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Review

Molecular trees: from syntheses towards applications[†]

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Summary – Molecular trees, also called dendrimers, arborols, cauliflowers, cascades or hyperbranched molecules, have been synthesized since their first observation in 1978 by divergent, convergent or combined methods, with various functions on the branches. The potential applications of these nanoscopic molecules are in the fields of biology (gene therapy, virus mimicking and vectorization) and molecular materials sciences (new polymers, adhesion, liquid crystals, *etc*).

molecular tree / dendrimer / cascade molecule / synthesis / applications of dendrimers

Contents

Abbreviations

amu:	atomic molecular unit
A_p:	protected function A
AIDS:	acquired immunodeficiency syndrome
B_p:	protected function B
BOC:	*t*-butoxycarbonyl
Cp:	η^5-cyclopentadienyl
CPK:	Corey-Pauling-Koltun
DCC:	dicyclohexylcarbodiimide
DEC:	1-[3-(dimethylamino)propyl]-3-ethyl carbodiimide hydrochloride
DNA:	desoxyribonucleic acid
FAB:	fast atom bombardment
nm:	nanometer
PAMAM:	polyamidoamine
R:	alkyl, allyl or benzyl
RNA:	ribonucleic acid
SDS:	sodium dodecyl sulfate
SEC:	size exclusion chromatography
SEC-LALLS:	SEC coupled with low-angle laser light scattering
THF:	tetrahydrofuran
TOF MALDI:	time-of-flight matrix-assisted laser-desorption ionization
Trp:	tryptophan
TTF:	tetrathiafulvalene

[†] Dedicated to Professor René Dabard, Director of the "Institut national des sciences physiques" of Rennes, on the occasion of his retirement.

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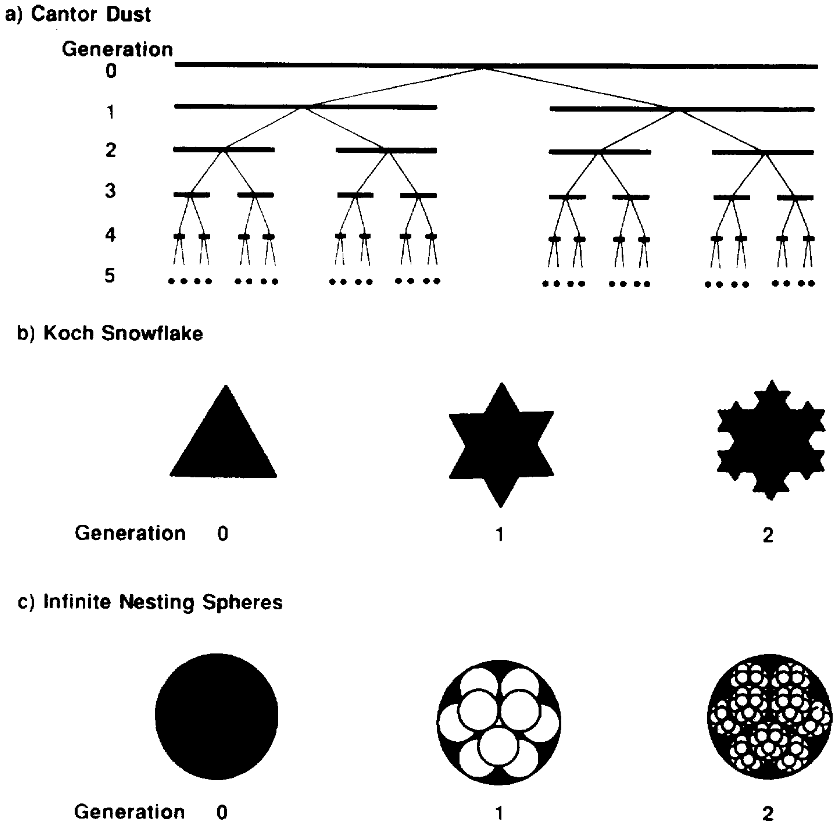


Fig 1. a) Bifurcation of a line segment with connectivity paths to define Cantor dust; b) bifurcation of a triangle (two-dimensions) to define Koch snowflakes; c) fitting of a sphere (three dimensions) to define a series of infinite nesting spheres. Adapted from ref 16.

Introduction

Whereas chemists have been synthesizing *well-defined small molecules* for about two centuries, the emergence of supramolecular chemistry [1, 2], chemistry beyond the molecule, initiated by Lehn [1], now addresses goals involving *well-defined macromolecules* relevant to biochemistry. Such large molecular assemblies can provide biomimetic functions, such as electron transfer in proteins [3] (*ie* photosynthesis [4]) or biocatalysis [5]. They can also be designed and constructed by chemists following abiotic systems. Classical polymers are related to such assemblies but are not so well defined. Molecular trees, however, are constructed from a small polyfunctional core by a branching reaction, generation after generation, according to a principle analogous to the fractal geometry of Mandelbrot [6-13] illustrated in scheme 1 [14].

The trees can rapidly reach a high number of branches, but remain well-defined molecules until a certain number of generations. De Gennes and Hervet [15] have predicted that the external surface of a molecular tree becomes saturated because of the dense packing when it reaches a given number of generations. This depends on the topology and the length of the segment added at each generation. If the construction is continued beyond this point, defects start to appear and the molecular object is no longer well defined (see section *The De Gennes dense-packing model*). By taking into account this fundamental limiting principle, chemists have been able to synthesize and characterize very large molecular trees with up to 10 generations.

The new emerging science of molecular trees [16-23], also called cascade molecules [19], dendrimers [16, 20], arborols [18, 21], and cauliflower polymers, is attractive because these giant molecules are aesthetically pleasing and synthetically challenging. Considerable synthetic efforts have recently been achieved and the interest has now turned towards applications [17b, 20].

One of the most fascinating aspects, however, is the relevance to genealogy and the chemistry of life (see, for instance fig 2), despite the abiotic aspect of the architectural construction [16, 20]. Tomalia pointed out that, as in biochemistry, the starting point is a germ (seed) for the construction. A remarkable comparison between the abiotic and biological molecular construction pathways lies in the replication of DNA. Proceeding one step further, we may then consider the transfer of information from generation to generation starting with the initial core. Obviously, the topological features of the tree and its surface intimately depend on the nature and topology of both the core and the segment added at each generation. In biochemistry, molecular information is transferred from DNA to RNA in the course of the transcription process. The self-replication of DNA is

Table I. Molecular trees: historial background.

Date	Author	Event	Reference
1920	Staundiger	Macromolecular hypothesis	49
1941	Flory	Theory of gestation	36
1944	Melville	First suggestion of tree-like molecules	40
1952	Flory	Non-linear polymerization (fig 1)	50
1956	Erlander, French	Hyperbranched dextrin structure of amylopectin (fig 2)	51
1978	Vögtle	Concept of structure-perfect cascade molecules and their first synthetic analogues	19
1982	Maciejewski	Concept of dense packing for cascade polymers	52
1983	Denkewalter	Reported synthesis of poly(lysine) molecular trees with asymmetrical branch junctions	53
1983	De Gennes, Hervet	Calculation of starburst, dense-packed generation limit for poly(amidoamine) molecular trees	15
1983	Tomalia	First successful synthesis of a symmetrical branched high-molecular-weight dendritic polymer	54,55
1985	Newkome	Synthesis of a 27-arborol	56
1989	Rebrov	First organo-Si dendrimers	57
1990	Fréchet	Convergent method for the synthesis of molecular trees	58,59
1990	Miller	Convergent method for the synthesis of molecular trees	60
1990	Tomalia	First comprehensive review on dendrimers	16
1991	Moore	First purely hydrocarbon dendrimer	61
1992	Balzani	Inorganic molecular trees	62,63
1992	Astruc	Organometallic molecular trees	64,65
1994	Majoral	Large neutral molecular trees based on phosphorus	66,67
1994	Labarre	Cyclophosphazenic dandeleon dendrimers	68,69

effected with this information transfer, leading to proliferation through successive generations according to a geometric progression [24]. This principle was extended by Mullis [25] to polymerase chain reactions, an abiotic commercial synthesis of DNA. This powerful principle of abiotic replicating synthesis *in vitro* has recently been applied to a virus [26] and this technique thus has a great future. Specifically, the molecular information that is transferred from generation to generation in the construction of molecular trees, starting from the initial core includes, as noted by Tomalia, the *size, shape, surface, topology and flexibility* [16]. The chemists should be able to manipulate these parameters for the design of discrete molecular trees of *nanoscopic dimensions* (*ie* 1 to 100 nm) [27, 28]. This type of concept in abiotic systems can be compared to those of molecular recognition [1] and structure-directed synthesis (resulting from "self assembly" or "supramolecular structures") [29-35], which do not involve genealogy.

Historically, the construction of tree-like molecular architectures was preceded by the pioneers time of polymer science (table I), and the origins of the molecular branching can be traced back to the network theory of Flory [36, 37] (fig 3) and Stockmayer [38, 39]. As early as 1944, Melville delivered a paper on January 12 to the Faraday Society stating that "someone [will discover] a general method for inducing branching of the chains of atoms without allowing such chains to be linked up into a three-dimensional network" [40]. Cascade theory was treated mathematically leading to a statistical treatment of the networks [41-43]. The first cascade molecules were reported by Vögtle in 1978, who has highlighted the area twice recently [17]. After the high-generation lysine trees of Denkewalter (1989) [53], the first strategy for the systematic construction of symmetrically branched trees was published in 1984 by Tomalia [44-48], who also coined the term starbust dendrimer^{TM} and published a magnificient review in 1990 [16]. In 1985, Newkome synthesized his first arborols (table I) [18, 56].

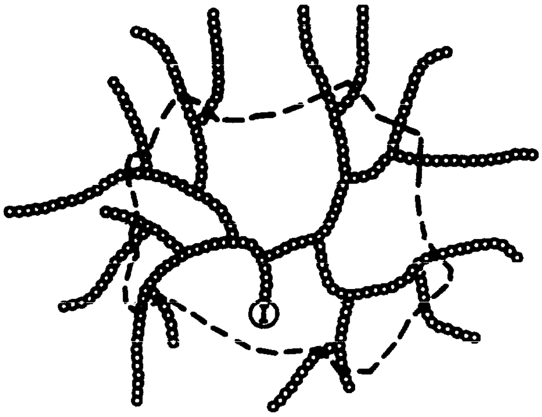


Fig 2. Dendritic branching topology of amylopectin.

Synthetic strategies (see scheme 1)

The divergent method

Organic synthetic methods have actually focused on two kinds of strategies: the divergent method and the

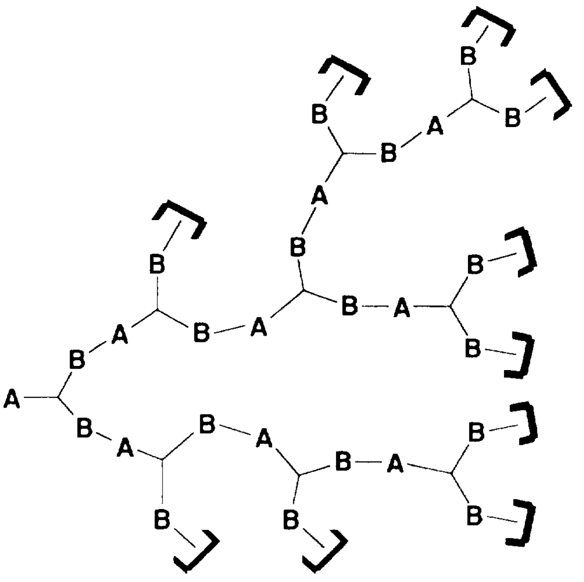


Fig 3. An illustration of Flory's highly branched polymer, which is formed via trifunctional, AB_2-type monomers.

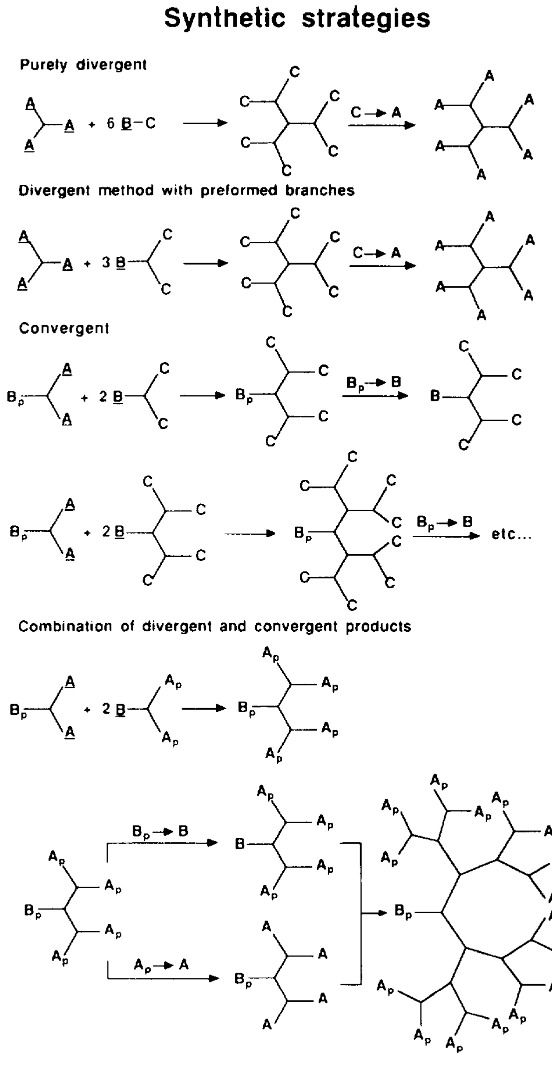
convergent method. In the former, each branch bearing a terminal function is divided into several branches. The same function is introduced at the end of the new branches in order to continue the division process for another generation. If N_c is the number of branches in the initial core and N_b is the number of branches into which the branches are divided, the total number of branches of the tree is $Z = N_c \cdot N_b^G$, G being the number of generations.

The divergent method was developed by the groups of Denkewalter [53], Tomalia [16, 70] and Newkome [21]; Tomalia achieved the first successful synthesis of ideal highly branched polyamidoamine (PAMAM) dendrimers through the 10th generation (scheme 2) with a defined number of surface groups (table I).

Table II. Relative molecular mass M_r, number of monomer units, number of terminal groups, predicted diameters (CPK models), and hydrodynamic diameter (determined by size exclusion chromatography) for starburst (PAMAM dendrimers as a function of generation). Adapted from ref 20.

Generation	M_r	Monomer units	Terminal groups	Diameters [Å] CPK [a]	SEC
0	359	3	3	9.6 (19.2)	10.8
1	1 043	9	6	12.8 (28.8)	15.8
2	2 411	21	12	17.6 (41.6)	22.0
3	5 147	45	24	24.1 (52.2)	31.0
4	10 619	93	48	30.6 (65.6)	40.0
5	21 563	189	96	38.5 (81.6)	53.0
6	43 451	381	192	47.5 (91.2)	67.0
7	87 227	765	384	61.8 (104.0)	80.0
8	174 779	1 533	768	78.0 (117.0)	92.0
9	349 883	3 069	1 536	98.0 (130.0)	105.0
10	700 091	6 141	3 072	123.0 (143.0)	124.0

[a] CPK = Corey-Pauling-Koltun; the first value refers to a three-dimensional contracted model, the value in parentheses to a three-dimensional extented model.



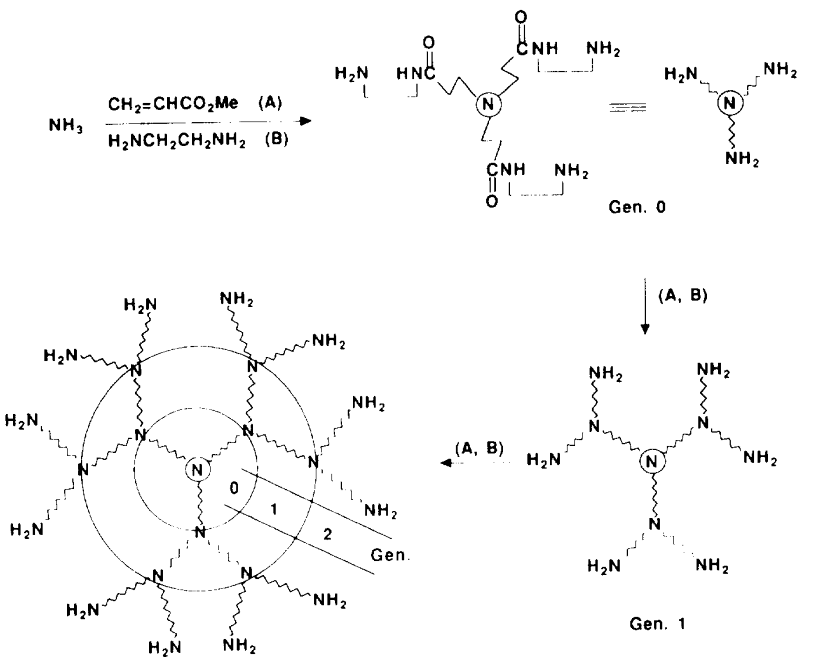
Scheme 1

These syntheses have been extended to linear polyamine cores and linear polyethylenimine cores [71-74].

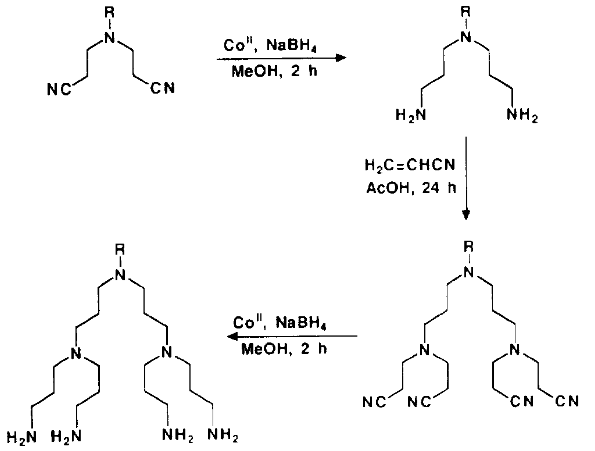
Interestingly, the pioneering cascade molecules of Vögtle used a related scheme involving the Michael addition of acrylonitrile to amines (scheme 3) [19]. This powerful method has now led to higher generations (up to five), high scales and a potentially commercial process. Indeed, the groups of Meijer and Mülhaupt have elegantly improved the reduction step of the construction by Vögtle and produced large-scale syntheses of now easily accessible molecular trees [75-77] (scheme 3b).

A variety of synthetic schemes were reported by Newkome, which also use the Michael addition of acrylonitrile or the related ester $CH_2{=}CHCO_2$-*t*-Bu on nitromethane or polyols (scheme 4) to build cores (scheme 4) [78-80].

Polyacylchloride or polycarboxylic acid cores were allowed to react with aminotriester cores for iterative synthesis (scheme 5) [81].



Scheme 2. Synthetic scheme for starburst PAMAM dendrimers [16].



Scheme 3a. The original cascade synthesis of polyamines reported by Vögtle *et al* [19].

Similarly, 1,3,5-benzenetricarbonyl trichloride was allowed to react with aminotriesters such as $H_2NC(CH_2OCH_2CH_2CO_2Et)_3$ obtained by reaction of $H_2NC(CH_2OH)_3$ with acrylonitrile and KOH in dioxane, giving the tris-nitrile, followed by reaction with anhydrous HCl in refluxing EtOH [79, 82].

The molecular trees of Denkewalter [53] (scheme 6) represent the first examples of well-defined, monodisperse dendritic polymers until generation 10. The core is a benzhydrylamine and the construction proceeds with an activated ester of amino protected L-lysine as the branching agent [83] (scheme 6). These molecular trees have been fixed on a Merrifield resin by Tam *et al* [84, 85]. Generation 10 has 2 048 terminal groups and its diameter reaches about 100 Å according to measurements made by intrinsic viscosity or small-angle X-ray scattering, as shown by Aharoni [86, 87].

Early arborols from Newkome's group start from polyhydroxy or polybromide cores [18, 21, 56, 88, 89] (schemes 7 and 8).

A remarkable all-carbon series of trees called the iptycenes, with either benzene or triptycene as the initiator core, was obtained by Hart [90-95] (scheme 9).

Compact and congested polyether trees with short branches were obtained by Tomalia [72]. This synthesis starts with $C(CH_2Br)_4$ with a masked pentaerythritol (bicyclic orthoester). Three hydroxy groups per terminal group were obtained after deprotection (scheme 10). Given this dense packing, branching defects become progressively higher from generation 2 to generation 3.

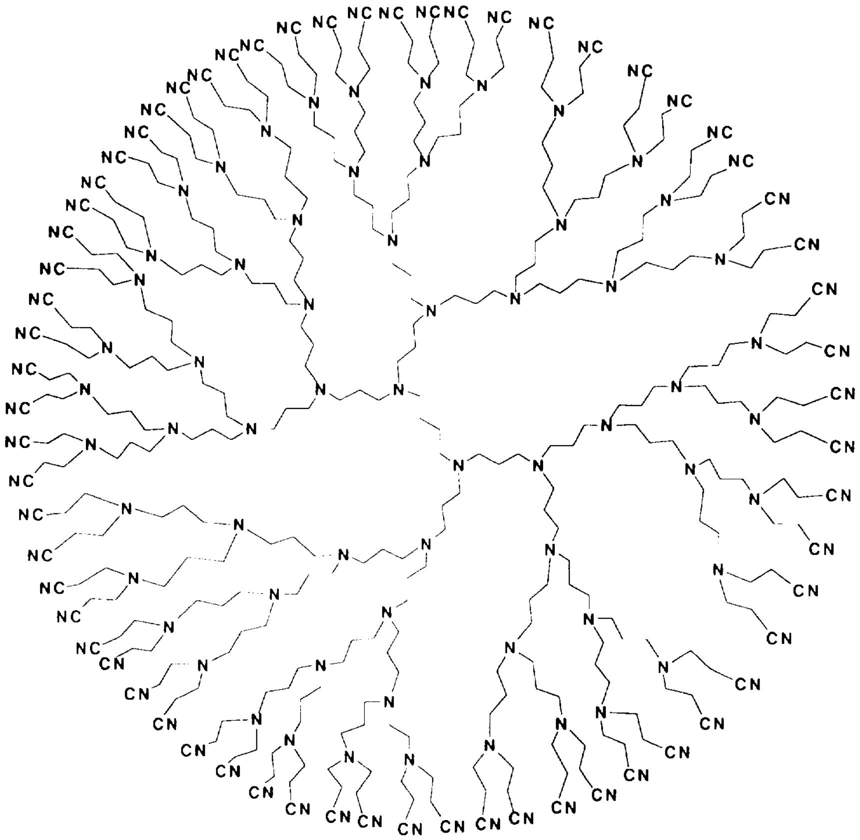
Polythioether analogues were synthesized, but the number of hydroxyl surface groups did not triple due to the steric effects [96].

Masamune [97] has achieved the synthesis of high-molecular-weight silicon molecular trees of up to 14 790 amu (atomic molecular unit) (scheme 11).

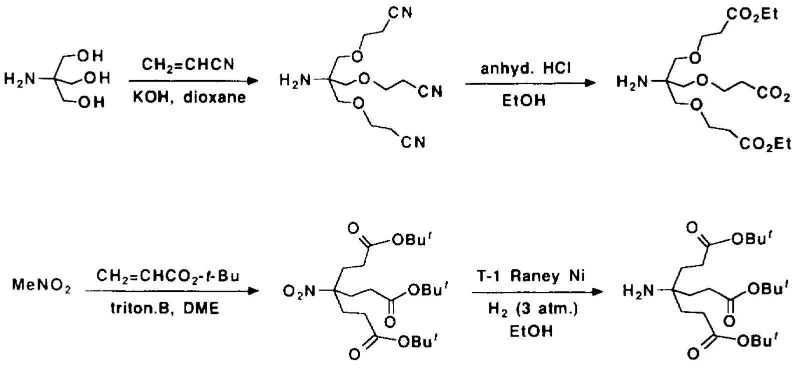
Roovers [98] also reported carbosilane molecular trees synthesized via repetitive Pt-catalyzed addition of dichloromethylsilane to an alkene and nucleophilic substitution at the terminal chorosilane group with vinylmagnesium bromide. Molecular trees up to 64 terminal groups and 6 016 amu (4th generation) were synthesized (scheme 12).

Starting from tetraallylsilane (rather than the tetravinylsilane above), van der Made [99, 100] reached a polysilane molecular tree with up to 972 end groups (73 912 amu, 5th generation) using repetitive alkenylation-hydrosilylation cycles (scheme 13).

Similarly, using tetravinylsilane Seyferth's group [101] synthesized an organosilicon molecular tree with 324 Si-H bonds (scheme 14).



Scheme 3b. Poly(propylen imine) dendrimer with diaminobutane core [76].



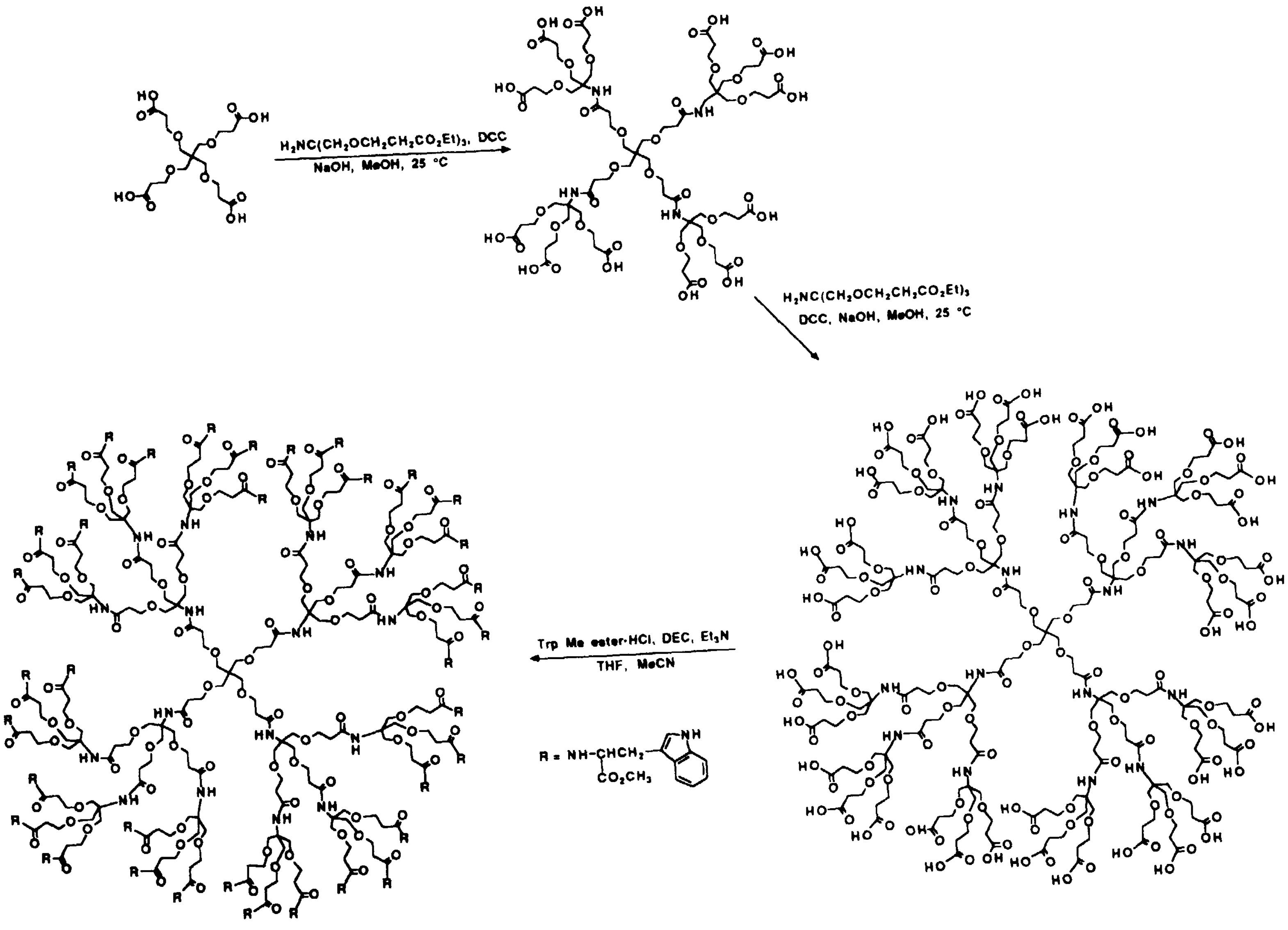
Scheme 4. References 78 and 79.

Zhdanov *et al* [57] performed an early synthesis of a tree with 46 Si atoms. This synthesis started from the reaction of CH_3SiCl_3 with $(EtO)_2(CH_3)SiONa$ and subsequently $SOCl_2$, and continued by repetitive reaction steps using these two reagents.

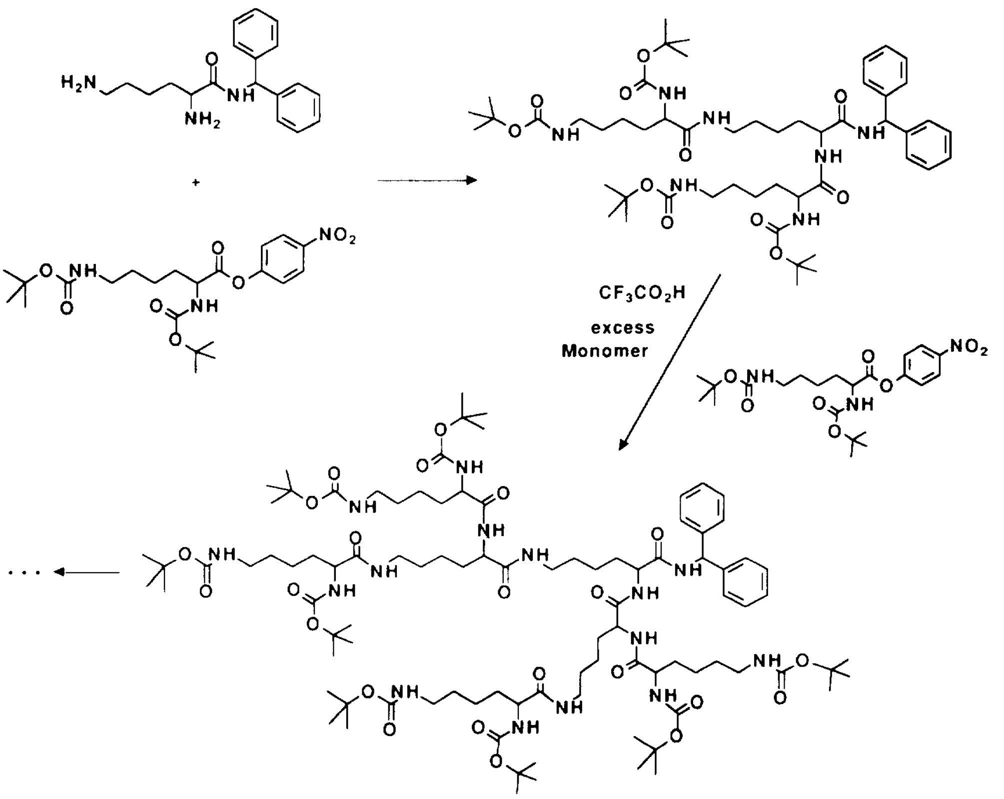
The convergent method

The convergent method (scheme 1) was reported independently by Fréchet [58, 59, 102] and Miller [60]. It is a useful sophistication yielding efficient paths to highly branched molecular trees. It consists of using a heterobifunctional core with, for example, three functional groups, of the type AB_2, in such a way that A_p is a protected form of a function A which reacts with B. An early example is represented in scheme 15. The largest tree made according to this scheme has 192 branches (40 689 amu).

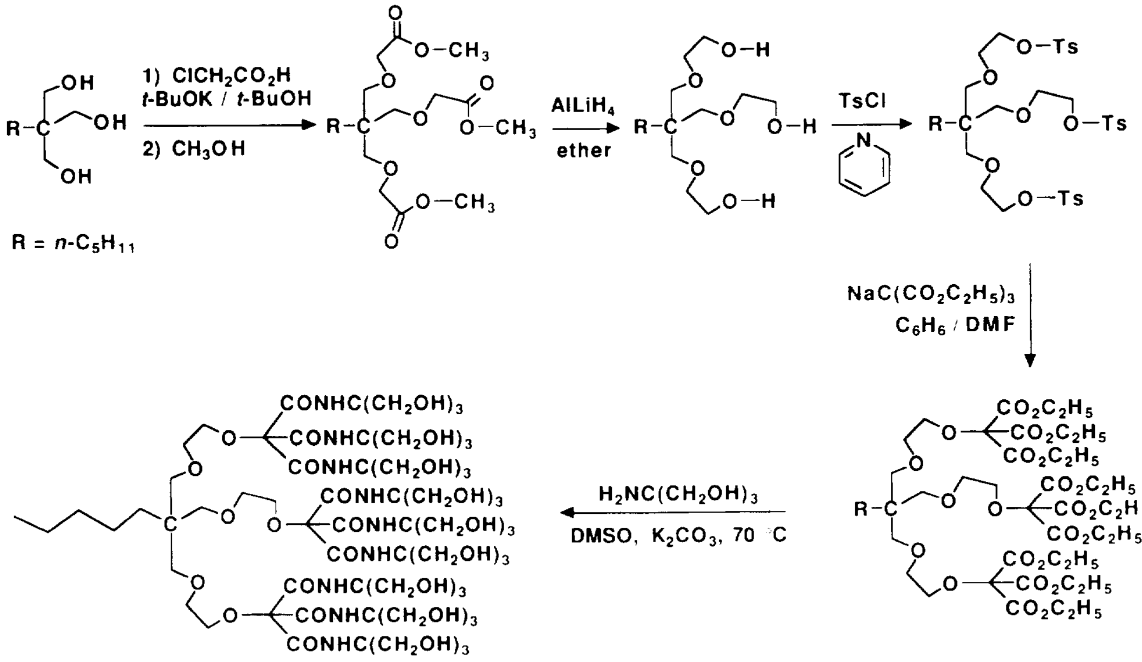
Viscosity studies [103] indicate a maximum for the third generation whereas the refractive index has a minimum around the second generation. These results indicate a monotonic decrease in density from the center to the outskirts, supporting the theoretical model of higher density inside the tree than at the outer surface [104]. Extended cores were also designed to minimize steric hindrance affording higher molecular weights, up



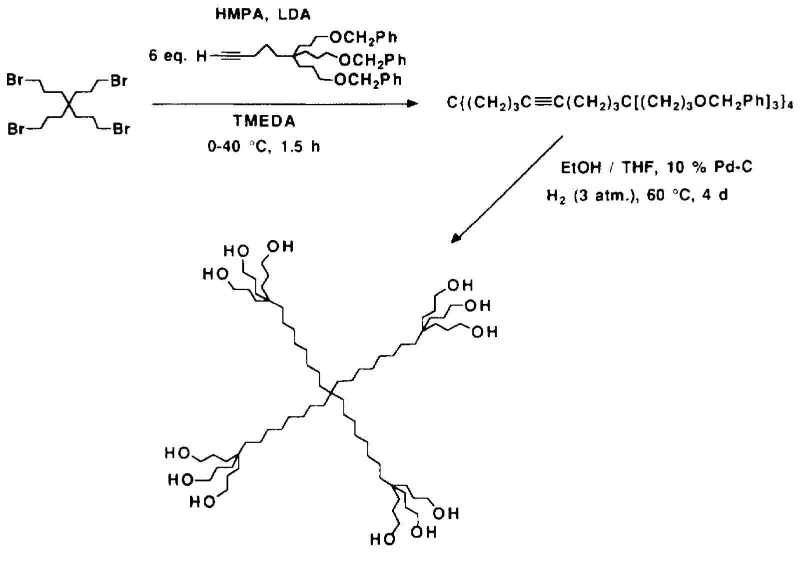
Scheme 5. Reference 81.



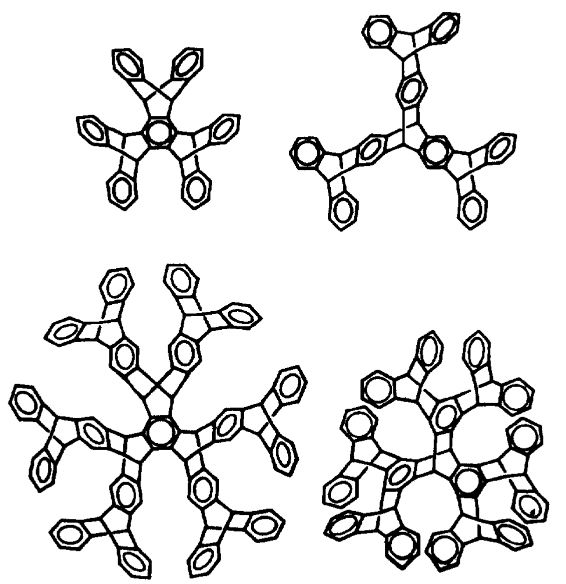
Scheme 6. Synthesis of lysine-based dendrimers by Denkewalter *et al* [53].



Scheme 7. References 18 and 21.



Scheme 8. References 18 and 21.



Scheme 9. Hydrocarbon dendrimers (iptycenes): heptaiptycene, nonaiptycene, nonadecaiptycene and supertriptycene [95].

to 8 420 amu [105] (scheme 16). The control of surface functionality with cyano, bromo and carboxymethyl groups was reported [106, 107].

The iterative convergent synthesis of polyamide molecular trees was achieved by coupling (DCC/DMAI) a secondary amine to a N-BOC (t-butoxycarbonyl) protected aminodicarboxylic acid (scheme 17). The highest molecular weight was 5 082 amu [108].

Miller and Neenan [60] reported a first convergent synthesis in 1990, using 1,3,5-trisubstituted benzene (scheme 18).

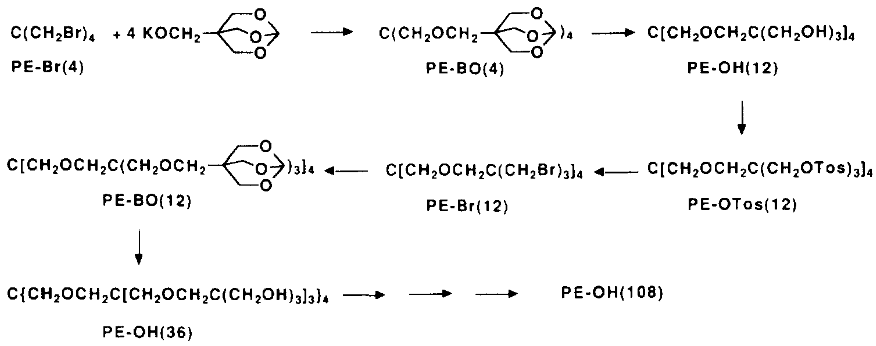
Miller's group has also reported an astute convergent synthesis of polyaryl molecular trees based on Pd-catalyzed aryl-aryl coupling [109] (scheme 19). Polypentafluorophenyl analogues were synthesized according to the same scheme.

Polyaryl trees with ester linking moieties were also synthesized by Miller's group [110] (scheme 20). The largest tree of this kind has 46 phenyl groups and a molecular weight of 5 483 amu. Another convergent synthesis of extended aryl ester dendrimers has been reported [111].

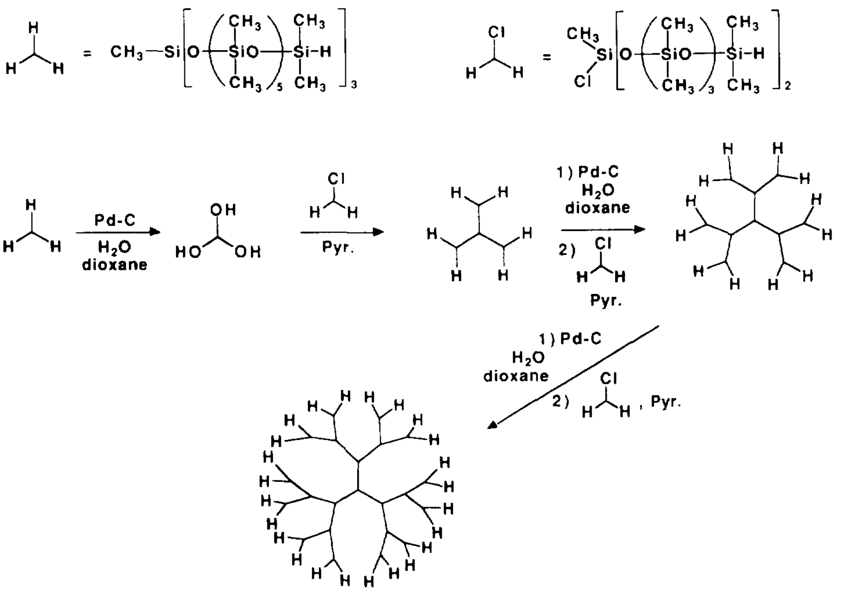
Variations of the convergent method are known to increase the number of branches. For instance, trees prepared by the convergent method were attached to a polyfunctional core, a technique called "double-stage growth" [105] or the branch-monomer approach [105, 112]. In a similar way, Wilkins and Moore [107] combined the convergent and divergent methods with the same substrate, using double protection, to grow trees rapidly. The reaction of a four-branch tree AB_{p4} with four-branch tree A_pB_4 easily yields a 16-branch tree A_pB_{p16} and so on. For instance, these authors unsuccessfully attempted the reaction of AB_{p16} with A_pB_{16} to produce A_pB_{254} with phenylacetylene units. However, a modified version of A_pB_{16} with t-butyl endings instead of phenylethynyl produced a remarkable 255-branch tree in 80% yield (characterized by TOF MALDI mass spectrometry); this is the largest known hydrocarbon tree. The author called this method the double exponential dendritic growth (the number of branches is $n = 2^G - 1$, G = the number of generations) (see scheme 1, above).

Finally, if a monomer AB_n is allowed to polymerize by reaction between A and B sites, it does so according to a tree-like geometry. Many such polymers have been prepared and this area has been reviewed [20]. Special types include the so-called comb-burst dendrimers reported by Tomalia [20]. This strategy involves reiterative grafting of "reactive end group" polymer chains to form tree-like polymers [113].

In summary, if we wish to compare purely divergent and purely convergent methods, we should note that the



Scheme 10. Synthetic scheme for starburst polyether (PE) dendrimers [72].



Scheme 11. Construction of a three-directional silicon-based cascade using a versatile silicon hydroxylation and coupling scheme [97].

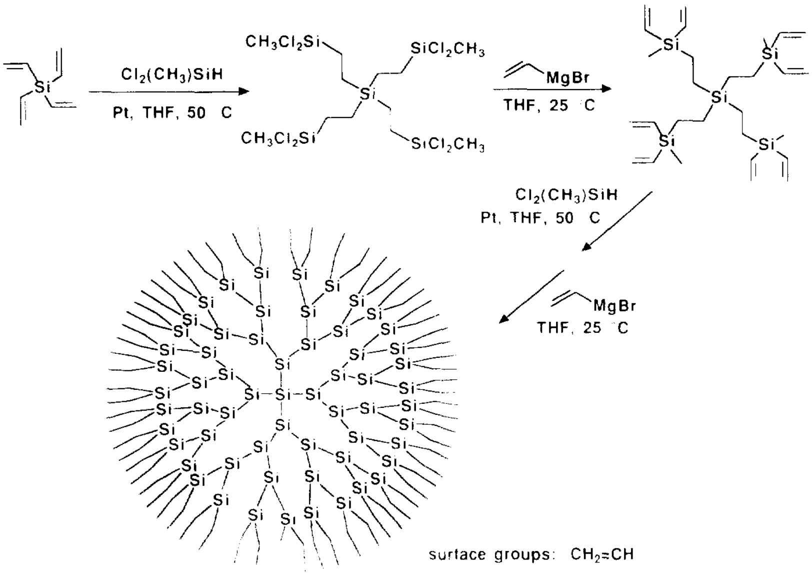
divergent approach suffers from defects on the surface because of the higher number of branches as the generation number increases. Excess reagent is needed and the necessary elimination of this excess may be a problem. On the other hand, the convergent approach suffers from steric constraints when the "dendrons" supposed to be attached to the core become too large. In any case, the number of steps to obtain a given molecular tree using either method is the same and these methods can be combined with each other.

Charged molecular trees and micellar aspects

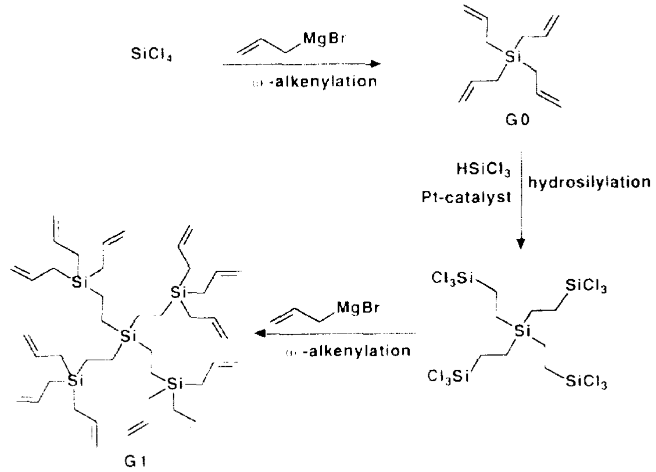
Molecular trees can be considered and used as micelles or inverted micelles. Newkome, whose arborols (trees with alcohol branches) are well known, enhanced the water solubility of the 36-arborol by oxidation of the terminal hydroxy groups to carboxylic acid with $RuO_2/NaIO_4$, followed by generation of the polymethylammonium carboxylate salt in order to study the micellar properties by UV spectroscopy of guest molecules (pinacyanol chloride, phenol blue and naphthalene) (scheme 21). Fluorescence life-time decays were measured using diphenylhexatriene as a probe [114].

The monodispersity, absence of intermolecular aggregation and molecular size were investigated by electron micrography. Photophysical studies of electron transfer on the anionic micelle surface were performed by Tomalia and Turro [115]. Sodium dodecylsulfate (SDS; C-12) and carboxylate-terminated half-generation PAMAM dendrimer [73, 116] were compared. Fluorescence probe experiments used luminescence quenching of the excited state of $Ru(bipy)_3^{2+}$ with methyl viologen. The results were in accord with previous studies indicating that lower generation PAMAM dendrimers (generation < 3.5) had a more dome-like shape than those of higher generations, which were found to be spherical [115-119].

Polyphosphonium and polyammonium molecular trees were synthesized by Engel and Rengan [120-122]. The polyphosphonium trees [120] were synthesized by reacting tri-[(methoxymethyl)phenyl]phosphine with an alkyl halide or bromo-4-(methoxymethyl)benzene and $NiBr_2$ which gave three- or four-directional cores. The



Scheme 12. Synthesis of four-directional silane cascades via Pt-mediated hydrosilylation of alkenes [98].



Scheme 13. References 99 and 100.

next step involved the transformation of the benzyl ether group to a benzyl iodide using ISiMe$_3$ followed by addition of tri-[(4-methoxymethyl)phenyl]phosphine (scheme 22). The 36-branch tree is insoluble in H$_2$O, but soluble in MeCN and alcohols.

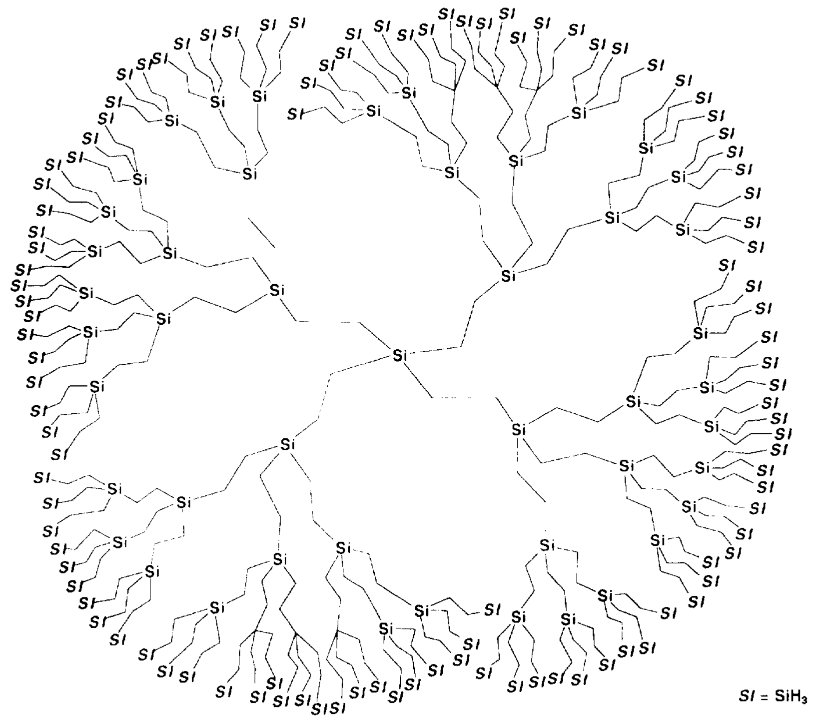
The polyammonium tree [121] was synthesized similarly by reaction of triethanolamine with either an alkyl halide or 2-chloroethanol to give a three- or four-directional core. The polyol was then tosylated in pyridine and treatment with excess triethanolamine gave the 36-branch tree (scheme 22).

The surfactant aspect of dendritic block copolymers has been emphasized [123]. The reactivity of organic anions has been promoted by placing a quaternary ammonium on dendrimers [124].

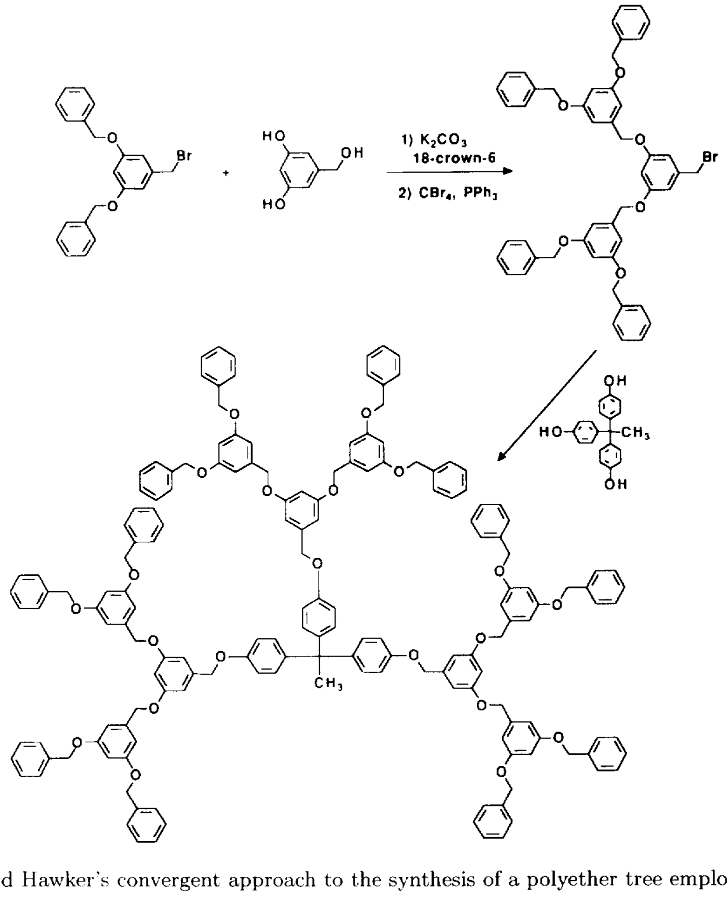
Given the tremendous utility of micelles [125-127], we can predict that the micellar aspect of molecular trees has a bright future. For instance, the range of concentration in pyrene solubilized by dendrimers is much higher than for usual micelles in aqueous media [119, 128].

Molecular trees containing special functional groups: crowns, C_{60}, porphyrins, sugars, boron clusters and TTF

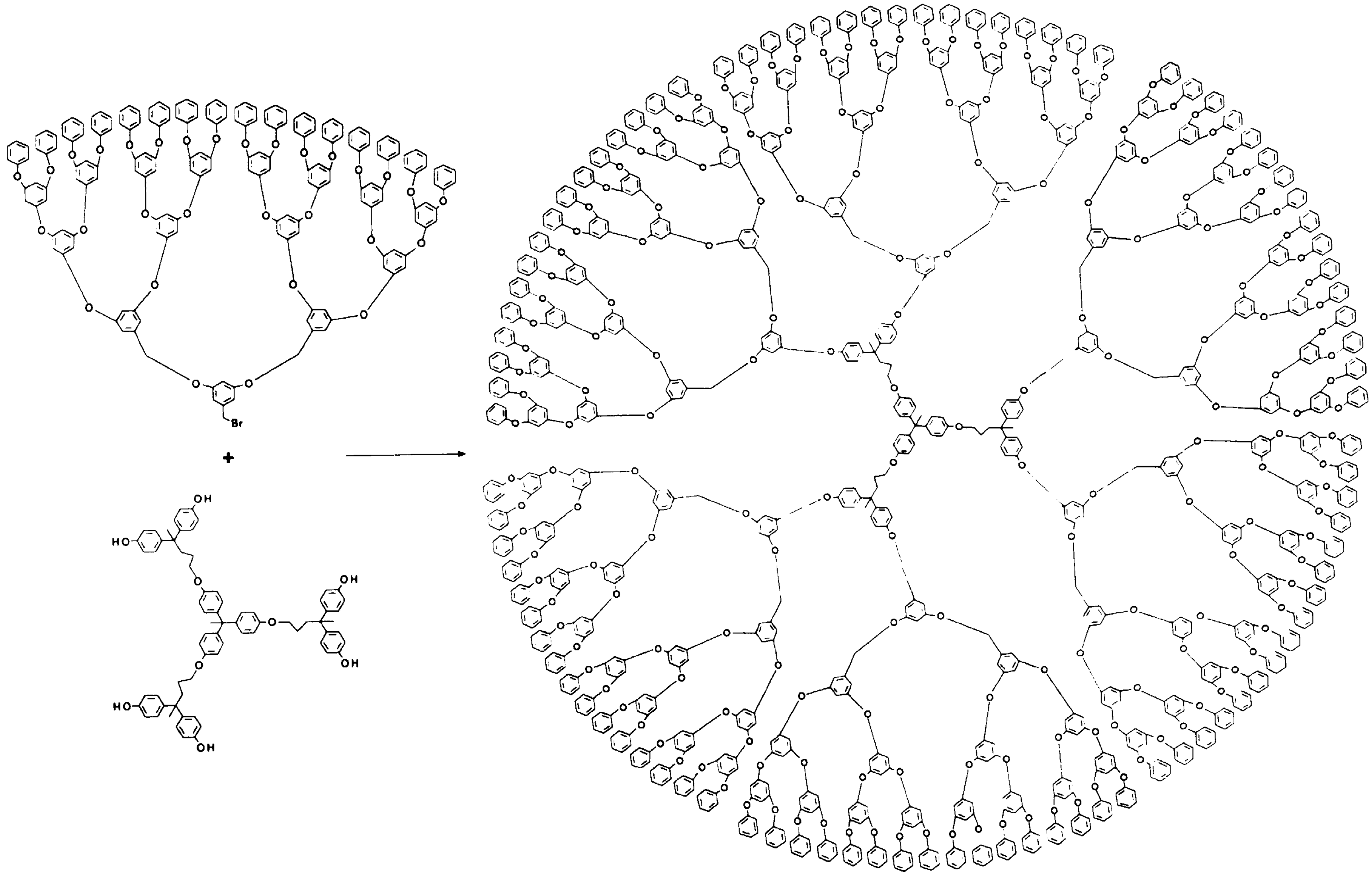
The synthesis of crowned molecular trees, which are potentially ion-complexing agents, was reported by Shinkai [129] using a convergent approach. Tetraoxodiazacrown was prepared in four steps from the monosubstituted N-benzyloxycarbonyldiazacrown ether, and then acylated via the mixed anhydride method (pivaloyl chloride/NEt$_3$/THF) using the N-benzyl-ester-protected diacid monomer. Reaction of the compound formed with 1,3,5-benzenetricarbonyle trichloride and NEt$_3$ in THF gave a second generation polycrown ether (scheme 23).



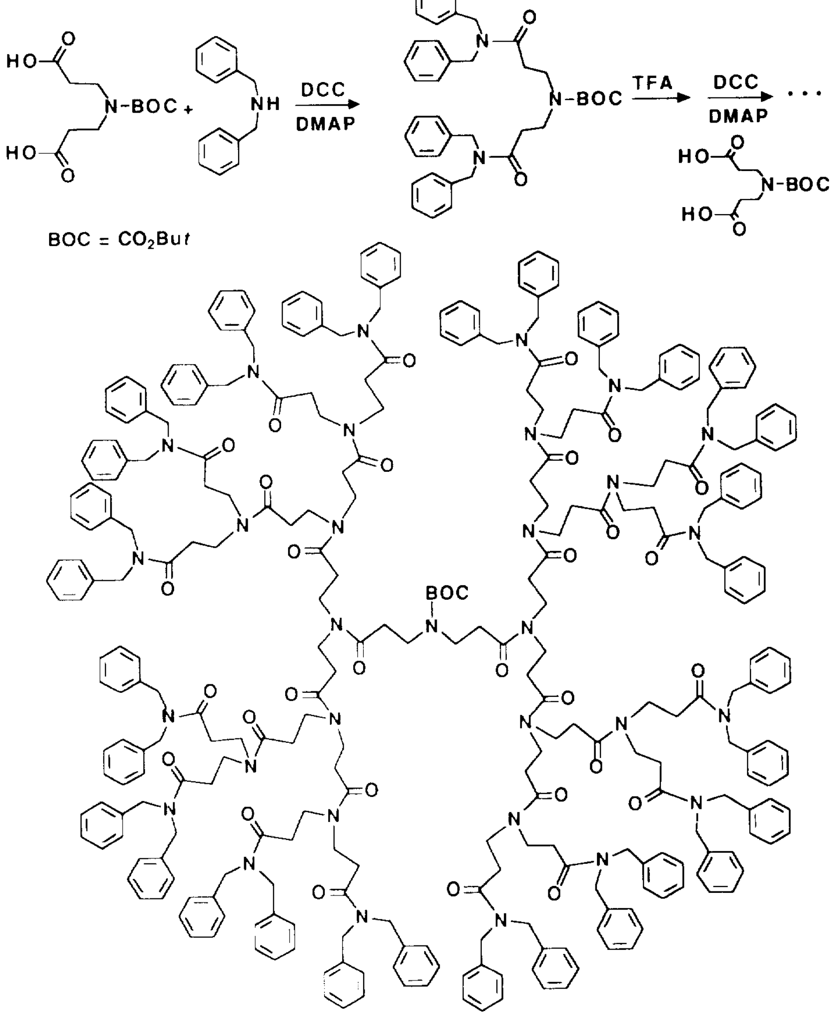
Scheme 14. Reference 101.



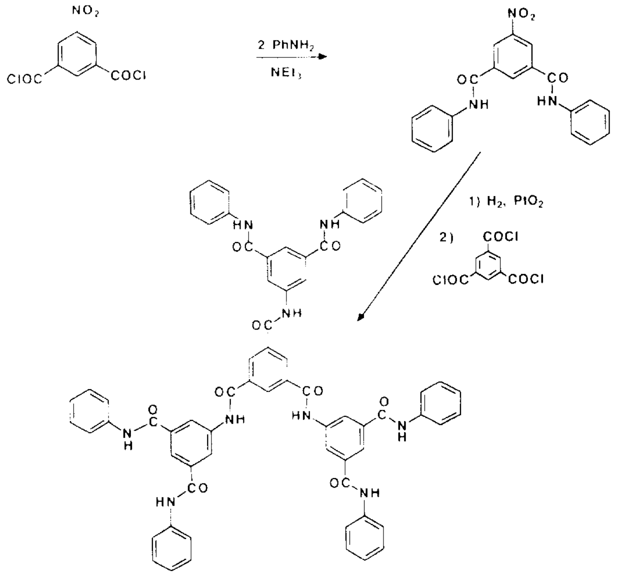
Scheme 15. Fréchet and Hawker's convergent approach to the synthesis of a polyether tree employing a three-dimensional trihydroxy core [59].



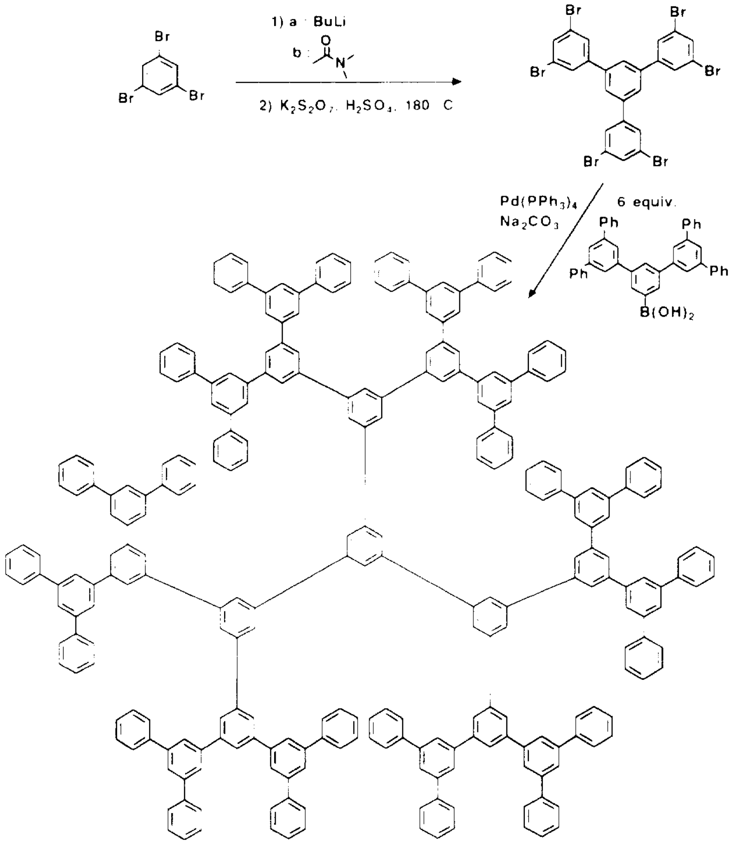
Scheme 16. Convergent strategy for the preparation of hypercores containing three-directional quaternary carbon branching centers, and flexible [-$(CH_2)_3$-] moieties [105].



Scheme 17. Convergent construction of a polyamide cascade using peptide chemistry for monomer connectivity [108].



Scheme 18. Convergent preparation of a three-directional polyaromatic tree using amide connectivity [60].



Scheme 19. Repetitive strategy used to construct a four-tier, three-directional hydrocarbon cascade using an extended hexabromide core [109].

Vögtle designed a molecular tree with a hexacyclen core (hexacyclen = hexaaza[18]crown-6): hexacyclen was linked using a branching unit obtained in a convergent way [130] (scheme 24).

The first molecular tree with a metal-porphyrin core was synthesized by Inoue [131]. Another example of porphyrin-centered molecular trees was synthesized by Diederich [132] using Newkome's divergent construction. The influence of the branches on the reduction potential of the zinc-porphyrin center was investigated by Gross and Louati [132] (scheme 25).

Functional dendrons (molecular trees prepared by the convergent method) have been attached to C_{60} [133, 134] (scheme 26).

Newkome synthesized molecular trees that contained a triple bond on each branch inside the tree. These triple bonds react with decaborane $B_{10}H_{14}$. A dodecaboron cluster could be made in this way and solubilized in water by sulfonate end groups [135, 136] (scheme 27).

Bryce reported a molecular tree with 12 tetrathiafulvalene endings. The voltammogram showed that the redox centers were independent [137] (scheme 28).

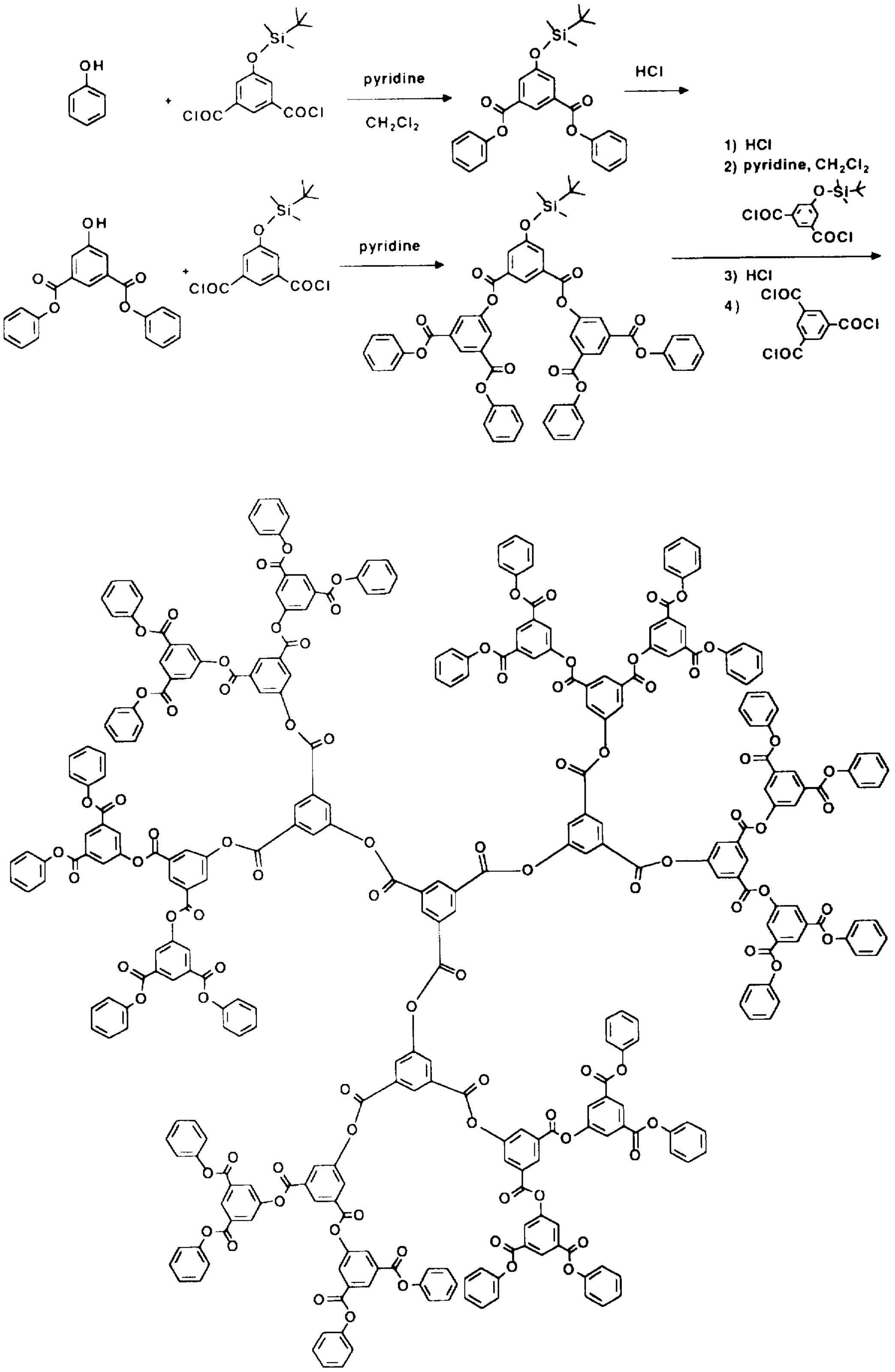
Inorganic and organometallic molecular trees

As well as the nitrogen, phosphorus and silicon based synthetic strategies described above (schemes 12–14 and 22), a variety of creative inorganic and organometallic synthetic strategies have been developed. The first neutral phosphorus-containing molecular trees were reported in 1994 by two groups from Toulouse led by Majoral and Labarre. Majoral's remarkable synthesis started by the reaction of $SPCl_3$ with the sodium salt of 4-hydroxybenzaldehyde and $H_2NN(Me)P(S)Cl_2$. Analogously, the starting point could also be $OPCl_3$. The only by-products were NaCl and water and the synthesis proceeded almost quantitatively (scheme 29) [66]. Trees with up to seven [67] (and even more [138]) generations could be made in this way and their endings could be functionalized with various groups including with crown ethers [67].

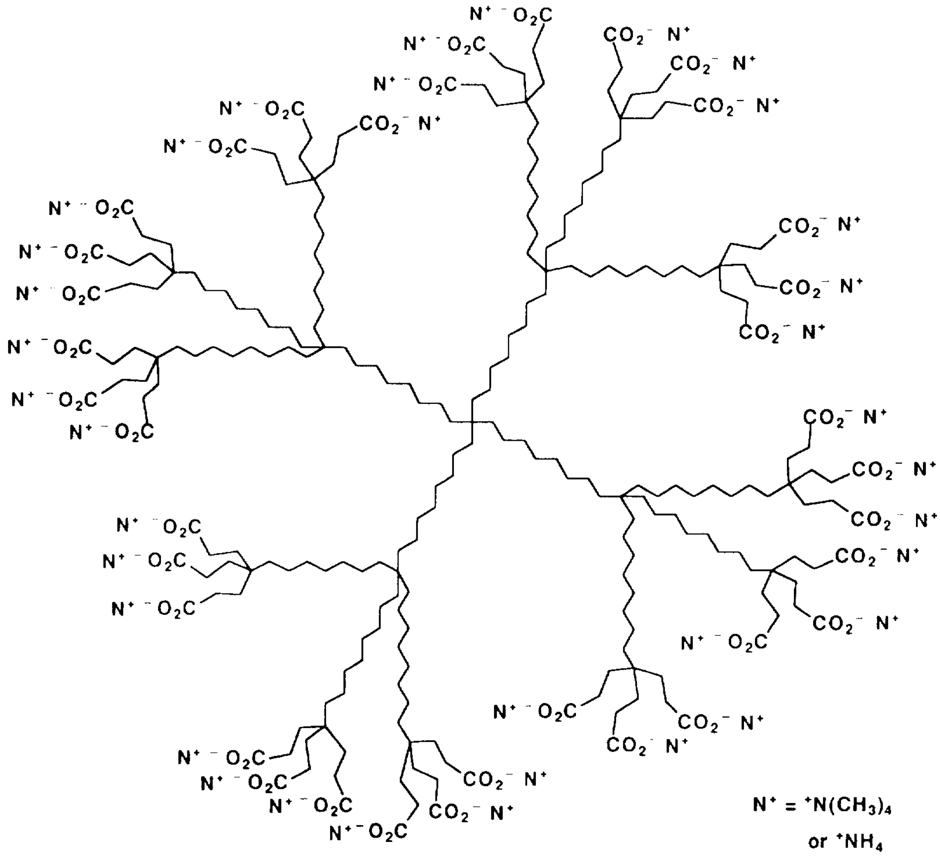
Labarre also performed a series of elegant dendritic syntheses using hexachlorocyclotriphosphazene as a core and long-chain diamines (scheme 30) [68, 69]. Polypodanes of this kind are rare, and so this strategy is especially astute. By linking two phosphazene cores by a diamine, decapodanes were made available and constitute starting materials for future design of cyclophosphazenic "dandeleon" dendrimers [69].

Similarly, Majoral has used the cyclophosphazene core $N_3P_3(OC_6H_4CHO)_6$ for a divergent dendrimer synthesis by successive reaction with $H_2NN(Me)H$, then R_2PCl until the third generation. Above this stage there are solubility problems [139].

The first inorganic transition-metal molecular trees were designed by Balzani's group, based on a divergent



Scheme 20. Preparation of a three-dimensional polyaryl cascade employing ester connectivity and rigid aromatic branching centers [110].



Scheme 21. Reference 114.

construction via ruthenium 2,3-bis(2-pyridyl)pyrazine units. Such molecular trees, which contain up to 22 ruthenium atoms, showed luminescent properties (scheme 31) [62].

Puddephatt reported a related strategy using a substituted bipyridine ligand. The method consisted of oxidative addition of a benzyl bromide to Pt^{II} followed by coordination of Pt^{II} by bipyridine (scheme 32) to make a Pt_{14} tree, but progression could not be continued because of steric hindrance. Using a tetrafunctional core, Puddephatt also made a Pt_{28} tree [140]. Majoral's large phosphorus dendrimers (*vide infra*) were recently coated with up to 48 $W(CO)_5$ units or 96 $Fe(CO)_4$ units [141a]. Large molecular trees with phosphine groups have been shown to give poly-gold complexes by the groups of Schmidbauer [141b] and Majoral [141a]. One interesting feature of these poly-gold complexes is an easier characterization by electronic microscopy.

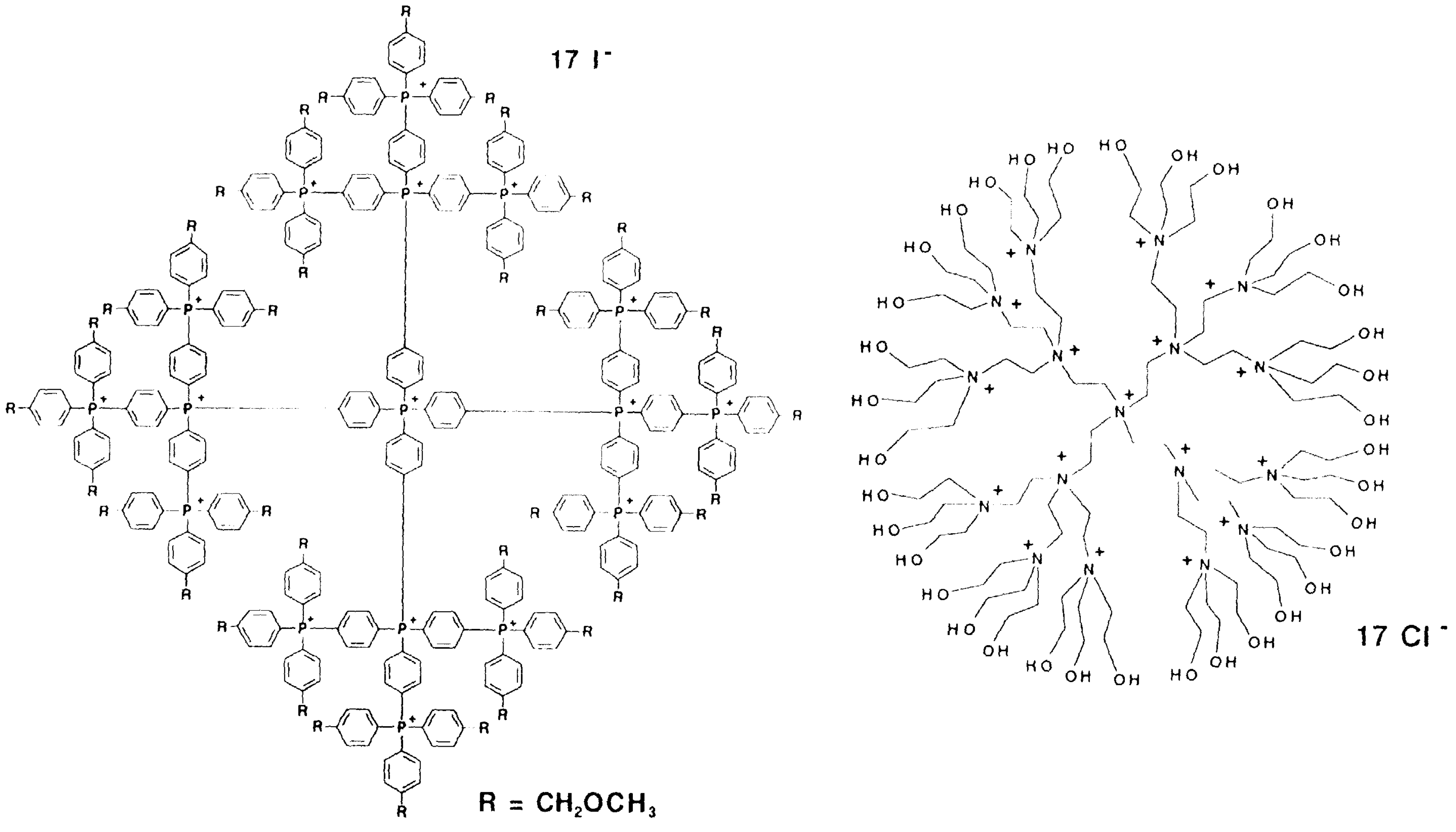
The $FeCp^+$-induced peralkylation [142-144], perallylation [145] and perbenzylation [143] of polymethyl aromatics gave the first construction of organometallic molecular trees [64].

$$[FeCp(arene)]^+PF_6^- \xrightarrow[\text{THF, 20-40°C}]{\text{RX, KOR}' \ (\text{R}' = \text{H or } t\text{-Bu})} [FeCp(arene\ R_n)]^+PF_6^-$$

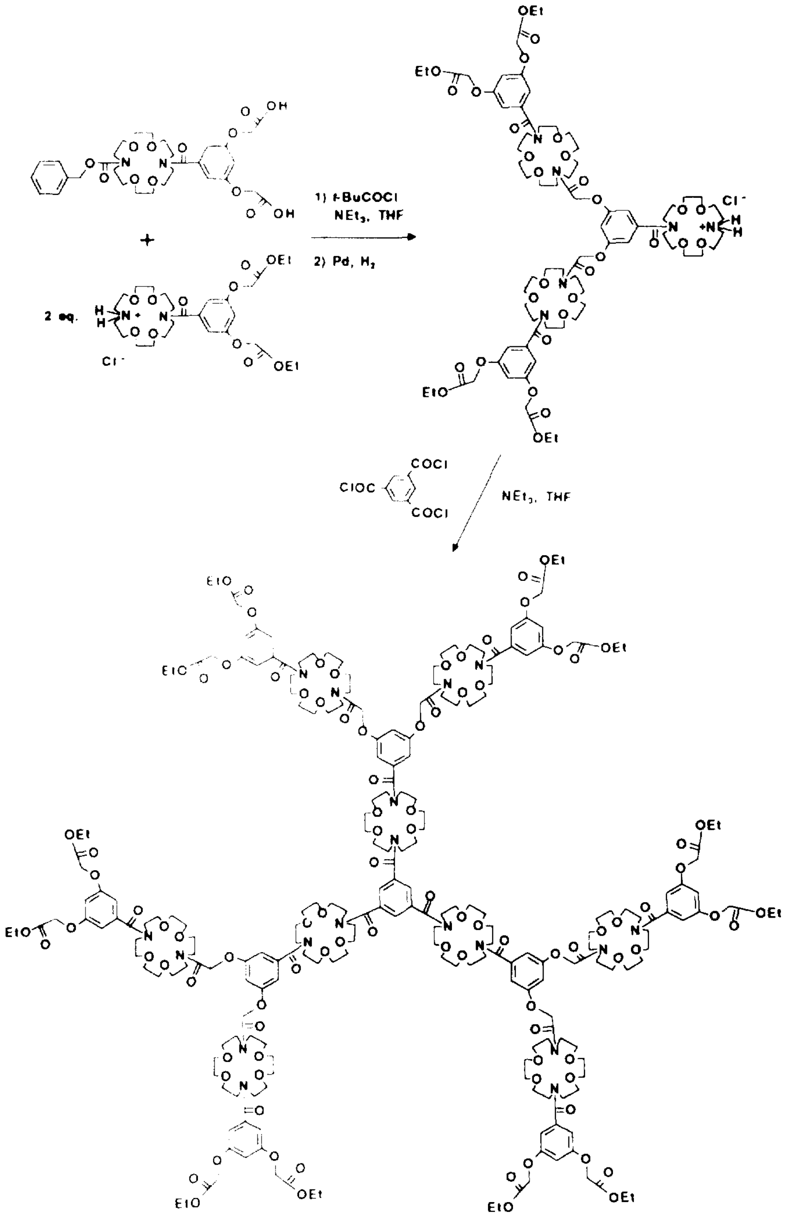
The reaction proceeds in one pot and can give up to 12 allyl branches [65] starting from the hexamethylbenzene complex.

Functionalized trees have been obtained with various topologies (scheme 33). The polyols, polyesters, polysilane, polyboranes, polyzirconanes, polyiodo, polyamines, polyammonium, polyphosphines, polyphosphonium, polyazide, polycyano and polyiron compounds were made available starting with the hydroelementation of the polyallyl derivatives [145, 146]. The poly-*para*-alkoxybenzylations of the C_6Me_6 complex also gave substituted tentacled derivatives with various endings including ferrocene and $[FeCp(arene)]^+$ [147]. Similarly an alkyl iodide terminated with a ferrocene moiety was used in the peralkylation of the C_6Me_6 complex [148] and living polymerization of star-shaped polystyrene has been achieved [149]. The polyiron complexes were designed to provide multielectronic redox centers at the same potential for multielectronic redox catalysis (scheme 34) [150]. Indeed the $[FeCp(arene)]^+$ system has been shown to be an active catalyst in the multielectronic electroreduction of NO_3^- to NH_3 [144]. Bard has recently pointed out the importance of such polyiron-sandwich systems in multielectron redox catalysis [151]. Molecular trees with 27 allyl branches can be obtained by such an organo-iron synthesis [152].

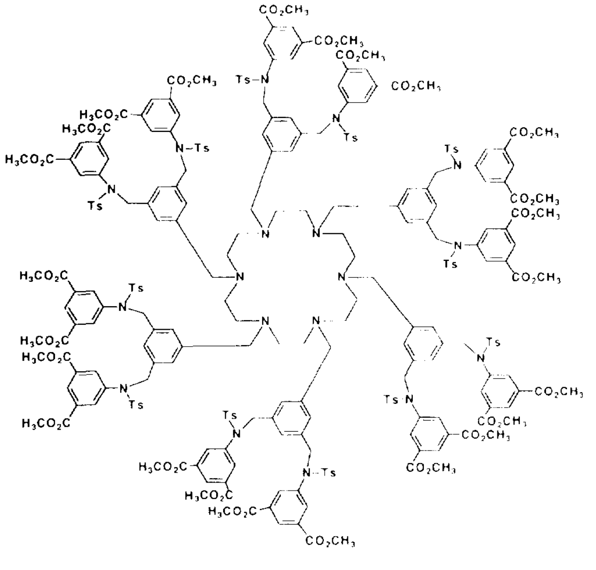
Organometallic silicon molecular trees with up to eight ferrocene groups (scheme 35) in which the redox



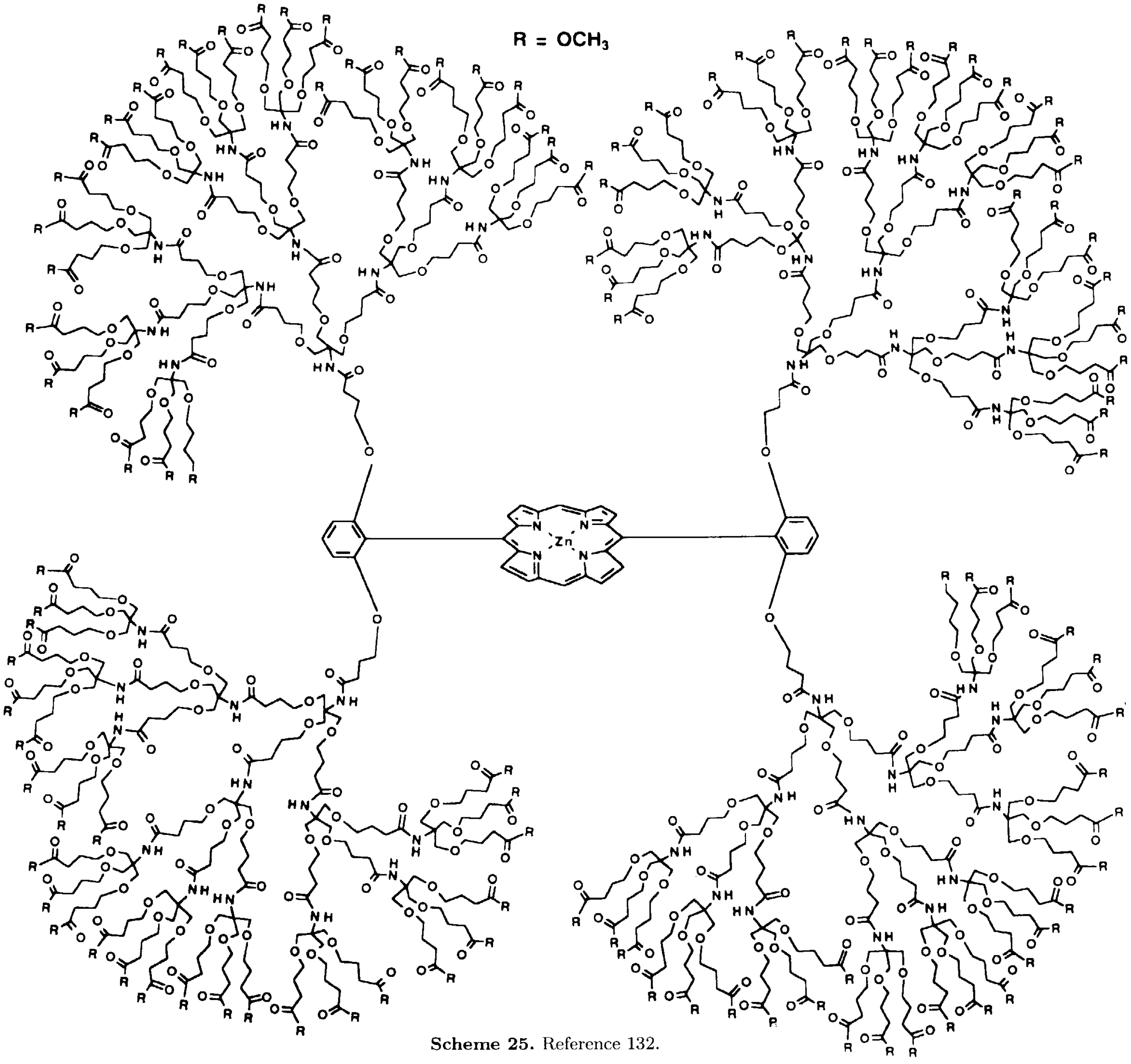
Scheme 22. Polyionic dendrimers using phosphonium and ammonium moieties as branching centers [120-122].



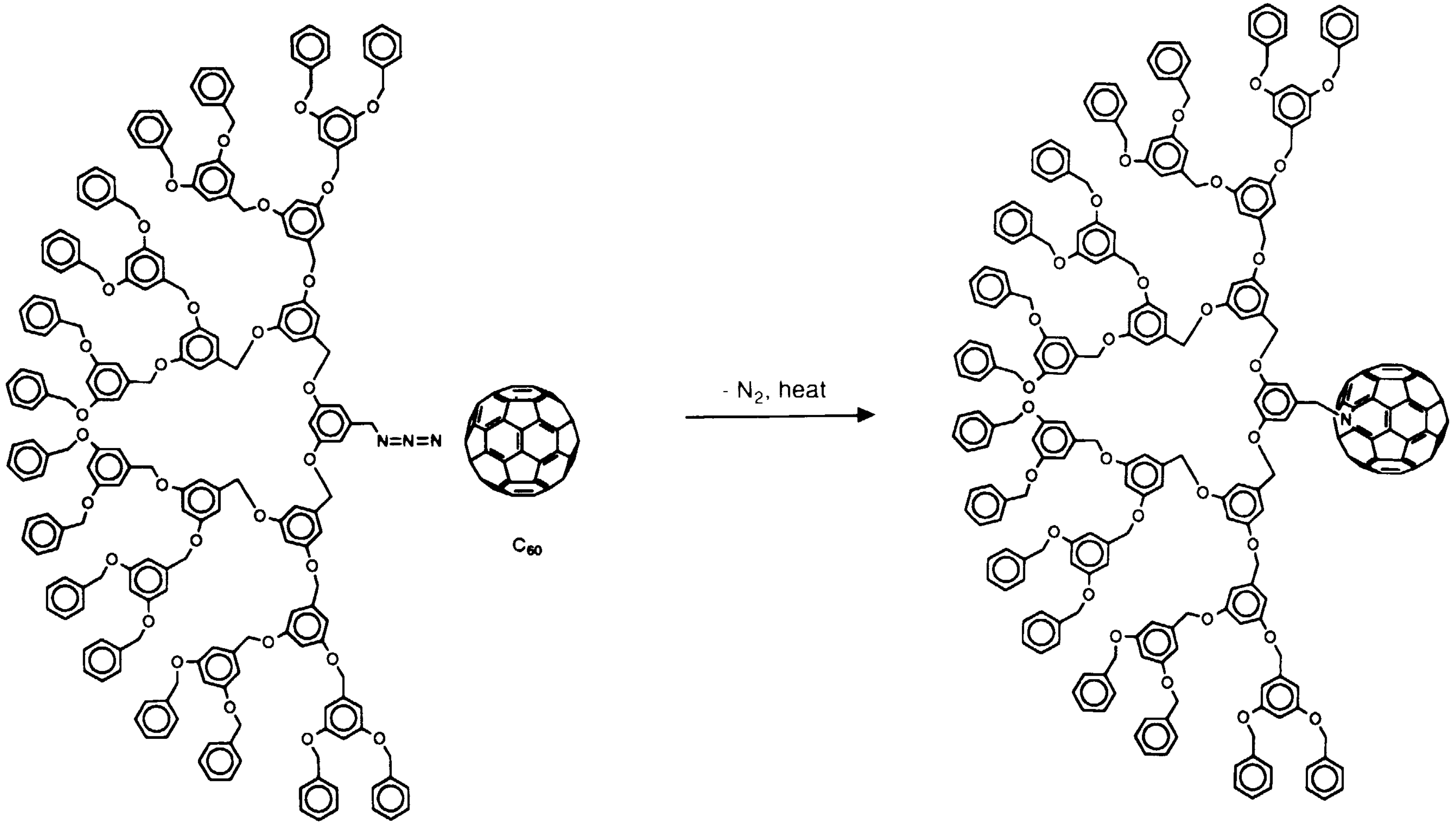
Scheme 23. The convergent construction of a three-dimensional crowned tree [129].



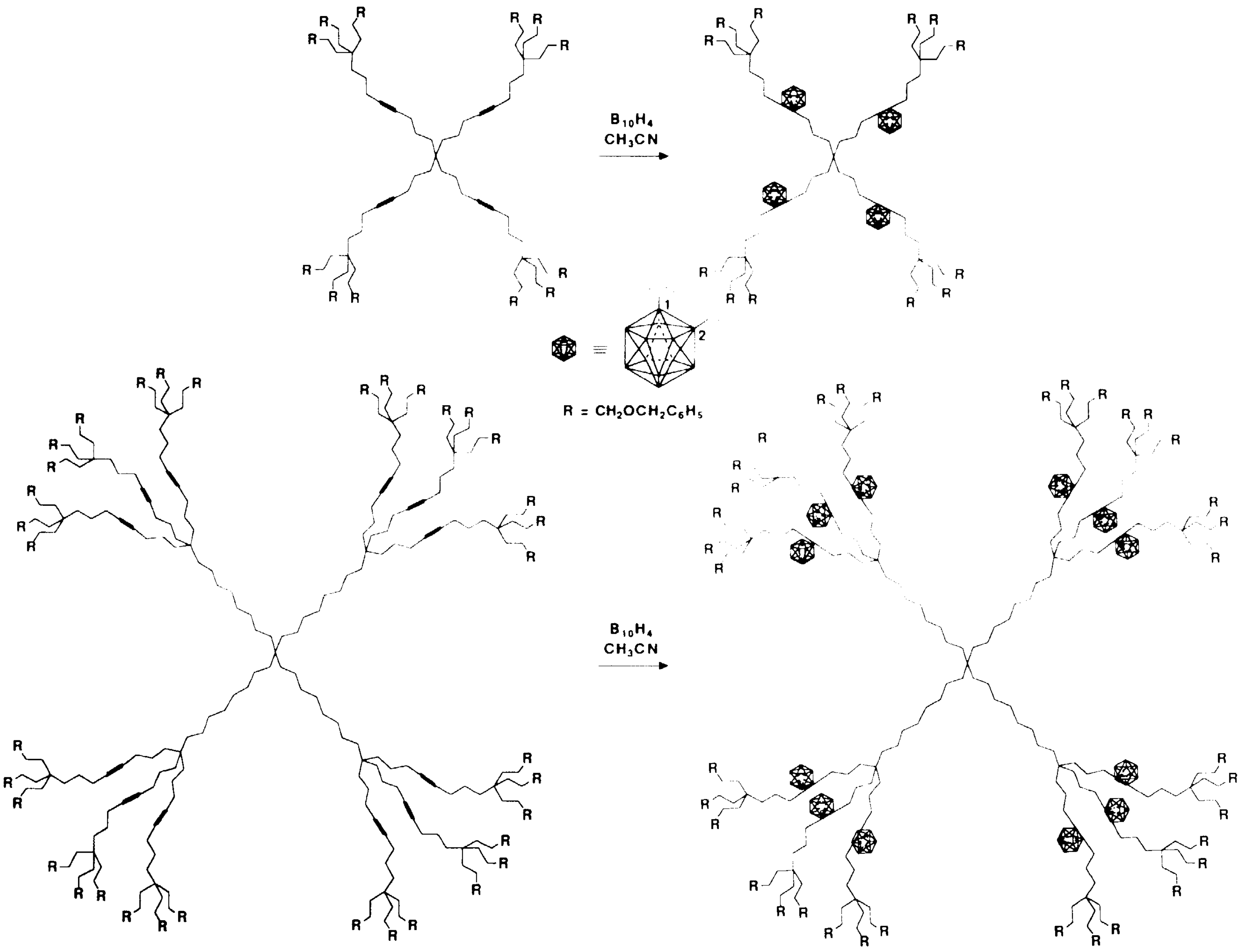
Scheme 24. Reference 130.



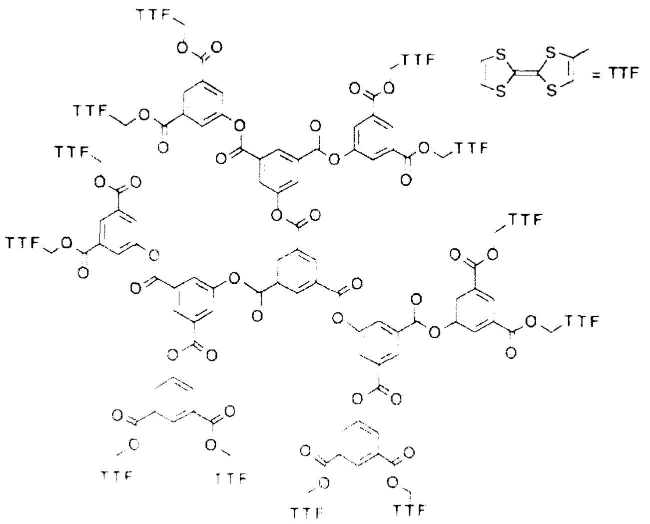
Scheme 25. Reference 132.



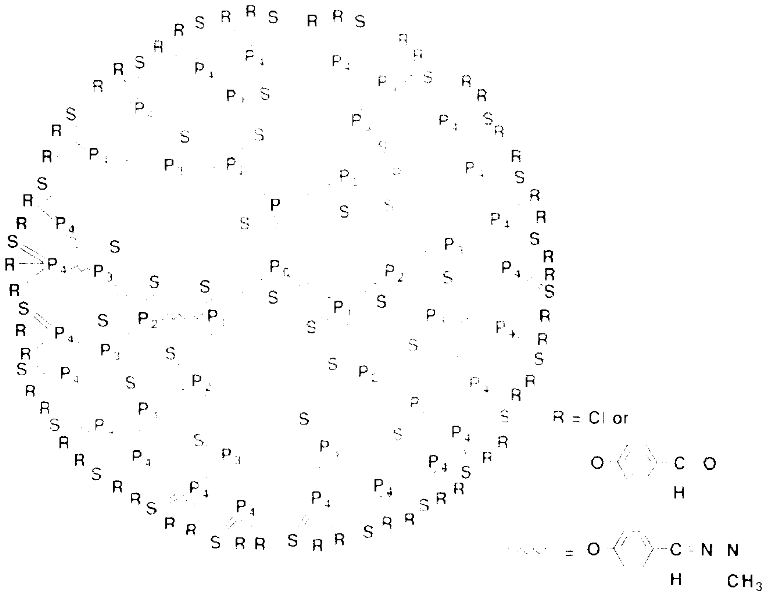
Scheme 26. Reference 134.



Scheme 27. Preparation of *o*-carborane superclusters by treatment of polyalkyne cascade precursors with $B_{10}H_{14}$. Also depicted is the *o*-carborane numbering [135]. R = $CH_2OCH_2C_6H_5$ (▬ = triple bond).



Scheme 28. Reference 147.



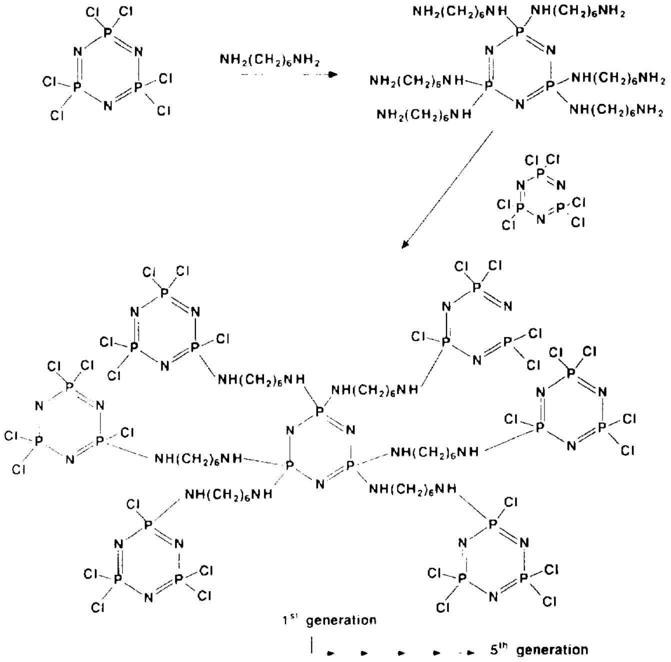
Scheme 29. Reference 66.

centers are equivalent have also been reported by the Madrid group [153]. Various molecular trees containing 12 transition-metal groups have been synthesized by attaching 12 metal groups to the branches. Newkome has reported the coordination of an arborol containing 12 inner triple bonds with [$Co_2(CO)_6$] [154], 12 terminal terpyridines have been coordinated to 12 ruthenium atoms [155]. Liao and Moss attached 12 [156], then 48 [$RuCp(CO)_2$] moieties using ending alkoxy branches [156]. The groups of van der Made and van Koten have reported a silane molecular tree also containing 12 nickel groups, which showed catalytic activity for the Kharash addition of polyhalogenoalkanes to carbon-carbon double bonds [157].

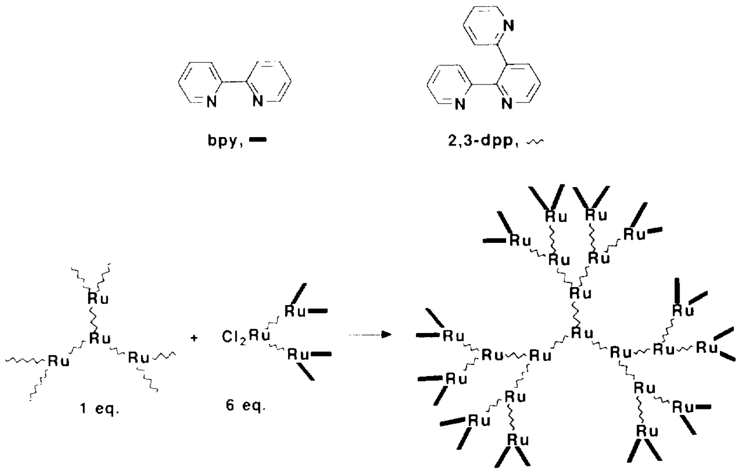
Dubois has reported the synthesis of molecular trees with up to 15 phosphorus atoms and the binding of five Pd^{II} groups to tripodal phosphines. A catalytic activity for CO_2 electro-reduction to CO in DMF was found [158]. Vögtle reported a polyimine (salen), which forms a trinuclear complex by reaction with cobalt salts [159]. Tomalia's dendrimers have been functionalized by carboxylate groups and then coordinated to Cu^{II} for ESR studies [115b].

Chiral molecular trees

Small chiral cores for molecular trees were synthesized by perfunctionalization of pentamethylcobalticinium [65, 160] and pentamethylrhodicinium [161, 162]. With small R groups, such as methyl and ethyl, it was found that the molecules are unidirectional at room temperature but coalescence in the ^1H NMR spectra indicated rotation of the isoalkyl groups at higher temperatures



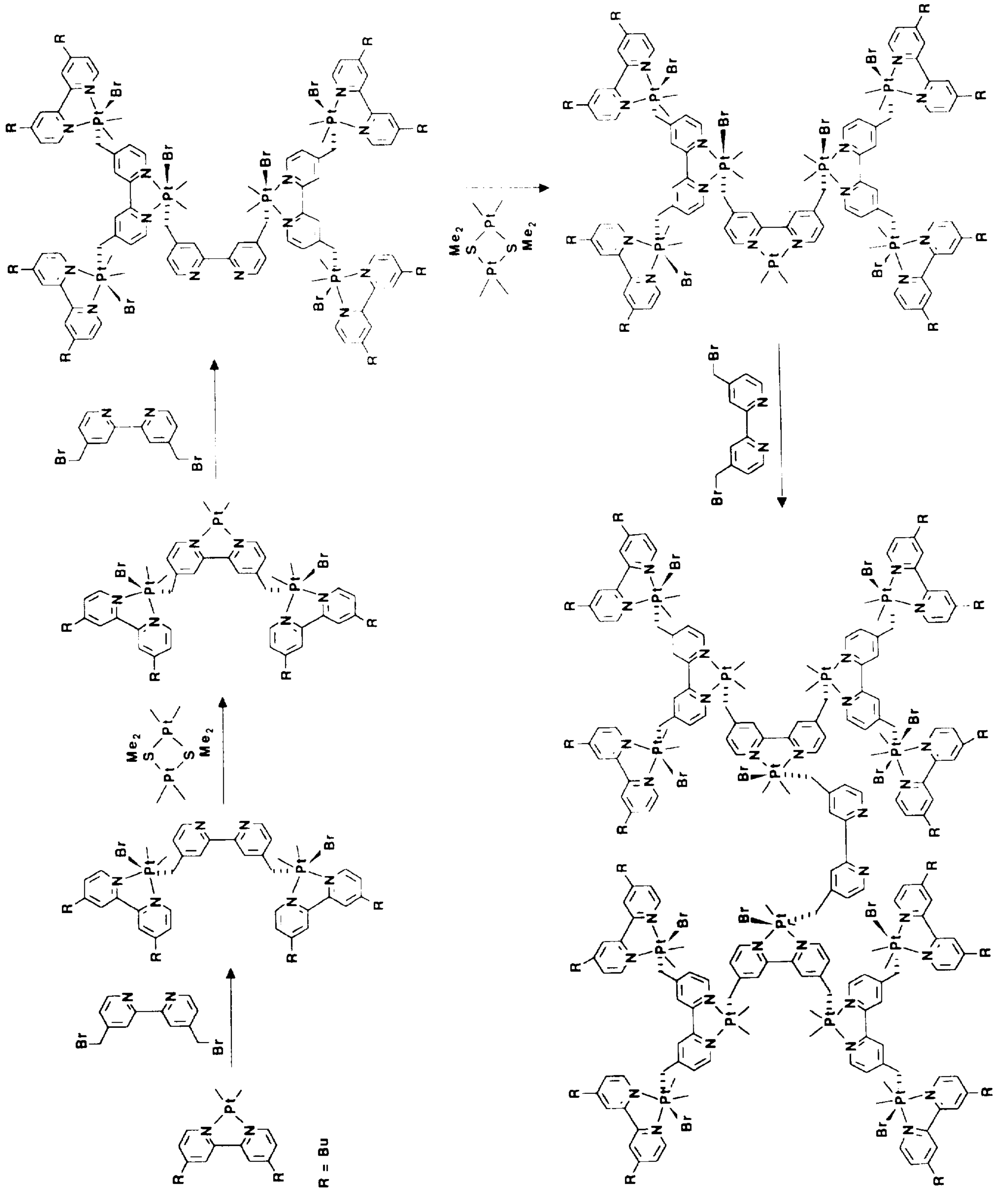
Scheme 30. Reference 69.



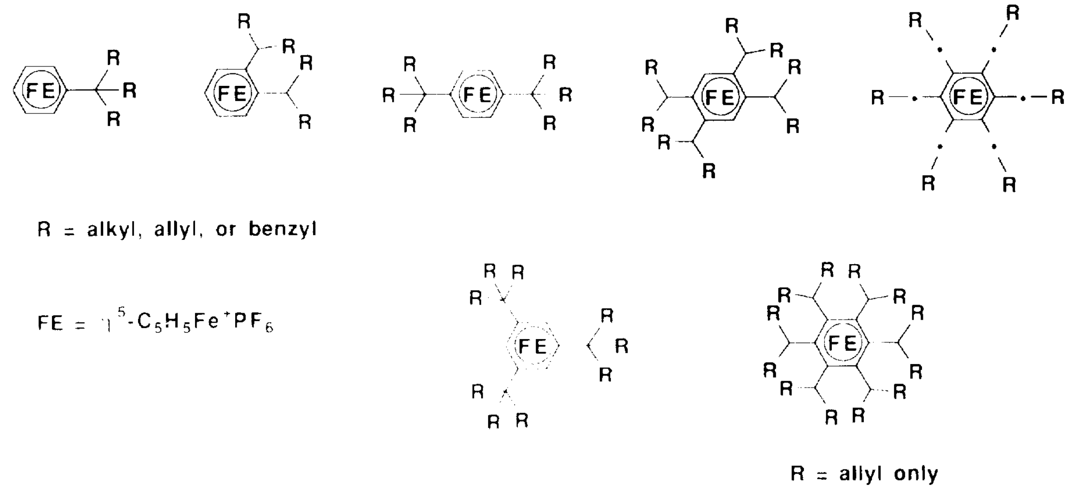
Scheme 31. Reference 62.

corresponding to a loss of chirality [160]. With larger R groups, such as allyl or benzyl (scheme 36), the coalescence is not found below the decomposition temperature and occurs anyway above 120°C at 200 MHz. The flexibility is thus more restricted and the chirality could indeed be blocked with bulky groups [160, 162].

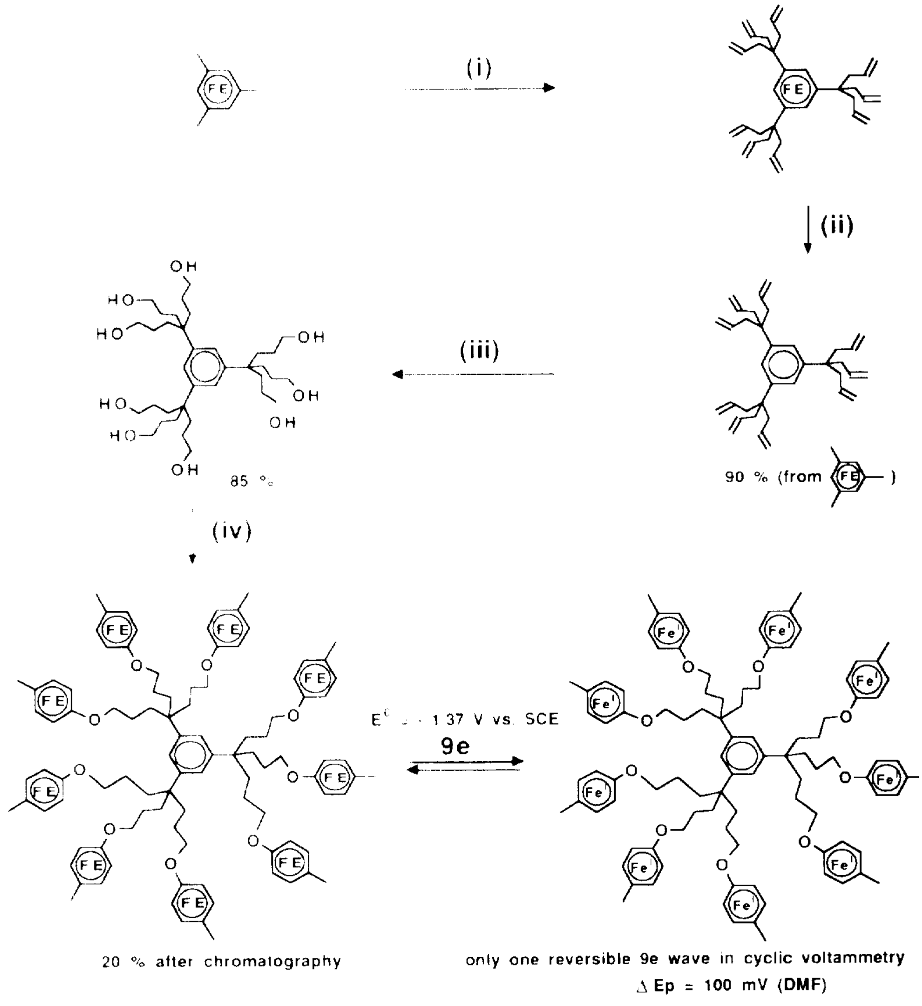
The first report of purely organic chiral trees was published by Newkome [81], who attached tryptophan units to the branches of a second-generation tree. Seebach [163, 164] published chiral cores in trees containing 12 aryl branches. The optical activity of trees with chiral cores decreases with the increasing size of the tree. When the tree is fully chiral, the optical activity corresponds to that of the core. Further work is required to know whether a chiral tree can provide enantiomeric host-guest recognition or can have a chiral shape. Which strategy should be most efficient for this purpose (chiral core or chiral branches or both (or a chiral core with different chiral or achiral branches)) is not yet clear. Meijer [165] has investigated the properties of trees based on the chiral pentaerythritol core; he also showed that chiral trees with chiral terminating branches have low or vanishing optical activity. The structure (size and shape) of the cavities inside molecular trees should be an important parameter for host-guest interactions and resulting medical applications [166]. Several other papers reported trees with chiral branches [167-169]. In particular, Brunner has developed a very elegant approach to enantioselective catalysis using optically active expanded chelate phosphines with dendritic structures for which he coined the term "dendrizyme" [169-174].



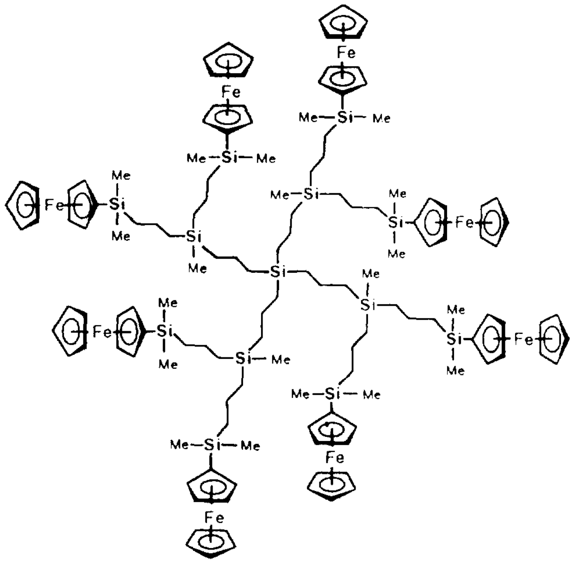
Scheme 32. Reference 140.



Scheme 33. Reference 61



Scheme 34. (i) CH_2CHCH_2Br, KOH, DME, 20°C, 9 days; (ii) MeCN, PPh_3 (1 equiv), visible light, 7 h, 25°C; (iii) disiamylborane, THF, 20°C, 1 day, H_2O_2 30%, NaOH 3M, 50°C, 1 h; (iv) $[Fe(Cp)(\eta^6\text{-}p\text{-}CH_3\text{-}C_6H_4F)]^+PF_6^-$, K_2CO_3, Bu_4NBr, THF/DMSO 80:20, 20°C, 3 days (FE $=\eta^5\text{-}C_5H_5Fe^+$, PF_6^-) [150].



Scheme 35. Reference 153.

Characterization and physical properties

Classical analytical and spectroscopic techniques are also useful for the characterization of molecular trees: elemental analysis, infrared, NMR (especially ^{13}C and heteronuclei if any). X-ray data have been used for the identification of cores [132, 175] and even for second-generation silicon dendrimers [101].

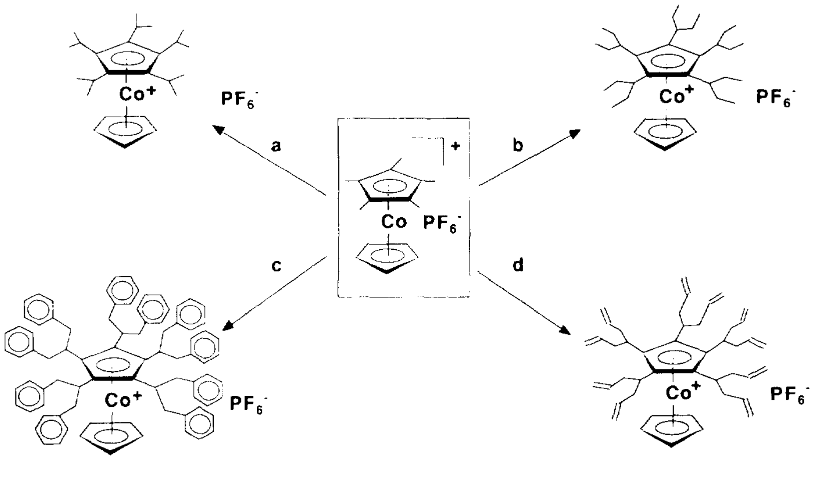
Size exclusion chromatography (SEC) is a commonly used technique as in the case of polymers. It has been coupled to low-angle laser light scattering (SEC-LALLS) [176]. The inconvenience of using common linear polymers such as polystyrene as standards has recently been overcome by Tomalia who proposed the dendrimers themselves as standards [177]. Molecular weights of molecular trees are indeed well defined unlike those of polymers, and the shape is more adequate for comparison [178].

Since elemental analysis does not easily allow us to distinguish defects, it is important, for a good level of characterization, to record the appropriate mass spectra. The mass spectral techniques used for molecular trees include fast atom bombardment (FAB), laser desorption and electrospray, at least up to a certain generation. Time of flight (TOF) matrix-assisted desorption ionization (MALDI) is probably one of best mass spectral techniques for molecular trees [179]. Another useful technique for designing a tree before its synthesis is computer-assisted molecular simulation (eventually comparison for CPK models for small trees). The calculation of structures can be made using, for instance, the molecular modeling package MAD [66, 68, 180a].

Other more rarely used techniques include vapor-phase osmometry, electrophoresis, electron microscopy, atomic-force microscopy, scanning-tunnel microscopy, titration (polyamines), fluorescence probe analysis and intrinsic viscosity measurements [20].

Defects that have been detected include branch defects, intramolecular looping, intermolecular bridging, intermolecular looping and intermolecular mixed bridging-looping [20]. ^{13}C NMR and electrospray mass spectrometry are considered to be the best techniques to investigate branch defects. Trees without defects are monodisperse (index = 1.0). Trees with defects are polydispersed (indices > 1.0). SEC is the technique of choice to determine the polydispersity index. For instance, the PAMAM trees of Tomalia have been found to have a polydispersity of 1.08 for generation 10 [20].

The melt viscosity behavior of dendrimers has been shown to be primarily a function of molecular weight, revealing a profile with no critical molecular weight (up to 85 000 amu). In this range, a value of 1.1 is obtained, indicating the premise that branching and surface congestion prevent significant tangling between separate dendritic macromolecules [180b]. These results contrast with those found earlier with PAMAM dendrimers [103] (*cf*, section *The convergent method*).



Scheme 36. a: MeI, *t*-BuOK, THF; b: EtI, KOH, DME; c: $PhCH_2Br$, *t*-BuOK, THF; d: C_3H_5Br, *t*-BuOK, THF [162].

Topology and chemistry of the surface and cavities

The De Gennes dense-packing model

De Gennes and Hervet [15] predicted that surface congestion occurs in a molecular tree after a certain generation. The surface area A_Z per terminal group is given by equation [1] in which Z is the number of terminal groups, A_D the total surface of the tree, N_Z the number of surface groups Z per generation, r the radius of the tree, N_c the number of core branches, N_b the number of branches at each generation and G the number of generations.

$$A_Z = \frac{A_D}{N_Z} \alpha \frac{r^2}{N_c N_b G} \quad [1]$$

This relationship indicates that A_Z decreases as the number of generations G increases. When A_Z reaches the cross-sectional area corresponding to the van der Waals radii, the "dense-packed" generation is reached. This means that further generations have defects. This prediction was verified with Tomalia's PAMAM trees. A simple equation [2] was proposed by De Gennes and Hervet to account for this principle for PAMAM trees. G_l is the dense-packed (limit) generation and P is the length of the branch-cell segment.

$$G_l \approx 2.88(\ln P + 1.5) \quad [2]$$

According to this equation, the dense-packed generation for PAMAM trees is between 10 and 11.

There is notable constrast between star-branched macromolecules and symmetrically branched trees. In star-branched polymers the branch densities are highest near the initiator core (fig 4) whereas in trees it is highest on the periphery as noted above.

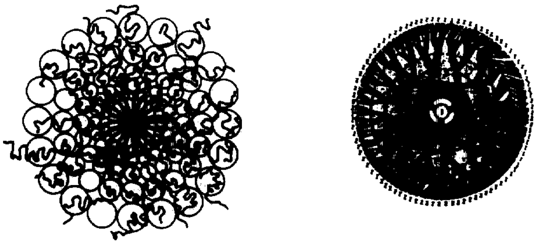


Fig 4. Comparison of the densities in star polymers (left) and dendrimers (rignt) adapted from refs 16 and 18.

Above generation 4, the PAMAM trees are spherical, but below this generation they have hemispherical dome shapes (from computer-assisted molecular modeling) [16, 181].

The surface congestion is also indicated by viscosity and refractive index measurements which decline or increase beyond generation 4 because of reduced interaction between the surface groups and the solvent [181].

Other theoreticians have proposed a different repartition of density in the dendrimers in which not all the functions are located on the surface, with extremities of the branches which turn inside the dendrimers [182, 183]. In dendrimers with surface azobenzene units, UV irradiation causes changes in the shape and size of the dendrimers due to reversible E-Z isomerization (the E isomer is thermodynamically more stable) [184].

Surface reactions

The divergent construction of the trees involve the division of a branch into N_b branches without defect until the generation G. Besides these reactions, which are relevant to the construction, many surface reactions have been performed on the branches [16]: protonation of amines (titration), electrophile-nucleophile reactions, complexation of the terminal functional groups by metal ions (alkali metals, transition metals), introduction of chiral groups. Cationic and anionic terminal groups have been formed to obtain water-soluble trees. The nature of the external group is essential for the solubility and for micellar and inclusion properties. The attachment of catalysts and groups with specific properties is currently under study (see sections *Charged molecular trees and micellar aspects, Inorganic and organometallic molecular trees* and *Liquid crystalline properties and layers*). Finally, the surface behavior of trees can be compared with those of vesicles and viruses; this biomimetism could be of great interest. Small viruses have many identical protein groups, which are symmetrically located around their RNA and are responsible for their function and protection [20].

Biomimetic catalysis has been found with dendrimers functionalized by amine surface groups for aminolysis of phenyl esters (as in microgels) [185]. With hydrophilic dendrimer surfaces covered with 36 tetraalkylammonium iodide, local substrate concentrations are increased, leading to rate acceleration in decarboxylation and hydrolysis reactions [186].

Dendrimers have been used by Tomalia as linker molecules to radiolabel antibodies [187]. Dendrimer-coupled antibodies are attractive alternatives to the double-antibody immune complexes currently used in many solid-phase immunoassays [188]. The coupling of dendrimers to antibodies was reproducible and the covalently linked antibodies retain full antigen-binding affinity both in solution and when immobilized on the solid phase. The coupling methods are applicable to the coupling of a wide range of other molecules of interest in diagnosis.

Dendrimers have been reported as synthetic vectors for transporting genetic materials into mammalian cells [48].

Biological dendrimers are biocompatible (non-toxic) and can recognize biological components. For instance, thymidines and adenonise-based dendrimers selectively recognize RNA branches and can detect and quantify viruses such as AIDS [189].

A water-soluble dendrimer with a thiosialoside surface can mimic the effect of some antibodies of glycoprotein type in order to increase the inhibiting capacities of the α-sialoside group against the cold-virus [190].

Cavities and their chemistry

The density of the symmetrically branched PAMAM trees of Tomalia reaches a minimum for generation 4 whereas that of asymmetrically branched trees of the Denkewalter type remains constant as a function of generation (fig 5) [73].

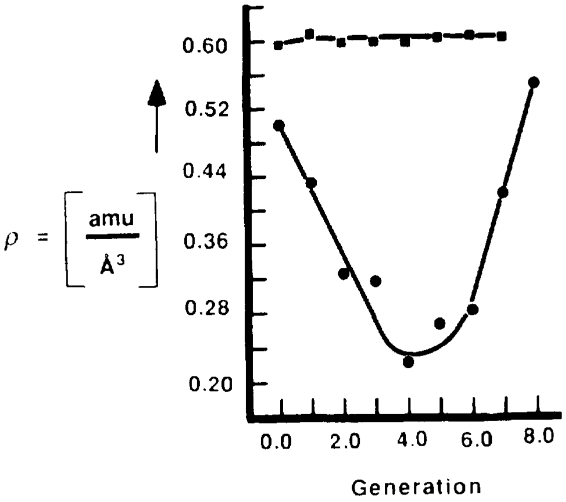


Fig 5. Dependence of density ρ on generation for symmetrically branched and asymmetrically branched trees; ■, Denkewalter trees (unsymmetrical branch cells); •, starburst PAMAM trees (symmetrical branch cells). Reproduced from ref 13.

Trees with large surface groups will also present large cavities. Clathrates have been characterized in chiral trees by Seebach [163, 164]. Trees with cavities have been characterized [166, 181, 191]. Guests include dyes, spin markers and fluorescence markers. In this way, trees are supramolecular compounds in which the guests can be reversibly bound by H bonding; pH-dependent release of guests has been demonstrated, indicating a potential for pharmaceuticals (drug release or targeting).

The topology of the core itself is of course of great importance for the size of cavities. The molecular trees show great promise for drug transport with pharmaceutical applications [192]. Encapsulation of guest molecules has indeed been studied in detail. The inclusion of 2,4-dichlorophenoxyacetic acid and acetylsalicylic acid in PAMAM dendrimers functionalized by alanine groups at their surface has been monitored by NMR; the relaxation time T_1 is decreased by the encapsulation [115]. Dendritic boxes with closed surfaces were constructed by the group of Meijer via the reaction of 64-branch poly(propyleneimine) molecular trees with chiral protected amino-acids. The guest molecules were captured in the course of this construction reaction, and then the diffusion of the guest molecules was immeasurably slow [191].

Transport due to the interaction of guest substances in dendritic cavities has been used for agrochemical [193] or medicinal [194] purposes. For instance, alkyl 4-hydroxybenzoate, which is used against coughs, has been transported by PAMAM dendrimers and separated by capillary electrophoresis [195].

Zn porphyrin deuterated dendrimers can trap small molecules such as vitamin K_3 whereas large quenchers cannot enter inside the dendrimer [131].

Liquid crystalline properties and layers

Liquid crystalline properties for molecular trees were first reported in 1988 by Friberg [196]. Vögtle pointed out that many molecular trees should be able to form discotic phases because of their round, flattened shape. Liquid crystalline properties are known for classical polymers. For instance, Kim reported dendritic polymers having hyperbranched aromatic polyamide structures which have lyotropic liquid-crystalline properties. Birefringence was observed for carboxy-acid-terminated polymers in amide solutions and poly(methylester) [197]. Optimization of clarification points was attempted [198]. Liquid crystalline dendritic polymers have been reported [199-204], especially by Percec [199-203]. A remarkable example of Percec's liquid crystalline polymer is derived from 10-bromo-1-(4′-hydroxy-1,1′-biphenyl-4-yl)-2-(4-hydroxyphenyl)decane, an asymmetric three-dimensional compound, which is mesogenic because of its conformational isomerism (scheme 37). The polymer was obtained using phase-transfer catalysis (Bu_4NHSO_4, 10 M NaOH, 1,2-dichlorobenzene) and alkylation of the terminal groups. Transitions between the nematic and isotropic states were found to be between 20 and 50°C (R = *n*-octyl, *n*-hexyl), a range interesting for potential applications [201].

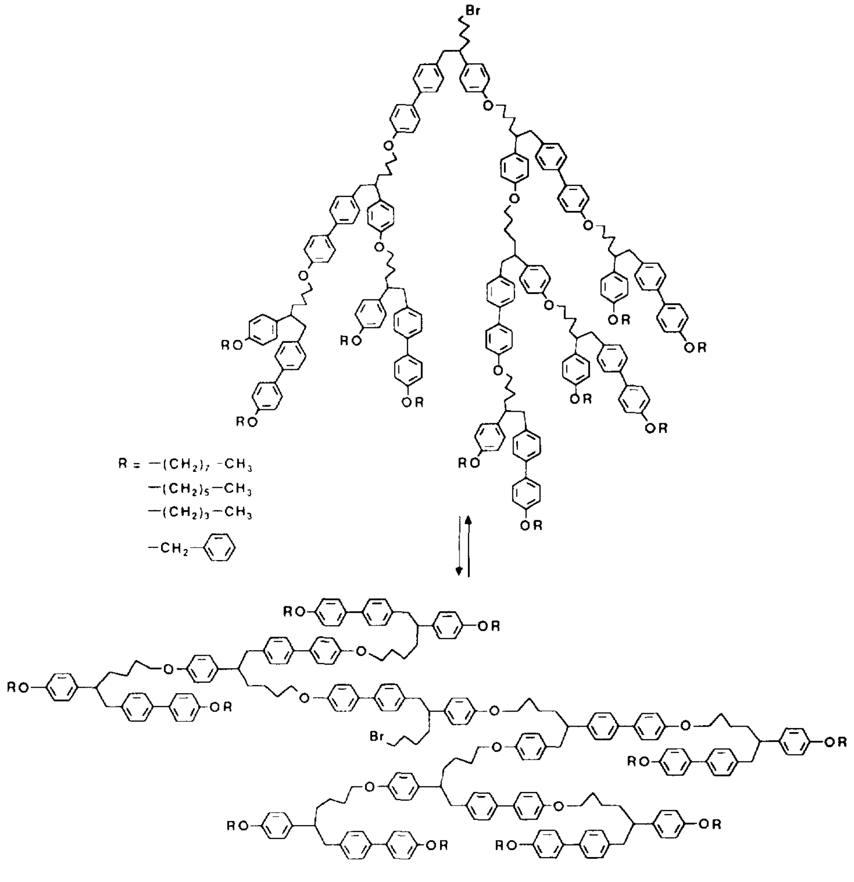
Repetitive treatment of PAMAM dendrimers (generation 6) with a silicon wafer coated with $PtCl_4^{2-}$ provided multilayers [205].

Conclusion: towards applications

Since the pioneering examples of Vögtle, the abiotic construction of molecular trees, whether it follows a divergent or convergent route, is relevant to genealogy, as pointed out by Tomalia, and the formation of living organisms. Comparisons have been made with liposomes and viruses. This biomimetism may be extremely powerful in the future to understand and control the behavior of these living organisms.

The importance of molecular trees also lies in their potential use as molecular micelles and inverted micelles [17b], as hosts for the transport of biologically important guests [16], as part of devices for energetically relevant water photosplitting catalysis, and for charge separation [17b], for multimetallic and polyredox catalysts. They have been designated as "nano-reactors" [117]. Applications have been sought in medicinal engineering, agrochemistry, photocopier toners, pharmacy, imaging [186, 206, 207], radiation therapy [208], gene therapy [209] and anti-cancer properties [17b].

The fixation of functional groups described in sections *Molecular trees containing special functional groups: crown, C_{60}, porphyrins, sugars, borons clusters, TTF* and *Liquid crystalline properties and layers* will lead to specific applications connected to redox, photochemical, photophysical and biological processes as well as to new kinds of catalysis. Encapsulation in dendritic



Scheme 37. Reference 201.

cavities (*cf* section *Topology and chemistry of the surface and cavities*) will allow drug vectorization.

As already shown in our own work [149], the chemistry of trees is also relevant to polymer chemistry. This is true in many ways. It is possible to start polymerization from a multibranch tree (core) as reported in the case of polystyrene [149]. One may, on the other hand, start the generation-after-generation construction from a polymer core as shown by Tomalia [16]. Both approaches should yield high-molecular-weight macromolecules. Large molecular trees should also be considered as polymers in their own right. Thus, whereas new cores [210] and building blocks [211, 212] continue to appear, it is certain that molecular trees have a future in polymer technology. They have very distinct topologies [213] and mechanical properties [214]. They are also attractive alternatives to μ-gels [215] given their physical reproducibility due to the regular iterative construction. It has been proposed that μ-gels could be used as fillers or additives for polymer matrices, and as stabilizers of high-impact polymers [213]. For electronics, a high glass transition temperature is required. Photoactive and electroactive dendrimers have been shown to exhibit this property [216]. Dendrimers can also be used in conjunction with other polymers to provide a good interaction between the two kind of branches [217]. Covalent linkage between polyethylene glycol and dendrimers gives good crystalline properties [218-220]. These associations find applications in the fields of resins [221] and surfactants [123]. The advantage of molecular trees over polymers has also been pointed out regarding viscosity and applications in high-resolution lithography, paint [222] and inks [223, 224]. Molecular trees are indeed likely to be much involved in nanotechnology [225-228], a concept now turned towards engineering [229]. Molecular assemblies with dimensions in the range 1–100 nm (10–1 000 Å) having 10^4–10^9 atoms (10^4–10^9 Da) are relevant to nanostructures (fig 6). Proteins such as insulin and hemoglobin are in this range (55 Å) as molecular trees (the spheroidal shapes of hemoglobin and molecular trees have also been compared). Abiotic self-organized assemblies belong to this class, for example, micelles, liquid crystals (*vide supra*), Langmuir-Blodgett films, molecular crystals, non-linear optical devices [230], bilayer membranes and molecular electronic devices [229, 231]. Molecular assemblies based on coordination, devised by Lehn [232] (helical Cu^{II}-polypyridine supramolecular structures) are the abiotic equivalent of DNA.

The scientists working at the interface between chemistry, polymer science, biology and physical chemistry involving transport of drugs or genes, immunology (*cf* section *Surface reactions*), catalysis and new molecular materials have started to embark on the investigation of applications. The engineering of multicomponent devices using these abiotic molecular assemblies for

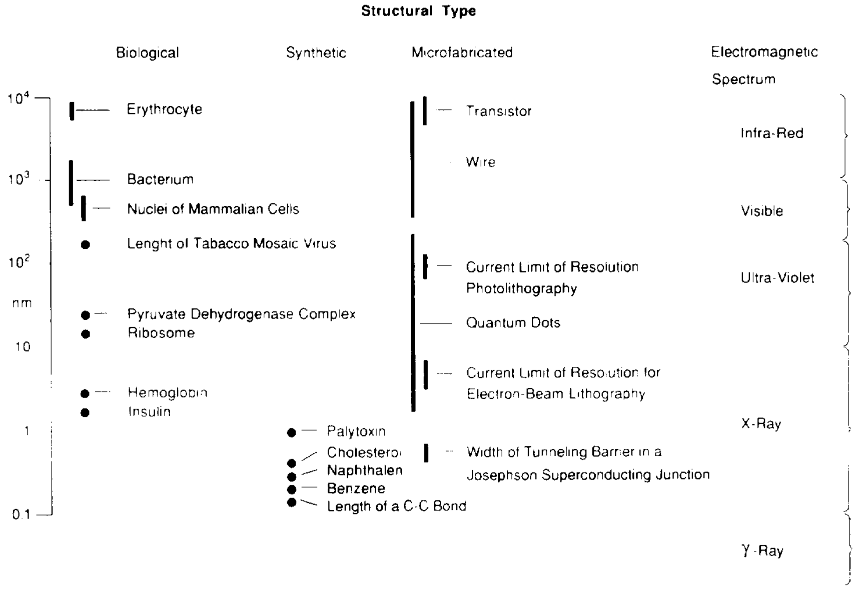
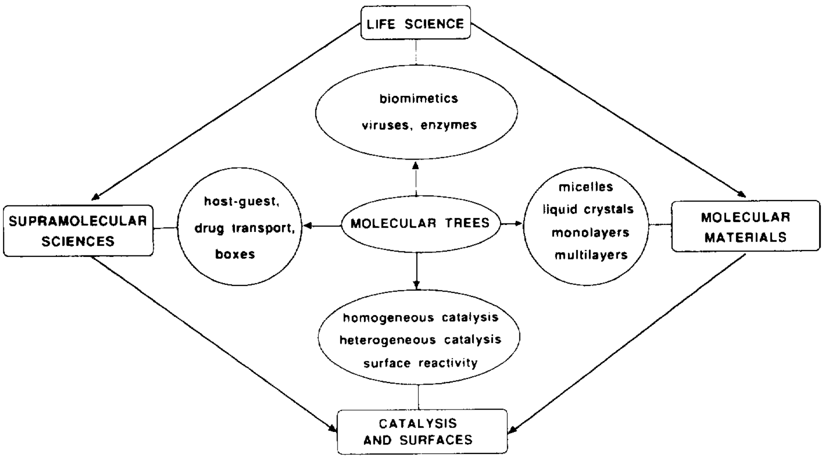


Fig 6. A comparison of the relative sizes of structures generated in biology, synthetic chemistry, and microfabrication. The scale (left) is logarithmic and the electromagnetic spectrum (right) is included as a reference. Both biology and microfabrication provide examples of structures with dimensions ranging 1 to 10^4 nm. Structures prepared by chemical synthesis may make it possible to obtain structures that have sizes of 10 to 10^3 nm. Reproduced from ref 230.



Scheme 38

determined functions will constitute an essential goal in the 21st century, including the underlying comparison with and inspiration from biological elements of comparable size, topology, and surface functional groups. Molecular trees, whose architecture and sizes offer enormous potential and variety, will undoubtedly take a major place in this nanoscopic context (scheme 38) [233–236].

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