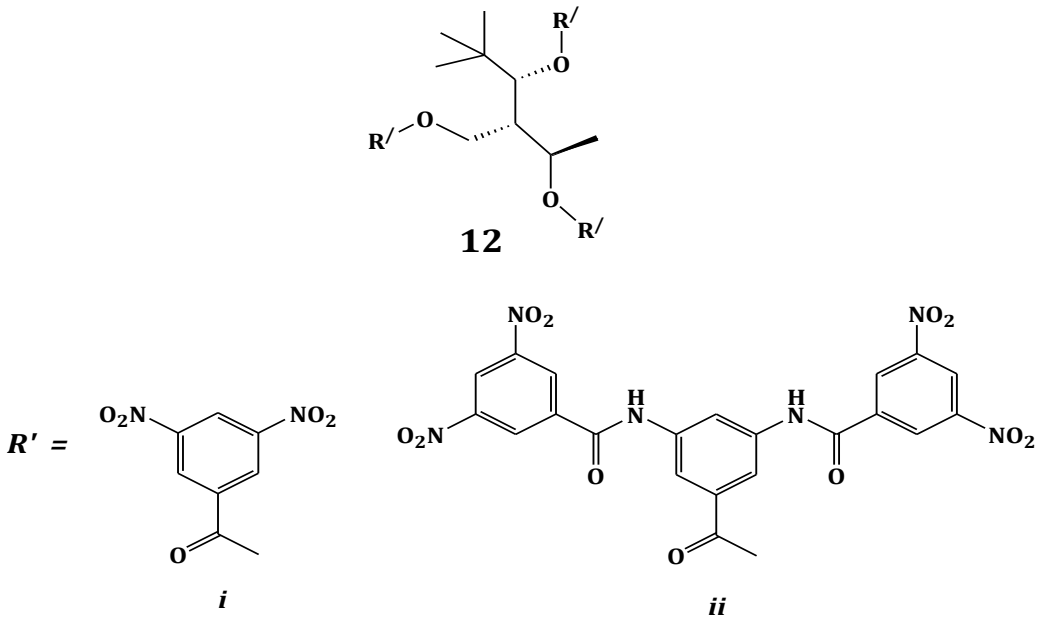


Figure 16: Chiral dendrimers based on a tris(hydroxymethyl)methane core unit and polyamide aromatic dendrons.

1.8.2 Dendrimers with chiral end groups:

In 1991, the first study on dendrimers possessing a chiral peripheral surface was reported by Newkome *et al.*[51] They produced polyether amide dendrimers up to the second generation with enantiomerically pure tryptophan moieties at the surface.[11] Their study observed that the chiral amino acid residues are independent from each other and do not induce any additional chiral substructure upon the dendritic framework.[51] Similar results were achieved by Chow and Mark[52] who explained the synthesis and studies of chiral dendritic fragments up to the third generation featuring L-tartrate derivatives between 4-*tert*-

butylphenyl end groups and the branching monomers. The molar rotation values of these tartrate-based dendrimers were directly proportional to the number of chiral units at the dendritic surface, indicating that the chiral units were independent of each other. Meijer *et al*. Reported[53] very interesting chiroptical properties of PPI dendrimer that was done with a range of tert-butyloxycarbonyl (Boc) protected amino acids (Figure 17). The optical rotation values observed for this series of chiral macromolecules reduced as the generation number of the dendrimer increased. This phenomenon was evident for all the amino acid dendrimer derivatives, but was most pronounced in the case of the dendrimers bearing sterically inhibited amino acids like *t*-Boc-L-lysine, *t*-Boc-L-phenylalanine, and *t*-Boc-L-tyrosine. This unanticipated behaviour could not be explained by the reduction of the amount of chromophores with respect to the molecular weight of the dendrimer, as this ratio remains constant throughout the series (the number of the amino acid residues and the molecular weight double in each new generation). In addition, other reasons, for example temperature and concentration, did not affect the optical rotation values observed for these dendrimers, as identical rotations were observed at different temperature and concentration. However, a reasonable dependence of the optical activity upon the solvent was observed, and this trend mirrored the solvent dependency of the optical rotation of the corresponding free amino acid. The spectroscopic data indicated that a change of the local environment around the peripheral amino acid was occurring at higher generation and was related to an increased packing density at the dendrimer surface. This dense peripheral packing is reinforced by multiple hydrogen bondings between the amide and carbamate groups of the amino acid and protecting group, respectively. The maintenance of the optical activity for each generation dendrimer when the carbamate moieties were changed with acetal groups that cannot form hydrogen bonds so readily, confirmed hydrogen bond formation at the PPI dendrimer surface. Since the chiroptical makeup of the amino acid residues at the PPI dendrimer peripheral surface proved sensitive to the local surroundings, it was argued that numerous chiral conformers are formed under non-equilibrium conditions, forced by the dense packing and hydrogen bonding. The difference of the protected amino acid at the

dendritic surface caused an internal compensation effect within the dendrimer, thus leading to a decrease in the optical activity values observed. This theory was confirmed by coupling more rigid chiral moieties (such as camphorsulfonyl amide and camphanic amid whose chiroptical properties are independent of the local environment) to the peripheral surface of PPI dendrimer backbone. In these cases the optical rotation values observed were constant for each generation number of the PPI dendrimers (Figure 17). The results obtained for these modified PPI dendrimers do not imply that the dendrimer surfaces possessing these rigid chiral units are not densely packed, but that the packing does not have an effect upon the conformational equilibrium and thus all the chiral molecules are able to adopt the same conformation.[38,53]

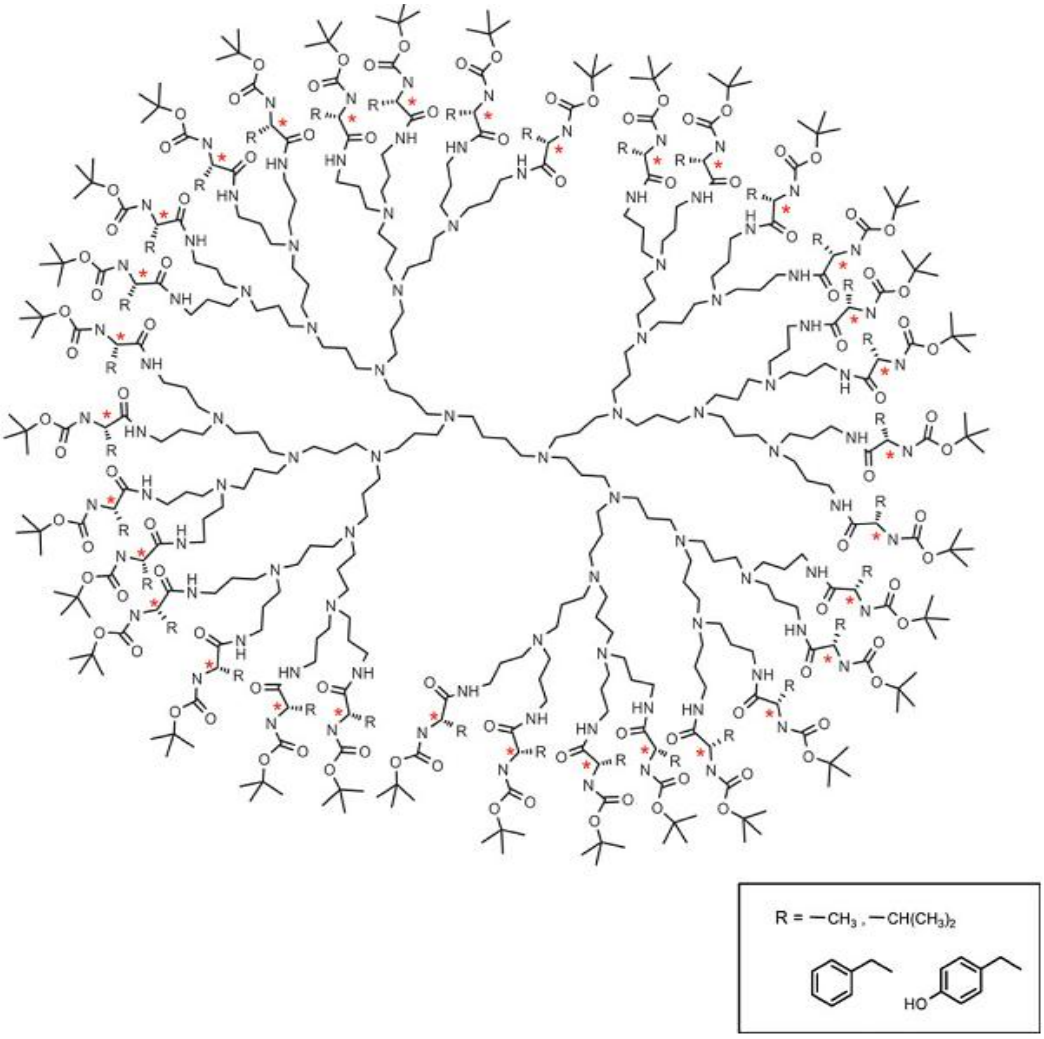
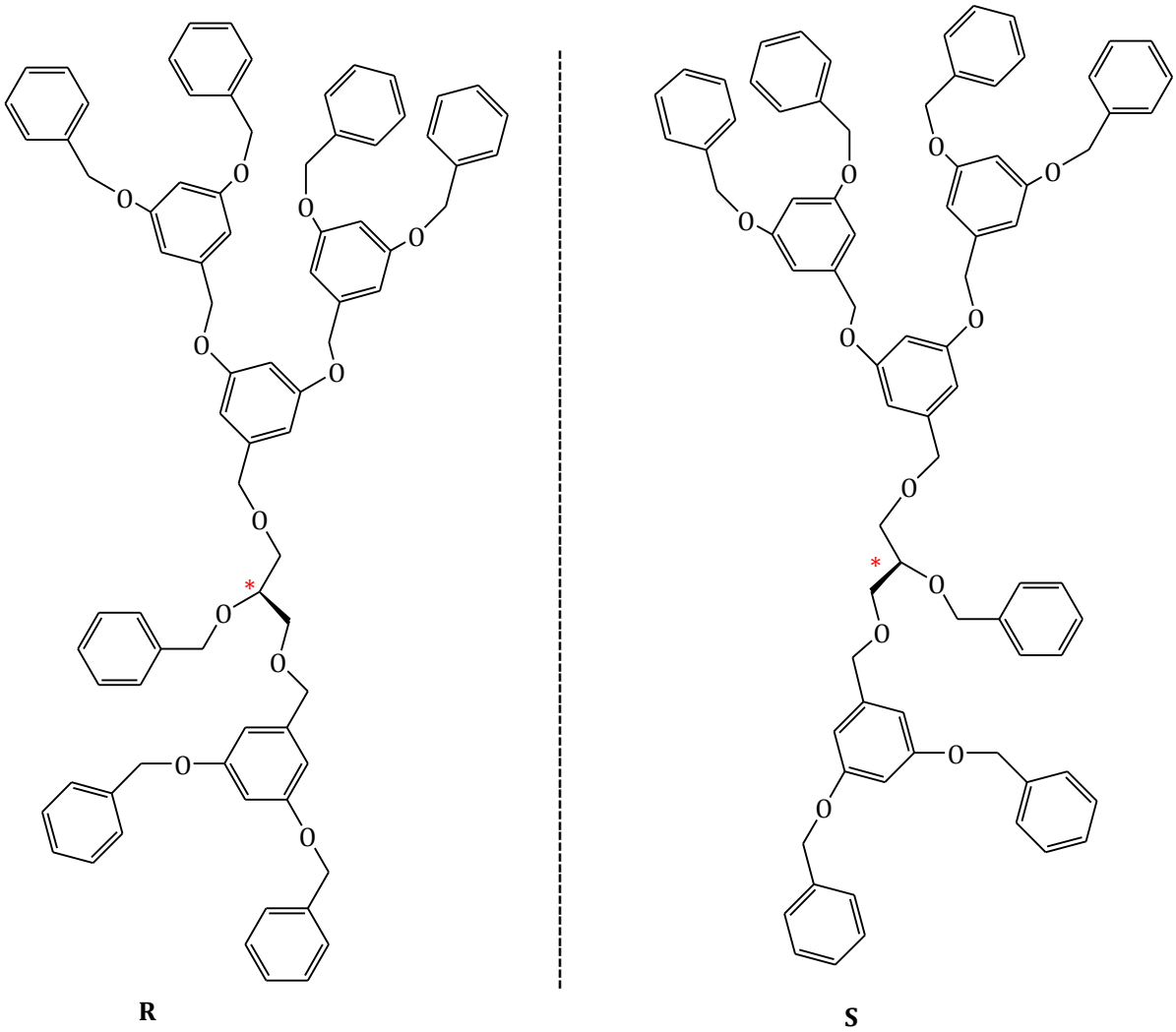


Figure 17: A chiral PPI dendrimer peripherally functionalised with tert-butyloxycarbonyl (Boc) protected amino acids.[4]

1.8.3 Dendrimers with an achiral core and different branches:

The first report of dendrimers with an achiral core and different branches was recorded by Meijer *et al.*[54]who researched the chiroptical properties of racemic dendrimers. The production involved linking a pentaerythritol core and diverse generations of aromatic polyether (Fréchet type)[20] dendrons. However, throughout his research the dendrimers still could not be isolated in their enantiomerically pure form when chiral HPLC analysis was used. Their incapability to achieve pure enantiomers meant that they were not capable of measuring the optical properties, but ^{1}H NMR spectroscopic researches showed that the resultant dendrimers have a stratified structure and the ordering of that was obvious when deuterated chloroform was utilized as solvent. The benzylic methylene protons of every different dendron resonated as separate sharp singlets. The presence of resolved signals in the ^{1}H NMR spectra for such similar methylene protons cannot be reasoned by the differentiation of electronic properties in each of the constitutionally different dendrons by the chiral core. Consequently, Meijer planned for these macromolecules to adopt an overall chiral shape in solution. Its structure depends on the solvent utilized. At the opposite of deuterated chloroform, the benzylic methylenes resonate as unresolved signals in both Deuterated benzene and 1-phenylazo -2-naphthol-d_5 solution (C_6D_5N).[54]Also, the Eindhoven-based group[55] have prepared enantiopure chiral dendrimers by linking different generations (the 0th, 1st and 2nd) of Fréchet type dendrons[20] and benzyl bromide monomer units to both enantiomers chiral glycerol derivatives 13(*R-S)*, respectively (Figure 18). Remarkably, the optical rotation analysis of these non-racemic glycerol derivatives has not shown any detectable optical activity. Molecular modeling research revealed that the two enantiomers depend on very similar conformations, and the chirality is in effect 'hidden'.[31, 54]



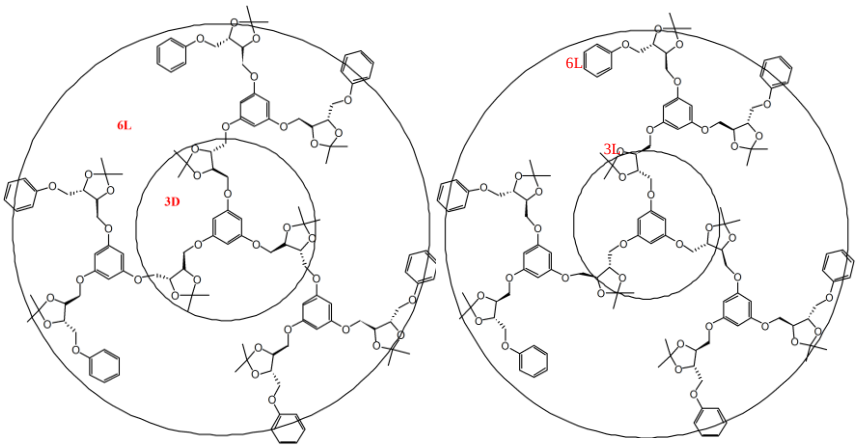
13

Figure 18: Eindhoven et al. chiral dendimer represent the first example reported for cryptochirality.[56]

1.8.4 Dendrimers featuring chiral branched units:

Chow et.al. [56] argued that chiral dendritic co-polymers bear more than one kind of chiral unit. They prepared dendrimers up to the second generation by using tartaric acid derivatives chiral spacer unit in both D and L forms between phloroglucinol branching units and by bringing together the achieved chiral tartrate units of both heterochiral 14 (Figure 19) and homochiral **15** (Figure 19) dendrimers configurations. The interesting point was observed that the carbon and proton spectra of the diastereomeric dendrimers were almost super-imposable, indicating that the central and peripheral phloroglucinol ring of the diastereoisomers existed in nearly the same chemical microenvironment irrespective of the configuration in the branches of

chiral. In addition, a preliminary study of the chiroptical properties showed that each of the chiral dendritic units contributed and was independent of the molar rotation with the same absolute value. A comparison of the CD spectra for each of the synthesised diastereoisomers containing L- and D- tartrate spacer units both in a reversed ratio and in different stations, unveiled that the 'end impact' was helpful when both the opposite chiral units were present in the same layer. The explanation for this was attributed to the idea that the external tartrate layers of the dendrimer were slightly different chiroptically from the internal layers.[56] Completely different results were found by Sharpless *et al*.[57] who argued that the production of chiral dendrimers that used benzene-1,3,5-tricarbonyl tri-chloride as the central core and asymmetric diol branching units up to the fourth generation derived from styrene. In this example, the molar rotation was proportional to the number of chiral units present, which shows the lack of any chiral secondary structure.



14 **15**

Figure 19: a) Hetero-chiral dendrimer incorporating tartaric acid linker units and phloroglucinol branching moieties. **b**) Homo-chiral dendrimer incorporating tartaric acid linker units and phloroglucinol branching moieties.

1.8.5 Chiral dendrimers with a chiral core, asymmetric branching units and optically active end groups:

Many dendritic systems exist with the characteristics of a chiral core, asymmetric branching unit, and optically active end group, like completely chiral dendrimers. [58] The first case of a dendrimer of this class was shown by Denkelwalter *et al.*[59] They produced poly(α,ε-L-lysine) dendrimers using a divergent approach. After this, the formation of many other dendrimer systems that were based on optically active natural construction blocks, for example amino acids[60] carbohydrates[61] and nucleosides,[62] have been reported. Notably, only a few extensive research efforts of the chiro-optical properties for systems of this class have been published in scholarly literature.[60,61,62,63] Tam *et al*. have shown [64] that the efficient formation of fully chiral dendrimers were based upon a tetravalent lysinil core peptide and peptide segments containing twenty amino acid each. The study of the optical properties of hyper-branched peptides revealed that exciton linked in the CD spectra corresponding to helical peptide conformation were elevated, as in the example of multi-peptide arm dendrimers in comparison with the analogous single strand peptide sequences. These CD data specify a fascinating class of cooperative reactions between dendrimer branches with a resulting formation of high stable conformation. The production of the first bile acid-derived chiral dendrons up to the second generation was reported by Maitra *et al.*[65]. In contrast to the polypeptide dendrimers shown by Tam *et al.*[64] chiral secondary construction was absent in these bile acid hyper-branched polymers as unveiled by the molar rotation values. These chiroptical properties were found to be proportional to the number of bile acid units present. The chiroptical studies showed that the molar rotation behaviour of these depsipeptide-based dendrimers linked with the amount of the dendrimers constituent chiral building blocks. The first case of an actuated configuration chiral substructure for fully chiral dendrimers was published by Seebach *et al*. who detailed the convergent construction of dendrimers incorporating derivatives of chiral tris(hydroxymethyl) methane units 8 (Figure 15). Seebach watched that when the chiral core with configuration (*R,S,R*) 8 (Figure 15) was joined with chiral dendrons of the first generation with either the *(R)*

or *(S)* configuration at the benzylic stereogenic center, the reaction proceeded in an efficient manner. However, when the same (R,S,R) core 8 was joined with the second generation chiral dendrons (Figure 15), only the branches with (*S*) 16 configuration at the benzylic stereogenic center gave the trisubstituted result; however, under the forced condition, the dendrons with (*R*) configuration 17 (figure 20) gave only the disubstituted result. Interestingly, when both the second generation dendrons with *(R)* or (*S*) configuration 16 and 17 (figure 20), respectively, were linked to the central chiral core that had the opposite conformation (*S,R,S*), triply branched dendrimers were synthesized. In addition, the combination of diastereomeric second generation polyether dendrons of this class and a variety of analogous chiral core systems have shown a degree of variability in the reaction efficiencies between the chiral core and dendrons. Some combinations led to the capable configuration of the fully substituted dendrimers but other dendrons/core combinations did not. In some of these systems, the only configuration that differs is that at the central core, thereby suggesting that a different macromolecular recognition process is in operation, giving either a fit or misfit of the chiral components. The itemized studies of the chiroptical properties of these hyper-branched macromolecules explained that the specific rotation and molecular ellipticity of all the dendrimers synthesized as a part of this study were comparable to the predicted values calculated by a simple summation of the values achieved from model compounds that were structurally related to the building blocks in different positions within the dendritic system. The only exception of this series of full chiral dendrimers was the second generation dendrimer with (*R,S,R*) configuration at the central core and dendrons having the (*S*)-configuration at the benzylic centers, whose special rotation and molecular ellipticity deviate clearly from the values expected and had a reversed sign from negative to positive. This result could further reveal the presence of the chosen macroscopic chiral conformation that contributes to the optical activity.[66]

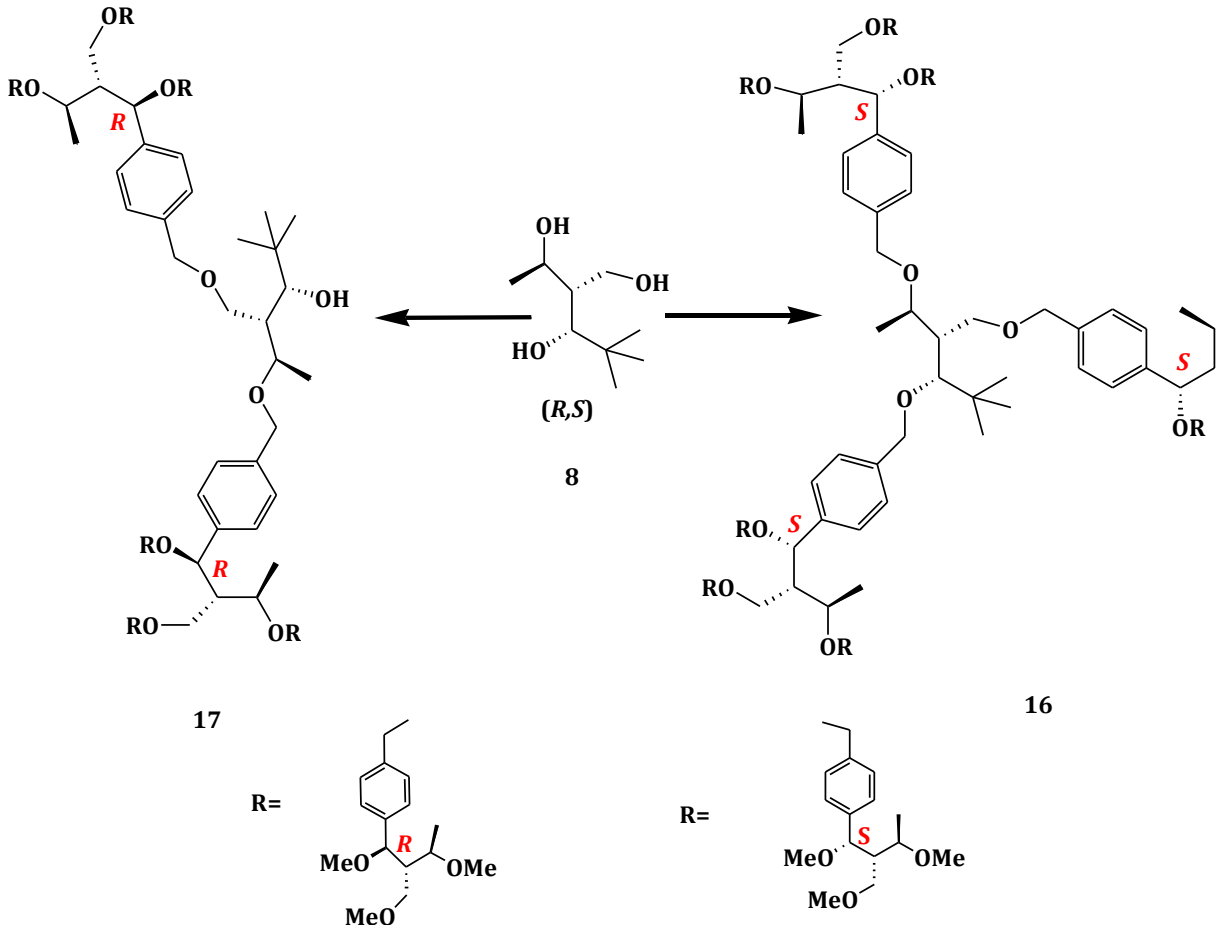


Figure 20: Seebach *et al*. induced conformational chiral substructure for fully chiral dendrimers.[67]

1.9 Binaphthyl-based chiral dendrimers:

In 1971, racemic 1,1-binaphthyl was discovered by Pincock et al. to undergo unprompted resolution to create the optically active R or S enantiomer when this R or S enantiomer was crystallized after melting.[67] A lot of crystallization experiments of rac-1,1-binaphthyl were studied, and the possibility to synthesise of the R or S enantiomer was improved about the same. The 1,1-binaphthyl-based chemistry was often used as the starting material to chiral compounds.[69] The feature of this compound is that there is some position to prepare binaphthyl derivatives because the presence of selective functional (3,3; 4,4 and 6,6-positions) and hydroxyl groups could be easily changed to other functional groups. For the reason of the importance of the 1,1-binaphthyl, much interest has been dedicated to preparing it in an optically pure yield and a lot of techniques have published. One of these ways is the utilization of (8*S*,9*R*)-(-)- *N* -benzylcinchonidinium chloride to resolve racemic BINOL into its optically pure *(R)* and *(S)*-enantiomers (Figure 21). There is great interest because of its efficiency and simplicity when utilized, and high optical purity could be had by using this method. The chiral configuration of BINOL is thermally stable. [70,71,72,73]

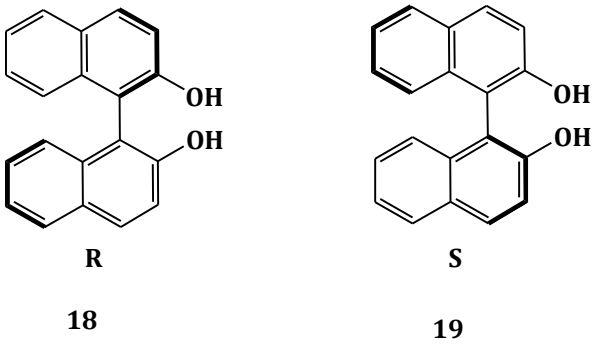


Figure 21: optical of racemic BINOL

Even now the monomeric chiral binaphthyl compounds are an active research subject and multiple binaphthyl units has coupled with many different generations to form molecular and polymers of specific constructions and properties. Over a decade ago, more research was mounted to find a use of BINOL to build a configuration of various chiral polymers, macrocycles, dendrimers and functional BINOLs, which discovered applications of these materials in asymmetric catalysis and studied their optical and electrical properties. [74]

Chapter Two

2. Results and Discussion:

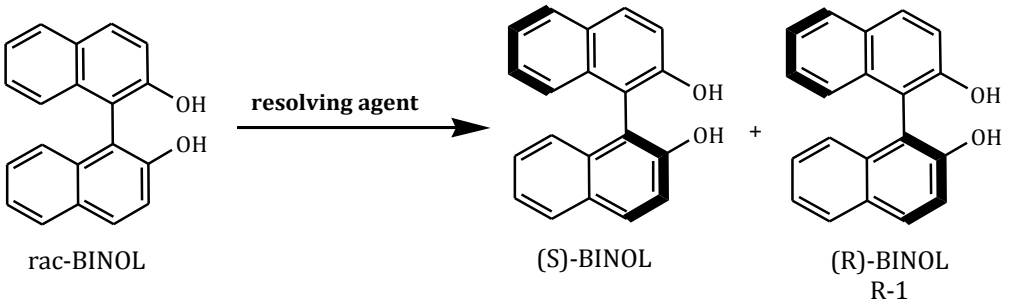
2.1 Research objective:

The aim of the research was to contribute to synthesis of some novel chiral dendrimers based on 1,1'-binaphthyl derivatives. Chiral dendrimers have important potential uses in drug delivery, catalysis (including enantioselective catalysis), as catalyst supports, phase transfer catalysts, and as membrane reactors, as well as a variety of other applications.

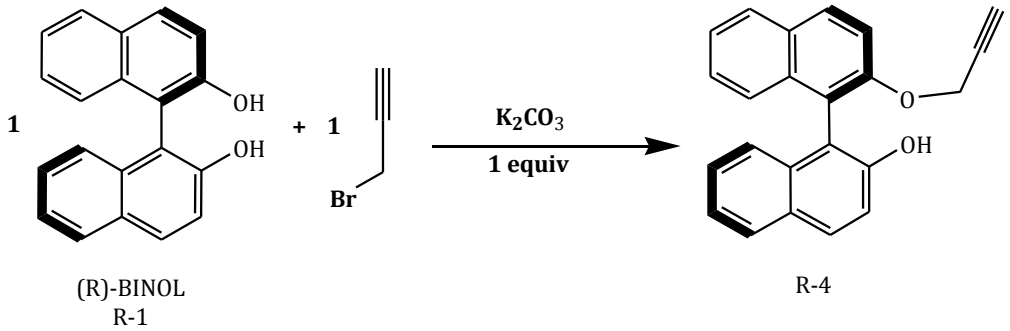
2.2 Routes of work:

2.2.1 Summary of route for synthesis of chiral bionapthol core:

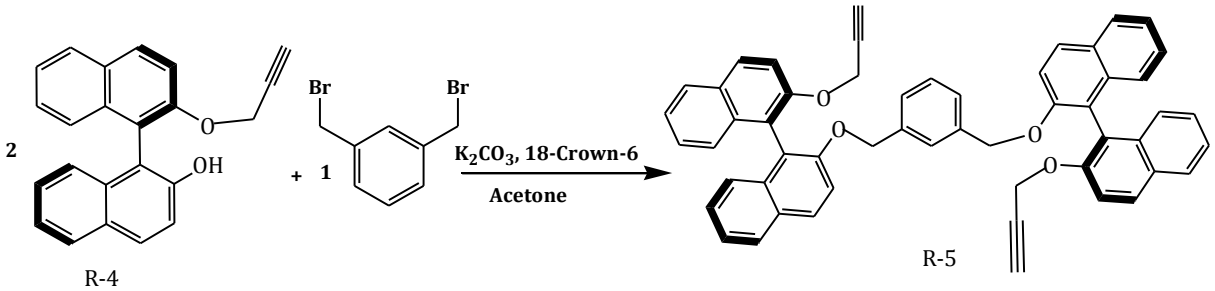
The project work started from *rac*-2,2-dihydroxy-1,1-binaphthyl and required the complete resolution into its optically pure *(R)* and *(S)*-enantiomers by the use of a chiral resolving agent (Scheme 1).[75] The isolated *(R)*-enantiomer was then reacted with propargyl bromide (Scheme 2).[2] The resulting mono-propargyl system was then dimerized with 1,3-bis(bromomethyl)benzene (Scheme 3) or 1,6-dibromohexane as the connector between two *(R)*-enantiomeric binaphtols (Scheme 4)[77] Finally, attempts were undertaken to synthesise 1,3-bis(*(R)*-2-methoxy-2'-propagyloxy-1,1'-binaphthly) benzene R-5 and 1,3-bis*((R)*-2-oxo-2'-propagyloxy-1,1'-binaphthly)hexane R-6 with 2nd generation Fréchet-type dendron 5 (Scheme 5),(Scheme 6) .[77]



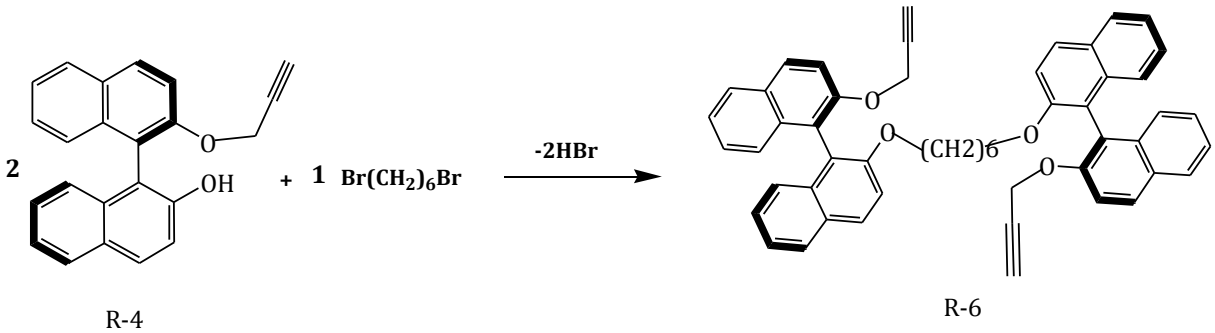
Scheme 1. Resolution of *rac*-BINOL into its enantiomers R-1.



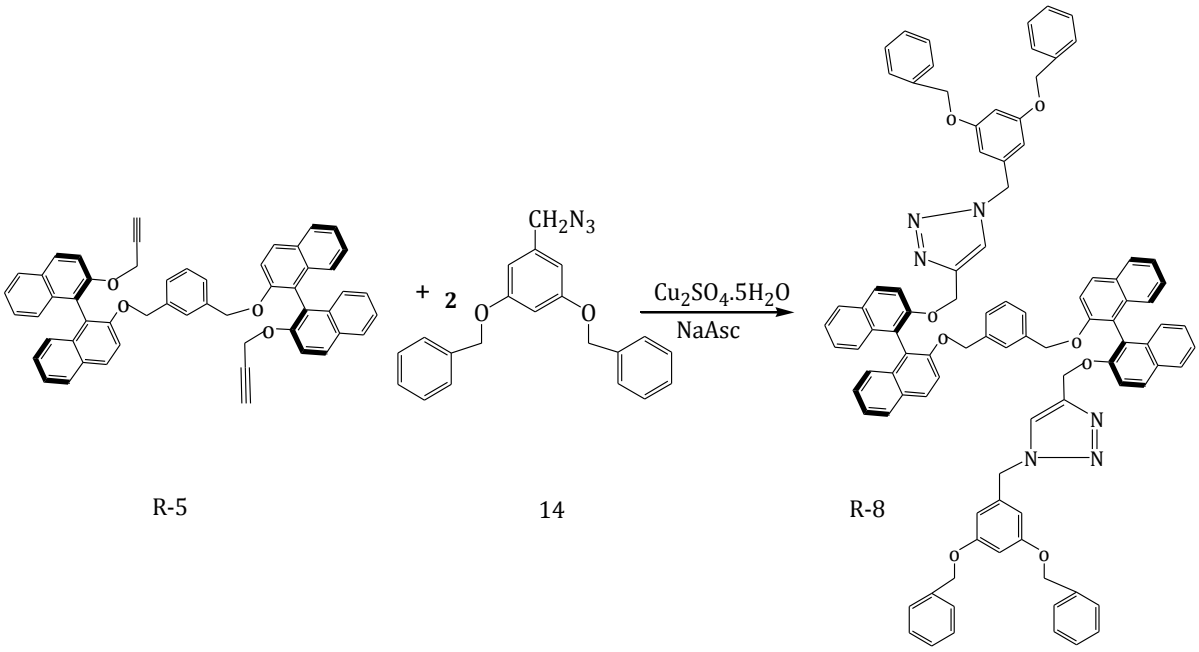
Scheme 2. Synthesis of (*R*)-2-hydroxy-2'-propargyloxy-1,1'-binaphthyl R-2.



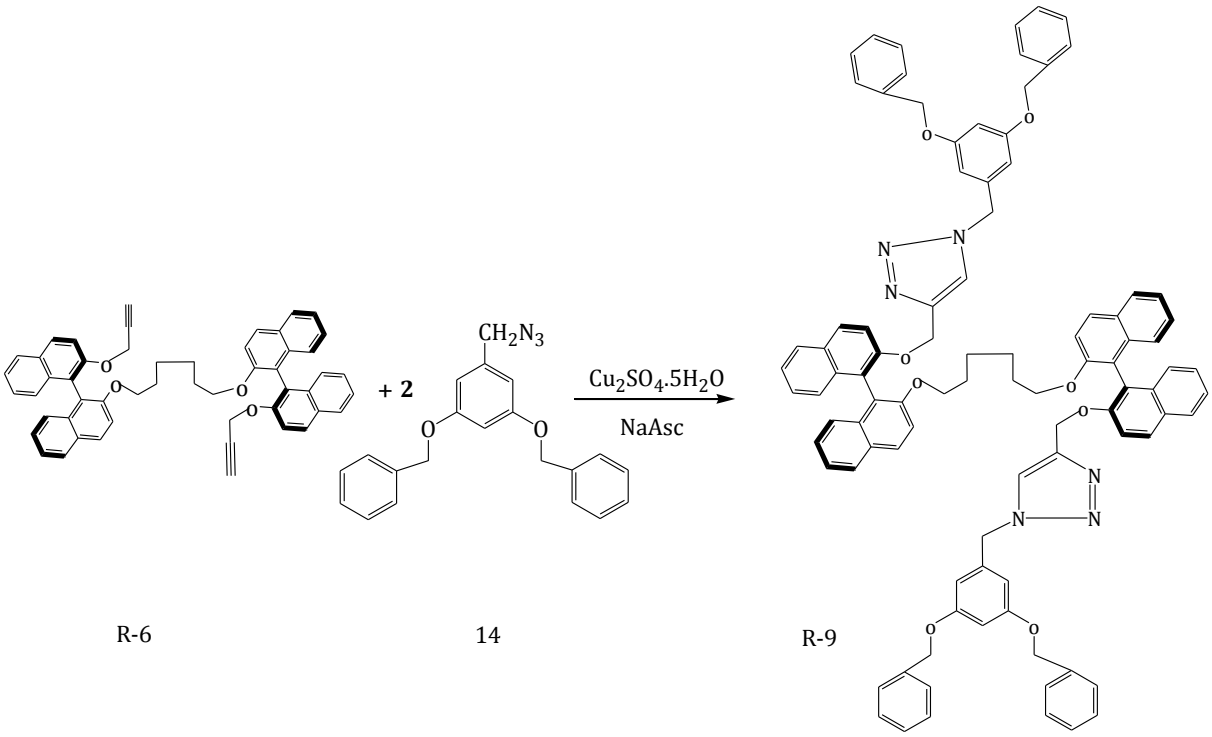
Scheme 3. Synthesis of 1,3-Bis((*R*)-2-methoxy-2'-propargyloxy-1,1'-binaphthly)benzene R-5.



Scheme 4. Synthesis of 1,3-Bis((*R*)-2-oxo-2'-propargyloxy-1,1'-binaphthly)hexane R-6.



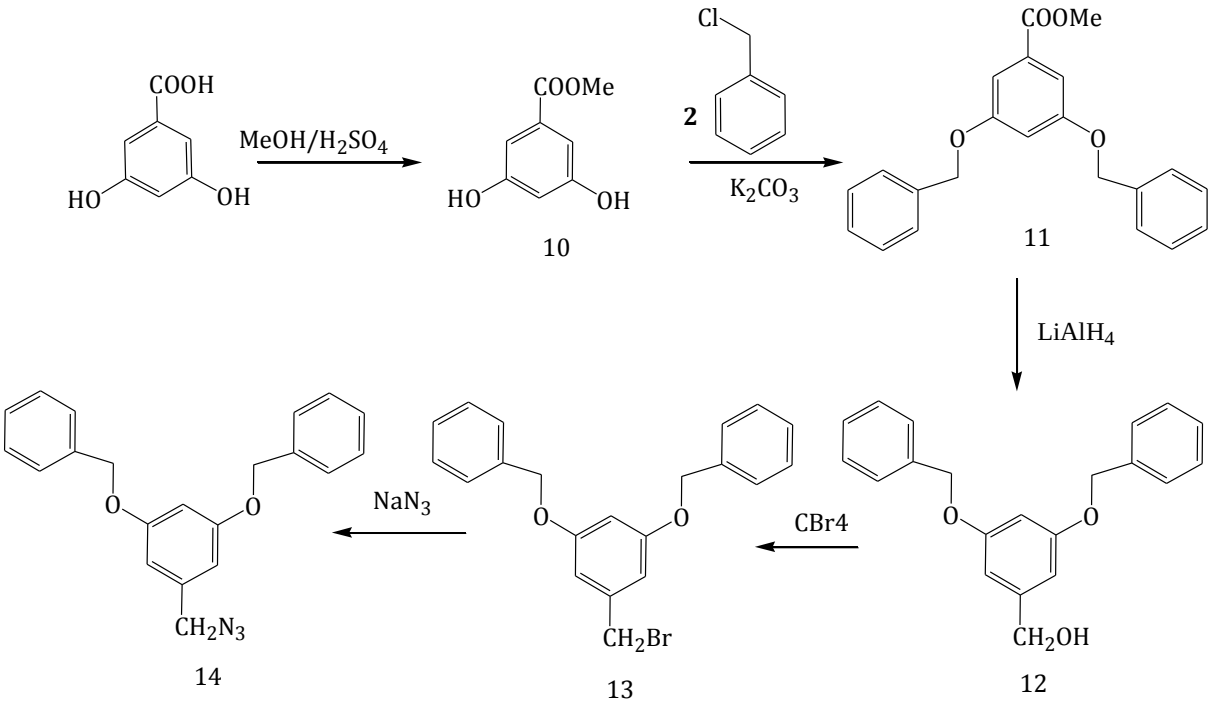
Scheme 5. Synthesis of R-8



Scheme 6. Synthesis of R-9

2.2.2 Summary of synthesis of dendron:

Fréchet-type dendritic benzylazide was synthesized by a route starting with the reaction of 3,5-dihydroxybenzoic acid with methanol to obtain methyl 3.5-dihydroxy-benzoate 10.[75] The resulting product was then to be reacted with benzyl chloride to give ester 11[78] followed by reduction with lithium aluminium hydride to obtain alcohol 12.[79] The resulting alcohol was then to be was treated with carbon tetrabromide to give 3,5-dibenzyloxybenzylbromide 13[80] and thence reacted with sodium azide to give azide as symmetric dendron 14 (Scheme 7).[81]

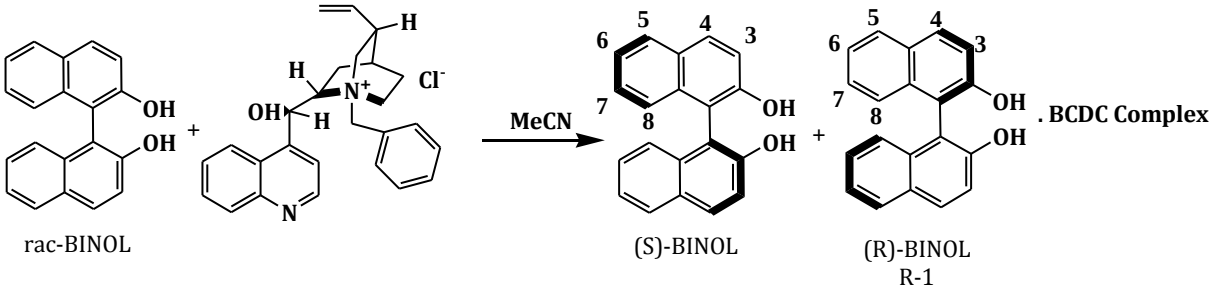


Scheme 7. Synthesis of Fréchet type dendron.

2.3 Synthesis of Core:

2.3.1 Resolution of racemic BINOL into its optically pure enantiomers S-BINOL and R-BINOL: [75]

There are many methods which have been reported [82,83,84,85] Racemic BINOL has been resolved into its optically pure *(R)* and *(S)* enantiomers according to the reported method by *Cai et al.*[86] using resolving agent as of (8*S*,9*R*)-(-)-N-benzyl-cinchonidinium chloride to give the (*S*)-enantiomer from the reaction mother solvent and (*R*)-enantiomer after washing the complex in hot methanol and then extraction, giving the enantiomers in 41 % and 37 % yields respectively (Scheme 8)



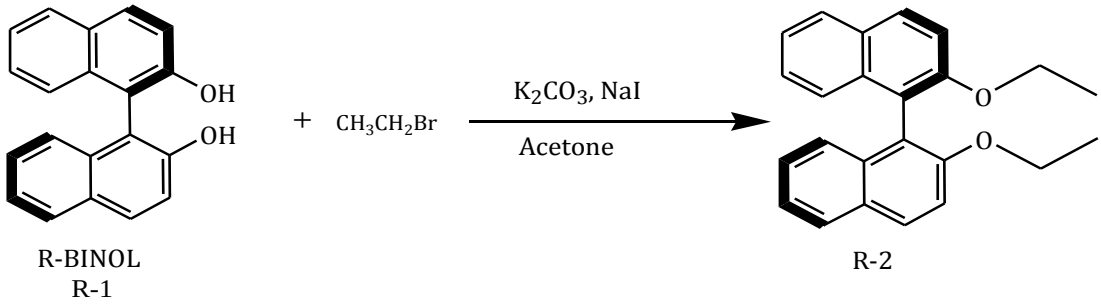
Scheme 8. Resolution of *rac*-BINOL into its enantiomers.

The structures of both (*R*)-BINOL and (*S*)-BINOL were confirmed using ^{1}H and ^{13}C NMR and H-COSY. NMR spectrum of both enantiomers showed one singlet peak for the hydroxyl group at 4.96 ppm and the aromatic region for the protons showed six peaks at 7.06-7.88 ppm. The specific optical rotation $[\alpha]^{22}$ of (R)-BINOL is +38.3 (c =0.3, DCM).

2.3.2 Synthesis of (*R*)-2,2'-diethoxy-1,1'-binaphyl R-2: [87]

The first approach employed protection of both hydroxyls. To protect the hydroxyl groups in *R*-1,1'-binaphthyl-2,2'-diol R-2, the binol was reacted with two equivalents of bromomethane in the presence of anhydrous potassium carbonate with sodium iodide as catalysis. This Williamson etherification reaction afforded *R*-2,2'-

diethoxy-1,1-binaphyl R-2 light yellow needles in 85 % yield after recrystallization from petroleum ether/dichloromethane (Scheme 9).



Scheme 9. Synthesis of R-2

Formation of *R*-1,1'-binaphthyl-2,2'-diol R-2 was confirmed using ^1H, ^{13}C NMR H-COSY and HQMC and the product data are fully consistent with the literature.[87] Important peaks in the ^1H NMR spectrum of R-2 are the three methyl protons of the (OCH_2CH_3) group, appearing as a very clear triplet signal at 0.96 ppm and the two methylene protons of the (OCH_2CH_3) groups giving rise to a multiplet signal at 3.94 ppm. In addition, the ^1H NMR spectrum (R-2) shows peaks in the aromatic region for six protons at 7.05 -7.85 ppm (Figure 22). The specific optical rotation $[\alpha]^{22}$ of R-2 is +40.3 (c =0.3, DCM).

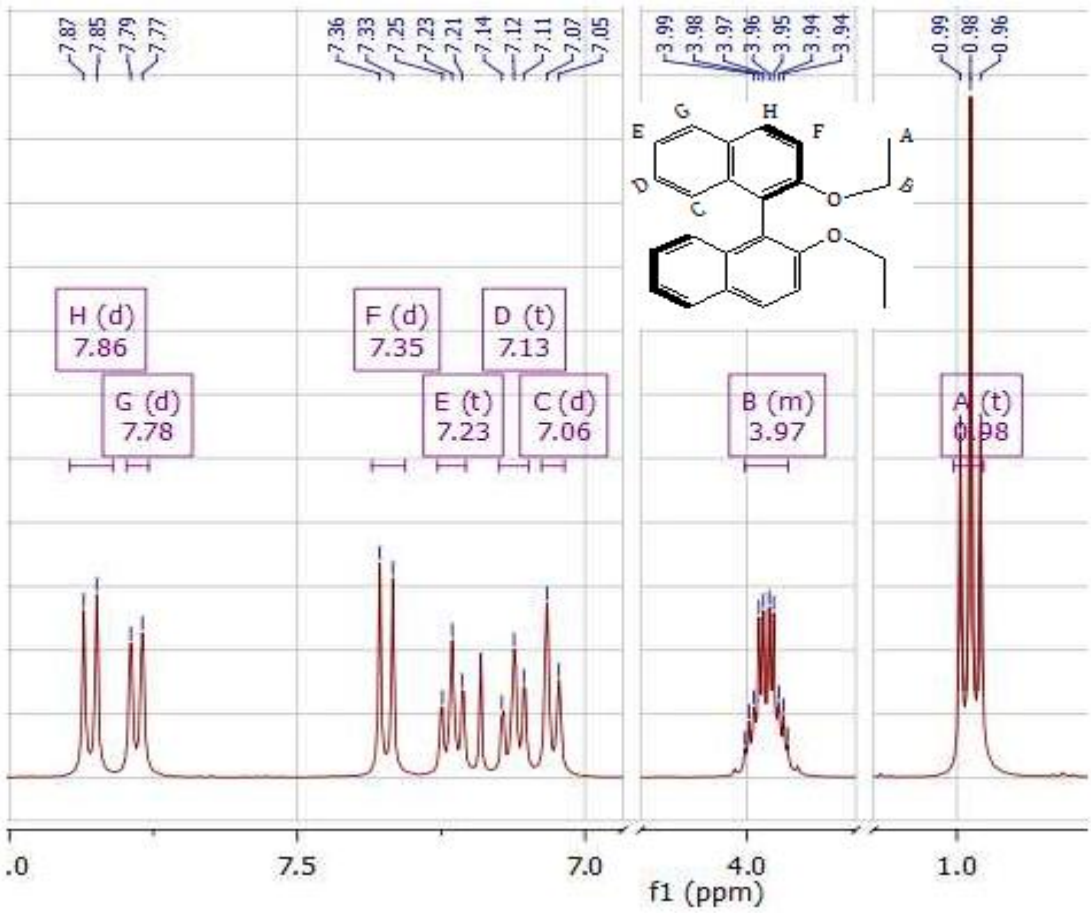
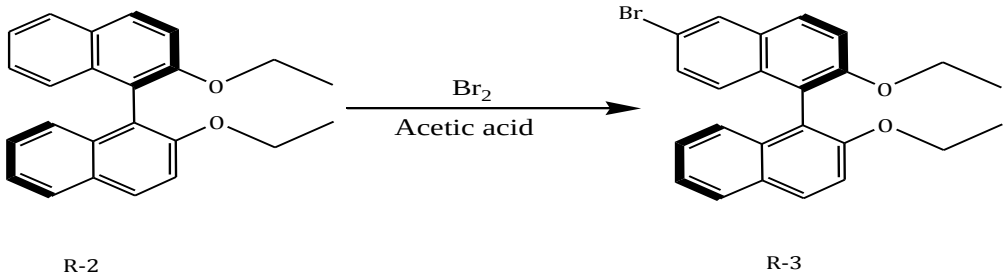


Figure 22: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of R-2

2.3.3 Synthesis of (*R*)-6-Bromo-2,2'- diethoxy-1,1'-binaphyl R-3: [77]

R-6-Bromo-2,2'-diethoxy-1,1'-binaphyl R-3 was obtained by reaction of a solution of *R*-2,2'-diethoxy-1,1'-binaphthyl R-2 in dichloromethane at -78 °C with a slowly added solution of bromide in dichloromethane, with stirring under nitrogen. Hydrobromic acid was removed by bubbling nitrogen over five hour, after which the crude mixture was treated with 10 % $NaHSO_4$, and then basified with potassium carbonate. The remaining solid was purified by column chromatography on silica gel eluting with hexane/dichloromethane to obtain pure R-3 as white solid in 92 % yield (Scheme 10).



Scheme 10. Synthesis of *R*-6-Bromo-2,2'- diethoxy-1,1'-binaphyl R-3

The product was confirmed using ^{1}H, ^{13}C NMR H-COSY and HQMC and the product data are fully consistent with the literature.[77] The ^{1}H NMR spectrum showed the methyl protons of the (OCH_2CH_3) as a triplet signal at 0.97 ppm and other one at 0.99 ppm as triplet. The methylene protons of the (OCH_2CH_3) groups as a multiplet at 3.93-4.00 ppm. However, the aromatic region for the protons showed only eleven protons at 6.87-7.93 ppm with disappearance of the position 6 signal, but with the survival of proton 6' (Figure 23). In addition the ^{13}C was showed at 123.5, ppm, to C (6) which couple with Br but in the position C (6') was recorded at 129.7 ppm, this difference is due to the impact of bromyl group as electron withdrawing group. In addition the Mass spectra (MS) was recorded 420.1 $(M+H)^{+}$. The specific optical rotation $[\alpha]^{22}$ of R-3 = +45.3 (c =0.4, DCM).

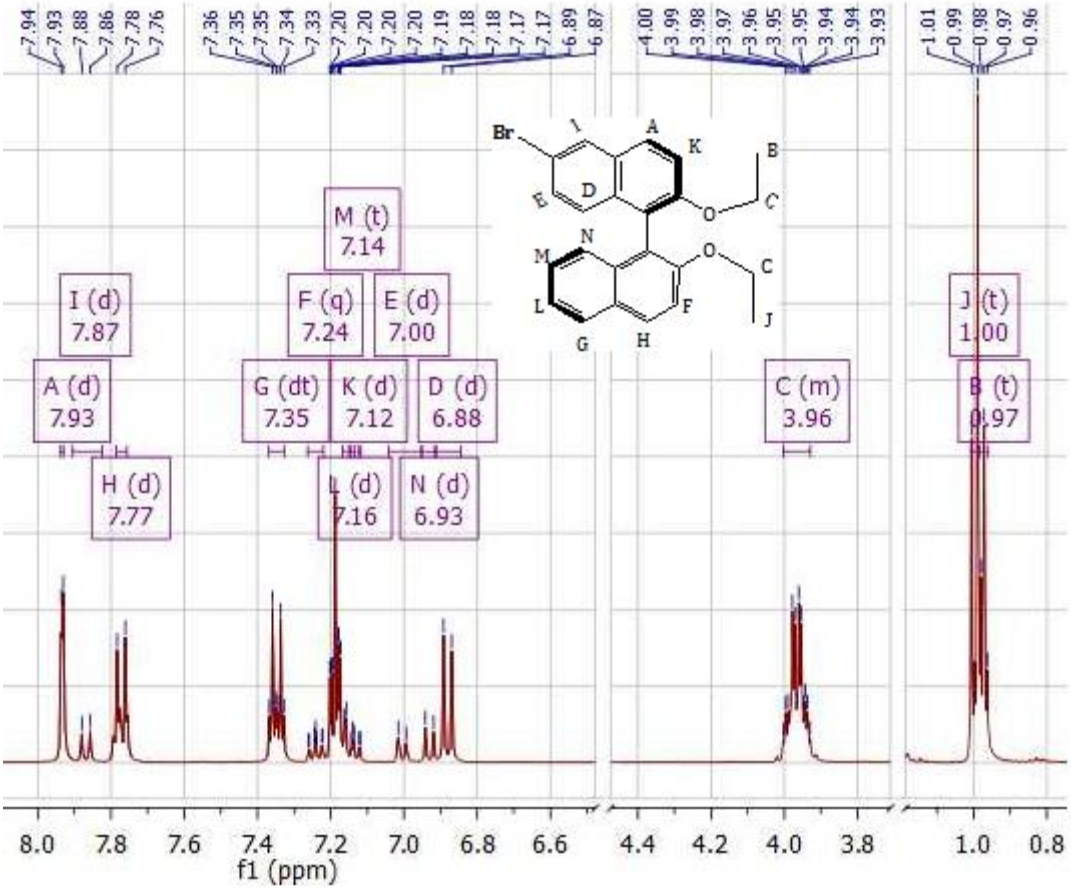
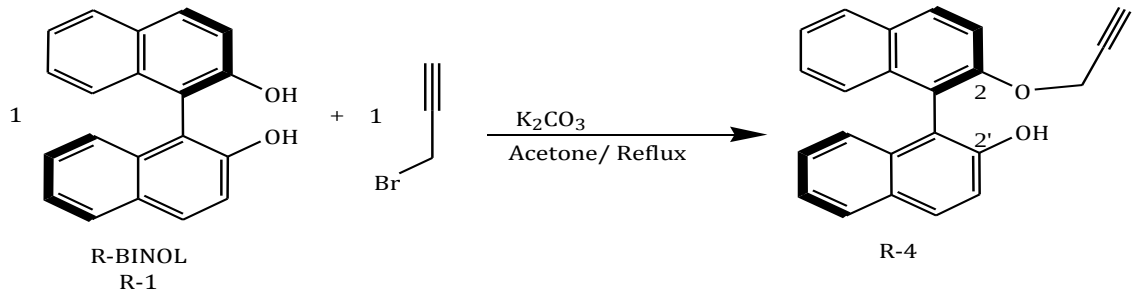


Figure 23: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of R-3

2.3.4 Synthesis of (*R*)-2-hydroxy-2'-propargyloxy-1,1'-binaphthyl R-4: [88]

(*R*)-2-hydroxy-2'-propargyloxy-1,1'-binaphthyl R-4 was prepared using alkylation of *R*-BINOL (Williamson synthesis) by using one equivalent of propargyl bromide in the presence of one equivalent of potassium carbonate in acetone, allowed to reflux with stirring for 36 h. Mono-ether R-4 was obtained in 83 % yield (Scheme 11).



Scheme 11. Synthesis of (*R*)-2-hydroxy-2'-propargyloxy-1,1'-binaphthyl R-4.

The structure of (*R*)-2-hydroxy-2'-propargyloxy-1,1'-binaphthyl R-4 was confirmed using ^{1}H, ^{13}C NMR H-COSY and HQMC. The ^{1}H NMR spectrum showed high multiplicity for the signals of the aromatic protons which is attributed to the difference in the chemical environment around the two naphthyl rings this arises because of the impact of different functional group in position 2 and 2', in contrast to *rac*-BINOL. In addition, the characteristic signals for the acetylene proton, the methylene protons and the aromatic hydroxyl group were observed. The methylene protons appear as diastereotopic to give a quartet pattern similar to *rac* -BINOL as shown (Figure 24). The specific optical rotation $[\alpha]^{22}$ of R-4 = +43.7 (c =0.25, DCM).

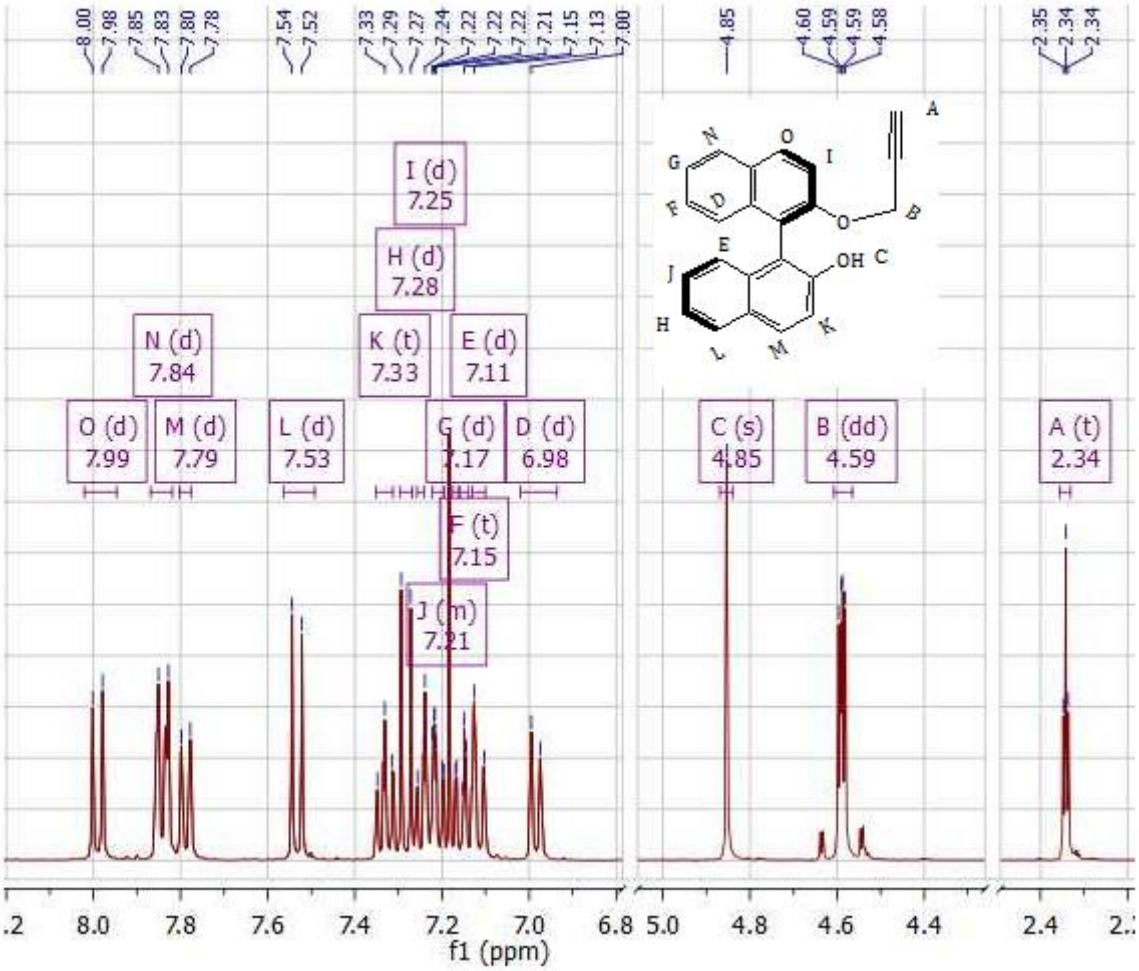
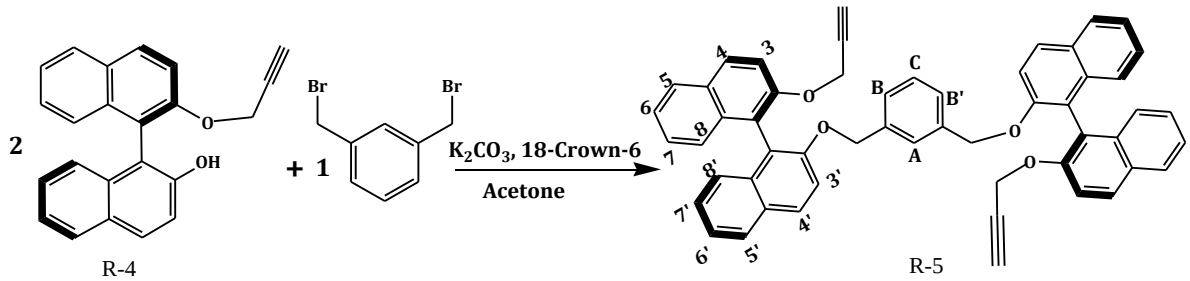


Figure 24: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of R-4

2.3.5 Synthesis of 1,3-Bis((*R*)-2-methoxy-2'-propargyloxy-1,1'-binaphthly) benzene R-5:[77]

1,3-Bis((*R*)-2-methoxy-2'-propargyloxy-1,1'-binaphthly)benzene R-5 was prepared by reaction with 1,3-bis(bromomethyl)benzene, using potassium carbonate and 18-Crown-6 as catalysis in acetone. The reaction mixture was judged complete by TLC after 24 h. After work up the resulting product was purified by flash column chromatography using silica gel eluting with dichloromethane to obtain novel compound R-5 in 85 % yield (Scheme 12).



Scheme 12. Synthesis of 1,3-Bis((*R*)-2-methoxy-2'-propargyloxy-1,1'-binaphthly)benzene R-5.

1,3-Bis((*R*)-2-methoxy-2'-propargyloxy-1,1'binaphthly)benzene R-5 was confirm-ed using ^{1}H, ^{13}C NMR H-COSY and HQMC, with comparison to R-4. The ^{1}H NMR spectrum showed the characteristic signals for the proton of (H^{A}) in benzene ring as a singlet at 6.44 ppm, the protons of (H^{B}) appeared as doublet at 6.69 whilst the protons of (H^{C}) in benzene ring appeared as a triplet at 6.82 ppm. In addition, the aromatic region for the protons showed six peaks at 7.04-7.88 ppm. However, the aromatic hydroxyl group signal of proton was completely absent (Figure 25). The specific optical rotation $[\alpha]^{22}$ of R-5 = +73.6 (c =0.3, DCM).

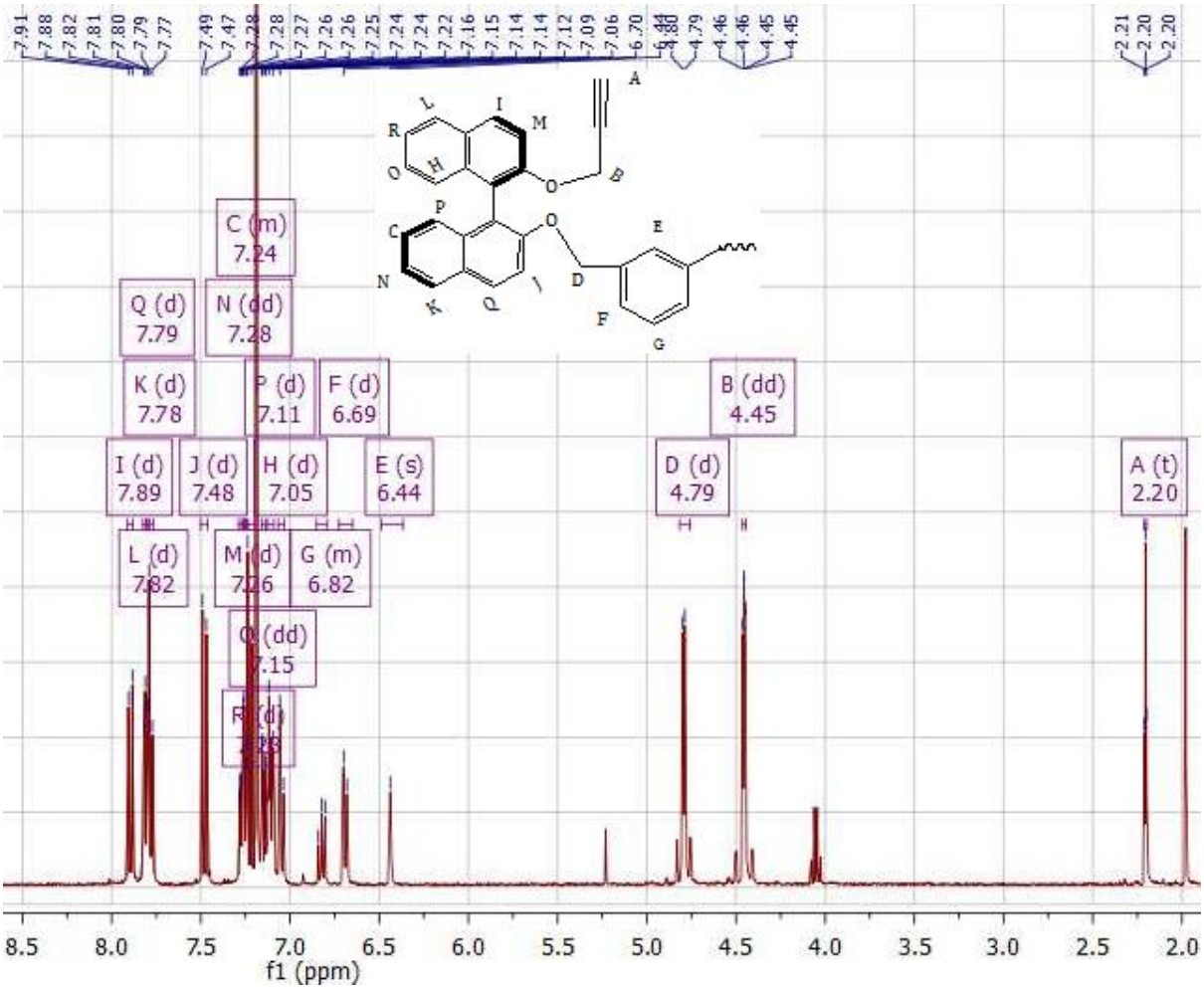
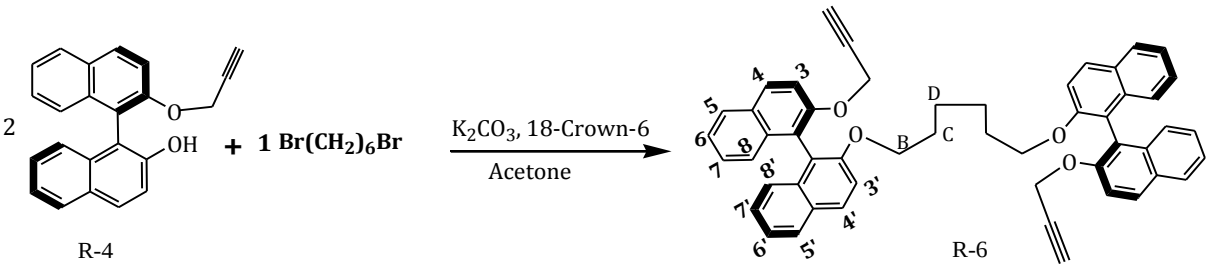


Figure 25: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of R-5

2.3.6 Synthesis of 1,3-Bis((*R*)-2-oxo-2'-propargyloxy-1,1'-binaphthly)hexane R-6[77]

1,3-Bis((*R*)-2-oxo-2'-propargyloxy-1,1'-binaphthly)hexane R-6 was prepared from R-4. To a mixture of potassium carbonate and 18-Crown-6 as catalysis was added acetone, and the reaction was stirred at 56 °C 15 min, when R-4 was added, and then after 30 min 1,6-dibromohexane was added. The mixture was allowed to reflux with stirring for 24 hour, till the reaction mixture was judged complete by TLC. After work up, the resulting product was purified by flash column chromatography using silica gel eluting with dichloromethane to obtain novel compound R-6 in 75 % yield (Scheme 13).



Scheme 13. Synthesis of 1,3-Bis((*R*)-2-oxo-2'-propargyloxy-1,1'-binaphthly)hexane.

1,3-Bis((*R*)-2-oxo-2'-propargyloxy-1,1'-binaphthly)hexane R-6 was confirmed using ^{1}H, ^{13}C NMR H-COSY and HQMC also compared to R-4. The ^{1}H NMR spectrum showed characteristic signals for the proton of (H^{D}) in the hexyl chain appeared as triplet at 1.02 ppm, the protons of (H^{C}) appeared as a multiplet at 1.15 ppm and the protons of (H^{B}) in hexane chain appeared as a triplet at 3.63 ppm. In addition, the aromatic region for the protons shows six peaks at 6.97-7.87 ppm. Furthermore, the impact of the different functional groups in position 2 and 2' was observed in the signals of the aromatic protons, due to the difference in the chemical environment around the naphthyl rings. However, the aromatic hydroxyl group signal of proton was completely absent as shown in (Figure 26). The specific optical rotation $[\alpha]^{22}$ of R-6 = +65.3 (c =0.4, DCM).

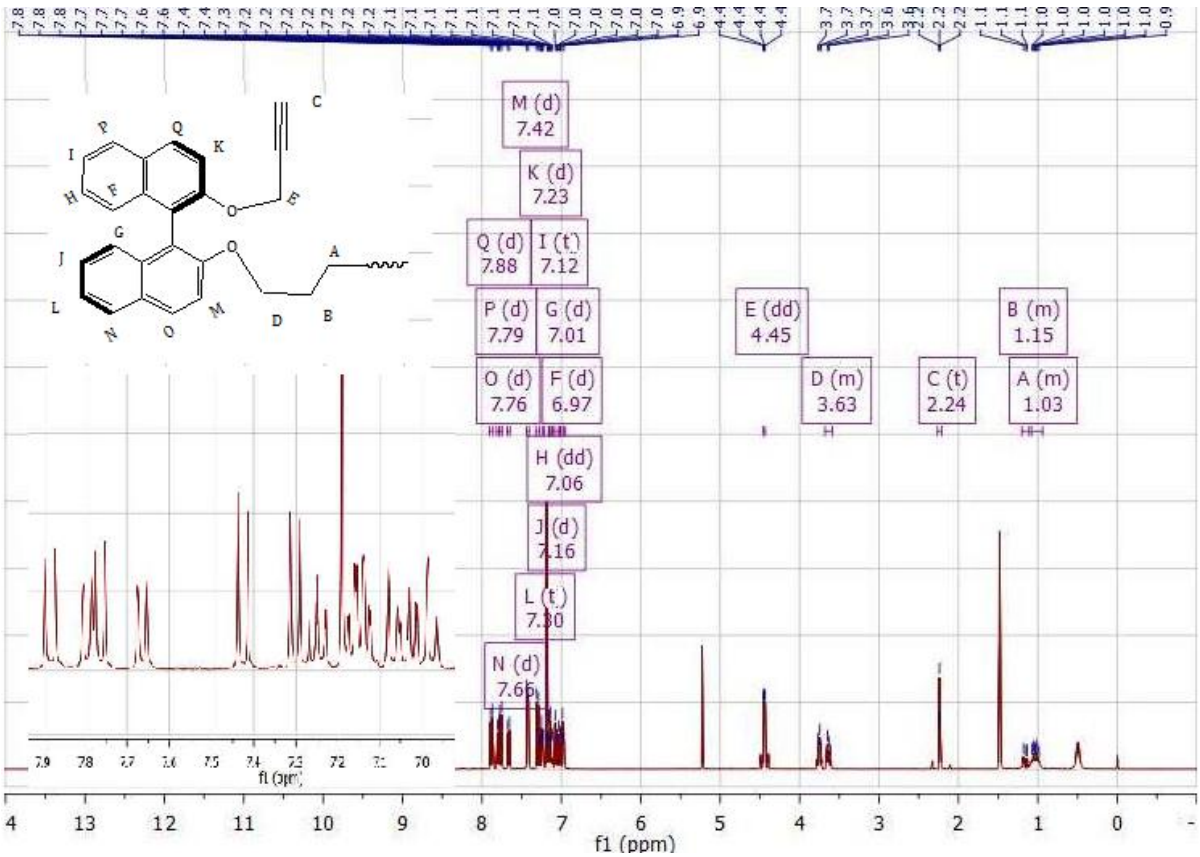
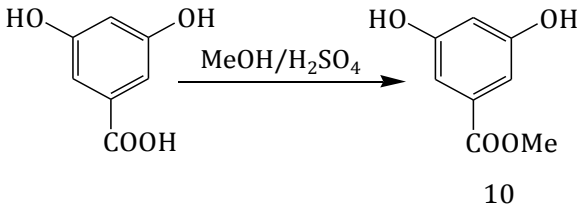


Figure 26: ^{1}H NMR spectrum (400 MHz, CDCl3) of R-6

2.4 Synthesis of Dendron:

2.4.1 Synthesis of methyl-3, 5-dihydroxybenzoate 10:[75,78]

Methyl-3,5-dihydroxybenzoate 10 was prepared by reaction of a solution 3,5-dihydroxy-benzoic acid in methanol in the presence of sulphuric acid for 7 hour. The product was purified by recrystallization from water to obtain compound 10 as white crystals in 73 % yield (Scheme 14).

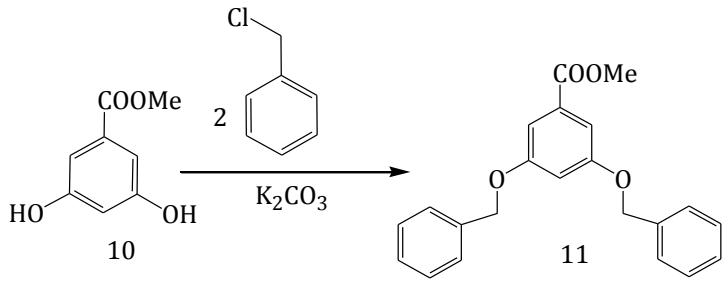


Scheme 14. Synthesis Methyl-3,5-dihydroxybenzoate

The 3,5-dihydroxybenzoic acid 10 structure was confirmed using ^{1}H, ^{13}C NMR H-COSY and HQMC, compared to starting material and the ^{1}H NMR spectrum showed the characteristic signals for the proton of methyl group was appeared at 3.82 ppm.

2.4.2 Synthesis of methyl-3,5-dibenzyloxybenzoate 11: [78,79,85]

Reaction for 72 hour of methyl 3.5-dihydroxybenzoate 11 with two equivalents from benzyl chloride and in the presence of anhydrous potassium carbonate as catalysis in acetone. The residue was purified by recrystallization from ethanol to obtain a methyl-3,5-dibenzyloxy-benzoate **11** as colourless needle crystals in 80 % yield (Scheme 15).

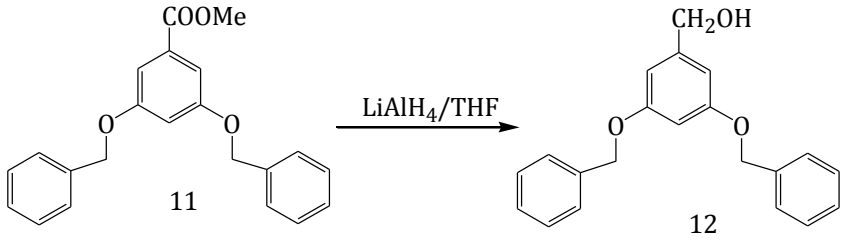


Scheme 15. Synthesis methyl 3,5-dibenzyloxybenzoate 11.

Methyl 3,5-dibenzyloxybenzoate 11 has been confirmed using ^{1}H, ^{13}C NMR H-COSY and HQMC also compared to starting material and the ^{1}H NMR spectrum was observed the characteristic signals for the aromatic hydroxyl group signal of proton was disappeared completely and the aromatic region for the protons appears peaks at 6.89-7.45 ppm.

2.4.3 Synthesis of 3,5-dibenzyloxybenzyl alcohol 12: [78,79,80]

Reduction of ester 11 using lithium aluminium hydride in dry THF at 0-5 °C the residue was recrystallized from a mixture of petroleum ether and dichloromethane to obtain 3,5-dibenzyloxybenzyl alcohol **12** as pure white solid in 95 % yield (Scheme 16).

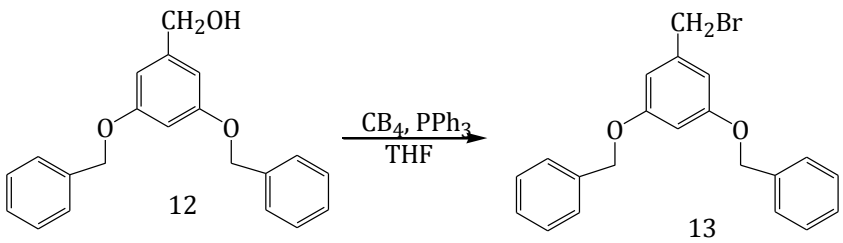


Scheme 16. Synthesis 3,5-dibenzyloxybenzyl alcohol 12.

The formation of 3,5-dibenzyloxybenzyl alcohol 12 was confirmed using ^{1}H, ^{13}C NMR H-COSY and HQMC. The ^{1}H NMR spectrum was appeared as triplet at 1.63 ppm for the aliphatic hydroxyl group and the doublet signal at 4.67 ppm for the terminal methylene group. On the contrary, in the compound **11** which the singlet signal at 3.92 ppm.

2.4.4 Synthesis of 3,5-dibenzyloxybenzyl bromide 13:[78]

3,5-Dibenzyloxybenzyl bromide 13 was prepared by bromination reaction of alcohol 12 using carbon tetrabromide and triphenylphosphine in dry THF for 5 hour at room temperature. After purification by flash column chromatography to obtain **13** as pure white powder in 75 % yield (Scheme 17).

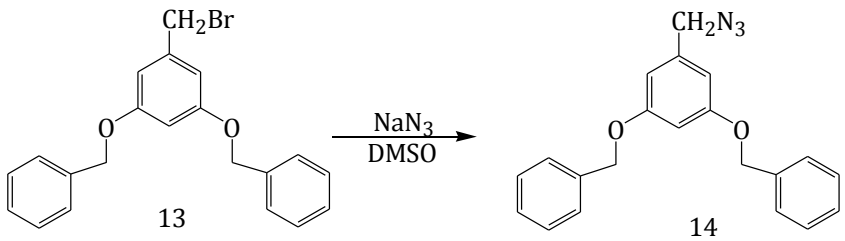


Scheme 17. Synthesis 3,5-dibenzyloxybenzyl bromide 13.

3,5-dibenzyloxybenzyl bromide has been confirmed using ^{1}H, ^{13}C NMR, H-COSY and HQMC also compared to starting material and the ^{1}H NMR spectrum was observed the characteristic signals for the proton of methyl group was appeared at 4.44 ppm and the hydroxyl group was disappeared.

2.4.5 Synthesis of 3,5-dibenzyloxybenzyl azide 14:[81]

3,5-Dibenzyloxybenzyl bromide 13 with NaN_3 in dimethylsulfoxide to obtain 3,5-dibenzyloxybenzyl azide **14** as colorless oily product in 97 % yield (Scheme 18).



Scheme 18. Synthesis 3,5-dibenzyloxybenzyl azide 14.

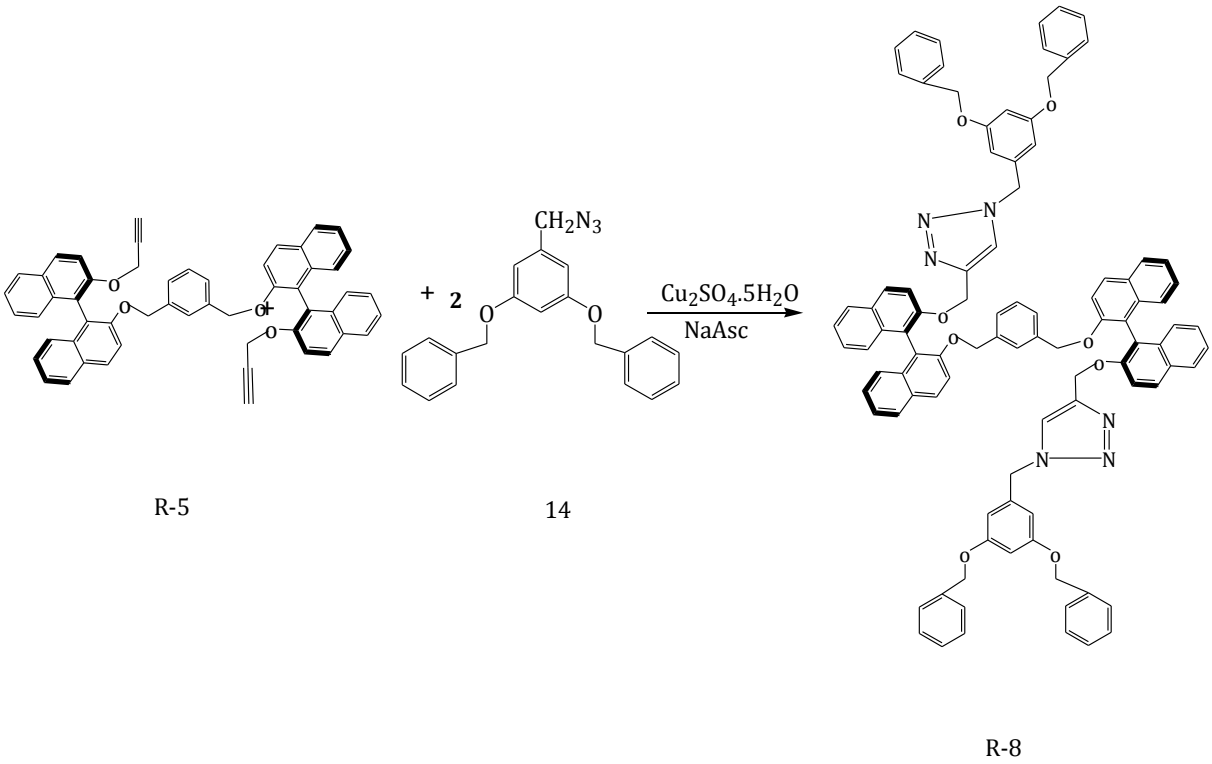
Formation of methyl 3,5-dibenzyloxybenzoate was confirmed using ^{1}H NMR, and the ^{1}H NMR spectrum was observed the characteristic signals for the methylene group which appears as singlet at 4.30 ppm. Also the protons *p*-H and *o*-H peaks are similar to 2, 3 and 4, but with small differences in the chemical shifts.

2.5 Problems and discuss reactions:

2.5.1 Attempt to synthesis of 1,3-Bis((*R*)-2-methoxy-2'-propagyloxy-1,1'-binaphthly) benzene R5 with 2nd generation 14:

1,3-Bis((*R*)-2-methoxy-2'-propargyloxy-1,1'-binaphthly) benzene R-5 in THF-H_2O (4:1) has been added to 2 equiv 3,5-dibenzyloxybenzyl azide 14 in (ratio 1:2) in the present of $Cu_2SO_4.5H_2O$ and NaAsc and the solution was stirred at room temperature for 72h (scheme 19). The reaction mixture was judged complete by TLC (Chloroform/ Petroleum ether 1:1) but has been still doubted remains the although shown for signs of the presence of production but not as wished. The solution which was extracted with DCM (2x25 ml), and the combined organic layers were dried ($MgSO_4$) and removed and it was purified by flash column chromatography using silica gel by DCM then *vacuo* to obtain product. After the result was checked by using ^{1}H, ^{13}C NMR. The ^{1}H NMR spectrum was not showed. It was a challenging target to get the product R-8. However,

maybe for spatial crowding and the large molecular weight was a hindrance to achieving the goal and certainly we need probably needs some changes to conditions.

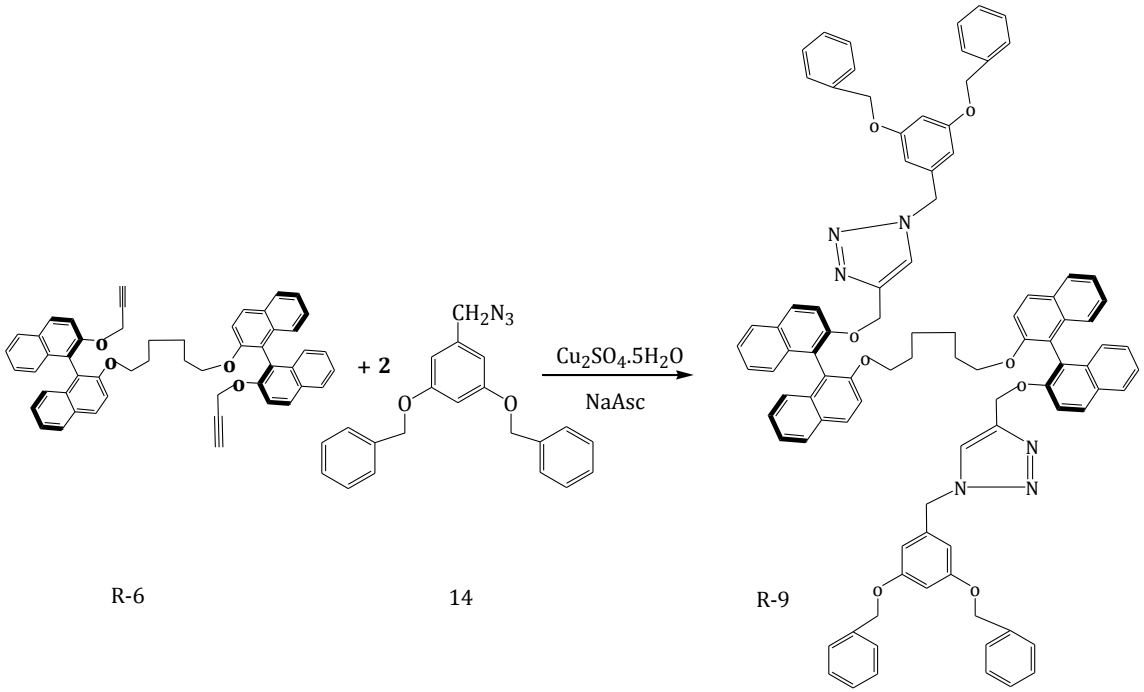


Scheme 19. Synthesis of R-8

2.5.2 Attempt to synthesis of 1,3-Bis((*R*)-2-oxo-2'-propargyloxy-1,1'-binaphthly) hexane R-6 with 2nd generation 14:

1,3-Bis((*R*)-2-oxo-2'-propargyloxy-1,1'-binaphthly)hexane R-6 in THF-H_2O (4:1) has been added to 2 equiv 3,5-dibenzyloxybenzyl azide 10 in (ratio 1:2) in the present of $Cu_2SO_4.5H_2O$ and NaAsc and the solution was stirred at room temperature for 72h (scheme 20). The reaction mixture was judged complete by TLC (Chloroform/ Petroleum ether 1:1) but has been still doubted remains the although shown for signs of the presence of production but not as wished. The solution which was extracted with DCM (2x25 ml), and the combined organic layers were dried ($MgSO_4$) and removed and it was purified by flash column chromatography using silica gel by DCM then *vacuo* to obtain product. It was a challenging target to get the product **R-9**. However, maybe for

spatial crowding and the huge molecular weight was a hindrance to achieving the goal and certainly we need probably needs some changes to conditions.



Scheme 20. Synthesis of R-9

2.6 Conclusion:

The main of objective of this research was to synthesise some novel chiral dendrimers based on 1,1'-binaphthyl derivatives. The projected started from *rac*-BINOL which has often been used as the starting material to chiral compounds because the hydroxyl groups can be easily changed to other functional groups, plus isolation of optically pure (*R*) and (*S*) by the use of a chiral resolving agent is a scalable procedure. In the current work, the isolated *(R)*-enantiomer was reacted with propargyl bromide to generate the mono-propargyl system. The mono-propargyl system was dimerized with two different compounds as the connector between these two *(R)*-enantiomeric binaphtols and attempts were undertaken to synthesise both of them with a 2nd generation Fréchet-type dendron. Fréchet-type dendritic benzylazide was successfully

synthesized by a route starting with the reaction of 3,5-dihydroxybenzoic acid as symmetric dendron.

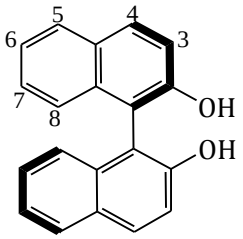
The reactions of core monfunctionalization and dimerization have been achieved and confirmed by ^{1}H, ^{13}C NMR, Mass spectra, elements analysis and Infrared spectra, confirming these targets to be pure compounds. However, all attempts to couple the modified core units and have so far proved problematic. It was challenging to obtain these novel targets, but almost certainly some changes to conditions will in future work complete synthesis of these novel dendrimers.

Chapter Three

3. Expermental Section:

The chemicals used were obtained from commercial sources and used as received without more purification, except for THF and DCM which were dried by distillation from calcium hydride. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra were recorded at 100 NMR on a Bruker DPX 400 spectrometer, expressed in ppm (δ) relative to trimethylsilane (TMS) as an internal standard. Mass spectra (MS) were recorded using a Micromass Platform II spectrometer using an electrospray ionization source. Infrared spectra were obtained by using ALPHA-P FTIR spectrometer. Aluminium-backed TLC plates (silica gel 60 F_{245}) were 0.2mm thickness. Normal silica gel 60(particle size 0.035-0.070mm) was made use of column chromatography. Melting points were determined using Stuart Scientific SMP10 apparatus and are uncorrected.

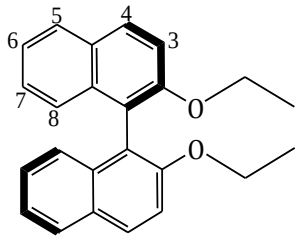
Resolution of 2,2'-dihydroxy-1,1'-binaphthyl into its enantiomers:[75]



A 50 mL round-bottom flask was charged with rac-BINOL (500 mg, 1.75 mmol) and to this was added a chiral (8S,9R)-(-)-N-benzylcinchonidinium (450 mg, 0.964 mmol) in MeCN (20 mL). The suspension was refluxed for 4 h then stirred at room temperature overnight, and then cooled in ice bath (0-5 °C) for 2 h, filtered, and the resulting filtrate was concentrated to dryness, then redissolved in ethyl acetate (50 mL) and 1N HCl (20 mL). This white solid which separated was washed with 1N HCl (2x10 mL) and brine (10 mL). The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated in *vacuo* to obtain (***S***) enantiomer (41%) as a light white solid. Mp: 211-214 °C (lit.[89]) The solid from filtration above was washed with MeCN (30 mL) and the solid then moved into a 250 mL flask, MeOH (50 mL) was added and the mixture refluxed overnight. After cooling to room temperature, the mixture was filtered and the

solid was washed with (30 mL) MeOH and the solid was then suspended in a mixture of ethyl acetate (30 mL) and 1N HCl (20 mL) and stirred till complete dissolution occured (10 mL). The organic layer was separated, washed with 1N HCl (20 mL), brine (10 mL) and then separated, dried ($MgSO_4$), filtered, and concentrated in *vacuo* to obtain (***R***) enantiomer (37%) as white powder. Mp: 215-217 °C (lit.[89]); Both enantiomers were recorded: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.96 (s, 2H,OH), 7.06 (d, *J*=8.4 Hz, 2H, H^8), 7.21 (t, *J*=6.8 Hz, 2H, H^7), 7.28 (d, *J*=6.8 Hz, 2H, H^6), 7.28 (t, *J*=9.2 Hz, 2H, H^3), 7.80 (d, *J*=7.2 Hz, 2H, H^5), 7.88 (d, J=7.6 Hz, 2H, H^4). ^{13}C NMR. (100MHz, $CDCl_3$): 110.8, 117.8, 124.1, 124.2, 127.5, 128.4, 129.5, 131.5, 133.4, 152.8. IR *υ*max cm^{-1}: 3429, 3507, 3056, 1617, 1594, 1510. ($C_{20}H_{14}O_2$), M.W: 286.3g/mol. ES-MS m/z; 287.2 $(M+H)^+$. $[\alpha]^{22}$ = +38.33 (c =0.3, DCM).

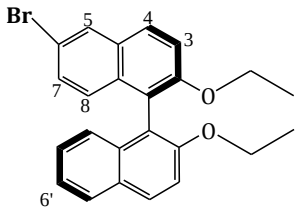
Synthesis of R-2,2'-diethoxy-1,1'-binaphyl R-2: [90]



To a 100 mL round-bottom flask equipped with a condenser was added 1,1'-bi naphthyl-2,2'-diol (100 mg, 0.349 mmol), bromoethane (76.14 mL, 0.698 mmol), K_2CO_3 (20 mg, 0.145 mmol), NaI (10 mg, 0.0667 mmol) and acetone (20 mL). The mixture was allowed to reflux with stirring under N_2 for 48 h, until the reaction was judged to be complete as monitored by TLC (Hexane/EtOAc 1:1). After cooling the reaction mixture was filtered, poured into water (10 mL) and extracted with DCM (2x10 mL). The solvent was removed in *vacuo*. The remaining yellow crude solid (135 mg) was recrystallisated from a mixture of petroleum ether (40-60) and DCM (1:1.5) to obtain **R-2** (105 mg, 85 %) as light yellow needles. M.pt: 132-134 °C (lit.[90]); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.96 (t, *J*=7.2, 6H,CH_3), 3.94-4.00 (m, 4H, OCH_2), 7.05 (d, J=7.2 Hz, 2H, H^8), 7.11 (t, *J*=6.8 Hz, 2H, H^7), 7.21 (t, *J*=6.8 Hz, 2H, H^6), 7.33 (d, *J*=9.2 Hz, 2H, H^3), 7.77 (d, *J*=8.0 Hz, 2H, H^5), 7.85 (d, *J*=7.6 Hz, 2H, H^4). ^{13}C NMR. (100 MHz, $CDCl_3$): 15.0, 65.2, 115.9, 120.6, 123.4,

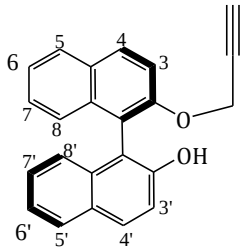
125.5, 126.1, 127.8, 129.1, 129.3, 134.2, 154.3. IR υmax cm^{-1}: 3060, 2990, 1610, 1570, 1190. ($C_{24}H_{22}O_2$), M.W: 342.4 g/mol. ES-MS m/z; 343.18 $(M+H)^+$. $[\alpha]^{22}$ = +40.3 (c =0.3, DCM).

Synthesis of R-6- Bromo-2,2'-diethoxy-1,1'-binaphthyl, R-3: [88]



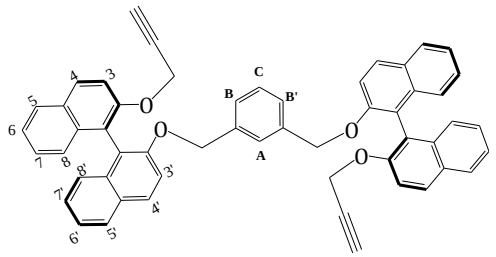
To a solution of R-2,2'-diethoxy-1,1'-binaphthyl R-2 (50 mg, 0.146 mmol) in DCM (20 mL) at -78 °C was added slowly a solution of Br_2 (0.15 mL, 0.146 mmol) in DCM under N_2. HBr was removed by bubbling nitrogen over 5 h, after which the crude mixture was treated with 10 % $NaHSO_4$, basified with K_2CO_3. The organic layer was washed with H_2O (2x5 mL), brine (5 mL) and extracted with DCM (2x10 mL), dried Mg_2SO_4, then chromatographed silica gel (Hexane/ DCM 4:1) to obtain **R-3** pure (55.9 mg, 91.5 %) as white solid. Mp: 70-71. °C (lit.[88]); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.97 (t, *J*=3.5, 3H, CH_3), 0.99 (t, *J*=3.6, 3H, CH_3), 3.93-4.00 (m, 4H, OCH_2), 6.87 (d, *J*= 9.0 Hz, 1H, H^8), 6.92 (d, *J*=9.0, 1H, $H^{8'}$), 6.99 (d, *J*=8.6 Hz, 1H, H^7), 7.12 (d, *J*= 1.3, 2H, H^3), 7.14 (t, *J*= 1.6, 1H, $H^{7'}$) 7.16 (d, *J*=2.1, Hz, 1H, $H^{6'}$), 7.24 (q, *J* = 8.1, 6.8, 1.2 Hz, 1H, $H^{3'}$), 7.35 (dt, *J*=9.0, 3.5 Hz, 1H, $H^{5'}$), 7.76 (d, *J*=9.0 Hz, 1H, $H^{4'}$), 7.86 (t, *J*=9.0 Hz, 1H, H^5), 7.93 (t, *J*=1.9 Hz, 1H, H^4). ^{13}C NMR. (100 MHz, $CDCl_3$): 14.9, 15.0, 65.1, 115.6, 116. 5, 116.7, 123.5, 125.2, 126.2, 127.1, 127.4, 127.9, 128.2, 128.5, 129.3, 129.4, 129.5, 129.7, 129.82, 154.5. IR υmax cm^{-1}: 3060, 2979, 1615, 1583, 1342, 1292, 1234. ($C_{24}H_{21}BrO_2$), M.W: 420.3 g/mol. ES-MS m/z; 420.1 $(M+H)^+$. $[\alpha]^{22}$ = +45.3 (c =0.4, DCM).

Synthesis of *(R)*-2-hydroxy-2'-propargyloxy-1,1'-binaphthyl R-4: [77]



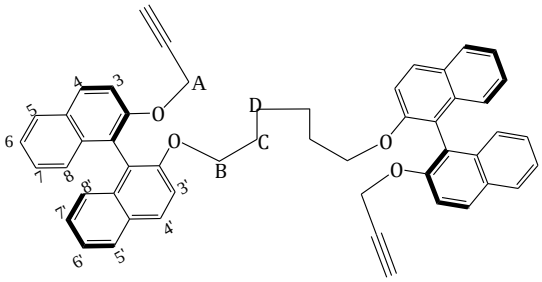
To a 100 mL round-bottom flask equipped with a condenser was added 1,1'-binaphthyl R-1(100 mg, 0.349 mmol), propargyl bromide (0.0311 mL, 0.349 mmol), K_2CO_3 (50 mg, 0.362 mmol) and acetone (20 mL) the mixture was allowed to reflux with stirring for 36 h, after which TLC (Hexane/ EtOAc 3:1) and indicated no remaining starting material. The resulting solution was extracted with DCM (2 x10 mL), the solvent dried (Mg_2SO_4) and removed in *vacuo* to obtain **R-4** as white solid (83 mg, 83 %)**.** Mp: 75-76 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.34 (t, *J*=2.4 Hz, 1H, C≡CH), 4.54-4.63(d,d, *J*=4, 2.4 Hz, 2H,OCH_2) 4.85 (s, Hz, 1H, OH), 6.97 (d, *J*=8.5 Hz, 1H, H^8), 7.10 (d, *J*=9.1 Hz, 1H, $H^{8'}$), 7.15 (t, *J*=8.4 Hz, 1H, H^7), 7.17 (t, *J*=8.0 Hz, 1H, H^6), 7.20 (t, *J*=8.4 Hz, 1H, $H^{7'}$), 7.25 (d, *J*=5.6 Hz, 1H, H^3), 7.28 (d, *J*=8.9 Hz, 1H, $H^{6'}$), 7.31 (d, *J*=6.9 Hz, 1H, $H^{3'}$), 7.52 (d, *J*=9.1 Hz, 1H, $H^{5'}$), 7.78 (d, *J*=8.1 Hz, 1H, $H^{4'}$), 7.83 (d, *J*=9.0 Hz, 1H, H^5), 7.98 (d, *J*=9.2 Hz, 1H, H^4).^{13}C NMR. (100 MHz, $CDCl_3$): 75.9, 78.7, 114.6, 115.8, 117.2, 117.6, 123.3, 124.7, 124.9, 125.2, 126.5, 127.4, 128.1, 128.2, 129.1, 130.0, 130.1, 130.8, 133.7, 134.0, 151.2, 153.8. IR υmax cm^{-1}: 3500, 3277, 2120, 1618, 1589, 1505, 1205, 1127. ($C_{23}H_{16}O_2$), M.W:324.4 g/mol. ES-MS m/z; 325.2 $(M+H)^+$. $[\alpha]^{22}$ = +43.7 (c =0.3, DCM).

Synthesis of 1,3-Bis((*R*)-2-methoxy-2'-propargyloxy-1,1'-binaphthly) benzene R-5: [77]



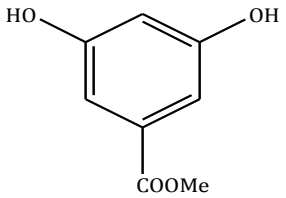
To a 50 mL round-bottom flask containing a mixture of potassium carbonate (50 mg, 0.362 mmol) and 18-Crown-6 (20 mg, 0.757 mmol), was added acetone (20 mL) in one portion. The reaction was stirred at 56 °C a further 15 min then R-4 (100 mg, 0.308 mmol) was added, and after a further 30 min was added 1,3-bis(bromomethyl)benzene (40.7 mg, 0.154 mmol). The mixture was allowed to reflux with stirring for 24 h, till the reaction mixture was judged complete by TLC (chloroform/petroleum ether 1:1). The resulting solution was extracted with ethyl acetate (2x15 mL), the combined organic layers were dried (Mg_2SO_4), solvents removed and the resulting product was purified by flash column chromatography using silica gel by DCM to obtain a compound **R-5**, (120 mg, 85 %) as a white solid. Mp: 86-88 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20 (t, *J*=2.4 Hz, 2H, C≡CH), 4.45 (d,d, *J*=3.2, 2.4 Hz, 4H,OCH_2-C), 4.79 (d, *J*=4.8 Hz, 4H,OCH_2-Ph), 6.44 (s, 1H, H^A), 6.69 (d, *J*=7.6, 1H, H^B), 6.82 (t, J=7.6, 1H, H^C), 7.04 (d, *J*=8.0 Hz, 2H, H^8), 7.09 (d, *J*=10.2 Hz, 2H, $H^{8'}$), 7.13 (t, *J*=7.8 Hz, 2H, H^7), 7.22 (t, *J*=9.0 Hz, 2H, H^6), 7.24 (t, *J*=5.2 Hz, 2H, $H^{7'}$), 7.25 (d, *J*=1.6 Hz, 2H, H^3), 7.27 (d,d, *J*=5.2 Hz, 2H, $H^{6'}$), 7.47 (d, *J*=9.0 Hz, 2H, $H^{3'}$), 7.77 (d, *J*=7.6 Hz, 2H, $H^{5'}$), 7.79 (d, *J*=8.2 Hz, 2H, $H^{4'}$), 7.81 (d, *J*=3.2 Hz, 2H, H^5), 7.88 (d, *J*=8.9 Hz, 2H, H^4).^{13}C NMR (125.8 MHz, $CDCl_3$) δ 154.0, 137.4, 134.1, 134.0, 129.4, 129.2, 127.9, 126.4, 125.8, 125.6, 125.5, 124.0, 123.8, 116.0, 115.8, 79.3, 75.3, 71.0. IR υmax cm^{-1}: 3279, 2119, 1620, 1589, 1505, 1456, 1430, 1327, 1214. ($C_{54}H_{38}O_4$), M.W:750.9g/mol. ES-MS m/z; 753.3 $(M+H)^+$. $[\alpha]^{22}$ = +73.6 (c =0.3, DCM).

Synthesis of 1,3-Bis((*R*)-2-oxo-2'-propargyloxy-1,1'-binaphthly)hexane R-6: [77]



To a 50 mL round-bottom flask containing a mixture of potassium carbonate (50 mg, 0.362 mmol) and 18-Crown-6 (20 mg, 0.757 mmol), was added acetone (20 mL) in one portion. The reaction was stirred at 56 °C a further 15 min then R-4 (100 mg, 0.308 mmol) was added, and after a further 30 min was added 1,6-dibromohexane (37.6 mg, 0.154 mmol). The mixture was allowed to reflux with stirring for 24 h, untill the reaction was judged complete by TLC (Chloroform/Petroleum ether 1:1). The resulting solution was extracted with ethyl acetate (2x15 mL), and the combined organic layers were dried (Mg_2SO_4) and solvents removed in *vacuo*. The resulting crude product was purified by flash column chromatography using silica gel elating with DCM and *vacuo* to obtain a compound **R-6** (103 mg, 74.9 %) as a yellow sticky. 1H NMR (400 MHz, $CDCl_3$) δ 1.02 (m, 4H, CH_2^D), 1.15 (m, 4H, CH_2^C), 2.24 (t, *J*=2.4 Hz, 2H, C≡CH), 3.63 (m, 4H, CH_2^B), 4.45 (d, *J*=2.4 Hz, 4H, CH_2^A), 6.97 (d, *J*=8.0 Hz, 2H, $2H^8$), 7.01 (d, *J*=6.4 Hz, 2H, $2H^{8'}$), 7.06 (t, *J*=6.2 Hz, 2H, $2H^7$), 7.12 (t, *J*=7.6 Hz, 2H, H^6), 7.16 (t, *J*=6.4 Hz, 2H, $H^{7'}$), 7.23 (d, *J*=8.0 Hz, 2H, H^3), 7.30 (t, *J*=8.8 Hz, 2H, $H^{6'}$), 7.42 (d, *J*=9.2 Hz, 2H, $H^{3'}$), 7.66 (d, *J*=8.0 Hz, 2H, $H^{5'}$), 7.76 (d, *J*=8.8 Hz, 2H, $H^{4'}$), 7.79 (d, *J*=8.4 Hz, 2H, H^5), 7.87 (d, *J*=9.2 Hz, 2H, H^4). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 134.1, 129.4, 129.0, 127.8, 126.3, 126.2, 125.5, 125.5, 123.9, 123.6, 116.1, 115.8, 79.4, 75.21, 69.5, 29.1, 25.0. 24.8; IR *υ*max cm^{-1}: 3281, 2929, 2860, 1742, 1619, 1590, 1505, 1458, 1328, 1215. $C_{54}H_{42}O_4$, M.W:730.9 g/mol. ES-MS m/z; 753.3 $(M+Na)^+$. $[\alpha]^{22}$ = +65.3 (c =0.4, DCM).

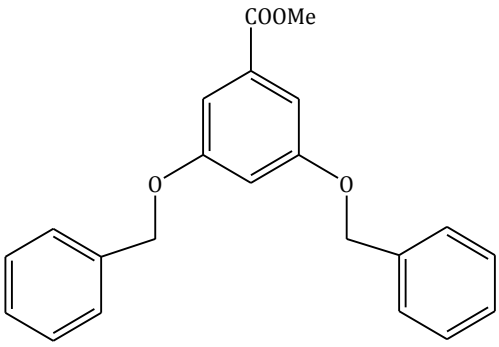
Synthesis of methyl 3,5-dihydroxybenzoate 10: [75]



10

To a 100 mL round-bottom flask a solution of 3,5-dihydroxybenzoic acid (1 g, 6.49 mmol) in methanol (20 mL), H_2SO_4 (20 mL, 375.2 mmol) was added and the reaction was refluxed with stirring, then concentrated to obtain the crude product as a white solid. The residue was dissolved in water (5 mL), extracted with diethyl ether (2x5 mL), dried (Mg_2SO_4), filtered solvent removed in *vacuo* and the residue was recrystallized from water (10 mL) to obtain **10** as white crystals (800 mg, 73.3 %). M.pt 175-177 °C (Lit. [78]). ^{1}H NMR (400 MHz, DMSO): δ 3.82 (s, 3H, CH_3), 6.45 (s, 1H, *p*-Ph) 6.80 (d, *J*=2.4, 2H, *o*-Ph), 9.65 (s, 2H, OH). ^{13}C NMR (100 MHz, DMSO): 52.0, 107.0, 107.1, 131.2, 158.5, 166.2. IR *υ*max cm^{-1}: 3353, 3228, 2994, 1684, 1596. ($C_8H_8O_4$) M.W= 168.16 g/mol. ES-MS m/z; 169.l $(M+H)^+$.

Synthesis of methyl 3,5-dibenzyloxybenzoate 11:[78,79]

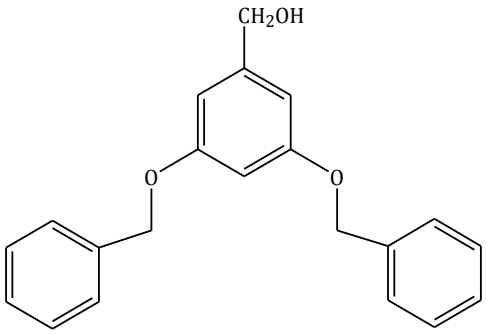


11

A solution of methyl 3.5-dihydroxybenzoate 10 (500 mg, 2.97 mmol), benzyl chloride (6.84 mL, 5.95 mmol, 2 equiv.) and K_2CO_3 (200 mg, 1.45 mmol) in acetone (20 mL) the mixture was refluxed with stirring for 72 h, after which the mixture was diluted with water (10 mL), extracted with DCM (10 mL), washed with water (2 x 15 mL) and brine (10 mL), and dried by ($MgSO_4$). Solvents were removed in *vacuo* and product recrystallized from ethanol (20 mL) to

obtain **11** as colourless needle crystals (828 mg, 80 %). M.pt 79-81 °C (Lit.[79]). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.92 (s, 3H, OCH_3), 5.09 (s, 4H, O-CH2-Ph), 6.89 (t, J=2.4 Hz, 1H, *p*-H of Ar-COOMe), 7.22 (d, J=2.4 Hz, 2H, *o*-H of Ar-COOMe), 7.34-7.45 (m, 10H, PhH). ^{13}C NMR (100 MHz, $CDCl_3$): 51.3, 69.9, 106.9, 108.1, 127.8, 128.1, 128.7, 131.8, 136.1, 159.8. IR *υ*max cm^{-1}: 3227, 1686, 1599, 1485, 1295, 1101. ($C_{22}H_{20}O_4$) M.W = 348.40 g/mol. ES-MS m/z: 349.3 $(M+H)^+$.

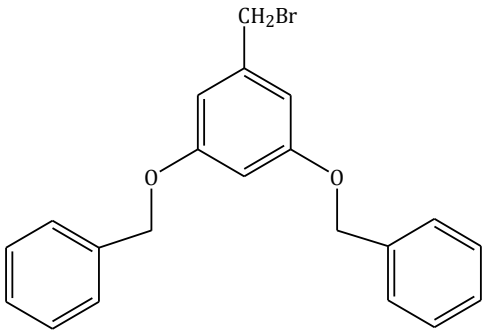
Synthesis of 3,5-dibenzyloxybenzyl alcohol 12:[78,7,91]



12

A solution of ester 2 (500 mg, 1.44 mmol) in dry THF (20 mL) was slowly added over 1 h to $LiAlH_4$ (57.7 mg, 1.52 mmol) suspended in dry THF (20 mL) with stirring under nitrogen at 0-5 °C. The mixture was stirred at room temperature overnight after which TLC confirmed completion. It was cooled to 0-5 °C and water (5 mL) was added dropwise, and pH adjusted to 7 using 1N HCl. The mixture was filtered, diethyl ether (5 mL) was added and the organic layer was separated, dried ($MgSO_4$) and the solvent removed. The product was recrystallized from a mixture of petroleum ether and DCM (2:1) to obtain **12** as pure white solid (438 mg, 95 %). M.pt 83-85 °C (Lit.[91]). ^{1}H NMR(400 MHz , $CDCl_3$:): δ 1.63 (t, *J*=6.0 Hz, 1H, OH), 4.67 (d, *J*=6.0 Hz, C-OH), 5.07 (s, 4H, $PhCH_2O$), 6.57 (t, *J*=2.4 Hz, 1H, *p*-ArH to CH_2OH), 6.65 (d, *J*=2.4 Hz, 2H, *o*-Ar-H to CH_2OH), 7.33-7.46 (m, 10H, PhH). ^{13}C NMR (100 MHz, $CDCl_3$): 65.4, 70.1, 72.1, 73.8, 101.3, 105.7, 127.6, 127.7, 128.0, 128.4, 128.5, 128.6, 129.6, 136.8, I43.4, 160.2; IR *υ*max cm^{-1}: 3282, 3030, 2904, 2864, 1590, 1442, 1284, 1146. ($C_{21}H_{20}O_3$) M.W= 320.4 g/mol. ES-MS *m/z*: 321.0 $(M+Na)^+$.

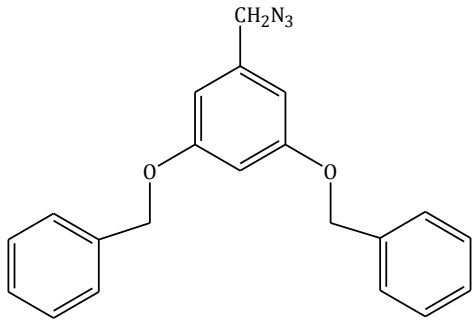
Synthesis of 3,5-dibenzyloxybenzyl bromide 13:[78]



13

To a solution of 3,5-dibenzyloxybenzyl alcohol 3 (300 mg, 0.94 mmol) a dry THF 30 mL, was added carbon tetrabromide (386 mg, 1.16 mmol) with stirring under nitrogen. After stirring for 15 min, triphenylphosphine (311 mg, 1.17 mmol) was added, the mixture stirred for 5 h at room temperature after which TLC confirmed completion. The reaction mixture was partitioned in a mixture of water (10 mL) and DCM (10 mL). The organic layer was washed with water (2x10 mL) and brine (5 mL). The organic layer was separated, dried over ($MgSO_4$), filtered, and concentrated in *vacuo* to obtain the crude product. The crude product was purified by flash column chromatography using silica gel (petrolum ether/ethyl acetate 4:1) to give **13** as white powder (270 mg, 75 %). M.pt 87-89 °C (Lit.[91]). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.44 (s, 2H, CH_2Br), 5.05 (s, 4H, $PhCH_2O$), 6.57 (t, *J*=2.4 Hz, 1H, *p*-Ar-H), 6.67 (d, *J*=2.4 Hz, 2H, *o*-Ar-H), 7.34-7.46 (m, 10H, Ph-H). ^{13}C NMR (100 MHz, $CDCI_3$): 33.6, 70.2, 101.7, 108.1, 127.6, 128.1, 128.7, 136.8, 143.7, 160.1. IR *υ*max cm^{-1}: 3280, 3030, 2925, 2871, 1592, 1497, 1372, 1295, 1151. ($C_{21}H_{19}O_2Br$), M.W= 383.28 g/mol. ES-MS *m/z*: 385 $(M+H)^+$.

Synthesis of 3,5-dibenzyloxybenzyl azide 14: [81]



A solution of 3,5-dibenzyloxybenzyl bromide 13 (150 mg, 0.39 mmol) and NaN_3 (38 mg, 0.58 mmol) in DMSO (10 mL) was heated to reflux 130 °C for 24 h with stirring, after which TLC confirmed completion. The reaction mixture was poured on to water (15ml) to give a suspended white solution which was extracted with ethyl acetate (2x15 mL), dried ($MgSO_4$) and then solvent removed in *vacuo* to obtain **14** as colourless oil (130 mg, 96.5 %). ^{1}H NMR (400 MHz, $CDCI_3$): δ 4.30 (s, 2H, CH_2N), 5.07 (s, 4H, $PhCH_2O$), 6.59 (d, *J*=2.4, 2.0Hz, 2H, *o*-ArH), 6.61 (t, *J*=2.4 Hz, 1H, *p*-ArH), 7.34-7.46 (m, 10H, PhH). ^{13}C NMR (100 MHz, $CDCl_3$): 54.9, 70.2, 101.8, 107.2, 127.6, 128.1, 128.7, 136.6, 137.7, 160.3. IR *υ*max cm^{-1}: 3032, 2872, 2094, 1593, 1448, 1374, 1345, 1292, 1147 ($C_{21}H_{19}N_3O_2$), M.W=345.4 g/mol. ES-MS *m/z*: 368.0 $(M+Na)^+$.

REFERENCE:

1. Tomalia, D. A. Sci. Amer. 1995, 62, 272.

2. Vögtle, F.; Buhlein, E.; Wehner, W. Synthesis 1978, 155.

3. Tomalia, D. A.; Baker, H.; Dewald, J. R.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Poly. J.* **1985,** *17,* 117.

4. Fritz Vögtle, G. R. a. N. W. *Dendrimer Chemistry;* WILEY-VCH Verlag GmbH & Co. KGaA,Weinheim: KGaA, Weinheim, **2009**.

5. Tomalia, D. A.; Baker, H.; Dewald, J. R.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J. Soc. Poly. Sci. **1984**, 65.

6. D. A. Tomalia, J. R. Dewald, *U.S. Pat*ent, 4,871,779, **1989**.

7. D. A. Tomalia, J. R. Dewald, *U.S. Pat*ent, 4,857,599, **1989**.

8. Mendenhall, G. D.; Liang, S. X.; Chen., E. H. T. *J. Org. Chem.* **1990,** *55,* 3697.

9. Newkome, G. R.; Moorefield, C. N. *J. Chem. Soc., Chem. Commun.* **1994,** 2139.

10. Klajnert, B. M. *Bryszewska, Acta Biochimica Polonica* **2001,** *48,* 199.

11. Vögtle, F.; Richardt, G.; Werner, N. *Dendrimer Chemistry;* WILEY-VCH, 2009; p 15.

12. Newkome, G. R.; Yao, Z.; Baker, G. R.; Gupta, V. K. *J. Org. Chem.* **1985,** *50,* 2003.

13. Newkome, G. R.; Hu, Y.; Saunders, M. J.; Fronczek, F. R. *Tetrahedron Lett.* **1991,** *32,* 1133.

14. Mendenhall, G. D.; Liang, S. X.; Chen, E. H. T. *J. Org. Chem.* **1990,** *55,* 3697.

15. Newkome, G. R. *Advances in dendritic macromolecules* 1994; Vol. 1, 3.

16. Hecht, S.; Fréchet, J. M. *Angew. Chem. Int. Ed. Engl.* **2001,** *40,* 74.

17. Hawker, C. J.; Fréchet, J. M.; Gitsov, C. J.; Leon, I. *Macromol. Sci. Pure Appl. Chem.* **1999,** 1399.

18. Moorefield, C. N.; Newkome, G. R. *Advances in Dendritic Macromolecules;*, 1994; Vol. 1, Ch.4.

19. Tomalia, D. A.; Dewald, J. R. 631,337, 1986.

20. Hawker, C. J.; Fréchet, J. M. *J. Chem. Soc., Chem. Commun.* **1990,** 1010.

21. Fréchet, J. M.; Tomalia, D. A. *Dendrimers and other Dendritic Polymers;* ch. 4.

22. Moorefield, C. N.; Newkome, G. R. *Advances in Dendritic Macromolecules;*, 1994; Vol. 1, 5.

23. Wooley, K. L.; Hawker, C. J.; Fréchet, J. M. *J. Am. Chem. Soc.* **1991,** *113*, 4252.

24. Samija, M. P.; Guillemette, V.; Dasgupta, M.; Kakkar, A. K. *J. Am. Chem. Soc.* **1999,** *121,* 1968.

25. Newkome, G. R.; Moorefield, C. N.; Baker, G. R.; Johnson, A. L.; Behera, R. K. *Angew. Chem. Int. Ed. Engl.* **1991,** *30,* 1176.

26. Lehn, J. M. *Angew. Chem. Int. Ed. Engl.* **1988,** *27,* 89.

27. Fréchet, J. M.; Tomalia, D. A. *Dendrimers and other Dendritic Polymers;* ch. 2, p 23.

28. Kawaguchi, T.; Walke, K. L.; Wilkins, C. L.; Moore, J. S. *J. Ame. Chem. Soc* **1995,** *117,* 2159.

29. Zeng, F.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1996,** *118,* 5326.

30. Tomalia, D. A.; Naylor, A. M.; Goddard, W. A. *Angew. Chem.* **1993,** *122,* 214.

31. Miller, T. M.; Neenan, T. X. *Chem. Mat.* **1990,** *2,* 346.

32. Fréchet, J. M.; Tomalia, D. A. *Dendrimers and other Dendritic Polymers.;* pp ch 10,11,12,13.

33. Cram, D. J. *Angew. Chem. Int. Ed. Engl.* **1988,** *27,* 1009-1020.

34. Seyferth, D.; Son, D. Y.; Rheingold, A. L.; Ostrander, R. L. *Organometallics* **1994,** *13,* 2682-2690.

35. Laliberte, D.; Maris, T.; Sirois, A.; Wuest, J. *Organic Letters.* **2003,** *5*, 4787.

36. Gandhi, P.; Huang, B.; Gallucci, J.; Parquette, J. *Organic Letters* **2001,** *3*, 3129.

37. Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendritic Molecules.,* 1st ed.; VCH, Weinheim, 1996;37.

38. Bosman, A. W.; Janssen, H. M.; Meijer, E. W. *Chem. Rev.* **1999,** *99,* 1665.

39. Romagnoli, B.; Hayes, W. *J. Mater. Chem.* **2002,** *12,* 767.

40. Kreiter, R.; Kleij, A. W.; Gebbink, R. M. *Top. Curr. Chem.* **2001,** *127,* 163.

41. Fréchet, J. M.; Tomalia, D. A. *Dendrimers and other Dendritic Polymers.;* ch 19.

42. Duncan, R. *J. Am. Chem. Soc.* **1999,** *217,* 141

43. Sigal, G. B.; Mammen, M.; Dahmann, G.; Whitesides, G. M. *J. Am. Chem. Soc.* **1996,** *118,* 3789.

44. Bielinska, A. U.; Kukowska, J. F.; Tomalia, D. A.; Baker, J. R. *Nucleic Acids Res.* **1996,** *24,* 2176.

45. Reichardt, C.; Erfurt, H.; Harms, K.; Schäfer, G. *Eur. J. Org. Chem.* **2002,** 439-452.

46. Reek, J. N. H.; Groot, D. d.; Oosterom, G.; Kamer, P. C. J. *Reviews in Molecular Biotechnology.* **2002,** *90,* 159.

47. Matthews, O. W.; Shipway, A. N.; Stoddart, J. F. *Prog. Polym. Sci.* **1998,** *23,* 1.

48. Chow, H. F.; Mak, C. C. *J. Org. Chem.* **1997,** *62,* 5116.

49. Seebach, D.; Lapierr, J. M.; Greiveldinger, G.; Skobridis, K. *Helv. Chim. Acta.* **1994,** *77,* 1673.

50. Buda, A. B.; Heyde, T. A. H.; Mislow, K. *Angew. Chem. Int. Ed. Engl.* **1992,** *31,* 989.

51. Gennes, P. G.; Hervet, H. *J. Phys. Lett. Fr.* **1993,** *44,* 351.

52. Newkome, G. R.; Lin, X.; Weis, C. D. *Tetrahedron: Asymmetry* **1991,** *2,* 957.

53. Chow, H.-F.; Mak, C. C. *Tetrahedron Lett.* **1996,** *37,* 5935.

54. Jansen, J. F. G. A.; Peerlings, H. W.; de Brabander-van den Berg, E. M. M.; Meijer, E. W. *Angew. Chem., Int. Ed. Engl.* **1995,** *34,* 1206.

55. Kramers, J. A.; Meijer, E. W. *J. Org. Chem.* **1994,** *59,* 4262.

56. Peerlings, H. W. I.; Struijk, M. P.; Meijer, E. W. *Chirality* **1998,** *10,* 46.

57. Chow, H.-F.; Mak, C. C. *Pure Appl. Chem.* **1997,** *69,* 483.

58. Chang, H.-T.; Chen, C.-T.; Kondo, T.; Siuzdak, G.; Sharpless, K. B. *Angew.Chem. Int. Ed. Engl.* **1996,** *35,* 182.

59. Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999,** *64,* 7202.

60. R. G. Denkelwalter, J. F. Kole, W. J. Lukasavage, **1982**, *US Pat,* 4,360,646.

61. Twyman, L. I. J.; Beezer, A. E.; Mitchell, J. C. *Tetrahedron Lett.* **1994,** *35,* 4423.

62. Ashton, P. R.; Boyd, S. E.; Brown, C. L.; Nepogodiev, S. A.; Meijer, E. W.; Peerlings, H. W. I.; Stoddart, J. F. *Chem. Eur. J.* **1997,** *3,* 3974.

63. Hudson, R. H. E.; Damha, M. J. *J. Am. Chem. Soc.* **1993,** *115,* 2119.

64. Roy, R.; Kim, J. M. *Angew. Chem. Int. Ed. Engl.* **1999,** *38,* 369.

65. Posnett, D. N.; McGrath, H.; Tam, J. P. *J. Biol. Chem.* **1988,** *263,* 1717.

66. Balasubramanian, R.; Rao, P.; Maitra, U. *Chem. Commun.* **1999,** 2353.

67. Murer, P. K.; Lapierre, J.-M.; Greiveldinger, G.; Seebach, D. *Helv. Chim. Acta.* **1997,** *80,* 1648.

68. Pincock, R. E.; Perkins, R. R.; Ma, A. S.; Wilson, K. R. *Science* **1971,** *174,* 1018.

69. Whitesell, J. K. *Chem. Rev.* **1989,** *89,* 1581.

70. Pu, L. *Chem. Rev.* **1998,** *98,* 2405–2494.

71. Truesdale, L. K. *Org. Synth.* **1988,** *13,* 67.

72. Fabbri, D.; Delogu, G.; De Lucchi, O. *J. Org. Chem.* **1993,** *58,* 1748.

73. Hu, Q.-S.; Vitharana, D. R.; Pu, L. *Tetrahedron: Asymmetry* **1995,** *6,* 2123.

74. Noji, M.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1994,** 7983.

75. Kyba, E. P.; Gokel, G. W.; de Jong, F.; Koga, K.; Sousa, L. R.; Siegel, M. G.; Kaplan, L.; Sogah, G. D. Y.; Cram, D. J. *J. Org. Chem.* **1977,** *42,* 4173-4184.

76. Fumio, T.; Kazuhiro, Y.; Shunji, H.; Shinji, T.; Spyros, C.; Irene, M. M. *Org.Biomol.Chem*. **2004,** *2,* 449-451.

77. Vains, J. B.; Regnouf, D. *Tetrahedron Letters* **2001,** *42,* 6507-6509.

78. Kőszegi, É.; Grün, A.; Bitter, I. *Supramolecular Chemistry.* **2008,** *6,* 565-572.

79. Xie, D.; Jiang, M.; Zhang, G.; Chen, D. *Chemistry European Journal* **2007,** *13,* 3346-3353.

80. Khrushcheva, N. S.; Sokolov, V. I. *Russ. Chem. Bull., Int. Ed.* **2004,** *4,* 830-833.

81. Thakkar, K.; Geahlen, R. L.; Cushman, M. *J. Med. Chem.* **1993,** *36,* 2950-2955.

82. Malkoch, M.; Schleicher, K.; Drockemnmuller, E.; Hawker, C. J.; Russell, T. P.; Wu, P.; Fokin, V. V. *Macromolecules* **2005,** *38,* 3663-3678.

83. Cram, D. J.; Sogah, D. Y. *J. Am. Chem. Soc.* **1985,** *107*, 8301–8302.

84. Kazlauskas, R. J. *Org. Syn.* **1991,** *70,* 60-67.

85. Wang, M.; Liu, S. Z.; Liu, J.; Hu, B. F. *J. Org. Chem.* **1995,** *60,* 7364–7365.

86. Brunel, J. M.; Buono, G. *J. Org. Chem.* **1993 ,** *58*, 7313–7314.

87. Cai, D.; Hughes, D.; Verhoeven, T. R.; Reider, D. J. *Tetrahedron Lett.* **1995,** *36*, 7991-7994.

88. Stock, H. T.; Kellogg, R. M. *J. Org. Chem.* **1996,** *61*, 3093–3105.

89. Vains, J.; Bernard, R. d. *Tetrahedron Letters* **2001,** *42,* 6507-6509.

90. Kyba, E. P.; Gokel, G. W.; Koga, F. D. J. . K. . S. L. R.; Siegel, M. G.; Kaplan, L.; Sogah, G. D. Y.; Cram, D. J. *J. Org. Chem.* **1977,** *42,* 4173–4184.

91. Stock, H. T.; Kellogg, R. M. *J. Org. Chem.* **1996,** *61*, 3093–3105.

92. Thakkar, K.; Geahlen, R. L.; Cushman, M. *J. Med. Chem.* **1993,** *36,* 2950-2955.

93. D. A. Tomalia, J. R. Dewald, *U.S. Pat*ent, 4,507,466, **1985**.

94. D. A. Tomalia, J. R. Dewald, *U.S. Pat*ent, 4,568,737, **1986**.

95. D. A. Tomalia, J. R. Dewald, *U.S. Pat*ent, 4,587,329, **1986**.

96. Chaumette, J. L.; Laufersweiler, M. J.; Parquett, J. R. *J. Org. Chem.* **1998,** *63,* 9399.

97. D. A. Tomalia, J. R. Dewald, *U.S. Pat*ent, 4,694,064, **1986**.

98. D. A. Tomalia, J. R. Dewald, *U.S. Pat*ent, 4,737,550, **1987**.

99. D. A. Tomalia, J. R. Dewald, *U.S. Pat*ent, 4,713,975, **1987**.

100. Kim, Y. H. *Macromol. Symp.* **1994,** *77,* 21.

101. Tomalia, D. A.; Naylor, A. M.; Goddard, W. A. *Angew. Chem., Int. Ed. Engl.* **1990,** *29,* 138.

102. Hawker, C. J.; Fréchet, J. M. *J. Am. Chem. Soc.* **1990,** *112*, 7638.

103. Chow, H.; Mak, C. *J. Chem. Soc. Perkin Trans. 1* **1994,** 2223.

104. Wooley, K. L.; Hawker, C. J.; Fréchet, J. M. *Angew. Chem., Int. Ed. Engl.* **1994,** *33,* 82.

105. Spindler, R.; Fréchet, J. M. *J. Chem. Soc., Chem. Commun.* **1993,** 913.

106. Ishida, Y.; Jikei, M.; Kakimoto, M. *Macromolecules.* **2000,** *33,* 3202.

107. Moor, R.; Vögtle, F. *Chem. Ber.* **1993,** *126,* 2133.

108. Newkome, G. R.; He, E. F.; Moorefield, C. N. *Chem. Rev.* **1999,** *99,* 1689.

109. Fischer, M.; Vögtle, F. *Chem. Soc. Rev.* **1998,** *27,* 233.

110. Astruc, D.; Chardac, F. *Chem. Rev.* **2001,** *101,* 2991.

111. Singh, P. *Bioconj. Chem.* **1998,** *9,* 54.

112. Langer, R. *Chem. Eng. Sci.* **1995,** *13,* 4109.

113. Esfand, R.; Tomalia, D. A. *Drug Discovery Today.* **2001,** *6*, 427.

114. Kukowska, J. F.; Raczka, E.; Chen, A.; Rymaszewski, C. L.; Baker, J. R. *Hum. Gene Therapy* **2000,** *11,* 1385.

115. Liu, Y.; Chen, Y.; Li, B.; Wada, T.; Inoue, Y. *Chem. Eur. J.* **2001,** *7,* 2528-2535.

116. Winnik, F. M.; Davidson, A. R.; Breton, M. P. 089,475, 1992.

117. Castagnola, M.; Cassiano, L.; Lupi, A.; Messana, I.; Patamia, M.; Rabino, R.; Rossetti, D. V.; Girdina, B. *J. Chromatogr.* **1999,** *694*, 463.

118. Seebach, D.; Murer, P. *Angew. Chem. Int. Ed. Engl.* **1995,** *34,* 2116.

119. Lescanec, R. L.; Muthukumar, M. *Macromolecules.* **1990,** *23,* 2280.

120. Chow, H.-F.; Mak, C. C. *J. Chem. Soc., Perkin Trans.* 1 **1997,** *1,* 91.

121. Miklis, P.; Cagin, T.; Goddard, W. A. *J. Am. Chem. Soc.* **1997,** *119,* 7458.