Chiral Dendrimers

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The synthesis of chiral dendrimers from various building blocks, their – difficult – structure determinations, and their – potential – use in physiological applications, in bioassays, and in enantioselective catalysis are reviewed.

Keywords: Chiral dendrimers, dendrimers, asymmetric synthesis, asymmetric catalysis.

1 Introduction

From the atomic to the macroscopic level chirality is a characteristic feature of biological systems and plays an important role in the interplay of structure and function. Originating from small chiral precursors complex macromolecules such as proteins or DNA have developed during evolution. On a supramolecular level chirality is expressed in molecular organization, e.g. in the secondary and tertiary structure of proteins, in membranes, cells or tissues. On a macroscopic level, it appears in the chirality of our hands or in the asymmetric arrangement of our organs, or in the helicity of snail shells. Nature usually displays a preference for one sense of chirality over the other. This leads to specific interactions called *chiral recognition*.

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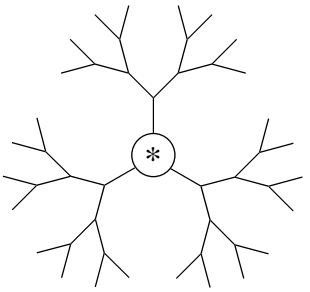
For organic chemists large chiral molecules offer not only a synthetic challenge but also access to a large spectrum of new molecules. The introduction of each new stereogenic center increases the possible number of different molecules by a factor of two. Therefore ten stereogenic centers already lead to 2^{10} or 1024 possible different stereoisomers. The – seemingly minor – change of configuration on a single stereogenic center may be sufficient to change the shape and the function of a whole macromolecule. The influence of chiral units on supramolecular structures and possible applications of such molecules in areas such as catalysis, (bio)sensor research, optical devices etc. are thus worth studying.

Chiral dendrimers are a class of compounds which offer the possibility to investigate the impact of chirality in macromolecular systems. Their specific properties are based on their well defined highly ordered structures with nanoscopic dimension (in this report we refer to *dendrimers* if the molecule has a core with at least three branches attached and a defined structure; otherwise we will use the term *dendritic compound*).

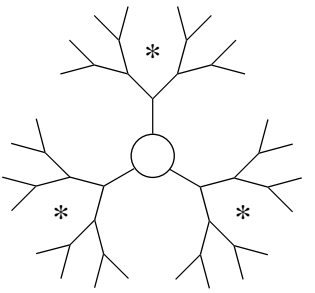
Chiral dendrimers should differ from achiral ones by showing the following properties: (a) their overall shape could be chiral and not spherical; (b) the arrangement of the functional groups on their surface could be chiral; (c) chiral substructures within a chiral dendrimer should be detectable by optical measurements (cf. helices in peptides). Interactions between chiral dendrimers and other chiral molecules should also be detectable by optical or kinetic measurements and interactions with small molecules should be enantioselective (chiral recognition). Functional groups in the cavity region which are able to form noncovalent bonds (cf. amino or amide groups, metal complexes, charge-transfer components etc.) may form active sites for catalytic reactions (enzyme models).

As previously reported [1] there are various possibilities of rendering a dendrimer chiral, see Fig. 1.

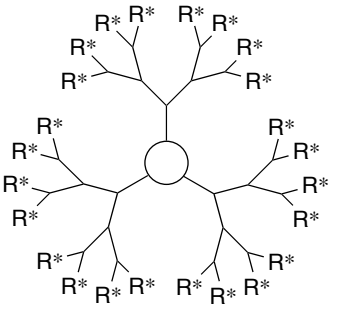
Here we review the development in and the manifold contributions to the area of chiral dendrimers [2] during the past ten years. The next section (Sect. 2) focuses on the synthesis and the properties of chiral dendrimers which are built of essentially unaltered natural building blocks. Their composition often resembles natural macromolecular systems and therefore opens possibilities for biological and medicinal applications. A variety of chiral dendrimers has been synthesized, containing amino acids, carbohydrates, nucleic acids and other natural chiral components. In part three we will focus on chiral dendrimers which have been synthesized mainly with the aim to investigate the influence of stereogenic centers on the entire structure of the molecule. Either by asymmetric synthesis or by modifying molecules from the pool of chiral building blocks dendritic structures of up to the fourth generation have been obtained. In part four first applications of chiral dendrimers in asymmetric catalysis are described. Several dendrimers bearing different catalytically active sites have been prepared for improving catalytic activity in homogeneous and heterogeneous catalysis.



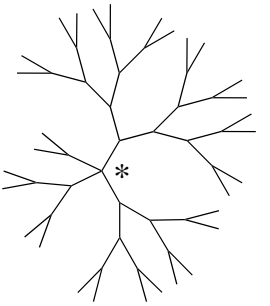
dendrimer with a chiral core
(achiral or chiral branches)



dendrimer with chiral building blocks
as spacers or branching units (achiral core)



dendrimer with chiral peripheral units
(achiral or chiral core and building blocks)



dendrimer with different achiral branches
attached to a non-planar core

Fig. 1. Introduction of one or more than one stereogenic elements (center, axis, plane or helix) leads to different types of chiral dendrimers

2
Chiral Dendrimers and Dendritic Compounds Containing Unaltered Natural Building Blocks

2.1
Dendritic Compounds Built of or Containing Amino Acids

Amino acids and peptides have played a key role in research on chiral dendrimers. The formation of amide bonds has been an extremely well-studied reaction of the past decades and there is a rich palette of suitable coupling reagents. The highly developed protecting group methodology for amino and carboxy functionalities makes amino acids versatile building blocks for the construction of chiral systems. It is therefore not surprising that, already in 1981, Denkewalter et al. reported for the first time on the synthesis of dendritic poly(α,ε-L-lysines) [3–5]. Starting with the reaction between benzhydrylamine and the monomeric building block *N*,*N*′-bis(*tert*-butoxycarbonyl)-L-lysine nitrophenyl ester, repetition of a simple coupling and deprotection sequence led

to lysine polypeptides containing more than 1000 terminal groups at the 10th generation. As an example, a 2nd-generation dendron (**1**) with four terminal groups, is shown in Fig. 2. Although the dendritic structure has not been exactly proven, the physical characterization by Aharoni et al. [6, 7] demonstrated that this compound was monodisperse. Due to their protecting groups, the Denkewalter dendritic lysine derivatives have a hydrophobic surface. Chapman et al. used poly(ethylene glycol, PEG) as a polymer support for the synthesis of similar dendra. Starting from soluble PEG, hydraamphiphiles of up to the 8th generation (polymeric surfactants, see **2** in Fig. 2) have been obtained [8, 9]. By deprotection with trifluoroacetic acid the hydrophilic NH_2-groups can be set free to change the character of the dendrimers completely. By saponification of the glycine ester bond, the PEG chains have been readily cleaved from the dendritic part of the molecule.

Polypeptide dendrimers of 1st and 2nd generation have also been synthesized by Mitchell et al. [10]. They used L-glutamic acid, protected by benzyloxycarbonyl groups and activated as bis(succinyl)ester, as branching units. In contrast to Denkewalter, they chose a convergent growth strategy by treating the

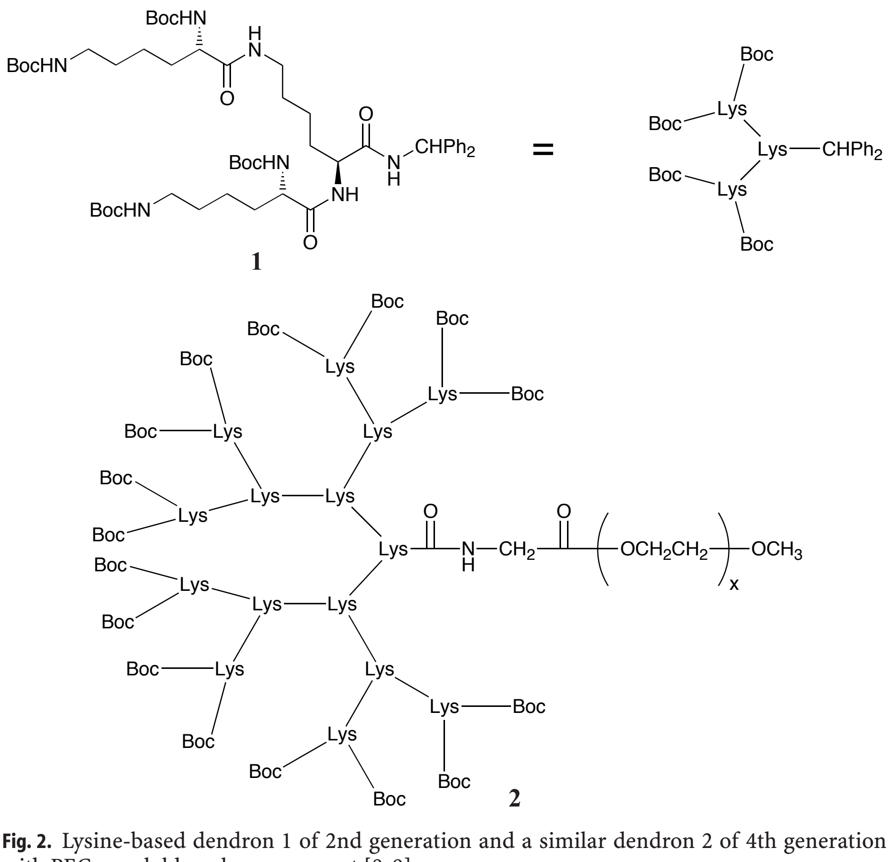


Fig. 2. Lysine-based dendron 1 of 2nd generation and a similar dendron 2 of 4th generation with PEG as soluble polymer support [8, 9]

diester with L-diethyl-glutamate and subsequently deprotecting the *N*-termini of the resulting 1st-generation dendron. The compounds obtained are monodisperse and have been fully characterized by MS, NMR and elemental analysis. Unfortunately no CD or ORD spectra have been reported.

Other types of branched peptide dendrimers, known as *m*ultiple *a*ntigen *p*eptides (MAPs), have been synthesized to mimic proteins for applications, for instance as synthetic vaccines, serodiagnostics, peptide inhibitors and intracellular delivery vehicles. Since this concept has been recently described in detail elsewhere [11], only the conceptual framework will be briefly presented here. Tam and coworkers have developed a dendritic core based on lysine units for the construction of MAPs [12–15] (Fig. 3). Carrying antigens at their periphery these MAPs have been designed to increase antigenicity and immunogenicity of peptides.

One common approach to the preparation of such dendritic peptides is stepwise solid-phase synthesis, which allows to reach the desired branching level [13, 16]. The selected peptide antigen is then added, again stepwise, to the resin-bound lysine core matrix to create the MAP dendron. However, this has not turned out to be a suitable procedure for obtaining dendritic macromolecular products with high purity. Modular approaches were also ineffective due to the poor solubility of the protected segments and the sluggish coupling rates. Tam et al. have therefore developed a more efficient approach for forming dendritic compounds, using unprotected peptides as building blocks and chemoselective "ligation" methods (which they refer to as orthogonal coupling). Examples of this approach include conjugation through thioalkylation, thiol-disulfide exchange, thioester and oxime formation, thiazolidine and oxazolidine ring formation, hydrazone, reverse proteolysis, and fragment coupling ("domain ligation"). Fig. 4 illustrates the synthesis of such a MAP derivative with three different ligation methods. The tetravalent lysine-based core peptide **5** carrying glyoxyl end groups has been directly coupled with a model peptide (VA20), which is derived from the surface protein of feline immunodeficiency virus and

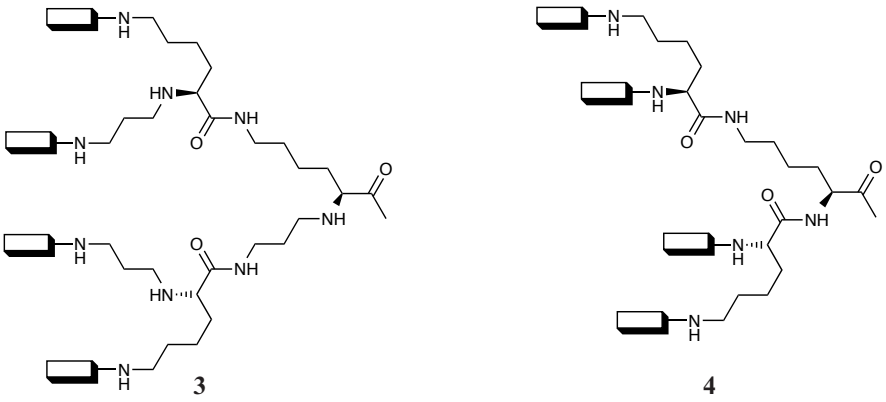


Fig. 3. Different MAPs based on lysine units. The open bars represent antigens [11]

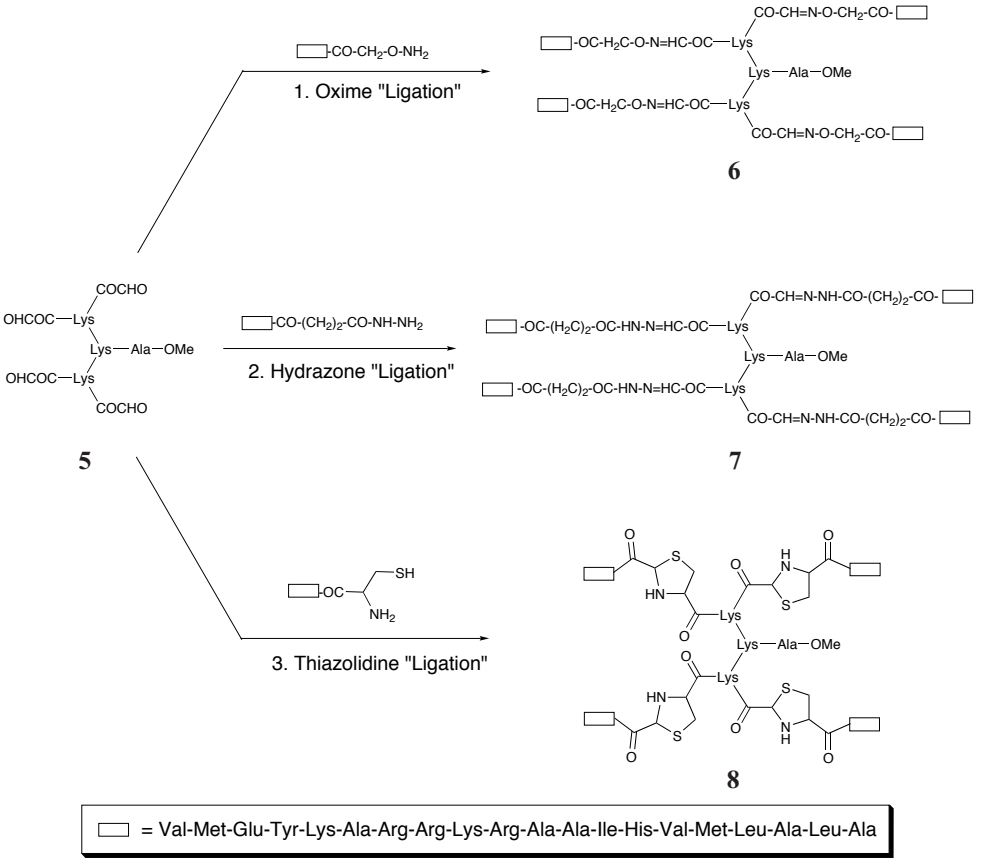


Fig. 4. Lysine-based core peptide **5** coupled with the model peptide VA 20 (represented by open boxes) by various "ligation" methods [17]

which consists of 20 amino acid residues. For the smooth coupling with the aldehyde groups of dendron **5**, VA20 has been elongated with (aminooxy)acetyl (→ **6**), monohydrazide succinyl (→ **7**), or cysteinyl groups (→ **8**) [17]. The circular dichroism (CD) spectra indicate a stronger helical structure of the dendritic peptides compared with the peptide monomer VA20. Cooperative interactions between the branches of the helical peptides might result in a more rigid overall structure.

Recently, Tam et al. extended their orthogonal "ligation" concept, using the thermodynamically driven formation of a thiazolidine ring for the synthesis of dendritic compounds that carry *cyclic* peptides at the surface, which were designated *m*ultiple *c*yclic *a*ntigen *p*eptides (McAPs) [18, 19].

The first example of a "grafted" dendrimer carrying non-racemic amino acid moieties at the surface has been reported in 1991 by Newkome et al. [20]. A four-directional core molecule, which they prepared from pentaerythrol [21], has been elongated with the branching units *tris*[carboxyethoxymethyl]amino-

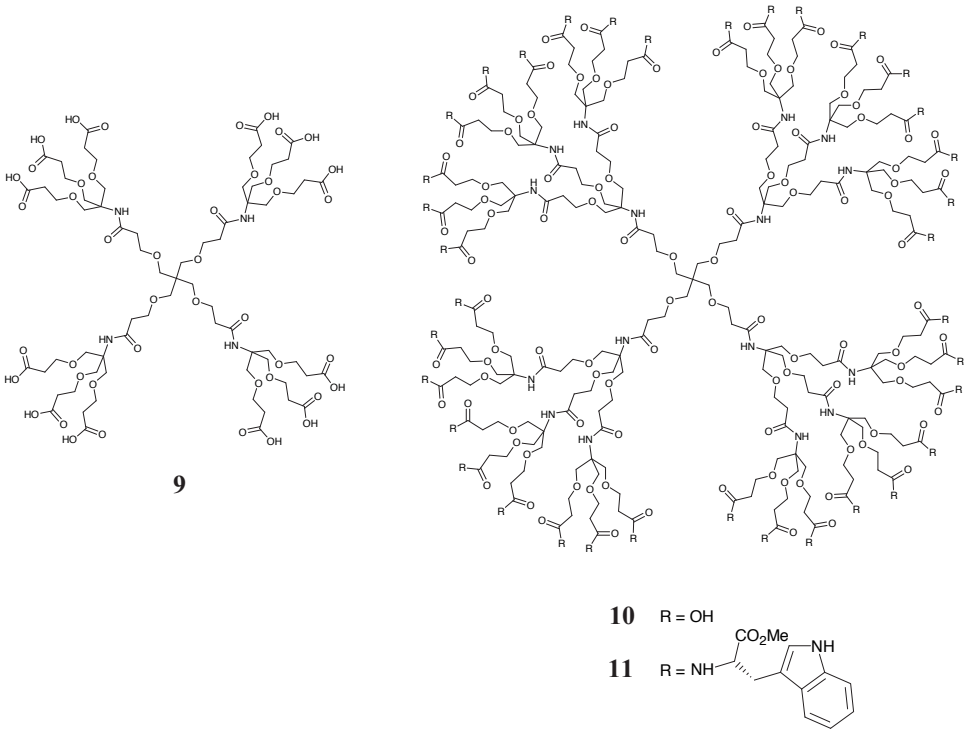


Fig. 5. Dodeca acid **9** and 2nd-generation dendrimers **10** and **11** as examples of "grafted" dendrimers [20]

methane, using standard DCC peptide coupling conditions, to give, after hydrolysis, the dodeca acid **9** (Fig. 5). Similarly, the 2nd-generation dendrimer **10** has been obtained, which could be modified by treatment with tryptophane methyl ester to give dendrimer **11**.

The molar ellipticity of these dendrimers was found to increase proportional to the number of chiral end groups. This is to be expected, in the absence of interactions between the terminal tryptophane moieties. No higher-generation dendrimers of this type have been reported. Other amino-acid-containing chiral dendrimers have been described by Meijer et al. who attached various amino acid derivatives to the periphery of poly(propylene imine) dendrimers (see Sect. 3) and more recently by Liskamp et al. (modification of polyamide dendra) [22] and Ritter et al. (synthesis of "grafted" polymerizable dendrimers containing L-aspartic acid components) [23].

2.2 Glycodendrimers

The important role saccharides play in biology, especially in recognition processes, led researchers to work on the development of multivalent so-called "neoglycoconjugates"; the numerous biological roles of cell surface oligosaccharides

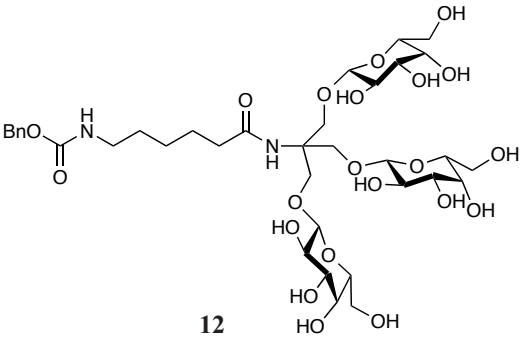


Fig. 6. Simple triply branched molecule with carbohydrates at the periphery (carbohydrate "cluster") [28]

have been reviewed in detail [24, 25]. Nevertheless it is worth to mention that, because of the weak nature of carbohydrate-protein interactions, only the large number and the multiplicity of these interactions led to measurable effects [26]. In addition it was found that only a few terminal sugar moieties are necessary to bind to the receptors. The linear increase of sugar density in these neoglycoconjugates led to a logarithmic growth of the binding affinity called "cluster-effect" [27].

Due to these observations, simple glycomimetics presenting the desired sugar moieties at the surface, should replace complex natural oligosaccharides which are only accessible through laborious syntheses. This has been demonstrated to be the case by Y.C. Lee et al. who synthesized the minimal "cluster" **12** (Fig. 6) [28] which already showed a "cluster-effect". During the last decade, various glycopolymers with *O*-, *S*-, and *C*-α-sialosides have been prepared, using copolymerization or "grafting"-methods. More complex structures contained e.g. sialyl *Lewis*^{x} (S*Le*^{x}) or a related 3′-sulfo-*Lewis*^{x} analog. The work in this area has been reviewed extensively [29].

Glycodendrimers [29–32] are supposed to be suitable molecules to fill the gap existing between these high molecular weight polydisperse glycoconjugates (glycopolymers) and small clusters. Due to the possibility to control the size, the molecular weight and the shape, a myriad of glycodendrimers can be envisioned and, in fact, synthesized. This novel class of glycoconjugates can be divided into two subgroups: bi- or tri-directional dendritic compounds and spherical dendrimers that can be built up either by a divergent or a convergent approach.

In 1993, the first synthesis of such neoglycoconjugates was published by Roy et al. [33, 34]. Doubly-branching polylysine dendra of up to 4 generations were prepared by solid-phase synthesis (Wang resin). The terminal amino groups were transformed into electrophilic *N*-chloroacetyl groups by treatment with *N*-chloroacetylglycylglycine hydroxybenzotriazolester to give the corresponding chlorides (cf. **13**, Fig. 7). They were functionalized with peracetylated glycosyl derivatives bearing thiol groups and, in a final step, they were cleaved from the support with trifluoroacetic acid. Thiolated glycosides were chosen in order to obtain dendritic glycosyl compounds that would be resistant to the action of glycohydrolases. After deprotection, dendritic glycosyl compounds

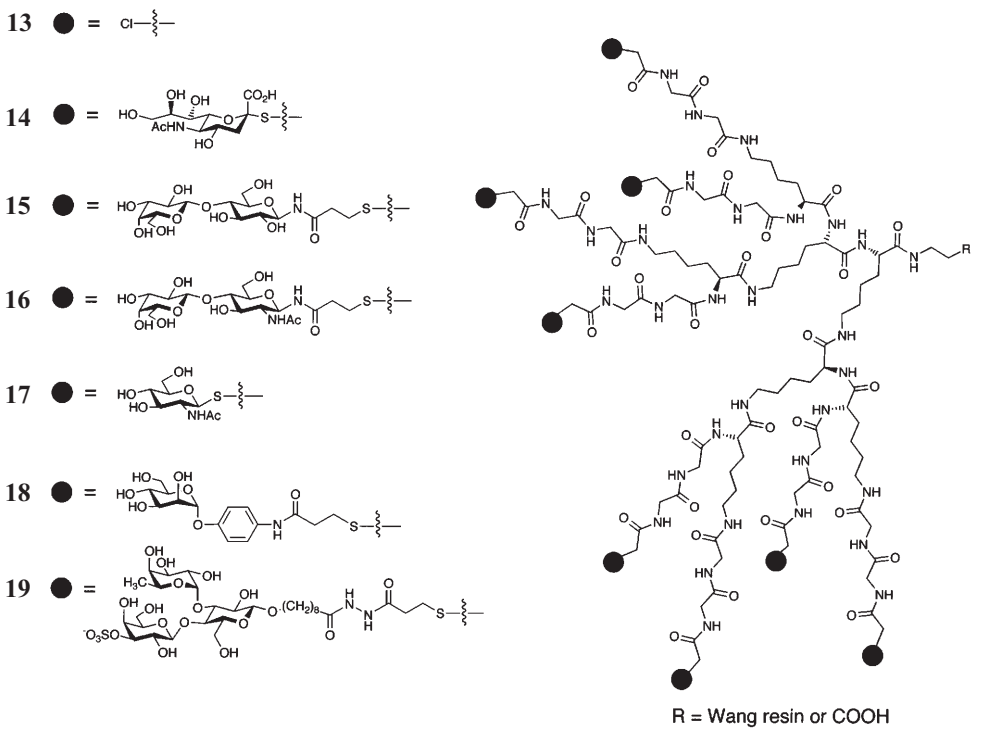


Fig. 7. Doubly-branching polylysine dendra functionalized with a chloroalkyl group and with various glycosides [33–39]

were obtained, carrying α-thiosialosides **14** [35], β-D-lactosides **15**, *N*-acetyllactosamines **16** [36], 1-thio β-D-*N*-acetylglycosamines **17** [37], α-D-mannosides **18** [38], or 3′-sulfo *Lewis*^{x}-glycosides **19** [39] (Fig. 7). These products were fully characterized, mainly by ^{1}H-NMR and mass spectrometry.

An alternative synthesis of compound **16**, using an enzymatic approach and starting from peracetylated 1-*S*-acetyl-1-thio-β-D-*N*-acetylglycosamine, has also been realized [37]. All the lysine dendra have been tested in *e*nzyme-*l*inked-*l*ectin-*a*ssays (ELLA) and showed strong biological activities. Especially compound **19**, containing the 3′-sulfo-*Lewis*^{x}-epitope, an active analogue of S*Le*^{x}, was found to be very active, showing an IC_{50}-value towards L-selectin of ca. 1 µM, 625 times higher than the corresponding monovalent compound [39]. Roy et al. also prepared triply branching dendra such as **20** that were synthesized with gallic acid as core and tetraethyleneglycol amine spacers using the above mentioned functionalization with thiolated glycosyl derivatives [40] (Fig. 8). Similar compounds built from phosphotriester backbones have also been synthesized [41]; they were tested as inhibitors of *vicia villosa* binding to asialoglycophorin. The results indicated a 3 to 10-fold enhanced affinity, thus supporting the "cluster-effect".

Okada et al. were the first to synthesize so-called "sugar-balls" [42]. They functionalized commercially available 3rd- and 4th-generation PAMAM-den-

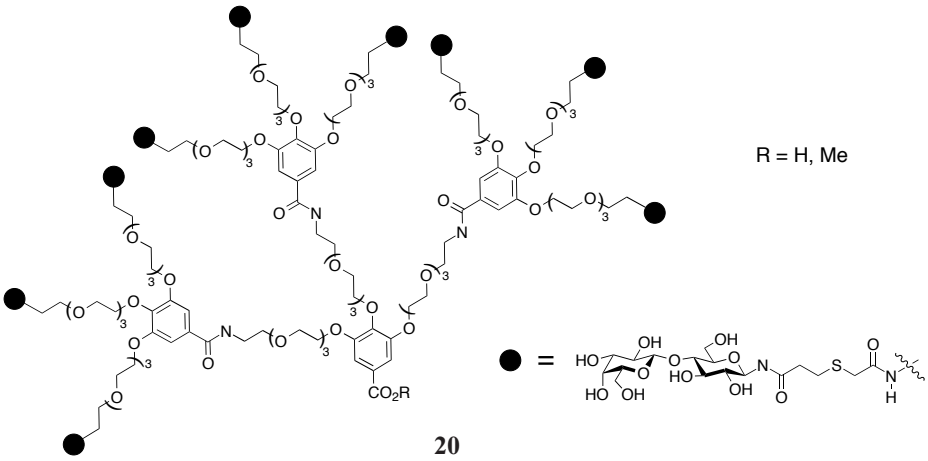


Fig. 8. Triply branching dendron functionalized at the surface with a glycosyl derivative [40]

drimers, bearing 24 or 48 amino groups at the surface, with disaccharide lactones of lactose (*O*-*β*-D-galactopyranosyl-(1,4)-D-glucono-1,5-lactone) via amide bond formation (**21**, Fig. 9). The resulting dendrimers showed strong interactions with the lectin *concanavalin A*.

Recently, the Okada group described a new class of polymerization systems [43]: oligoglycopeptide-type sugar-balls were obtained by a "radial growth polymerization" (RGP) of *α*-amino acid *N*-carboxyanhydrides with PAMAM dendrimers of different generations.

Using peracetylated glycosyl isothiocyanates of *β*-D-glucose, *α*-D-mannose, *β*-D-galactose, *β*-cellobiose, and *β*-lactose, Lindhorst and Kieburg synthesized tetra-, hexa- and octa-valent PAMAM dendrimer derivatives. Using these glycosyl isothiocyanates, dendrimers, bearing a wide variety of sugars at the surface, were readily obtained [44]. Very recently, the same group published the synthesis of small dendrimers, applying the same coupling strategy that does not rely on the use of protecting groups [45].

In a more recent paper, Roy et al. reported on the synthesis and biological properties of mannosylated Starburst™ dendrimers [46]. In addition to the presence of good biological properties in ligand- and inhibitor-tests, these dendrimers were shown to constitute novel biochromatography materials of high affinity for the rapid and easy isolation and purification of carbohydrate-binding proteins from crude mixtures.

Stoddart et al., in a collaboration with Meijer, synthesized "sugar-balls" by modification of poly(propylene imine) dendrimers [47]. An attachment of carboxyl derivatives of D-galactose and D-lactose to the amino surface groups has been achieved by means of amide bond formation, using the *N*-hydroxysuccinimide coupling procedure. The acetate protecting groups, that are still necessary to avoid undesired reactions in the coupling step, have been deprotected under standard Zemplen deacylation conditions, followed by treatment with an aqueous NaOH solution. The interpretation of the ^{13}C-NMR spectra allowed the

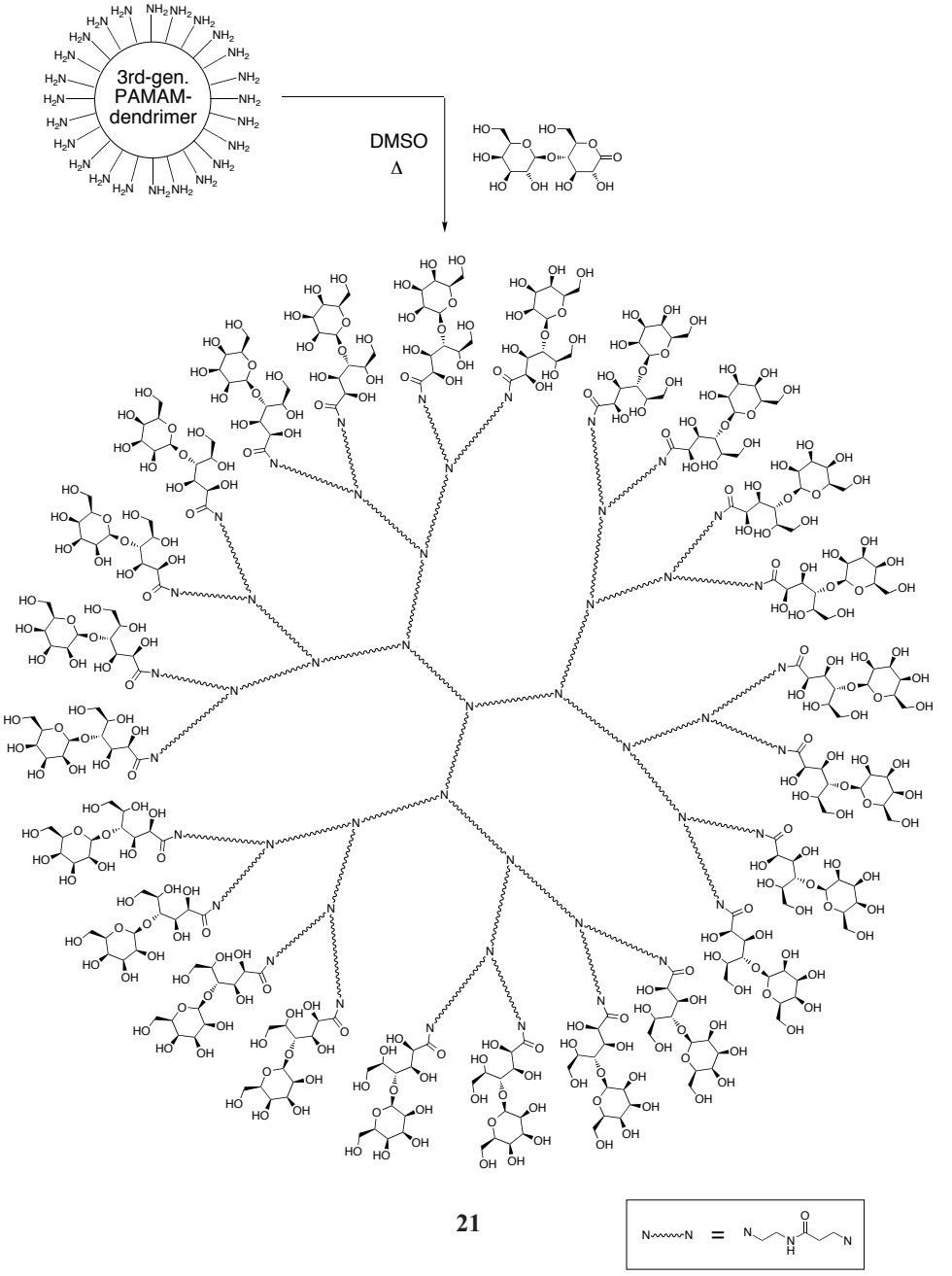


Fig. 9. 3rd-Generation PAMAM-dendrimer functionalized with disaccharide end groups [42]

authors to conclude that the resulting glycodendrimers do not contain any serious defects as a result of the chemical manipulations and that the degree of functionalization by the small saccharides seems to be very high. The statistical defects present in these structures are a result of the divergent nature of the synthesis of poly(propylene imine) dendrimers. Until now no details about biological properties have been reported.

A convergent approach leading to monodisperse glycodendrimers was used by Stoddart et al. [48]. Their strategy involved the synthesis of a triglycosylated derivative of tris(hydroxymethyl)methylamine (TRIS), the introduction of a glycine-derived spacer and 3,3′-iminodipropionic-acid-derived branching units on to the TRIS derivative by amide bond formation, the subsequent coupling of these dendrons with a trifunctional 1,3,5-benzenetricarboxylic acid derivative, used as a core, and finally the deprotection of the saccharide units. An example of an 18-mer (**22**), carrying 18 saccharide units at the periphery is shown in Fig. 10. In this case, the isolated compounds were shown to be monodisperse, an advantage of the convergent approach.

More recently, the above described route was extended by Stoddart et al. to even larger structures [49]. However, due to steric hindrance during the cou-

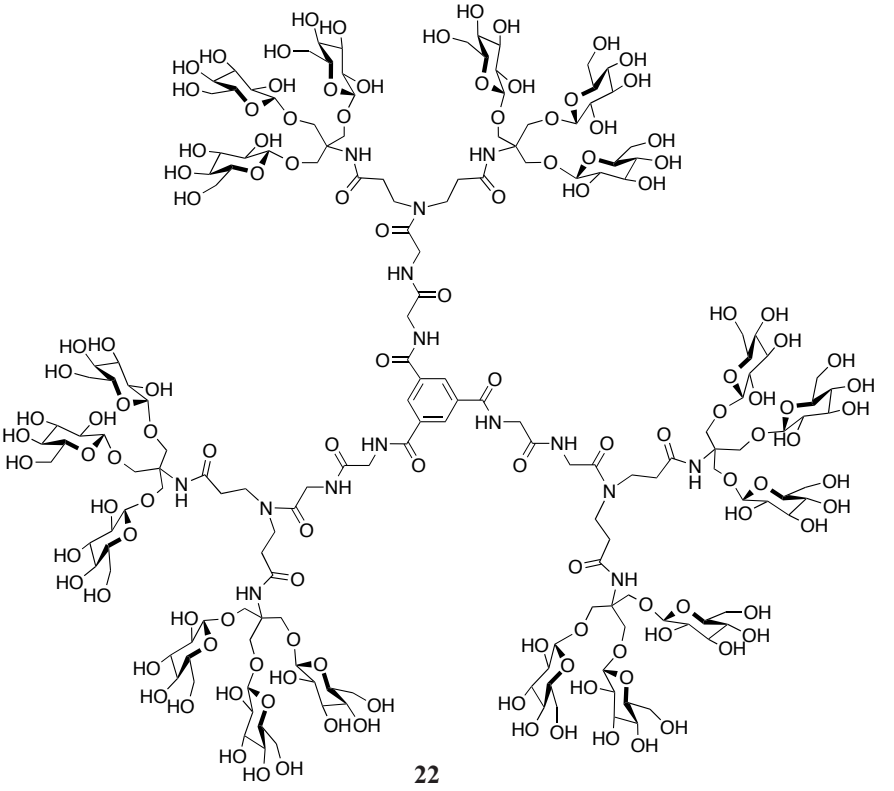


Fig. 10. Glycodendrimer with triglycosylated TRIS end groups [48]

pling of the large dendrons to the core (a limitation of the convergent approach), the strategy had to be sligthly modified. The biggest molecules contained up to 36 saccharide units with a calculated molecular weight of 14965 Da. The reduced activities of the focal point in dendritic wedges may probably be circumvented by using non-protected carbohydrate moieties [50]. The first biological evaluations of representatives of this class of glycodendrimers furnished promising results [51]. The same group also started a project to synthesize "fully-carbohydrate"-derived dendrimers [52].

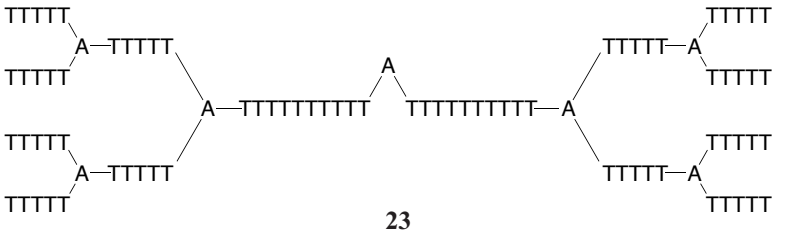
In summary, glycodendrimers with a wide variety of shapes, core molecules and carbohydrate residues are now available. A combination of both, the convergent and the divergent approach, seems to be the best strategy to build up these dendritic structures. As far as there exist no X-ray structures of biologically important glycoproteins and lectins, the biological testing of these new classes of neoglycoconjugates can help to obtain structural information about carbohydrate ligands and *c*arbohydrate *r*ecognition *d*omains (CRDs) of lectins. The glycodendrimers are envisaged as potentially useful therapeutic agents in the prevention of bacterial and viral infections and could also find application in the development of cancer drugs. In order to reach these important goals, the toxicological and immunochemical properties of the compounds have yet to be evaluated.

2.3 Chiral Dendrimers Based on Nucleic Acids

Less attention than to dendrimers containing amino acids or carbohydrates has been paid to dendrimers containing nucleic acids. Hudson and Damha reported on the synthesis of a 3rd-generation dendron containing 87 nucleotides (**23**, Fig. 11) [53]. On the surface of controlled-pore glass they synthesized, by a convergent procedure, oligonucleotides from thymidine. By coupling of two adjacent polymer-bound nucleotide chains with a tetrazole-activated adenosine 2′,3′-bis(phosphoramidite) derivative the 1st generation was obtained. Further elongation and coupling steps led, after cleavage from the polymer support, to the 87-mer **23**. Besides this synthetic work, commercial applications (for pharmaceuticals [54] or for signal amplification) and labeling in DNA blots [55] have so far been described.

The latter is an interesting example of self-organizing chiral dendrimers. The construction of the dendrimer is based on the natural property of nucleic acids to recognize and specifically bind to complementary sequences. Pairwise hybridization of two designed DNA strands results in the formation of large "monomers" which have four single stranded "arms" and a double stranded "waist" (**24**, Fig. 12).

The surface of each layer has two types of single stranded arms (e.g. one 3′ → 5′and one 5′ → 3′ strand) which can bind to other monomers to render 1st- and 2nd-generation "dendrimers" **25** and **26**. Therefore the molecular scaffold grows exponentially with each sequential layer of hybridization. If an oligonucleotide contains a sequence complementary to those at the surface of these networks it should be hybridized. The remaining free sequences from the other type of arms then bind in a standard nucleic acid blot (after they are bound to



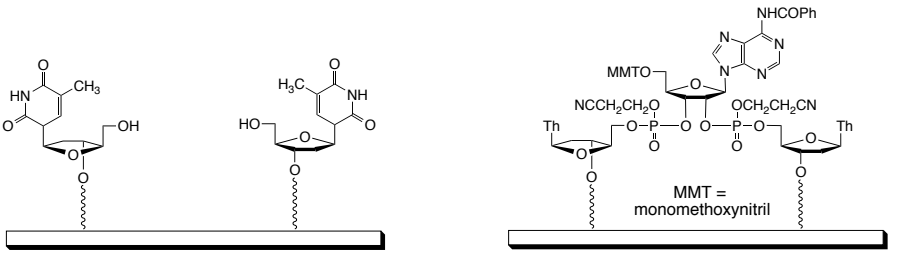


Fig. 11. Dendron **23** of 3rd generation containing 87 nucleotides. Two key intermediates in the synthesis of dendra such as **23**. The box represents long-chain alkylamine controlled-pore glass [53]

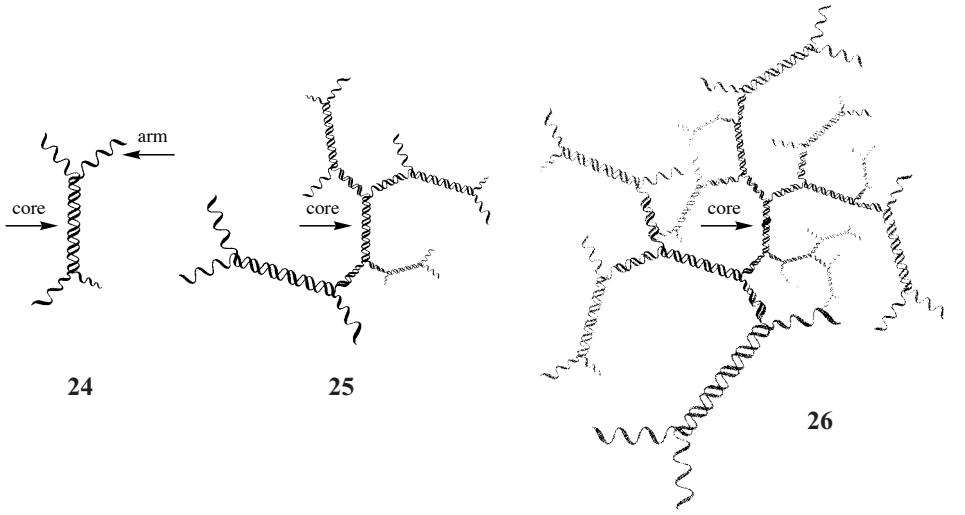
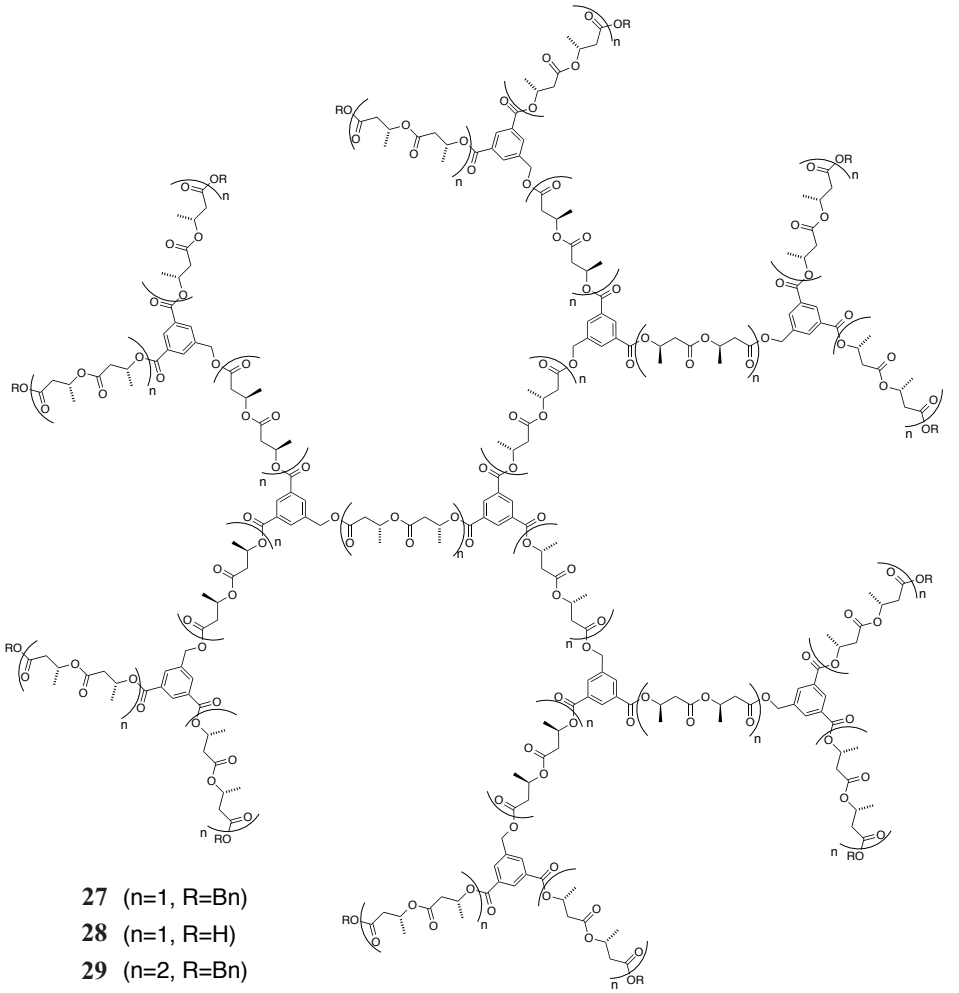


Fig. 12. DNA "core" and DNA dendrimers of "generations" 1 to 3 [55]

the target) to hundreds of so-called "label molecules". The signals of blots that were probed using oligonucleotides with dendrimers showed amplification of over 100-fold when compared to identical blots probed with the specific oligonucleotide alone [55].

2.4
Chiral Dendrimers Containing Oligo-(3-Hydroxybutanoate) Units

In our group, several dendrimers based on (*R*)-3-hydroxybutanoic acid (HB) have been prepared [56–58]. The dendrimers were synthesized by the convergent strategy. Trimesic acid has been used as core unit and the benzyl esters of the dimer and the tetramer of HB as elongation units. In such a way dendrimers of 1st and 2nd generation (**27**–**30**) have been constructed (Fig. 13). Since poly(*R*)-3-hydroxybutanoic acid (PHB) is known to be biodegradable [59, 60] the stability of the dendrimers **27**–**30** was tested in the presence of PHB-de-



27 (n=1, R=Bn)
28 (n=1, R=H)
29 (n=2, R=Bn)
30 (n=2, R=H)

Fig. 13. Chiral dendrimers of 2nd generation from trimesic and (*R*)-3-hydroxy-butanoic acid [56, 57]

polymerase. It was shown that the benzyl-protected dendrimer with dimeric HB-elongation units was not degraded by the depolymerase whereas the free acid was a surprisingly good substrate for the enzyme, even though the simple dimeric HB is not [58]. All deprotected dendrimers with tetrameric HB-elongation units were degraded very well. The rate of the first degradation step was about one hundred times faster than the degradation of dendrimers with dimeric HB-elongation units. An esterase, a lipase and a protease were shown to be able to degrade the dendritic compounds as well [56].

3
Dendrimers Containing Synthetic Chiral Building Blocks

Because of their high molecular weight and their defined structure, dendrimers offer themselves for studying the "expression of chirality" on a macromolecular level. The construction of configurationally uniform macromolecules is otherwise a complex task but can be achieved more easily with dendrimers because of repetitive synthesis from identical (chiral) building blocks. Comparison of optical rotation values and circular dichroism (CD) spectra should demonstrate what influence there is of the chiral building blocks on the structure of the whole dendrimer.

The stereogenic centers of chiral dendrimers synthesized so far are either generated by asymmetric synthesis, or they are derived from molecules of the pool of chiral building blocks. The only investigation on chiral dendrimers, consisting of achiral building blocks exclusively, was published by Meijer et al., who synthesized dendrimers such as **31** [61] (Fig. 14). This compound ows its chiral-

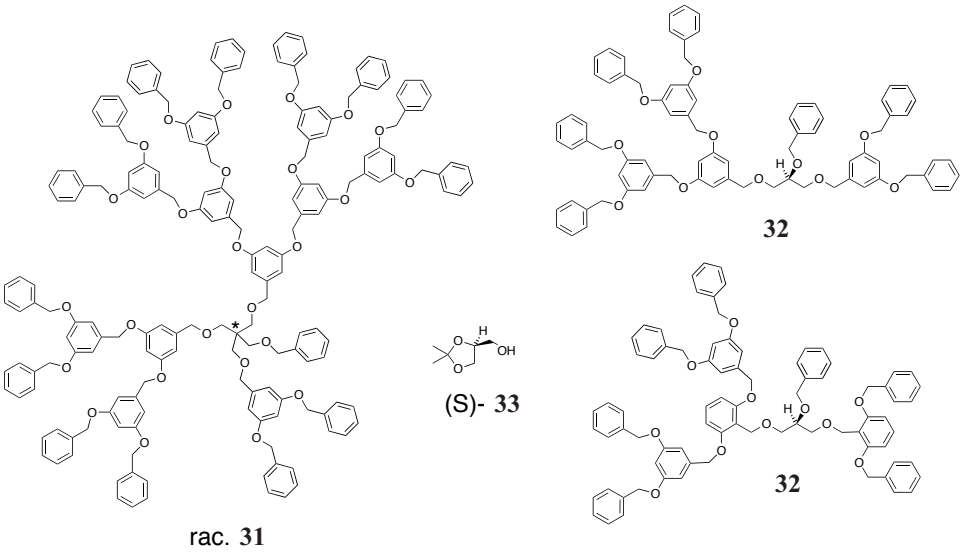


Fig. 14. Chiral dendrimers **31** (prepared as racemic mixture) with a core chirality center. Compounds **32** and **34** are derived from (*S*)-solketal **33** as enantiopure precursor [61, 64, 66]

ity to four achiral Fréchet-type [62] branches of different generations, which are attached to a pentaerythrol core [63]. Unfortunately the enantiomers of the racemic compound **31** could not be separated. By another route the chiral compound **32** was synthesized, starting from the chiral glycerol derivative (*S*)-solketal **33** [64]. Even though all intermediate products of the steps leading to **32** were optically active, the final product **32** was not (**32** was thus designated as being "cryptochiral" [65], a terrible term, considering that chirality is the geometrical property of an entity which is non-superimposable with its mirror image, and that an optically active compound must consist of chiral molecules, but that a compound consisting of chiral molecules needs not be optically active !).

The conformational flexibility and the lack of difference of the electronic properties of the polyether branches in **32** have been forwarded to explain this zero rotation. Therefore a similar dendrimer **34** has been prepared which carries a more sterically demanding branch, leading to a more rigid structure [66]: interestingly, this dendrimer indeed exhibited a very small but measurable optical activity, which underlines the thesis that "nanoscopic chirality" depends on the rigidity of the investigated structure.

In their studies on so-called dendritic boxes [67–69] Meijer et al. also modified achiral poly(propylene imine) dendrimers with several protected amino acids. The resulting dendrimers of generations 1 to 5 showed no constant optical activity per chiral end group. Rather, a decrease with increasing generation number was observed (Fig. 15). This effect has been most pronounced with the aromatic amino acids (*S*)-tyrosine and (*S*)-phenylalanine, and it is in contrast to results described by Newkome et al. [20] who found a comparable contribution of chiral appendages to the optical rotation in a series of dendrimers of different generations. There is no obvious explanation for the unexpected chiroptical behavior of the dendritic boxes garnished with amino-acid-derived groups, but racemization or "dilution effects" [70] can be excluded. In model studies, the contribution to the optical activity of the *N*-BOC-(*S*)-phenylalanine end groups has been shown to be very sensitive to the local environment and, therefore, also to the solvent. From ^{13}C-NMR relaxation-time measurements [67] a "solid-phase" behavior of the peripheral groups on going to higher generations is indicated. Thus, the local environment of the *N*-BOC-(*S*)-phenylalanine end groups changes when they are getting closer to each other. According to the authors' interpretation, the end groups in a dense packing seem to adopt "frozen-in" conformations with contributions to the optical rotation that internally cancel each other to give a resulting average of almost zero. Evidence for these conformational changes has also been derived from UV/VIS spectroscopic data [70].

When *t*-butoxy methoxy benzyl acetate groups are attached to the same dendrimers, which are similar in shape to but less dependent on the solvent than the phenylalanine moieties, a roughly constant optical rotation per end group is obtained for all generations [2]. In this case the contributions to optical activity of the end groups seem to be additive and insensitive to differences in packing.

In another experiment, alkyl chains have been introduced as spacers between the surface NH_2 groups of the dendrimer and the *N*-BOC-(*S*)-phenylalanine groups. In this case, too, the optical activity per end group remained constant for both, the dendrimer of the 1st (with four end groups) and of the 5th generation

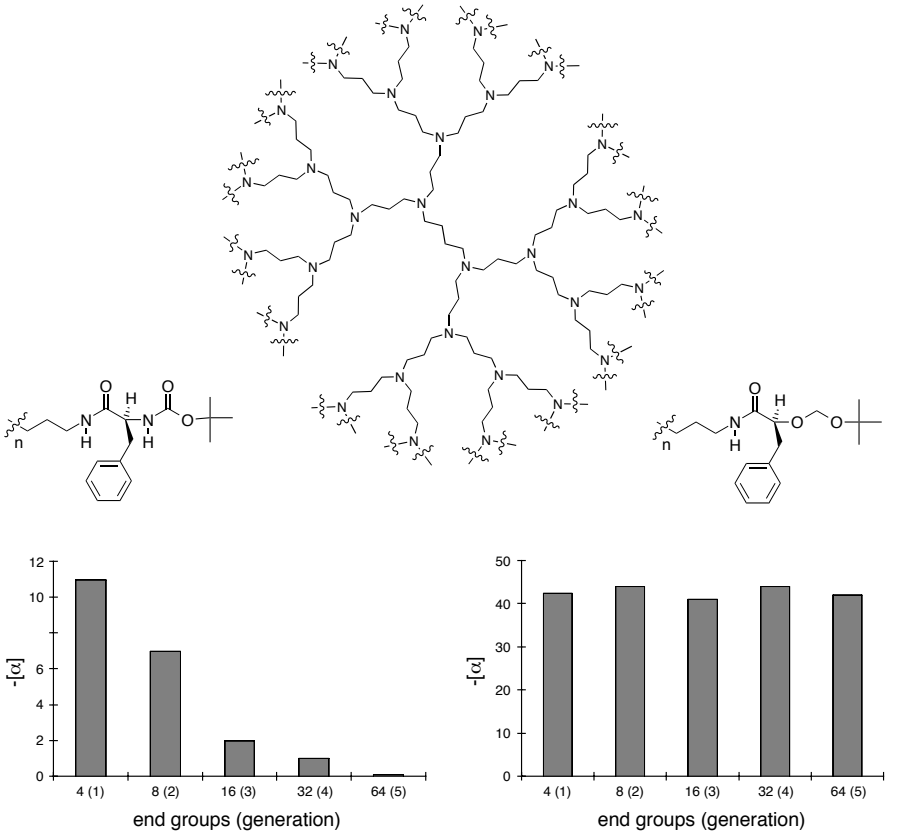


Fig. 15. Optical activities of poly(propylene imine) dendrimers, functionalized at the periphery with protected phenylalanine or *t*-butoxy methoxy benzyl acetate groups, depend on the number of end groups [2]

(with 64 end groups). Obviously, the end groups can now freely adopt their preferred conformation. After all, an *N*-BOC-(*S*)-phenylalanine group may be considered a suitable terminal group to determine the (local) density of a dendrimer surface.

Vögtle et al. have prepared chiral poly(imine) dendrimers of various generations by condensation of non-racemic 5-formyl-4-hydroxy[2.2]paracyclophane moieties with poly(amine) dendrimers [71]. They have found that the optical activity of these dendrimers was nearly constant with increasing generation number.

The first dendrimers with stereogenic centers generated by asymmetric reactions rather than being derived from natural chiral building blocks were prepared by Sharpless et al. [72]. With the goal "to find reliable strategies for the efficient construction of dendrimers and to introduce chiral cavities into these compounds", they synthesized chiral 1,2-diols as branching units. Starting from *para*- or *meta*-(chloromethyl)-phenyl substituted acetonides (from enantio-

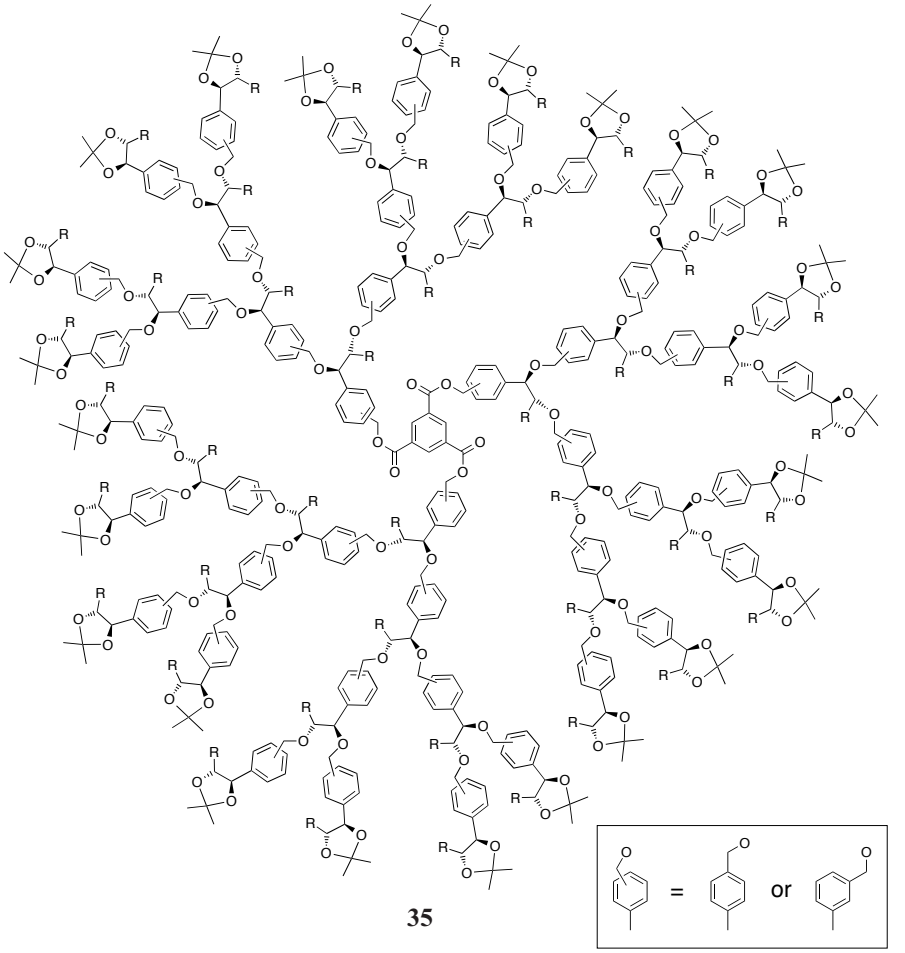


Fig. 16. Chiral 4th-generation dendrimers from *para*- or *meta*-(chloromethyl)-phenyl substituted acetonides and a 1,3,5-benzenetricarboxylic acid center piece [72]

selective dihydroxylations) they were able to synthesize chiral polyether dendrimers up to the 4th generation (**35**, Fig. 16), following a convergent "double exponential dendrimer growth" approach [73], which implies direct coupling of four 2nd-generation dendra with a 2nd-generation dendron, skipping the third generation.

A similar approach, employing the same asymmetric dihydroxylation reaction to synthesize chiral doubly branching monomers **36** – **39** has been described by McGrath et al. (Fig. 17) [74]. In their reactivity, monomers **36** and **37** are similar to Fréchet-type [62] branching units since each possesses two phenolic and one benzylic hydroxy group. With these building blocks dendrimers of up to the 3rd generation (**40**) have been synthesized, using, again, the achiral 1,3,5-benzenetricarbonyl moiety as core [75]. Now, OH groups on the stereogenic centers

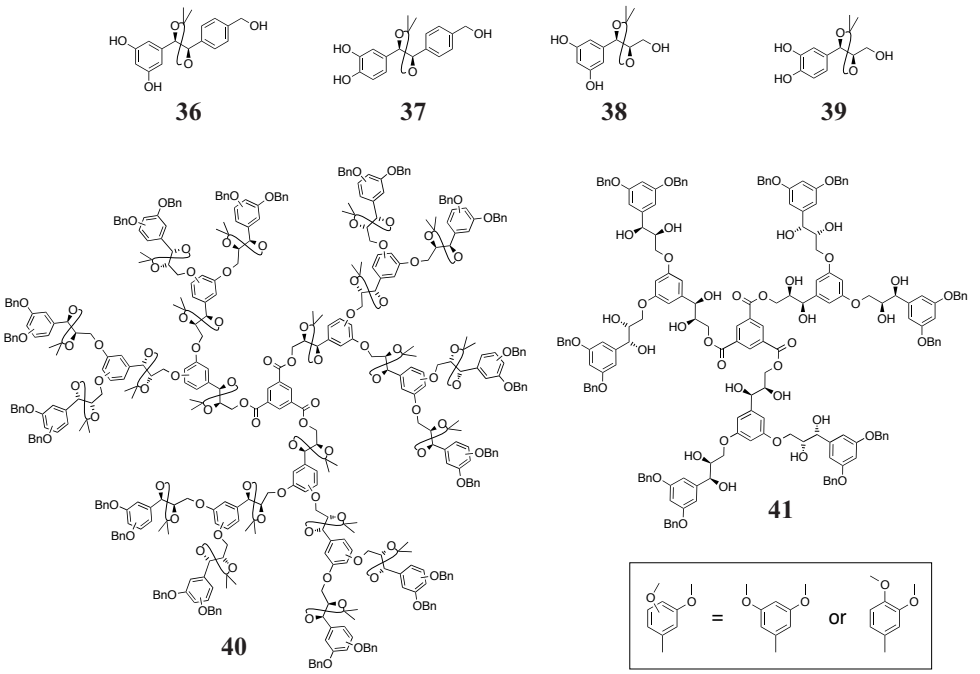


Fig. 17. Chiral acetonide building blocks **36**–**39**, protected 3rd-generation dendrimer **40** and deprotected 2nd-generation dendrimer **41**, derived from enantioselectively dihydroxylated styrenes and cinnamic alcohols [74–76]

in the inner part of the dendrimers are not the branching points used to combine the monomer units by etherification; rather, they are introduced in the acetonide-protected form, and thus, after deprotection, they are ready for reactions and interactions with each other or with other compounds: the free hydroxy groups can give rise to either *intramolecular* interactions between two branches or to *intermolecular* interactions between the dendrimer and other molecules (host-guest chemistry). As an example, the 2nd-generation chiral dendrimer **41** is shown in Fig. 17 [76]. Of course, the solubility of dendrimer **41** with 18 hydroxy groups in non-polar organic solvents is very low. As a possible application, these dendrimers, which should have the ability to anchor metal complexes, could be used for asymmetric synthesis. On the other hand, their hydroxyester functionality is expected to render them sensitive to H^+ or Lewis acid catalyzed transesterifications (the OH to CO distances of 5 and 6 atoms are ideal for acyl shifts !).

McGrath et al. have also thoroughly studied the chiroptical properties of dendrimers such as **40**. They compared the optical activities of the series of 1st-, 2nd- and 3rd-generation compounds of type **40**, considering the molar rotation per chiral unit ($[\Phi]_D/n$) [75]. A big difference of the values was found between the generations which could possibly indicate chiral conformations inside the dendrimers, that enhance the optical rotation values per unit when

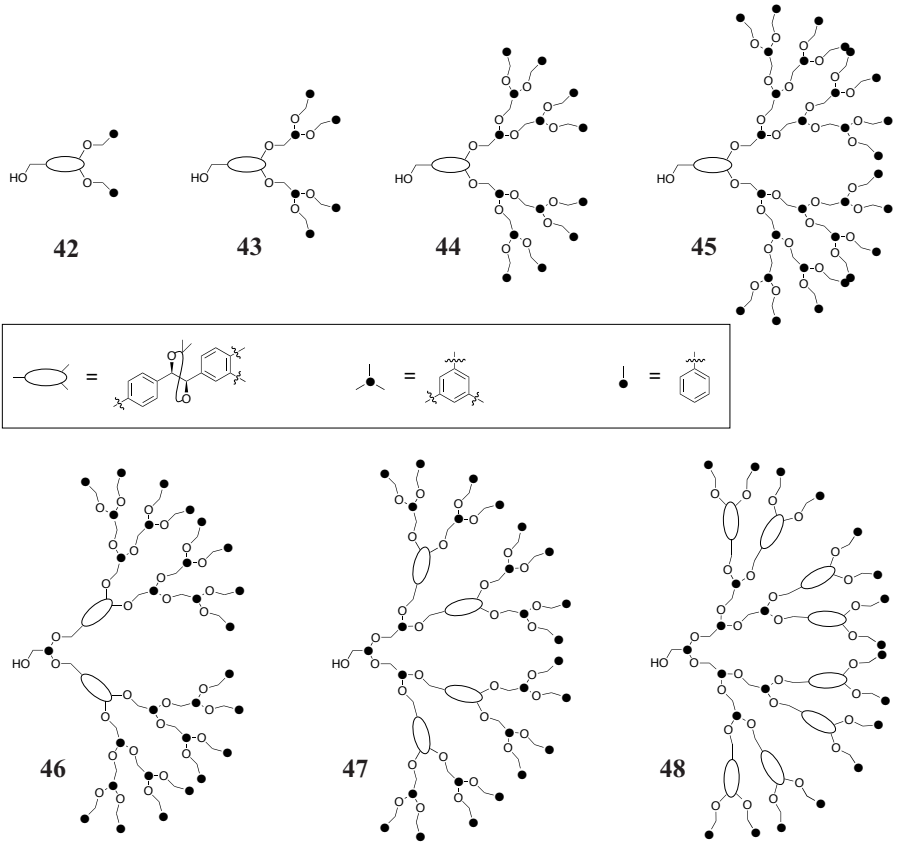


Fig. 18. Series of dendra **42 – 45** of 1st to 4th generation containing a chiral branching unit in the first shell and 4th-generation dendra 45 – 48 containing a chiral branching unit in different shells [77]

going to larger molecules. But as it was found in the case of the "fully chiral" dendrimers prepared by Seebach et al. (see later in this chapter) they also discovered that slight changes in constitution are causing these effects. By adding the molar rotation values of three model compounds (representing the core, the interior and the peripheral units) the calculated molar rotations agreed with the observed values (with deviations of less than 15%). To find out how the location of individual chiral units affects the chiroptical properties of single branches, they prepared two series of up to 4th-generation dendra (Fig. 18) [77]. In one series they attached Fréchet-type [62] benzyl aryl ether branches of 0th to 3rd generation to a chiral acetonide-protected hydrobenzoin unit (→ **42 – 45**). No increase of the molar optical activity of these dendra was observed with increasing size of the achiral branches.

In a next series of experiments McGrath et al. synthesized and compared some 4th-generation dendra **45 – 48**, where the chiral unit(s), when placed in the

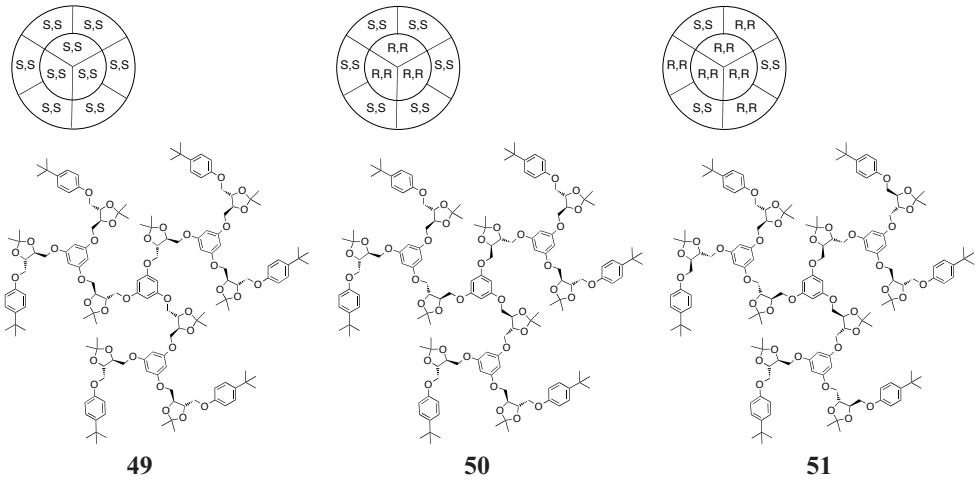


Fig. 19. A series of 2nd-generation dendrimers with chiral spacers derived from (*R,R*)- or (*S,S*)-tartaric acid. Note that the (*R,R*)-threitol-acetonide building blocks in **49 – 51** are derived from (*S,S*)-tartaric acid, and vice versa [78 – 80]

interior shells (**46** and **47**), have a larger influence on the molar optical activity per chiral unit than when placed at the periphery or in the center. However the authors are not yet fully convinced that this is not also a constitutional effect and further studies in this area are under way.

Other studies to investigate the relationship between the "stereo-spatial" [78] properties of chiral building blocks and the overall chiroptical properties of the entire dendrimer, they are part of, were performed by Chow et al. [78 – 80]. They synthesized different chiral 2nd-generation dendrimers by the convergent approach, using enantiopure threitol derivatives as spacers between achiral 1,3,5-benzenetriol (phloroglucine) derived branching units (Fig. 19). By combining spacers derived from (*R,R*)- or (*S,S*)-tartaric acid they were able to construct what they call "homo dendrimer" **49** [80] which contains only spacers of (*S,S*)-configuration and "layer-block dendrimers" **50** and **51** with combinations of spacers of opposite chirality sense. These dendrimers could, similarly to those of McGrath et al. [76], be hydrolyzed to (chemically stable) polyhydroxylated compounds.

The molar rotation of the dendrimers **49 – 51** is proportional to the excess of (*R,R*)- or (*S,S*)-threitol units. This means that the chiroptical effects of threitol building blocks of opposite chirality cancel out each other. For the "homo dendrimers" an average positive molar optical rotation value of 146 for each (*R,R*)-threitol unit was calculated whereas a value of –185 resulted for each (*S,S*)-threitol building block. From CD spectra of dendrimers of the types **49 – 51** it could be derived that the chiroptical effect of an (*S,S*)-chiral unit in the outer shell of the dendrimer did not compensate that of a (*R,R*)-chiral unit in the inner shell [81], a result which led the authors to state that the different dendritic layers are "chiroptically slightly different" [80].

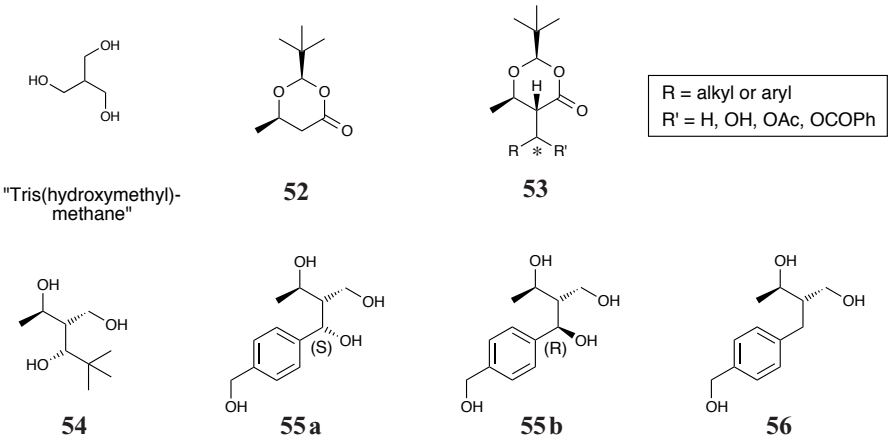


Fig. 20. Enantiopure chiral building blocks **54**–**56** and intermediates **52** and **53** obtained from 3-(*R*)-hydroxy-butanoate [1, 83–88]

At the beginning of investigations on chiral dendrimers in our own group was the question of how to synthesize chiral, non-racemic derivatives of "tris(hydroxymethyl)-methane" [82], which we wanted to use as dendrimer center pieces. We have developed efficient diastereoselective syntheses of such triols [83–85] from (*R*)-3-hydroxybutanoic acid, readily available from the biopolymer PHB [59, 60] (cf. Sect. 2.4). To this end, the acid is converted to the dioxanone **52** [86, 87], from which various alkylation products and different aldol adducts of type **53** were obtained selectively, via the enolate (Fig. 20). These compounds have been reduced to give a variety of enantiopure chiral building blocks for dendrimers, such as the core unit **54**, triply branching units **55a** and **55b** or doubly branching unit **56** [1, 88].

In 1994 we published the first chiral dendrimers built from chiral cores and achiral branches [1, 89], see for instance dendrimer **57** with a core from hydroxybutanoic acid and diphenyl-acetaldehyde and with twelve nitro-groups at the periphery (Fig. 21). As had already been observed with starburst dendrimers, compound **57** formed stable clathrates with many polar solvent molecules, and it could actually only be isolated and characterized as a complex [2 · (**57** · EtOAc · (8 H_2O))]. Because no enantioselective guest-host complex formation could be found, and since compounds of type **57** were poorly soluble, and could thus not be easily handled, we have moved on and developed other systems to investigate how the chirality of the core might be influencing the structure of achiral dendritic elongation units.

Following the convergent procedure, dendrimers of type **58**, **59** and **60** have been prepared from the chiral core triol **54** and achiral Fréchet-type [62] benzylic branch bromides. In the series of dendrimers with aromatic spacers (**60**) and without spacers (**58**), the optical activity $[\alpha]_D$ decreased on going from the 1st (not shown in Fig. 21) to the 2nd generation, whereas with aliphatic spacers

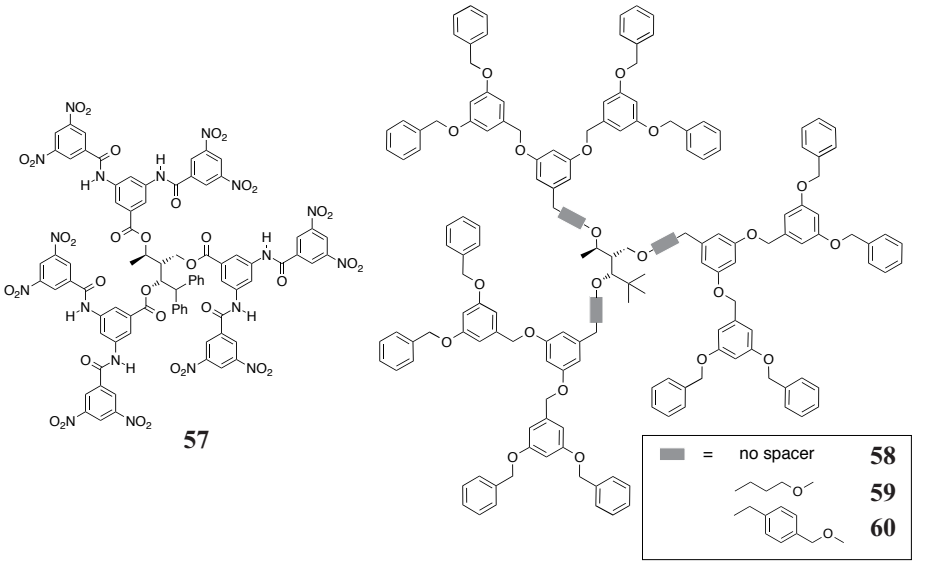


Fig. 21. 1st-Generation dendrimer **57** with nitro groups at the periphery and 2nd-generation dendrimers **58**–**60** used for optical and ^{1}H-NMR measurements [1, 89]

(**59**) hardly any optical activity could be detected at all. Obviously, no chiral substructures (which would contribute to the optical activity) are present in the achiral branches, and there is merely a kind of dilution effect upon the optical activity: for the dendrimers with aromatic spacers the *molar* optical rotation values $[\Phi]_d$ are constant. An anomaly was observed only with the two dendrimers containing no spacer: the *molar* rotation doubled when going from generation 1 to generation 2 (i.e. **58**). Also, the signals of the diastereotopic benzylic H-atoms observed in the ^{1}H-NMR spectra can be taken as a measure for the degree of dissimilarity of their environment: the heterotopic benzylic H-atoms become isochronous when going from the inner to the outer layer of the 2nd-generation dendrimers of type **59** and **60**. Again, the dendrimer **58** without spacers is an exception, in that there were no singlets for any of the sets of analogous benzylic H-atoms.

In order to continue our studies about the influence of chiral building blocks on the overall shape of dendrimers, the synthesis of "fully chiral" dendrimers (with stereogenic centers in the core and in all branching units) became the next goal. To obtain a dense shell even with low-generation dendrimers, triply branching units like **55** (see Fig. 20) with stereogenic centers at every branching point [1, 88, 90] were chosen. The synthetic limit turned out to be reached with the 2nd generation. During the synthesis a remarkable case of diastereoisomer differentiation (i.e. chiral recognition) was observed (Fig. 22).

When branch bromide **61**, consisting of four type-**55a** building blocks of (*S*)-configuration at the benzylic stereogenic centers, was coupled with the chiral triol **54**, dendrimer **63** was obtained in 51% yield after purification. With the

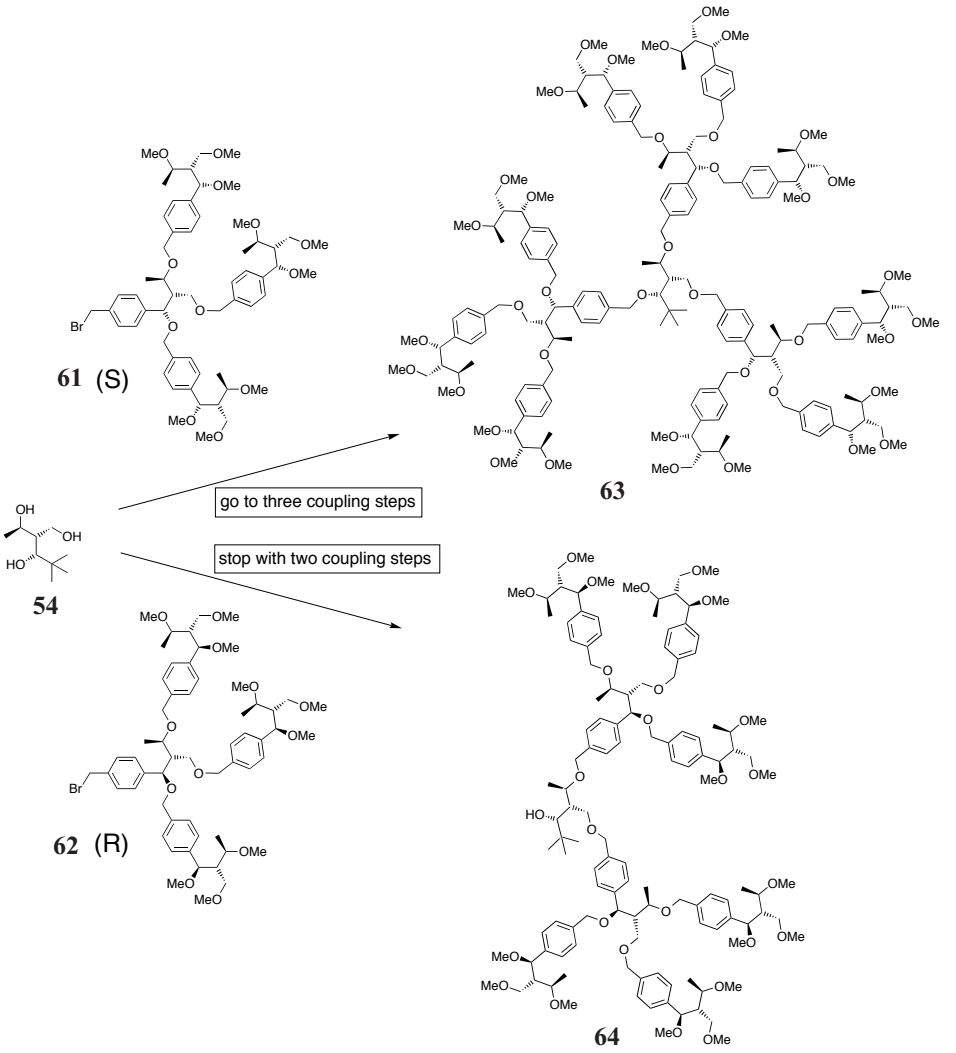


Fig. 22. The influence of different configurations in the dendritic branch bromides **61** and **62** on coupling with the same chiral core **54** [88, 90]

diastereomeric branch bromide **62**, however, that differs from **61** only by having (*R*)-configuration at the four benzylic centers, only two branches could be coupled to give dendritic alcohol **64**; even under forcing conditions, the corresponding dendrimer was not formed to any detectable degree. With the enantiomeric center triol *ent*-**54**, on the other hand, both, the (*S*)- and the (*R*)-branches reacted to give the desired dendrimers (**65**, **66** in Fig. 23).

Further work has revealed, that some combinations of diastereoisomeric 2nd-generation branch bromides (**61**, **62**, **67**, **68**) and various cores (**54**, *ent*-**54**, **69**) smoothly reacted to give the desired dendrimers (**63**, **65**, **66**, **74**, **75**) whereas

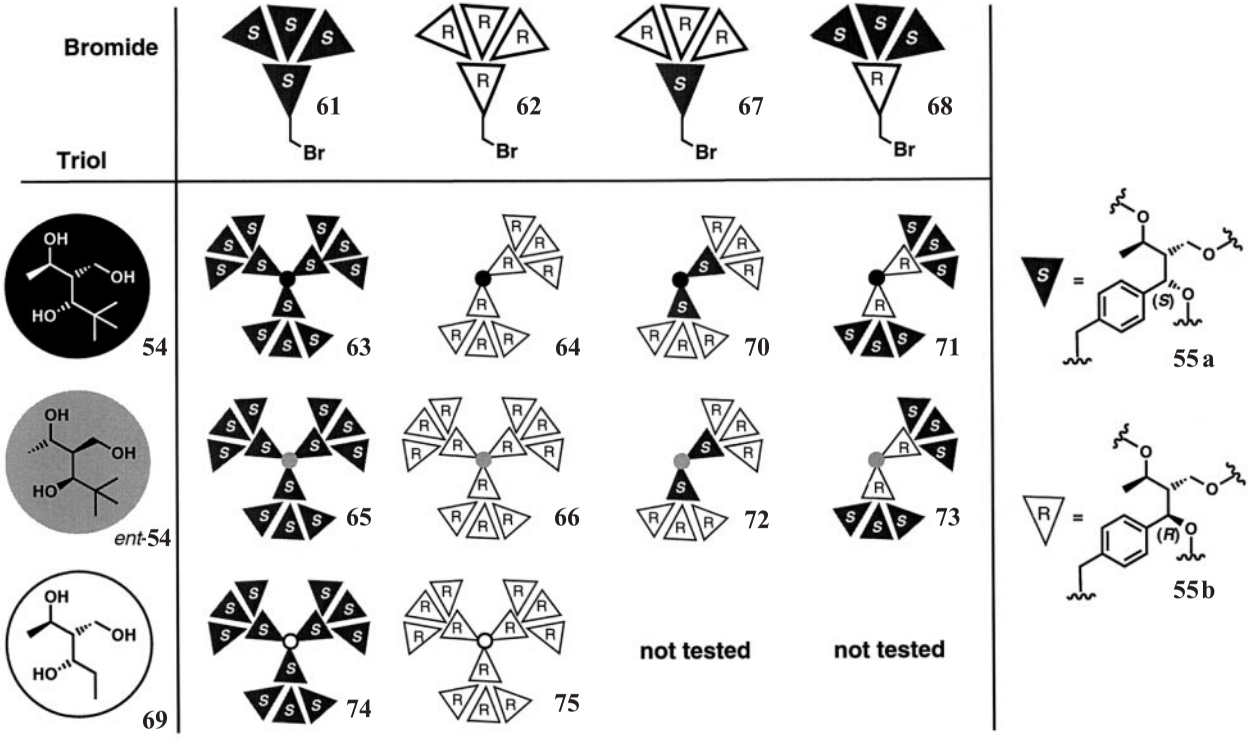


Fig. 23. Formation of various 2nd-generation dendrimers or dendritic compounds using branch building blocks of (*S*)- or (*R*)-configuration at the benzylic centers [90]. Three of the eight combinations tested by us led to dendrimer formation (products **63, 65, 66**) while five halted at the stage of the doubly coupled products **64, 70 – 73**, cf. Fig. 22. Core molecule **69** has less hindered OH groups and is, of course, not an isomer of **54** and *ent*-**54**

others (see **64**, **70**, **71**, **72**, **73**) did not (Fig. 23). With a switch of configuration at (some of) the benzylic centers of the branches the conformation of the branch and/or of the doubly coupled dendritic alcohols of type **64** must be altered in such a way that the third etherification may take place or be entirely blocked.

Considering the distance from the core OH groups to the stereogenic center(s) at which there is a configurational difference (17 bonds in the case of **70** vs **63**, of **72** vs **65**, and of **73** vs **66**) this recognition phenomenon might be called "outrageous". The components are able to discriminate between each other and show either a fit or a misfit (coupling or no coupling). Since the numerous single bonds in these dendritic structures have low energy barriers for rotation and hence the molecules have even more numerous conformations separated by shallow energy surfaces we [90] consider it impossible to reproduce and thus rationalize the observed phenomenon, for instance by molecular modelling. The coupling combinations shown in Fig. 23 are but a (minimal) few, considering the fact that of the 10^{11} possible stereoisomers (which exist of a molecule with 39 independent stereogenic centers) we have tested the synthesis of only eight.

Comparison of the optical activity showed that the dendrimer **63** with branches of (*S*)-configuration has a specific rotation and a molecular ellipticity which clearly deviate from the expected values [88, 90]. All other 2nd-generation dendrimers (even those with additional spacers between the branches and the core) have specific rotations that are comparable to those expected by simple addition of appropriate values for their building blocks. The deviation may therefore signal the presence of chiral conformational substructures in the 2nd-generation dendrimer **63**.

Besides MALDI-TOF mass spectroscopy, by which the monodispersity of all the above described dendritic compounds was proven, ^{1}H-NMR spectroscopy was again found to be a most informative characterization method, since most signals from the hydrogens at the different stereogenic centers have unique shifts. The resonances from analogous protons of the peripheral, interior and central units were always well separated and shifted towards lower field on going from outside to inside (for detailed discussion see our recent full paper [90]).

Another possibility to find out more about the structure of these dendrimers was chosen by incorporating fluorine atoms. The use of ^{19}F-NMR spectroscopy offered an additional tool to study the conformation of the dendrimer, especially with the fluorines attached close to the stereogenic centers [91]. Following our previously developed methods [92], fluorine-containing 1st- and 2nd-generation chiral dendrimers such as **76** were synthesized (Fig. 24).

The CF_3 groups not only had interesting effects upon certain synthetic steps on the way to such dendrimers [93], but also could be used as probes: the ^{19}F-NMR spectra which were measured in different solvents and at different temperatures exhibited a clear-cut difference between the inner CF_3 groups and those close to the periphery.

It turned out that with the sterically demanding triply branching building blocks no dendrimers larger than of 2nd generation could be prepared. We therefore switched to dendrimers with analogous doubly branching building units (see **56** in Fig. 20) as our target molecules. The components for the

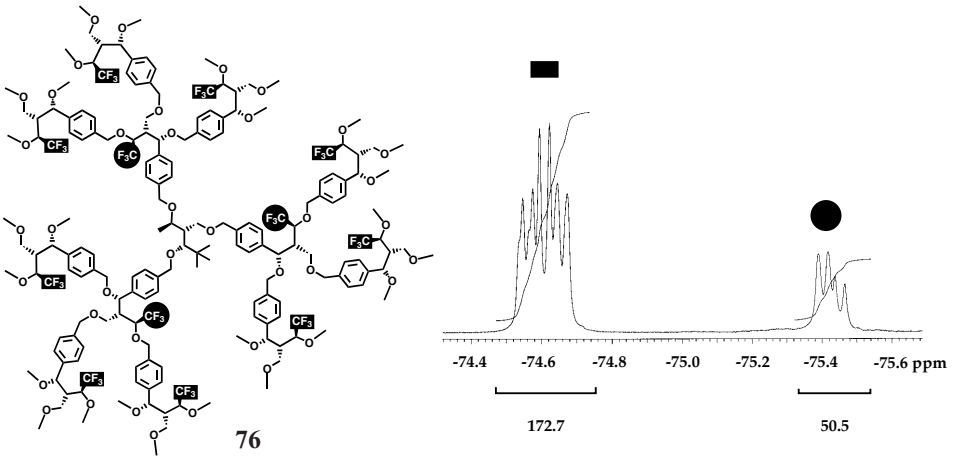
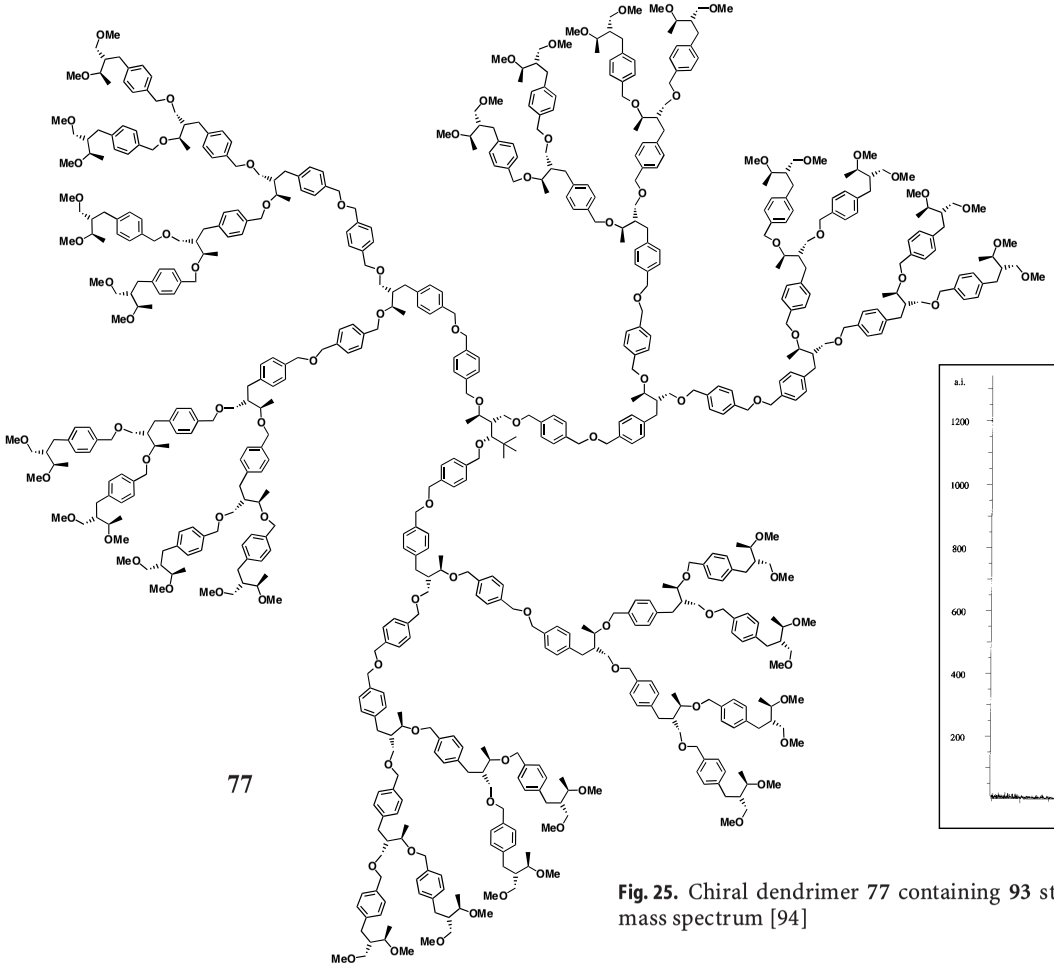


Fig. 24. Fluorine-containing 2nd-generation dendrimer **76** and ^{19}F-NMR spectrum showing the different chemical environment in the two dendrimer-layers [91]

branches are available by alkylation of the enolate of **52** with a benzylic bromide. Using a convergent strategy, "fully chiral" branches of up to 5th and dendrimers of up to 4th generation have been synthesized [88, 94, 95]. Dendrimer **77** was built from a triol with an aromatic elongating group and from 45 (24 peripheral, 21 interior) doubly branching units. It contains 93 stereogenic centers (and, thus, is one out of 10^{28} possible stereoisomers) and is monodisperse (Fig. 25).

By ^{13}C-NMR spin-lattice relaxation time measurements, it was shown that the segmental mobility of the peripheral units of all dendrimers of this type (1st up to 4th generation) is higher than that of the interior units [95]. This result is comparable to that obained by similar measurements with achiral dendrimers [96, 97]. By size-exclusion chromatography we tried to estimate the size of these dendrimers. By assuming that the molecules have a spherical shape and by using the intrinsic viscosity values, a diameter of five nanometers has been calculated for dendrimer **77**. Polarimetry showed, that even for dendrimers with so many stereogenic centers, the overall specific rotation $[\alpha]_D$ can be derived as arithmetic sum of increments of suitable model compounds resembling the building blocks. As shown in Fig. 26, compound **78** was used as reference for the elongated core, **79** for the interior and **80** for the peripheral building blocks.

A comparison of the thus calculated with the measured specific rotations of the 0th- to 4th-generation dendrimers of this kind gave a close resemblance, with a curve, approaching asymptotically a limiting value (Fig. 26). It was also shown that the shape of this curve was independent of solvent, concentration and temperature. This was not the case when CD spectra of these dendrimers were compared (Fig. 27): in solvents such as CH_2Cl_2 and *t*-butyl methyl ether a constant rise of the Cotton effect was observed, which correlates with the increasing amount of benzene chromophores in the dendrimers. However, in the



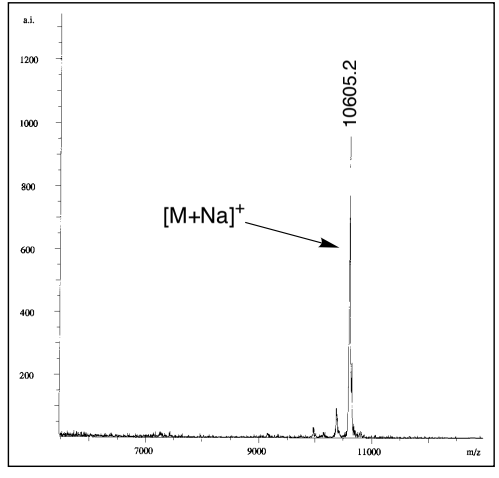
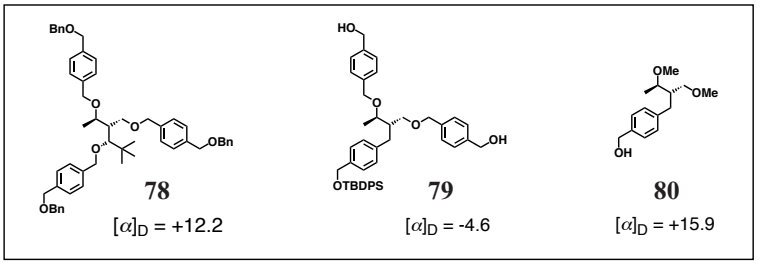


Fig. 25. Chiral dendrimer **77** containing **93** stereogenic centers and its MALDI-TOF mass spectrum [94]



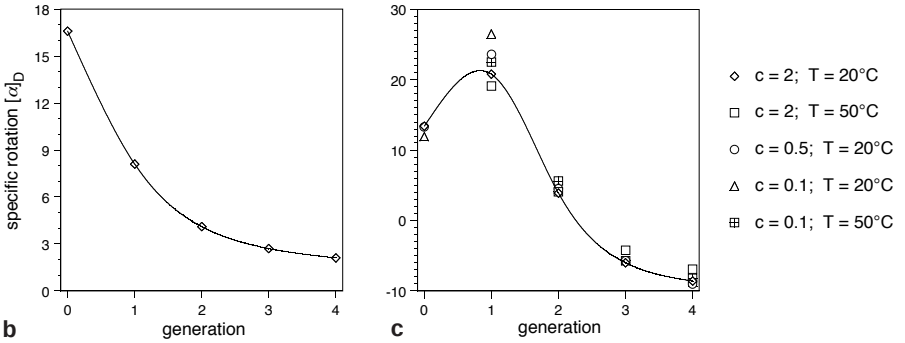


Fig. 26. **a** Specific optical rotations for the model building blocks for "core" **78**, "interior building block" **79** and "peripheral unit" **80** of dendrimers of type **77**; **b** calculated average optical rotations for the doubly branching dendrimers of 0th to 4th generation; **c** measured optical rotations in $CHCl_3$ at different temperatures and concentrations [94]

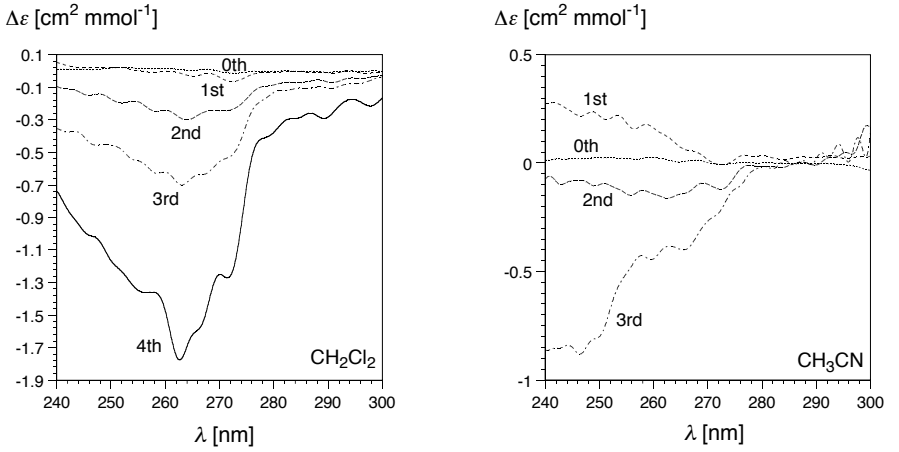


Fig. 27. CD spectra of "fully chiral" dendrimers (0th up to 4th generation of type **77**) in CH_2Cl_2 and in CH_3CN [94]

more polar solvent CH_3CN, dendrimer **77** was not soluble and the curves found for lower generation dendrimers changed shape (*and* sign) from generation to generation. To date, this effect could not be rationalized.

In conclusion, we have learned a lot from studying chiral dendrimers, about the behavior of such large chiral molecules and about the contributions of the different building blocks to the whole structure. It remains a great challenge to rationalize the origin of the dramatic diastereoselectivity effects observed in the synthesis of certain chiral dendrimers.

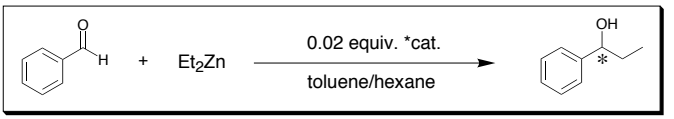
4
Chiral Dendrimers in Catalysis

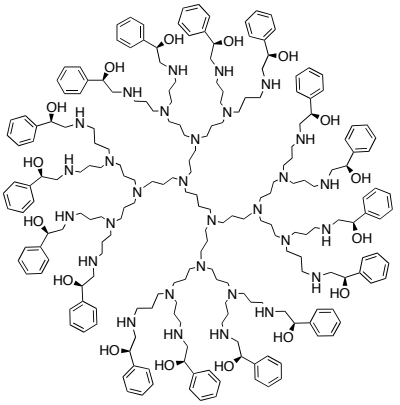
Due to their regular shape and their controllable surface and size dendrimers show promising properties as carriers for catalytically active sites. Such dendrimers with achiral ligands attached to their periphery were first described by van Koten et al. [98]. They prepared polycarbosilane dendrimers with diamino arylnickel(II) complexes on the surface to catalyze the Kharash addition of polyalkanes to double bonds. Compared to the smaller monomers, commonly used in homogeneous catalysis, dendrimeric molecules should be more easily recovered after the reaction because of their size and their stable shape and constant volume (e.g. by ultrafiltration). In this way, dendrimers combine the advantages of homogeneous catalysis (i.e. fast kinetics and good accessibility to the active sites) and heterogeneous catalysis (i.e. easy recovery) [99].

To catalyze asymmetric transformations, catalytically active sites can be incorporated in different areas of a dendrimer: a) chiral sites at the periphery, b) chiral sites in cavities or at the core, c) achiral sites which are surrounded by chiral branches in the interior of the dendrimer.

The rate of a catalytic reaction depends on the rate of diffusion of both substrates and products to and from the catalytic sites. Therefore it is of outmost importance that the catalytically active sites are freely accessible for reactions. Only dendrimers of *low* generation number can possibly be expected to be suitable carriers for catalytically active sites, especially when these are located in the interior. In high-generation dendrimers with crowded surfaces catalytic activity of an internal site would be prevented. On the other hand, a crowded surface will not only hinder access to an interior ligand site but will also cause steric hindrance between groups attached to it and thus prevent high reactivity of sites at the periphery.

The latter effect has been demonstrated by Meijer et al., who attached chiral aminoalcohols to the peripheral NH_2-groups of poly(propylene imine) dendrimers of different generations [100]. In the enantioselective addition of diethylzinc to benzaldehyde (mediated by these aminoalcohol appendages) both the yields and the enantioselectivities decreased with increasing size of the dendrimer (Fig. 28). The catalyst obtained from the 5th-generation dendrimer carrying 64 aminoalcohol groups at its periphery showed almost no preference for one enantiomer over the other. This behavior coincides with the absence of measurable optical rotation as mentioned in Sect. 3 above. The loss of activity and selectivity was ascribed to multiple interactions on the surface which were





Poly(propylene imine) dendrimer of
3rd generation with 16 end groups

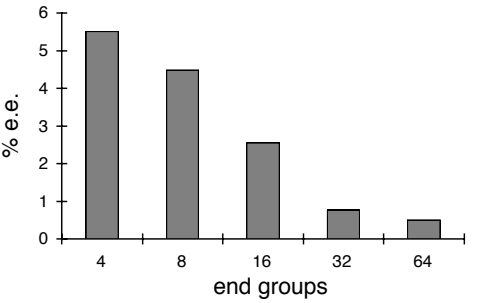


Fig. 28. Dependence of enantioselectivity from the number of generations or endgroups in the enantioselective addition of Et_2Zn to benzaldehyde, using 0.02 equiv. amino alcohol equivalents in each case [100]

proposed to cause steric hindrance and formation of different conformers of the terminal groups, so that opposite selectivities result.

Brunner et al. attached chiral branches to non-chiral catalytically active sites. With the aim to influence the enantioselectivity of transition metal catalyzed reactions they synthesized several dendritically enlarged diphosphines such as **81** [101] (Fig. 29). In situ prepared catalysts from $[Rh(cod)Cl]_2$ and **81** have been tested in the hydrogenation of (α)-*N*-acetamidocinnamic acid. After 20 hours at 20 bar H_2-pressure (Rh/substrate ratio 1:50) the desired product was obtained with an enantiomer ratio of 51:49.

In another reaction dendritic pyridine derivatives such as **82** or **83** were tested as co-catalysts for enantioselective cyclopropanation of styrene with ethyl diazoacetate [102]. Using catalyst **82**, enantiomer ratios of up to 55:45 were obtained. However, with catalyst **83** bearing larger branches yields and selectivities did not increase. The relatively low selectivities were rationalized by the presence of a large number of different conformations that this non-rigid system may adopt.

Bolm et al. attached single achiral Fréchet-type branches of up to the 3rd generation to a chiral pyridyl alcohol, but practically no influence was observed on the selectivity of the catalyzed reaction [103].

In our group, dendrimers carrying the catalytically active part either on the periphery or in the core were investigated. In both cases $\alpha,\alpha,\alpha',\alpha'$-*t*etra*a*ryl-1,3-*d*ioxolane-4,5-*d*imethan*ol*s (TADDOLs) have been employed as ligands in chiral

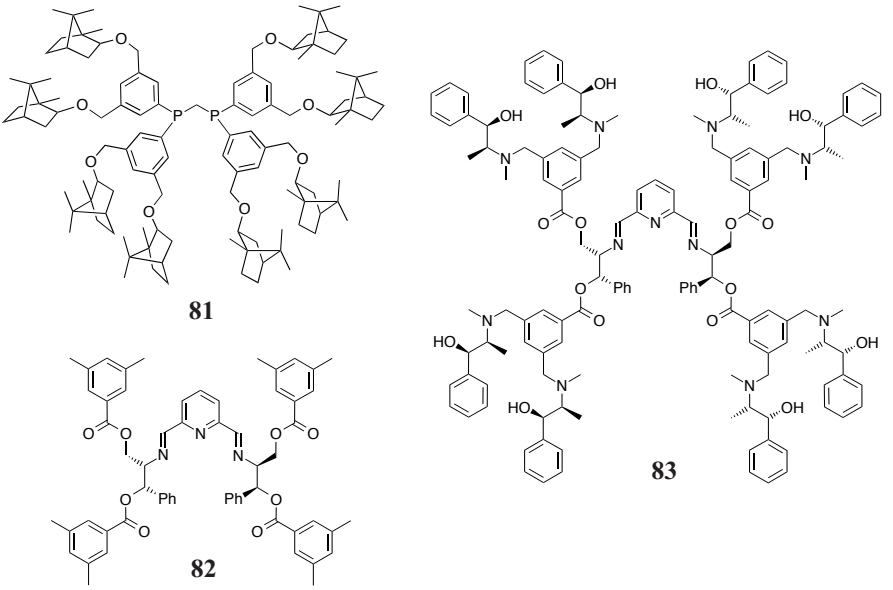


Fig. 29. Dendritically enlarged diphosphine **81** and pyridine derivatives **82** and **83** tested for enantioselective catalytic hydrogenations and cyclopropanations [101, 102]

active sites (Fig. 30), since a large variety of catalytic and stoichiometric enantioselective transformations had been shown to be possible with TADDOLate metal complexes [104].

Attached to the periphery of a 1st-generation dendrimer, $Ti(OCHMe_2)_2$-complexes of the six TADDOL moieties in **84** catalyze – in homogeneous solution – the enantioselective addition of diethylzinc to benzaldehyde with about the same selectivity ((*S*):(*R*) 97:3) as do six monomeric TADDOL units [105], but, with a molecular weight of only 3833 Da, dendrimer **84** had to be separated by column chromatography rather than by ultrafiltration methods.

Dendrimers of various sizes with the TADDOL placed in the center have also been prepared. By attaching achiral or chiral branches to the aryl rings of the central TADDOL a series of up to 3rd-generation dendrimers (as an example see **85**) was obtained. By using the titanate of low-generation dendrimers of this type in homogeneous catalysis it was shown that the branches had only a minor influence on the selectivity and rate of the catalyzed reaction. Dendritic branches can be of advantage to change the properties of a catalyst: thus octylgroups attached to the periphery of dendritic TADDOLs cause their complexes to be very well soluble in apolar media.

To increase efficiency and ease of product separation from reaction mixtures, we also prepared styryl-substituted TADDOL-dendrimers that can act as crosslinkers in styrene suspension polymerizations, and thus lead to beads with intimately incorporated TADDOL sites [106, 107]. Due to the presence of the conformationally flexible dendritic spacers between the chiral ligand and the poly-

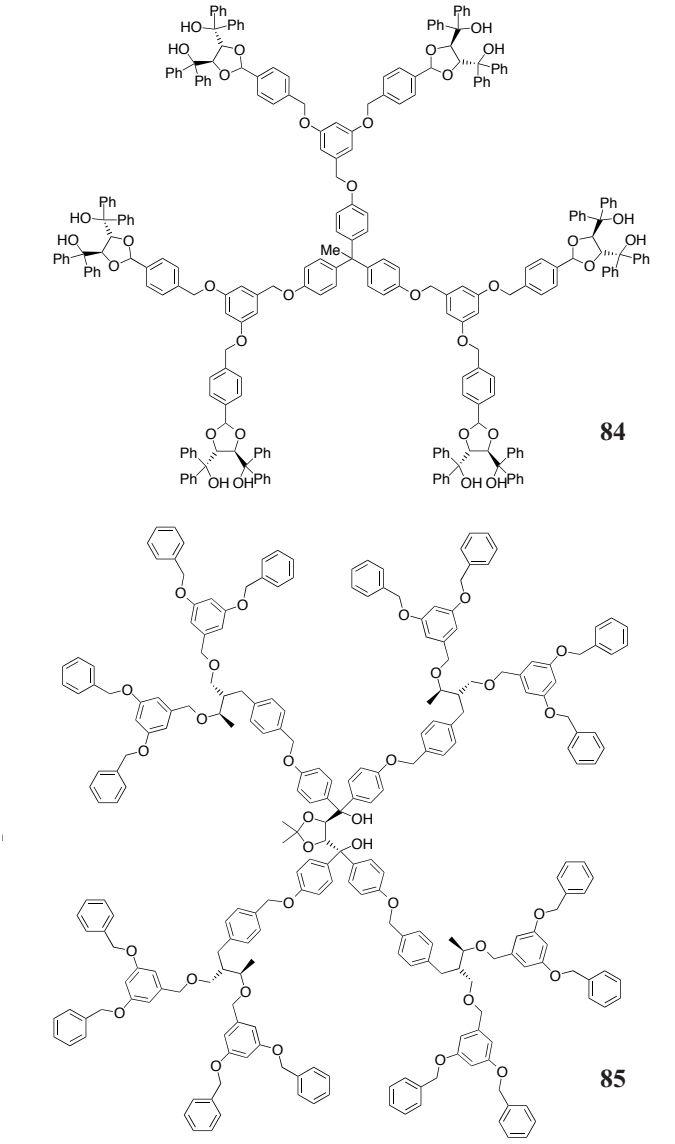


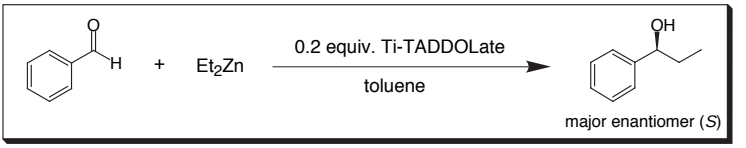
Fig. 30. Dendritic TADDOL derivatives carrying the catalytically active site either at the periphery (**84**) or in the center (**85**) [105, 106]

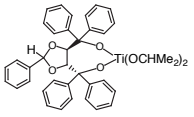
mer backbone(s), such cross-linked insoluble polymers were expected to have readily accessible TADDOL sites and thus provide catalytic activity comparable to that of soluble analogs.

Following a procedure previously employed for simple styryl TADDOLs [105], dendritic styryl-substituted TADDOLs were copolymerized with styrene

and loaded with $Ti(OCHMe_2)_4$. The beads thus obtained were tested in the catalysis of the enantioselective addition of Et_2Zn to PhCHO under the usual conditions [105, 108–110] (these first polymer particles which have been prepared with a crosslinking dendrimer do (because of the high degree of crosslinking) not swell in organic solvents which in less crosslinked polymers normally would be considered [111] a sign for poor solvent penetration and thus for poor properties as carriers of polymer-bound active sites or reagents!).

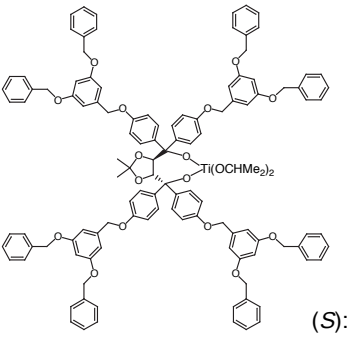
Employing 0.2 equiv. of polymer-bound dendritic Ti-TADDOLates of type **89** (1st and 2nd generation) enantioselectivities up to 98:2 were observed (Fig. 31). This value is comparable to those obtained in heterogeneous reactions using non-dendritic, polymer-bound analogs **88** (er up to 98,5:1,5 [105]) and with the



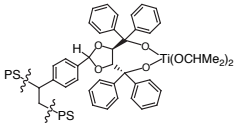


86
(*S*):(*R*) 99:1

Homogeneous



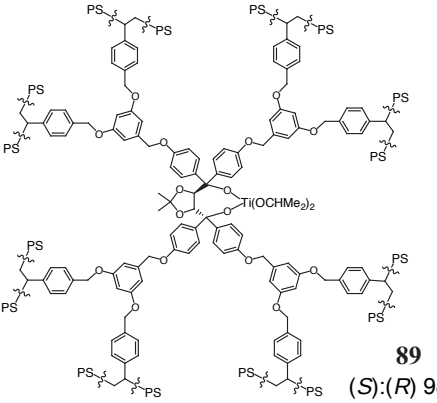
87
(*S*):(*R*) 98:2



88
(*S*):(*R*) 98.5:1.5

Heterogeneous

(PS=polystyrene chain)



89
(*S*):(*R*) 98:2

Fig. 31. Selectivity comparison for the enantioselective addition of Et_2Zn to benzaldehyde using different dendritic and non-dendritic homogeneous and heterogeneous Ti-TADDOLates as chiral catalysts [107, 110]. (*S*):(*R*) ratios refer to the 1-phenyl-propanol formed

corresponding homogeneous reactions using dendritic TADDOLate **87** (er up to 98:2) or the simple TADDOLate **86** (er up to 99:1 [108]). For the dendrimer-crosslinked polymers the selectivity increased from the 0th to the 1st generation, whereas with the 2nd generation no further improvement of the enantioselectivity was observed.

A comparison of the rates showed that the polymer-bound Ti-TADDOLate **88** and the dendritic polymer **89** catalyze the Et_2Zn-to-PhCHO addition at a similar fast rate as the monomeric TADDOLate **86** and the dendritic TADDOLate **87** in homogeneous solution [107, 112]. Further experiments also with other ligands are being carried out in our laboratories.

Along another line of work in our group (*S*,*S*)-1,4-bis(dimethylamino)-2,3-dimethoxy butane (DDB), which had been used as cosolvent in asymmetric synthesis [113], was tested as a core moiety for a dendritic amine catalyst. The conformationally flexible DDB-core, which has been synthesized in five steps from diethyl tartrate was coupled with different branches to give dendritically expanded diamines **90**–**92** (molecular weight 3800 Da) [114] (Fig. 32).

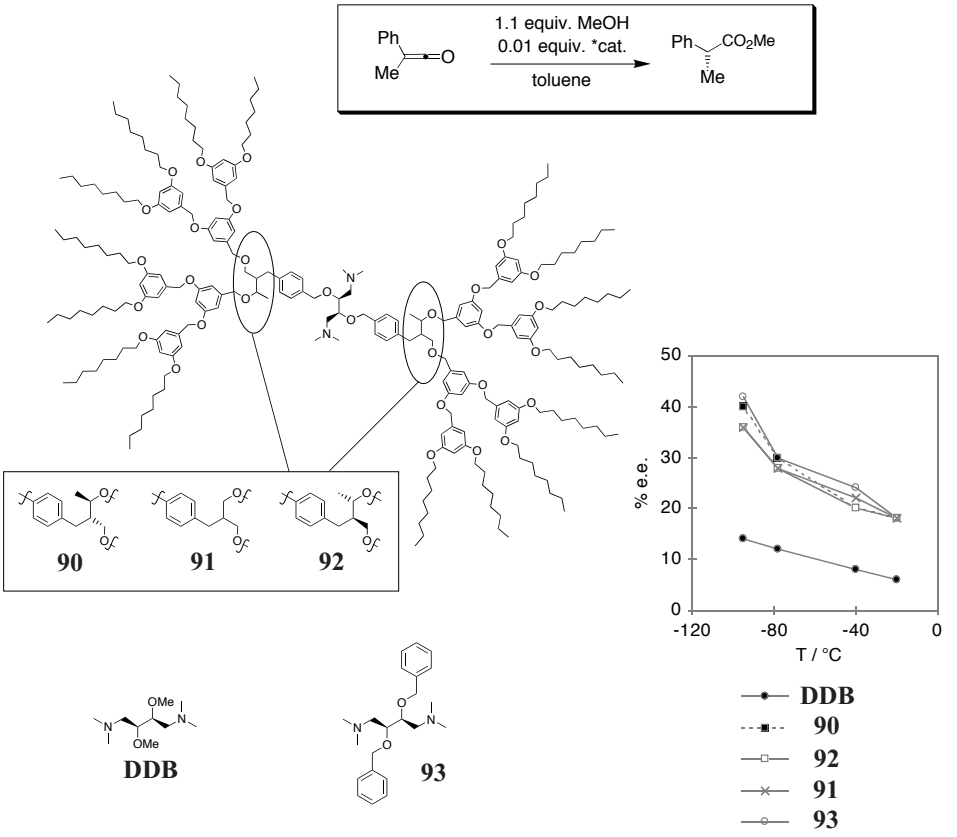


Fig. 32. Dendritically enlarged diamines **90**–**92** and benzylated ligand **93** (DDB analogs) in the enantioselective addition of methanol to ketene using 0.01 equiv. catalyst [114]

These dendritic compounds have been tested in several base-catalyzed reactions, e. g. the addition of ketene to chloral or the Michael-addition of thiophenol to cyclohexenone. In these cases the dendritically expanded DDB provided only minor differences in enantioselectivity, as compared to the monomeric DDB. However, when compound **90** was used to catalyze the enantioselective addition of methanol to methyl phenyl ketene, the selectivity, with which (*R*)-methyl-2-propionate was formed, increased by a factor of three. Also the diastereoisomer **92**, which differs from **90** by containing a branch building block of opposite chirality, and the dendritically enlarged ligand **91** with achiral branches catalyze the reaction more selectively than DDB. This particular ketene reaction includes an enantioselective protonation, i. e. the catalyst is directly involved in the enantio-differentiating step. Since the stereogenic centers of the branching units are remote from the reaction center(s) it follows that the entire dendritic wedge or parts thereof influence the stereochemical outcome of the reaction. The experimental results show that the stereogenic centers of the branching units, which are remote from the reaction center(s) seem to have only minor influence on the reaction. Therefore it was proposed that the size of the whole dendritic branch or parts thereof influence the stereochemical outcome of the reaction. Indeed, when employing non-dendritic dibenzyl ether **93**, an effect on the selectivity was found which is similar to that generated by dendritic elongation.

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