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PROEFSCHRIFT

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Aan mijn ouders
Voor Julianne

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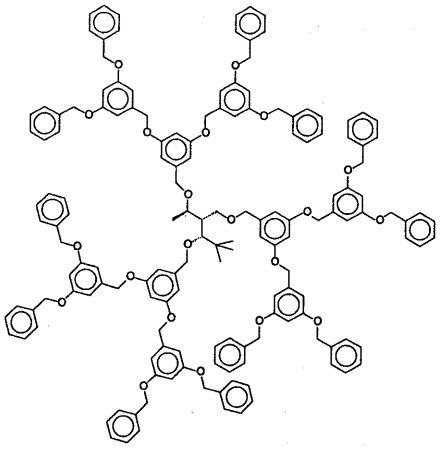
1 Chirality in dendritic architectures

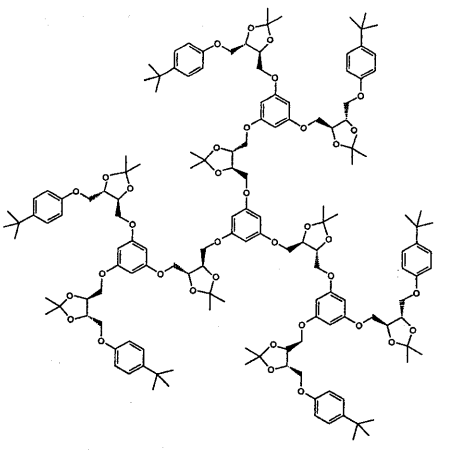
1.1 Introduction

Both symmetry and asymmetry in molecular objects have always attracted the interest of chemists.[1] Three-dimensional symmetry in macromolecular or nanosized structures is created within the field of dendrimers and hyperbranched polymers. Dendrimers or cascade molecules are highly branched macromolecules that are synthesized stepwise, and are characterized by a well-defined number of generations and end groups. They are generally described as spherical structures possessing a high degree of symmetry.[2] By now combining the high degree of symmetry in these dendrimers with chirality (or asymmetry), in fact a contradiction in terms is introduced. The different concepts and approaches to chirality of dendritic architectures are discussed as well as how these chiral features are expressed in the specific properties of this new class of macromolecules.

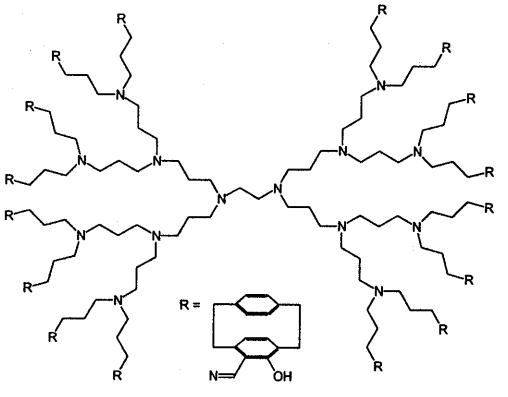
The first report on chiral dendrimers dates back to 1979, when Denkewalter described a divergent procedure for high molecular weight dendrimers based on the amino acid lysine.[3] Since that time numerous publications appeared on the issue of chirality and dendrimers, using either natural or man-made chiral building blocks. Seebach was the first to classify the various possibilities of building chiral dendrimers based on where the chirality is introduced in the molecule.[4] Due to the recent accounts on the synthesis and properties of chiral dendrimers, we have slightly modified and expanded Seebach's classification. We differentiate between a chiral dendrimer based on 1) chirality of the core only, 2) chirality of the branching unit only, 3) chirality of the end group only, 4) chirality in two or three of these building blocks, 5) constitutionally different branches attached to a chiral core, 6) a chiral object with a rigid chiral conformation, but without any stereocenters or chiral units, 7) interactions with chiral ligands, not covalently attached. All of the chiral dendrimers reported so far are members of one of the above classes, although no examples are yet known within classes 6 and 7. A selected anthology of chiral dendrimers and their classification is given in Figure 1.



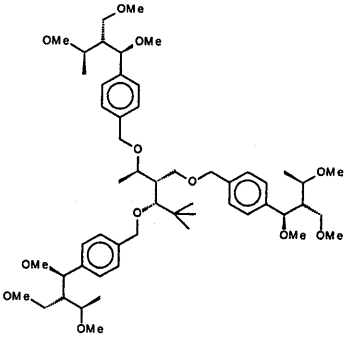
Class 1. A chiral core.[4]



Class 2. Chiral branching units.[5]



Class 3. Planar dissymmetrical end groups.[6]



Class 4. Chiral core and end groups.[4]

Figure 1. *A selected anthology of chiral dendrimers and their classification.*[4,5,6]

1.2 Challenges of chiral dendrimers

Not only do chiral dendrimers have a high scientific value for the basic understanding of fundamental stereochemical issues, they also have many features that will be of crucial importance to other fields where dendrimers are thought to be useful. Many of the interesting properties and applications foreseen for chiral dendrimers are the result of typical dendrimer properties, like: 1) a well-defined, three-dimensional architecture with a restricted conformational freedom at higher generations, 2) a large number of reactive end groups at the periphery of the dendrimer, and 3) the guest–host properties of dendrimers. When chirality is

now introduced into these highly branched architectures, it is interesting to raise the following questions and to investigate whether some of the challenges can be brought within the realm of reality: a) Is there a role in biological systems for well-defined nanosized structures with a periphery of natural products and encapsulated guests? b) Can dendritic chiral objects close the gap between molecular and macroscopic chirality? c) Are the surfaces of fractal nature and is it possible to use these curved chiral surfaces? d) Is chiral clathration possible by making use of chiral recognition in dendritic guest–host systems? e) Is it possible to develop efficient dendrimer-based catalysts for asymmetric synthesis?

Finally, it is of interest to know whether the chiroptical properties, e.g. optical rotation, of dendrimers differ from their linear macromolecular counterparts. The importance of chirality in linear polymers is generally accepted and for further information the reader is referred to an excellent review.[7]

1.2.1 Biocompatibility of dendrimers derived from natural products

The most straightforward way to introduce chirality into dendritic architectures is by using natural products, like amino acids, nucleotides and carbohydrates as building blocks or as end groups. These dendrimers can act as models for biomacromolecules, while additional features emerge from their possible biocompatibility and availability for interactions with other bioreactive species, including (modeling of) enzymatic activity.

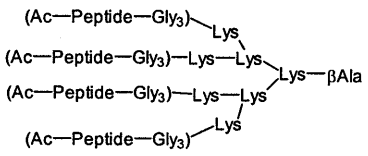


Figure 2. *Tam's all-peptide dendrimer.*[8a]

By far the most intriguing approach to these dendrimers is the use of AB_2 building blocks to construct highly branched macromolecules, based on natural products only.[9,10] Following Denkewalter's first report,[3] Tam reported on all-peptide based dendrimers.[8] These dendrimers (Figure 2) were made to study their possible role in biological systems and no specific chirality issues were raised. It is, however, interesting to study how the conformations and hydrogen-bonding patterns of these dendritic macromolecules differ from their linear counterparts, and circular dichroism can be used here. More advanced branched structures with helical peptide structures have also been described,[11] as well as structures

bearing amino acids in the building blocks.[12] The search for dendritic polysaccharides is inspired by the presence of these molecules in natural tissues. Several groups have been successful in preparing all-saccharide dendrimers and have expressed their interest to study the inhibition of infectious diseases.[13] This interest is based on the notion that simple saccharide derivatives are not active, while clustered saccharides (neoglycoconjugates) are.

Assuming that the biological compatibility is only due to the presence of amino acids and saccharides at the periphery of the dendrimer, poly(amidoamine) dendrimers,[14] arborols,[15] arborol-like[16] and poly(propylene imine) dendrimers[17] have been prepared with amino acids and saccharides as end groups.[18]

With the dendrimers made out of, or decorated with, natural products in hand, it should be possible to investigate the enzymatic cleavage of these groups from the packed dendrimer surface. However, only unsuccessful attempts are known.[19] Recently, an enzymatic hydrolysis was studied on a lactic acid-based dendrimer as reported by Seebach.[20] The enzymatic hydrolysis proved to be much faster for the dendrimers built from the tetrameric elongation unit (n = 4) compared to the dimeric analog (n = 2).

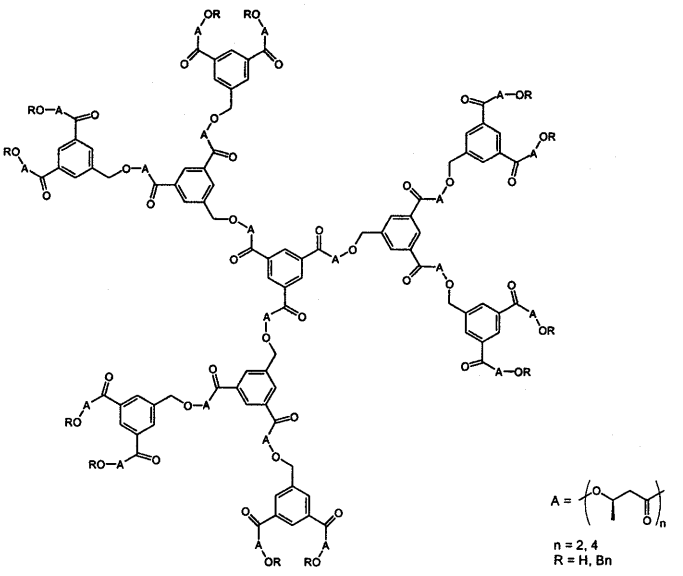


Figure 3. *An enzymatically degradable lactic acid-based dendrimer.*[20]

1.2.2 Chiral objects

The relationship between macroscopic chirality of objects and intrinsic chirality of molecules has puzzled many scientists for decades. When we compare these two forms of chirality (e.g. the mirror image relationship of our hands versus the identical configurations of the molecules in both hands), we recognize that somewhere in the growth of matter the molecular chirality is overruled by other packing phenomena. This effect is well-documented and accepted for crystallization.[21] However, it is less well-known for more disordered structures, despite the fact that a number of chiral aggregates and polymers can switch between diastereoisomeric conformers, while the configuration at the stereocenters remains unaffected.[22,23] In this paragraph we advertise that chiral dendrimers are an attractive class of compounds to shine light on the issue of chiral objects in general.

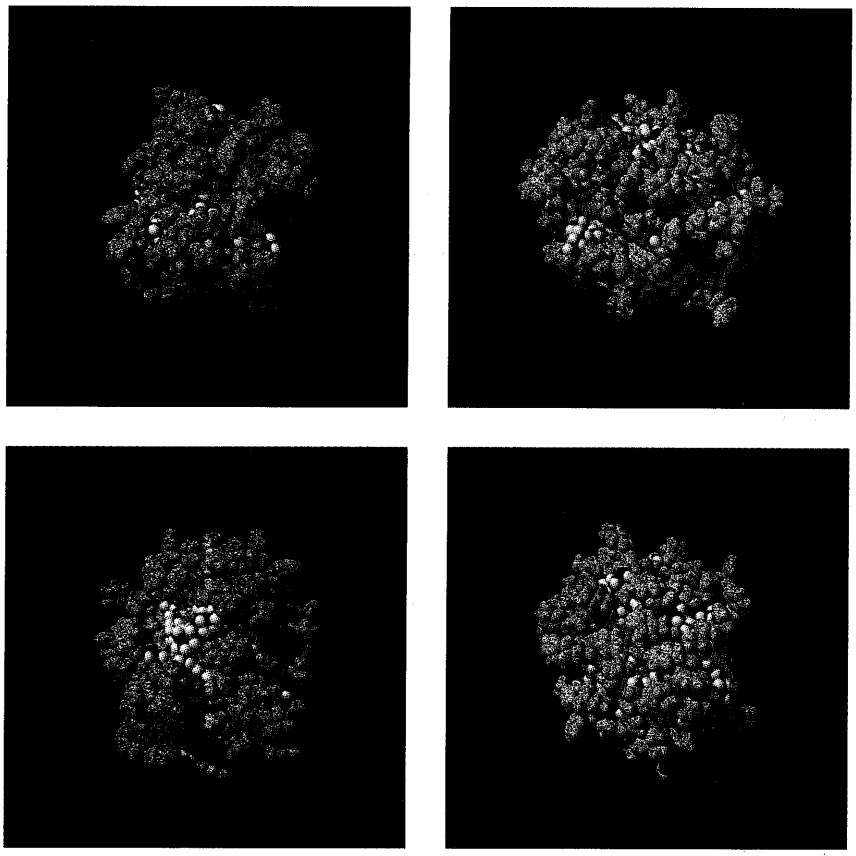


Figure 4. *Four conformations of the dendritic box that possess macroscopic chirality.*

The most appealing form of a chiral dendrimer is based on the arguments of Green and Garetz concerning the chirality of atactic polystyrene.[24] Since each molecule of polystyrene is chiral by definition due to its atactic nature, it will be present in a mixture of stereoisomers without its mirror image enantiomer present, due to statistical improbability. As a result of the flexibility of the polystyrene chain, the detection of chirality is only theoretical. However, there are possibilities that dendrimers can bring this notion within the realm of reality and this makes the class 6 of chiral dendrimers worthwhile mentioning. Supposing that high generation dendrimers with highly packed surfaces have indeed very rigid conformations, each dendrimer conformation is chiral and kinetically stable, while it is statistically improbable that its mirror image is present.[24,25] It should be possible to study these dendrimers with a variety of recently introduced nanometer-scale spectroscopic tools, like SNOM, AFM, etc. In order to illustrate this type of chirality, four different conformations of the dendritic box, as generated by computer, are given in figure 4. It now depends on the rigidity of the dendritic object whether the chirality can be addressed.

The second class of chiral objects is based on chiral dendrimers of class 5 in which constitutionally different branches are attached to a (chiral) core. Kremers and Meijer have investigated this type of chirality by synthesizing two dendrimers in which four Fréchet-wedges of different generation are attached to a core based on pentaerythritol (Figure 5).[26] A multi-step synthesis afforded both compounds in the racemic form. Unfortunately, these dendrimers could not be obtained in enantiomerically pure form, since all separation techniques available were unable to discriminate between enantiomers of this kind.

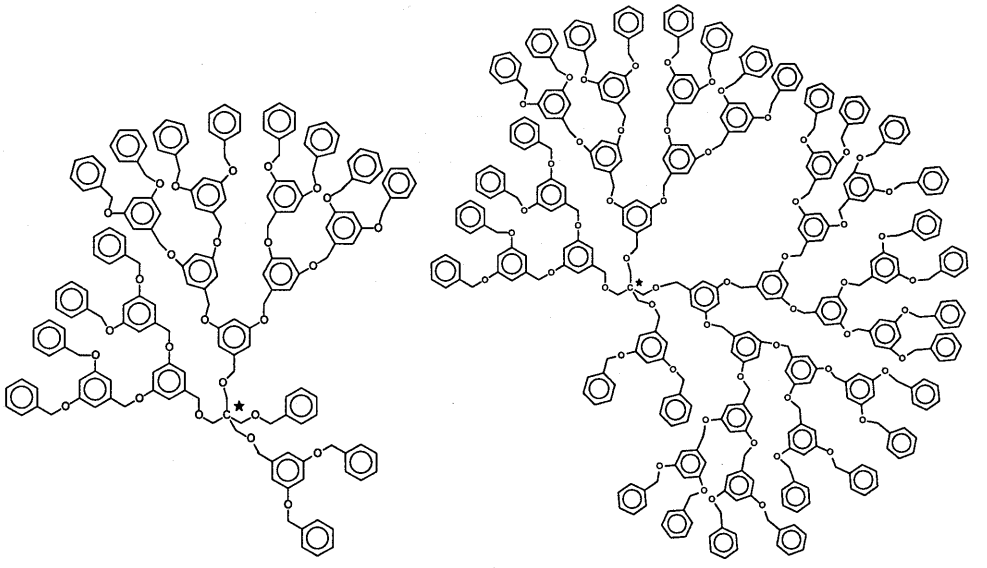


Figure 5. *Kremers' chiral objects.*[26]

A rapidly increasing number of papers addresses the formation of well-defined dendrimers made out of chiral building blocks, and their optical activity is used to study interactions within the dendrimers. Seebach[4] has reported on a number of compounds based on this principle, where chirality stems from the core, or both from the core and the branching units. In a fundamental study to address the contributions of the different chiral units to the overall optical activity, Chow[5] synthesized layered dendrimers incorporating both configurations of tartaric acid derivatives. He indicated that the optical activity was determined by the number of *R*- and *S*-tartaric acid units and that the individual chiral units did not influence each other. McGrath[27] and Sharpless[28] recently reported on several chiral objects. Especially the work of McGrath *et al.* is of great value, because they have addressed in detail the difficult analysis of optical rotation of dendrimers with chirality present in all layers of the dendrimer (Figure 6).[27] Using a series of model compounds, it was shown that the optical activity of a building block is dependent on where the unit is positioned in the dendrimer and that the optical rotation is not just additive, because the chemical identity of a unit in the core changes with increasing generation. Hence, small deviations from additivity are explained by the constitutional differences between the units.[27c,d] Here, high molecular weight dendrimers and linear polymers differ significantly. Within linear polymers the chiral repeating units are similar, whereas the same chiral repeating units within a dendrimer are constitutionally and environmentally different.

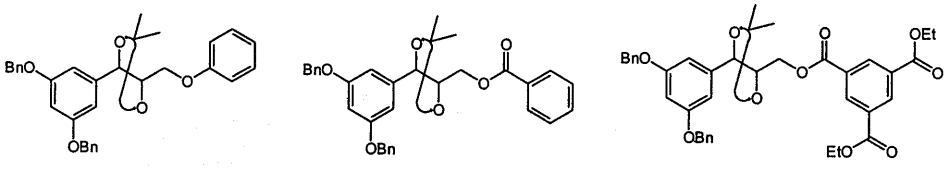


Figure 6. *Model compounds used to determine the optical activity of the McGrath dendrimers.*[27c,d]

1.2.3 Chiral surfaces

Over the last decades much attention has been focused on two-dimensional surface interactions, especially those of Langmuir–Blodgett films. When dendrimers that are approaching their sterically induced stoichiometry are modified on the surface with chiral end groups, we are dealing with a curved surface in which the end groups are positioned with the help of covalent bonds. This can lead to very specific interactions between the various end groups, since on a curved surface it is almost impossible to obtain crystalline-like properties. A large number of reports is dealing with the properties of these curved surfaces, but only a few reports make use of chiral units, while deviant behavior in the chiroptical properties of these chiral dendrimers can be expected.

The first example of a chiral dendrimer of class 3 is reported by the group of Newkome,[15] who has modified his arborols with the enantiomerically pure amino acid tryptophane (Figure 7).

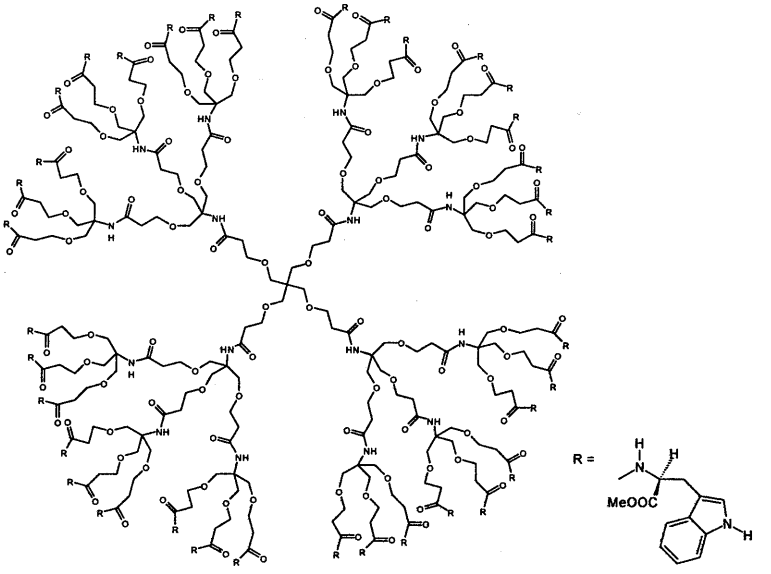


Figure 7. *Newkome's arborols, modified with enantiomerically pure tryptophane.*[15]

The modification was performed for a number of generations, but no peculiarities in the chiroptical behavior were found (the optical activity per end group was roughly constant for all generations). The same constant optical rotation per end group was observed within a series of other dendrimers,[29] including saccharide-modified poly(propylene imine) dendrimers.[17a]

When, however, studying the dendritic boxes,[17b,c] in which the poly(propylene imine) dendrimers were modified with various N-*t*-BOC protected amino acids, it was shown that the optical activity decreased when going to higher generations of dendrimer. This issue will be discussed in chapter 2.

1.2.4 Chiral clathration

Guest–host interactions and clathration in a dendritic architecture are intriguing properties of dendrimers, especially if they can be achieved with chiral recognition. No

experiments using chiral dendrimers and enantioselective clathration have been reported so far, but a small number of related experiments are worth mentioning. An induced circular dichroism (ICD) can be observed when achiral guest molecules are encapsulated into the chiral dendritic box. The ICD-effects found are small and in agreement with the conformationally disordered shell of the dendritic box.[17b,c] However, these ICD spectra could be used to discuss the possible orientational order of the guest encapsulated, and an exciton–coupled ICD spectrum (Figure 8) was recorded in the case of 4 molecules of Rose Bengal in the dendritic box.[30] It is regarded as a real challenge to study the interaction of chiral guest molecules with the many chiral dendritic hosts now available as discussed above in the section of chiral objects.

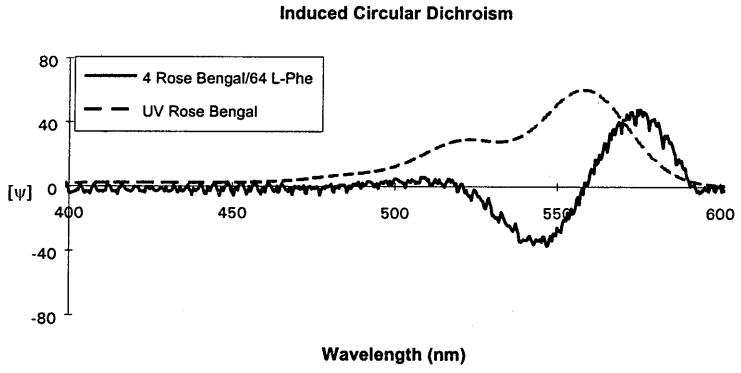


Figure 8. *Induced CD effect for encapsulated Rose Bengal in the dendritic box.*[30]

That the area of stereoselectivity can be extremely fruitful is illustrated with the exciting example from the group of Seebach, in which high diastereoselectivity in the formation of chiral dendrimers is observed.[31] A chiral triol core was brought into reaction with dendritic wedges differing only in chirality in the building blocks (Figure 9). With the combination of the chiral core and one form of the building block, they observed that three wedges were attached to the triol core, whilst in the other combination of the chiral core with the other building block only two wedges were attached. A large number of reference experiments were performed to verify this observation.

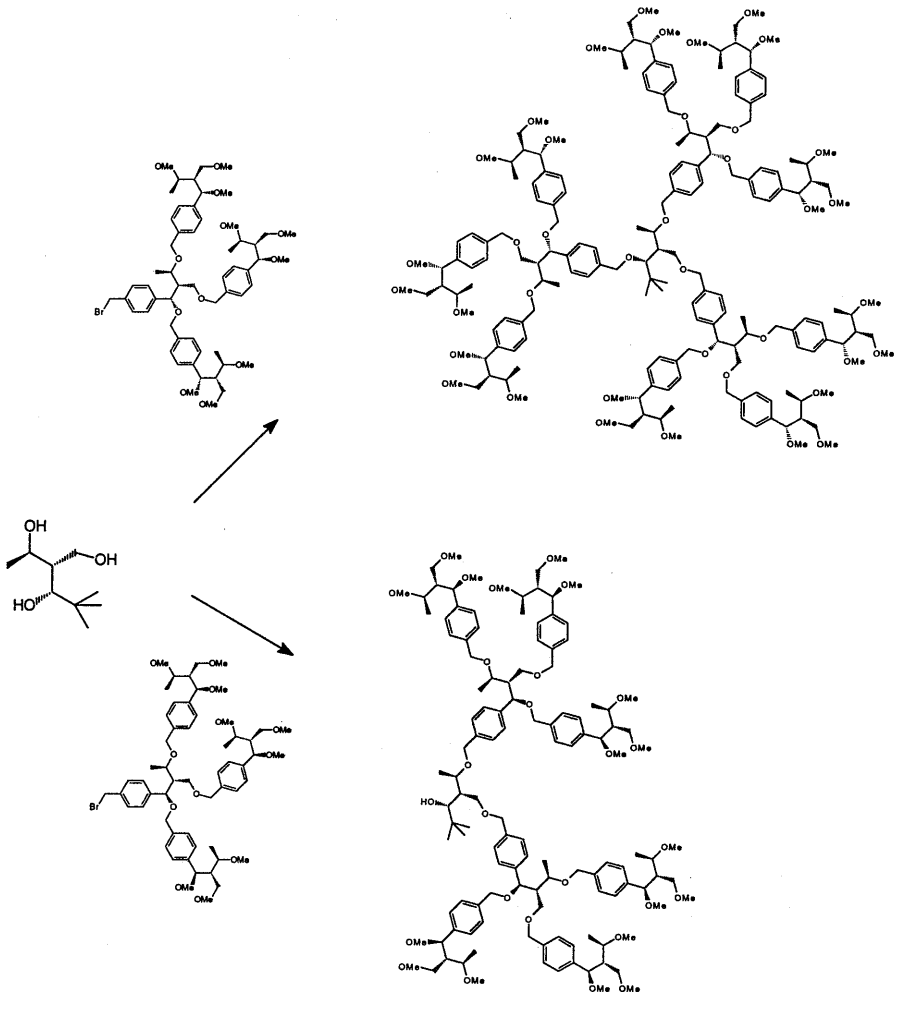


Figure 9. *Seebach's diastereoselectively formed dendrimers.*[31]

The field of enantioselectivity in clathration,[32] encapsulation and dendrimer formation is still in its infancy, but the potentials are very exciting, both scientifically (e.g. modeling enzymatic activity and molecular recognition) and technologically (e.g. separation of enantiomers and sensors).

1.2.5 Catalysis

Dendrimers have been proposed to become important carriers for catalysts due to the homogeneous nature of the systems with most of the catalytic sites exposed to the solvent on the one hand, and the facile isolation of these three-dimensional nanosized systems by (ultra)filtration techniques on the other hand.[33] The first report in this area is described by the group of Van Koten,[33a] using dendritic aryl nickel complexes as catalysts for the Kharash addition of tetrachloromethane to methyl methacrylate. Obviously, asymmetric catalysis will not only be of general interest, but will also show the scope and limitations of this approach in more detail. Initial results with low-generation chiral dendrimers have shown that these multi-substituted molecules act as simple models, but are also far from structures that can be isolated by ultrafiltration.[34–39] The largest structures, however still relatively small, in which asymmetric catalysis is reported are described by Bolm,[35] who uses three generations of Fréchet-type dendritic wedges to which an amino alcohol is attached (Figure 10). This catalytically active core is used in the addition of diethylzinc to benzaldehyde. The enantiomeric excess (e.e.) in these cases proved to be independent of the dendrimer generation used (approx. 85% e.e.). However, so far, filtration techniques have not been reported successful with these structures.

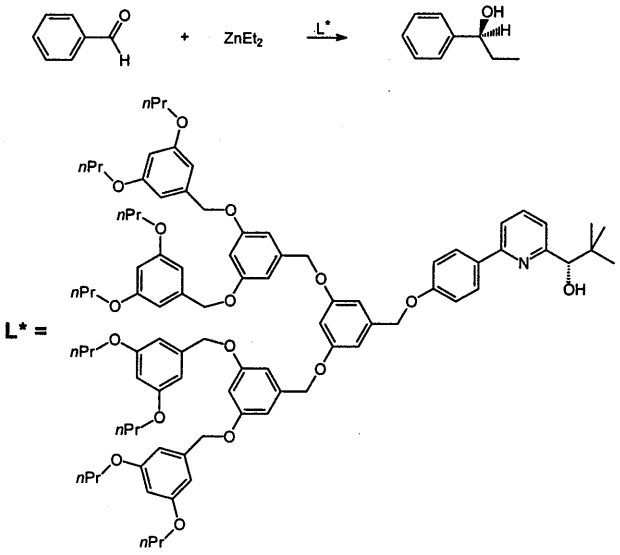


Figure 10. *Bolm's catalyst used in the addition of diethylzinc to benzaldehyde.*[35]

This field of research can be regarded as "polymer supported chemistry revisited", and hence, we have to compare the results found with dendrimers to those found with modified linear macromolecules. However, we expect that by proper design the chiral dendritic

catalysts will have a great future. Unfortunately, a large number of trial and error experiments, of which many will have negative results only, will have to be performed before the scope and limitations are known.

1.3 Aim and scope of the thesis

The aim of the research is to use the contradictory combination of symmetrical dendrimers with chirality to fill the gap between macroscopic and molecular chirality and thereby get a better understanding of the relation of chirality with the conformation of dendritic nanosized structures. The study of chirality in dendritic architectures is only in its infancy, but the initial reports have already shown that many intriguing stereochemical issues are involved.[40] A number of hypotheses is proposed to explain the chiroptical properties (optical rotations, etc.) found for dendrimers with chirality in the core, the branching unit and/or the end groups. It is clear from the chiroptical studies of chiral dendrimers that they differ in many aspects from their linear macromolecular counterparts. Besides the more fundamental approach to chiral objects, these dendrimers can also be very promising in other fields of interest like e.g. catalysis, molecular recognition and biocompatibility.

Modification of poly(propylene imine) dendrimers with N-*t*-BOC protected amino acids has led to the discovery of the dendritic box.[17b,c] These structures were also useful to study end group interactions in the highly curved dendritic surfaces. In *chapter 2* the chiroptical features of these compounds are described, showing a decrease in optical activity on going to the higher generations of dendrimer.[17b,40,41] This observation could be rationalized by the presence of multiple hydrogen-bonding interactions and dense surface packing for chiral end groups that can adopt different conformations in different chemical environments. Therefore, this chiral unit is proposed to be useful as a probe to study interactions.

This chiral probe is used in *chapter 3* in a homologous series of chiral linear N,N'-alkylene diamides.[42] Within this series specific hydrogen-bonding interactions are observed for the 1,5-pentamethylene derivative, as could be deduced from ^{1}H- and ^{13}C-NMR and IR spectroscopy as well as by chiroptical studies.

Synthetic approaches towards possible biological applications of saccharide-coated poly(propylene imine) dendrimers are described in *chapters 4* and *5*. Direct modifications of the peripheral primary amine end groups with galactose, lactose and even clustered trisgalactoside units are described in *chapter 4*.[17a] Biological studies revealed that the best binding properties are observed for less densely packed systems, which prompted us to synthesize spacer-armed glucodendrimers.[43] These systems are also useful for studying amphiphilic behavior and are described in *chapter 5*.

Chiral dendritic objects are the subject of *chapters 6* to *8*. In *chapter 6* an enantiomerically pure dendrimer is described built from Fréchet-type dendritic wedges, attached to a chiral solketal core.[44] No detectable optical activity was found for this compound as could be concluded from optical rotation, ORD and CD measurements. Therefore, this compound can be referred to as being *cryptochiral*. An explanation for this observation can be given in terms of conformational flexibility. Chiral objects built from enantiomerically pure axially chiral bisnaphthol to which Fréchet-type dendritic wedges are attached are described in *chapter 7*.[45] Results from this study revealed a high degree of conformational flexibility in this type of systems. Conformational rigidity has been introduced by the use of backfolding dendritic wedges (*chapter 8*).[46] Modification of enantiomerically pure solketal with these backfolding wedges yielded a compound that, in contrast to the isomer described in chapter 6, showed optical activity. This indicates that these backfolding wedges introduce conformational rigidity. Axially chiral bisnaphthol modified with these wedges showed a larger molar rotation compared to their normal Fréchet-type analogs, also indicative for a higher degree of rigidity.

In *chapter 9* a convenient method for the construction and isolation of isocyanates is described, by a reaction of the corresponding primary amines with di-*t*-butyltricarbonate.[47] It was even possible to convert all generations of poly(propylene imine) dendrimers into isocyanate-functionalized compounds, which were highly reactive towards primary and secondary alcohols and amines. The utility of this method is exemplified in the modification of the peripheric primary amine end groups of the poly(propylene imine) dendrimers with a chiral isocyanate to yield urea-based dendrimers. Finally, new polycarbamate/urea dendrimers are constructed, starting from an asymmetrical diisocyanate building block, in a one-pot procedure to yield advanced structures in a fast and convenient way.[48]

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2 Chiral dendritic surfaces

Summary

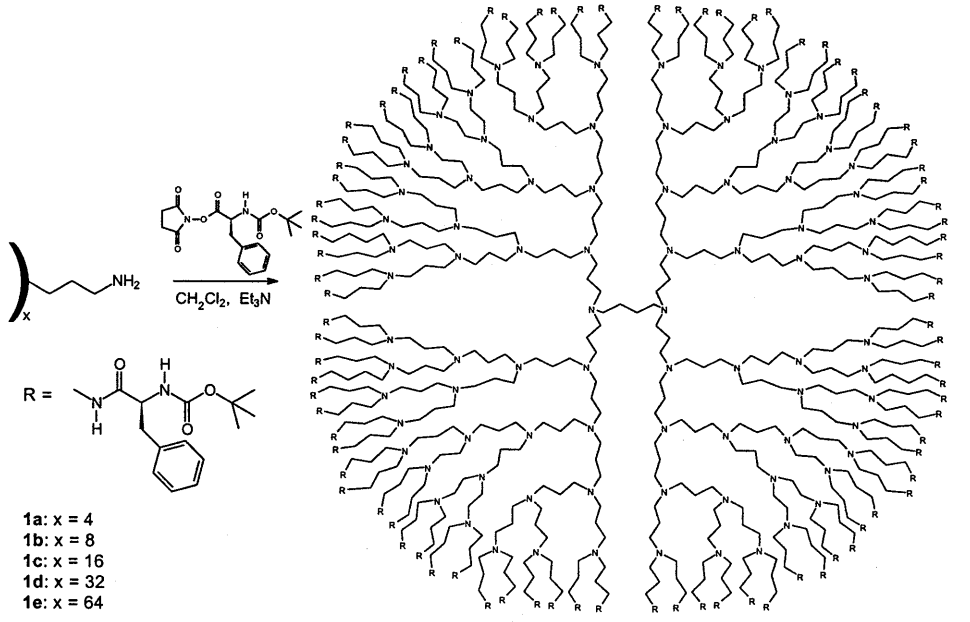
The modification of the peripheral primary amines of poly(propylene imine) dendrimers with enantiomerically pure amino acids is described, leading to the formation of the "dendritic box". The chiroptical properties of these compounds reveal a decrease in optical activity on going to higher generations of modified dendrimers. From chiroptical studies of a model compound, the corresponding N'-propyl-N-t-BOC-L-phenylalaninamide, it is shown that the optical activity strongly depends on the solvent used, which can be ascribed to conformational changes in the molecule. This in turn is probably due to the possibility of hydrogen-bonding interactions. The specific influence of these interactions has been studied by replacing the carbamate functionality by an acetal moiety, in which these multiple hydrogen-bonding interactions are limited. Dendrimers modified with this acetal chiral unit show a constant optical rotation for all generations, and the optical rotation of the corresponding model compound is solvent independent. Finally, the influence of packing density has been determined by the insertion of a long alkyl-chain spacer between the dendrimer surface and the chiral amino acid end group. These compounds show the same optical rotation for the dendrimers of the first and fifth generation, indicating that in this case the chiral end group can adopt its preferred conformation. These findings have been used to explain the results obtained in a first approach to use chiral dendrimers as catalysts for asymmetric synthesis.

2.1 Introduction

As outlined in the first chapter of this thesis, dendrimers decorated at the surface with chiral groups can give structures suitable for fundamental chiroptical studies, as well as for applications in areas like e.g. catalysis or biology.[1] The first example of chiral globular nanosized dendrimer was reported by the group of Newkome,[2] who modified his arborols of various generation with enantiomerically pure tryptophane. No peculiarities were found in the chiroptical properties of these compounds as the optical activity was roughly constant for all

generations. The same constant optical rotation per end group was observed in several other chiral dendrimers.[3]

The divergently synthesized dendrimers are most frequently employed for the construction of chiral dendritic surfaces, due to their availability and their large number of reactive end groups. One of the most employed dendrimers with this respect, that is even commercially available, is the poly(propylene imine) dendrimer,[4] which has been developed at DSM. These dendrimers are built from a 1,4-diaminobutane core, in an iterative procedure consisting of a Michael-addition with acrylonitrile and subsequent hydrogenation to the corresponding amines. The first generation poly(propylene imine) dendrimer contains 4 primary amine end groups. When repeating these step sequences of Michael-addition and hydrogenation, dendrimers of up to the fifth generation with 64 primary amine end groups (DAB-*dendr*-$(NH_2)_{64}$) are obtained. The highly reactive primary amine end groups are ideal for modifications and this has led to a number of appealing structures. When modifying these dendrimers with enantiomerically pure N-*t*-BOC protected amino acids, as was first performed by Johan Jansen in our group, nanosized structures were obtained that proved to be very useful to encapsulate guest molecules: *the dendritic box* (Scheme 1).[5]



Scheme 1. *N-t-BOC-L-Phe modified poly(propylene imine) dendrimers* ***1a–1e.***[5]

It proved to be not only possible to encapsulate a variety of molecules, but it was even possible to perform a selective liberation of encapsulated small molecules, leaving larger dye

molecules encapsulated in a perforated box (when only the BOC protective groups were removed using formic acid).[6] When encapsulating achiral dye molecules (e.g. Rose Bengal) into this dendritic box, an induced CD effect could be measured.[7] Not only the encapsulation was of much interest to us, but also the chiroptical features of the box proved to be very exciting. The investigation presented here was triggered by the observation that the specific optical rotation of DAB-*dendr*-(NH-*t*-BOC-L-Phe)$_x$, **1a–1e**, vanishes to almost zero on going from dendrimers of the first generation ($[\alpha]_D = -11$, c = 1, $CHCl_3$) with four end groups to dendrimers of the fifth generation ($[\alpha]_D = -0.1$, c = 1, $CHCl_3$) with 64 end groups (Figure 1 and Table 1).[8] A more thorough investigation employing a variety of different amino acid derivatives revealed that this decrease was a general phenomenon for all amino acids studied (Table 1).[8] However, this decrease was less pronounced for the smaller amino acids, such as alanine and valine. As the number of chiral end groups per weight unit (measure for the optical rotation) is roughly independent of the generation (in each generation both the number of end groups and the molecular weight double), the decrease in optical rotation is not due to the reduction of the number of chiral chromophores. It has also been established that neither concentration, solvent nor temperature effects are causing this decrease in optical rotation.[8] Finally, the absence of racemization has been demonstrated by HPLC analysis of the amino acids after acid-catalyzed hydrolysis of the modified dendrimers.[8]

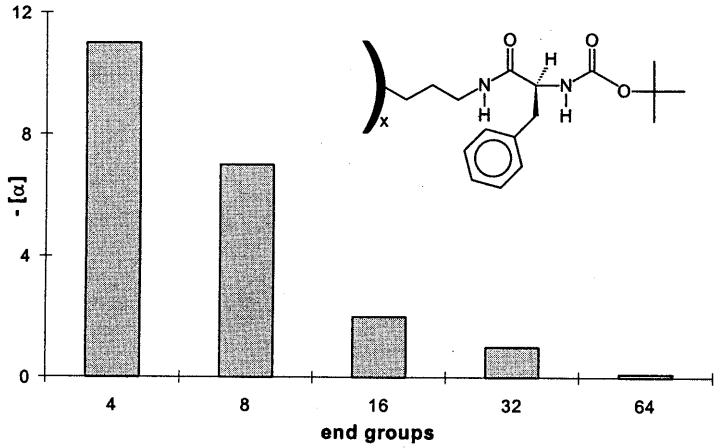


Figure 1. *Optical rotation (error appr. ±0.2) versus number of end groups for dendrimers* ***1a–1e*** *as measured in $CHCl_3$ (c = 1).*

Table 1. *Optical rotations ($[\alpha]_D^{20}$, c = 1) for amino acid modified dendrimers.*[8]

BOC amino acid (solvent)	Number of end groups (generation)				
	4 (1)	8 (2)	16 (3)	32 (4)	64 (5)
L-alanine ($CHCl_3$)	–24	–25	–26	–33	–14
L-valine ($CHCl_3$)	–39	–31	–27	–28	–22
L-leucine ($CHCl_3$)	–28	–23	–21	–13	–10
L-methionine ($CHCl_3$)	–16	–12	–11	–10	–2
L-(*S*)-benzylcysteine ($CHCl_3$)	+56	+42	+26	+13	+5
ε-(*Z*)-L-lysine ($CHCl_3$)	–28	–8	–3	–1	0.0
L-phenylalanine ($CHCl_3$)	–11	–7	–2	–1	–0.1
D-phenylalanine ($CHCl_3$)	+10	+7	+2	+1	+0.1
L-tyrosine (DMSO)	+19	+9	+1	–0.2	–0.1

In this chapter, we report on the details of the peculiar chiroptical properties of these dendritic boxes in order to find an explanation for their anomalous behaviour by means of model studies and investigation of the influence of multiple hydrogen-bonding interactions in combination with dense packing of the surface end groups. These data are also used to explain the results obtained in a first approach to use chiral dendrimers as catalysts in asymmetric synthesis.

2.2 Poly(propylene imine) dendrimers modified with chiral end groups

2.2.1 N-*t*-BOC protected amino acid terminated dendrimers

In order to rationalize the decreasing trend in the chiroptical response of the dendritic box, first circular dichroism (CD) and optical rotary dispersion (ORD) studies in conjunction with absorption spectroscopy have been undertaken (Figure 2).

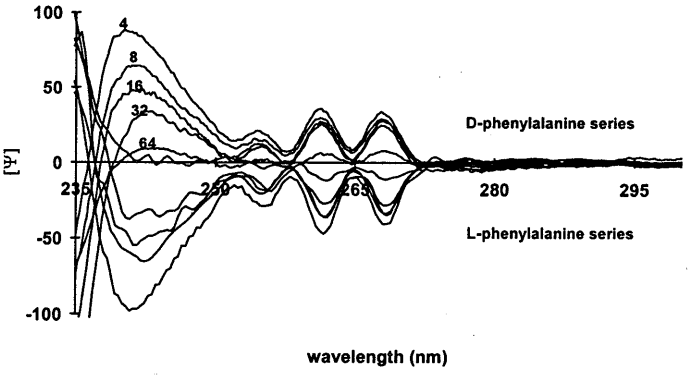


Figure 2. *CD spectra of N-t-BOC-L-phenylalanyl dendrimers* ***1a–1e.***

From these measurements it becomes clear that the Cotton Effects (CEs) in the CD spectra are strongly influenced by the generation. The π–π^* transitions of the phenyl group (at λ = 255, 260 and 270 nm) only decrease dramatically from the fourth to the fifth generation, while the n–π^* transitions of the carbamate functionality (at λ = 240 nm) show a gradual decrease on going from the first to the fifth generation dendrimer. The absorption of the latter also shifts slightly to higher wavelengths going to higher generations of dendrimer. These measurements were performed in $CHCl_3$ as a solvent, which limits the spectral range to a wavelength of 235 nm. Therefore, the n–π^* transition of the newly formed amide bond (at approximately λ = 215 nm) was measured in trifluoroethanol. This also showed a decrease, but, this decrease was less pronounced than for the carbamate absorption.

In order to get a better understanding about the factors governing this anomalous behavior we first performed a model study on a monomeric unit for the dendrimers; N'-propyl-N-*t*-BOC-L-phenylalaninamide, **2**. For this model compound the optical rotation was determined in solvents of different polarity (Figure 3).

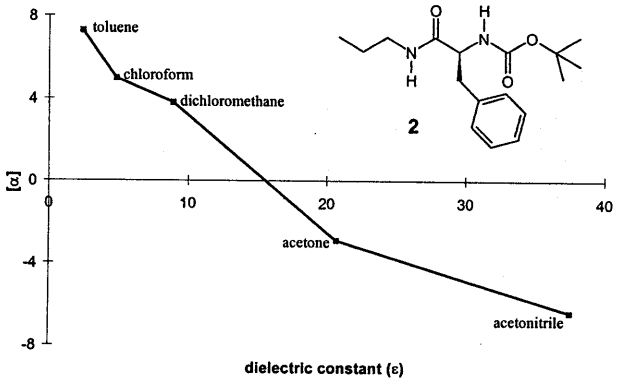


Figure 3. *The optical rotation ($[\alpha]_D$) of model compound 2 in various solvents (c = 1).*

These data show that on going from an apolar solvent like toluene ($[\alpha]_D$ = +7.3) to a polar solvent like acetonitrile ($[\alpha]_D$ = –6.4), the optical rotation changes from a positive to a negative value, indicating that the optical rotation of this compound has a strong dependency on the chemical environment. This type of behavior has been observed before for compounds that can either interact intramolecularly or with the solvent, as was nicely shown for nicotine, which exhibits a strong solvent and concentration dependency on the chiroptical response.[9] Despite the fact that these effects have been known for almost a century, full understanding of the underlying principles is still lacking. This solvent dependency may rely on hydrogen-bonding interactions. Each solvent may cause a different preferred conformation for the solute and each conformation may correspond to its own optical rotation.

2.2.2 Influence of multiple hydrogen-bonding interactions

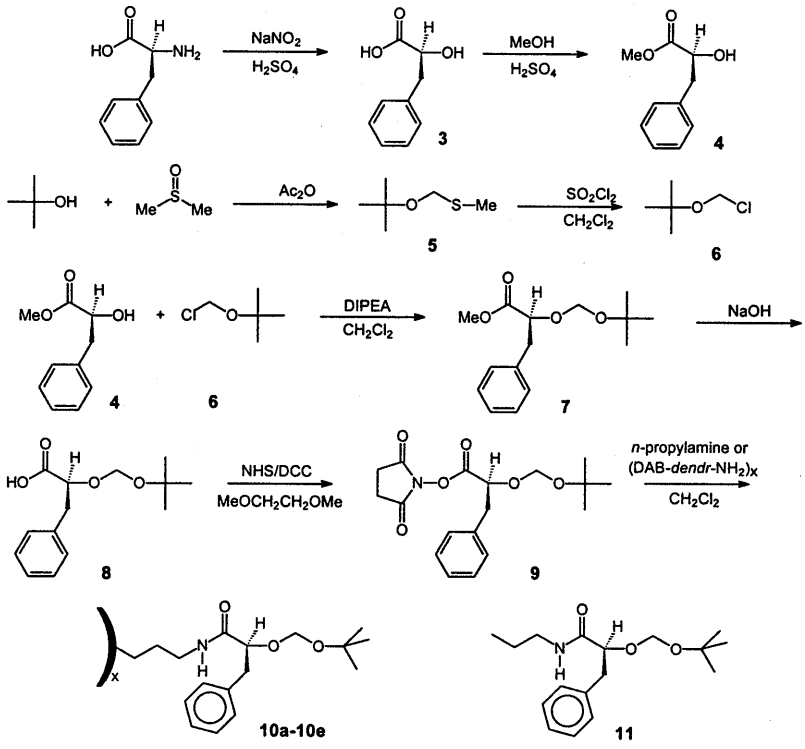
In model compound **2**, two functional groups are capable of undergoing strong hydrogen-bonding interactions: the carbamate and the amide moiety. For a modified dendrimer of the fifth generation with 64 end groups this would imply that 128 hydrogen bonding donor groups and 128 hydrogen bonding acceptor groups are present in one molecule. The influence of multiple hydrogen-bonding interactions was investigated by replacing the carbamate functionality by an acetal moiety to construct dendrimers **10a–10e** (Scheme 2).

For the synthesis of these dendrimers first L-phenylalanine was converted into hydroxy acid **3** by reaction with a diluted solution of sulfuric acid and sodium nitrite. Hydroxy acid **3** could be obtained in a 45% yield.[10] HPLC analysis using a chiral stationary phase proved that the conversion was almost complete (only a very small amount of

remaining L-phenylalanine (approx. 0.6%) was identified) and that the enantiomeric excess (e.e.) of **3** exceeded 99.5%. Methyl ester **4** was obtained in a nearly quantitative yield from **3** by an acid-catalyzed esterification.

The *t*-butyl chloromethyl ether **6**, which was used for the functionalization of the newly formed alcohol functionality of **4**, was synthesized in a two-step procedure following a literature procedure.[11] First, methyl thioether **5** was synthesized by the reaction of *t*-butanol with DMSO in the presence of acetic anhydride. Treatment of **5** with sulfuryl chloride afforded crude chloromethyl ether **6**, which was used as such for the functionalization of **4**.

The protected compound **7** was formed in a 87% yield by the reaction of chloromethyl ether **6** with methyl ester **4**, using CH_2Cl_2 as a solvent and DIPEA as a base. Subsequent saponification of the methyl ester, yielding **8** in a 92% yield, followed by a reaction with N-hydroxysuccinimide (NHS) under the influence of DCC,[12] afforded activated ester **9** in a 97% yield. The activated ester **9** was used for coupling to the poly(propylene imine) dendrimers to yield the acetal functionalized dendrimers **10a–10e**. Model compound **11** was obtained by the reaction of activated ester **9** with *n*-propylamine.



Scheme 2. *Synthesis of acetal functionalized dendrimers **10a–10e** (x = 4, 8, 16, 32, 64) and model compound **11**.*

Characterization of the dendrimers was accomplished by ^{1}H-NMR, ^{13}C-NMR and IR spectroscopy. Signals in ^{1}H-NMR spectra were much less broadened compared to the amino acid dendrimers **1a–1e**. ^{13}C-NMR signals were well-resolved and did not change a lot for the different generations of dendrimers. In IR spectroscopy the newly formed amide bond can be found at a wavenumber of 1660 cm^{-1}. ^{13}C-NMR proved to be a very useful tool for investigating the completeness of the reaction as a signal for unreacted CH_2NH_2 resonates at 40 ppm (whereas reacted ones resonate at 37–38 ppm). For none of the dendrimers **10a–10e** a signal could be detected at 40 ppm in ^{13}C-NMR spectroscopy.

When the optical rotation was measured for model compound **11**, it was found that despite fluctuations in the optical rotation, this compound exhibits a large negative value in all solvents studied (Figure 4). Hence, the amide acetal unit possesses an environmentally independent optical rotation, making this unit attractive for studying its optical properties when attached to a dendritic surface.

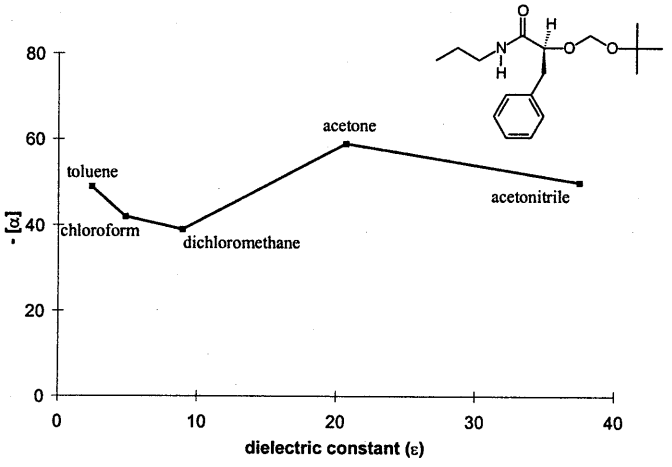


Figure 4. *Optical rotation of model compound 11 in various solvents (c = 1) at room temperature.*

The results of the optical rotation, measured in $CHCl_3$, for all generations of dendrimers are listed in table 2, depicted in figure 5 and, indeed, proved to be constant for all generations of dendrimers ($[\alpha]_D = -42 \pm 2$, $CHCl_3$).

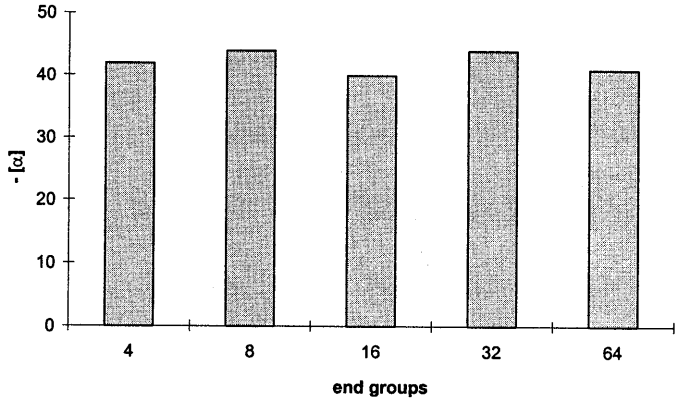


Figure 5. *Optical rotation versus number of end groups for acetal dendrimers **10a–10e**.*

Table 2. *Yields and optical rotations for acetal functionalized dendrimers **10a–10e**.*

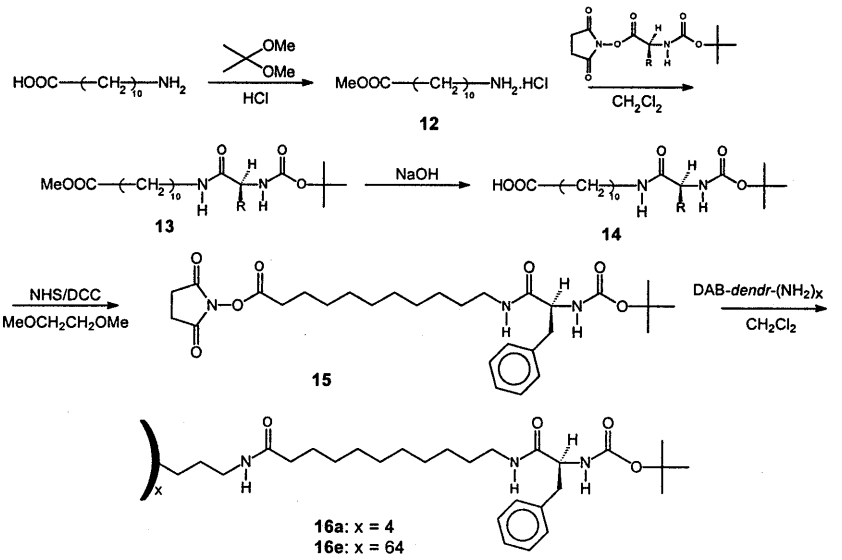
Compound	Yield (%)	$[\alpha]_D^{20}$ (c = 1, $CHCl_3$)
10a	100	–42
10b	78	–44
10c	74	–40
10d	93	–44
10e	70	–41

With this set of experiments we have shown that for the chiral amide-acetal group the optical rotation remains constant for all generations of dendrimers. The steric demands of both substituents are estimated to be similar. Therefore, this is in sharp contrast to the results obtained for the sensitive N-*t*-BOC-L-phenylalanyl group that gives rise to a decrease in optical activity when going to higher generations of dendrimers. This result does not imply that the acetal functionalized end groups are not densely packed, but it is less sensitive for difference in packing, which is in good agreement with the solvent dependence of the model compound. A relatively large shift of both NH (carbamate and amide) resonances of approximately 0.6 ppm was observed for **1a–1e** in ^{1}H-NMR[13], whereas for dendrimers **10a–10e** only a marginal shift in NH (only amide) absorption is observed of 0.1 ppm. NMR-relaxation experiments for compounds **1a–1e** indicated a solid-like behavior for the higher generations.[5] Also, results from IR studies in solution indicated a higher degree of hydrogen-bonding interactions present for higher generations of dendrimers.[13] This indicates that cooperative effects may be influenced by the packing density over the surface of the

dendrimer. Modification of these dendrimers with camphanic chloride and camphorsulfonyl chloride also yielded products with a constant optical rotation for all generations of dendrimers.[8] Especially the conformationally rigid camphorsulfonamides gave exciting results as in this case the NH shift change in ^{1}H-NMR amounted up to 0.6 ppm going from the dendrimer of the first up to the fifth generation, which is comparable to the shifts observed for the densely packed BOC protected amino acid dendrimers.[13] This implies that dense packing for the camphorsulfonamides is also likely, but that this does not give rise to a decrease in optical activity.

2.2.3 Influence of packing density

From the discussion above, we can conclude that N-*t*-BOC protected amino acids in the dendritic box constitute a special case and can be used to probe the local environment of the dendrimer periphery. The issue of dense packing at the dendrimer periphery is further investigated by the introduction of an alkyl-chain spacer between the N-*t*-BOC-L-phenylalanyl unit and the dendrimer surface (Scheme 3).



Scheme 3. *Synthesis of alkyl-chain spacer precursors **12–15** and dendrimers **16a** and **16e**.*

The synthesis of these compounds is rather straightforward and starts with the conversion of 11-aminoundecanoic acid into the methyl ester hydrochloric acid salt **12**, which could be obtained in a 92% yield.[14] The amine functionality was reacted with the N-

succinimidyl activated ester of N-*t*-BOC-L-phenylalanine to yield **13** in a 99% yield. Saponification of the methyl ester, yielding **14**, followed by a reaction with NHS, under the influence of DCC in dimethoxyethane as a solvent[12] afforded the N-succinimidyl activated ester **15**, which could be obtained in 48% yield after crystallization. The alkyl-chain spacer-armed dendrimers **16a** and **16e** could be obtained by the reaction of activated ester **15** with the poly(propylene imine) dendrimers of the first and fifth generation in yields of 71 and 80%, respectively. The completeness of the reaction was monitored by ^{1}H- and ^{13}C-NMR spectroscopy. IR spectroscopy is also indicative for the formation of the products as the newly formed amide bond appears at a wavenumber of 1650–1690 cm^{-1}.

The optical activity remains constant for both spacer-armed dendrimers at $[\alpha]_D^{20} = +4$, approximately, which is in sharp contrast to the normal dendritic box dendrimers in which a decrease from $[\alpha]_D^{20} = -11$ to -0.1 was observed (Figure 6).

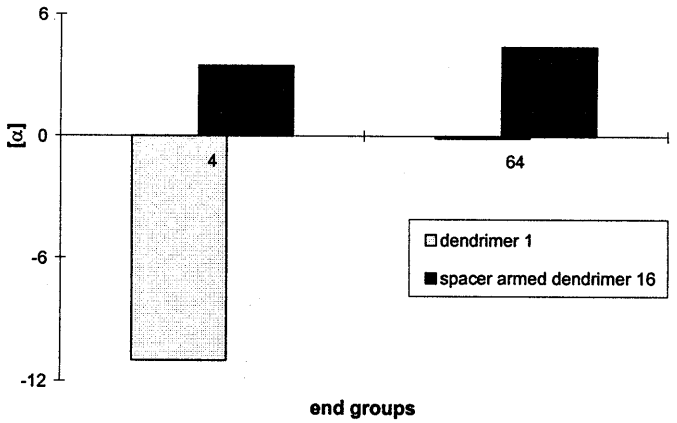


Figure 6. *The influence of packing density: comparison of dendrimers **1a** and **1e** with alkyl-chain spacer-armed dendrimers **16a** and **16e**.*

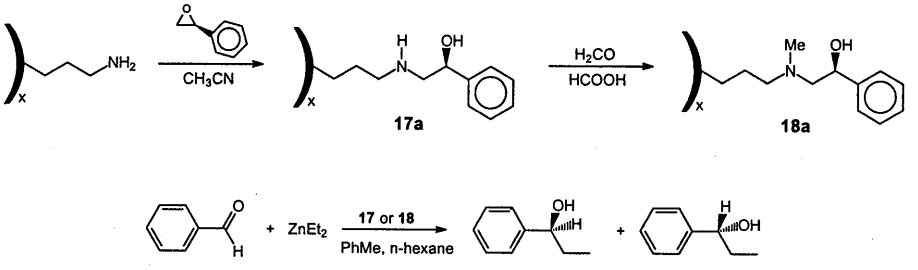
Comparing the optical rotation of dendrimer **16e** in various solvents with different polarity, revealed the same trend as found for model compound **2**, giving rise to positive values for the optical rotation in chloroform and dichloromethane and a negative value for acetone. A quantitative comparison proved to be impossible due to mass effects. However, these results indicate that when introducing an alkyl-chain spacer, the chiral end group is free to adopt its preferred conformation. Calculations of the average area available per end group, when assuming extended chain conformations, were performed. A comparison of the dendritic box, **1e**, with alkyl-chain spacer-armed dendrimer **16e** indicates an increase of the available area per end group by a factor 4 in the case of the spacer-armed dendrimer. Hence,

these results confirm the hypothesis that the N-*t*-BOC-L-phenylalanyl unit is informative to probe the local density of a dendrimer surface.

2.3 Asymmetric catalysis based on poly(propylene imine) dendrimers

The poly(propylene imine) dendrimers were also considered in a first approach as the macromolecular support for catalysts in asymmetric synthesis. We used the diethylzinc addition to benzaldehyde as a model reaction, since many experimental parameters are known for this reaction and it requires an amino alcohol as the chiral ligand, a functionality that can easily be introduced at the dendritic surface. For this purpose we modified the primary amine end groups of the dendrimers into a chiral amino alcohol functionality, based on a ring-opening reaction of enantiomerically pure *R*-phenyloxirane in acetonitrile.[1a,15] This reaction afforded a mixture of functionalized compounds, **17**. The reaction product consists of unsubstituted starting material, α-ring-opened mono- and disubstituted products and a small amount of β-ring-opened products. This mixture was not purified, but was used as such. Also the methylated mixture of compounds, **18**, were synthesized from **17** by a methylation, performed by a reaction with formic acid and formaldehyde (Scheme 4).[1a,15] Despite the presence of different isomers and adducts in the products, no large differences between the various generations have been observed. Hence, for a feasibility study towards the influence of generation on catalytic activity, the ill-defined dendrimers can be used. In scheme 4 the ideal mono α-ring-opened products **17a** and **18a** are depicted.

These dendrimer mixtures **17** and **18** were used as catalysts in the addition of diethylzinc to benzaldehyde (Scheme 4)[16] and the resulting yields and enantiomeric excess (e.e.) values are depicted in Table 3.



Scheme 4. *Preparation of catalysts 17 and 18 and use in the addition of diethylzinc to benzaldehyde.*

Table 3. *Modified poly(propylene imine) dendrimer mixtures **17** and **18** as catalysts in the addition of diethylzinc to benzaldehyde.*

	17		**18**	
end groups	yield (%)	e.e. (%)	yield (%)	e.e. (%)
1	82	36	86	27
2	75	36	77	25
4	54	11	86	25
8	58	9	64	24
16	63	13	57	18
32	49	10	70	18
64	57	7	68	18

In all cases studied, both the chemical yield and the enantiomeric excess decreased with increasing dendrimer generation. Although it proved to be very difficult to obtain catalytically active dendrimers in high purity, it is proposed that the loss of activity is caused by multiple interactions on the dendritic surface, an explanation that seems reasonable based on the results reported in the first part of this chapter. As a result of the more dense packing of the end groups at the periphery of higher generations, a number of different conformations can be envisaged resulting in the presence of different catalytic sites. A possible solution for this problem can be found by introducing an alkyl-chain spacer between the surface of the dendrimer and the chiral group that acts as the catalyst. We already showed that this spacer minimizes the interactions between the chiral end groups and that this type of molecules can easily be isolated by membrane filtration.[5,17]

2.4 Discussion and conclusion

The chiroptical features of modified N-*t*-BOC protected amino acid terminated poly(propylene imine) dendrimers proved to be not trivial, as a decreasing trend could be observed from measurements of the optical rotation, ORD and CD when going to higher generation dendrimers. Studying the optical rotation of a model compound with this respect revealed a high dependency of the optical rotation on the solvent used, indicative for the presence of different conformations in different solvents, possibly governed by hydrogen bonding.

The influence of multiple hydrogen-bonding interactions on the different conformations was investigated by replacing one hydrogen-bonding unit, the carbamate moiety, by an acetal functionality, which is unable to undergo multiple hydrogen-bonding. The chiroptical features of these acetal functionalized dendrimers showed a constant value for all generations of modified dendrimers. When comparing these results with the amino acid terminated dendrimers reported by Newkome,[2] based on amide–ester end groups, we can conclude that the carbamate functionality itself plays a crucial role on the decrease in optical activity. This could also be deduced from the CD data for the N-*t*-BOC protected amino acids that revealed a gradual decrease for the intensity of the n–π* transition of the carbamate functionality and a much less pronounced decrease for the intensity of the π–π* transition of the phenyl group and the n–π* transition of the amide bond (Figure 2). Also, the substantial bond rotational flexibility of the NH–CO in the carbamate group (at room temperature) is supposed to play a crucial role, as for these functionalized dendrimers two partly overlapping NH resonances can be observed in ^{1}H-NMR. Experiments were performed to investigate the effect of the replacement of the carbamate by an amide moiety (acetyl protected), which contains an NH–CO bond of enhanced rotational rigidity. Preliminary chiroptical studies revealed a decrease of approximately 50% on going from the first to the fifth generation dendrimer. However, at this stage a full understanding of the processes involved in these nanosized structures is difficult, and for a better understanding of the processes involved we should limit ourselves to model studies, which are the subject of chapter 3.

The influence of dense packing on the decrease in optical activity was investigated by the introduction of an alkyl-chain spacer between the dendrimer surface and the chiral end group. The local surface concentration of amino acids decreases by a factor 4 for the dendrimer of the fifth generation upon the introduction of this spacer. Chiroptical studies revealed a constant optical rotation for dendrimers of the first and the fifth generation. Comparing these results with model compound **2** (Figure 3) revealed that the chiral end groups in the alkyl-chain spacer-armed dendrimers can adopt their preferred conformation.

In conclusion, evidence is presented for the decrease in optical activity for the amino acid terminated dendrimers, which can be discussed in terms of conformational rigidity of the chiral unit in combination with multiple hydrogen-bonding interactions and dense surface packing of the end groups. Although in great detail these experiments have contributed to a better understanding of the chiroptical properties of these highly curved dendritic surfaces, a satisfying rationalization for this phenomenon is still lacking. One of the possible explanations that can account for this decrease relates to the observations with model compound **2** (Figure 3). It is now proposed that the polarity locally present in the densely packed shell of the dendrimer is intermediate between the polarity of dichloromethane ($[\alpha]_D > 0$) and acetone ($[\alpha]_D < 0$), which leads to an optical rotation between these values and,

therefore, going to zero. This phenomenon has been observed before in literature and is referred to as "accidental cryptochirality".[18] However, the decrease in optical activity can also be explained in terms of conformational order or disorder on the dendrimer surface. Conformational order could be deduced from the fact that it is known from amino acids that the density of racemic crystals is lower than that of their enantiomerically pure counterparts,[19] which would imply a pairwise interlocking of end groups on the dendrimer surface. The supposed conformational changes in the dendritic box has recently been the subject of molecular dynamics studies.[20] Conformational disorder could also explain the decrease in optical activity following Green's insights in the chiroptical features of chiral polymers.[21] No matter what the correct explanation is, this N-*t*-BOC-L-phenylalanyl chiral unit can be very useful as a probe to study interactions in these types of nanosized structures.

2.5 Experimental section

General

All solvents were of c.p. quality, except those used as reaction solvent which were of p.a. quality. Melting points are uncorrected and were determined with a Jeneval microscope equipped with a Linkam hot stage. NMR spectra were run on a Bruker AM-400 spectrometer at frequencies of 400.1 MHz and 100.6 MHz for ^{1}H- and ^{13}C- nuclei, respectively. TMS was used as an internal standard and δ-values are given in ppm. IR-spectra were taken on a Perkin Elmer 1600 series FT-IR and data are given in cm^{-1}. ORD/CD measurements were performed on a Jasco 600 spectropolarimeter and $[\alpha]_D^{20}$ data were measured on a Jasco DIP-370 digital polarimeter. Elemental analyses were run on a Perkin Elmer 2400 series II machine. GC analyses were performed using a Perkin Elmer machine with a chiral stationary phase.

General procedure for the modification of the poly(propylene imine) dendrimers with N-succinimidyl activated esters

The poly(propylene imine) dendrimer (about 80 mg, approximately 1.0 mmol primary amine end groups) was dissolved in CH_2Cl_2 (8 mL) and triethylamine (0.1 mL) was added. To the stirred solution the N-succinimidyl activated ester was added (1.01 eq per amine end group) and stirring was continued overnight at room temperature. The reaction mixture was extracted with a saturated aqueous Na_2CO_3 solution (5 x 50 mL) (typically approximately 3 h were needed for a complete separation of the layers). The organic layer was dried with Na_2SO_4, and the solvent evaporated to yield the functionalized dendrimers.

N-*t*-BOC-L-Phenylalanyl modified poly(propylene imine) dendrimers, 1a–1e

Following the general procedure for the coupling of the poly(propylene imine) dendrimers with activated esters compounds **1a–1e** were obtained as white foams. Optical rotations are listed in Table 1. ^{1}H-NMR spectra showed considerable broadening of the peaks, even at elevated temperatures.

Typical resonances in ^{13}C-NMR are listed below for the first generation dendrimer (**1a**). Absorptions for all other dendrimers are roughly the same. ^{13}C-NMR (**1a**, $CDCl_3$): δ 25.8 ($NCH_2(CH_2)_2CH_2N$), 26.6 (CH_2CH_2NH), 28.1 (CH_3, BOC), 37.4 and 39.3 (CH_2NH and CH_2Ph), 51.1 ($CH_2CH_2CH_2NH$), 53.5 ($NCH_2(CH_2)_2CH_2N$), 55.6 (C*H), 79.2 (C-*ipso*, BOC), 126.2, 128.0, 129.2 (PhCH), 137.1 (PhC-*ipso*), 155.7 ($NHCO_2$), 172.0 (NHCO).

N'-propyl-N-*t*-BOC-L-phenylalaninamide, 2

The title compound was prepared following the general procedure to yield **2** as a white, amorphous solid in a quantitative yield. m.p. 116 °C. ^{1}H-NMR ($CDCl_3$): δ 0.80 (t, J = 7.1 Hz, 3H, CH_3CH_2), 1.38 (m, 11H, CH_3CH_2, $C(CH_3)_3$), 2.99–3.16 (m, 4H, CH_2NH, CH_2Ph), 4.46 (br, 1H, C*H), 5.67 (br d, J = 8.1 Hz, 1H, NHC*H), 6.80 (s, 1H, CH_2NH), 7.19–7.26 (m, 5H, PhH). ^{13}C-NMR ($CDCl_3$): δ 11.1 (CH_3CH_2), 22.3 (CH_3CH_2), 28.0 ($C(CH_3)_3$), 38.8, 40.9 (CH_2NH, CH_2Ph), 55.7 (C*H), 79.4 (C-*ipso*, BOC), 126.4, 128.1, 129.1 (PhCH), 136.9 (PhC-*ipso*), 155.4 ($NHCO_2$), 171.4 (NHCO). IR (KBr): ν 3342 (NH stretch), 3062 (=C–H stretch, phenyl), 2966 (CH_3 stretch), 2932 (CH_2 stretch), 1685 and 1657 (C=O stretch). $[\alpha]_D^{20}$ = +7.3 (c = 1.0, PhMe), +5.0 (c = 1.0, $CHCl_3$), +3.8 (c = 1.0, CH_2Cl_2), –2.9 (c = 1.0, Me_2CO), –6.4 (c = 1.0, MeCN).

***S*-2-Hydroxy-3-phenylpropionic acid, 3**[10]

To a stirred and cooled (0–5 °C) sulfuric acid solution (4 mL H_2SO_4 in 100 mL water) of L-phenylalanine (16.54 g, 100.1 mmol), a solution of $NaNO_2$ (10.3 g, 0.15 mol in 30 mL of water) was added dropwise over a period of 1 h. The reaction mixture was stirred for 2 days at 5 °C. The solvent was evaporated and diethyl ether was added to the white suspension. The solution was filtered and washed with diethyl ether. Evaporation of the solvent yielded pure **3** (7.74, 46.6 mmol, 47%) as a white solid. HPLC analysis using a chiral stationary phase showed an e.e. > 99.5%. m.p. 126 °C. ^{1}H-NMR ($CDCl_3$): δ 3.01 (dd, J = 14.0 and 7.2 Hz, 1H, H_aH_bPh), 3.21 (dd, J = 14.0 and 4.3 Hz, 1H, H_aH_bPh), 4.52 (dd, J = 7.2 and 4.3 Hz, 1H, C*H), 7.22–7.39 (m, 5H, PhH). ^{13}C-NMR ($CDCl_3$): δ 40.1 (CH_2Ph), 71.0 (C*H), 127.2, 128.6, 129.5 (PhCH), 135.8 (PhC-*ipso*), 177.6 (CO_2H). IR (KBr): 3424 (OH stretch), 1740 (C=O stretch), 1308 (OH deformation, sec. alcohol), 1093 (C–O stretch, sec. alcohol). $[\alpha]_D^{20}$ = –30 (c = 1.02, $CHCl_3$). Anal. Calc. for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 64.83; H, 6.33.

Methyl *S*-2-hydroxy-3-phenylpropionate, 4

A mixture of **3** (4.72 g, 28.4 mmol) and a catalytic amount of H_2SO_4 (0.5 mL) in methanol (50 mL) was stirred and heated under reflux overnight. The solvent was evaporated and water (40 mL) and diethyl ether (40 mL) were added. The layers were separated and the water layer was extracted with diethyl ether (2 x 30 mL). The organic layers were combined, dried with Na_2SO_4 and the solvent evaporated to yield pure **4** (5.06 g, 98%) as a white crystalline solid. m.p. 48 °C. ^{1}H-NMR ($CDCl_3$): δ 2.95 (br. s, 1H, OH), 2.95 (dd, J = 13.8 and 6.8 Hz, 1H, H_aH_bPh), 3.11 (dd, J = 14.0 and 4.5 Hz, 1H, H_aH_bPh), 3.76 (s, 3H, OCH_3), 4.44 (dd, J = 6.8 and 4.6 Hz, 1H, C*H), 7.20–7.40 (m, 5H, PhH). ^{13}C-NMR ($CDCl_3$): δ 40.5 (CH_2Ph), 52.4 (OCH_3), 71.2 (C*H), 126.8, 128.4, 129.4 (PhCH), 136.2 (PhC-*ipso*), 174.5 (C=O). IR (KBr): ν 3262 (OH stretch), 3029 (=C–H stretch, phenyl), 2950 (CH_3 stretch), 1748 (C=O stretch), 1604, 1498 (C=C stretch, phenyl), 1109 (C–O stretch, sec. alcohol). $[\alpha]_D^{20}$ = –8 (c = 1.02, $CHCl_3$). Anal. Calc. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.73; H, 6.28.

t-Butoxymethyl methyl thioether, 5[11]

A mixture of *t*-butanol (50 mL), DMSO (300 mL) and acetic anhydride (200 mL) was allowed to stand for 6 days. Then, this reaction mixture was carefully added to aqueous saturated $NaHCO_3$ (300 mL). To this mixture NaOH (40 g, 1.0 mol) and diethyl ether (400 mL) were added and stirred overnight at room temperature. An additional portion of NaOH (40 g, 1.0 mol) was added. The layers were separated and the water layer was extracted with diethyl ether (3 x 150 mL). The organic layers were combined and subjected to a column filtration (250 g SiO_2, hexane/Et_2O = 2:1, R_f = 0.89). Careful evaporation of the solvent furnished crude **5** (31.20 g) as a low boiling liquid, which was used as such in the next reaction step. ^{1}H-NMR ($CDCl_3$): δ 1.26 (s, 9H, $C(CH_3)_3$), 2.18 (s, 3H, SCH_3), 4.51 (s, 2H, CH_2). ^{13}C-NMR ($CDCl_3$): δ 14.0 (SCH_3), 27.4 ($C(CH_3)_3$), 66.6 (CH_2), 74.3 ($C(CH_3)_3$). IR (KBr): ν 2975 (CH_3 stretch), 2920 (CH_2 stretch).

t-Butyl chloromethyl ether, 6[11]

To a stirred solution of **5** (4.69 g, 35 mmol) in freshly distilled CH_2Cl_2 (100 mL), a solution of SO_2Cl_2 (6.5 g, 48 mmol) in CH_2Cl_2 (25 mL) was added dropwise. After stirring overnight at room temperature the solvent was carefully evaporated. This furnished crude **6** (4.29 g) as a low boiling liquid, which was used as such in the next reaction step. ^{1}H-NMR ($CDCl_3$): δ 1.33 (s, 9H, $C(CH_3)_3$), 4.61 (s, 2H, CH_2). ^{13}C-NMR ($CDCl_3$): δ 28.0 ($C(CH_3)_3$), 77.6 (CH_2Cl), 78.3 ($C(CH_3)_3$).

Methyl *S*-2-*t*-butoxy methoxy-3-phenylpropionate, 7

To a stirred mixture of **4** (1.81 g, 10 mmol) and di-isopropylethylamine (DIPEA, 8 mL) in CH_2Cl_2 (8 mL), **6** (4.0 g, 33 mmol) was added and stirring was continued for 7 days. The reaction mixture was poured into water (50 mL) after which CH_2Cl_2 (50 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The organic layers were combined, dried with Na_2SO_4 and the solvent evaporated to give crude **7**, which was subjected to column chromatography (200 g SiO_2, hexane/EtOAc = 5:1, R_f = 0.35) to furnish **7** (2.33 g, 87%) as a slightly yellow oil. ^{1}H-NMR ($CDCl_3$): δ 1.08 (s, 9H, $C(CH_3)_3$), 2.99 (dd, J = 13.8 and 8.1 Hz, 1H, H_aH_bPh), 3.06 (dd, J = 13.8 and 5.1 Hz, 1H, H_aH_bPh), 3.67 (s, 3H, OCH_3), 4.46 (dd, J = 8.1 and 5.1 Hz, 1H, C*H), 4.68 and 4.76 (2 x d, J = 7.9 Hz, 2H, OCH_2O), 7.18–7.33 (m, 5H, PhH). ^{13}C-NMR ($CDCl_3$): δ 28.1 ($C(CH_3)_3$), 39.1 (CH_2Ph), 51.6 (OCH_3), 74.6 ($C(CH_3)_3$), 76.0 (C*H), 88.0 (OCH_2O), 126.2, 128.2, 129.4 (PhCH), 136.8 (PhC-*ipso*), 172.6 (C=O). IR (KBr): ν 2974 (CH_3 stretch), 1752 (C=O stretch), 1194 (C–O stretch, ester), 850 ((CH_3)$_3$CO stretch). $[\alpha]_D^{20}$ = –63 (c = 1.03, $CHCl_3$).

***S*-2-*t*-Butoxy methoxy-3-propionic acid, 8**

To a stirred NaOH solution (1 M, 50 mL), **7** (0.60 g, 2.24 mmol) was added and stirring was continued for 4 h. The reaction mixture was washed with diethyl ether (2 x 25 mL) and the aqueous phase was subsequently acidified with HCl to a pH of about 2. Extraction of the acidified mixture with diethyl ether (2 x 25 mL), drying of the combined organic layers with Na_2SO_4 and evaporation of the solvent furnished pure **8** (0.52 g, 92%) as a white solid. m.p. 61 °C. ^{1}H-NMR ($CDCl_3$): δ 1.11 (s, 9H, $C(CH_3)_3$), 3.00 (dd, J = 14.1 and 8.5 Hz, 1H, H_aH_bPh), 3.17 (dd, J = 14.1 and 4.2 Hz, 1H, H_aH_bPh), 4.45 (dd, J = 8.5 and 4.2 Hz, 1H, C*H), 4.69 and 4.77 (2 x d, J = 7.7 Hz, 2H, OCH_2O), 7.20–7.34 (m, 5H, PhH), 9.30 (s, 1H, CO_2H). ^{13}C-NMR ($CDCl_3$): δ 28.0 ($C(CH_3)_3$), 38.7 (CH_2Ph), 75.3 ($C(CH_3)_3$), 76.8 (C*H), 89.4 (OCH_2O), 126.6, 128.2, 129.4 (PhCH), 136.7 (PhC-*ipso*), 176.3 (C=O). IR (KBr): ν 3446 (OH stretch), 2980 (CH_3 stretch), 1741 (C=O stretch), 1601, 1504 (C=C stretch, phenyl). $[\alpha]_D^{20}$ = –49 (c = 0.99, $CHCl_3$).

N-Succinimidyl *S*-2-*t*-butoxy methoxy-3-phenylpropionate, 9[12]

To a stirred and cooled (0–5 °C) solution of **8** (2.58 g, 10.2 mmol) and N-hydroxysuccinimide (1.23 g, 10.3 mmol) in dimethoxyethane (13 mL), DCC (2.32 g, 11.2 mmol) was added. The reaction mixture was stirred overnight at 4 °C. The white precipitate was filtered off, the filtrate was evaporated to dryness and subsequently crystallized from 2-propanol, which furnished pure **9** (3.50 g, 97%) as a white solid. m.p. 78 °C. ^{1}H-NMR ($CDCl_3$): δ 1.08 (s, 9H, $C(CH_3)_3$), 2.82 (s, 4H, CH_2 Suc), 3.13 (dd, J = 14.2 and 8.4 Hz, 1H, H_aH_bPh), 3.27 (dd, J = 14.1 and 4.6 Hz, 1H, H_aH_bPh), 4.47-4.82 (m, 3H, C*H and OCH_2O), 7.22–7.38 (m, 5H, PhH). ^{13}C-NMR ($CDCl_3$): δ 25.5 (CH_2 Suc), 28.1 ($C(CH_3)_3$), 39.2 (CH_2Ph), 74.1 (C*H), 75.1 ($C(CH_3)_3$), 89.1 (OCH_2O), 126.9, 128.3, 129.6 (PhCH), 135.8 (PhC-*ipso*), 167.7 (*C*OC*H), 168.7 (C=O Suc). IR (KBr): ν 2980 (CH_3 stretch), 1741 (C=O stretch), 1092 (C–O stretch, ether). $[\alpha]_D^{20}$ = –56 (c = 0.96, $CHCl_3$). Anal. Calc. for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.64, N, 4.01. Found: C, 62.28; H, 7.07, N, 4.02.

Acetal functionalized poly(propylene imine) dendrimers, 10a–10e

These compounds were obtained following the general procedure by coupling of activated ester **9** with the dendrimers to furnish **10a–10e** as amorphous glass-like compounds. The yields and optical rotations are listed in Table 2. The absorptions in ^{1}H-NMR of these compounds exhibited much less broadening compared to compounds **1a–1e**. To give an indication about absorptions in ^{1}H-NMR and ^{13}C-NMR the data for **10a** are listed below. ^{1}H-NMR (**10a**, $CDCl_3$): δ 1.13 (s, 36H, $C(CH_3)_3$), 1.31 (m, 4H, $NCH_2(CH_2)_2CH_2N$), 1.48 (m, 8H, $NCH_2CH_2CH_2N$), 2.27 (m, 12H, CH_2NCH_2), 2.95 (dd, J = 14.0 and 7.2 Hz, 4H, H_aH_bPh), 3.17 (dd, J = 14.1 and 3.9 Hz, 4H, H_aH_bPh), 3.25 (m, 8H, CH_2NH), 4.34 (dd, J = 7.1 and 3.9 Hz, 4H, C*H), 4.62 and 4.68 (2 x d, J = 7.1 Hz, 8H, OCH_2O), 6.90 (t, J = 5.8 Hz, 4H, NH), 7.17–7.27 (m, 20H, PhH). ^{13}C-NMR (**10a**, $CDCl_3$): δ 24.4 ($NCH_2(CH_2)_2CH_2N$), 26.5 (CH_2CH_2NH), 28.0 (CH_3), 37.2 and 38.4 (CH_2NH and CH_2Ph), 51.2 ($CH_2CH_2CH_2NH$), 53.5 ($NCH_2(CH_2)_2CH_2N$), 74.2 ($C(CH_3)_3$), 77.8 (C*H), 88.8 (OCH_2O), 126.1, 127.7, 129.4 (PhCH), 137.0 (PhC-*ipso*), 171.3 (NHCO).

N-Propyl *S*-2-*t*-butoxy methoxy-3-phenylpropionanamide, 11

The title compound was prepared following the general procedure for the coupling of amines to activated esters to furnish **11** as a white solid in a quantitative yield. m.p. 70 °C. ^{1}H-NMR ($CDCl_3$): δ 0.73 (t, J = 7.4 Hz, 3H, CH_3CH_2), 1.04 (s, 9H, $C(CH_3)_3$), 1.32 (m, 2H, CH_3CH_2), 2.85 (dd, J = 14.0 and 7.1 Hz, 1H, H_aH_bPh), 3.06 (m, 3H, H_aH_bPh, CH_2NH), 4.24 (dd, J = 7.1 and 3.9 Hz, 1H, C*H), 4.50 and 4.61 (2 x d, J = 7.1 Hz, 2H, OCH_2O), 6.56 (t, J = 5.2 Hz, 1H, NH), 7.04–7.18 (m, 5H, PhH). ^{13}C-NMR ($CDCl_3$): δ 10.9 (CH_3CH_2), 22.3 (CH_3CH_2), 27.9 ($C(CH_3)_3$), 38.2, 40.2 (CH_2NH, CH_2Ph), 74.0 ($C(CH_3)_3$), 77.9 (C*H), 88.8 (OCH_2O), 126.0, 127.6, 129.3 (PhCH), 136.9 (PhC-*ipso*), 171.2 (C=O). IR (KBr): ν 2971 (CH_3 stretch), 1658 (C=O stretch). $[\alpha]_D^{20}$ = –49 (c = 1.0, PhMe), –42 (c = 0.93, $CHCl_3$), –39 (c = 0.93, CH_2Cl_2), –59 (c = 0.90, Me_2CO), –50 (c = 0.86, MeCN).

Methyl 11-aminoundecanoate.HCl salt, 12[14]

To a stirred suspension of 11-aminoundecanoic acid (5.03 g, 25.0 mmol) in 2,2-dimethoxypropane (250 mL) concentrated hydrochloric acid (25 mL) was added. The mixture was allowed to stand overnight at room temperature, during which considerable darkening occurred. The solvent was evaporated, the residue taken up in a minimal amount of methanol and subsequently precipitated with

diethyl ether. The white precipitate was filtered off and dried to yield pure **12** (5.76 g, 92%). m.p. 159–161 °C. ^{1}H-NMR ($CDCl_3$): δ 1.28–1.39 (m, 12H, CH_2 spacer), 1.60 (quintet, J = 7.2 Hz, 2H, CH_2), 1.78 (quintet, J = 7.4 Hz, 2H, CH_2), 2.30 (t, J = 7.5 Hz, 2H, CH_2CO_2Me), 2.99 (sextet, J = 7.2 Hz, 2H, $CH_2NH_2.HCl$), 3.67 (s, 3H, CH_3), 8.25 (s, 3H, $NH_2.HCl$). ^{13}C-NMR ($CDCl_3$): δ 24.9, 26.4, 27.6, 28.9, 29.0, 29.1, 29.2, 34.0 (CH_2 spacer), 39.9 ($CH_2NH_2.HCl$), 51.4 (CH_3), 174.2 (C=O). IR (KBr): ν 2920, 2850 (CH_2 stretch), 1725 (C=O stretch), 1178 (C–O stretch, ester). Anal. Calc. for $C_{11}H_{26}ClNO_2$: C, 57.24; H, 10.41; N, 5.56. Found: C, 57.23; H, 10.22; N, 5.54.

Methyl 11-(N-*t*-BOC-L-phenylalanyl)aminoundecanoate, 13

To a stirred solution of **12** (1.2612 g, 5.009 mmol) and Et_3N (2 mL) in CH_2Cl_2 (50 mL) N'-succinimidyl N-*t*-BOC-L-phenylalaninate (1.8345 g, 5.06 mmol) was added. Stirring was continued overnight at room temperature and the reaction mixture was subsequently extracted with aqueous saturated Na_2CO_3 (5 x 40 mL), dried with Na_2SO_4 and evaporated to dryness to yield **13** (2.30 g, 99%) as a white amorphous solid. m.p. 106 °C. ^{1}H-NMR ($CDCl_3$): δ 1.18–1.37 (m, 14H, CH_2 spacer), 1.41 (s, 9H, $C(CH_3)_3$), 1.62 (quintet, J = 7.1 Hz, 2H, CH_2 spacer), 2.30 (t, J = 7.5 Hz, CH_2CO_2Me), 2.98–3.17 (m, 4H, CH_2Ph, CH_2NH), 3.67 (s, 3H, CO_2CH_3), 4.28 (br, 1H, C*H), 5.16 (s, 1H, NH), 5.78 (s, 1H, NH), 7.20–7.31 (m, 5H, PhH). ^{13}C-NMR ($CDCl_3$): δ 24.9, 26.7, 29.0, 29.1, 29.2, 29.3, 34.0 (CH_2 spacer), 28.2 ($C(CH_3)_3$) 38.8, 39.4 (CH_2NH, CH_2Ph), 51.4 (CO_2CH_3), 56.0 (C*H), 79.9 ($C(CH_3)_3$), 126.8, 128.5, 129.2 (PhCH), 136.9 (PhC-*ipso*), 155.3 ($NHCO_2$), 170.9, 174.2 (CONH, CO_2Me). IR (KBr): ν 3341, 3311 (NH stretch), 2918, 2850 (CH_2 stretch), 1731 (C=O stretch, ester). 1684, 1655 (C=O stretch, amide). $[\alpha]_D^{20}$ = +3.0 (c = 0.60, $CHCl_3$).

11-(N-*t*-BOC-L-phenylalanyl)amidoundecanoic acid, 14

A stirred solution of **13** (2.0 g, 4.3 mmol) in THF (10 mL) was treated with aqueous NaOH (2.0 g, 50 mmol, in 25 mL of water). The reaction mixture was stirred overnight at room temperature and subsequently acidified with hydrochloric acid to pH 3. The acidified reaction mixture was extracted with Et_2O (3 x 25 mL). The organic layers were combined, dried with Na_2SO_4 and evaporated to dryness to yield **14** (2.0 g, quant) as a white solid. (Traces of solvents were still present, that proved to be very hard to remove.) ^{1}H-NMR ($CDCl_3$): δ 1.07–1.27 (m, 14H, CH_2 spacer), 1.30 (s, 9H, $C(CH_3)_3$), 1.56 (quintet, J = 7.4 Hz, 2H, CH_2 spacer), 2.26 (t, J = 7.4 Hz, 2H, CH_2CO_2H), 2.91–3.11 (m, 4H, CH_2NH, CH_2Ph), 4.35 (br, 1H, C*H), 5.83 (d, J = 7.6 Hz, 1H, $NHCO_2$), 6.64 (s, 1H, CONH), 7.10–7.19 (m, 5H, PhH), 9.80 (br s, 1H, CO_2H). ^{13}C-NMR ($CDCl_3$): δ 24.6, 26.5, 28.9, 29.0 (2 x), 29.1, 29.2, 33.9 (CH_2 spacer), 28.1 ($C(CH_3)_3$), 38.7, 39.3 (CH_2NH, CH_2Ph), 55.8 (C*H), 79.8 ($C(CH_3)_3$), 126.5, 128.2, 129.1 (PhCH), 136.7 (PhC-*ipso*), 155.7 ($NHCO_2$), 171.7, 177.7 (NHCO, CO_2H). IR (KBr): ν 3341 (NH stretch), 2923, 2852 (CH_2 stretch), 1685, 1657 (C=O stretch, amide). $[\alpha]_D^{20}$ = –0.3 (c = 1.8, $CHCl_3$).

N'-Succinimidyl 11-(N-*t*-BOC-L-phenylalanyl)amidoundecanoate, 15[12]

To a stirred and cooled (0–5 °C) solution of **14** (1.79 g, 3.99 mmol) and N-hydroxysuccinimide (0.475 g, 4.13 mmol) in dimethoxyethane (5 mL) DCC (0.83 g, 4.02 mmol) was added. The reaction mixture was stirred overnight at 4 °C, after which the white precipitate was removed by filtration. The residue was concentrated *in vacuo* and crystallized from 2-propanol to yield **15** (1.05 g, 48%) as a white solid. (Traces of solvents were still present, that proved to be very hard to remove.) ^{1}H-NMR ($CDCl_3$): δ 1.14–1.40 (m, 14H, CH_2 spacer), 1.40 (s, 9H, $C(CH_3)_3$), 1.74 (quintet, J = 7.3 Hz, 2H, CH_2 spacer), 2.60 (t, J = 7.4 Hz, 2H, CH_2CO_2 Suc), 2.83 (s, 4H, CH_2 Suc), 3.00–3.17 (m, 4H, CH_2NH,

CH_2Ph), 4.28 (br, 1H, C*H), 5.46 (d, J = 8.3 Hz, 1H, $NHCO_2$), 6.35 (s, 1H, CONH), 7.20–7.33 (m, 5H, PhH). ^{13}C-NMR ($CDCl_3$): δ 24.3, 26.6, 28.5, 28.8, 29.0 (2 x), 29.1, 30.7 (CH_2 spacer), 25.4 (CH_2 Suc), 28.1 ($C(CH_3)_3$), 38.7, 39.3 (CH_2NH, CH_2Ph), 55.7 (C*H), 79.8 ($C(CH_3)_3$), 126.6, 128.3, 129.2 (PhCH), 136.8 (PhC-*ipso*), 155.3 ($NHCO_2$), 168.6, 171.1 (NHCO, CO_2 Suc), 169.3 (CO Suc). IR (KBr): ν 3369 (NH stretch), 2919, 2852 (CH_2 stretch), 1794 (C=O stretch), 1687 (C=O stretch, amide). $[\alpha]_D^{20} = -0.5$ (c = 2.3, $CHCl_3$).

Spacer-armed poly(propylene imine) dendrimers, 16a and 16e

These compounds were synthesized using activated ester **15** in the standard coupling procedure with the poly(propylene imine) dendrimers of the first and fifth generation to yield **16a** and **16e**, respectively. In ^{1}H-NMR the signals considerably broadened. Typical resonances in ^{13}C-NMR are listed for **16a**, while the absorptions for **16e** were also at approximately the same δ-values. ^{13}C-NMR (**16a**, $CDCl_3$): δ 24.7 ($NCH_2(CH_2)_2CH_2N$), 26.7 (CH_2CH_2NH), 25.7, 26.6, 29.0, 29.2 (2x), 36.4, 37.8, 38.8, 39.2 (CH_2 spacer, CH_2Ph, CH_2NH) 28.0 (CH_3, BOC), 51.6 ($CH_2CH_2CH_2NH$), 53.5 ($NCH_2(CH_2)_2CH_2N$), 55.7 (C*H), 79.4 (C-*ipso*, BOC), 126.4, 128.1, 129.1 (PhCH), 136.8 (PhC-*ipso*), 155.3 ($NHCO_2$), 171.2 and 173.3 (NHCO). IR (KBr): ν 3328 (NH stretch), 2927, 2852 (CH_2 stretch), 1687, 1654 (C=O stretch, amide).

General procedure for the phenyloxirane modified poly(propylene imine) dendrimers, 17[15]

To a solution of the poly(propylene imine) dendrimers (approximately 0.25 g) in acetonitrile (5 mL) was added *R*-phenyloxirane (1.0 eq per primary amine end group). The mixture was allowed to stand for 6 months at room temperature, during which time a viscous oil precipitated from the solution. The solvent was evaporated to yield **17** as a highly viscous syrup. The composition of the products was partly unsubstituted, α-ring-opened mono- and disubstituted and in addition also a small amount of β-ring-opening was observed.

General procedure to methylated phenyloxirane modified dendrimers, 18[15]

A solution of dendrimer **17** (approximately 0.3 g) in formic acid (5 mL) and formaldehyde (37% solution, 3.5 mL) was stirred at 100 °C for 2 days after which the mixture was concentrated *in vacuo*. Then another portion of formic acid (5 mL) and formaldehyde solution (3.5 mL) was added and again heated to 100 °C for 1 day, after which the mixture was again concentrated. This latter procedure was repeated once more after which a NaOH solution (1 M, 25 mL) was added. Solid NaOH (2.0 g, 50 mmol) was added and the solution extracted with CH_2Cl_2 (3 x 25 mL). The organic layers were combined, dried with Na_2SO_4 and concentrated *in vacuo* to yield the methylated dendrimers **18**.

General procedure for the catalyzed addition of diethylzinc to benzaldehyde

To a stirred solution of catalyst **17** or **18** (2 mol%) in toluene (1.1 mL) was added diethylzinc (1 M solution in *n*-hexane, 5 mL). Stirring was continued for 2 h, after which the mixture was cooled to –10 °C. Then benzaldehyde was added (0.10 mL) and stirring was continued for 2 days at room temperature, after which the reaction mixture was poured in a hydrochloric acid solution (1 M, 25 mL), followed by extraction with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried with Na_2SO_4 and evaporated to dryness. Analysis of the products was performed by GC, using a chiral stationary phase. Yields and e.e. values are listed in Table 3.

2.6 References

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3 Hydrogen-bonding interactions in chiral N,N'-alkylene diamides

Summary

*A homologous series of chiral N,N'-alkylene diamides **10–17** is described, made from linear alkylene diamines (1,2-diaminoethane up to 1,9-diaminononane), and enantiomerically pure N-t-BOC-L-phenylalanine. IR spectroscopy in solution, ^{1}H-, and ^{13}C-NMR spectroscopy, as well as chiroptical studies revealed that within this series of compounds, bearing two amide and two carbamate functionalities per molecule, large differences in hydrogen-bonding interactions are present in solution. In a hydrogen-bond breaking solvent, like DMSO, no anomalies were observed within the series, as was proven by ^{1}H- and ^{13}C-NMR spectroscopy and chiroptical studies. However, when measuring in a CH_2Cl_2 or a $CHCl_3$ solution, in the specific case of 1,5-pentamethylene derivative **13**, deviant behavior with respect to hydrogen-bonding interactions is observed. The experimental results clearly indicate conformational differences between **13** and all other compounds. The introduction of chirality enables us to study interactions with chiroptical techniques confirming the IR and NMR data as well as the solubility.*

3.1 Introduction

Protein folding as well as the molecular scaffolding of oligo- and polyamides has inspired many groups to study the role of hydrogen-bonding interactions in these processes. Model compounds are often studied in order to gain detailed insight into the conformation of these nanoscopic structures.[1–2] Much attention has been focused on understanding the formation of α-helices and β-hairpins.[3–7] The formation of a β-turn in proteins is caused by hydrogen-bonding interactions between the NH and CO groups of the first and fourth amino acid, leading to the formation of two 10-membered rings in an intramolecular fashion (Figure 1).[7]

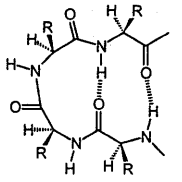


Figure 1. *Formation of a β-turn in a tetrapeptide.*[7]

Besides the amide bond, commonly known from protein chemistry, conformational effects of other hydrogen-bonding species have also been reported, including e.g. ureas[8] and oxalamides.[9] With respect to the aforementioned diamides and diureas, applications are reported in organic gels,[10–12] which are formed as a consequence of formation of intermolecular hydrogen-bonded three-dimensional networks. A report by Feringa *et al.*[11] deals with linear alkyl diureas that are capable of gelating various apolar solvents. Recently, Hanabusa[12] reported on structures consisting of linear alkyl diamides bearing protected amino acids, which proved to be very useful for the gelation of both polar and apolar solvents.

A large number of oligoamide- and oligourea-based structures have been reported incorporating hydrogen-bonding interactions,[3–6,13] but, for a better understanding of the hydrogen-bonding processes involved, we limit ourselves here to a number of examples dealing with di- and triamido and di- and triurea-based structures. Fundamental in this respect are the studies performed by Still[14] and Gellman,[15] who reported large differences in hydrogen-bonding capacity in a homologous series (1 up to 6 carbon atoms) of linear alkyl diamides (**1**, Figure 2). In these structures two carbonyl groups are present besides only one NH group, which enabled them to gain more insight into the hydrogen-bonding properties of these compounds, by studying NMR and IR spectroscopy in solution. IR spectroscopy in a CH_2Cl_2 solution is a nice tool to differentiate between non-hydrogen-bonded species, at a wavenumber of 3450–3460 cm^{-1}, and hydrogen-bonded species, at a wavenumber of 3300–3330 cm^{-1}. Within the series the tetramethylene compound, **2**, showed the strongest hydrogen-bonding interactions, as could be deduced from IR spectroscopy in dilute solution, and leads intramolecularly to the formation of a nine-membered ring.

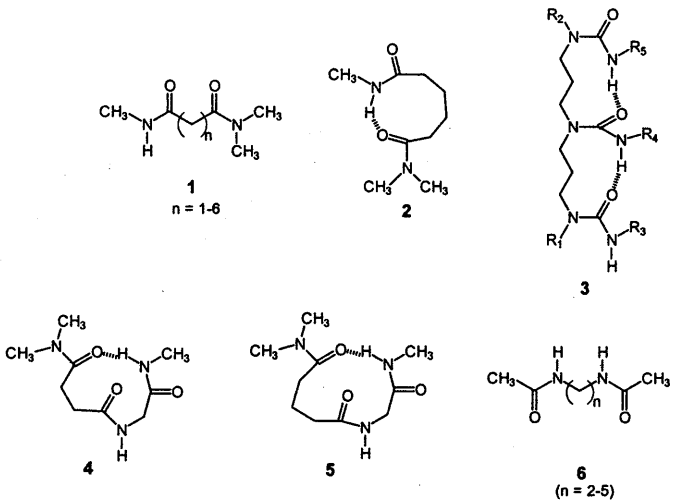


Figure 2. *Hydrogen-bonding studies in model compounds 1–6.*[8,14–17]

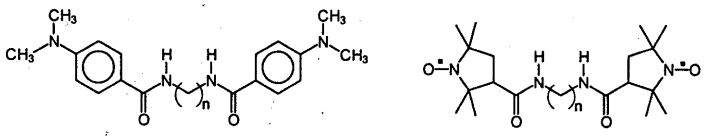
Nowick *et al.*[8] reported on triurea-based structures, constructed from a triamine as the starting material (Figure 2). Strong intramolecular hydrogen-bonding interactions, leading to the formation of two 10-membered rings, were observed for **3**, as was deduced from ^{1}H-NMR and IR spectroscopy in solution.

Gung *et al.*[16] recently reported on the folding pattern of triamides **4** and **5**, bearing three carbonyl and two NH moieties. The interesting feature with respect to these structures is that various ring sizes are theoretically possible. This was investigated in more detail by NMR and IR spectroscopy in solution, and revealed a tendency to form 10- and 11-membered rings for **4** and **5**, respectively.

Solid-state crystallographic and quantum mechanical studies were performed on a homologous series of aliphatic diamides (**6**) by Puigallí *et al.*[17] For an even number of methylene units *all-trans* single direction hydrogen-bonds were formed in the crystals, leading to stretched systems, whereas for an odd number of methylene units folding of the structure was observed.

In relation to these structures, work in our group was performed based on modification of a series of linear alkylene diamines (Figure 3) with N,N-dimethylaminobenzoic acid (**7**)[18] and 3-carboxyproxyl (**8**).[19] The solubility of **7** in DMSO and chloroform showed large differences within the series, whereas the pentamethylene derivative was by far better soluble than the others, presumably due to intramolecular hydrogen bonding, leading to a 10-membered ring. ESR, IR and NMR studies in solution for **8**,

however, revealed a trend in which the tetramethylene diamide derivative showed deviant behavior, leading preferentially to the formation of a nine-membered ring.

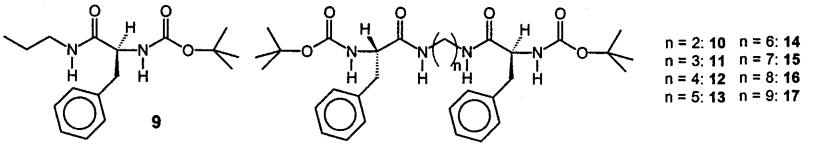


7 (n = 3-5) 8 (n = 2-9)

Figure 3. *Symmetrical alkylene diamides 7 and 8.*[18–19]

All of these studies reveal that for amide- and/or urea-based structures intramolecular hydrogen-bonding occurs in solution, especially when a nine- up to eleven-membered ring is formed. At this stage, however, even for these relatively simple model compounds no clear trend can be found and, therefore, this behavior is proposed to be highly dependent on the substituents present on the amide and urea functionality.

In chapter 2 we reported on the chiroptical features of the N'-propyl-N-*t*-BOC-L-phenylalaninamide, **9** (Figure 4), being a molecule with a strong solvent-dependent optical rotation.[20] This unit is proposed to be useful in probing the conformation of molecules capable of undergoing hydrogen-bonding interactions, as has been illustrated from the modification of the poly(propylene imine) dendrimers with this environmentally sensitive chiral unit.[20,21] All generations of dendrimers followed a trend in which the increased local concentration of N-*t*-BOC-L-phenylalanine groups led to a decrease in the optical activity and, in more detail, in the π–π^* transition of the phenyl group and the n–π^* transition of the carbamate functional group. The 1,4-butylene diamide model possesses deviant chiroptical behavior and is, in contrast to all other molecules, barely soluble in $CHCl_3$.



9

n = 2: **10** n = 6: **14**
n = 3: **11** n = 7: **15**
n = 4: **12** n = 8: **16**
n = 5: **13** n = 9: **17**

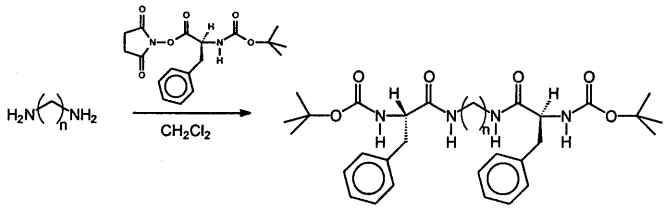
Figure 4. *Model compound* ***9***[20] *and diamides* ***10–17****.*

In this chapter, we describe a homologous series of linear alkylene diamides **10–17** (Figure 4) for which the hydrogen-bonding interactions were studied using ^{1}H- and ^{13}C-NMR spectroscopy, IR spectroscopy in solution as well as optical rotation, optical rotatory dispersion (ORD) and circular dichroism (CD) in dilute solution.

3.2 Results

3.2.1 Synthesis and characterization of diamides 10–17

We have synthesized the homologous series of linear N,N'-alkylene diamides **10–17** by a reaction of linear diamines (from 1,2-diaminoethane up to 1,9-diaminononane) with N'-succinimidyl N-*t*-BOC-L-phenylalaninate (Figure 5).



n=2: **10** n=6: **14**
n=3: **11** n=7: **15**
n=4: **12** n=8: **16**
n=5: **13** n=9: **17**

Figure 5. *Synthesis of linear N,N'-alkylene diamides **10–17**.*

All these derivatives could be obtained as white amorphous solids in excellent yields and were fully characterized by ^{1}H- and ^{13}C-NMR spectroscopy as well as FT-IR spectroscopy and elemental analysis (and in some cases EI-MS). Melting points could not be determined due to the decomposition of the compounds by the thermal elimination of the BOC group at approximately 190 ^{0}C.

The solubility of these compounds proved to be excellent in DMSO. In apolar solvents, like dichloromethane and chloroform, the solubility was markedly lower for all compounds within this series, except for **13**, which was readily soluble in these solvents. Unfortunately, the solubility cannot be expressed in a concentration, because temperature-dependent gelation occurred.[10–12] However, these compounds proved to be no general organic gelators as in many cases the compounds precipitated or crystallized on standing. The deviant solubility behavior of **13** in the series studied was investigated in more detail with other techniques.

^{1}H-NMR spectroscopy, performed in $CDCl_3$ shows two resonances for the N–H protons of all compounds (Table 1). The absorption of the carbamate functionality varies between δ = 5.16 and 5.57 ppm for all compounds, except for **13**, where it is found at δ = 5.97 ppm. The absorption of the amide NH lies in the range δ = 5.91–6.68 ppm, except again for **13**, where it is found at δ = 7.49 ppm. These results indicate that **13** possesses the highest

δ-values for both N–H absorptions present, indicative for the strongest hydrogen-bonding properties in $CDCl_3$. Also, the δ-values for the amide proton of **11**, **14**, **15** and **17** and the δ-values of the carbamate NH-proton of **14**, **15** and **17** are at slightly lower field than the others, but are less significantly different than **13**.

A similar, but, much less pronounced trend is found in ^{13}C-NMR spectroscopy, (Table 1) for the two carbonyl resonances. The carbamate C=O absorption is found at δ = 155.4–155.6 ppm, except for **13** (155.9 ppm). The amide C=O absorption resonates in the range δ = 171.0–171.7 ppm, except for **13** (172.3 ppm).

The concentration dependency of the NH absorptions and the CO absorptions in NMR could not be determined, due to the poor solubility of most compounds in $CDCl_3$.

Table 1. δ-*Values (ppm) for the NH and CO absorptions of diamides **10–17** (in $CDCl_3$).*

Compound	NH resonance in ^{1}H-NMR		CO resonance in ^{13}C-NMR	
	δ (amide)	δ (carbamate)	δ (amide)	δ (carbamate)
10	5.91	5.19	171.7	155.6
11	6.68	5.16	171.7	155.6
12	6.29	5.21	171.5	155.6
13	7.49	5.97	172.3	155.9
14	6.61	5.57	171.6	155.6
15	6.71	5.54	171.5	155.6
16	6.00	5.19	171.1	155.6
17	6.41	5.44	171.2	155.4

IR spectroscopy in solution enables differentiation between hydrogen-bonded and non-hydrogen-bonded species, as the non-hydrogen-bonded amide N–H stretching vibrations are found at wavenumbers of 3420 cm^{-1}, whereas for hydrogen-bonded amides these are found at approximately 3340 cm^{-1}. In order to enable a good comparison, we studied compounds **12**, **13** and **14** in a 5 mM CH_2Cl_2 solution (Figure 6). The most intense absorption attributed to hydrogen-bonded atoms is found for **13**, in which also a shift of the absorption to 3310 cm^{-1} is observed, indicative for stronger hydrogen-bonding interactions.

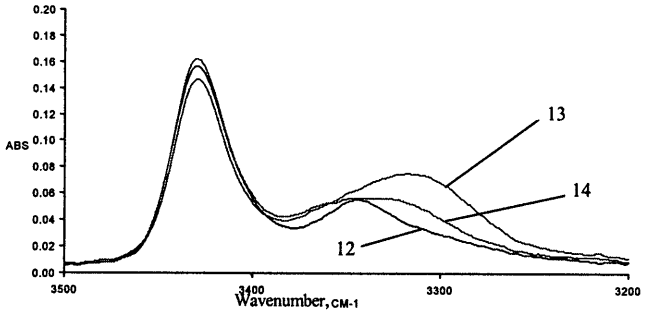


Figure 6. *IR spectra of a 5 mM CH_2Cl_2 solution at room temperature for diamides 12–14.*

The IR data show that also in this case the hexamethylene derivative, **14**, exhibits a significant absorption for the hydrogen-bonded species, which is in good agreement with the findings from the NH shift in ^{1}H-NMR in a $CDCl_3$ solution (Table 1). However, clearly the effect is the strongest in the case of pentamethylene **13**. In IR spectroscopy in the solid state no significant trend can be observed for the amide and carbamate absorptions at wavenumbers of 1655, 1685 and 3340 cm^{-1}. The absorption at 3340 cm^{-1} indicates that in the solid state all compounds are completely hydrogen-bonded. When comparing our results to the literature data of similar compounds,[14–16,18,19] it is proposed that for **13** the intramolecular hydrogen-bonded species is preferably formed, which would imply the formation of a ten-membered ring *via* the amides. Differentiation between intra- and intermolecular hydrogen-bonding interactions require measurements at various concentrations, however, this proved to be impossible on account of the low solubility of these compounds. Less pronounced interactions are also observed for the hexamethylene derivative, which would give rise to an 11-membered ring. However, the carbamate functionalities present in structures **10–17**, allow to achieve cooperativity yielding a large variety of structures.

3.2.2 Chiroptical properties of diamides 10–17

The introduction of chirality might act as an additional tool to study differences in interactions within the series. For this purpose the molar rotation of these compounds was determined in two solvents with different action on hydrogen-bonding interactions: CH_2Cl_2 and DMSO. The results of these studies are shown in Table 2.

Table 2. *Molar rotations in CH_2Cl_2 and DMSO for diamides **10–17**.*

Compound	Molec. Formula	Calc. Molec. Mass	$[\Phi]_D^{20}$ (c = 0.5, CH_2Cl_2)	$[\Phi]_D^{20}$ (c = 0.5, DMSO)
10	$C_{30}H_{42}N_4O_6$	554.69	+72	+122
11	$C_{31}H_{44}N_4O_6$	568.71	+80	+114
12	$C_{32}H_{46}N_4O_6$	582.74	+146	+122
13	$C_{33}H_{48}N_4O_6$	596.77	0	+131
14	$C_{34}H_{50}N_4O_6$	610.79	+37	+122
15	$C_{35}H_{52}N_4O_6$	624.82	+56	+131
16	$C_{36}H_{54}N_4O_6$	638.85	+83	+115
17	$C_{37}H_{56}N_4O_6$	652.88	+46	+118

The molar rotations measured in DMSO show a roughly constant value for all compounds in the range between +114 and +131. This can be explained by taking into account that DMSO is well-known for its hydrogen-bond breaking capability. Hence, no interactions can take place, neither intra- nor intermolecularly, and therefore, no unusual behavior is expected in this series when measuring in this solvent. Optical rotatory dispersion (ORD) measurements in DMSO showed the same trend for all compounds. When measuring the optical rotation in CH_2Cl_2, however, large differences between the various derivatives are observed, as values range from 0 up to +146. Most pronounced in this series is the value of **13** as this compound has no detectable optical activity in this solvent. Also, low values for the molar rotation are observed for **14**, **15** and **17** in this solvent. The same trend, employing CH_2Cl_2 as solvent, could be found in ORD. In the specific case of **13** no optical activity could be detected over the whole range of wavelengths measured. In order to gain detailed insight into the contribution of each chromophore on the overall optical activity, the compounds **12–14** were studied in circular dichroism (CD) in a CH_2Cl_2 solution (Figure 7).

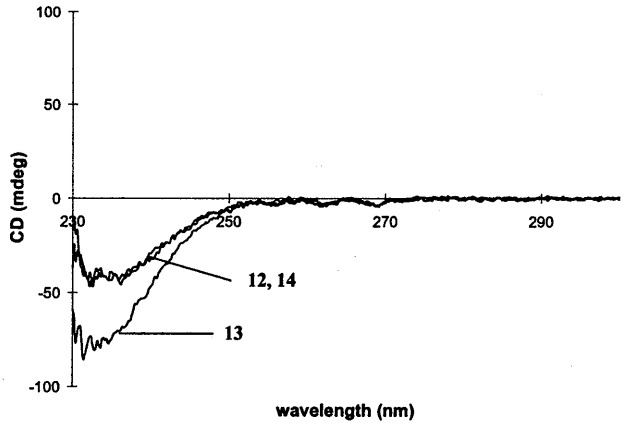


Figure 7. *CD spectra in CH_2Cl_2 for diamides 12–14.*

The Cotton Effects (CEs) for the π–π* transition of the phenyl group (λ = 255–275 nm) are relatively small and are roughly the same for all derivatives, but the CE of the n–π* transition of the carbamate functionality (λ = 240 nm) is the largest for **13**. Apparently, the combination of positive and negative CEs results into a zero optical rotation. This indicates that there are conformational differences between **13** and all other compounds, which is expressed in the absorption of the carbamate functionality.

3.3 Discussion and conclusion

The homologous series of amides **10–17** obtained from linear alkyl diamines derivatized with N-*t*-BOC-L-phenylalanine could be easily synthesized and characterized. With a variety of techniques we have investigated the possibilities of hydrogen-bonding interactions. Within this series no peculiarities in terms of solubility, chiroptical features, and NMR and IR spectroscopy were found in a hydrogen-bond breaking solvent like DMSO. However, when using solvents like CH_2Cl_2 or $CHCl_3$ large differences within the series are observed. The solubility for pentamethylene derivative **13** is by far best in these solvents. From ^{1}H- as well as ^{13}C-NMR measurements in $CDCl_3$, the resonances for both hydrogen-bonding units, the amide and the carbamate, were at higher δ-values for **13**, indicating a higher degree of hydrogen-bonding. Higher δ-values were also observed for compounds **14**, **15** and **17**, but the effect was less pronounced in these cases. Following Still and Gellmann's insights into model diamides,[14–15] IR measurements in CH_2Cl_2 as a solvent (a strategy commonly used to study hydrogen-bonding interactions) indicate the presence of a higher

degree of hydrogen-bonding in **13**. Also compound **14** showed strong hydrogen-bonding interactions, but the effect was less pronounced. The special findings for **13** and to some extent also for **14**, **15**, and **17**, are emphasized by measurements of the optical rotation and ORD, as no detectable optical activity was observed in the case of **13** and low values for **14**, **15** and **17**, when measuring in CH_2Cl_2. CD measurements indicate that conformational differences are present in **13**. When comparing these results with the literature data on similar compounds we have indications that this behavior is strongly dependent on the end group present.[14-19]

The formation of a ten-membered ring, as is most likely the case for **13**, is comparable with the formation of a β-turn in peptides as described in the literature,[7] suggesting that we are dealing with these hairpin structures in compound **13**.

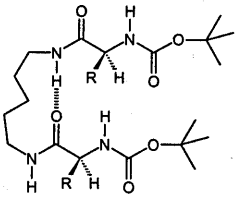


Figure 8. *Proposed β-turn formation in compound 13.*

So far, not much attention has been paid on the formation of larger ring sizes, as is the case for compounds **14**, **15** and **17**, leading to 11-, 12- and 14-membered rings, besides intermolecular interactions. We also have to take in account the fact, however, that the carbamate functionalities can support the intramolecular hydrogen-bonded species.

By introducing chirality as an additional tool we have been able to gain more insight in the conformation of diamides **10–17**. By CD measurements, we are able to differentiate between the two hydrogen-bonding species (amide and carbamate functionality) in CD.

3.4 Experimental section

General

All solvents were of c.p. quality, except those used as reaction solvent which were of p.a. quality. NMR spectra were run on a Bruker AM-400 spectrometer at frequencies of 400.1 MHz and 100.6 MHz for ^1H- and ^{13}C- nuclei, respectively. TMS was used as an internal standard and δ-values are given in ppm. IR-spectra were taken on a Perkin Elmer 1600 series FT-IR and data are given in cm^{-1}.

ORD/CD measurements were performed on a Jasco 600 spectropolarimeter and $[\alpha]_D^{20}$ data were measured on a Jasco DIP-370 digital polarimeter. Elemental analyses were run on a Perkin Elmer 2400 series II machine. EI-MS measurements were performed at the University of Berkeley.

N,N'-1,2-Ethylenebis(N''-*t*-BOC-L-phenylalaninamide), 10

To a solution of 1,2-ethylenediamine (27.8 mg, 0.463 mmol) in CH_2Cl_2 (10 mL) with Et_3N (0.1 mL) was added N'-succinimidyl N-*t*-BOC-L-phenylalaninate (341.3 mg, 0.943 mmol). This mixture was stirred overnight at room temperature during which a white precipitate was formed. Work-up was accomplished by the addition of CH_2Cl_2 (70 mL) and extraction of the organic phase with aqueous saturated Na_2CO_3 (5 x 30 mL). The organic layer was dried with Na_2SO_4 and the solvent evaporated to furnish pure **10** (0.18 g, 0.325 mmol, 70%) as a white solid. ^{1}H-NMR ($CDCl_3$): δ 1.42 (s, 18H, CH_3), 2.92–3.19 (m, 8H, C*H*$_2$NH, C*H*$_2$Ph), 4.13 (dd, *J* = 14.5 and 7.7 Hz, 2H, C*H), 5.09 (br d, *J* = 7.1 Hz, 2H, N*H*BOC), 5.65 (br, 2H, CH$_2$N*H*), 7.17–7.35 (m, 10H, PhH). ^{13}C-NMR ($CDCl_3$): δ 28.3 (CH_3, BOC), 38.9 (CH_2NH, CH_2Ph), 56.1 (C*H), 80.1 (C-*ipso*, BOC), 127.0, 128.6, 129.1 (PhCH), 136.8 (PhC-*ipso*), 155.6 (CO, BOC), 171.8 (CH$_2$NH*C*O). IR (KBr): ν 3334 (NH stretch), 2936 (CH_2 stretch), 1685 and 1656 (C=O stretch), 1545 and 1516 (C=C stretch), 1387 and 1367 (C(CH$_3$)$_3$ vibration). $[\alpha]_D^{20}$ = +13 (c = 0.49, CH_2Cl_2), +22 (c = 0.50, DMSO). Anal. Calcd. for $C_{30}H_{42}N_4O_6$: C, 64.96; H, 7.63; N, 10.10. Found: C, 64.77; H, 7.65; N, 9.97. EI-MS Calcd.: 554.3. Found: 554 $[M]^+$, 463 $[M–C_7H_6]^+$, 454 $[M–BOC]^+$, 381 [M-BOC–*t*BuOH]$^+$, 363 $[M–BOC–C_7H_6]^+$, 120 $[H_2NCHCH_2Ph]^+$, 91 $[C_7H_6]^+$.

N,N'-1,3-Propylenebis(N''-*t*-BOC-L-phenylalaninamide), 11

To a solution of 1,3-diaminopropane (53.8 mg, 0.726 mmol) in CH_2Cl_2 (10 mL) with Et_3N (0.1 mL) was added N'-succinimidyl N-*t*-BOC-L-phenylalaninate (535.0 mg, 1.476 mmol). This mixture was stirred overnight at room temperature during which a white precipitate was formed. Work-up was accomplished by the addition of CH_2Cl_2 (70 mL) and extraction of the organic phase with aqueous saturated Na_2CO_3 (5 x 30 mL). The organic layer was dried with Na_2SO_4 and the solvent evaporated to furnish pure **11** (0.35 g, 0.615 mmol, 85%) as a white solid. ^{1}H-NMR ($CDCl_3$): δ 1.39 (s, 18H, CH_3), 2.97–3.11 (m, 8H, C*H*$_2$NH, C*H*$_2$Ph), 4.32 (br, 2H, C*H), 5.16 (br d, *J* = 6.5 Hz, 2H, N*H*BOC), 6.68 (br, 2H, CH$_2$N*H*), 7.19–7.29 (m, 10H, PhH). ^{13}C-NMR ($CDCl_3$): δ 28.3 (CH_3, BOC), 28.9 (CH_2-3), 36.3, 38.5 (CH_2NH, CH_2Ph), 56.0 (C*H), 80.1 (C-*ipso*, BOC), 126.8, 128.6, 129.3 (PhCH), 136.7 (PhC-*ipso*), 155.6 (CO, BOC), 171.7 (CH$_2$NH*C*O). IR (KBr): ν 3343 (NH stretch), 2933 (CH_2 stretch), 1687 and 1658 (C=O stretch), 1550 and 1520 (C=C stretch), 1391 and 1366 (C(CH$_3$)$_3$ vibration). $[\alpha]_D^{20}$ = +14 (c = 0.49, CH_2Cl_2), + 20 (c = 0.50, DMSO). Anal. Calcd. for $C_{31}H_{44}N_4O_6$: C, 65.47; H, 7.80; N, 9.85. Found: C, 65.43; H, 7.87; N, 9.80. EI-MS Calcd.: 568.3. Found: 568 $[M]^+$, 477 $[M–C_7H_6]^+$, 468 $[M–BOC]^+$, 395 [M–BOC–*t*BuOH]$^+$, 377 $[M–BOC–C_7H_6]^+$, 120 $[H_2NCHCH_2Ph]^+$, 91 $[C_7H_6]^+$.

N,N'-1,4-Butylenebis(N''-*t*-BOC-L-phenylalaninamide), 12

To a solution of 1,4-diaminobutane (211.0 mg, 2.394 mmol) in CH_2Cl_2 (25 mL) with Et_3N (0.4 mL) was added N'-succinimidyl N-*t*-BOC-L-phenylalaninate (1759.8 mg, 4.856 mmol). This mixture was stirred overnight at room temperature during which a white precipitate was formed. Work-up was accomplished by the addition of CH_2Cl_2 (70 mL) and extraction of the organic phase with aqueous saturated Na_2CO_3 (5 x 30 mL). The organic layer was dried with Na_2SO_4 and the solvent evaporated to furnish pure **12** (1.26 g, 2.16 mmol, 90%) as a white solid. ^{1}H-NMR ($CDCl_3$): δ 1.28 (m, 4H, CH_2-

2,3), 1.38 (s, 18H, CH_3), 2.97–3.23 (m, 8H, CH_2NH, CH_2Ph), 4.35 (br, 2H, C*H), 5.23 (br, 2H, NHBOC), 6.33 (br, 2H, CH_2NH), 7.20–7.30 (m, 10H, PhH). ^{13}C-NMR ($CDCl_3$): δ 26.1 (CH_2-2,3), 28.3 (CH_3, BOC), 38.7 (CH_2NH, CH_2Ph), 56.0 (C*H), 80.1 (C-*ipso*, BOC), 126.8, 128.6, 129.3 (PhCH), 136.9 (PhC-*ipso*), 155.6 (CO, BOC), 171.5 (CH_2NHCO). IR (KBr): ν 3343 (NH stretch), 1687 and 1658 (C=O stretch), 1550 and 1520 (C=C stretch), 1391 and 1366 ($C(CH_3)_3$ vibration). $[\alpha]_D^{20}$ = +25 (c = 0.30, CH_2Cl_2), +21 (c = 0.51, DMSO). Anal. Calcd. for $C_{32}H_{46}N_4O_6$: C, 65.96; H, 7.96; N, 9.61. Found: C, 66.04; H, 8.10; N, 9.65.

N,N'-1,5-Pentylenebis(N''-*t*-BOC-L-phenylalaninamide), 13

To a solution of 1,5-diaminopentane (207.5 mg, 2.031 mmol) in CH_2Cl_2 (25 mL) with Et_3N (0.1 mL) was added N'-succinimidyl N-*t*-BOC-L-phenylalaninate (1488.3 mg, 4.107 mmol). This mixture was stirred overnight at room temperature during which a white precipitate was formed. Work-up was accomplished by the addition of CH_2Cl_2 (70 mL) and extraction of the organic phase with aqueous saturated Na_2CO_3 (5 x 30 mL). The organic layer was dried with Na_2SO_4 and the solvent evaporated to furnish pure **13** (1.20 g, 2.011 mmol, 99%) as a white solid. ^{1}H-NMR ($CDCl_3$): δ 1.19 (m, 2H, CH_2-3), 1.33 (s, 18H, CH_3, BOC), 1.38 (m, 4H, CH_2-2,4), 2.87–3.30 (m, 8H, CH_2NH, CH_2Ph), 4.74 (br, 2H, C*H), 5.97 (br d, *J* = 8.3 Hz, 2H, NHBOC), 7.18–7.22 (m, 10H, PhH), 7.50 (br, 2H, CH_2NH). ^{13}C-NMR ($CDCl_3$): δ 24.6 (CH_2-3), 28.2 (CH_3, BOC), 28.6 (CH_2-2,4), 39.1, 39.5 (CH_2NH, CH_2Ph), 55.5 (C*H), 79.3 (C-*ipso*, BOC), 126.2, 128.0, 129.3 (PhCH), 137.1 (PhC-*ipso*), 155.8 (CO, BOC), 172.3 (CH_2NHCO). IR (KBr): ν 3340 (NH stretch), 2932 (CH_2 stretch), 1687 and 1654 (C=O stretch), 1522 (C=C stretch), 1391 and 1365 ($C(CH_3)_3$ vibration). $[\alpha]_D^{20}$ = 0 (c = 0.50, CH_2Cl_2), +22 (c = 0.50, DMSO). Anal. Calcd. for $C_{33}H_{48}N_4O_6$: C, 66.42; H, 8.11; N, 9.39. Found: C, 66.44; H, 8.20; N, 9.46.

N,N'-1,6-Hexylenebis(N''-*t*-BOC-L-phenylalaninamide), 14

To a solution of 1,6-diaminohexane (57.6 mg, 0.496 mmol) in CH_2Cl_2 (10 mL) with Et_3N (0.1 mL) was added N'-succinimidyl N-*t*-BOC-L-phenylalaninate (380.9 mg, 1.051 mmol). This mixture was stirred overnight at room temperature during which a white precipitate was formed. Work-up was accomplished by the addition of CH_2Cl_2 (70 mL) and extraction of the organic phase with aqueous saturated Na_2CO_3 (5 x 30 mL). The organic layer was dried with Na_2SO_4 and the solvent evaporated to furnish pure **14** (0.29 g, 0.475 mmol, 96%) as a white solid. ^{1}H-NMR ($CDCl_3$): δ 1.21 (m, 4H, CH_2-3,4), 1.37 (m, 22H, CH_3, CH_2-2,5), 2.95–3.17 (m, 8H, CH_2NH, CH_2Ph), 4.42 (br, 2H, C*H), 5.57 (br d, *J* = 6.4 Hz, 2H, NHBOC), 6.61 (br, 2H, CH_2NH), 7.20–7.28 (m, 10H, PhH). ^{13}C-NMR ($CDCl_3$): δ 25.3 (CH_2-3,4), 28.2 (CH_3, BOC), 28.8 (CH_2-2,5), 38.4, 39.0 (CH_2NH, CH_2Ph), 55.9 (C*H), 79.7 (C-*ipso*, BOC), 126.6, 128.3, 129.3 (PhCH), 137.0 (PhC-*ipso*), 155.6 (CO, BOC), 171.6 (CH_2NHCO). IR (KBr): ν 3335 (NH stretch), 2932 (CH_2 stretch), 1689 and 1652 (C=O stretch), 1522 (C=C stretch), 1390 and 1366 ($C(CH_3)_3$ vibration). $[\alpha]_D^{20}$ = +6 (c = 0.50, CH_2Cl_2), +20 (c = 0.51, DMSO). Anal. Calcd. for $C_{34}H_{50}N_4O_6$: C, 66.86; H, 8.25; N, 9.17. Found: C, 66.59; H, 8.33; N, 9.06. EI-MS Calcd.: 610.4. Found: 610 $[M]^+$, 519 $[M–C_7H_6]^+$, 510 $[M–BOC]^+$, 437 $[M–BOC–t\text{BuOH}]^+$, 419 $[M–BOC–C_7H_6]^+$, 120 $[H_2NCHCH_2Ph]^+$, 91 $[C_7H_6]^+$.

N,N'-1,7-Heptylenebis(N''-*t*-BOC-L-phenylalaninamide), 15

To a solution of 1,7-diaminoheptane (67.5 mg, 0.518 mmol) in CH_2Cl_2 (10 mL) with Et_3N (0.1 mL) was added N'-succinimidyl N-*t*-BOC-L-phenylalaninate (381.9 mg, 1.054 mmol). This mixture was stirred overnight at room temperature during which a white precipitate was formed. Work-up was

accomplished by the addition of CH_2Cl_2 (70 mL) and extraction of the organic phase with aqueous saturated Na_2CO_3 (5 x 30 mL). The organic layer was dried with Na_2SO_4 and the solvent evaporated to furnish pure **15** (0.31 g, 0.496 mmol, 96%) as a white solid. ^{1}H-NMR ($CDCl_3$): δ 1.21 (m, 6H, CH_2-3,4,5), 1.38 (m, 22H, CH_3, CH_2-2,6), 2.94–3.21 (m, 8H, C*H*$_2$NH, C*H*$_2$Ph), 4.46 (br, 2H, C*H), 5.54 (br, 2H, N*H*BOC), 6.71 (br, 2H, CH_2N*H*), 7.18–7.27 (m, 10H, PhH). ^{13}C-NMR ($CDCl_3$): δ 26.3 (CH_2-3,4,5), 28.3 (CH_3, BOC), 28.8 (CH_2-2,6), 39.1 (CH_2NH, CH_2Ph), 55.8 (C*H), 79.7 (C-*ipso*, BOC), 126.5, 128.3, 129.3 (PhCH), 137.0 (PhC-*ipso*), 155.6 (CO, BOC), 171.5 (CH_2NH*C*O). IR (KBr): ν 3339 (NH stretch), 2930 (CH_2 stretch), 1689 and 1655 (C=O stretch), 1522 (C=C stretch), 1390 and 1366 ($C(CH_3)_3$ vibration). $[\alpha]_D^{20}$ = +9 (c = 0.51, CH_2Cl_2), +21 (c = 0.50, DMSO). Anal. Calcd. for $C_{35}H_{52}N_4O_6$: C, 67.28; H, 8.39; N, 8.97. Found: C, 66.90; H, 8.46; N, 8.82. EI-MS Calcd.: 624.4. Found: 624 $[M]^+$, 533 $[M–C_7H_6]^+$, 524 $[M–BOC]^+$, 451 [M–BOC–*t*BuOH]$^+$, 433 [M–BOC–C_7H_6]$^+$, 120 $[H_2NCHCH_2Ph]^+$, 91 $[C_7H_6]^+$.

N,N'-1,8-Octylenebis(N''-*t*-BOC-L-phenylalaninamide), 16

To a solution of 1,8-diaminooctane (69.1 mg, 0.479 mmol) in CH_2Cl_2 (10 mL) with Et_3N (0.1 mL) was added N'-succinimidyl N-*t*-BOC-L-phenylalaninate (356.0 mg, 0.982 mmol). This mixture was stirred overnight at room temperature during which a white precipitate was formed. Work-up was accomplished by the addition of CH_2Cl_2 (70 mL) and extraction of the organic phase with aqueous saturated Na_2CO_3 (5 x 30 mL). The organic layer was dried with Na_2SO_4 and the solvent evaporated to furnish pure **16** (0.30 g, 0.470 mmol, 98%) as a white solid. ^{1}H-NMR ($CDCl_3$): δ 1.20 (m, 8H, CH_2-3,4,5,6), 1.34–1.55 (m, 22H, CH_3, CH_2-2,7), 3.00–3.20 (m, 8H, C*H*$_2$NH, C*H*$_2$Ph), 4.29 (br, 2H, C*H), 5.19 (br, 2H, N*H*BOC), 6.00 (br, 2H, CH_2N*H*), 7.17–7.32 (m, 10H, PhH). ^{13}C-NMR ($CDCl_3$): δ 26.1 (CH_2-3,4), 28.3 (CH_3, BOC), 28.5 (CH_2-5,6), 29.1 (CH_2-2,7), 38.9, 39.3 (CH_2NH, CH_2Ph), 56.1 (C*H), 80.0 (C-*ipso*, BOC), 126.8, 128.5, 129.3 (PhCH), 136.9 (PhC-*ipso*), 155.6 (CO, BOC), 171.1 (CH_2NH*C*O). IR (KBr): ν 3339 (NH stretch), 2930 (CH_2 stretch), 1682 and 1658 (C=O stretch), 1527 (C=C stretch), 1393 and 1366 ($C(CH_3)_3$ vibration). $[\alpha]_D^{20}$ = +13 (c = 0.50, CH_2Cl_2), +18 (c = 0.50, DMSO). Anal. Calcd. for $C_{36}H_{54}N_4O_6$: C, 67.68; H, 8.52; N, 8.77. Found: C, 67.74; H, 8.62; N, 8.64. EI-MS Calcd.: 638.4. Found: 638 $[M]^+$, 547 $[M–C_7H_6]^+$, 538 $[M–BOC]^+$, 465 [M–BOC–*t*BuOH]$^+$, 447 [M–BOC–C_7H_6]$^+$, 120 $[H_2NCHCH_2Ph]^+$, 91 $[C_7H_6]^+$.

N,N'-1,9-Nonylenebis(N''-*t*-BOC-L-phenylalaninamide), 17

To a solution of 1,9-diaminononane (93.4 mg, 0.590 mmol) in CH_2Cl_2 (10 mL) with Et_3N (0.1 mL) was added N'-succinimidyl N-*t*-BOC-L-phenylalaninate (435.2 mg, 1.201 mmol). This mixture was stirred overnight at room temperature during which a white precipitate was formed. Work-up was accomplished by the addition of CH_2Cl_2 (70 mL) and extraction of the organic phase with aqueous saturated Na_2CO_3 (5 x 30 mL). The organic layer was dried with Na_2SO_4 and the solvent evaporated to furnish pure **17** (0.38 g, 0.582 mmol, 99%) as a white solid. ^{1}H-NMR ($CDCl_3$): δ 1.20 (m, 10H, CH_2-3,4,5,6,7), 1.38 (m, 22H, CH_3, CH_2-2,8), 3.00–3.20 (m, 8H, C*H*$_2$NH, C*H*$_2$Ph), 4.37 (br, 2H, C*H), 5.45 (d, *J* = 7.3 Hz, 2H, N*H*BOC), 6.41 (br, 2H, CH_2N*H*), 7.18–7.29 (m, 10H, PhH). ^{13}C-NMR ($CDCl_3$): δ 26.5 (CH_2-4,5,6), 28.3 (CH_3, BOC), 28.8 (CH_2-3,7), 29.1 (CH_2-2,8), 38.9, 39.2 (CH_2NH, CH_2Ph), 55.9 (C*H), 79.7 (C-*ipso*, BOC), 126.6, 128.3, 129.2 (PhCH), 136.9 (PhC-*ipso*), 155.4 (CO, BOC), 171.2 (CH_2NH*C*O). IR (KBr): ν 3342 (NH stretch), 2927 (CH_2 stretch), 1686 and 1656 (C=O stretch), 1522 (C=C stretch), 1391 and 1366 ($C(CH_3)_3$ vibration). $[\alpha]_D^{20}$ = +7 (c = 0.50, CH_2Cl_2), +18 (c = 0.50, DMSO). Anal. Calcd. for $C_{37}H_{56}N_4O_6$: C, 68.07; H, 8.64; N, 8.58. Found: C, 68.11; H, 8.84; N, 8.46.

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4 Synthesis of glycodendrimers by the modification of poly(propylene imine) dendrimers

Summary

The use of preformed poly(propylene imine) dendrimers (DAB-dendr-$(NH_2)_x$) for the rapid and facile construction of high molecular weight carbohydrate-coated dendrimers (glycodendrimers) is demonstrated. An efficient attachment of derivatives of D-galactose, lactose and a clustered trisgalactoside, via a short spacer arm, to the primary amine end groups of all generations (1 to 5) of DAB-dendr-$(NH_2)_x$ has been achieved through amide bond formation using the N-succinimidyl activated ester coupling procedure. Acetates have been employed as protecting groups in order to avoid side reactions at the coupling stage. Deacetylation leads to the target glycodendrimers. The regularity of the glycodendrimers has been proven by NMR spectroscopy, while the molecular weights of the low-generation carbohydrate-coated dendrimers have been determined by mass spectrometry. Modifications of DAB-dendr-$(NH_2)_x$ with biologically active carbohydrates afford a new and simple approach to high molecular weight compounds which may be considered as neoglycoconjugates with perfectly symmetrical structures and with much promise as multivalent ligands that can be involved in carbohydrate–protein interactions.

4.1 Introduction

Many of the unique properties of dendrimers, like dense surface packing and controlled architecture, are only observed at dendrimers of higher generation,[1–3] stressing the need for large dendrimers that have an almost perfect structure. For this purpose, mostly divergently synthesized dendrimers are used in view of their availability on a reasonably large scale, even for the higher generations. Modifications of these dendrimers at the periphery have led to the disclosure of e.g. unimolecular (inverted) micelles,[4] catalysts,[5] metallodendrimers[6] and dendritic boxes.[1] Also biomolecules, such as peptides,[7] antibodies,[8] oligonucleotides[9] and mono- and oligosaccharide residues[10] have been attached to dendritic scaffolds. Many of the unique dendritic properties, like guest–host interactions and dense

surface packing, only arise at higher generations of dendrimers, indicating that cooperative effects are present in these nanosized structures.[1–4,11] These cooperative recognition effects are even more prominent in biology, especially when clustering effects within a molecule are important.[11] Therefore, dendrimers are good candidates for investigating biological processes where these cooperative effects might be operating.

In recent years, several groups have described[12–16] their particular approaches to the construction of carbohydrate-containing dendrimers or —as they have become known— glycodendrimers.[17] This new family of neoglycoconjugates has proven to be extremely useful when studying multiple carbohydrate–protein interactions. The enhancement in binding of saccharide residues to protein receptors as a result of increasing the saccharide 'valency' is a well-known phenomenon in glycobiology,[11] which is often referred to as the cluster glycoside or multivalent effect. It has already been shown that some carbohydrate-containing dendrimers possess much higher activities in binding towards lectins than their corresponding individual saccharide residues. It has also been observed, that the optimum number of saccharide residues which induce the most pronounced effect is relatively small,[18] whereas large glycodendrimers do not show significant increase in biological activity. However, so far all studies of the glycodendrimer biological activity were carried out *in vitro* and the situation may be different *in vivo* where the potential of large glycodendrimers mimicking carbohydrate-containing biomolecules still needs to be investigated.

In this chapter, we describe our results on the modification of DAB-*dendr*-$(NH_2)_x$[19] involving the multiple attachment of saccharide units *via* a short spacer terminated with carboxylic acid end groups to the peripheral primary amines, *i.e.* the carbohydrate–dendrimer linkages are constructed *via* amide bonds. The approach combines the use of commercially available dendrimers, simple saccharide derivatization and standard coupling techniques to yield advanced structures.

4.2 Results and discussion

4.2.1 Modification of DAB-*dendr*-$(NH_2)_x$ with lactose and galactose residues

As the basis for our modifications we used the poly(propylene imine) dendrimers (DAB-*dendr*-$(NH_2)_x$)[19] **1a**–**5a** (Figure 1) of the first up to the fifth generation with 4, 8, 16, 32, and 64 primary amine end groups, respectively. We had noticed that a very successful modification of dendrimer **5a** had been achieved using N-succinimidyl activated esters of amino acids,[1] and therefore, we decided to use the same mild coupling method for the construction of the carbohydrate-coated dendrimers (Figure 1).

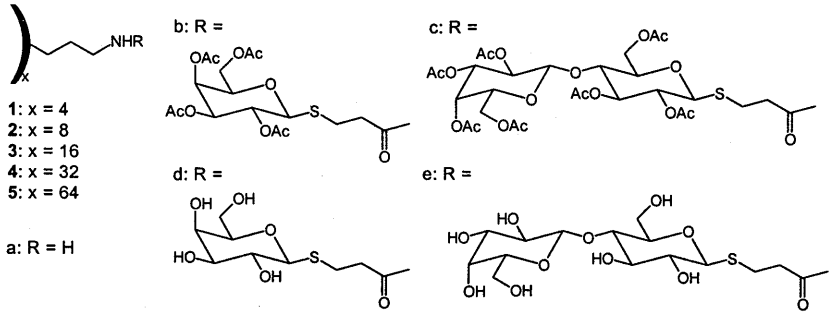
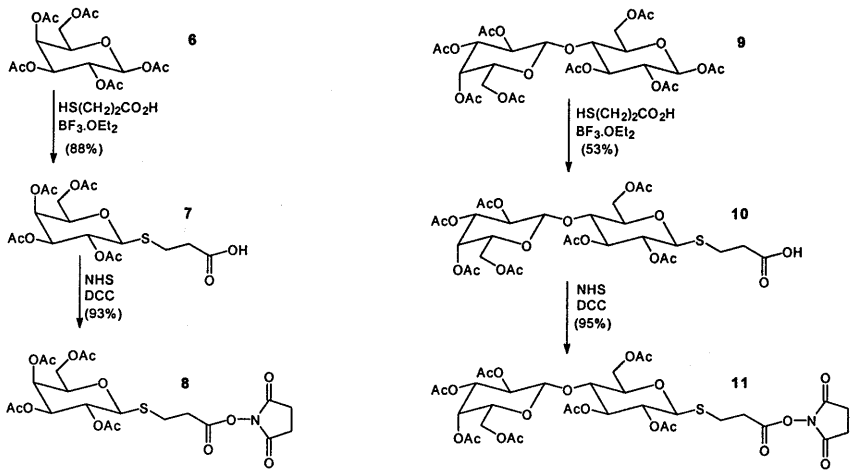


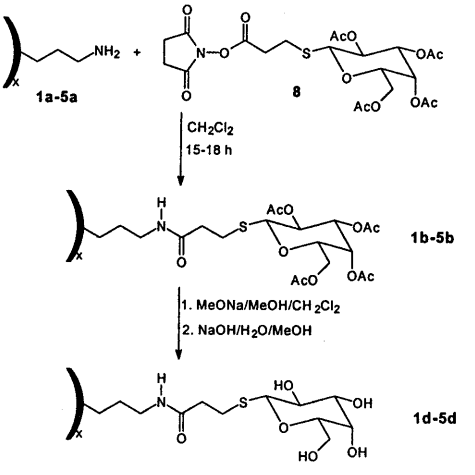
Figure 1. *Poly(propylene imine) dendrimers **1a–5a** and glycodendrimers **1b/e–5b/e**.*

Before the coupling of saccharide and dendrimer, two carbohydrates (D-galactose and lactose) were converted into their acetylated spacer-armed derivatives containing an activated ester as the reactive end group (Scheme 1). A simple and efficient procedure[20] ($HSCH_2CH_2CO_2H$ / $BF_3{\cdot}OEt_2$ / CH_2Cl_2, 20 °C, 5 h) afforded the thioglycoside **7** in a high yield starting from 1,2,3,4,6-penta-O-acetyl-β-D-galactopyranose **6**. Employing very similar conditions, lactose octaacetate[21] **9** has been transformed into **10** in a 53% yield. The N-succinimidyl activated esters **8** and **11** have been prepared from **7** and **9**, respectively, by condensation of these carboxylic acid derivatives with N-hydroxysuccinimide under the influence of DCC ($MeOCH_2CH_2OMe$, 0–5 °C, 18 h).[22] The acetyl protection of the hydroxyl groups was essential for the efficient coupling of activated esters to the dendrimers; after the attachment of the saccharides to the dendrimers, they were removed.



Scheme 1. *Synthesis of N-succinimidyl activated esters of D-galactose and lactose for attachment to the poly(propylene imine) dendrimers.*

The coupling of the activated esters **8** and **11** with the DAB-*dendr*-$(NH_2)_x$ (Scheme 2) was carried out using one molar equivalent of the activated ester for every primary amine end group present in the dendrimers. Reactions were performed in CH_2Cl_2 at 25 °C for 15–18 h to give carbohydrate dendrimers **1b/c–5b/c** (Figure 1), which were isolated after vigorous washing of the diluted (CH_2Cl_2) reaction mixtures with saturated aqueous Na_2CO_3. No starting materials or acids derived from **8** or **11** could be detected, following this particular work-up procedure. Deprotection of the acetates in **1b/c–5b/c** was achieved by subjecting them to standard Zemplén deacetylation,[23] followed by treatment with aqueous NaOH. The deacetylated products were completely soluble in water and their desalination was achieved successfully in all cases using GPC.



Scheme 2. *Synthetic strategy towards glycodendrimers, exemplified for the specific case of* ***1d–5d.***

4.2.2 Structure determination of the galacto- and lacto-dendrimers

The introduction of saccharide moieties into dendrimers **1a–5a** has been evident from the NMR spectra of the coupling products. ^{13}C-NMR spectra were more characteristic than ^{1}H-NMR spectra. Both galactose and lactose units of acetylated glycodendrimers **1b/c–5b/c** revealed one set of well-resolved signals in the region of δ = 60–101 ppm (6 or 12, for **1b–5b** or **1c–5c**, respectively). Chemical shifts of the same type of carbon atoms of saccharide residues of synthesized dendrimers practically coincided (Table 1). These signals can be assigned on the basis of unambiguous peak assignment from ^{13}C-NMR spectra of the monosaccharide precursors **7** and **10**. The latter has been performed using COSY and CH-NMR correlation experiments. Acetyl protecting groups are also clearly registered as two sets

of peaks located around δ = 20 and in a region of δ = 169–170 ppm. Close to the latter region a signal of the newly formed NHCO group is detected (δ = 170.7–171.0 ppm). All signals of the inner part of acetylated glycodendrimers are situated in a separate area of the ^{13}C-NMR spectra. These are signals assigned to the thiopropionic linker as well as to CH_2-links of propylenediamine fragments which appear in three different regions (Table 1). Signals of the central diaminobutane core are weak and overlapping with the above mentioned signals, although in ^{13}C-NMR spectra of the first generation dendrimer, **1b** and **1c**, they can be identified (δ 24.6 ppm CH_2CH_2N and 53.5 ppm CH_2CH_2N). For the CH_2 group next to the newly formed amide bond (CH_2CH_2NHCO) there is an absorption at δ = 37.3–37.9 ppm and for the spacer between the dendrimer and the saccharide there are absorptions at δ = 26.3–26.8 ppm (SCH_2) and δ = 36.5–36.9 ppm (CH_2CONH).

Table 1. *^{13}C-NMR spectroscopic data (ppm) for acetylated glycodendrimers **1b/e–5b/e**.*

Resonance	Galactose dendrimers **1b–5b**	Lactose dendrimers **1c–5c**[a]
C-1	84.2–84.4	83.7–84.1 (*Glc*)
		100.6–100.9 (*Gal*)
C-2	66.8–67.2	69.9–70.1 (*Glc*)
		68.8–69.0 (*Gal*)
C-3	71.3–71.5	73.4–73.6 (*Glc*)
		70.6–70.8 (*Gal*)
C-4	67.0–67.2	75.3–75.9 (*Glc*)
		66.4–66.5 (*Gal*)
C-5	74.0–74.3	76.5–76.7 (*Glc*)
		70.3–70.5 (*Gal*)
C-6	61.1–61.3	61.6–61.8 (*Glc*)
		60.5–60.6 (*Gal*)
SCH_2	26.3–26.5	26.6–26.8
CH_2CONH	36.5–36.8	36.7–36.9
$CONHCH_2$	37.4–37.9	37.3–37.8
CH_2NCH_2	50.8–51.5	50.0–51.3
	51.3–53.5	51.1–53.5
$CH_2CH_2CH_2$	26.4–26.8	26.6–26.8

[a]For lactose units in **1c–5c**, the chemical shifts are given for glucose (*Glc*) and galactose (*Gal*) residues in separate rows.

^{1}H-NMR spectra of glycodendrimers **1b/c–5b/c** with attached acetylated sugar units have been inspected for characteristic signals of acetyl, amide, and pyranose ring protons. However, well-resolved spectra were only obtained for low-generation modified dendrimers (see for example ^{1}H-NMR spectra of **1b** and **1c** in the experimental section), whereas for high molecular weight compounds considerable broadening of the lines was observed.

IR-spectra of compounds **1b/c–5b/c** are almost identical for each series, differing a little in the intensities of the selected bands. A strong absorption at 1655 cm^{-1} is characteristic for the newly formed amide bond.

In order to determine molecular masses of carbohydrate-modified dendrimers **1b/c–5b/c** liquid secondary ion mass spectrometry (LSI-MS) has been applied and molecular peaks of dendrimers with four and eight saccharide end groups, **1b**, **2b**, **1c**, and **2c**, have been successfully registered (Table 2).

Table 2. *Mass spectroscopic data for the glycodendrimers.*

Compound	Molecular Formula	Calc. Mol. Mass	Mass Spectroscopic Data	
			LSI-MS	MALDI-TOF-MS
1b	$C_{84}H_{128}N_6O_{40}S_4$	1988.7	1990 $[M+H]^+$	1990 $[M+H]^+$
2b	$C_{176}H_{272}N_{14}O_{80}S_8$	4118.6	4143 $[M+Na]^+$	4124 $[M+H]^+$
3b	$C_{360}H_{560}N_{30}O_{160}S_{16}$	8378.3	8401 $[M+Na]^+$	8402 $[M+Na]^+$
1c	$C_{132}H_{192}N_6O_{72}S_4$	3142.1	3143 $[M+H]^+$	3143 $[M+H]^+$
			3165 $[M+Na]^+$	
2c	$C_{272}H_{400}N_{14}O_{144}S_8$	6424.3	6448 $[M+Na]^+$	6433 $[M+H]^+$
1d	$C_{52}H_{96}N_6O_{24}S_4$	1316.5		1319 $[M+H]^+$
				1341 $[M+Na]^+$
2d	$C_{112}H_{208}N_{14}O_{48}S_8$	2774.2		2777 $[M+H]^+$
				2799 $[M+Na]^+$
1e	$C_{76}H_{136}N_6O_{44}S_4$	1964.8		1989 $[M+Na]^+$
2e	$C_{160}H_{288}N_{14}O_{88}S_8$	4070.7		4097 $[M+Na]^+$
16a[a]	$C_{228}H_{328}N_{14}O_{132}$	5376.0	5399 $[M+Na]^+$	
16b[a]	$C_{132}H_{232}N_{14}O_{84}$	3358.5		3387 $[M+Na]^+$

[a]Compounds **16a** and **16b** are described in section 4.2.4.

A satisfactory result has also been obtained for dendrimer **3b** with 16 acetylated monosaccharide units using LSI-MS, again showing essentially the presence of a single molecule without statistical defects. This observation is in agreement with the ESI-MS of the starting materials.[19c] Molecular masses of heavier molecules **3c**, **4b/c**, and **5b/c** cannot be determined by LSI-MS as a consequence of limitations of the technique. To tackle this

problem, MALDI-TOF mass spectrometry has been attempted for these compounds, but again reliable determination of molecular masses proved to be impossible. However, statistical defects as a result of the divergent parent dendrimer are obviously present.[19c] In contrast, lower molecular weight compounds **1b**, **2b**, **3b**, **1c**, and **2c** exhibit good MALDI-TOF mass spectra which contain only peaks of both $[M+Na]^+$ and $[M+K]^+$ ions.

The structure of unprotected carbohydrate dendrimers **1d/e–5d/e** has also been analyzed by means of NMR spectroscopy and mass spectrometry. ^{13}C-NMR spectra of these compounds (Table 3) measured in D_2O showed a great similarity in specific parts of the spectra when they are grouped either by the nature of the involved sugar unit or by the nature of the DAB-*dendr*-$(NH_2)_x$. In the first case the resonance of carbon nuclei either of galactose or lactose residues appear as a set of 6 or 12 signals, respectively (Table 1), the chemical shifts of the corresponding signals being absolutely identical. Therefore, the nature of the dendritic core does not influence the spectral properties of the carbohydrate units. At the same time, signals of poly(propylene imine) parts of glycodendrimers **1d/e–5d/e** are characteristic for compounds built from DAB-*dendr*-$(NH_2)_x$ of the same generation. These signals reveal as sets of 5–9 peaks of different intensity at δ = 21–56 ppm, which have a specific location for dendrimers of a certain generation. The relative simplicity of this part of the spectra for compounds **1d/e–5d/e** justifies to suggest that the dendritic skeleton does not contain any serious defects as a result of chemical manipulation (*e.g.* basic treatment in the process of working up or deacetylation). Signals of the amide carbonyl group (δ = 177.3–177.4 ppm) are also observed very distinctively.

Table 3. *^{13}C-NMR spectroscopic data (ppm) of glycodendrimers **1d/e–5d/e, 16b and 17b.***

Resonance	**1d–5d**	**1e–5e**	**16b–17b**[a]
Saccharide part	64.0, 71.5, 72.3, 76.6, 81.6, 88.8	63.1, 63.8, 71.2, 73.6, 74.7, 75.2, 78.1, 78.5, 81.1, 81.3, 88.0, 105.6	63.7, 71.3, 73.4, 75.2, 77.8, 106.2
$CH_2CH_2CH_2$	21.6–24.7	21.5–23.3	21.5–23.3
SCH_2	26.0–26.2	26.1–26.2	-
$CONHCH_2CH_2$	29.1–29.3	28.9–29.2	24.3
$CH_2CONHCH_2$	38.0–39.0	38.9–39.0	38.8
CH_2NCH_2	52.4–55.2	52.4–55.2	52.3–55.2
$CH_2CONHCH_2$	177.3–177.4	177.2–177.3	178.8–178.9

[a]Trisgalactosidedendrimers **16b** and **17b** (described in section 4.2.4), δ 26.0, 37.2–37.3, 37.5, 45.4, 62.6, 70.3, 173.6–173.7 ppm.

When ^{1}H-NMR spectra of synthesized glycodendrimers were recorded at 25 °C in D_2O, they exhibited extreme broadening of all signals. Elevated temperatures (100 °C) and $(CD_3)_2SO$ as a solvent have been employed in an attempt to overcome this problem, and some improvements of spectral quality, particularly for the first, small member of each series, have been achieved (interpretations of ^{1}H-NMR spectra of **1d** and **1e** are given in the experimental section). The assignment of the spectra of **1d** and **1e** may be used as a basis for the assignment of the larger dendrimers, but the last still reveal poorer resolution decreasing quickly when switching from low to high generation dendrimers. It is worth mentioning that when ^{1}H-NMR spectra of the original DAB-*dendr*-$(NH_2)_x$ **1a–5a** were measured under the same conditions, this dramatic difference of the spectral quality of lower and higher generation dendrimers was not observed.

Mass-spectrometric analysis was successful for low molecular weight glycodendrimers **1d**, **2d**, **1e** and **2e** using the MALDI-TOF technique only (Table 2). In these cases the $[M+Na]^+$ ion was registered as the main peak in the region of mass higher than 1 kDa.

Chiroptical features of glycodendrimers have been studied by polarimetry, and it was revealed that specific optical rotation of compounds in each series of galactose or lactose dendrimers remained nearly constant (Table 4). Such chiroptical behavior of glycodendrimers is not unexpected, but it is in sharp contrast with the significant decrease of optical rotation for the amino acid modified DAB-*dendr*-$(NH_2)_x$ with increasing dendrimer generation.[1]

Table 4. *Yields and specific optical rotation for the acetylated glycodendrimers* ***1b/c–5b/c*** *and free glycodendrimers* ***1d/e–5d/e.***

Acetylated glycodendrimers			Unprotected glycodendrimers		
Compound	Yield (%)	$[\alpha]_D^{20}$ ($CHCl_3$)	Compound	Yield (%)	$[\alpha]_D^{20}$ (H_2O)
1b	96	–4.5 (c = 1.0)	**1d**	87	+8.2 (c = 0.9)
2b	100	–4.8 (c = 1.0)	**2d**	85	+5.1 (c = 1.0)
3b	99	–4.9 (c = 1.0)	**3d**	88	+6.3 (c = 1.0)
4b	100	–5.8 (c = 1.0)	**4d**	74	+5.6 (c = 1.0)
5b	97	–5.5 (c = 1.0)	**5d**	69	+7.5 (c = 1.0)
1c	97	–5.5 (c = 1.0)	**1e**	78	+0.5 (c = 1.1)
2c	97	–7.2 (c = 1.0)	**2e**	79	0 (c = 1.2)
3c	100	–8.0 (c = 1.0)	**3e**	73	+0.2 (c = 1.1)
4c	94	–8.5 (c = 1.0)	**4e**	69	0 (c = 1.1)
5c	93	–7.7 (c = 1.1)	**5e**	64	+1 (c = 1.2)

The methodology described above relied upon the reactivity of multiple amino groups on the dendrimer surface. The full characterization, including mass spectrometry, of the first, second and third generation glycodendrimers allows the unambiguous assignment of completely functionalized molecules without statistical defects: perfect organic molecules. The confident results of detailed spectroscopic analyses, without mass spectrometry, allows the conclusion that extremely high values of functionalizations are obtained. However, it is obvious that a small number of statistical defects are present at least in the same order as in the starting poly(propylene imine) dendrimers.[19c] The number of saccharide units incorporated into the glycodendrimers has been estimated by combustion analyses, which gave reasonable ratios of the content of carbon to sulfur (Table 5), whereas absolute results of microanalyses were not correct as can be expected for these hygroscopic compounds.

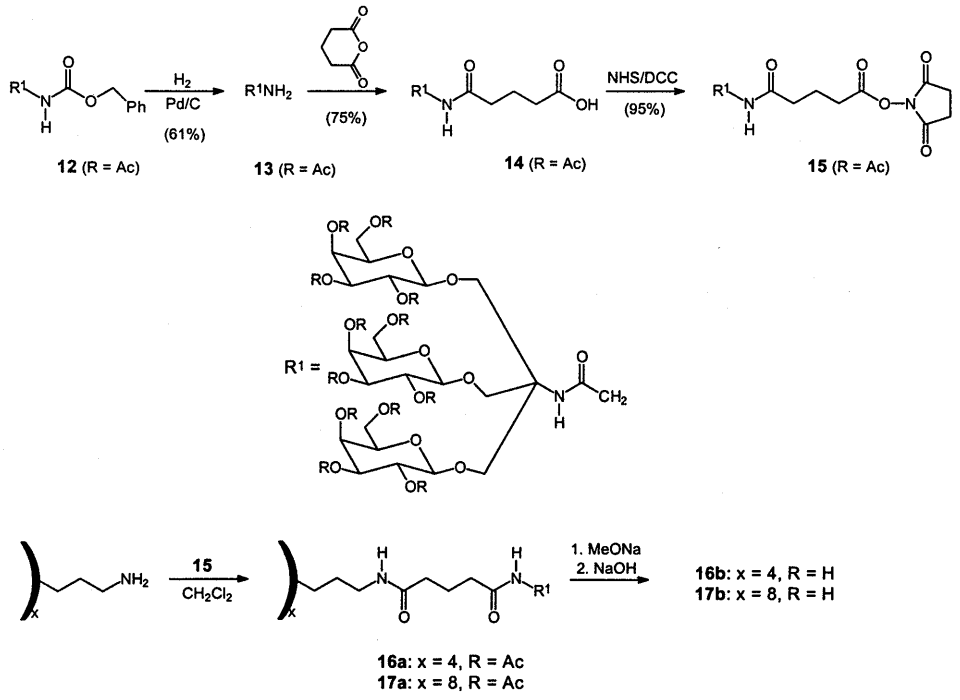
Table 5. *Microanalytical data (C/S ratio) for the free glycodendrimers* ***1d–5d*** *and* ***1e–5e.***

Compound	Molecular formula	%C : %S	
		Calculated	Found
1d	$C_{52}H_{96}N_6O_{24}S_4$	4.87	4.92
2d	$C_{112}H_{208}N_{14}O_{48}S_8$	5.25	5.40
3d	$C_{232}H_{432}N_{30}O_{96}S_{16}$	5.43	5.56
4d	$C_{472}H_{880}N_{62}O_{192}S_{32}$	5.53	5.68
5d	$C_{952}H_{1776}N_{126}O_{384}S_{64}$	5.57	5.66
1e	$C_{76}H_{136}N_6O_{44}S_4$	4.87	4.92
2e	$C_{160}H_{288}N_{14}O_{88}S_8$	7.49	7.67
3e	$C_{328}H_{592}N_{30}O_{176}S_{16}$	7.68	7.65
4e	$C_{664}H_{1200}N_{62}O_{352}S_{32}$	7.77	7.71
5e	$C_{1336}H_{2416}N_{126}O_{704}S_{64}$	7.82	7.81

Certainly, completeness of functionalization of amino groups by saccharides may depend upon the structure of the latter and large oligosaccharides may reveal a tendency to random and incomplete attachment.

4.2.3 Construction of trisgalactoside modified DAB-*dendr*-$(NH_2)_x$

In this section a clustered trisgalactoside[24] is used for modification of the first two generations of DAB-*dendr*-$(NH_2)_x$-dendrimers, **1a** and **2a** (Scheme 3). To introduce a carboxylic acid end group spacer arm to **12**, it was N-deprotected (H_2, 10% Pt/C, 40 °C, 8 h) to give amine **13**, which was acylated with glutaric anhydride, affording compound **14** in a 46% overall yield. Condensation of **14** with N-hydroxysuccinimide by the standard procedure[22] yielded activated ester **15** in a nearly quantitative yield. Reactions of dendrimers **1a** and **2a** with 4 or 8 equivalents of **15**, have been carried out under the same conditions as described earlier and afforded compounds **16a** and **17a** in 92 and 84% yield, respectively.



Scheme 3. *Synthesis of activated ester 15 and dendrimers 16 and 17.*

Deacetylation of **16a** and **17a** (1. MeONa/MeOH, 2. NaOH/H_2O–MeOH, 22 °C, 8 h) has led to carbohydrate dendrimers **16b** and **17b** bearing 12 and 24 monosaccharide residues, respectively.[23] Due to the high degree of symmetry in **16a/b–17a/b** rather simple NMR spectra were obtained, as was also the case for the galacto- and lacto-dendrimers (Tables 1 and 3). The internal noncarbohydrate part of the glycodendrimers was revealed most distinctly in ^{13}C-NMR spectra of the compounds recorded in D_2O. Except for the difference due to a different kind of linker there was a good agreement between chemical shifts of CH_2-group signals in spectra of **16b** and **17b** and signals of analogous galacto- and lacto-dendrimers (Tables 1 and 3). LSI-MS and MALDI-TOF mass-spectrometry have confirmed the structure of low generation dendrimers **16a** an **16b** (Table 2). Also, for these compounds no peculiarities in chiroptical behaviour were found as the optical rotation, $[\alpha]_D = 0$ in both cases.

4.3 Conclusion

By the current study we have demonstrated that modification of readily available DAB-*dendr*-$(NH_2)_x$ by mono- and disaccharides as well as by a clustered trisgalactoside can

be achieved using a common amide bond formation strategy. Notwithstanding the fact that exhaustive characterization of high molecular weight carbohydrate dendrimers represents a real challenge because of their polymeric nature, there is no indication for the presence of serious structural defects in these compounds. The use of acetylated saccharides at the stage of attachment to dendritic cores did not create steric hindrance interfering with the realization of condensation reactions. Obviously, after removal of protecting groups, the space between sugar residues increases, which should allow free motion of the latter due to a flexible spacer connecting the carbohydrates to the dendrimer. We successfully used spacer arms in the syntheses of galacto- and lacto-dendrimers. It is expected that the efficiency of attachment will be adversely affected by the application of a longer spacer-arm. From the biological standpoint an elongation of a spacer-arm may have a very positive effect on the ability of a carbohydrate dendrimer to form a strong complex with a protein receptor, as such elongation can provide an optimal distance between the carbohydrate ligands to guarantee optimal binding. Our results concerning the introduction of spacer-arms of various length between the dendrimer surface and the saccharide end groups are described in the next chapter.

4.4 Experimental section

General

Chemicals, including lactose and 1,2,3,4,6-penta-O-acetyl-β-D-galactose, were purchased from Aldrich. Poly(propylene imine) dendrimers **1a–5a** were supplied by DSM Research (The Netherlands). Compound **12** was prepared following a literature procedure.[21] For deacetylation reactions, anhydrous methanol was prepared by reflux over Mg and distillation. Thin layer chromatography (TLC) was carried out on aluminum sheets precoated with Kieselgel 60 F_{254} (Merck). The plates were inspected by UV light and developed with 5% H_2SO_4 in EtOH at 120 °C. Column chromatography was carried out using silica gel 60 F (Merck 40–63 μm). Gel permeation chromatography (GPC) was performed on a column (80 × 1.6 cm with V_0 ~ 60 mL) packed with Fractogel TSKHW-40(S) (Merck) in water. Fractions were monitored using a Differential Refractometer 141 supplied by Waters. ^{1}H-NMR Spectra were recorded on either a Bruker AC300 (300 MHz) spectrometer or a Bruker AMX400 (400 MHz) spectrometer with either the solvent reference or TMS as internal standards. ^{13}C-NMR Spectra were recorded on a Bruker AC300 (75.5 MHz) or a Bruker AMX400 (100.6 MHz) spectrometer using the PENDANT pulse train. Optical rotations were measured at 22±2 °C on a Perkin-Elmer 457 polarimeter. IR-spectra were taken on a Perkin-Elmer 1600 series FT-IR and data are given in cm^{-1}. Liquid secondary ion mass spectra (LSI-MS) were recorded on a VG Zabspec mass spectrometer equipped with a cesium gun operating at ~ 30 keV. Matrix assisted laser desorption ionization/time-of-flight mass spectra (MALDI-TOF-MS) were recorded on a Kratos Kompact MALDI III instrument using a 2,5-dihydroxybenzoic acid matrix. Microanalyses were performed at the University of North London Microanalytical Services.

3-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosylthio)propionic acid, 7

The title compound was prepared from the β-acetate **6** according to the literature[20] to afford a colorless oil in a yield of 88%. R_f = 0.67 (PhMe/EtOAc/AcOH = 80:19:1). ^{1}H-NMR ($CDCl_3$): δ 1.97, 2.04, 2.05, 2.14 (4 × s, 4 × 3H, CH_3CO), 2.74 (m, 2H, SCH_2CH_2), 2.93 (m, 2H, SCH_2CH_2), 3.91 (m, 1H, H-5), 4.08 (dd, $J_{5,6a}$ = 6.5 Hz, $J_{6a,6b}$ = 11.2 Hz, 1H, H-6a), 4.14 (dd, $J_{5,6b}$ = 7.0 Hz, 1H, H-6b), 4.53 (d, $J_{1,2}$ = 9.8 Hz, 1H, H-1), 5.03 (dd, $J_{2,3}$ = 10.0 Hz, $J_{3,4}$ = 3.5 Hz, 1H, H-3), 5.21 (pt, $J_{1,2} \approx J_{2,3}$ = 10 Hz, 1H, H-2), 5.41 (dd, $J_{4,5}$ = 1.0 Hz, 1H, H-4). ^{13}C-NMR ($CDCl_3$): δ 20.3, 20.4, 20.5 ($COCH_3$), 25.1 (SCH_2), 35.0 (CH_2CO_2H), 61.6 (C-6), 67.1 (C-2), 67.3 (C-4), 71.8 (C-3), 74.5 (C-5), 84.6 (C-1), 169.0–170.4 (4 x C, CH_3CO), 175.9 (CO_2H). $[\alpha]_D$ = –9 (c = 1.0, $CHCl_3$). A small portion of **7** was deacetylated by 0.1 M MeONa in MeOH, followed by deionization with Amberlite IR-120 (H^+), to give crude 3-(β-D-galactopyranosylthio)propionic acid. ^{1}H-NMR (D_2O): δ 2.67 (m, 2H, SCH_2CH_2), 2.87 (m, 2H, SCH_2CH_2), 3.44 (pt, $J_{1,2} \approx J_{2,3}$ = 9.7 Hz, 1H, H-2), 3.53 (d, $J_{3,4}$ = 3.4 Hz, 1H, H-3), 3.56–3.61 (m, 2H, H-5, H-6a), 3.65 (dd, $J_{5,6b}$ = 8.6 Hz, $J_{6a,6b}$ = 12.0 Hz, 1H, H-6b), 3.86 (dd, 1H, H-4), 4.38 (d, 1H, H-1). ^{13}C-NMR (D_2O): δ 27.7 (SCH_2), 37.5 (SCH_2CH_2), 63.6 (C-6), 71.3 (C-4), 72.1 (C-2), 76.45 (C-3), 81.4 (C-5), 88.6(C-1), 179.0 (C=O). MALDI-TOF-MS: *m/z* Calc. for $C_9H_{16}O_7S$: 268.1. Found: 290 $[M+Na]^+$.

N-Succinimidyl-3-(2,3,4,6-tetra-O-acetyl-β-D-galacto-pyranosylthio)propionate, 8

DCC (3.5 g, 17 mmol) and N-hydroxysuccinimide (1.9 g, 16.5 mmol) were added to a solution of **7** (7.2 g, 16.5 mmol) in $MeO(CH_2)_2OMe$ (50 mL) and the mixture was stirred at 0–10 °C for 20 h. The side product was removed by filtration, the filtrate was concentrated *in vacuo*, and the residue was dissolved in $CHCl_3$ (150 mL). The solution was filtered again, the filtrate was concentrated to *ca.* 50 mL and then poured into cyclohexane (250 mL). After decantation of the solvent, the remaining viscous oil was dissolved in a minimal amount of chloroform and precipitated again in cyclohexane. The solvent was decanted and the remaining oil was dried to give a white foam, **8** (7.1 g, 93%). R_f = 0.64 (PhMe/EtOAc = 7:3). ^{1}H-NMR ($CDCl_3$): δ 2.00, 2.06, 2.08, 2.17 (4 × s, 4 × 3H, CH_3CO), 2.86 (s, 4H, CH_2 of Suc), 2.96–3.17 (m, 4H, SCH_2CH_2), 3.97 (m, 1H, H-5), 4.14 (m, 2H, H-6a, H-6b), 4.59 (d, $J_{1,2}$ = 9.9 Hz, 1H, H-1), 5.07 (dd, $J_{2,3}$ = 10.0 Hz, $J_{3,4}$ = 3.3 Hz, 1H, H-3), 5.23 (pt, 1H, H-2), 5.44 (d, 1H, H-4). ^{13}C-NMR ($CDCl_3$): δ 20.5, 20.6 (2 x), 20.7 ($COCH_3$), 24.7 (SCH_2), 25.5 (CH_2 of Suc), 32.7 (CH_2CO_2-Suc), 61.6 (C-6), 66.9 (C-2), 67.2 (C-4), 71.7 (C-3), 74.5 (C-5), 84.1 (C-1), 167.0 (CH_2CO_2-Suc), 168.9 (C=O of Suc), 169.7, 170.0, 170.2, 170.5 (CH_3CO). $[\alpha]_D$ = –8.3 (c = 1.08, $CHCl_3$). MALDI-TOF-MS: *m/z* Calc. for $C_{21}H_{27}O_{13}NS$: 533.1. Found: 555 $[M+Na]^+$, 571 $[M+K]^+$.

3-[2,3,6-Tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-β-D-galacto-pyranosyl)-β-D-glucopyranosyl thio]propionic acid, 10

A solution of lactose heptaacetate **9** (13.0 g, 19.2 mmol, a mixture of α/β isomers, 1.0/3.7, prepared by acetylation of lactose with Ac_2O/NaOAc and 3-thiopropionic acid (6.7 mL, 77 mmol) in CH_2Cl_2 (100 mL) was treated with $BF_3{\cdot}OEt_2$ (3.5 mL, 28 mmol) and the mixture was left to stand for 5 h at room temperature, before being diluted with CH_2Cl_2 (100 mL) and washed with 1 M HCl (3 x 40 mL). The organic layer was dried, filtered and concentrated *in vacuo*. The product was isolated by column chromatography (PhMe/EtOAc/AcOH = 80:18:2) to afford **10** (7.4 g, 53%). R_f = 0.34 (PhMe/EtOAc/AcOH = 80:19:1). ^{1}H-NMR ($CDCl_3$): δ 1.97, 2.05, 2.12, 2.15 (4 × s, 7 × 3H, CH_3CO), 2.70 (m, 2H, CH_2CO_2H), 2.84 (m, 1H, SCHaHb), 2.94 (m, 1H, SCHaHb), 3.66 (m, 1H, H-5 Glc), 3.83 (pt, $J_{3,4} = J_{4,5}$ = 9.2 Hz, 1H, H-4 Gal), 3.91 (pt, $J_{5,6a} \approx J_{5,6b}$ = 7.5 Hz, 1H, H-5 Gal), 4.10 (m, 3H, H-6a Glc, H-6a Gal, H-6b Gal), 4.49 (m, 1H, H-6b Glc), 4.51 (d, $J_{1,2}$ = 7.6 Hz, 1H, H-1 Gal),

4.53 (d, $J_{1,2}$ = 9.2 Hz, 1H, H-1 Glc), 4.92 (pt, $J_{1,2} \approx J_{2,3}$ = 9.2 Hz, 1H, H-2 Glc), 4.99 (dd, $J_{2,3}$ = 10.4 Hz, $J_{3,4}$ = 3.4 Hz, 1H, H-3 Gal), 5.09 (dd, 1H, H-2 Gal), 5.19 (pt, 1H, H-3 Glc), 5.32 (d, 1H, H-4 Glc). ^{13}C-NMR ($CDCl_3$): δ 20.3, 20.4, 20.5 ($COCH_3$), 25.1 (SCH_2), 35.0 (CH_2CO_2H), 60.7 (C-6 Gal), 62.1 (C-6 Glc), 66.6 (C-4 Gal), 69.0 (C-2 Gal), 70.0 (C-2 Glc), 70.5 (C-5 Gal), 70.8 (C-3 Gal), 73.5 (C-3 Glc), 76.0 (C-4 Glc), 76.5 (C-5 Glc), 83.6 (C-1 Glc), 101.8 (C-1 Gal), 169.0–170.4 (7 x C, CH_3CO), 175.9 (CO_2H). $[\alpha]_D$ = –11 (c = 1.32, $CHCl_3$). MALDI-TOF-MS: *m/z* Calc. for $C_{29}H_{40}O_{19}S$: 724.2. Found: 747 $[M+Na]^+$, 763 $[M+K]^+$.

N-Succinimidyl 3-[2,3,6-tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-β-D-glucopyranosylthio]propionate, 11

Compound **10** (5.9 g, 8.1 mmol) was treated with NHS (0.95 g, 8.1 mmol) and DCC (1.83 g, 8.9 mmol) in $MeO(CH_2)_2OMe$ (25 mL) for 7 h at 0–5°C and the product was isolated, as described for the preparation of **8,** to give the ester **11** (6.3 g, 95%). R_f = 0.30 (PhMe/EtOAc/AcOH = 80:19:1. ^{1}H-NMR ($CDCl_3$): δ 1.97, 2.05, 2.12, 2.15 (4 × s, 7 × 3H, CH_3CO), 2.75–3.01 (m, 8H, $SCH_2CH_2CO_2$Suc), 3.61 (m, 1H, H-5 Glc), 3.72 (pt, $J_{3,4}$ = $J_{4,5}$ = 9.0 Hz, 1H, H-4 Gal), 3.85 (pt, $J_{5,6a}$= $J_{5,6b}$ = 7.5 Hz, 1H, H-5 Gal), 4.00–4.10 (m, 4H, H-6a, H-6b Glc, H-6a, H-6b Gal), 4.45 (d, $J_{1,2}$ = 7.6 Hz, 1H, H-1 Gal), 4.51 (d, $J_{1,2}$ = 9.0 Hz, 1H, H-1 Glc), 4.88 (pt, $J_{1.2} \approx J_{2,3}$ = 9.0 Hz, 1H, H-2 Glc), 4.90 (dd, $J_{2,3}$ = 10.0 Hz, $J_{3,4}$ = 3.4 Hz, 1H, H-3 Gal), 5.02 (dd, 1H, H-2 Gal), 5.16 (pt, 1H, H-3 Glc), 5.28 (d, 1H, H-4 Glc). ^{13}C-NMR ($CDCl_3$): δ 20.3–20.6 (7 x C, $COCH_3$), 24.5 (CH_2CO_2-Suc), 25.4 (SCH_2), 32.6 (CH_2CO_2-Suc), 60.6 (C-6 Gal), 61.9 (C-6 Glc), 66.9 (C-4 Gal), 68.8 (C-2 Gal), 70.0 (C-2 Glc), 70.4 (C-5 Gal), 70.8 (C-3 Gal), 73.3 (C-3 Glc), 75.9 (C-4 Gal), 76.5 (C-5 Glc), 83.3 (C-1 Glc), 100.6 (C-1 Gal), 167.0 (CH_2CO_2), 168.9 (CO Suc), 169.5–170.3 (CH_3CO). $[\alpha]_D$ = –11.7 (c = 1.04, $CHCl_3$). MALDI-TOF-MS: *m/z* Calcd. for $C_{33}H_{43}NO_{21}S$: 821.2. Found: 844 $[M+Na]^+$, 860 $[M+K]^+$.

General procedure for coupling of activated esters with PA-dendrimers.

To a solution of DAB-*dendr*-$(NH_2)_x$ dendrimer (about 50 mg that corresponds to approximately 0.16, 0.065, 0.03, 0.014, and 0.007 mmol of dendrimers **1a**, **2a**, **3a**, **4a**, and **5a,** respectively) in CH_2Cl_2 (10 mL), the activated ester **8** or **11** (0.65, 0.53, 0.48, 0.45, and 0.45 mmol for reactions with **1a**, **2a**, **3a**, **4a**, and **5a,** respectively) was added and the mixture was stirred for 18 h at room temperature. After dilution with CH_2Cl_2 (40 mL), the solution was washed with saturated aqueous Na_2CO_3 (5 x 30 mL, usually 1–3 h was required for the complete separation of layers), dried over Na_2SO_4, filtered and the filtrate concentrated to give a white solid foam which was dried *in vacuo*. Yields and $[\alpha]_D$ values are given in Table 4. ^{13}C-NMR and mass spectroscopic data are listed in Tables 1 and 2, respectively. To give an indication about the absorptions in ^{1}H-NMR spectra the data of compounds **1b** and **1c** are listed below.

Galactodendrimer 1b

^{1}H-NMR ($CDCl_3$): δ 1.35 (br m, 4H, $NCH_2(CH_2)_2CH_2N$), 1.58 (br m, 8H, $NCH_2CH_2CH_2N$), 1.92, 1.99, 2.00, 2.10 (4 x s, 48H, Ac) 2.25–2.55 (m, 20H, CH_2NCH_2 and CH_2NHCO), 2.82–3.02 (m, 8H, SCH_2), 3.21 (br m, 8H, CH_2CONH), 3.90 (pt, $J_{5,6a} \approx J_{5,6b}$ = 6 Hz, 4H, H-5 Gal), 4.03 (dd, $J_{5,6a}$ = 6.0 Hz, $J_{6a,6b}$ = 11 Hz, 4H, H-6a Gal), 4.11 (dd, $J_{5,6b}$ = 6.0 Hz, 4H, H-6b Gal), 4.52 (d, $J_{1,2}$ = 9.5 Hz, 4H, H-1 Gal), 5.00 (dd, $J_{2,3}$ = 9.5 Hz, $J_{3.4}$ = 3.0 Hz, 4H, H-3 Gal), 5.13 (pt, $J_{1,2} \approx J_{2,3}$ = 9.5 Hz, 4H, H-2 Gal), 5.37 (d, 4H, H-4 Gal), 6.80 (t, J = 5.0 Hz, 4H, NH).

Lactodendrimer 1c

^{1}H-NMR ($CDCl_3$): δ 1.39 (br m, 4H, $NCH_2(CH_2)_2CH_2N$), 1.63 (br m, 8H, $NCH_2CH_2CH_2N$), 1.97, 2.05, 2.06, 2.07, 2.10, 2.14 (6 x s, 84H, Ac), 2.33–2.50 (m, 20H, CH_2NCH_2 and CH_2NHCO), 2.86 (m, 4H, SCHaHb), 2.99 (m, 4H, SCHaHb), 3.28 (br m, 8H, CH_2CONH), 3.66 (m, 4H, H-5 Glc), 3.82 (pt, $J_{3,4} \approx J_{4,5}$ = 9.5 Hz, 4H, H-4 Glc), 3.93 (pt, $J_{5,6a} \approx J_{5,6b}$ = 6,8 Hz, 4H, H-5 Gal), 4.06–4.17 (m, 12H, H-6a Glc, H-6a Gal, H-6b Gal), 4.56 (d, $J_{1,2}$ = 8 Hz, 4H, H-1 Gal), 4.57 (d, $J_{1,2}$ = 10.0 Hz, 4H, H-1 Glc), 4.60 (br d, $J_{6a,6b}$ = 11 Hz, 4H, H-6b Glc), 4.91 (pt, $J_{1,2} \approx J_{2,3}$ = 9.5 Hz, 4H, H-2 Gal), 4.99 (dd, $J_{2,3}$ = 10.2 Hz, $J_{3,4}$ = 3.4 Hz, 4H, H-3 Gal), 5.11 (dd, $J_{1,2}$ = 8.0 Hz, $J_{2,3}$ =10.2 Hz, 4H, H-2 Gal), 5.21 (dd, $J_{2,3} \approx J_{3,4}$ = 9.5 Hz, 4H, H-3 Glc), 5.36 (d, $J_{3,4}$ = 3.4 Hz, 4H, H-4 Gal), 6.93 (br t, J = 5.3 Hz, 4H, NH).

General procedure for deacetylation of protected carbohydrate dendrimers 1b/c–5b/c.

A solution of acetylated glycodendrimer (200–400 mg) in a mixture of dry CH_2Cl_2 (2 mL) and dry MeOH (3 mL) was treated with 1 M MeONa in MeOH (0.5 mL) and stirred for about 15 min at room temperature. A white precipitate was formed and the mixture was concentrated *in vacuo* and the residue was dissolved in water (5–8 mL) and MeOH (1–2 mL). The solution was stirred overnight at room temperature, before being neutralized with 1 M HCl to pH 6, concentrated to 1 mL and subjected to GPC in H_2O. All fractions, which were detected by differential refractometry and eluted before salt, were collected, combined, concentrated and freeze-dried from H_2O to give white powders. The yields and $[\alpha]_D$ values are listed in Table 4, ^{13}C-NMR spectra of **1d/e–5d/e** are given in Table 3, mass spectroscopic data are listed in Table 2, and the C/S ratios from elemental analytical data are listed in Table 5. To give an indication about the absorptions in ^{1}H-NMR spectra, the data of compounds **1d** and **1e** are listed below.

Galactodendrimer 1d

^{1}H-NMR (100 °C, $(CD_3)_2SO$): δ 1.82 (m, 4H, $NCH_2CH_2CH_2CH_2N$), 1.92 (m, 8H, $NCH_2CH_2CH_2NHCO$), 2.46 (m, 8H, SCH_2CH_2CONH), 2.79–2.92 (m, 8H, SCH_2), 3.05–3.23 (2 x m, 12H and 8H, CH_2NCH_2 and CH_2NHCO), 3.35 (dd, $J_{2,3}$ = 9.3 Hz, $J_{3,4}$ = 3.4 Hz, 4H, H-3), 3.42 (pt, $J_{1,2} \approx J_{2,3}$ = 9.3 Hz, 4H, H-2), 3.44 (ddd, $J_{4,5}$ = 1.1 Hz, $J_{5,6a} = J_{5,6b}$ = 6,0 Hz, 4H, H-5), 3.55 (dd, $J_{6a,6b}$ = 13.2 Hz, 8H, H-6a, H-6b), 3.77 (dd, $J_{3,4}$ = 3.4 Hz, $J_{4,5}$ = 1.1 Hz, 4H, H-4), 4.27 (d, $J_{1,2}$ = 9.3 Hz, 4H, H-1), 7.78 (bs, 4H, NH). IR (KBr): ν 3395 (OH and NH stretch), 2962 (CH_2 stretch), 1654 (C=O stretch amide).

Lactodendrimer 1e

^{1}H-NMR (100 °C, $(CD_3)_2SO$): δ 1.82 (m, 4H, $NCH_2CH_2CH_2CH_2N$), 1.92 (m, 8H, $NCH_2CH_2CH_2NHCO$), 2.46 (m, 8H, SCH_2CH_2CONH), 2.79–2.92 (m, 8H, $SCH_2CH_2CO_2$), 3.05–3.23 (2 x m, 12H and 8H, CH_2NCH_2 and CH_2NHCO), 3.34–3.43 (m, 20H, H-2 and H-3 Gal, H-3, H-4, H-5 Glc), 3.48 (m, 4H, H-5 Gal), 3.55–3.63 (m, 8H, H-6a and H-6b Gal), 3.67 (dd, $J_{5,6a}$ = 4.8 Hz, $J_{6a,6b}$ = 12.4 Hz, 4H, H-6a Glc), 3.71 (dd, $J_{3,4}$ = 2.8 Hz, $J_{4,5}$ = 1.4 Hz, 4H, H-4 Gal), 3.82 (dd, $J_{5,6b}$ = 2.5 Hz, 4H, H-6b Glc), 4.23 (d, $J_{1,2}$ = 7.3 Hz, 4H, H-1 Gal), 4.23 (d, $J_{1,2}$ = 9.6 Hz, 4H, H-1 Glc), 7.80 (bs, 4H, NH). IR (KBr): ν 3396 (OH and NH stretch), 2943 (CH_2 stretch), 1659 (C=O stretch amide).

N'-[Tris(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyloxymethyl)methyl]glycinamide, 13

A solution of **12**[24] (3.08 g, 2.36 mmol) in EtOAc (30 mL) was hydrogenated over Pd/C (10%, 0.5 g) at 30 °C for 10 h, filtered through Celite and concentrated. The residue was subjected to column chromatography (SiO_2, EtOAc:EtOH 99:1 to 94:6) to give **13** (1.57 g, 61%). R_f = 0.20 ($CHCl_3$:Me_2CO = 5:1). ^{1}H-NMR ($CDCl_3$): δ 1.97, 2.05, 2.06, 2.15 (4 × s, 36H, $COCH_3$), 3.27 (s, 2H, NH_2), 3.82 (d, J = 10.0 Hz, 3H, C(quat)C*Ha*Hb), 3.91 (m, 4H, Ha Gly, H-5), 4.08–4.21 (m, 8H, H_b Gly, C(quat)CHa*Hb*, H-6a, H-6b), 4.42 (d, $J_{1,2}$ = 7.9 Hz, 3H, H-1), 5.01 (dd, $J_{2,3}$ = 10.2 Hz, $J_{3,4}$ = 3.2 Hz, 3H, H-3), 5.13 (dd, 3H, H-2), 5.37 (d, 3H, H-4), 7.20 (s, 1H, C(quat)NH). ^{13}C-NMR ($CDCl_3$): δ 20.5, 20.6 (2 x), 20.8 ($COCH_3$), 45.3 (CH_2NH_2), 58.7 (C(quat)), 61.0 (C-6), 68.1 (C(quat)CH_2), 66.9 (C-4), 69.0 (C-2), 70.6 (C-3), 70.7 (C-5), 101.4 (C-1), 169.4, 170.0, 170.2, 170.4 (CH_3CO), 173.0 (CONH). $[\alpha]_D$ = –14.3 (c = 1.05, $CHCl_3$); MALDI-TOF-MS *m/z*: Calc. for $C_{48}H_{68}N_2O_{31}$: 1168.4. Found: 1191 $[M+Na]^+$, 1208 $[M+K]^+$.

4-{N'-[Tris(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyloxymethyl)methyl]methylamino-carbonylmethylaminocarbonyl}butanoic acid, 14

Glutaric anhydride (170 mg, 1.5 mmol) was added to a solution of the amine **13** (1.57 g, 1.34 mmol) in CH_2Cl_2 (10 mL), and the mixture was stirred for 4 h at 20 °C, concentrated, and the product was purified by column chromatography (SiO_2, EtOAc:EtOH 99:1 to 94:6) to afford the corresponding acid **14** (1.28 g, 75%); R_f = 0.39 ($CHCl_3$:Me_2CO = 5:1). ^{1}H-NMR ($CDCl_3$): δ 1.96–2.02 (m, 11H, $COCH_3$ and $CH_2CH_2CH_2$), 2.09, 2.18 (2 × s, 27H, 2 × $COCH_3$), 2.37–2.46 (m, 4H, $CH_2CH_2CH_2$), 3.78 (d, $J_{Ha,Hb}$ = 10.3 Hz, 3H, C(quat)C*Ha*Hb), 3.87 (dd, J = 4.8, J = 6.8, 1H, Ha Gly), 3.97 (pt, $J_{5,6a} \approx J_{5,6b}$ = 7 Hz, 3H, H-5), 3.98 (m, 1H, Hb Gly), 4.14 (dd, $J_{5,6a}$ = 6.1 Hz, $J_{6a,6b}$ = 11.2 Hz, 3H, H-6a), 4.14 (d, 3H, C(quat)CHa*Hb*), 4.20 (dd, $J_{5,6b}$ = 6.7 Hz, 3H, H-6b), 4.45 (d, $J_{1,2}$ = 7.7 Hz, 3H, H-1), 5.05 (dd, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = 3.3 Hz, 3H, H-3), 5.13 (dd, 3H, H-2), 5.40 (d, 3H, H-4), 6.39 (s, 1H, C(quat)NH), 6.94 (t, J = 5.2 Hz, 1H, NH Gly). ^{13}C-NMR ($CDCl_3$): δ 20.3, 20.4, 20.5, 20.6 (CH_3CO and $CH_2CH_2CH_2$), 32.7, 34.6 ($CH_2CH_2CH_2$), 42.6 (CH_2 Gly), 59.3 (C(quat)), 60.9 (C-6), 66.8 (C-4), 67.9 (C(quat)CH_2), 68.9 (C-2), 70.4 (C-3), 70.7 (C-5), 101.2 (C-1), 169.5 (NHCO Gly), 169.4, 169.8, 170.0, 170.2 (CH_3CO), 172.7 (C(quat)NH*CO*), 175.9 (CO_2H). $[\alpha]_D$ = –14.0 (c = 1.04, $CHCl_3$). MALDI-TOF-MS *m/z*: Calc. for $C_{53}H_{74}N_2O_{34}$; 1282.4. Found: 1306 $[M+Na]^+$, 1321 $[M+K]^+$. Elem. anal.: Calcd. C, 49.61; H, 5.81; N, 2.18. Found: C, 49.68; H, 5.71; N 2.08.

N-Succinimidyl 4-{N'-[tris(2,3,4,6-tetra-O-acetyl-β-D-galacto-pyranosyloxymethyl)methyl]-methylaminocarbonylmethylaminocarbonyl}butanoate, 15

A solution of the acid **14** (1.11 g, 0.87 mmol), DCC (206 mg, 1.0 mmol), and N-hydroxysuccinimide (103 mg, 0.9 mmol) in $MeO(CH_2)_2OMe$ (10 mL) was stirred for 17 h at 4–10 °C. The workup procedure, which was analogous to that described for **8**, afforded a syrupy mass of the activated ester **15** (1.14 g, 95%). ^{1}H-NMR ($CDCl_3$): δ 1.99 (s, 11H, $COCH_3$, $CH_2CH_2CH_2$), 2.08 (s, 18H, $COCH_3$), 2.17 (s, 9H, $COCH_3$), 2.42 (t, J = 7.2 Hz, 2H, CH_2CH_2CONH), 2.73 (t, J = 7.2 Hz, 3H, CH_2CO_2-Suc), 3.77–3.82 (m, 4H, Ha Gly, C(quat)C*Ha*Hb), 3.96–4.01 (m, 4H, Hb Gly, H-5), 4.11–4.22 (m, 9H, C(quat)CHa*Hb*, H-6a, H-6b), 4.44 (d, $J_{1,2}$ = 7.8 Hz, 3H, H-1), 5.03 (dd, $J_{2,3}$ = 10.4 Hz, $J_{3,4}$ = 3.4 Hz, 3H, H-3), 5.13 (dd, 3H, H-2), 5.39 (d, 3H, H-4), 6.23 (s, 1H, C(quat)NH), 6.56 (m, 1H, NH Gly). ^{13}C-NMR ($CDCl_3$): δ 20.2, 20.3, 20.4, 20.5 (CH_3CO, $CH_2CH_2CH_2$), 25.3 (CH_2 Suc), 29.7, 33.8 ($CH_2CH_2CH_2$), 42.8 (CH_2 Gly), 58.9 (C(quat)), 60.9 (C-6), 67.8 (C(quat)CH_2), 66.7 (C-4), 68.7 (C-2), 70.3, 70.5 (C-3, C-5), 101.2 (C-1), 168–171.8 (C=O). $[\alpha]_D$ = –13.4 (c = 1.0, $CHCl_3$).

Glycodendrimer 16a

This compound was prepared starting from **1a** (22 mg, 0.07 mmol) and **15** (398 mg, 0.228 mmol) according to the general procedure for coupling of activated esters with PA-dendrimers. Yield 340 mg (90%), ^{1}H-NMR ($CDCl_3$): δ 1.40 (br m, 4H, $NCH_2(CH_2)_2CH_2N$), 1.64 (m, 8H, $NCH_2CH_2CH_2N$), 1.98 (br s, 20H, $COCH_3$ and $COCH_2CH_2CH_2CO$), 2.08, 2.17 (2 × s, 36H, CH_3CO), 2.22–2.45 (m, 28H, $COCH_2CH_2CH_2CONH(CH_2)_2CH_2NCH_2$), 3.26 (m, 8H, CH_2NHCO), 3.78 (d, 3H, $J_{Ha,Hb}$ = 10.2 Hz, C(quat)CHaHb), 3.86 (m, 4H, Ha Gly), 3.98 (pt, $J_{5,6a} \approx J_{5,6b} \approx 7$ Hz, 12H, H-5), 4.11–4.21 (m, 28H, H-6a, H-6b, C(quat)CHa*Hb*), 4.46 (d, $J_{1,2}$ = 7.7 Hz, 12H, H-1), 5.05 (dd, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = 3.3 Hz, 12H, H-3), 5.13 (dd, 12H, H-2), 5.39 (d, 12H, H-4), 6.28 (s, 4H, C(quat)NH), 6.84 (t, J = 5 Hz, 4H, NHCO Gly), 7.09 (t, J = 5 Hz, 4H, NHCO dendrimer). ^{13}C-NMR ($CDCl_3$) δ 20.4, 20.5, 20.6, 20.7 (CH_3CO and $COCH_2CH_2CH_2CO$), 25.8, 27.0 ($CH_2CH_2CH_2$), 33.8, 34.9, 35.3, 38.2 ($COCH_2CH_2CH_2CO$, $CH_2CONHCH_2$), 42.7 (CH_2 Gly), 49.3, 52.0 (CH_2NCH_2), 59.2 (C(quat)), 67.0 (C-6), 66.8 (C-4), 68.0 (C(quat)CH_2), 68.9 (C-2), 70.4 (C-3), 70.6 (C-5), 101.2 (C-1), 168.8 (NHCO dendrimer), 169.3, 169.9, 170.0, 170.3 (CH_3CO), 172.6, 172.8, (C(quat)NHCO, NHCO Gly). $[\alpha]_D$ = –11.6 (c = 1.0, $CHCl_3$). MALDI-TOF-MS (Table 2).

Glycodendrimer 17a

This compound was prepared as described previously for **16a** starting from **2a** and **15** in a 84% yield. $[\alpha]_D$ = –11.6 (*c* = 1.0, $CHCl_3$).

Glycodendrimer 16b

This compound was prepared in 74% yield by deacetylation of **16a** as described in the general procedure. ^{1}H-NMR ($(CD_3)_2SO$, 100 °C): δ 1.74–1.93 (m, 20H, $NCH_2CH_2CH_2NHCO$, $COCH_2CH_2CH_2CO$, $NCH_2CH_2CH_2CH_2N$), 2.12–2.24 (m, 16H, $COCH_2CH_2CH_2CO$), 3.06–3.20 (m, 20H, CH_2NCH_2 and CH_2NHCO), 3.30–3.40 and 3.52–3.65 (2 x m, 48H, H-2, H-3, H-5, H-6), 3.69 (m, 20H, CH_2 Gly and H-4), 3.83 (d, J = 10 Hz, 12H, C(quat)CHaHb), 4.06 (d, 12H, C(quat)CHa*Hb*), 4.17 (d, $J_{1,2}$ = 8 Hz, 12H, H-1), 6.85 (s, 4H, NHCO Gly), 7.65 (br s, 8H, $NHCO(CH_2)_3CONH$). $[\alpha]_D$ = +0.3 (*c* = 1.2, H_2O). ^{13}C-NMR and MS data are listed in Tables 3 and 2, respectively.

Glycodendrimer 17b

This compound was prepared as described for **16b** in 67% yield. $[\alpha]_D$ = 0 (c = 1.0, H_2O). The ^{13}C-NMR spectroscopic data are listed in Table 3.

4.5 References

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5 Synthesis of spacer-armed glucodendrimers based on the modification of poly(propylene imine) dendrimers

Summary

The use of poly(propylene imine) dendrimers (DAB-dendr-$(NH_2)_x$) with reactive primary amine end groups proved to be very useful for the construction of saccharide surface-coated dendrimers. For this purpose, amide bonds were introduced by a reaction of the primary amine end groups of the dendrimers with N-succinimidyl activated esters of spacer-armed, acetyl-protected thioglucopyranoside units. The linear alkyl-chain spacer between the dendrimer surface and the saccharide units was varied in length from 1 via 5 to 10 carbon atoms. These spacer-arms were introduced to determine the influence of local saccharide surface concentration variations on the dendrimer properties. After modification of the dendrimers with these saccharide units, the acetyl protecting groups were removed. Purification of these derivatives was accomplished by dialysis either in water or in aqueous methanol. The solubility of the resulting glucodendrimers proved to be strongly dependent on the hydrophobic part, i.e. the alkyl-chain spacers in the molecule. Therefore, these nanosized multivalent structures, which could be more appropriate for studying carbohydrate–protein interactions, might also be very useful for investigating amphiphilic properties.

5.1 Introduction

Dendrimers are very promising candidates for applications in biology, especially when cooperative and clustering effects within a molecule are of importance.[1–5] Since the first patents by Denkewalter,[6] many structures have been reported based on dendrimers with biologically active appendages such as antibodies,[7] amino acids[1,2,8] and saccharide residues. With respect to the multivalent cooperative effects, saccharide-coated dendrimers (glycodendrimers) have been proven very useful in studying carbohydrate–protein interactions. Recently, a series of papers describing these saccharide dendrimers appeared in the literature. Okada's[9] 'sugar-balls' as well as Lindhorst's[10] dendrimers were designed for

this purpose, using the PAMAM dendrimers as starting material. Stoddart *et al.*[11] have developed their own saccharide-based dendrimers, and biological studies have been performed on these structures.[11e] In chapter 4 we have already reported on the modification of poly(propylene imine) dendrimers with saccharide residues.[12] Roy and coworkers[13] recently disclosed from a biological study, carried out by them, that clustered saccharides were much more active in an inhibitory lectin binding study than the corresponding free saccharide moieties, emphasizing the importance of cooperative effects in these clustered neoglycoconjugates. Unfortunately, these effects were only observed with relatively small molecules. Larger structures exhibited no significant activity, most likely as a result of the fact that the local saccharide concentration is too large, leading to inefficient binding to the specific carbohydrate binding sites in the protein. Analogous results were obtained by Seebach[14] in the enzymatic hydrolysis of his biologically active ester-based dendrimers, where hydrolysis only proved to be possible in the case of less crowded systems. In this chapter, we report on the synthesis of large dendritic structures with variations of the "local saccharide concentration" on the dendrimer surface. Control of "local concentration" was achieved by the introduction of a linear alkyl chain spacer between the dendrimer surface and the saccharide units. By varying the linear alkyl-chain spacer length from 1, *via* 5 to 10 carbon atoms we were also able to study the relationship between structure and water solubility. With the unimolecular micelle concept[15] in mind, it is also reasonable to investigate the hydrophilic and hydrophobic interactions within this type of structures, since we are increasing the hydrophobic character of the molecule upon going to longer alkyl-chain spacer lengths.

5.2 Results and discussion

5.2.1 Synthetic strategy

As the basis for our modification, we used the divergently synthesized poly(propylene imine)dendrimers,[16] which are well-known for their ease of undergoing alterations at the peripheral primary amine groups. Here, we studied the modification of the dendrimer of the first generation (**1a**) with 4 primary amine end groups and of the fifth generation (**1b**) with 64 end groups (Figure 1). Although the end groups are reactive toward many reagents, we chose a mild coupling method well-known from peptide chemistry, namely, the reaction with the N-succinimidyl activated ester, to smoothly afford amide bonds. Previously, we have used this coupling method successfully for the construction of the unimolecular micelles,[15] the dendritic box[1,2] and derivatized saccharide dendrimers.[12] This synthetic strategy implies the

use of acetyl protecting groups on the saccharide unit to circumvent side reactions during subsequent chemical modifications. These acetyl protecting groups can be easily removed after attachment of the monosaccharide units to the dendrimers, by standard deprotection techniques, and finally lead to compounds **9a–9c** (Figure 1).

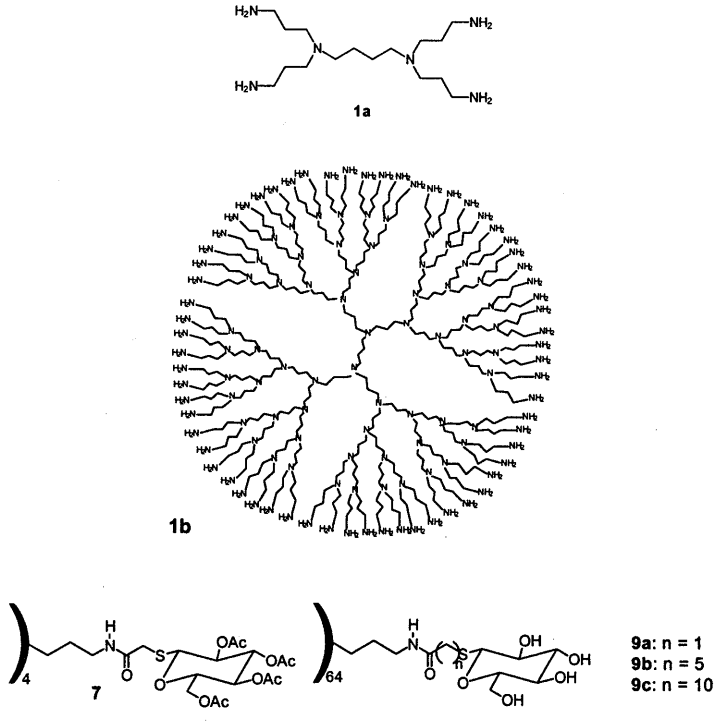
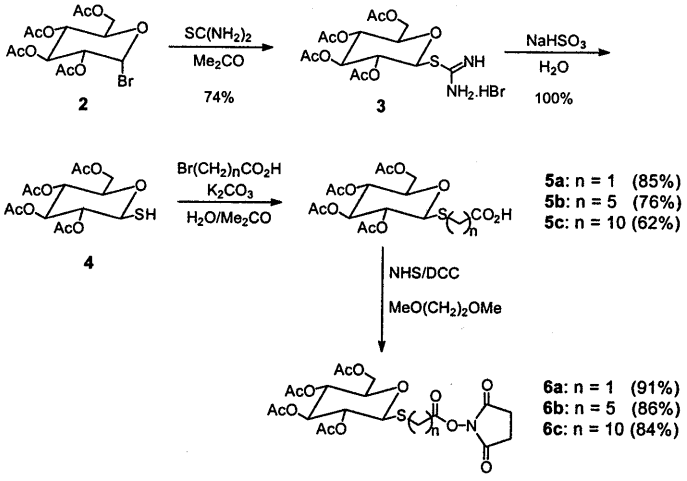


Figure 1. *Structural formulas of the first (**1a**) and fifth generation (**1b**) poly(propylene imine) dendrimers and glucodendrimers 7 and **9a–9c**.*

5.2.2 Saccharide residues

D-(+)-Glucose was used as the source of the saccharide precursors (Scheme 1 and Table 1). Starting from bromo-2,3,4,6-tetra-O-acetyl-α-D-glucopyranose **2**, the thiouronium salt **3** was prepared by a reaction with thiourea in acetone, following a literature procedure.[17] The salt was converted into the corresponding mercaptane by reaction of **3** with sodium hydrogensulfite in water, to furnish **4** in a quantitative yield.[18] Compound **4** was the key intermediate in the synthesis of all spacer-armed thioether-linked saccharide residues.[19] They could be prepared by reaction of **4** with bromoacetic acid to give **5a**, 6-bromohexanoic acid to give **5b** and 11-bromoundecanoic acid to give **5c** using K_2CO_3 as a base.[18] Purification of these compounds was accomplished by column chromatography to furnish **5a**, **5b** and **5c** in

yields of 85, 76 and 62%, respectively. The N-succinimidyl activated esters **6a**, **6b** and **6c** were obtained by a reaction of **5a**, **5b** and **5c** with N-hydroxysuccinimide under the influence of DCC in dimethoxyethane as a solvent[20] in yields of 91, 87 and 84%, respectively.



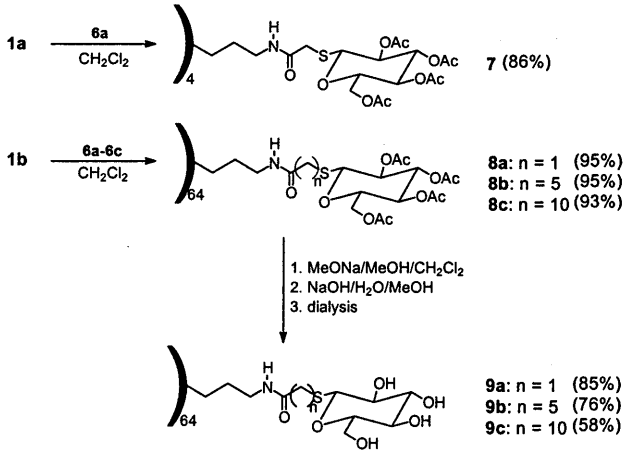
Scheme 1. *Syntheses of 1-thio-β-D-glucopyranose derivatives **6a–6c** for attachment to the poly(propylene imine) dendrimers.*

Table 1. *Yields, optical rotations and mass spectral data for the dendrimer precursors.*

Compound	Yield (%)	$[\alpha]_D^{20}$ (c = 1, CH_2Cl_2)	Calculated molec. mass	MALDI-TOF-MS
4	100	+3.6	364.1	365[M+H]$^+$ 387[M+Na]$^+$
5a	85	–48	422.1	445[M+Na]$^+$ 467[M+2Na]$^+$
5b	76	–33	478.2	501[M+Na]$^+$
5c	62	–29	548.2	571[M+Na]$^+$ 593[M+2Na]$^+$
6a	91	–59	519.1	541[M+Na]$^+$ 557[M+2Na]$^+$
6b	87	–24	575.2	597[M+Na]$^+$
6c	84	–20	645.3	668[M+Na]$^+$ 685[M+K]$^+$

5.2.3 Saccharide modified poly(propylene imine) dendrimers

The desired acetylated glucodendrimers were obtained by coupling of the N-succinimidyl esters **6a–6c** to the poly(propylene imine) dendrimers (**1a** and **1b**) using CH_2Cl_2 as the solvent (Scheme 2). Purification was accomplished by extraction of the diluted reaction mixtures with saturated aqueous Na_2CO_3. The glucodendrimer **7** was constructed as a model compound from the first generation dendrimer (**1a**) modified with **6a**. This compound was fully characterized by ^{1}H-NMR, ^{13}C-NMR and IR spectroscopy and by MALDI-TOF-MS. Likewise, the other glucodendrimers **8a–8c** were synthesized (Scheme 2) starting from the fifth generation dendrimer with 64 primary amine end groups (**1b**) by reaction with the activated esters **6a–6c**, using the same reaction conditions and work-up procedure. Removal of the acetyl protecting groups was accomplished by standard Zemplén deacetylation,[21] leading to **9a–9c**, which could be purified by dialysis either in water (for **9a** and **9b**) or in aqueous methanol (for **9c**).



Scheme 2. *Coupling of the appropriate saccharide units with the primary amine end groups of the dendrimers.*

5.2.4 Structure determination of the glucodendrimers

Successful coupling between the activated esters **6a–6c** and dendrimers **1a** and **1b** was established by NMR and IR spectroscopy. Compound **7** was fully characterized using ^{1}H- and ^{13}C-NMR spectroscopy, as well as IR spectroscopy and MALDI-TOF-MS. In the ^{1}H-NMR spectrum signals for the CH_2 part of the dendrimer resonate at δ = 1.45, 1.69, 2.47, 2.51 and 3.28, whereas the newly formed amide bond NH protons give a triplet at δ = 7.34. Also the absorptions of the saccharide part, as well as of the acetyl-protecting groups, appear as a set

of well-resolved signals (δ = 3.27–5.24 ppm and δ = 2.01–2.09 ppm, respectively). The ^{13}C-NMR spectrum of **7** shows characteristic signals for the dendrimer part at δ = 24.0, 26.2, 38.0, 51.0 and 53.2 ppm. The absorptions of the methyl carbon atoms of the acetyl protecting groups are found in the region 20.5–20.7 ppm, whereas the saccharide part resonates as a set of 6 signals between 62 and 83 ppm. The carbonyl absorptions of the newly formed amide bond, as well as the acetyl protecting groups, overlap in the region of δ = 169–171 ppm. In the IR spectrum, the newly formed amide bond features an absorption band at a wavenumber of 3388 cm^{-1}. Characterization of this compound by MALDI-TOF-MS nicely showed peaks at *m/z* 1937 and 1959, corresponding to the $[M+H]^+$ and $[M+Na]^+$ species, respectively. The assignment of the resonances for the saccharide part in the NMR spectra was based on the unambiguous peak assignments that could be deduced from COSY and XHCORRD measurements carried out on compound **5a**. No large ^{1}H- and ^{13}C-NMR spectral shifts of the succinimide esters **6a–6c** and the dendrimers **7** and **8a–8c** were observed, compared to the spectra of **5a**.

Dendrimers **8a–8c** were characterized solely by ^{13}C-NMR and IR spectroscopy, since in the ^{1}H-NMR spectra the absorptions were considerably broadened with signals overlapping, even when the spectra were recorded at elevated temperatures.[12] The saccharide part is found in each case as six separate, nicely resolved signals in the region of δ = 62–83 ppm. Signals for the spacer part of the molecule resonate at δ = 25–36 ppm. The newly-formed amide bond is characterized by a signal in the same region (δ = 168.9–170.7), as that for the acetyl protecting groups. Typical absorptions for the dendrimer part of the molecules in the ^{13}C-NMR spectrum are found at δ = 24 and 53 ppm approximately, together with an absorption at δ = 37 ppm (CH_2NH). ^{13}C-NMR spectra also provide information on the completeness of the reaction, since unreacted CH_2NH_2 functions should give rise to signals at δ = 40 ppm. In the cases of dendrimers **8a–8c**, no signal could be detected in this region, indicating that the reaction was at least near completion.

Deprotection of the acetyl groups was performed using the standard Zemplén procedure,[21] furnishing dendrimers **9a–9c** in yields of 85, 76 and 58%, respectively. Characterization of these compounds was accomplished by ^{13}C-NMR spectroscopy. Well-resolved spectra were obtained (Figure 2) for **9a** and **9b** in D_2O as the solvent, whereas for **9c**, difficulties were encountered as a result of the low solubility of this compound both in D_2O and CD_3OD. The best solubility has been obtained so far with mixtures of D_2O and CD_3OD at elevated temperatures (60 °C). However, even at this temperature, the sample remained turbid. The ^{13}C-NMR spectrum of **9c** shows some well-resolved absorptions for the saccharide part in the range of δ = 63–87 ppm. The absorptions arising from the spacer part, as well as from the dendrimer part, are considerably broadened compared to those in the other glucodendrimers, especially for the carbonyl group, which appears as a very broad signal

around 177 ppm in the ^{13}C-NMR spectrum. Generally for the deprotected compounds **9a–9c**, the signals attributable to the dendrimer part are located at δ-values of approximately 25, 39 and 53 ppm, whereas the signals corresponding to the spacer part range from 27 to 38 ppm. The saccharide part of the spectra represent a set of well-resolved signals between δ = 63–87 ppm, and the amide carbonyl absorption is observed in the region of 175–180 ppm. Completeness of deprotection could be deduced from the disappearance of the signals in the regions 20–21 and 169–171 ppm.

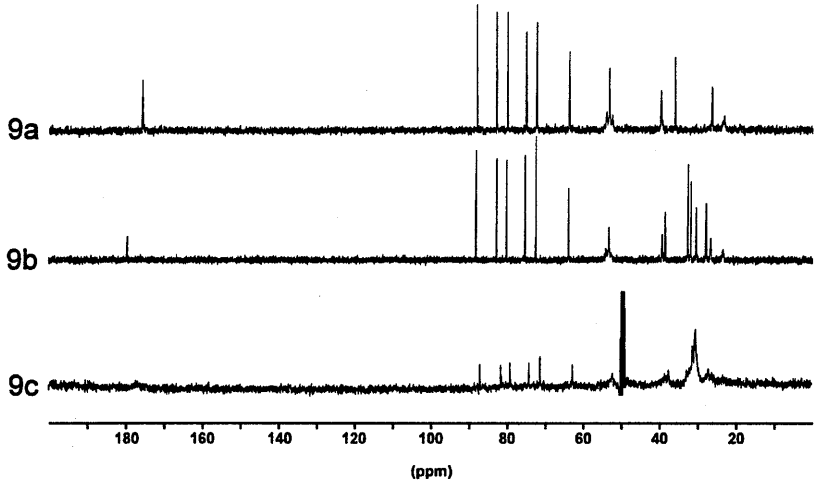


Figure 2. *The ^{13}C-NMR spectra of glucodendrimers **9a–9c**.*

The chiroptical properties of these compounds (Table 2) were studied by polarimetry. However, for a good comparison it is better to calculate the molar rotations per saccharide unit ($[\Phi]_D/n$) for these compounds. The optical rotation of **9c** could not be determined on account of its poor solubility and turbidity of the solution. From the molar rotation per end group, ranging from –108 to –191, no clear trend can be observed within this series.

Table 2. *Yields and chiroptical data of the spacer armed glucodendrimers.*

Compound	Yield (%)	$[\alpha]_D^{20}$	Calculated molec. mass	$[\Phi]_D/n$
7	86	–34 (c = 1, CH_2Cl_2)	1,934.10	–164
8a	95	–37 (c = 0.5, $CHCl_3$)	33,048.89	–191
8b	95	–28 (c = 0.6, $CHCl_3$)	36,639.93	–160
8c	93	–17 (c = 0.6, $CHCl_3$)	41,128.25	–109
9a	85	–31 (c = 1.8, H_2O)	22,287.50	–108
9b	76	–29 (c = 2.3, H_2O)	25,878.36	–117
9c	58	–	30,366.93	–

5.3 Conclusion

In this chapter, we have described the successful preparation of spacer-armed poly(propylene imine) glucodendrimers based on a modification of the peripheral primary amine groups with N-succinimidyl activated esters of various alkyl-chain spacer-armed thioglucoside species to form amide bonds. The linear spacer length between the dendrimer surface and the saccharide units has been varied from 1 *via* 5 to 10 carbons in order to study the effect of a decrease in the "local saccharide concentration" on the dendritic surface. On account of the fact that the parent higher generations of poly(propylene imine) dendrimers exhibit some degree of polydispersity,[16c] dendrimers **8a–8c** and **9a–9c** cannot be characterized using the normal mass spectrometric techniques. However, model compound **7** could still be fully characterized by ^{1}H- and ^{13}C-NMR spectroscopic techniques as well as by IR spectroscopy and MALDI-TOF-MS. Similarly, the dendrimers of the fifth generation could be synthesized and characterized. The (near) completeness of the reaction was monitored using ^{13}C-NMR spectroscopy. Deprotection of these dendrimers was achieved by the standard Zemplén deacetylation techniques.[21] The reaction products were purified using dialysis in water (**9a** and **9b**) or aqueous methanol (**9c**). No signals could be detected corresponding to the acetyl groups in ^{13}C-NMR spectra.

In conclusion, we have described a synthetic approach toward globular nanosized structures with varying surface densities of biologically active saccharide residues, thus making interactions with specific carbohydrate binding sites in proteins possible. Moreover, these compounds should be very useful in probing hydrophilic and hydrophobic interactions since the hydrophobic part of the molecule increases on going to the longer alkyl-chain spacers. This feature was exemplified by the solubility behavior of the dendrimer with the C-10 spacer arm, which proved to be barely soluble both in water and methanol.

5.4 Experimental section

General

Compound **2** was obtained from Aldrich and **3** was prepared following a literature procedure.[17] The poly(propylene imine) dendrimers **1a–1b** were supplied by DSM Research (The Netherlands). Thin layer chromatography (TLC) was performed on aluminum sheets coated with Kieselgel 60 F_{254} (Merck). The plates were developed by treatment with 5% H_2SO_4 in EtOH at 120 °C. Column chromatography was carried out using silica gel 60 F (Merck 40–63 μm). Dialysis was performed using Medicell dialysis tubing with size 2 Inf Dia 18/32" - 14.3 mm and a molecular weight cutoff of 12,000–14,000 Dalton. Melting points are uncorrected and were determined with a Jeneval microscope equipped with a Linkam hot stage. Optical rotations ($[\alpha]_D^{20}$) were measured with a Jasco DIP-370 digital polarimeter. NMR spectra were recorded on a Bruker AM-400 spectrometer at frequencies of 400.1 MHz and 100.6 MHz for ^{1}H- and ^{13}C-nuclei, respectively. Tetramethylsilane (TMS) was used as an internal standard and data are given in ppm. IR-spectra were taken on a Perkin Elmer 1600 series FT-IR and data are given in cm^{-1}. Matrix assisted laser desorption ionization/time of flight mass measurements (MALDI-TOF-MS) were recorded on a Kratos Kompact MALDI III instrument using a 2,5-dihydroxybenzoic acid matrix. The mass spectral data for compounds **4–6** are listed in Table 1.

2,3,4,6-Tetra-O-acetyl-1-thio-β-D-glucopyranose, 4

To a solution of **3** (9.75 g, 20.0 mmol) in water (100 mL) an aqueous solution of sodium bisulfite (10.50 g, 10.0 mmol in 35 mL of water) was added. This mixture was allowed to stand for 5 min and subsequently placed in an ice bath for 2 h. A white precipitate was formed which was extracted with CH_2Cl_2 (3 x 50 mL). The organic layers were combined, washed with water (2 x 25 mL) and dried with Na_2SO_4. Evaporation of the solvent furnished pure **4** (7.29 g, 100%) as a white solid. m.p. 118 °C. ^{1}H-NMR ($CDCl_3$): δ 2.01, 2.03, 2.07, 2.09 (4 x s, 4 x 3H, CH_3CO), 2.34 (d, J = 10.0 Hz, 1H, SH), 3.75 (ddd, $J_{4,5}$ = 9.9 Hz; $J_{5,6a}$ = 4.7 Hz; $J_{5,6b}$ = 2.2 Hz, 1H, H-5), 4.13 (dd, $J_{6a,6b}$ = 12.4 Hz; $J_{5,6b}$ = 2.0 Hz, 1H, H-6b), 4.26 (dd, $J_{6a,6b}$ = 12.4 Hz; $J_{5,6a}$ = 4.8 Hz, 1H, H-6a), 4.57 (pt, $J_{1,SH} \approx J_{1,2}$ = 9.9 Hz, 1H, H-1), 4.98 (pt, $J_{1,2} \approx J_{2,3}$ = 9.5 Hz, 1H, H-2), 5.11 (pt, $J_{3,4} \approx J_{4,5}$ = 9.7 Hz, 1H, H-4), 5.20 (pt, $J_{2,3} \approx J_{3,4}$ = 9.4 Hz, 1H, H-3). ^{13}C-NMR ($CDCl_3$): δ 20.5, 20.6 (CH_3CO), 61.9 (C-6), 68.0 (C-4), 73.4 (2 x, C-2, C-3), 76.2 (C-5), 78.6 (C-1), 169.2, 169.5, 170.0, 170.5 (CH_3CO). IR (KBr): ν 2969 and 2890 (CH_3 stretch), 1741 (C=O stretch), 1240 ($OCOCH_3$ stretch). $[\alpha]_D^{20}$ = +3.6 (c = 1.07, CH_2Cl_2).

1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosylthio)acetic acid, 5a

To a stirred solution of **4** (1.82 g, 5.00 mmol) and bromoacetic acid (0.70 g, 5.0 mmol) in acetone (5 mL) a K_2CO_3 solution (0.69 g, 5.0 mmol in 5 mL of water) was added. Stirring was continued for 2 h, after which the reaction mixture was acidified with acetic acid (0.5 mL) and subsequently extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification of the residue was accomplished by column chromatography (SiO_2: PhMe:EtOAc:AcOH, 50:50:2. R_f = 0.3), which furnished pure **5a** (1.80 g, 85%) as a white solid. m.p. 123–124 °C. ^{1}H-NMR ($CDCl_3$): δ 2.02, 2.04, 2.07, 2.10 (4 x s, 4 x 3H, CH_3CO), 3.33, 3.57

(2 x d, J = 15.4 Hz, 2H, CH_2CO_2H), 3.76 (ddd, $J_{4,5}$ = 10.0 Hz; $J_{5,6a}$ = 4.5 Hz; $J_{5,6b}$ = 2.3 Hz, 1H, H-5), 4.15 (dd, $J_{6a,6b}$ = 12.4 Hz; $J_{5,6b}$ = 2.2 Hz, 1H, H-6b), 4.22 (dd, $J_{6a,6b}$ = 12.5 Hz; $J_{5,6a}$ = 4.7 Hz, 1H, H-6a), 4.69 (d, $J_{1,2}$ = 10.0 Hz, 1H, H-1), 5.07 (pt, $J_{1,2} \approx J_{2,3}$ = 9.5 Hz, 1H, H-2), 5.11 (pt, $J_{3,4} \approx J_{4,5}$ = 9.8 Hz, 1H, H-4), 5.26 (pt, $J_{2,3} \approx J_{3,4}$ = 9.3 Hz, 1H, H-3), 10.62 (s, 1H, CO_2H). ^{13}C-NMR ($CDCl_3$): δ 20.5, 20.6 (CH_3CO), 30.9 (CH_2CO_2H), 61.8 (C-6), 68.0 (C-4), 69.5 (C-2), 73.5 (C-3), 75.9 (C-5), 82.1 (C-1), 169.4, 169.5, 170.1, 170.9 (CH_3CO), 174.7 (CO_2H). IR (KBr): ν 3167 (CO_2H stretch), 2967 (CH_3 stretch), 1745, 1255 (C=O stretch), 1227 ($OCOCH_3$ stretch). $[\alpha]_D^{20}$ = –48 (c = 0.99, CH_2Cl_2).

6-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosylthio)hexanoic acid, 5b

To a stirred solution of **4** (3.64 g, 10.0 mmol) and 6-bromohexanoic acid (1.95 g, 10.0 mmol) in acetone (10 mL) a K_2CO_3 solution (1.38 g, 10.0 mmol in 10 mL of water) was added. Stirring was continued for 2.5 h, after which the reaction mixture was acidified with acetic acid (0.5 mL) and subsequently extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was evaporated. Purification of the residue was accomplished by column chromatography (SiO_2: chloroform:AcOH, 98:2, R_f = 0.3), which furnished pure **5b** (3.65 g, 76%) as a white solid. m.p. 82–83 °C. ^{1}H-NMR ($CDCl_3$): δ 1.44 (quintet, J = 7.7 Hz, 2H, $CH_2CH_2CH_2CO_2H$), 1.64 (septet, J = 7.4 Hz, 4H, $CH_2CH_2CH_2CH_2CO_2H$), 2.01, 2.03, 2.06, 2.09 (4 x s, 4 x 3H, CH_3CO), 2.36 (t, J = 7.4 Hz, 2H, CH_2CO_2H) 2.68 (m, 2H, SCH_2), 3.71 (ddd, $J_{4,5}$ = 10.0 Hz; $J_{5,6a}$ = 4.8 Hz; $J_{5,6b}$ = 2.3 Hz, 1H, H-5), 4.14 (dd, $J_{6a,6b}$ = 12.4 Hz; $J_{5,6b}$ = 2.2 Hz, 1H, H-6b), 4.25 (dd, $J_{6a,6b}$ = 12.4 Hz; $J_{5,6a}$ = 4.9 Hz, 1H, H-6a), 4.48 (d, $J_{1,2}$ = 10.0 Hz, 1H, H-1), 5.03 (pt, $J_{1,2} \approx J_{2,3}$ = 9.4 Hz, 1H, H-2), 5.09 (pt, $J_{3,4} \approx J_{4,5}$ = 9.9 Hz, 1H, H-4), 5.23 (pt, $J_{2,3} \approx J_{3,4}$ = 9.3 Hz, 1H, H-3), 10.45 (s, 1H, CO_2H). ^{13}C-NMR ($CDCl_3$): δ 20.6, 20.7 (CH_3CO), 24.1, 28.0, 29.2, 29.6 (CH_2-spacer), 33.7 (SCH_2), 62.1 (C-6), 68.2 (C-4), 69.7 (C-2), 73.8 (C-3), 75.8 (C-5), 83.5 (C-1), 169.4, 170.2, 170.7 (CH_3CO), 179.2 (CO_2H). IR (KBr): ν 2955 (CH_3 stretch), 1744, 1720 and 1260 (C=O stretch), 1233 ($OCOCH_3$ stretch). $[\alpha]_D^{20}$ = –33 (c = 0.97, CH_2Cl_2).

11-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosylthio)undecanoic acid, 5c

To a stirred solution of **4** (4.75 g, 13.0 mmol) and 11-bromoundecanoic acid (3.45 g, 13.0 mmol) in acetone (13 mL) a K_2CO_3 solution (1.80 g, 13.0 mmol in 13 mL of water) was added. Stirring was continued for 90 min, after which the reaction mixture was acidified with acetic acid (0.5 mL) and subsequently extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was evaporated. Purification of the residue was accomplished by column chromatography (SiO_2: PhMe:EtOAc:AcOH, 80:20:2, R_f = 0.32), which furnished pure **5c** (4.43 g, 62%) as a white solid. m.p. 87–88 °C. ^{1}H-NMR ($CDCl_3$): δ 1.27 (br, 12H, CH_2-spacer), 1.61 (m, 4H, $CH_2CH_2CO_2H$, SCH_2CH_2), 2.01, 2.03, 2.06, 2.09 (4 x s, 4 x 3H, CH_3CO), 2.35 (t, J = 7.4 Hz, 2H, CH_2CO_2H), 2.67 (m, 2H, SCH_2), 3.72 (ddd, $J_{4,5}$ = 9.9 Hz; $J_{5,6a}$ = 4.7 Hz; $J_{5,6b}$ = 2.2 Hz, 1H, H-5), 4.13 (dd, $J_{6a,6b}$ = 12.4 Hz; $J_{5,6b}$ = 2.1 Hz, 1H, H-6b), 4.25 (dd, $J_{6a,6b}$ = 12.4 Hz; $J_{5,6a}$ = 4.8 Hz, 1H, H-6a), 4.49 (d, $J_{1,2}$ = 10.0 Hz, 1H, H-1), 5.03 (pt, $J_{1,2} \approx J_{2,3}$ = 9.7 Hz, 1H, H-2), 5.09 (pt, $J_{3,4} \approx J_{4,5}$ = 9.7 Hz, 1H, H-4), 5.23 (pt, $J_{2,3} \approx J_{3,4}$ = 9.3 Hz, 1H, H-3), 10.20 (s, 1H, CO_2H). ^{13}C-NMR ($CDCl_3$): δ 20.6, 20.7 (CH_3CO), 24.7, 28.7, 29.0, 29.0, 29.1, 29.3, 29.3, 29.5, 30.0 (CH_2-spacer), 33.9 (SCH_2), 62.2 (C-6), 68.3 (C-4), 69.9 (C-2), 73.9 (C-3), 75.8 (C-5), 83.6 (C-1), 169.4, 170.3, 170.7 (CH_3CO), 179.1 (CO_2H). IR (KBr): ν 2926 (CH_3 stretch), 2853 (CH_2 stretch), 1746 and 1707 (C=O stretch), 1228 ($OCOCH_3$ stretch). $[\alpha]_D^{20}$ = –29 (c = 1.00, CH_2Cl_2).

N-Succinimidyl-1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylthio)acetate, 6a

To a stirred and cooled (0–5 °C) mixture of **5a** (1.66 g, 3.92 mmol) and N-hydroxysuccinimide (0.48 g, 4.17 mmol) in dimethoxyethane (8 mL) DCC (0.97 g, 4.70 mmol) was added. The mixture was stirred overnight, the solids were filtered off and the solvent was evaporated. The residue was precipitated twice from cyclohexane, yielding **6a** (1.86 g, 91%) as a viscous syrup. ^{1}H-NMR ($CDCl_3$): δ 2.01, 2.03, 2.07, 2.09 (4 x s, 4 x 3H, CH_3CO), 2.89 (s, 4H, CH_2-Suc), 3.56, 3.86 (2 x d, J = 15.4 Hz, 2H, SCH_2), 3.80 (ddd, $J_{4,5}$ = 10.0 Hz; $J_{5,6a}$ = 4.5 Hz; $J_{5,6b}$ = 2.3 Hz, 1H, H-5), 4.15 (dd, $J_{6a,6b}$ = 12.4 Hz; $J_{5,6b}$ = 2.2 Hz, 1H, H-6b), 4.21 (dd, $J_{6a,6b}$ = 12.5 Hz; $J_{5,6a}$ = 4.7 Hz, 1H, H-6a), 4.85 (d, $J_{1,2}$ = 10.0 Hz, 1H, H-1), 5.04 (pt, $J_{1,2} \approx J_{2,3}$ = 9.5 Hz, 1H, H-2), 5.11 (pt, $J_{3,4} \approx J_{4,5}$ = 9.8 Hz, 1H, H-4), 5.25 (pt, $J_{2,3} \approx J_{3,4}$ = 9.3 Hz, 1H, H-3). ^{13}C-NMR ($CDCl_3$): δ 20.3, 20.4 (CH_3CO), 25.3 (CH_2-Suc), 27.7 (SCH_2), 61.7 (C-6), 67.9 (C-4), 69.6 (C-2), 73.3 (C-3), 75.5 (C-5), 81.3 (C-1), 165.0 (SCH_2CO_2), 169.0 (CO-Suc), 169.4, 169.6, 170.0, 170.8 (CH_3CO). IR (KBr): ν 2946 (CH_3 and CH_2 stretch), 1740 (C=O stretch), 1223 ($OCOCH_3$ stretch). $[\alpha]_D^{20}$ = –59 (c = 5, CH_2Cl_2).

N-Succinimidyl-6-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylthio)hexanoate, 6b

To a stirred and cooled (0–5 °C) solution of **5b** (1.39 g, 2.90 mmol) and N-hydroxysuccinimide (0.333 g, 2.90 mmol) in dimethoxyethane (5 mL) DCC (0.60 g, 2.91 mmol) was added. This mixture was stirred overnight, the solids were filtered off and the solvent was evaporated. The residue was precipitated twice from cyclohexane, yielding **6b** (1.45 g, 87%) as a glass-like compound. ^{1}H-NMR ($CDCl_3$): δ 1.51 (qui, J = 7.6 Hz, 2H, $CH_2CH_2CH_2CO_2$), 1.63 (m, 2H, SCH_2CH_2), 1.76 (qui, J = 7.5 Hz, 2H, $CH_2CH_2CO_2$), 2.01, 2.03, 2.06, 2.09 (4 x s, 4 x 3H, CH_3CO), 2.63 (t, J = 7.4 Hz, 2H, CH_2CO_2) 2.68 (m, 2H, SCH_2), 2.88 (s, 4H, CH_2-Suc), 3.75 (ddd, $J_{4,5}$ = 10.0 Hz; $J_{5,6a}$ = 4.8 Hz; $J_{5,6b}$ = 2.3 Hz, 1H, H-5), 4.13 (dd, $J_{6a,6b}$ = 12.4 Hz; $J_{5,6b}$ = 2.2 Hz, 1H, H-6b), 4.24 (dd, $J_{6a,6b}$ = 12.4 Hz; $J_{5,6a}$ = 4.9 Hz, 1H, H-6a), 4.53 (d, $J_{1,2}$ = 10.0 Hz, 1H, H-1), 5.02 (pt, $J_{1,2} \approx J_{2,3}$ = 9.4 Hz, 1H, H-2), 5.07 (pt, $J_{3,4} \approx J_{4,5}$ = 9.9 Hz, 1H, H-4), 5.23 (pt, $J_{2,3} \approx J_{3,4}$ = 9.3 Hz, 1H, H-3). ^{13}C-NMR ($CDCl_3$): δ 20.3, 20.4 (CH_3CO), 23.7, 27.4, 28.8, 29.3, 30.4 (CH_2-spacer), 25.3 (CH_2-Suc), 61.9 (C-6), 68.0 (C-4), 69.6 (C-2), 73.5 (C-3), 75.4 (C-5), 83.1 (C-1), 168.3 (CO_2-Suc), 169.2 (CO-Suc), 169.2, 169.3, 170.0, 170.5 (CH_3CO). IR (KBr): ν 2941 (CH_3 stretch), 2862 (CH_2 stretch), 1740 (C=O stretch), 1224 ($OCOCH_3$ stretch). $[\alpha]_D^{20}$ = –24 (c = 3.0, CH_2Cl_2).

N-Succinimidyl-11-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylthio)undecanoate, 6c

To a stirred and cooled (0–5 °C) solution of **5c** (2.03 g, 3.70 mmol) and N-hydroxysuccinimide (0.46 g, 4.00 mmol) in dimethoxyethane (10 mL) DCC (0.90 g, 4.36 mmol) was added. This mixture was stirred overnight, the solids were filtered off and the solvent was evaporated. The residue was precipitated twice from cyclohexane, yielding **6c** (2.00 g, 84%) as a glass-like compound. ^{1}H-NMR ($CDCl_3$): δ 1.29 (m, 12H, CH_2-spacer), 1.61 (m, 2H, SCH_2CH_2), 1.73 (qui, J = 7.2 Hz, 2H, $CH_2CH_2CO_2$-Suc), 2.01, 2.03, 2.06, 2.09 (4 x s, 4 x 3H, CH_3CO), 2.61 (t, J = 7.3 Hz, 2H, CH_2CO_2-Suc), 2.68 (m, 2H, SCH_2), 2.86 (s, 4H, CH_2-Suc), 3.77 (ddd, $J_{4,5}$ = 9.9 Hz; $J_{5,6a}$ = 4.7 Hz; $J_{5,6b}$ = 2.2 Hz, 1H, H-5), 4.12 (dd, $J_{6a,6b}$ = 12.4 Hz; $J_{5,6b}$ = 2.1 Hz, 1H, H-6b), 4.23 (dd, $J_{6a,6b}$ = 12.4 Hz; $J_{5,6a}$ = 4.8 Hz, 1H, H-6a), 4.56 (d, $J_{1,2}$ = 10.0 Hz, 1H, H-1), 5.01 (pt, $J_{1,2} \approx J_{2,3}$ = 9.7 Hz, 1H, H-2), 5.06 (pt, $J_{3,4} \approx J_{4,5}$ = 9.7 Hz, 1H, H-4), 5.22 (pt, $J_{2,3} \approx J_{3,4}$ = 9.3 Hz, 1H, H-3). ^{13}C-NMR ($CDCl_3$): δ 19.9, 20.0, 20.1 (CH_3CO), 23.9, 28.0, 28.4, 28.6, 28.7, 29.0, 29.3, 30.2 (CH_2-spacer), 25.0 (CH_2-suc), 61.6 (C-6), 67.8 (C-4), 69.3 (C-2), 73.2 (C-3), 75.0 (C-5), 82.7 (C-1), 168.2, 168.8, 168.9, 169.2, 169.6 170.0 (C=O). IR (KBr): ν 2929 (CH_3 stretch), 2855 (CH_2 stretch), 1739 (C=O stretch), 1223 ($OCOCH_3$ stretch). $[\alpha]_D^{20}$ = –20 (c = 7.3, CH_2Cl_2).

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To a solution of **1a** (73.7 mg, 0.233 mmol) in CH_2Cl_2 (10 mL) **6a** (483.5 mg, 0.931 mmol) was added and the reaction mixture was stirred overnight. After dilution with CH_2Cl_2 (40 mL), the solution was washed with saturated aqueous Na_2CO_3 (5 x 30 mL, usually 1–3 h was required for the complete separation of layers), dried over Na_2SO_4, filtered and concentrated to give **7** (0.38 g, 86%) as a white foam. ^{1}H-NMR ($CDCl_3$): δ 1.45 (m, 4H, $NCH_2CH_2CH_2CH_2N$), 1.69 (qui, J = 6.5 Hz, 8H, $NCH_2CH_2CH_2NH$), 2.01, 2.04, 2.07, 2.09 (4 x s, 48H, CH_3CO), 2.47 (m, 4H, $NCH_2CH_2CH_2CH_2N$), 2.51 (qui, J = 6.3 Hz, 8H, $NCH_2CH_2CH_2NH$), 3.28 (m, 8H, $NCH_2CH_2CH_2NH$), 3.27 and 3.47 (2 x d, J = 15.6 Hz, 8H, CH_2CONH), 3.79 (ddd, $J_{4,5}$ = 10.0 Hz; $J_{5,6a}$ = 4.5 Hz; $J_{5,6b}$ = 2.3 Hz, 4H, H-5), 4.14 (dd, $J_{6a,6b}$ = 12.4 Hz; $J_{5,6b}$ = 2.1 Hz, 4H, H-6b), 4.23 (dd, $J_{6a,6b}$ = 12.4 Hz; $J_{5,6a}$ = 4.7 Hz, 4H, H-6a), 4.70 (d, $J_{1,2}$ = 10.0 Hz, 4H, H-1), 5.04 (pt, $J_{1,2} \approx J_{2,3}$ = 9.5 Hz, 4H, H-2), 5.10 (pt, $J_{3,4} \approx J_{4,5}$ = 9.7 Hz, 4H, H-4), 5.24 (pt, $J_{2,3} \approx J_{3,4}$ = 9.4 Hz, 4H, H-3), 7.34 (t, J = 5.5 Hz, 4H, NH). ^{13}C-NMR ($CDCl_3$): δ 20.5, 20.6, 20.7 (CH_3CO), 24.0 ($NCH_2CH_2CH_2CH_2N$), 26.2 ($NCH_2CH_2CH_2NH$), 33.7 (SCH_2), 38.0 (CH_2NH), 51.0 ($NCH_2CH_2CH_2NH$), 53.2 ($NCH_2CH_2CH_2CH_2N$), 61.8 (C-6), 68.0 (C-4), 69.7 (C-2), 73.5 (C-3), 75.8 (C-5), 83.3 (C-1), 168.9, 169.4, 169.4, 169.9, 170.5 (C=O). IR (KBr): ν 3388 (NH stretch), 2946 (CH_3 and CH_2 stretch), 1753 (C=O stretch), 1226 ($OCOCH_3$ stretch). $[\alpha]_D^{20}$ = –34 (c = 1.2, CH_2Cl_2). MALDI-TOF-MS *m/z*: 1937 $[M+H]^+$, 1959 $[M+Na]^+$: $C_{80}H_{120}N_6O_{40}S_4$ (1932.7).

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To a solution of **1b** (188.0 mg, 0.0262 mmol) in CH_2Cl_2 (10 mL) **6a** (872 mg, 1.68 mmol) was added and the reaction mixture was stirred overnight. After dilution with CH_2Cl_2 (40 mL), the solution was washed with saturated aqueous Na_2CO_3 (5 x 30 mL, usually 1–3 h was required for the complete separation of layers), dried over Na_2SO_4, filtered and concentrated to give **8a** (0.82 g, 95%) as a slightly yellow foam. ^{13}C-NMR ($CDCl_3$): δ 20.3, 20.4, 20.5 (CH_3CO), 22.9, 26.3 (CH_2CH_2N), 33.2 (CH_2-spacer), 37.6 (CH_2NH), 50.7, 51.2 (CH_2NCH_2), 61.7 (C-6), 67.8 (C-4), 69.5 (C-2), 73.3 (C-3), 75.4 (C-5), 82.7 (C-1), 169.1, 169.6, 170.2 (C=O); IR (KBr): ν 3388 (NH stretch), 2947 (CH_3 and CH_2 stretch), 1752 (C=O stretch), 1223 ($OCOCH_3$ stretch). $[\alpha]_D^{20}$ = –37 (c = 0.54, $CHCl_3$).

Glucodendrimer 8b

To a solution of **1b** (204.2 mg, 0.0285 mmol) in CH_2Cl_2 (10 mL) **6b** (1.05 g, 1.82 mmol) was added and the reaction mixture was stirred overnight. After dilution with CH_2Cl_2 (40 mL), the solution was washed with saturated aqueous Na_2CO_3 (5 x 30 mL, usually 1–3 h was required for the complete separation of layers), dried over Na_2SO_4, filtered and concentrated to give **8b** (0.99 g, 95%) as a slightly yellow foam. ^{13}C-NMR ($CDCl_3$): δ 20.1, 20.3 (CH_3CO), 24.9, 28.0, 28.9, 30.4, 35.6 (CH_2-spacer), 26.0 (CH_2CH_2N), 36.8 (CH_2NH), 50.4 (CH_2NCH_2), 61.6 (C-6), 67.8 (C-4), 69.4 (C-2), 73.3 (C-3), 75.2 (C-5), 83.0 (C-1), 168.8, 168.9, 169.5, 170.0 (CH_3CO), 173.1 (CONH); IR (KBr): ν 3316 (NH stretch), 2941 and 2860 (CH_3 and CH_2 stretch), 1755 (C=O stretch), 1228 ($OCOCH_3$ stretch). $[\alpha]_D^{20}$ = –28 (c = 0.55, $CHCl_3$).

Glucodendrimer 8c

To a solution of **1b** (202.6 mg, 0.0283 mmol) in CH_2Cl_2 (10 mL) **6c** (1.17 g, 1.81 mmol) was added and the reaction mixture was stirred overnight. After dilution with CH_2Cl_2 (40 mL), the solution was washed with saturated aqueous Na_2CO_3 (5 x 30 mL, usually 1–3 h was required for the complete

separation of layers), dried over Na_2SO_4 , filtered and concentrated to give **8c** (1.08 g, 93%) as a slightly yellow foam. ^{13}C-NMR ($CDCl_3$): δ 20.3, 20.5 (CH_3CO), 24.3 ($CH_2CH_2CH_2NCH_2$), 25.7, 28.6, 29.0, 29.4, 29.8, 36.3 (CH_2-spacer), 26.9 ($NCH_2CH_2CH_2NH$), 37.4 (CH_2NH), 51.0 and 51.9 (CH_2NCH_2), 61.9 (C-6), 68.1 (C-4), 69.6 (C-2), 73.6 (C-3), 75.5 (C-5), 83.3 (C-1), 169.1, 169.2, 169.8, 170.3 (CH_3CO), 173.7 (NHCO). IR (KBr): ν 3422 (NH stretch), 2928 and 2854 (CH_3 and CH_2 stretch), 1756 (C=O stretch), 1228 ($OCOCH_3$ stretch). $[\alpha]_D^{20} = -17$ (c = 0.56, $CHCl_3$).

Glucodendrimer 9a

A solution of **8a** (0.21 g, 6.5 μm) in a mixture of dry CH_2Cl_2 (2 mL) and dry MeOH (3 mL) was treated with 1 M MeONa in MeOH (0.5 mL) and stirred for about 15 min at room temperature. A white precipitate was formed, the mixture was concentrated and the residue was dissolved in water (6 mL) and MeOH (1 mL). The solution was stirred overnight at room temperature, before being neutralized with 1 M HCl to pH 6, concentrated to 1 mL and subjected to dialysis in water. Evaporation of the solvent furnished pure **9a** (0.17 g, 85%) as a glass-like compound. ^{13}C-NMR (D_2O): δ 23.2, 26.3 (CH_2CH_2N), 36.0 (CH_2-spacer), 39.7 (CH_2NH), 52.4, 53.2, 53.9 (CH_2NCH_2), 63.7 (C-6), 72.2, 75.0, 79.9, 82.7 (C-2, C-3, C-4, C-5), 87.9 (C-1), 175.6 (CONH). IR (KBr): ν 3421 (NH stretch), 2924 (CH_2 stretch), 1752 (C=O stretch). $[\alpha]_D^{20} = -31$ (c = 1.8, H_2O).

Glucodendrimer 9b

A solution of **8b** (427 mg, 11.7 μm) in a mixture of dry CH_2Cl_2 (2 mL) and dry MeOH (3 mL) was treated with 1 M MeONa in MeOH (0.5 mL) and stirred for about 15 min at room temperature. A white precipitate was formed, the mixture was concentrated and the residue was dissolved in water (6 mL) and MeOH (1 mL). The solution was stirred overnight at room temperature, before being neutralized with 1 M HCl to pH 6, concentrated to 1 mL and subjected to dialysis in water. Evaporation of the solvent furnished pure **9b** (0.23 g, 76%) as a glass-like compound. ^{13}C-NMR (D_2O): δ 23.4, 26.6 (CH_2CH_2N), 27.8, 30.4, 31.8, 32.5 (CH_2-spacer), 38.5 (SCH_2), 39.3 (CH_2NH), 53.2, 54.0 (CH_2NCH_2), 63.8 (C-6), 72.4, 75.2, 80.1, 82.7 (C-2, C-3, C-4, C-5), 88.1 (C-1), 179.5 (CONH). IR (KBr): ν 3416 (NH stretch), 2927 (CH_2 stretch), 1755 (C=O stretch). $[\alpha]_D^{20} = -29$ (c = 2.27, H_2O).

Glucodendrimer 9c

A solution of **8c** (558 mg, 13.6 μm) in a mixture of dry CH_2Cl_2 (2 mL) and dry MeOH (3 mL) was treated with 1 M MeONa in MeOH (0.5 mL) and stirred for about 15 min at room temperature. A white precipitate was formed, the mixture was concentrated and the residue was dissolved in water (6 mL) and MeOH (1 mL). The solution was stirred overnight at room temperature, before being neutralized with 1 M HCl to pH 6, concentrated to 1 mL and subjected to dialysis in a water/methanol mixture (1:1). Evaporation of the solvent furnished pure **9c** (0.24 g, 58%) as a glass-like compound. ^{13}C-NMR (D_2O/CD_3OD): δ 22.4, 25.6 (CH_2CH_2N), 27.0, 30.0, 30.6, 30.8, 31.1, 31.2 (CH_2-spacer), 37.3 (SCH_2), 38.0 (CH_2NH), 52.0 (CH_2NCH_2), 62.7 (C-6), 71.2, 74.2, 79.1, 81.5 (C-2, C-3, C-4, C-5), 86.9 (C-1), 176.9 (CONH). IR (KBr): ν 3425 (NH stretch), 2929 (CH_2 stretch), 1751 (C=O stretch).

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6 Cryptochirality in chiral objects with a dendritic architecture

Summary

*The synthesis and characterization of S-2-benzyloxy-1-[3,5-bis(3,5-dibenzyloxy-benzyloxy)benzyloxy]-3-(3,5-dibenzyloxy-benzyloxy)-propane (**S-7**) is described. The chirality originates from the linkage of three constitutionally different dendritic wedges, varying only in size, to a chiral glycerol derived core, S-(+)-solketal. Despite the enantiomeric purity, **S-7** lacks any detectable optical activity in terms of optical rotation, ORD and CD measurements and may be regarded as a macromolecular analog of the well-known organic molecules with "accidental degeneracy" or "cryptochirality".*

6.1 Introduction

Any object that is not superimposable with its mirror image can be referred to as being chiral, as was first coined by Lord Kelvin,[1] rediscovered by Whyte[2] and later firmly reintroduced into the stereochemical literature by Cahn, Ingold and Prelog[3] and by Mislow *et al.*,[4] who also introduced the terms *accidental degeneracy* and *cryptochirality.*[4] Both terms are proposed to be related to the lack of any detectable optical activity from enantiomerically pure molecules. A number of classical examples are given in figure 1; chiral molecules **1**, **2**, **3**, and **4** were introduced by Wynberg,[5] Mosher,[6] Baer[7] and Mislow,[8] respectively. The chirality in these molecules originates from a very small chemical difference between two or more substituents attached to the central chiral carbon atom, or the rotational axis in the specific case of **4**.

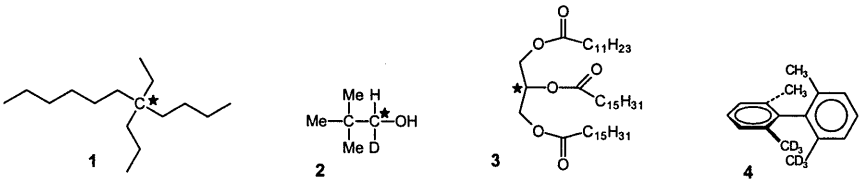


Figure 1. *Cryptochiral compounds 1–4.*[5–8]

We were very intrigued by the geometries of chiral objects with dendritic architectures, possibly leading to enantiomerically pure compounds with an accidental degeneracy similar to the ones shown in figure 1, but now based on a dendritic architecture. From the pioneering days of dendrimer chemistry, the design and synthesis of chiral dendritic objects intrigued many groups.[9] However, most of these examples deal with compounds consisting of more than one stereocenter. For a more fundamental stereochemical approach our group focused the attention towards dendritic molecules bearing only one stereocenter, as was exemplified by Kremers in molecules **5** and **6**.[10] (Figure 2).

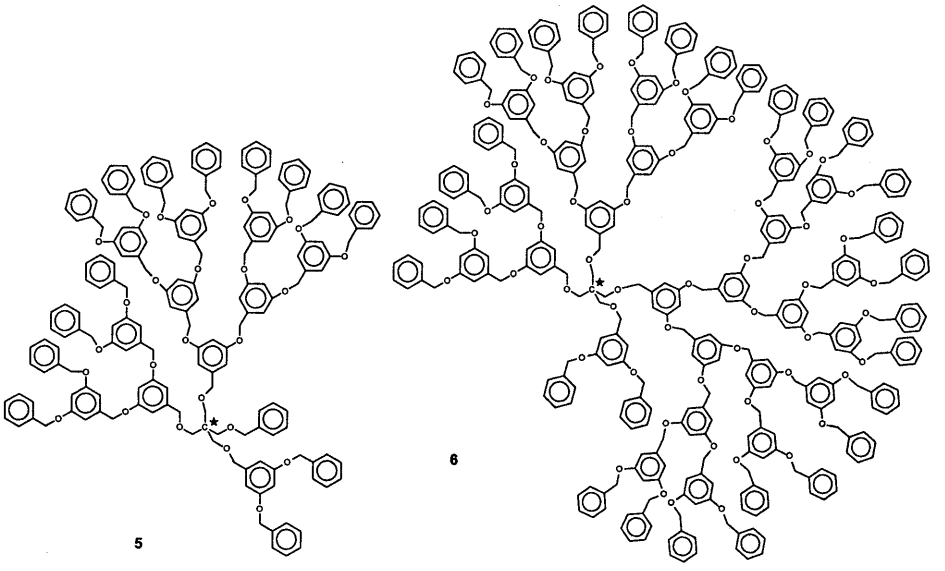


Figure 2. *Racemic chiral dendrimers 5 and 6.*[10]

Molecules **5** and **6**[10] were prepared in the racemic form, making use of a stepwise modification of the four alcohol functionalities of the pentaerythritol core with Fréchet-type dendritic wedges[11] in a convergent synthetic route. Neither **5** nor **6** could be resolved, hampering any detailed chiroptical study. This stays in sharp contrast to the fact that the resonances attributed to the CH_2-protons of the pentaerythritol core can be seen separately in ^{1}H-NMR spectroscopy, indicating a chemical difference being present between the various substituents. The degree of chirality in this type of chiral dendrimers decreases upon going from **5** to **6** and further, following Mislow's insights into the degree of chirality.[4,8]

In order to allow for a detailed chiroptical study, the enantiomers ***S*-7** and ***R*-7** (Figure 3) have been designed and prepared. These chiral dendritic objects, can be obtained by using a triol derivative, *S*-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol (*S*-(+)-solketal),[12] as a chiral starting material. The chirality in dendrimer **7** stems from the fact that now the two primary

alcohol functionalities of the glycerol core are substituted with Fréchet-type dendritic wedges of different generation.

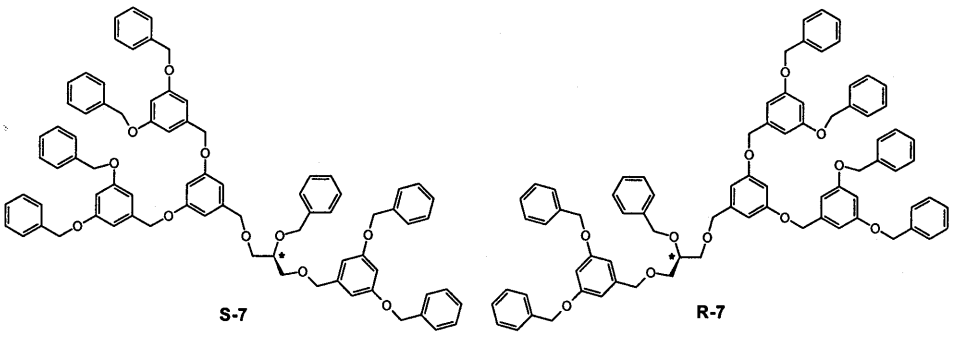


Figure 3. *Enantiomeric chiral dendrimers **S-7** and **R-7**.*

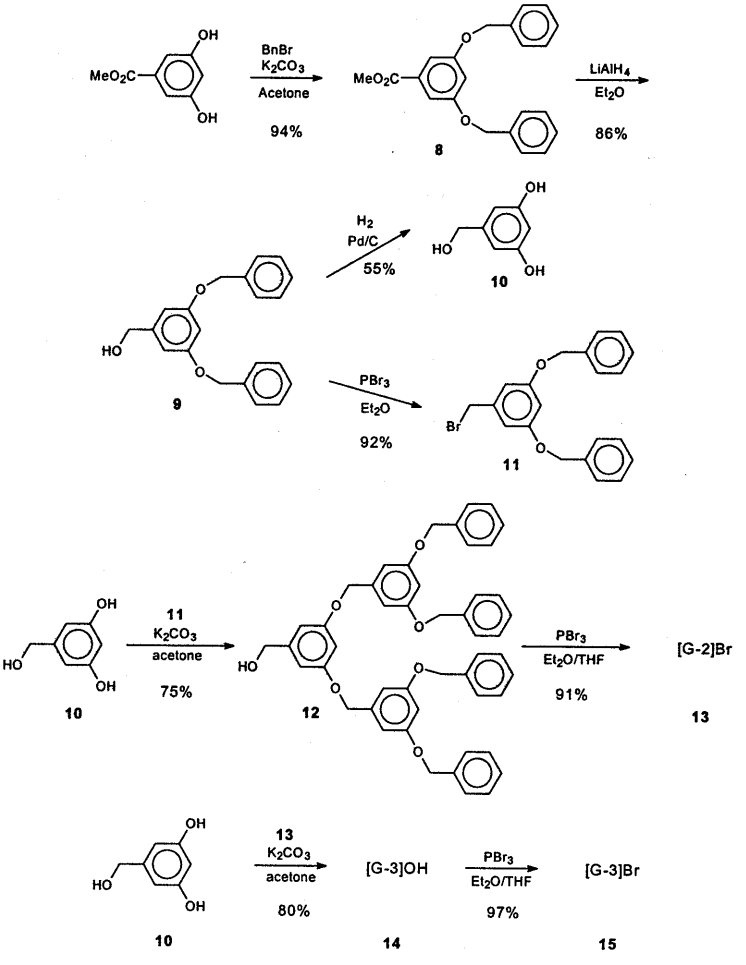
In this chapter, we describe the synthesis and chiroptical features of ***S*-7**, and will show that it represents a macromolecular analog of compounds exhibiting *accidental degeneracy* or *cryptochirality*.[4,13]

6.2 Results

6.2.1 Synthesis of the Fréchet-type dendritic wedges

The dendritic wedges used for the construction of chiral dendrimer **7** are synthesized as introduced by Fréchet[11] (Scheme 1). Methyl 3,5-dibenzyloxybenzoate **8** is synthesized in a 94% yield by reaction of methyl 3,5-dihydroxybenzoate with benzyl bromide using acetone as a solvent, K_2CO_3 as a base and 18-crown-6 as the phase transfer catalyst. The methyl benzoate **8** was subsequently converted into first generation alcohol **9** by a $LiAlH_4$ reduction. This alcohol was a key precursor as it could be used as the starting material for the synthesis of building block **10** as well as for the construction of the first generation bromide **11**. Building block **10** was obtained in a 55% yield by a hydrogenation in methanol as a solvent using Pd/C as the catalyst. The first generation bromide was obtained by treatment of **9** with PBr_3 in diethyl ether, rendering **11** as a nice, crystalline solid in a 92% yield. A reaction between building block **10** and 2 equivalents of bromide **11** in acetone as solvent, K_2CO_3 as base and 18-crown-6 as phase transfer catalyst furnished the second generation alcohol **12** in a 75% yield after crystallization. The second generation bromide was obtained by treatment of alcohol **12** with PBr_3 in a mixture of diethyl ether and THF. Pure **13** was obtained in a 91%

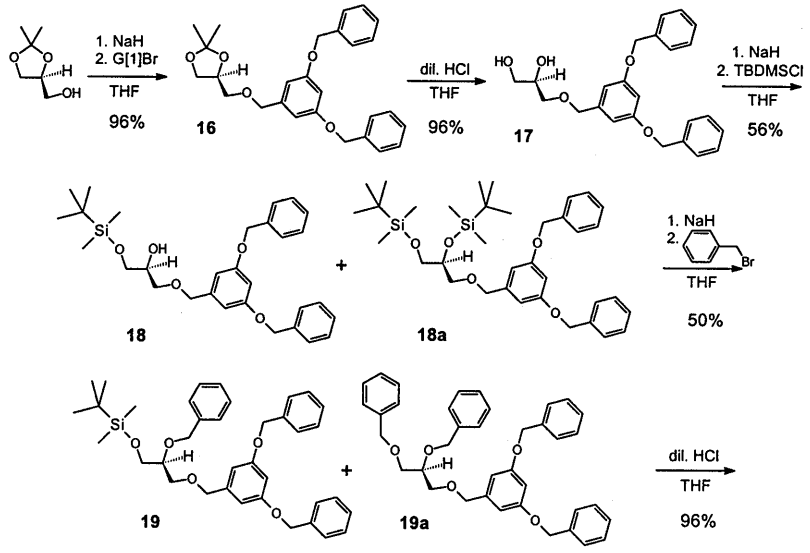
yield by precipitation of the reaction mixture with methanol. The third generation alcohol, **14**, was obtained by a reaction of 2 equivalents of bromide **13** with building block **10** using K_2CO_3 as base and 18-crown-6 as phase transfer catalyst in acetone as the solvent. A considerable amount of carbon–carbon coupling was observed as a side reaction, as is also known from the literature.[11] Purification of **14** was accomplished by column chromatography followed by precipitation in diethyl ether. Bromination to **15** was performed in a 97% yield by reaction of alcohol **14** with PBr_3 in a diethyl ether/THF mixture. Bromides **13** and **15** were prepared using a very convenient method, differing from that in the literature.[11] For the construction of chiral dendrimer **7** only benzyl bromide, and the first and second generation bromide, **11** and **13** were employed.

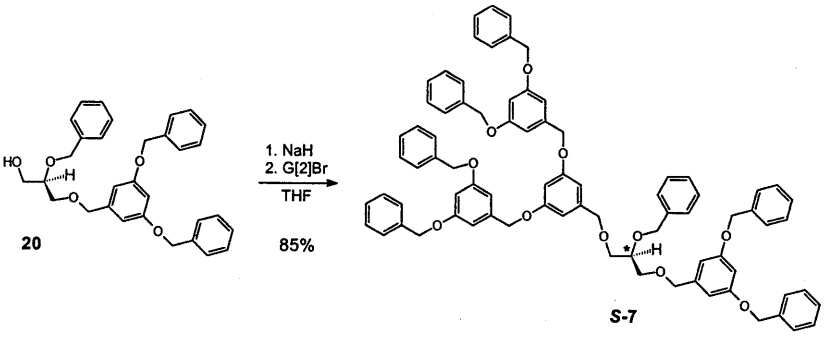


Scheme 1. *Synthesis of the Fréchet-type dendritic wedges.*[11]

6.2.2 Synthesis of the chiral dendrimer

Enantiomerically pure *S*-(+)-solketal[12] was used as the starting material for both enantiomers of **7**. The synthetic route for ***S*-7** is depicted in scheme 2. The route is designed with the aim to prevent racemization of the chiral core occurring during modifications as an enantiomerically pure chiral dendrimer is required. First the primary alcohol of *S*-(+)-solketal is coupled with the first generation of bromide, **11** ([G-1]-Br) to render **16** in a 96% yield. Hydrolysis of the ketal under acidic conditions to **17**, followed by a selective protection of the newly generated primary alcohol in the presence of the secondary one with TBDMSCl yielded **18** in 54% yield. Also 17% of diprotected product **18a** was formed, which could not be separated from **18** by column chromatography, and the mixture was therefore used as such in the following reaction step. Hence, during the etherification of the secondary alcohol with benzyl bromide ([G-0]-Br) to **19**, also an amount of the smaller chiral dendrimer **19a** was formed, which was also used for chiroptical studies. Acid-catalyzed deprotection of the TBDMS group yielded pure **20**. The final step in the synthesis of chiral dendrimer ***S*-7** was a Williamson coupling of **20** with the second generation bromide, **13** ([G-2]-Br). Dendrimer ***S*-7** was purified by column chromatography. *S*-(+)-Solketal was also used to prepare ***R*-7** (Figure 3) just by changing the sequence of attachment of the [G-1] and [G-2] in the aforementioned synthetic route. Synthetic and spectroscopic data for ***R*-7** are not included in this chapter, but the spectroscopic data proved to be the same for both enantiomers. All spectroscopic data of the new products are in full agreement with the assigned structures.





Scheme 2. *Synthetic route to optically pure dendrimer **S**-7.*

6.3 Chiroptical properties

All chiral molecules, except for ***S*-7**, ***R*-7** and the smaller dendrimer **19a**, synthesized in this study show optical activity in solution. Chiral dendrimer ***S*-7** has $[\alpha]_D^{20} = 0.00 \pm 0.01$ (c = 11, $CHCl_3$), while its precursor alcohol **20** still exhibited an $[\alpha]_D^{20} = +9.6$ (c = 0.86, CH_2Cl_2). Circular dichroism (CD), ultraviolet (UV) and optical rotatory dispersion (ORD) measurements were performed to gain more insight into the optical activity of the new low-generation dendrimer with structural chirality. Over the complete wavelength range, using 10 cm cells and at the highest possible concentrations in hexane, no indications for any optical activity were found for ***S*-7**, as was also already the case for model compound **19a**. A typical example of a CD spectrum from ***S*-7**, with saturation at the high energy side, is shown in figure 4. Other solvents and lower temperatures did not affect the chiroptical behavior.

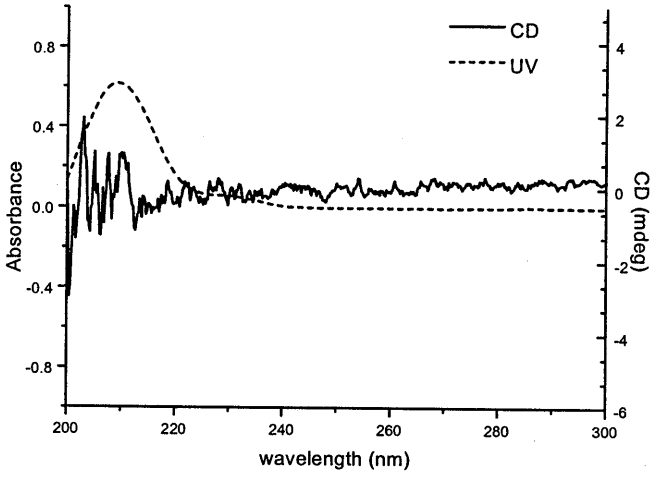


Figure 4. *UV and circular dichroism (CD) of chiral dendrimer **S**-7 in hexane.*

6.4 Discussion and conclusion

The synthetic procedure to chiral dendritic object ***S*-7** is straightforward, the yields are high (20% overall yield), and no indications for racemization are found. However, any detectable optical activity in ***S*-7** or ***R*-7** is lacking.

The first issue that can be raised is related to the degree of chirality[10,14] present in this dendritic structure. On the one hand the two different substituents at the glycerol core, attached *via* the primary alcohol functionalities, differ significantly in size, but on the other hand, they have a closely related structure. The degree of chirality on going to higher generation dendrimers (i.e. on going from **5** to **6**) decreases as was reported by Kremers[10] and Mislow.[14] However, this theory does not take into account the steric crowding effects and flexibility issues might be of crucial importance in dendrimers. Several reports deal with the flexibility/rigidity of dendrimers,[15] and so far it has become clear that the flexibility in these systems strongly influences their properties. In some cases it was even proven that the end groups of a number of dendrimers can be present over the whole volume of the dendrimer, and that the end group density is not different for core or periphery. The Fréchet-type dendritic wedges have been the subject of related studies.[16–18] Schlüter[16] reported on the crystal structure of the second generation wedge which crystallized in a disc-like shape with an occupied volume of 45%, suggesting that crowding effects are likely for the higher generation dendrimers. Wooley[17] showed with REDOR NMR relaxation experiments in the solid state of $^{13}C/^{19}F$ labelled dendritic wedges that backfolding occurred in these wedges, starting from generation 3. These two studies only describe results obtained from measurements in the solid state, but Aida[18] reported on results from measurements in solution. Azobenzene-based Fréchet-type dendrimers are described and starting from generation 3 anomalies were found in the photoisomerization properties, attributable to crowding effects in the dendrimer. It remains to be argued whether the effects of degree of chirality and steric crowding would eventually induce a detectable optical activity for analogs of **7** on going to higher generation substituents.

In the specific case of **7** with only small dendritic substituents, the lack of optical activity can be explained in a similar way as is done for the molecules depicted in figure 1.[5–8] Explanations invoking significant conformational freedom of the different substituents in **1** and vanishing electronic differences in the substituents in **1–4**, are both applicable to chiral dendrimer **7**. The significant conformational flexibility in **7** will lead to a vanishing enantiomeric difference between the geometries of ***S*-7** and ***R*-7**. This flexibility can also account for the failures to resolve dendrimers **5** and **6**. Therefore, these compounds are believed to be the macromolecular analogs of molecule **1** and can, therefore, be referred to as being *cryptochiral*.[4–8]

The flexibility present in the Fréchet-type dendrimers can be investigated in more detail when employing an axially chiral core as is described in chapter 7. A detectable optical activity may come from larger dendritic substituents as indicated in the discussion above, but also the degree of chirality plays a crucial role. In order to circumvent the issue of the degree of chirality, the wedges can be designed in such a way that interactions already play a crucial role for low dendrimer generations. This has been achieved by the introduction of the so-called backfolding wedges as is described in chapter 8.

6.5 Experimental section

General

All solvents were of c.p. quality, except those used as a reaction solvent which were of p.a. quality. THF was distilled over sodium/benzophenone prior to use. Column chromatography was performed with Merck silica gel 60 (particle size 0.063–0.200 mm). Melting points are uncorrected and were determined with a Jeneval microscope equipped with a Linkam hot stage. NMR spectra were run on a Bruker AM-400 spectrometer at frequencies of 400.1 MHz and 100.6 MHz for ^{1}H- and ^{13}C- nuclei, respectively. TMS was used as an internal standard and δ-values are given in ppm. The following abbreviations are used in the peak assignment: Ar refers to aromatic rings derived from 3,5-dihydroxybenzyl alcohol or bromide at the reactive center. Ar' and Ar'' refer to the aromatic rings derived from 3,5-dihydroxybenzyl alcohol, one and two generations remote from the reaction center, respectively. Ph refers to aromatic rings derived from benzyl alcohol. IR-spectra were taken on a Perkin Elmer 1600 series FT-IR and data are given in cm^{-1}. ORD/CD measurements were performed on a Jasco 600 spectropolarimeter and $[\alpha]_D^{20}$ data were measured on a Jasco DIP-370 digital polarimeter. LSI-MS spectra were recorded at the University of Birmingham with a VG ZabSpec mass spectrometer, using a *p*-nitrobenzyl alcohol matrix. Microanalyses were performed on a Perkin-Elmer 2400 Series II machine.

Methyl 3,5-dibenzyloxybenzoate, 8

A mixture of methyl 3,5-dihydroxybenzoate (155.2 g, 0.923 mol), potassium carbonate (256.6 g, 1.857 mol), benzyl bromide (322 g, 1.88 mol) and 18-crown-6 (9.1 g, 34 mmol) in acetone (1000 mL) was heated under reflux for 3 days, while vigorously stirred. The reaction mixture was allowed to cool to room temperature and the salts were removed by filtration. The filtrate was concentrated *in vacuo* and the resulting yellow oil was subjected to treatment with methanol (*ca.* 1.5 L), yielding **8** (303.51 g, 94%) as a white crystalline solid. m.p. 79–80 °C (lit.[10,11]: 77.5–79.5 °C). ^{1}H-NMR ($CDCl_3$): δ 3.89 (s, 3H, OCH_3), 5.06 (s, 4H, CH_2Ph), 6.80 (t, J = 2.2 Hz, 1H, ArH-4), 7.30 (d, J = 2.2 Hz, 2H, ArH-2,6), 7.33–7.43 (m, 10H, PhH). ^{13}C-NMR ($CDCl_3$): δ 52.2 (CH_3), 70.2 (CH_2Ph), 107.2 (ArC-4), 108.3 (ArC-2,6), 127.5, 128.1, 128.6 (PhCH), 132.0 (ArC-1), 136.4 (PhC-*ipso*), 159.7 (ArC-3,5), 166.8 (C=O). IR (KBr): ν 2947 and 2861 (CH_2 stretch), 1714 (C=O stretch, aromatic ester), 1597 and 1499 (C=C stretch), 1439 (CH_2 deformation), 1239 (CO stretch, arylalkyl ether). Anal. Calc. for $C_{22}H_{20}O_4$: C, 75.84; H, 5.79. Found: C, 75.81; H, 5.75.

3,5-Dibenzyloxybenzyl alcohol, [G-1]OH, 9

To a suspension of $LiAlH_4$ (34.83 g, 0.918 mol) in anhydrous diethyl ether (700 mL) was added dropwise a solution of **8** (300.0 g, 0.861 mol) in anhydrous diethyl ether (3.2 L) at such a rate to ensure gentle reflux. After the addition was complete, the reaction mixture was boiled under reflux for an hour and allowed to cool to room temperature. Subsequently ethyl acetate (50 mL), water (30 mL) and aqueous sodium hydroxide (10% w/v, 30 mL) were added carefully to the stirred reaction mixture. The precipitated salts were removed by filtration and the remaining solution was concentrated *in vacuo*. The residue was subjected to crystallization from a methanol/water mixure (95/5 v/v, 800 mL), yielding **9** (236.1 g, 86%) as a white crystalline solid. m.p. 83 °C (lit.[10,11]: 85–86 °C). ^{1}H-NMR ($CDCl_3$): δ 2.09 (t, J = 6.0 Hz, 1H, OH), 4.54 (d, J = 6.0 Hz, 2H, CH_2OH), 4.98 (s, 4H, CH_2Ph), 6.52 (t, J = 2.2 Hz, 1H, ArH-4), 6.58 (d, J = 2.2 Hz, 2H, ArH-2,6), 7.31–7.40 (m, 10H, PhH). ^{13}C-NMR ($CDCl_3$): δ 65.1 (CH_2OH), 69.9 (CH_2Ph), 101.2 (ArC-4), 105.6 (ArC-2,6), 127.4, 127.9, 128.5 (PhCH), 136.7 (PhC-*ipso*), 143.4 (ArC-1), 160.0 (ArC-3,5). IR (KBr): ν 3317 (OH stretch), 2903 and 2864 (CH_2 stretch), 1586 and 1497 (C=C stretch), 1444 (CH_2 deformation). Anal. Calc. for $C_{21}H_{20}O_3$: C, 78.73; H, 6.29. Found: C, 78.88; H, 6.28.

3,5-Dihydroxybenzyl alcohol, 10

In a Parr-apparatus, a solution of **9** (26.0 g, 81.2 mmol) in methanol (250 mL) was hydrogenated, using palladium on activated carbon (10% w/w, 1.0 g) as the catalyst. Upon completion of the reaction the catalyst was filtered off through a florisil column and the filtrate was concentrated *in vacuo* to yield a red solid, which was subjected to crystallization from acetonitrile (160 mL), yielding **10** (6.30 g, 55%) as slightly brown crystals. m.p. 192 °C (lit.[10,11]: 189 °C). ^{1}H-NMR (CD_3OD): δ 4.45 (s, 2H, CH_2OH), 5.95 (br s, 3H, OH), 6.18 (t, J = 2.2 Hz, 1H, ArH-4), 6.32 (d, J = 2.2 Hz, 2H, ArH-2,6). ^{13}C-NMR (CD_3OD): δ 65.1 (CH_2OH), 102.3 (ArC-4), 106.3 (ArC-2,6), 145.0 (ArC-1), 159.4 (ArC-3,5). IR (KBr): ν 3380 (OH stretch), 1600 and 1491 (C=C stretch), 1163 (CO stretch, phenol), 1019 (CO stretch, primary alcohol). Anal. Calc. for $C_7H_8O_3$: C, 60.00; H, 5.75. Found: C, 59.94; H, 5.75.

3,5-Dibenzyloxybenzyl bromide, [G-1]Br, 11

To a stirred and cooled (ice/salt bath) solution of **9** (90.5 g, 0.282 mol) in diethyl ether (1.4 L), phosphorus tribromide (25.8 g, 95.3 mmol) in diethyl ether (250 mL) was added dropwise over a period of 90 min. The reaction mixture was stirred overnight and subsequently poured on ice-cold water (1 L). The organic layer was separated and the aqueous layer extracted with diethyl ether (3 x 300 mL). The organic layers were combined and washed with saturated, aqueous sodium bicarbonate (2 x 300 mL) and water (1 x 300 mL). The organic layer was dried (Na_2SO_4), concentrated *in vacuo* and the residue subsequently recrystallized from hexane (1.6 L), yielding **11** (99.53 g, 92%) as a colorless crystalline solid. m.p. 90–91 °C (lit.[10,11]: 92–93 °C). ^{1}H-NMR ($CDCl_3$): δ 4.35 (s, 2H, CH_2Br), 4.96 (s, 4H, CH_2Ph), 6.52 (t, J = 2.2 Hz, 1H, ArH-4), 6.60 (d, J = 2.2 Hz, 2H, ArH-2,6), 7.29–7.39 (m, 10H, PhH). ^{13}C-NMR ($CDCl_3$): δ 33.5 (CH_2Br), 70.0 (CH_2Ph), 102.0 (ArC-4), 108.0 (ArC-2,6), 127.5, 128.0, 128.5 (PhCH), 136.5 (PhC-*ipso*), 139.7 (ArC-1), 159.9 (ArC-3,5). IR (KBr): ν 2926 and 2871 (CH_2 stretch), 1595 and 1498 (C=C stretch), 1446 (CH_2 deformation). Anal. Calc. for $C_{21}H_{19}BrO_2$: C, 65.81; H, 5.00. Found: C, 66.17; H, 5.00.

3,5-Bis(3,5-dibenzyloxy-benzyloxy)benzyl alcohol, [G-2]OH, 12

A vigorously stirred mixture of **10** (11.38 g, 81.2 mmol), **11** ([G-1]Br, 69.67 g, 182 mmol), potassium carbonate (28.3 g, 205 mmol) and 18-crown-6 (3.9 g, 15 mmol) in acetone (500 mL) was boiled under reflux for 2 days. The reaction mixture was allowed to cool to room temperature and the salts were filtered off. The filtrate was concentrated *in vacuo* and the residue crystallized from toluene/hexane (3:1 v/v, 200 mL) to furnish **12** (45.3 g, 75%) as a white solid. m.p. 111 °C (lit.[10,11]: 110–111 °C). ^{1}H-NMR ($CDCl_3$): δ 3.67 (br s, 1H, OH), 4.62 (br s, 2H, CH_2OH), 4.97 (s, 4H, ArOCH_2Ar'), 5.02 (s, 8H, Ar'OCH_2Ph), 6.51 (t, J = 2.2 Hz, 1H, ArH-4), 6.58 (t, J = 2.2 Hz, 2H, Ar'H-4), 6.61 (d, J = 2.2 Hz, 2H, ArH-2,6), 6.68 (d, J = 2.2 Hz, 4H, Ar'H-2,6), 7.30–7.42 (m, 20H, PhH). ^{13}C-NMR ($CDCl_3$): δ 65.1 (CH_2OH), 69.8 (ArOCH_2Ar'), 70.0 (Ar'OCH_2Ph), 101.2 (ArC-4), 101.4 (Ar'C-4), 105.6 (ArC-2,6), 106.3 (Ar'C-2,6), 127.5, 127.9, 128.5 (PhCH), 136.7 (PhC-*ipso*), 139.2 (Ar'C-1), 143.4 (ArC-1), 159.9 (ArC-3,5), 160.1 (Ar'C-3,5). IR (KBr): ν 3446 (OH stretch), 2922 and 2868 (CH_2 stretch), 1596 and 1497 (C=C stretch), 1452 (CH_2 deformation), 1040 (CO stretch, primary alcohol). Anal. Calc. for $C_{49}H_{44}O_7$: C, 79.01; H, 5.95. Found: C, 79.05; H, 5.93.

3,5-Bis(3,5-dibenzyloxy-benzyloxy)benzyl bromide, [G-2]Br, 13

To a stirred and cooled (ice/salt bath) suspension of **12** ([G-2]OH, 7.45 g, 10.0 mmol) in diethyl ether/anhydrous THF (30:2 v/v, 64 mL) was added dropwise a solution of phosphorus tribromide (1.75 g, 6.47 mmol) in diethyl ether (5 mL). The mixture was stirred overnight at room temperature after which methanol (150 mL) was added. The white precipitate was filtered off and washed with methanol and diethyl ether yielding **13** (7.31 g, 91%) as a white solid. m.p. 129–130 °C (lit.[10,11]: 129–130.5 °C). ^{1}H-NMR ($CDCl_3$): δ 4.40 (s, 2H, CH_2Br), 4.96 (s, 4H, ArOCH_2Ar'), 5.03 (s, 8H, Ar'OCH_2Ph), 6.51 (t, J = 2.2 Hz, 1H, ArH-4), 6.57 (t, J = 2.2 Hz, 2H, Ar'H-4), 6.61 (d, J = 2.2 Hz, 2H, ArH-2,6), 6.67 (d, J = 2.2 Hz, 4H, Ar'H-2,6), 7.30–7.42 (m, 20H, PhH). ^{13}C-NMR ($CDCl_3$): δ 33.4 (CH_2Br), 69.9 (ArOCH_2Ar'), 70.0 (Ar'OCH_2Ph), 101.5 (Ar'C-4), 102.1 (ArC-4), 106.2 (Ar'C-2,6), 108.1 (ArC-2,6), 127.4, 127.9, 128.4 (PhCH), 136.6 (PhC-*ipso*), 138.9 (Ar'C-1), 139.6 (ArC-1), 159.8 (ArC-3,5), 160.0 (Ar'C-3,5). IR (KBr): ν 3031 (=C–H stretch), 2863 (CH_2 stretch), 1596 and 1498 (C=C stretch), 1447 (CH_2 deformation). Anal. Calc. for $C_{49}H_{43}BrO_6$: C, 72.86; H, 5.37. Found: C, 73.14; H, 5.38.

3,5-Bis[3,5-bis(3,5-dibenzyloxy-benzyloxy)benzyloxy]benzyl alcohol, [G-3]OH, 14

A vigorously stirred mixture of **10** (0.70 g, 5.00 mmol), **13** ([G-2]Br, 8.48 g, 10.5 mmol), potassium carbonate (2.79 g, 20 mmol) and 18-crown-6 (0.56 g, 2.1 mmol) in acetone (50 mL) was boiled under reflux for 2 days. The mixture was allowed to cool to room temperature, the salts were filtered off and the filtrate concentrated *in vacuo*. Column chromatography of the residue (220 g SiO_2, CH_2Cl_2/hexane = 9:1, R_f = 0.2) and subsequent trituration with diethyl ether furnished **14** (6.36 g, 80%) as a white foam. ^{1}H-NMR ($CDCl_3$): δ 1.74 (t, J = 5.9 Hz, 1H, OH), 4.52 (d, J = 6.1 Hz, 2H, CH_2OH), 4.91 (s, 12 H, ArOCH_2Ar'; Ar'OCH_2Ar''), 4.97 (s, 16 H, Ar''OCH_2Ph), 6.51 (2 x t, J = 2.2 Hz, 3H, ArH-4; Ar'H-4), 6.54 (t, J = 2.2 Hz, 4H, Ar''H-4), 6.55 (d, J = 2.2 Hz, 2H, ArH-2,6), 6.63 (d, J = 2.2 Hz, 4H, Ar'H-2,6), 6.65 (d, J = 2.2 Hz, 8H, Ar''H-2,6), 7.25–7.42 (m, 40H, PhH). ^{13}C-NMR ($CDCl_3$): δ 65.1 (CH_2OH), 69.9 (ArOCH_2Ar'; Ar'OCH_2Ar''), 70.0 (Ar''OCH_2Ph), 101.2 (ArC-4), 101.5 (Ar'C-4; Ar''C-4), 105.7 (ArC-2,6), 106.3 (Ar'C-2,6; Ar''C-2,6), 127.5, 127.9, 128.5 (PhCH), 136.7 (PhC-*ipso*), 139.2 (Ar''C-1), 139.3 (Ar'C-1), 143.5 (ArC-1), 160.0 (ArC-3,5; Ar'C-3,5), 160.1 (Ar''C-3,5). IR (KBr): ν 3447 (OH stretch), 2927 and 2870 (CH_2 stretch), 1595 and 1497 (C=C stretch), 1451 (CH_2 deformation), 1053 (CO stretch, primary alcohol). Anal. Calc. for $C_{105}H_{92}O_{15}$: C, 79.13; H, 5.82. Found: C, 79.17; H, 5.79.

3,5-Bis[3,5-bis(3,5-dibenzyloxy-benzyloxy)benzyloxy]benzyl bromide, [G-3]Br, 15

To a stirred and cooled (ice/salt bath) suspension of **14** ([G-3]OH, 2.39 g, 1.50 mmol) in diethyl ether/anhydrous THF (4:1 v/v, 25 mL) was added dropwise a solution of phosphorus tribromide (0.55 g, 2.0 mmol) in diethyl ether (5 mL). Stirring was continued for 18 h after which methanol (60 mL) was added. The white precipitate was filtered off and washed with methanol and diethyl ether yielding **15** (2.40 g, 97%) as a white solid. ^{1}H-NMR ($CDCl_3$): δ 4.37 (s, 2H, CH_2Br), 4.92 (s, 4H, ArO*C*H_2Ar'), 4.94 (s, 8H, Ar'O*C*H_2Ar''), 5.01 (s, 16H, Ar''O*C*H_2Ph), 6.52 (t, J = 2.2 Hz, 1H, ArH-4), 6.53 (t, J = 2.2 Hz, 2H, Ar'H-4), 6.55 (t, J = 2.2 Hz, 4H, Ar''H-4), 6.60 (d, J = 2.2 Hz, 2H, ArH-2,6), 6.62 (d, J = 2.2 Hz, 4H, Ar'H-2,6), 6.66 (d, J = 2.2 Hz, 8H, Ar''H-2,6), 7.28–7.45 (m, 40 H, PhH). ^{13}C-NMR ($CDCl_3$): δ 33.6 (CH_2Br), 69.9 (ArO*C*H_2Ar'; Ar'O*C*H_2Ar''), 70.0 (Ar''O*C*H_2Ph), 101.5 (Ar'C-4; Ar''C-4), 102.1 (ArC-4), 106.3 (Ar''C-2,6), 106.4 (Ar'C-2,6), 108.2 (ArC-2,6), 127.5, 128.0, 128.5 (PhCH), 136.7 (PhC-*ipso*), 139.0 (Ar'C-1), 139.2 (Ar''C-1), 139.8 (ArC-1), 159.9 (ArC-3,5), 160.0 (Ar'C-3,5), 160.1 (Ar''C-3,5). IR (KBr) : ν 3030 (=C–H stretch), 2926 and 2871 (CH_2 stretch), 1596 and 1497 (C=C stretch), 1450 (CH_2 deformation). Anal. Calc. for $C_{105}H_{91}BrO_{14}$: C, 76.12; H, 5.54. Found: C, 76.20; H, 5.51.

***S*-1-O:2-O-Isopropylidene-3-(3,5-dibenzyloxy-benzyloxy)propane-1,2-diol, 16**

To a solution of *S*-(+)-solketal (3.0 g, 22 mmol) in anhydrous THF (120 mL) was added pentane-washed sodium hydride (0.82 g, 34 mmol). After stirring for 1 h, when the solution became very viscous, solid **11** ([G-1]-Br, 9.7 g, 25 mmol) was added and the mixture was heated under reflux for 18 h. Careful addition of water (10 mL) and evaporation of the solvent gave an oil, to which diethyl ether (150 mL) and water (150 mL) were added. The ether layer was separated, and the aqueous phase was extracted with diethyl ether (2 x 100 mL). The combined organic layers were dried with $MgSO_4$ and the solvent evaporated to give the crude residue, which was purified by column chromatography (400 g SiO_2). After the elution of [G-1]-Br had ceased (hexane/ethyl acetate = 4:1), the eluent was changed to pure ethyl acetate, to yield pure **16** (9.5 g, 96%) as a slightly yellow oil. ^{1}H-NMR ($CDCl_3$): δ 1.36, 1.42 (2 x s, 6H, CH_3), 3.44, 3.50 (2 x dd, J = 9.8 and 5.6 Hz, 2H, C*H*$_2$OCH$_2$Ar), 3.70, 4.02 (2 x dd, J = 8.2 and 6.4 Hz, 2H, CH_2 cyclic), 4.26 (qui, J = 5.9 Hz, 1H, C*H), 4.46, 4.51 (2 x d, J = 12.5 Hz, 2H, OC*H*$_2$Ar), 5.00 (s, 4H, ArOC*H*$_2$Ph), 6.54 (t, J = 2.2 Hz, 1H, ArH-4), 6.59 (d, J = 2.2 Hz, 2H, ArH-2,6), 7.30–7.42 (m, 10H, PhH). ^{13}C-NMR ($CDCl_3$): δ 25.3, 26.7 (CH_3), 66.7, 70.9, 73.2, 74.6 (CH_2 cyclic; *C*H$_2$OCH$_2$Ar; OCH$_2$Ar; C*H), 69.9 (OCH$_2$Ph), 101.3 (ArC-4), 106.4 (ArC-2,6), 109.3 (*C*(CH$_3$)$_2$), 127.4, 127.9, 128.5 (PhCH), 136.8 (PhC-*ipso*), 140.4 (ArC-1), 159.9 (ArC-3,5). IR (KBr): ν 2932 and 2870 (CH_2 stretch), 1595 and 1498 (C=C stretch), 1453 (CH_2 deformation), 1371 (C(CH$_3$)$_2$ deformation). $[\alpha]_D^{20}$ = +12.3 (c = 0.98, CH_2Cl_2).

***R*-3-(3,5-dibenzyloxy-benzyloxy)propane-1,2-diol, 17**

A mixture of **16** (8.6 g, 20 mmol) in aqueous hydrochloric acid (80 mL, 1 M) was heated under reflux overnight. The aqueous mixture was allowed to cool to room temperature and extracted with diethyl ether (3 x 75 mL). The organic layers were combined, dried with Na_2SO_4 and after evaporation of the solvent pure **17** (7.5 g, 96%) was obtained as a yellow oil. ^{1}H-NMR ($CDCl_3$): δ 2.92 (br s, 1H, OH), 3.28 (br s, 1H, OH), 3.44, 3.48 (2 x dd, J = 9.8 and 4.3 Hz, 2H, C*H*$_2$OCH$_2$Ar), 3.57, 3.66 (2 x dd, J = 11.5 and 4.8 Hz, 2H, C*H*$_2$OH), 3.84 (qui, J = 4.0 Hz, 1H, C*H), 4.43 (s, 2H, OC*H*$_2$Ar), 5.00 (s, 4H, ArOC*H*$_2$Ph), 6.53 (t, J = 2.2 Hz, 1H, ArH-4), 6.55 (d, J = 2.2 Hz, 2H, ArH-2,6), 7.27–7.40 (m, 10H, PhH). ^{13}C-NMR ($CDCl_3$): δ 63.8 (CH_2OH), 69.9 (OCH$_2$Ph), 70.7, 71.5, 73.2 (C*H; *C*H$_2$OCH$_2$Ar; OCH$_2$Ar), 101.3 (ArC-4), 106.5 (ArC-2,6), 127.4, 127.9, 128.5 (PhCH), 136.7 (PhC-*ipso*), 140.1 (ArC-1), 159.9 (ArC-3,5). IR (KBr): ν 3405 (OH stretch), 2924 and 2870 (CH_2

stretch), 1595 and 1497 (C=C stretch), 1452 (CH_2 deformation), 1059 (CO stretch, alcohol). $[\alpha]_D^{20}$ = +0.6 (c = 2.4, CH_2Cl_2).

S-1-(3,5-Dibenzyloxy-benzyloxy)-3-(*tert*-butyldimethylsilyloxy)propan-2-ol, 18

To a solution of **17** (8.2 g, 21 mmol) in anhydrous THF (200 mL) was added pentane-washed sodium hydride (1.35 g, 56 mmol). After stirring for 1 h, *tert*-butyldimethylsilyl chloride (3.2 g, 21 mmol) was added and the mixture was stirred for 2 h at room temperature. Addition of water (10 mL) and evaporation of the solvent gave an oil, which was dissolved in diethyl ether (250 mL). Washing with aqueous potassium carbonate (10% w/v, 150 mL) and brine (150 mL), drying over $MgSO_4$ and evaporation of the organic solvent yielded a crude oil. The oil was subjected to column chromatography (300 g SiO_2, hexane/ethyl acetate = 2:1), yielding a yellowish oil (8.5 g, 56%). This oil contained a mixture of **18** and the diprotected compound, **18a** in a ratio of 3:1. The mixture was used as such for the next reaction step. ^{1}H-NMR ($CDCl_3$): δ 0.15 (s, 6H, $Si(CH_3)_2$), 0.98 (s, 9H, $SiC(CH_3)_3$), 2.70 (br s, 1H, OH), 3.56, 3.60 (2 x dd, *J* = 9.7 and 5.0 Hz, 2H, CH_2OCH_2Ar), 3.71, 3.75 (2 x dd, *J* = 10.1 and 5.0 Hz, 2H, $CH_2OTBDMS$), 3.92 (quintet, *J* = 5.3 Hz, 1H, C*H), 4.54 (s, 2H, OCH_2Ar), 5.07 (s, 4H, $ArOCH_2Ph$), 6.63 (t, *J* = 2.2 Hz, 1H, ArH-4), 6.67 (d, *J* = 2.4 Hz, 2H, ArH-2,6), 7.37–7.49 (m, 10H, PhH). ^{13}C-NMR ($CDCl_3$): δ –5.5 ($Si(CH_3)_2$), 18.1 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 63.9, 70.6, 71.3, 73.1 (OCH_2Ar; C*H; $CH_2OTBDMS$; CH_2OCH_2Ar), 69.8 (OCH_2Ph), 101.1 (ArC-4), 106.4 (ArC-2,6), 127.3, 127.8, 128.4 (PhCH), 136.7 (PhC-*ipso*), 140.4 (ArC-1), 159.9 (ArC-3,5).

S-2-Benzyloxy-1-(3,5-dibenzyloxy-benzyloxy)-3-(*tert*-butyldimethylsilyloxy)propane, 19 and R-2,3-Dibenzyloxy-1-(3,5-dibenzyloxy-benzyloxy)propane, 19a

To a solution of **18/18a** (3.5 g, 6.5 mmol) in anhydrous THF (35 mL) was added pentane-washed sodium hydride (0.46 g, 19 mmol). After stirring for 1 h, benzyl bromide (1.78 g, 10 mmol) was added and the mixture stirred and heated under reflux overnight. Addition of water (10 mL) and evaporation of the solvent gave an oil, which was dissolved in diethyl ether (50 mL) and water (50 mL). The ether layer was separated and the aqueous phase was extracted with diethyl ether (2 x 50 mL). Drying of the combined organic layers with $MgSO_4$ and evaporation of the solvent yielded a crude oil. The oil was subjected to column chromatography (200 g SiO_2, hexane/ethyl acetate = 10:1), yielding **19** (1.96 g, 50%) as a colourless oil. Flushing with hexane/ethyl acetate 2:1 yielded **19a** as a slightly yellow oil (1.35 g).

19: ^{1}H-NMR ($CDCl_3$): δ 0.15 (s, 6H, $Si(CH_3)_2$), 0.99 (s, 9H, $SiC(CH_3)_3$), 3.64–3.82 (m, 5H, C*H, CH_2OCH_2Ar; $CH_2OTBDMS$), 4.57, 4.78 (2 x s, 2 x 2H, $C*HOCH_2Ph$; OCH_2Ar), 5.05 (s, 4H, $ArOCH_2Ph$), 6.64 (t, *J* = 2.0 Hz, 1H, ArH-4), 6.71 (d, *J* = 2.0 Hz, 2H, ArH-2,6), 7.30–7.49 (m, 15H, PhH). ^{13}C-NMR ($CDCl_3$): δ –5.5 ($Si(CH_3)_2$), 18.1 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 63.0 (CH_2-OTBDMS), 69.8 (OCH_2Ph), 70.1, 72.2, 73.1 (CH_2OCH_2Ar; OCH_2Ar; $C*HOCH_2Ph$), 78.9 (C*H), 101.1 (ArC-4), 106.3 (ArC-2,6), 127.3, 127.4, 127.5, 127.8, 128.1, 128.4 (PhCH), 136.8, 138.7 (PhC-ipso), 140.8 (ArC-1), 159.9 (ArC-3,5). IR (KBr): ν 3064 and 3031 (=C–H stretch), 2927 and 2856 (CH_2 stretch), 1595 and 1497 (C=C stretch), 1453 (CH_2 deformation), 1101 (CO stretch, ether). $[\alpha]_D^{20}$ = –1.8 (c = 1.6, CH_2Cl_2).

19a: ^{1}H-NMR ($CDCl_3$): δ 3.57 (m, 4H, CH_2OCH_2Ar; $C*HCH_2OPh$), 3.79 (qui, *J* = 5.0 Hz, 1H, C*H), 4.43, 4.48, 4.64 (3 x s, 3 x 2H, OCH_2Ar; OCH_2Ph), 4.93 (s, 4H, $ArOCH_2Ph$), 6.49 (t, *J* = 2.2 Hz, 1H, ArH-4), 6.54 (d, *J* = 2.2 Hz, 2H, ArH-2,6), 7.22–7.36 (m, 20H, PhH). ^{13}C-NMR ($CDCl_3$): δ 69.9 ($ArOCH_2Ph$), 70.2, 72.1, 73.1, 73.2 (OCH_2Ar; CH_2 core; core-OCH_2Ph), 77.2 (C*H), 101.1 (ArC-4),

106.3 (ArC-2,6), 127.4, 127.5, 127.6, 127.8, 128.2, 128.2, 128.4 (PhCH), 136.8, 138.2, 138.6 (PhC-*ipso*), 140.7 (ArC-1), 159.9 (ArC-3,5). IR (KBr): ν 2921 and 2863 (CH_2 stretch), 1595 and 1497 (C=C stretch), 1452 (CH_2 deformation), 1100 (CO stretch, ether). $[\alpha]_D^{20} = 0.00$ (c = 13.5, CH_2Cl_2).

_R_-2-Benzyloxy-3-(3,5-dibenzyloxy-benzyloxy)propan-1-ol, 20

A solution of **19** (1.6 g, 2.6 mmol) in THF (12 mL) and aqueous HCl (1 M, 12 mL) was heated under reflux for 18 h. After evaporation of the solvent, the mixture was taken up in diethyl ether (50 mL) and water (50 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (2 x 50 mL). The combined organic layers were dried with $MgSO_4$ and evaporated to dryness to yield **20** (1.21 g, 96%) as a colorless oil. ^{1}H-NMR ($CDCl_3$): δ 2.65 (br s, 1H, OH), 3.40–3.70 (m, 5H, C*H; CH_2OCH_2Ar; CH_2OH), 4.39 (s, 2H, OCH_2Ar), 4.53, 4.62 (2 x d, J = 11.9 Hz, 2H, C*HOCH_2Ph), 4.91 (s, 4H, ArOCH_2Ph), 6.52 (t, J = 2.2 Hz, 1H, ArH-4), 6.57 (d, J = 2.2 Hz, 2H, ArH-2,6), 7.18–7.35 (m, 15H, PhH). ^{13}C-NMR ($CDCl_3$): δ 62.2 (CH_2OH), 69.6 (ArOCH_2Ph), 69.8, 71.7, 72.9 (CH_2OCH_2Ar; C*HOCH_2Ph; OCH_2Ar), 78.0 (C*H), 101.0 (ArC-4), 106.1 (ArC-2,6), 127.2, 127.4, 127.4, 127.6, 128.1, 128.2 (PhCH), 136.6, 138.1 (PhC-*ipso*), 140.3 (ArC-1), 159.7 (ArC-3,5). IR (KBr): ν 3448 (OH stretch), 3063 and 3031 (=C–H stretch), 2921 and 2868 (CH_2 stretch), 1595 and 1497 (C=C stretch), 1452 (CH_2 deformation), 1059 (CO stretch, primary alcohol). $[\alpha]_D^{20} = +9.6$ (c = 0.86, CH_2Cl_2).

_S_-2-Benzyloxy-1-[3,5-bis(3,5-dibenzyloxy-benzyloxy)benzyloxy]-3-(3,5-dibenzyloxybenzyloxy) propane, _S_-7

To a solution of **20** (1.1 g, 2.2 mmol) in anhydrous THF (13 mL) was added pentane-washed sodium hydride (0.16 g, 6.7 mmol). After stirring for 2 h **13** ([G-2]-Br, 2.1 g, 2.6 mmol) was added and the mixture stirred and heated under reflux overnight. Addition of water (2 mL) and evaporation of the THF gave an oil, which was taken up in CH_2Cl_2 (50 mL) and water (50 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL). Drying of the combined organic layers over $MgSO_4$ and concentration yielded a crude oil (3.1 g). The oil (1.40 g) was subjected to column chromatography (75 g SiO_2, CH_2Cl_2/toluene = 1:1), yielding ***S*-7** (1.1 g, 85%) as a yellowish oil. ^{1}H-NMR ($CDCl_3$): δ 3.47, 3.52 (2 x dd, J = 10.1 and 5.0 Hz, 4H, CH_2OCH_2Ar,), 3.68 (qui, J = 5.0 Hz, 1H, C*H), 4.39, 4.40 (2 x s, 2 x 2H, OCH_2Ar), 4.61 (s, 2H, C*HOCH_2Ph), 4.83, 4.87 (2 x s, 2 x 4H, ArOCH_2Ar'; ArOCH_2Ph[G-1]branch), 4.92 (s, 8H, Ar'OCH_2Ph), 6.43 (m, 2 x 1H, ArH-4), 6.48 (t, J = 2.2 Hz, 2H, Ar'H-4), 6.50 (m, 2 x 2H, ArH-2,6), 6.58 (d, J = 2.2 Hz, 4H, Ar'H-2,6), 7.15–7.33 (m, 35H, PhH). ^{13}C-NMR ($CDCl_3$): δ 69.9, 70.0, 70.3, 72.2, 73.2 (CH_2), 77.3 (C*H), 101.2, 101.5 (ArC-4; Ar'C-4), 106.4 (ArC-2,6; Ar'C-2,6), 127.5, 127.6, 127.9, 128.0, 128.3, 128.5, 128.5 (PhCH), 136.7, 136.8, 138.6 (PhC-*ipso*), 139.3, 140.8 (ArC-1; Ar'C-1), 159.9, 160.0, 160.1 (ArC-3,5; Ar'C-3,5). IR (KBr): ν 3063 and 3031 (=C–H stretch), 2923 and 2868 (CH_2 stretch), 1595 and 1497 (C=C stretch), 1451 (CH_2 deformation), 1054 (CO stretch, ether). $[\alpha]_D^{20} = 0.00$ (c = 11.0, CH_2Cl_2). LSI-MS: Calc. for $C_{80}H_{74}O_{11}$: 1210.5. Found: 1211 $[M+H]^+$.

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7 Synthesis and characterization of axially chiral molecules containing dendritic substituents

Summary

*Enantiomerically pure axially chiral S-(–)-1,1'-bi-2-naphthol is used as a core material to which Fréchet-type dendritic wedges of the zeroth up to the fourth generation are attached, yielding the first axially chiral dendrimers **1–5**. The chiroptical features of these compounds were studied and this revealed an increasing molar rotation on going to higher generations of dendrimers, which can be attributed to a larger torsional angle between the naphthyl units, as a result of steric repulsions between the dendritic wedges. However, the effect is marginal, indicating the presence of a high degree of flexibility in these axially chiral dendrimers.*

7.1 Introduction

The use of stereocenters is the most frequently employed method for the introduction of chirality into a molecule. Since the first reports on chiral dendrimers much attention has been devoted to structures owing their chirality to the presence of such stereocenters in the molecule.[1] On the other hand, when looking at our classification on chiral dendrimers as outlined in the first chapter of this thesis, it is obvious that there are ample possibilities for introducing chirality. However, these have not yet been explored to their full extent.[2] Even more so, only one example is known to us dealing with the presence of chiral scaffolds bearing planar dissymmetry on a dendritic surface.[3]

In many studies the Fréchet-type[4] dendritic wedges and polyether dendrimers are employed, due to the high purity that can be obtained *via* the convergent approach. Our studies on chiral objects,[5] the studies reported by Schlüter on dendritic cylinders[6] and the REDOR NMR experiments by Wooley[7] have revealed that dendrimers using these Fréchet-wedges are of rather flexible nature and that interactions between the different groups are only present at very high generations of dendrimers.[7,8]

In our approach to axially chiral dendrimers we chose enantiomerically pure axially chiral *S*-(–)-1,1'-bi-2-naphthol[9] as a starting material. This axially chiral unit has already been proven useful in catalysis,[10] for studying host–guest properties,[11] and has also been proposed

useful in dendrimer synthesis.[12] Recently, a paper appeared in the literature in which Fréchet-type dendritic wedges were attached to the 6,6' positions of this axially chiral unit, however, no peculair chiroptical behavior was observed.[13] Chiroptical studies of the axially chiral unit have indicated that the chiroptical features are strongly dependent on the substituents attached, as was illustrated in a series of modified bridged 1,1'-binaphthyl-2,2'-diethers (Figure 1).[14] As could be deduced from the chiroptical features, the torsional angle between the two naphthyl units proved to be strongly dependent on the length of the alkyl-chain spacer between the two naphthyl units. (Table 1).

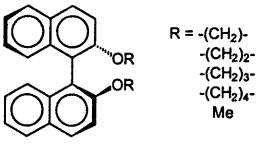


Figure 1. *Structural formula of the bridged S-1,1'-binaphthyl-2,2'-diethers.*[14]

Table 1. *Optical rotation and molar rotation of the bridged S-1,1'-binaphthyl-2,2'-diethers.*[14]

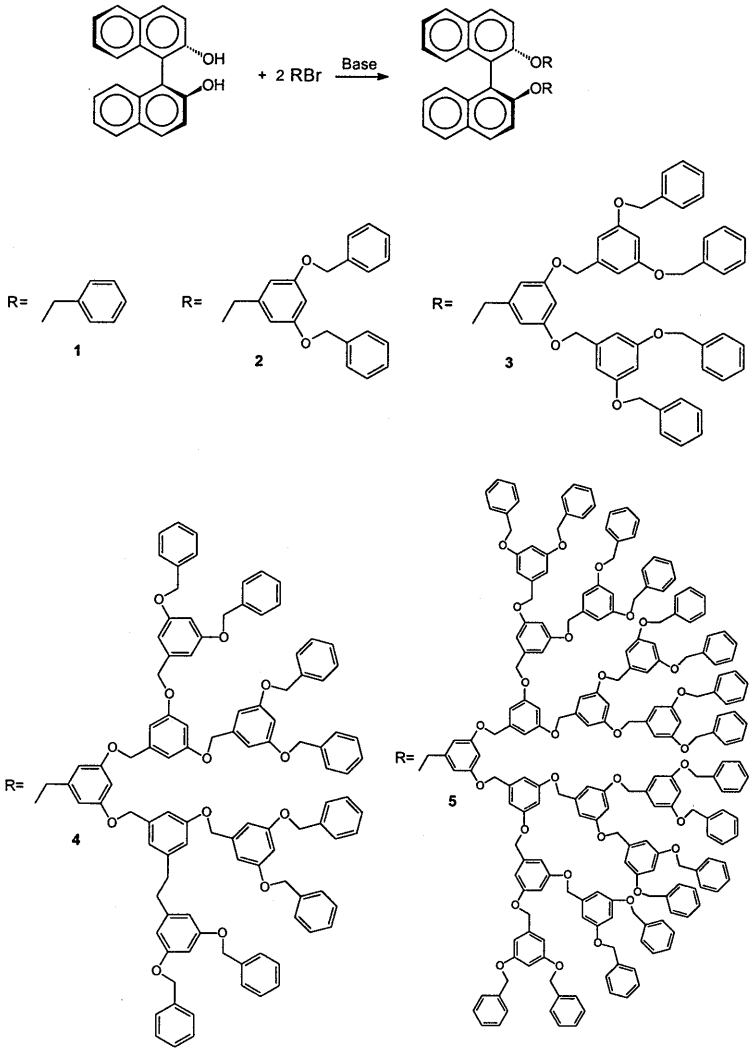
R	$[\alpha]_D^{20}$ ($CHCl_3$)	Molecular Formula	Calc. Molec. Mass	$[\Phi]_D$
$-(CH_2)-$	+779 (c = 1)	$C_{21}H_{14}O_2$	298.34	+2324
$-(CH_2)_2-$	+523 (c = 1)	$C_{22}H_{16}O_2$	312.37	+1634
$-(CH_2)_3-$	+431 (c = 1)	$C_{23}H_{18}O_2$	326.39	+1407
$-(CH_2)_4-$	+217 (c = 1)	$C_{24}H_{20}O_2$	340.42	+739
Me	–54 (c = 0.06)	$C_{22}H_{18}O_2$	314.38	–170

The axially chiral dendrimers **1–5** (Scheme 1) were prepared by a modification of the phenolic alcohol functionalities of the *S*-(–)-1,1'-bi-2-naphthol unit with Fréchet-type dendritic bromides, using the same coupling strategy as reported for the construction of the dendritic wedges.[4] The molar rotation of these dendrimers is used to probe the effect of steric hindrance of the wedges of different generation on the torsional angle of the binaphthyl unit.

7.2 Synthesis and characterization of axially chiral dendrimers 1–5

The synthesis of the axially chiral dendrimers **1–5** (Scheme 1) was performed, by applying the same strategy for the construction of the dendritic wedges as introduced by Fréchet,[4] employing *S*-(–)-1,1'-bi-2-naphthol as a core material. Except for the synthesis of **1**, which was performed in DMF as a solvent with NaH as a base, *S*-(–)-1,1'-bi-2-naphthol

(enantiomerically pure as proven by HPLC on a Pirkle column) was reacted with the bromide Fréchet-type dendritic wedges in the presence of potassium carbonate as base, acetone as solvent, and 18-crown-6 as the phase-transfer catalyst. Purification was accomplished by precipitation and/or column chromatography. HPLC analysis, on a chiral Pirkle column was used to check whether racemization had taken place during the reaction. This technique proved to be useless for the dendrimer-modified binaphthyls due to the lack of resolution, presumably owing to the flexible nature of these compounds. Therefore, we focused our attention toward a model compound, 2,2'-dimethoxy-1,1'-binaphthalene,[14] to ascertain that the synthetic procedure used for the alkylation did not lead to any racemization.



Scheme 1. *The S-(–)-1,1'-bi-2-naphthol-based dendrimers 1–5.*

All spectroscopic data in terms of ^{1}H-, ^{13}C-NMR, FT-IR, elemental analysis and LSI-MS/MALDI-TOF-MS are in full agreement with the assigned structures. Characterization with ^{13}C-NMR is based on an XHCORRD-correlation NMR experiment of 2,2'-dimethoxy-1,1'-binaphthalene, a compound well-documented in literature.[14] In the characterization of the dendrimers in ^{13}C-NMR the signal expected for the C-5 of the bisnaphthol unit is missing, probably due to an overlap with a signal corresponding to the phenyl end group of the dendritic wedge. Also the LSI-MS mass data (for compounds **1–4**) and the MALDI-TOF-MS data (for **5**) are in good agreement with the prepared structures (Table 2). However, for **4** a relatively small signal is present which has been attributed to a dendritic wedge of the third generation in which carbon–carbon coupling has occurred, a phenomenon well-documented in the literature.[4] In ^{1}H-NMR the absence of significant quantities of C-alkylation was proven.

Table 2. *Measured molar masses for axially chiral dendrimers 1–5.*

Compound	Molec. Formula	Calc. Mass	Mass Found
1	$C_{34}H_{26}O_2$	466.2	466 $[M]^+$
2	$C_{62}H_{50}O_6$	890.4	891$[M+H]^+$
			913 $[M+Na]^+$
3	$C_{118}H_{98}O_{14}$	1739.8	1739 $[M]^+$
4	$C_{230}H_{194}O_{30}$	3437.4	3461 $[M+Na]^+$
			4187 $[M+[G-2]+Na]^+$
5	$C_{454}H_{386}O_{62}$	6833.8	6874 $[M+K]^+$

7.3 Chiroptical properties of the dendrimers

For the chiroptical features of these compounds the molar rotation was determined for the dendrimers using CH_2Cl_2 as a solvent (Table 3) (Negative values for the optical rotation were also observed when using acetone or toluene as a solvent). Roughly constant values for the molar rotation as measured at 589 nm are obtained for the dendrimers of the zeroth and first generation of approximately –200, whereas an increase is observed to –271, –424 and –650 for dendrimers of the second, third and fourth generation, respectively. From compounds **1–5** also optical rotatory dispersion (ORD) and circular dichroism (CD) studies were performed. These studies confirmed the optical rotation data, but gave no additional information concerning the local chirality in the core or wedges. A typical CD spectrum for compound **2** is shown in Figure 2.

Table 3. *The optical rotation for bisnaphthol dendrimers 1–5.*

Compound	$[\alpha]_D^{20}$ (CH_2Cl_2)	Molec. Formula	Molecular Mass	$[\Phi]_D$
1	–45.5 (c = 0.47)	$C_{34}H_{26}O_2$	466.59	–212
2	–22.8 (c = 0.89)	$C_{62}H_{50}O_6$	891.09	–203
3	–15.6 (c = 1.74)	$C_{118}H_{98}O_{14}$	1740.07	–271
4	–12.3 (c = 1.01)	$C_{230}H_{194}O_{30}$	3438.03	–424
5	–9.5 (c = 0.57)	$C_{454}H_{386}O_{62}$	6833.99	–650

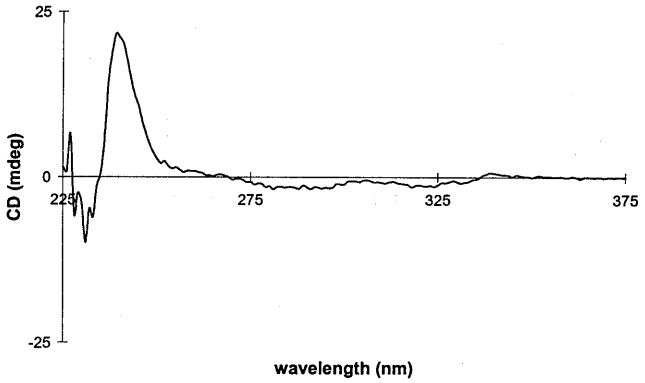


Figure 2. *Circular dichroism (CD) spectrum (measured in CH_2Cl_2) of compound 2.*

7.4 Discussion and conclusions

Comparison of the molar rotations of dendrimers **1–5** (Table 3) to the aforementioned alkyl ether bridged *S*-1,1'-binaphthyl-2,2'-diethers[14] (Table 1) learns that the latter exhibit positive values for the molar rotations ranging from +739 for the compound with a butylene spacer up to +2324 for the methylene spacer, suggesting that the torsional angle between the naphthyl units is smaller than 90^0 and decreases upon going to shorter spacer lengths.[14] The molar rotation of the model compound 2,2'-dimethoxy-1,1'-binaphthalene[14] (Table 1) was –170, which is comparable to the values of approximately –200 obtained for **1** and **2**. The negative value for the optical rotation of modified *S*-1,1'-bi-2-naphthol would indicate a torsional angle between the naphthyl units exceeding 90^0. When going to higher generation dendrimers **3–5** we observe an increasing molar rotation, which is related to a larger torsional

angle between the naphthyl units. The crystal structure of the second generation dendritic wedge as reported by Schlüter[6] indicated that this dendritic wedge crystallized in a flat orientation with an occupied volume of 45%, thus making interactions between the dendritic wedges in a bifunctional material plausible. Also REDOR-NMR relaxation experiments on $^{13}C/^{19}F$ labelled dendritic wedges pointed to backfolding for higher generations of dendrimers, even leading to inward folding of the end groups into the dendrimer.[7] These findings prompted us to conclude that due to steric interactions between the wedges the angle between the naphthyl units increases when going to higher generations of dendrimers, leading to a more negative molar rotation. A molecular modeling picture of **2** and **3** is presented in figure 3.

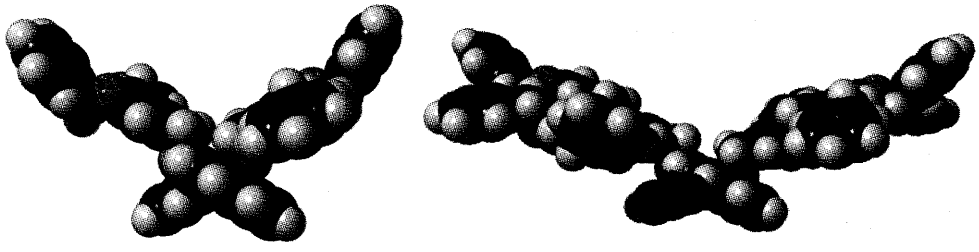


Figure 3. *Molecular modeling presentation of 2 and 3.*

However, when considering the increase in molar rotation from –203 (**2**) to –650 (**5**) and comparing these values with the results obtained for the conformationally rigid alkyl ether bridged systems (Table 1), we conclude that the difference in torsional angle is small, probably due to the high degree of conformational flexibility still present in the dendrimers. This is in agreement with the observation that we were not able to resolve the first generation axially chiral dendrimer on a chiral HPLC column and is also perfectly in line with the results obtained for the chiral dendritic objects as described in the previous chapter.

When using an axially chiral core, we have been able to gather information on the conformational flexibility and on crowding effects in solution for Fréchet-type dendritic wedges, thanks to the chiroptical properties. So far, only Aida[8] reported on the anomalous behavior in solution for higher generation Fréchet-type dendrimers in his photoresponsive dendrimers, that were also possibly caused by crowding effects. When modifying this axially chiral unit at the 6,6' positions with Fréchet-type dendritic wedges no change in optical rotation was observed.[13] A slight increase in the molar rotation per chiral unit, however, was reported by Chow[15] in his axially chiral binaphthol-based oligomers. In this specific case also a high degree of flexibility is present and no interactions between the chiral units could be detected.

7.5 Experimental section

General

All solvents were of c.p. quality, except those used as reaction solvent which were of p.a. quality. The Fréchet-type dendritic wedges[4] are synthesized as described in chapter 5. Column chromatography was performed with Merck silica gel 60 (particle size 0.063–0.200 mm). Melting points are uncorrected and were determined with a Jeneval microscope equipped with a Linkam hot stage. NMR spectra were run on a Bruker AM-400 spectrometer at frequencies of 400.1 MHz and 100.6 MHz for ^{1}H- and ^{13}C- nuclei, respectively. TMS was used as an internal standard and δ-values are given in ppm. The following abbreviations are used in the peak assignment: Ar refers to aromatic rings derived from 3,5-dihydroxybenzyl alcohol or bromide at the reactive center. Ar', Ar'' and Ar''' refer to the aromatic rings derived from 3,5-dihydroxybenzyl alcohol, one, two and three generations remote from the reaction center, respectively. Ph refers to aromatic rings derived from benzyl alcohol. IR-spectra were taken on a Perkin Elmer 1600 series FT-IR and data are given in cm^{-1}. ORD/CD measurements were performed on a Jasco 600 spectropolarimeter and $[\alpha]_D^{20}$ data were measured on a Jasco DIP-370 digital polarimeter. LSI-MS spectra for compounds **1–4** were recorded at the University of Birmingham with a VG ZabSpec mass spectrometer, using a *p*-nitrobenzyl alcohol matrix. MALDI-TOF-MS for **5** was run on a Voyager DE spectrometer with an α-cyano-4-hydroxycinnamic acid matrix at the University of Berkeley. Elemental analyses were run on a Perkin Elmer 2400 series II machine. The mass spectral data for compounds **1–5** are listed in table 2.

Binaphthalene dendrimer 1

To a solution of *S*-(–)-1,1'-bi-2-naphthol (0.57 g, 2.0 mmol) in DMF (30 mL) was added pentane-washed sodium hydride (0.30 g, 13 mmol). After stirring at room temperature for 1 h, benzyl bromide (0.70 g, 4.1 mmol) was added and the mixture was heated at 75 °C for 4 days. Then water (2 mL) was added to the mixture and the solvent was evaporated *in vacuo*, yielding the crude product, which was purified by column chromatography (toluene, Rf = 0.65). This furnished pure **1** (0.81 g, 87%) as a yellowish glass-like substance. ^{1}H-NMR ($CDCl_3$): δ 4.96 (s, 4H, CH_2Ph), 6.91 (dd, J = 7.4 and 1.7 Hz, 2H, PhH-*ortho*), 7.01–7.06 (m, 2H, PhH-*meta*), 7.05 (d, J = 9.0 Hz, 2H, H-8), 7.16 (ddd, J = 7.8, 6.4 and 1.1 Hz, 2H, H-7), 7.21 (t, J = 7.8 Hz, 2H, PhH-*para*), 7.26 (ddd, J = 8.0, 6.5 and 1.4 Hz, 2H, H-6), 7.34 (d, J = 9.0 Hz, 2H, H-3), 7.80 (d, J = 8.2 Hz, 2H, H-5), 7.84 (d, J = 9.0 Hz, 2H, H-4). ^{13}C-NMR ($CDCl_3$): δ 71.0 (CH_2Ph), 115.9 (C-3), 120.6 (C-1), 123.6 (C-6), 125.5 (C-8), 126.3 (C-7), 126.6, 127.2, 128.0, (PhCH), 127.8 (C-5), 129.2 (C-4), 129.4 (C-4a), 134.1 (C-8a), 137.5 (PhC-*ipso*), 154.0 (C-2). IR (KBr): ν 3057 (=C–H stretch), 2925 and 2866 (CH_2 stretch), 1621, 1590, 1506 (C=C stretch), 1452 (CH_2 deformation), 1270 (CO stretch, arylalkyl ether). $[\alpha]_D^{20}$ = –45.5 (c = 0.47, CH_2Cl_2). Anal. for $C_{34}H_{26}O_2$: Calc. C, 87.53; H, 5.62. Found C, 87.56; H, 5.74.

Binaphthalene dendrimer 2

A vigorously stirred mixture of *S*-(–)-1,1'-bi-2-naphthol (145 mg, 0.506 mmol), 3,5-dibenzyloxybenzyl bromide ([G-1]Br, 397.4 mg, 1.037 mmol), 18-crown-6 (0.03 g, 0.1 mmol) and potassium carbonate (2.5 g, 18 mmol) in acetone (40 mL) was heated under reflux for 2 days. The reaction mixture was allowed to cool to room temperature and the salts were removed by filtration. The filtrate was concentrated *in vacuo* and the residue was precipitated two times with methanol.

Removal of the last traces of solvent *in vacuo* yielded pure **2** (0.37 g, 83%) as a slightly yellow foam. ^{1}H-NMR: ($CDCl_3$): δ 4.60 (2 x d, J = 11.6 Hz, 8H, ArOCH_2Ph), 4.99 (s, 4H, CH_2Ar), 6.20 (d, J = 2.1 Hz, 4H, ArH-2,6), 6.35 (t, J = 2.1 Hz, 2H, ArH-4), 7.21–7.37 (m, 26H, PhH, H-6, H-7, H-8), 7.44 (d, J = 9.0 Hz, 2H, H-3), 7.77 (d, J = 8.0 Hz, 2H, H-5), 7.88 (d, J = 9.0 Hz, 2H, H-4). ^{13}C-NMR ($CDCl_3$): δ 69.7 (ArOCH_2Ph), 70.8 (CH_2Ar), 101.4 (ArC-4), 105.0 (ArC-2,6), 115.6 (C-3), 120.6 (C-1), 123.8 (C-6), 125.4 (C-8), 126.5 (C-7), 127.7, 127.9, 128.5 (PhCH), 129.3 (C-4a), 129.4 (C-4), 134.1 (C-8a), 136.8 (PhC-*ipso*), 139.9 (ArC-1), 153.9 (C-2), 159.7 (ArC-3,5). IR (KBr): ν 3031 (=C–H stretch), 2927 and 2868 (CH_2 stretch), 1595 and 1507 (C=C stretch), 1452 (CH_2 deformation), 1264 (CO stretch, arylalkyl ether). $[\alpha]_D^{20}$ = –22.8 (c = 0.89, CH_2Cl_2). Anal. for $C_{62}H_{50}O_6$: Calc. C, 83.57; H, 5.66. Found C, 83.76; H, 5.72.

Binaphthalene dendrimer 3

A vigorously stirred mixture of *S*-(–)-1,1'-bi-2-naphtol (143.6 mg, 0.502 mmol), 3,5-bis(3,5-dibenzyloxy-benzyloxy)benzyl bromide ([G-2]Br, 0.82 g, 1.02 mmol), 18-crown-6 (0.03 g, 0.1 mmol) and potassium carbonate (2.5 g, 18 mmol) in acetone (50 mL) was heated under reflux for 2 days. The reaction mixture was allowed to cool to room temperature and the salts were removed by filtration. The filtrate was concentrated *in vacuo* and was precipitated with methanol. Removal of the last traces of solvent *in vacuo* furnished pure **3** (0.85 g, 97%) as a slightly yellow foam. ^{1}H-NMR ($CDCl_3$): δ 4.47 (s, 8H, ArOCH_2Ar'), 4.93 (s, 20H, CH_2Ar, Ar'OCH_2Ph), 6.14 (d, J = 2.1 Hz, 4H, ArH-2,6), 6.28 (t, J = 2.1 Hz, 2H, ArH-4), 6.54 (t, J = 2.2 Hz, 4H, Ar'H-4), 6.57 (d, J = 2.2 Hz, 8H, Ar'H-2,6), 7.15–7.38 (m, 48H, PhH, H-3, H-6, H-7, H-8), 7.69 (dd, J = 8.5 and 1.5 Hz, 2H, H-5), 7.79 (d, J = 9.0 Hz, 2H, H-4). ^{13}C-NMR ($CDCl_3$): δ 69.5 (ArOCH_2Ar'), 69.9 (Ar'OCH_2Ph), 70.6 (CH_2Ar), 101.2 (ArC-4), 101.4 (Ar'C-4), 105.0 (ArC-2,6), 106.5 (Ar'C-2,6), 115.5 (C-3), 120.5 (C-1), 123.7 (C-6), 125.3 (C-8), 126.4 (C-7), 127.4, 127.9, 128.5 (PhCH), 129.3 (C-4a, C-4), 134.0 (C-8a), 136.7 (PhC-ipso), 139.1 (Ar'C-1), 139.8 (ArC-1), 153.7 (C-2), 159.5 (ArC-3,5), 160.0 (Ar'C-3,5). IR (KBr): ν 3061 and 3031 (=C–H stretch), 2927 and 2869 (CH_2 stretch), 1595 and 1497 (C=C stretch), 1451 (CH_2 deformation). $[\alpha]_D^{20}$ = –15.6 (c = 1.74, CH_2Cl_2). Anal. for $C_{118}H_{98}O_{14}$: Calc. C, 81.45; H, 5.68. Found C, 81.59; H, 5.73.

Binaphthalene dendrimer 4

A vigorously stirred mixture of *S*-(–)-1,1'-bi-2-naphthol (143.0 mg, 0.499 mmol), 3,5-bis[3,5-bis(3,5-dibenzyloxy-benzyloxy)benzyloxy]benzyl bromide ([G-3]Br, 1.68 g, 1.01 mmol), 18-crown-6 (0.03 g, 0.1 mmol) and potassium carbonate (2.5 g, 18 mmol) in acetone (50 mL) was heated under reflux for 2 days. The reaction mixture was allowed to cool to room temperature and the salts were removed by filtration. Column filtration (CH_2Cl_2/toluene = 4:1, Rf = 0.5) furnished pure **4** (1.35 g, 79%) as a slightly yellow foam. ^{1}H-NMR ($CDCl_3$): δ 4.41 (s, 8H, ArOCH_2Ar'), 4.84 (s, 16H, Ar'OCH_2Ar''), 4.92 (s, 36H, CH_2Ar, Ar''OCH_2Ph), 6.11 (d, J = 2.1 Hz, 4H, ArH-2,6), 6.23 (t, J = 2.1 Hz, 2H, ArH-4), 6.50–6.53 (m, 20H, Ar'H-2,6, Ar'H-4, Ar''H-4), 6.63 (d, J = 2.1 Hz, 16H, Ar''H-2,6), 7.16–7.32 (m, 86H, PhH, H-6, H-7, H-8), 7.35 (d, J = 9.0 Hz, 2H, H-3), 7.69 (d, J = 7.7 Hz, 2H, H-5), 7.77 (d, J = 9.0 Hz, 2H, H-4). ^{13}C-NMR ($CDCl_3$): δ 69.6 (ArOCH_2Ar'), 69.8 (Ar'OCH_2Ar''), 70.0 (Ar''OCH_2Ph), 70.5 (CH_2Ar), 101.0 (ArC-4), 101.5 (Ar''C-4), 101.6 (Ar'C-4), 105.1 (ArC-2,6), 106.3 (Ar''C-2,6), 106.6 (Ar'C-2,6), 115.5 (C-3), 120.6 (C-1), 123.8 (C-6), 125.3 (C-8), 126.5 (C-7), 127.5, 127.9, 128.5 (PhCH), 129.3 (C-4, C-4a), 134.1 (C-8a), 136.7 (PhC-*ipso*), 139.2 (Ar'C-1), 139.3 (Ar''C-1), 139.8 (ArC-1), 153.7 (C-2), 159.6 (ArC-3,5), 159.9 (Ar'C-3,5), 160.1 (Ar''C-3,5). IR (KBr): ν 3060 and 3030 (=C–H stretch), 2926 and 2869 (CH_2 stretch), 1595 and 1497 (C=C

stretch), 1451 (CH_2 deformation). $[\alpha]_D^{20}$ = –12.3 (c = 1.01, CH_2Cl_2). Anal. for $C_{230}H_{194}O_{30}$: Calc. C, 80.35; H, 5.69. Found C, 80.52; H, 5.73.

Binaphthalene dendrimer 5

A vigorously stirred mixture of *S*-(–)-1,1'-bi-2-naphthol (4.303 mg, 15.0 μmol), 3,5-bis{3,5-bis[3,5-bis(3,5-dibenzyloxy-benzyloxy)benzyloxy]benzyloxy}benzyl bromide ([G-4]Br, 103.5 mg, 30.9 μmol), 18-crown-6 (2.6 mg, 10 μmol) and potassium carbonate (180 mg, 1.3 mmol) in acetone (5 mL) was heated under reflux for 2 days. The reaction mixture was allowed to cool to room temperature and the salts were removed by filtration. Column chromatography (CH_2Cl_2/toluene = 5:1, R_f = 0.6) furnished pure **5** (56.8 mg, 55%) as a slightly yellow foam. ^{1}H-NMR ($CDCl_3$): δ 4.35 (s, 8H, ArOCH_2Ar'), 4.76 (s, 16H, Ar'OCH_2Ar''), 4.78 (s, 32H, Ar''OCH_2Ar'''), 4.86 (s, 68H, CH_2Ar, Ar'''OCH_2Ph), 6.08 (d, *J* = 2.1 Hz, 4H, ArH-2,6), 6.20 (t, *J* = 2.1 Hz, 2H, ArH-4), 6.46–6.48 (m, 28H, Ar'H-4, Ar''H-4, Ar'''H-4), 6.50 (d, *J* = 2.1 Hz, 8H, Ar'H-2,6), 6.57–6.59 (m, 48H, Ar''H-2,6, Ar'''H-2,6), 7.05–7.35 (m, 166H, PhH, H-6, H-7, H-8), 7.37 (d, *J* = 9.0 Hz, 2H, H-3), 7.67 (d, *J* = 7.7 Hz, 2H, H-5), 7.74 (d, *J* = 9.0 Hz, 2H, H-4). ^{13}C-NMR ($CDCl_3$): δ 69.5 (ArO*C*H_2Ar'), 69.8 (Ar'O*C*H_2Ar''), 69.8, 69.9 (Ar''O*C*H_2Ar''', Ar'''O*C*H_2Ph), 70.3 (*C*H_2Ar), 100.9 (ArC-4), 101.5 (Ar'C-4, Ar''C-4, Ar'''C-4), 105.1 (ArC-2,6), 106.3 (Ar''C-2,6, Ar'''C-2,6), 106.5 (Ar'C-2,6), 115.4 (C-3), 120.4 (C-1), 123.7 (C-6), 125.3 (C-8), 126.4 (C-7), 127.5, 127.9, 128.5 (PhCH), 129.3 (C-4, C-4a), 134.1 (C-8a), 136.7 (PhC-*ipso*), 139.1, 139.3 (Ar'C-1, Ar''C-1, Ar'''C-1), 139.8 (ArC-1), 153.6 (C-2), 159.5 (ArC-3,5), 159.8 (Ar'C-3,5), 159.9 (Ar''C-3,5), 160.0 (Ar'''C-3,5). IR (KBr): ν 3062 and 3030 (=C–H stretch), 2919, 2870 (CH_2 stretch), 1594 and 1497 (C=C stretch), 1449 (CH_2 deformation). $[\alpha]_D^{20}$ = –9.5 (c = 0.57, CH_2Cl_2). Anal. for $C_{454}H_{386}O_{62}$: Calc. C, 79.79; H, 5.69. Found C, 79.61; H, 5.80.

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8 Chiral dendrimers with backfolding wedges

Summary

Normally dendrimers are of flexible nature and have a branching pattern that forces the growth outward. However, when conformationally more rigid structures are desired, substitution patterns can be introduced that force the growth of the dendrimer inward. For this purpose we changed the substitution pattern of the Fréchet-type benzyl ethers from 3,5-dibenzyloxy to 2,6-dibenzyloxy. The effect of these conformationally more rigid analogs is illustrated with chiroptical studies. Firstly, a chiral dendrimer built from enantiomerically pure solketal to which backfolding wedges of various generation are attached, is presented. Secondly, dendrimers built from axially chiral S-(–)-1,1'-bi-2-naphthol modified with these backfolding wedges, is described. The chiroptical properties of both types of chiral dendrimers revealed conformational rigidity being present in this new type of dendritic wedges, even at low generations of dendrimer.

8.1 Introduction

The first reports on the synthesis and properties of dendrimers[1] initiated many studies towards this new class of highly branched macromolecules. A wide variety of synthetic routes has led to the production of a large number of new dendritic structures, even leading to compounds that are now commercially available.[1d–e,2] The branching pattern of many, if not all, of these dendrimers is designed to allow the growth of each next generation outward. As a result, dendrimers can be obtained which possess a highly packed periphery and cavities in the interior, allowing e.g. encapsulation of guest molecules.[3] For a number of divergently synthesized dendrimers it has now been established that a high degree of conformational flexibility is present within these nanosized structures.[4] Recently, Schlüter[5] reported on a crystal structure of the convergently synthesized second generation Fréchet-type[6] dendritic wedge, which revealed that this structure had a disc-like shape with an occupied volume of 45%, suggesting that backfolding may occur in higher generation dendrimers. In this context, Wooley[7] has proven by REDOR NMR relaxation experiments that the distances between a ^{19}F core and ^{13}C-labeled end groups reveal inward folding and even interpenetration of the end

groups in the dendrimers for the third, fourth and fifth generation Fréchet-type dendritic wedges could be observed. So far, conformational rigidity in these structures has only been found at higher generations of dendrimers.[8–10] Restricted flexibility at lower generations, however, has not yet been observed previously and may be of interest for many applications foreseen for dendrimers, e.g. molecular recognition and catalysis.[9,11] Also our search for an optically active chiral dendritic object, that owes its chirality to the presence of constitutionally different wedges attached to a central carbon atom, is highly hampered by this flexibility.[12] Previously, the enantiomerically pure dendrimer ***S*-1** was described (Figure 1), but no detectable optical activity was observed.[13,14] Moreover, the use of axially chiral *S*-(–)-1,1'-bi-2-naphthol as core material revealed the flexible nature of the Fréchet-type dendritic wedges.[15]

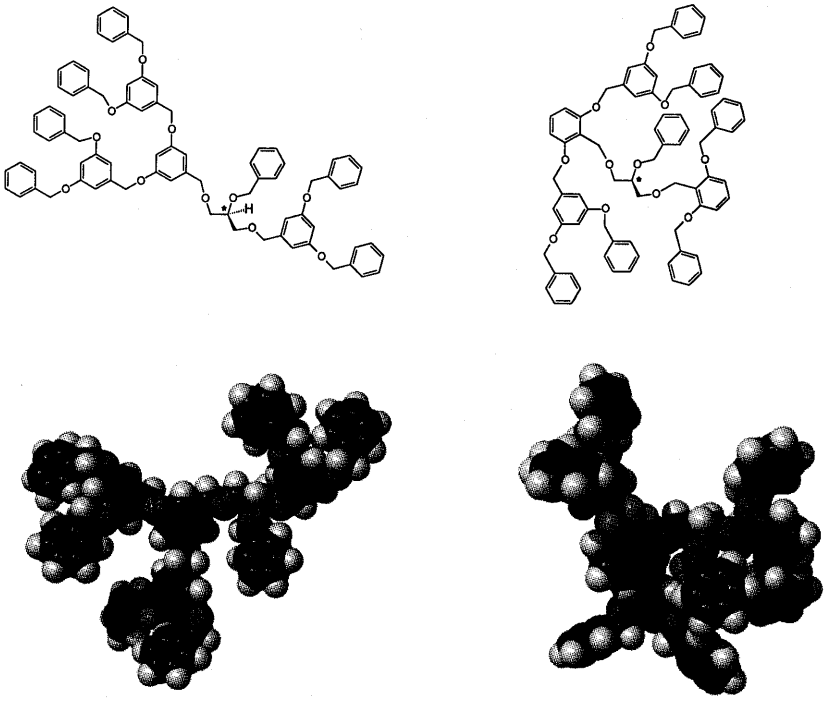
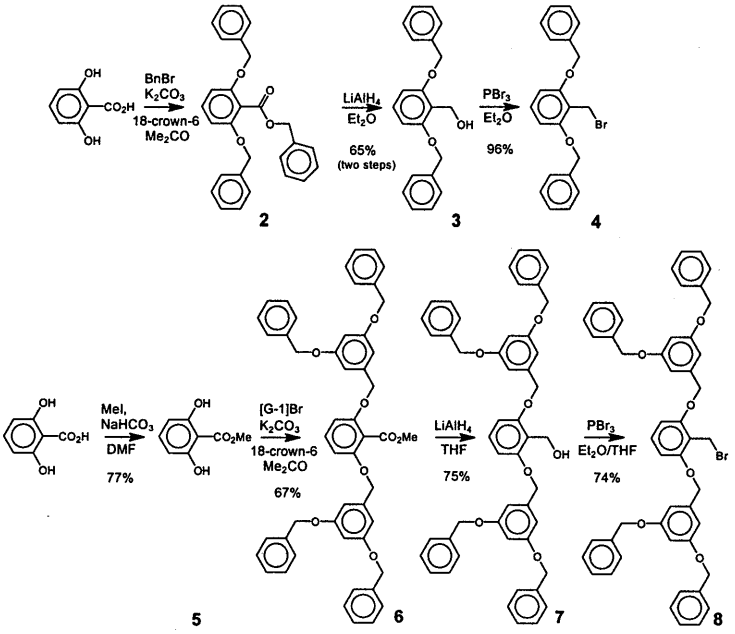


Figure 1. *Molecules **S*-1 (left side) and **S*-9 (right side).*

In this chapter, we present the concept of backfolding wedges for the synthesis of dendrimers with restricted flexibility, already at low generations. The effect of these wedges is illustrated by chiroptical data based on the modification of the Fréchet-type polybenzylether wedges by changing from a 3,5- to a 2,6-dibenzyloxy substitution pattern.

8.2 Synthesis of the backfolding wedges

2,6-Dihydroxybenzoic acid was used as a starting material for the synthesis of the first and second generation backfolding dendritic wedges (Scheme 1). The first generation was synthesized by a reaction of 2,6-dihydroxybenzoic acid with 3 equivalents of benzyl bromide, yielding benzyl 2,6-dibenzyloxybenzoate **2**, followed by a reduction with $LiAlH_4$ to 2,6-dibenzyloxybenzyl alcohol **3**. Subsequent bromination of **3** was accomplished by a reaction with PBr_3, yielding 2,6-dibenzyloxybenzyl bromide **4**, the first generation brominated backfolding dendrimer. For synthesizing the second generation backfolding dendritic wedge, first 2,6-dihydroxybenzoic acid was converted into methyl 2,6-dihydroxybenzoate **5** by a reaction with methyl iodide in DMF under the influence of $NaHCO_3$. In our first approach to backfolding, the normal Fréchet-type dendritic wedge of the first generation was brought into reaction with **5**, to yield **6**. After reduction to the corresponding benzyl alcohol **7**, the desired benzyl bromide **8** was obtained by reaction with PBr_3. The crystalline benzyl bromides **4** and **8** proved to be rather acid sensitive and compound **8** even decomposes upon standing in a chloroform solution.



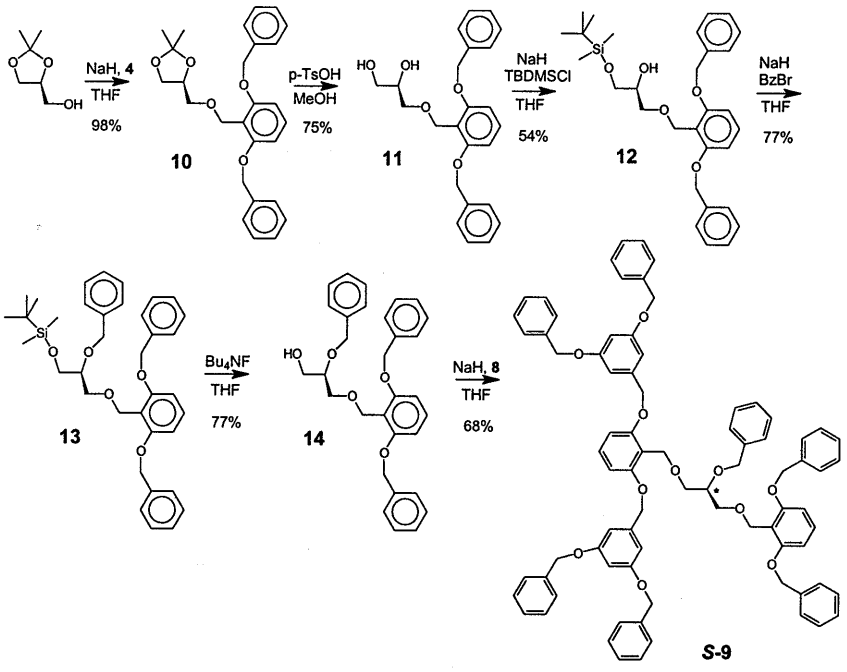
Scheme 1. *Synthetic route to the backfolding dendritic wedges.*

8.3 Backfolding dendrimer *S*-9

8.3.1 Synthetic strategy to *S*-9

To study the effect of backfolding dendritic wedges ***S*-9**, the conformationally more rigid isomer of ***S*-1**, has been synthesized (Figure 1). The conformational flexibility in ***S*-1** is based on the results obtained from a chiroptical study as there is no detectable optical activity in terms of ORD and CD spectroscopy or optical rotation,[13] and therefore, this compound can be referred to as being *cryptochiral*.[14]

The synthetic approach to chiral dendrimer ***S*-9** (Scheme 2), is similar to the synthesis of ***S*-1**, with normal Fréchet-type wedges, as reported previously.[13] However, due to the acid-sensitivity of the dendritic wedges, the use of strong acidic conditions in the synthetic route had to be circumvented. Enantiomerically pure *S*-(+)-solketal[16] ($[\alpha]_D^{20}$ = +15.2 (neat, 25 °C)) was used as a starting material for the synthesis of backfolding dendrimer ***S*-9**. The free alcohol functionality of the solketal was derivatized with the first generation backfolding bromide **4**, yielding **10**. Removal of the acetal protecting group was performed under mild acidic conditions, making use of a catalytic amount of *p*-toluenesulfonic acid in methanol, leading to diol **11**, a white crystalline solid. In order to differentiate between the two alcohol functionalities, a bulky protecting group was introduced by a reaction with NaH and TBDMS chloride. Only the desired monosubstituted product **12** and unreacted diol **11** could be obtained after the reaction. This mixture could be separated by washing with hexane in which only the desired product dissolved. The free secondary alcohol functionality was reacted with benzyl bromide (the zeroth generation dendrimer), yielding **13**. Subsequently, the TBDMS group was removed by reaction with Bu_4NF to yield precursor molecule **14**. In the final step the free primary alcohol functionality of **14** was reacted with the second generation backfolding bromide **8**, in a Williamson synthesis leading to target molecule ***S*-9**. Except for **11**, all chiral compounds were oils that had to be purified by column chromatography. All spectroscopic data are in full agreement with the proposed structures.



Scheme 2. *Synthetic route to chiral dendrimer **S-9**.*

8.3.2 Chiroptical properties of dendrimer *S*-9

Backfolding dendrimer ***S*-9** exhibited, in sharp contrast to ***S*-1**, an optical activity of $[\alpha]_D^{20} = +0.8$ (c = 2.2, CH_2Cl_2). A more thorough study was performed using ORD, UV and CD spectroscopy. The results of the ORD study are depicted in figure 2, showing a positive value for all wavelengths measured.

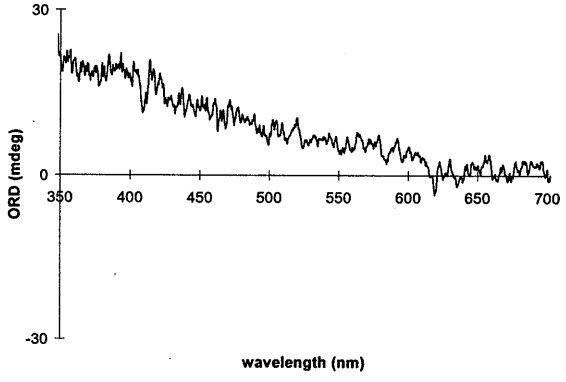


Figure 2. *ORD spectrum of chiral dendrimer **S-9** (c = 7, CH_2Cl_2) at room temperature.*

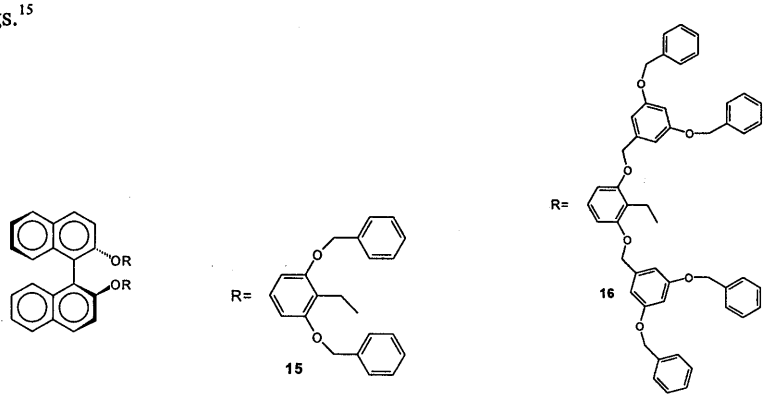
CD measurements (distilled CH_2Cl_2) were performed at wavelenghts λ = 320–220 nm. A very weak signal was found at λ = 280 nm, at a temperature of 15 ^{0}C, indicative for an induced chiral effect. However, at more elevated temperatures (30 ^{0}C) this signal vanished, indicating that the conformational flexibility/rigidity can be triggered by the temperature.

The difference in chiroptical effects for ***S*-1** and ***S*-9** is presumably the result of a higher degree of conformational rigidity in the latter (Figure 1). The conformational flexibility of ***S*-1** was demonstrated by the absence of detectable optical activity and could therefore be referred to as being *cryptochiral*.[14] Apparently, the flexibility present in the wedges, causes the differences between these wedges to become negligible. When introducing the backfolding wedges more rigidity is introduced, as could be deduced from the chiroptical features of the isomer of ***S*-1**, ***S*-9**. The limited flexibility in these backfolding wedges allows a differentiation between the wedges and hence expression of optical activity.

8.4 Axially chiral dendrimers

8.4.1 Synthesis and characterization of axially chiral dendrimers

For the synthesis of the axially chiral dendrimers enantiomerically pure *S*-(–)-1,1'-bi-2-naphthol[17] was used as the core, which was reacted[15] with the first (**4**) and second (**8**) generation backfolding wedge, to yield **15** and **16**, respectively (Scheme 3). The core material shows torsional angle dependent optical rotation, and is therefore ultimately suitable to study flexibility/rigidity of the backfolding wedges in comparison with the normal Fréchet-type analogs.[15]



Scheme 3. *The S-(–)-1,1'-bi-2-naphthol backfolding dendrimers **15** and **16**.*

The synthesis of the dendrimers is rather straightforward, but small amounts of impurities proved to be very hard to remove, leading to lower yields. All spectroscopic data in terms of ^{1}H-NMR and ^{13}C-NMR spectroscopy as well as IR spectroscopy, elemental analysis and MALDI-TOF-MS were in full agreement with the structures assigned to the compounds obtained. As was indicated previously,[15] racemization under these conditions is highly unlikely.

8.4.2 Chiroptical properties of axially chiral dendrimers 15 and 16

For the chiroptical features of the newly formed dendrimers the molar rotations were measured in CH_2Cl_2 as solvent and compared to the isomeric dendrimers built from the normal Fréchet-type dendritic wedges[15] (Table 1).

Table 1. *Optical rotation for the bisnaphthol dendrimers.*

compound[a]	$[\alpha]_D^{20}$ (CH_2Cl_2)	Calc. Molec. Mass	$[\Phi]_D$
[G-0]	–45.5 (c = 0.47)	466.59	–212
[G-1]	–22.8 (c = 0.89)	891.09	–203
[G-2]	–15.6 (c = 1.74)	1740.07	–271
[G-3]	–12.3 (c = 1.01)	3438.03	–424
[G-4]	–9.5 (c = 0.57)	6833.99	–650
15	–53.3 (c = 0.90)	891.09	–475
16	–23.2 (c = 1.74)	1740.07	–404

[a] Compounds [G-0] up to [G-4] are described in ref 15.

Also CD and ORD measurements were performed, but, these did not give any more detailed information. Unfortunately, an induced CD (ICD) effect could not be detected for these compounds. However, the data indicate that when applying a first generation backfolding wedge, the steric effect is even stronger than for the "normal" dendrimer of the third generation, from which also a backfolding effect was observed in REDOR NMR relaxation experiments.[7] When using the second generation backfolding wedge the effect becomes slightly less pronounced, possibly caused by the normal Fréchet-type dendritic part of the molecule that possesses a high degree of flexibility as was previously demonstrated in our chiral objects.[12–13] Nevertheless, it is shown that by introducing these small backfolding

wedges, crowding effects are introduced that up to now were only observed for higher generations of "normal" dendrimers.

8.5 Discussion and conclusion

In conclusion, we presented the concept of backfolding dendritic wedges (BF) by modifying the branching pattern of the Fréchet-type dendritic wedges from 3,5-dibenzyloxy ([G-x]) to 2,6-dibenzyloxy (BF[G-x]). The backfolding character of this new type of dendrimers is illustrated in chiral dendrimer ***S*-9** and in the axially chiral dendrimers **15** and **16**. The degree of chirality (as discussed in chapter 6) is not an issue of importance here as [G-x] and BF[G-x] are isomers and when comparing dendritic wedges of the same generation (as in ***S*-1** and ***S*-9**) primarily crowding effects are of importance.

The chiroptical properties of ***S*-9** indicate that these backfolding wedges increase the rigidity, as becomes apparent from the detectable optical activity and the induced CD effect. These findings were in sharp contrast with the results obtained for isomer ***S*-1** in which normal Fréchet-type dendritic wedges were used. The chirality in these compounds stems from the attachment of dendrimers of the first and second generation to the chiral glycerol-derived core. As could be deduced from studies presented in literature[5,7–10] crowding effects only arise at generations exceeding [G-3]. Therefore, it is most likely that for ***S*-1**, in which [G-1] and [G-2] are compared, no crowding effects are to be expected. As was shown by a chiroptical study for compound ***S*-9**, the backfolding wedges BF[G-1] and BF[G-2] show interactions possibly caused by crowding effects, as was proven by a nicely detectable optical activity, ORD measurements and even an induced CD (ICD) effect.

The introduction of these backfolding wedges also affects the flexibility in axially chiral dendrimers **15** and **16**. The results of these studies are compared with the results obtained for the normal Fréchet-type dendrimers.[15] In the former the larger molar rotation is the result of stronger steric interactions between the wedges, leading to a larger torsional angle between the naphthyl units. The obtained values for the molar rotation indicated that the backfolding/rigidifying effect of BF[G-1] is even larger than the effect of [G-3], in which the phenomenon of backfolding was reported before.[5,7–10]

Studies on Fréchet-type dendrimers as reported by Schlüter[5] and Wooley[7] contributed to a large extent to a better understanding of the backfolding character of the [G-x] wedges, but these studies were only performed in the solid state. It was demonstrated by Wooley[7] that the backfolding character of [G-x] in the solid state became prominent starting from [G-3], as was deduced from REDOR NMR experiments and modeling studies, but a quantitative study on the degree of backfolding proved to be difficult. The only report on studies in solution by

Aida,[10] dealing with the photoisomerization of azobenzene dendrimers of the Fréchet-type, described exciting packing phenomena starting from [G-3]. With this respect it is worthwhile noting that the most exciting results in dendrimers have been obtained with dense packing and interactions within these dendrimers.[3,8–10] With this in mind we have presented an easy route to come to the desired packing and rigidifying effects by the introduction of these BF[G-x] wedges. Also, the characterization of these small molecules is much more straightforward than for nanosized structures. This enables us to create more conformational rigidity at low generations which up to now was only possible at very high generations of dendrimers.

8.6 Experimental section

General

All solvents were of c.p. quality, except those used as reaction solvent which were of p.a. quality. THF was distilled over sodium/benzophenone prior to use. Column chromatography was performed with Merck silica gel 60 (particle size 0.063–0.200 mm). Melting points are uncorrected and were determined with a Jeneval microscope equipped with a Linkam hotstage. NMR spectra were run on a Bruker AM-400 spectrometer at frequencies of 400.1 MHz and 100.6 MHz for ^{1}H- and ^{13}C-nuclei, respectively. TMS was used as an internal standard and δ-values are given in ppm. The following abbreviations are used in the peak assignment: Ar refers to aromatic rings derived from 2,6-dihydroxybenzyl alcohol or bromide at the reactive center and Ar' refers to the aromatic rings derived from 3,5-dihydroxybenzyl alcohol one generation remote from the reaction center. Ph refers to aromatic rings derived from benzyl bromide. BN refers to resonances of the bisnaphthol core. IR-spectra were taken on a Perkin Elmer 1600 series FT-IR and data are given in cm^{-1}. ORD/CD measurements were performed on a Jasco 600 spectropolarimeter and $[\alpha]_D^{20}$ data were measured on a Jasco DIP-370 digital polarimeter. LSI-MS spectra were recorded at the University of Birmingham using a VG ZabSpec mass spectrometer, using a *p*-nitrobenzyl alcohol matrix MALDI-TOF-MS measurements were performed on a Voyager-DE machine at the University of Berkeley using an α-cyano-4-hydroxycinnamic acid matrix. Elemental analyses were performed on a Perkin Elmer 2400 series II machine.

2,6-Dibenzyloxybenzyl alcohol, 3

A mixture of 2,6-dihydroxybenzoic acid (15.4 g, 100 mmol), benzyl bromide (53 g, 0.31 mol), potassium carbonate (43.5 g, 0.31 mol) and 18-crown-6 (0.26 g, 1.0 mmol) in acetone (100 mL) was boiled under reflux overnight while vigorously stirred. The reaction mixture was allowed to cool to room temperature and the salts were removed by filtration. The filtrate was concentrated *in vacuo* yielding crude benzyl 2,6-dibenzyloxybenzoate **2**, as a yellow syrup, which was dissolved in anhydrous diethyl ether (200 mL). This solution was added dropwise to an argon blanketed suspension of $LiAlH_4$ (5.0 g, 0.13 mol) in diethyl ether (200 mL) at such a rate to ensure gentle reflux. The reaction mixture was boiled under reflux for one hour. After allowing the reaction

mixture to cool down to room temperature it was subsequently neutralized by the addition of ethyl acetate (10 mL) and aqueous sodium hydroxide (10% w/v, 10 mL). After removal of the salts by filtration and evaporation of the solvent, the residue was subjected to crystallization (toluene : hexane = 1:4, 300 mL), yielding **3** (20.72 g, 65%) as a white crystalline solid. m.p. 80–81 °C. ^{1}H-NMR ($CDCl_3$): δ 2.55 (t, J = 6.9 Hz, 1H, OH), 4.90 (d, J = 6.9 Hz, 2H, CH_2OH), 5.09 (s, 4H, CH_2Ph), 6.62 (d, J = 8.4 Hz, 2H, ArH-3,5), 7.17 (t, J = 8.3 Hz, 1H, ArH-4), 7.32 (t, J = 6.9 Hz, 2H, PhH-*para*), 7.38 (t, J = 7.7 Hz, 4H, PhH-*meta*), 7.42 (d, J = 6.9 Hz, 4H, PhH-*ortho*). ^{13}C-NMR ($CDCl_3$): δ 55.0 (CH_2OH), 70.4 (CH_2Ph), 105.5 (ArC-3,5), 118.0 (ArC-1), 127.2, 128.0, 128.6 (PhCH), 129.1 (ArC-4), 136.8 (PhC-*ipso*), 157.6 (ArC-2,6). IR (KBr): ν 3572 (OH stretch), 2942 and 2882 (CH_2 stretch), 1596 and 1496 (C=C stretch), 1451 (CH_2 deformation).

2,6-Dibenzyloxybenzyl bromide, 4

To a stirred and cooled (ice/salt bath) solution of **3** (8.02 g, 25.0 mmol) in diethyl ether (75 mL) was added dropwise a solution of phosphorus tribromide (2.5 g, 9.2 mmol) in diethyl ether (10 mL). After completion of the addition, the solution was stirred for another 30 min. The reaction mixture was poured in ice-cold water and the layers were separated. The organic layer was extracted with saturated aqueous sodium bicarbonate (1 x 25 mL). The organic layer was dried (Na_2SO_4) and the solvent evaporated *in vacuo*, yielding **4** (9.22 g, 96%) as a white solid, which colored slightly purple upon standing. ^{1}H-NMR ($CDCl_3$): δ 4.80 (s, 2H, CH_2Br), 5.15 (s, 4H, CH_2Ph), 6.58 (d, J = 8.4 Hz, 2H, ArH-3,5), 7.18 (t, J = 8.3 Hz, 1H, ArH-4), 7.32 (t, J = 7.3 Hz, 2H, PhH-*para*), 7.39 (dd, J = 7.1 and 1.6 Hz, 4H, PhH-*meta*), 7.49 (d, J = 7.1 Hz, 4H, PhH-*ortho*). ^{13}C-NMR ($CDCl_3$): δ 23.6 (CH_2Br), 70.3 (CH_2Ph), 105.3 (ArC-3,5), 115.4 (ArC-1), 127.1, 127.9, 128.6 (PhCH), 130.0 (ArC-4), 136.9 (PhC-*ipso*), 157.6 (ArC-2,6). IR (KBr): ν 3060 and 3027 (=C–H stretch), 2901 and 2861 (CH_2 stretch), 1598 and 1497 (C=C stretch), 1447 (CH_2 deformation).

Methyl 2,6-dihydroxybenzoate, 5

To a stirred mixture of 2,6-dihydroxybenzoic acid (7.73 g, 50.0 mmol) in DMF (50 mL) sodium bicarbonate (12.8 g, 152 mmol) and methyl iodide (4.8 mL, 77 mmol) were added. After one night another portion of methyl iodide (4.8 mL, 77 mmol) was added and stirring was continued for another 4 days at room temperature. The mixture was filtered, the solvent evaporated *in vacuo*, the residue subsequently taken up in CH_2Cl_2 and the suspension extracted with aqueous HCl (3 x 50 mL, 0.5 M) and saturated aqueous sodium bicarbonate (4 x 50 mL). The organic layer was dried, the solvent evaporated, and the solid residue sublimated at 0.2 mbar, yielding **5** (6.50 g, 77%) as a slightly yellow crystalline solid. m.p. 60–61 °C. ^{1}H-NMR ($CDCl_3$): δ 4.08 (s, 3H, CH_3), 6.49 (d, J = 8.2 Hz, 2H, ArH-3,5), 7.31 (t, J = 8.3 Hz, 1H, ArH-4), 9.66 (br s, 2H, OH). ^{13}C-NMR ($CDCl_3$): δ 52.0 (CH_3), 99.8 (ArC-1), 108.1 (ArC-3,5), 136.5 (ArC-4), 160.7 (ArC-2,6), 169.9 (C=O). IR (KBr): ν 3416 (OH stretch), 1575 and 1475 (C=C stretch), 1325 (OH deformation, phenol), 1196 (COH stretch, phenol).

Methyl 2,6-bis(3,5-dibenzyloxy-benzyloxy)benzoate, 6

A mixture of **5** (1.68 g, 10 mmol), 3,5-dibenzyloxybenzyl bromide ([G-1]Br, 8.05 g, 21.0 mmol), potassium carbonate (4.15 g, 30 mmol) and 18-crown-6 (0.26 g, 1.0 mmol) in acetone (50 mL) was boiled under reflux for 2 days, while vigorously stirred. The mixture was allowed to cool to room temperature and the salts were filtered off. The solvent was evaporated and the residue was subjected to column chromatography (250 g SiO_2, toluene/CH_2Cl_2 = 1:1, R_f = 0.15) yielding **6** (5.14 g, 67%) as

a slightly yellow viscous syrup. ^{1}H-NMR ($CDCl_3$): δ 3.90 (s, 3H, CH_3), 5.02 (s, 8H, CH_2Ph), 5.06 (s, 4H, CH_2Ar'), 6.54 (m, 4H, ArH-3,5, Ar'H-4), 6.66 (d, J = 1.9 Hz, 4H, Ar'H-2,6), 7.17 (t, J = 8.2 Hz, 1H, ArH-4), 7.20–7.45 (m, 20 H, PhH). ^{13}C-NMR ($CDCl_3$): δ 52.3 (CH_3), 70.0 (CH_2Ph), 70.3 (CH_2Ar'), 101.5 (Ar'C-4), 105.6 (Ar'C-2,6), 105.9 (ArC-3,5), 114.3 (ArC-1), 127.5, 128.0, 128.5 (PhCH), 131.0 (ArC-4), 136.8 (PhC-*ipso*), 139.3 (Ar'C-1), 156.3 (ArC-2,6), 160.1 (Ar'C-3,5), 166.6 (C=O). IR (KBr): ν 3088 and 3031 (=C–H stretch), 2946 and 2874 (CH_2 stretch), 1732 (C=O stretch, ester), 1595 and 1497 (C=C stretch), 1451 (CH_2 deformation).

2,6-Bis(3,5-dibenzyloxy-benzyloxy)benzyl alcohol, 7

A solution of **6** (3.63 g, 4.70 mmol) in anhydrous THF (30 mL) was added dropwise to an argon blanketed suspension of $LiAlH_4$ (0.3 g, 8 mmol) in anhydrous THF (30 mL) at such a rate to ensure mild reflux. This mixture was stirred overnight at room temperature and was subsequently neutralized with ethyl acetate (10 mL) and aqueous sodium hydroxide (10% w/v, 2 mL). The salts were filtered off and the solvent was removed *in vacuo* to yield **7** (2.62 g, 75%) as a viscous oil that crystallized slowly. m.p. 85–87 °C. ^{1}H-NMR ($CDCl_3$): δ 2.55 (t, J = 4.3 Hz, 1H, OH), 4.87 (d, J = 4.3 Hz, 2H, CH_2OH), 5.01 (s, 12 H, CH_2Ph and CH_2Ar'), 6.56 (d, J = 8.3 Hz, 2H, ArH-3,5 and t, J = 2.2 Hz, 2H, Ar'H-4), 6.66 (d, J = 2.2 Hz, 4H, Ar'H-2,6), 7.12 (t, J = 8.4 Hz, 1H, ArH-4), 7.25–7.50 (m, 20H, PhH). ^{13}C-NMR ($CDCl_3$): δ 54.9 (CH_2OH), 70.0 (CH_2Ph), 70.3 (CH_2Ar), 101.5 (Ar'C-4), 105.5 (ArC-3,5), 106.0 (Ar'C-2,6), 117.9 (ArC-1), 127.5, 127.9, 128.5 (PhCH), 129.1 (ArC-4), 136.5 (PhC-*ipso*), 139.2 (Ar'C-1), 157.4 (ArC-2,6), 160.1 (Ar'C-3,5). IR (KBr): ν 3581 (OH stretch), 3031 (=C–H stretch), 2927 and 2874 (CH_2 stretch), 1595 and 1497 (C=C stretch), 1448 (CH_2 deformation), 1048 (CO stretch, primary OH).

2,6-Bis(3,5-dibenzyloxy-benzyloxy)benzyl bromide, 8

To a stirred and cooled (ice/salt bath) suspension of **7** (0.74 g, 1.00 mmol) in diethyl ether/dry THF (3/1 v/v, 12 mL) was added dropwise phosphorus tribromide (0.25 g, 0.92 mmol) in diethyl ether (4 mL). Stirring of the cooled solution was continued for 2.25 h, and then methanol (70 mL) was added. Subsequent filtration of the white precipitate gave **8** (0.60 g, 0.74 mmol, 74%). ^{1}H-NMR ($CDCl_3$): δ 4.80 (s, 2H, CH_2Br), 5.05 (s, 8H, CH_2Ph), 5.08 (s, 4H, CH_2Ar'), 6.52 (d, J = 8.4 Hz, 2H, ArH-3,5), 6.57 (t, J = 2.2 Hz, 2H, Ar'H-4), 6.75 (d, J = 2.2 Hz, 4H, ArH'-2,6), 7.23 (t, J = 8.3 Hz, 1H, ArH-4), 7.30–7.55 (m, 20H, PhH). ^{13}C-NMR ($CDCl_3$): δ 24.0 (CH_2Br), 70.0 (CH_2Ar'), 70.1 (CH_2Ph), 101.8 (Ar'C-4), 105.2 (ArC-3,5), 105.8 (Ar'C-2,6), 127.5, 127.9, 128.6 (PhCH), 130.1 (ArC-4), 136.8 (PhC-*ipso*), 139.4 (Ar'C-1), 157.5 (ArC-2,6), 160.2 (Ar'C-3,5). IR (KBr): ν 3031 (=C–H stretch), 2927 and 2875 (CH_2 stretch), 1595 and 1497 (C=C stretch), 1450 (CH_2 deformation).

***S*-1-O:2-O-Isopropylidene-3-(2,6-dibenzyloxy-benzyloxy)propane-1,2-diol, 10**

To a solution of *S*-(+)-solketal (1.00 g, 7.57 mmol) in anhydrous THF (50 mL) was added pentane-washed sodium hydride (0.82 g, 34 mmol). After stirring for 1 h, **4** (3.26 g, 8.50 mmol) was added and the mixture was stirred overnight at room temperature. Careful addition of water (2 mL) and evaporation of the THF gave an oil, to which CH_2Cl_2 (50 mL) and water (50 mL) were added. The organic layer was separated, and the aqueous phase was extracted with diethyl ether (2 x 40 mL). The combined organic layers were dried with Na_2SO_4 and concentrated to give the crude product, which was purified by column chromatography (150 g SiO_2, hexane/ethyl acetate = 4:1, R_f = 0.15) yielding **10** (3.22 g, 98%) as a slightly yellow oil. ^{1}H-NMR ($CDCl_3$): δ 1.31, 1.37 (2 x s, 6H, CH_3), 3.46, 3.62 (2 x dd, J = 9.9 and 6.6 Hz, 2H, CH_2OCH_2Ar), 3.65, 3.93 (2 x dd, J = 8.2 and 6.5 Hz, 2H, CH_2

cyclic), 4.24 (quintet, J = 5.9 Hz, 1H, C*H), 4.75 and 4.80 (2 x d, J = 10.2 Hz, 2H, OCH_2Ar), 5.09 (s, 4H, CH_2Ph), 6.60 (d, J = 8.4 Hz, 2H, ArH-3,5), 7.17 (t, J = 8.4 Hz, 1H, ArH-4), 7.30 (t, J = 7.5 Hz, 2H, PhH-*para*), 7.35 (t, J = 7.3 Hz, 4H, PhH-*meta*), 7.43 (d, J = 7.7 Hz, 4H, PhH-*ortho*). ^{13}C-NMR ($CDCl_3$): δ 25.3, 26.7 (CH_3), 61.7, 67.2 (2 x CH_2 core), 70.3 (CH_2Ph), 71.1 (CH_2Ar), 74.5 (C*H), 105.4 (ArC-3,5), 109.0 (*C*(CH_3)$_2$), 115.0 (ArC-1), 127.1, 127.7, 128.4 (PhCH), 129.7 (ArC-4), 137.1 (PhC-*ipso*), 158.5 (ArC-2,6). IR (KBr): ν 3031 (=C–H stretch), 2932 and 2876 (CH_2 stretch), 1596 and 1497 (C=C stretch), 1453 (CH_2 deformation), 1370 (C(CH_3)$_2$ deformation), 1114 (CH_2OCH_2 stretch). $[\alpha]_D^{20}$ = + 11.2 (c = 3.6, CH_2Cl_2).

_R_-3-(2,6-Dibenzyloxy-benzyloxy)propane-1,2-diol, 11

To a stirred solution of **10** (3.22 g, 7.4 mmol) in absolute methanol (100 mL) a crystal of *p*-toluenesulfonic acid was added, causing the solution to turn yellow immediately. Solid sodium carbonate was added to the stirred solution when TLC showed complete conversion (approx. 2 days), causing the reaction mixture to turn colorless again. The solvent was removed *in vacuo* and the residue was taken up in CH_2Cl_2 and water. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The organic layers were combined and dried with Na_2SO_4. The solvent was removed *in vacuo* and the residue was subjected to crystallization from hexane/ethyl acetate (2:1 v/v, 75 mL), which furnished pure **11** (2.19 g, 75%) as a white crystalline solid. m.p. 86 ^{0}C. ^{1}H- NMR ($CDCl_3$): δ 2.11 (dd, J = 7.4 and 5.3 Hz, 1H, CH_2OH), 2.71 (d, J = 5.4 Hz, 1H, CHO*H*), 3.48–3.63 (m, 4H, CH_2OH, CH_2OCH_2Ar), 3.77 (qui, J = 5.0 Hz, 1H, C*H), 4.73 and 4.79 (2 x d, J = 10.1 Hz, 2H, CH_2Ar), 5.11 (s, 4H, CH_2Ph), 6.63 (d, J = 8.4 Hz, 2H, ArH-3,5), 7.21 (t, J = 8.4 Hz, 1H, ArH-4), 7.33 (t, J = 7.1 Hz, 2H, PhH-para), 7.39 (t, J = 7.5 Hz, 4H, PhH-*meta*), 7.43 (d, J = 7.0 Hz, 4H, PhH-*ortho*). ^{13}C-NMR ($CDCl_3$): δ 62.0, 64.3 (CH_2OH, *C*H_2OCH_2Ar), 70.2 (C*H), 70.5 (CH_2Ph), 71.9 (CH_2Ar), 105.5 (ArC-3,5), 114.7 (ArC-1), 127.3, 127.9, 128.6 (PhCH), 129.9 (ArC-4), 136.9 (PhC-*ipso*), 158.4 (ArC-2,6). IR (KBr): ν 3252 (OH stretch), 3032 (=C–H stretch), 2935 and 2878 (CH_2 stretch), 1600 and 1497 (C=C stretch), 1453 (CH_2 deformation), 1242 (arylalkyl ether stretch). $[\alpha]_D^{20}$ = –4.0 (c = 0.6, CH_2Cl_2).

_S_-1-(2,6-Dibenzyloxy-benzyloxy)-3-(*tert*-butyldimethylsilyloxy)propan-2-ol, 12

To a solution of **11** (1.58 g, 4.00 mmol) in anhydrous THF (10 mL) was added pentane-washed sodium hydride (0.958 g, 4.17 mmol). After stirring for 45 min, *tert*-butyldimethylsilyl chloride (0.61 g, 4.02 mmol) was added and stirring was continued for another 45 min at room temperature. The mixture was poured in diethyl ether (100 mL) and the organic layer was subsequently washed with aqueous potassium carbonate (10% w/v, 30 mL), brine (30 mL) and dried with Na_2SO_4. The solvent was removed *in vacuo* and the residue was subjected to hexane washing. Starting diol **11** could be recovered as a crystalline solid (0.50 g, 32%) and the product **12** was dissolved in hexane. Removal of the hexane yielded **12** (1.09 g, 2.14 mmol, 54%) as a colorless oil. ^{1}H-NMR ($CDCl_3$): δ 0.01 (s, 6H, Si(CH_3)$_2$), 0.86 (s, 9H, SiC(CH_3)$_3$), 2.59 (d, J = 4.4 Hz, 1H, OH), 3.46–3.62 (m, 4H, CH_2OTBDMS, CH_2OCH_2Ar), 3.82 (qui, J = 5.0 Hz, 1H, C*H), 4.79 (s, 2H, CH_2Ar), 5.12 (s, 4H, CH_2Ph), 6.62 (d, J = 8.4 Hz, 2H, ArH-2,6), 7.19 (t, J = 8.4 Hz, 1H, ArH-4), 7.32 (t, J = 6.9 Hz, 2H, PhH-*para*), 7.38 (t, J = 7.5 Hz, 4H, PhH-*meta*), 7.45 (d, J = 7.2 Hz, 4H, PhH-*ortho*). ^{13}C-NMR ($CDCl_3$): δ –5.5 (Si(*C*H_3)$_2$), 18.2 (Si*C*(CH_3)$_3$), 25.8 (SiC(*C*H_3)$_3$), 61.7, 64.2 (*C*H_2OCH_2Ar, *C*H_2OTBDMS), 70.4 (CH_2Ph), 70.5 (C*H), 70.9 (CH_2Ar), 105.5 (ArC-3,5), 115.1 (ArC-1), 127.1, 127.8 and 128.5 (PhCH), 129.7 (ArC-4), 137.1 (PhC-*ipso*), 158.5 (ArC-2,6). IR (KBr): ν 3483 (OH stretch), 3032 (=C–H stretch), 2927 and 2856 (CH_2 stretch), 1596 and 1498 (C=C stretch), 1453 (CH_2 deformation), 1113 (CH_2OCH_2 stretch). $[\alpha]_D^{20}$ = –1.5 (c = 1.0, CH_2Cl_2).

S-2-Benzyloxy-1-(2,6-dibenzyloxy-benzyloxy)-3-(*tert*-butyldimethylsilyloxy)propane, 13

To a solution of **12** (1.00 g, 1.96 mmol) in anhydrous THF (40 mL) was added pentane-washed sodium hydride (0.24 g, 10 mmol). After stirring for 1 h, benzyl bromide (0.52 g, 3.0 mmol) was added and the mixture stirred at room temperature for 2 days. Addition of water (2 mL) and evaporation of the THF gave an oil, which was dissolved in CH_2Cl_2 (50 mL) and water (50 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). Drying of the combined organic layers with Na_2SO_4 and evaporation of the solvent yielded a crude oil, which was subjected to column chromatography (45 g SiO_2, hexane/ethyl acetate = 10:1, R_f = 0.22), yielding **13** (0.90 g, 77%) as a colorless oil. ^{1}H-NMR ($CDCl_3$): δ 0.02 (d, J = 3.4 Hz, 6H, $Si(CH_3)_2$), 0.89 (s, 9H, $SiC(CH_3)_3$), 3.69 (m, 5H, CH_2OCH_2Ar, C*H, $CH_2OTBDMS$), 4.64 and 4.69 (2 x d, J = 11.9 Hz, 2H, C*HOCH_2Ph), 4.84 (s, 2H, CH_2Ar), 5.14 (s, 4H, $ArOCH_2Ph$), 6.65 (d, J = 8.4 Hz, 2H, ArH-3,5), 7.23 (t, J = 8.4 Hz, 1H, ArH-4), 7.25–7.50 (m, 15H, PhH). ^{13}C-NMR ($CDCl_3$): δ –5.5 and –5.4 ($Si(CH_3)_2$), 18.2 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 61.6, 63.7 ($CH_2OTBDMS$, CH_2OCH_2Ar), 70.4, 72.1 ($ArOCH_2Ph$, C*HOCH_2Ph, CH_2OAr), 79.1 (C*H), 105.6 (ArC-3,5), 115.5 (ArC-1), 127.0, 127.2, 127.6, 127.7, 128.1, 128.4 (PhCH), 129.6 (ArC-4), 137.3 ($ArOCH_2PhC$-*ipso*), 139.1 (C*HOCH_2Ph*C-ipso*), 158.6 (ArC-2,6). IR (KBr): ν 3031 (=C–H stretch), 2927 and 2856 (CH_2 stretch), 1596 and 1497 (C=C stretch), 1453 (CH_2 deformation), 1115 (CH_2OCH_2 stretch). $[\alpha]_D^{20}$ = +0.4 (c = 1.0, CH_2Cl_2).

R-2-Benzyloxy-3-(2,6-dibenzyloxy-benzyloxy)propan-1-ol, 14

To a stirred solution of **13** (0.82 g, 1.37 mmol) in THF (10 mL) was added a solution of Bu_4NF in THF (1 M, 6 mL). The reaction mixture was stirred at room temperature until TLC showed complete conversion (approx. 2 days). The solvent was evaporated, the residue taken up in CH_2Cl_2 (40 mL) and washed with brine (3 x 30 mL). The organic layer was dried with Na_2SO_4 and the solvent evaporated. The remaining viscous oil was subjected to column chromatography (80 g SiO_2, hexane/ethyl acetate = 2:1, R_f = 0.3) which furnished **14** (0.51 g, 77%) as a colorless viscous liquid. ^{1}H-NMR ($CDCl_3$): δ 2.25 (t, J = 5.2 Hz, OH), 3.53–3.64 (m, 4H, CH_2OCH_2Ar, CH_2OH), 3.69 (qui, J = 5.2 Hz, 1H, C*H), 4.51 and 4.61 (2 x d, J = 11.8 Hz, 2H, CH_2OCH_2Ar), 4.73 and 4.78 (d, J = 10.2 Hz, 2H, C*HOCH_2Ph), 5.08 (s, 4H, $ArOCH_2Ph$), 6.61 (d, J = 8.4 Hz, 2H, ArH-3,5), 7.19 (t, J = 8.4 Hz, 1H, ArH-4), 7.22–7.44 (m, 15H, PhH). ^{13}C-NMR ($CDCl_3$): δ 61.9, 63.3, 70.5, 71.8 (C*HOCH_2, CH_2OCH_2Ar, CH_2OH), 70.4 ($ArOCH_2Ph$), 77.5 (C*H), 105.5 (ArC-3,5), 114.9 (ArC-1), 127.2, 127.6, 127.7, 127.8, 128.3, 128.5 (PhCH), 129.8 (ArC-4), 137.1 ($ArOCH_2PhC$-*ipso*), 138.4 (C*HOCH_2Ph*C-ipso*), 158.5 (ArC-2,6). IR (KBr): ν 3460 (OH stretch), 3062 and 3031 (=C–H stretch), 2924 and 2873 (CH_2 stretch), 1596 and 1497 (C=C stretch), 1453 (CH_2 deformation), 1114 (CH_2OCH_2 stretch). $[\alpha]_D^{20}$ = +11.1 (c = 1.2, CH_2Cl_2).

S-2-Benzyloxy-1-[2,6-bis(3,5-dibenzyloxy-benzyloxy)benzyloxy]-3-(2,6-dibenzyloxy-benzyloxy) propane, S-9

To a solution of **14** (0.13 g, 0.27 mmol) in anhydrous THF (40 mL) was added pentane-washed sodium hydride (0.05 g, 2 mmol). After stirring for 1 h at room temperature, **8** (0.26 g, 0.32 mmol) was added, the mixture stirred and heated under reflux overnight. Addition of water (2 mL) and evaporation of the THF gave an oil, which was taken up in CH_2Cl_2 (50 mL) and water (50 mL). After separation of the organic phase, the aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL). Drying of the combined organic layers with Na_2SO_4 and evaporation of the solvent yielded a crude oil, which

was subjected to column chromatography (35 g SiO_2, CH_2Cl_2, R_f = 0.2) to yield ***S*-9** (0.22 g, 68%) as a slightly yellow viscous oil. ^{1}H-NMR ($CDCl_3$): δ 3.58–3.69 (m, 4H, C*HCH_2), 3.79 (qui, J = 5.5 Hz, 1H, C*H), 4.51 and 4.67 (2 x s, 4H, CH_2OCH_2OAr), 4.71 and 4.73 (2 x d, J = 10.3 Hz, 2H C*HOCH_2Ph), 4.89 and 4.90 (2 x s, 8H, $ArOCH_2Ph$, $ArOCH_2Ar'$), 4.91 (s, 8H, $Ar'OCH_2Ph$), 6.44 and 6.48 (2 x d, J = 8.4 Hz, 4H, ArH-3,5), 6.51 (t, J = 2.2 Hz, 2H, Ar'H-4), 6.64 (d, J = 2.2 Hz, 4H, Ar'H-2,6), 7.03–7.35 (m, 37H, ArH-4 and PhH). ^{13}C-NMR ($CDCl_3$): δ 61.4, 69.8, 70.1, 70.9, 71.0, 71.8 (CH_2), 77.4 (C*H), 101.3 (Ar'C-4), 105.4 and 105.6 (ArC-3,5), 105.8 (Ar'C-2,6), 115.4, 115.5 (ArC-1), 126.8, 126.9, 127.2, 127.4, 127.5, 127.8, 128.3, 128.4, 129.3, 129.4 (PhCH), 129.3, 129.4 (ArC-4), 136.7 ($Ar'OCH_2PhC$-*ipso*), 137.1 ($ArOCH_2PhC$-*ipso*), 139.1 ($C*HOCH_2PhC$-*ipso*), 139.7 (Ar'C-1), 158.4 (ArC-2,6), 159.9 (Ar'C-3,5). IR (KBr): ν 3031 (=C–H stretch), 2927 and 2872 (CH_2 stretch), 1596 and 1497 (C=C stretch), 1452 (CH_2 deformation), 1115 (CH_2OCH_2 stretch). $[\alpha]_D^{20}$ = +0.8 (c = 2.2, CH_2Cl_2). LSI-MS for $C_{80}H_{74}O_{11}$ (calculated mass: 1210.5). Found: 1233 $[M+Na]^+$, 1249 $[M+K]^+$, 1343 $[M+Cs]^+$.

S-2,2'-Bis(2,6-dibenzyloxy-benzyloxy)-1,1'-binaphthalene, 15

A vigorously stirred mixture of *S*-(–)-1,1'-bi-2-naphthol (143.4 mg, 0.501 mmol), **4** (383.8 mg, 1.001 mmol), 18-crown-6 (0.03 g, 0.1 mmol) and potassium carbonate (2.5 g, 18 mmol) in acetone (40 mL) was heated under reflux for 2 days. The reaction mixture was allowed to cool to room temperature and the salts were removed by filtration. The filtrate was concentrated *in vacuo* and the residue was subjected twice to column chromatography (30 g SiO_2, toluene, R_f = 0.24) to yield pure **15** (0.19 g, 43%) as a slightly yellow foam. ^{1}H-NMR ($CDCl_3$): δ 4.55, 4.66 (2 x d, J = 12.1 Hz, 8H, $ArOCH_2Ph$), 5.15, 5.24 (2 x d, J = 10.7 Hz, 4H, CH_2Ar), 6.25 (d, J = 8.3 Hz, 4H, ArH-3,5), 6.82–6.90 (m, 4H, BNH), 6.93 (t, J = 8.3 Hz, 2H, ArH-4), 7.21–7.37 (m, 22H, PhH, BNH), 7.51 (s, 4H, BNH), 7.63 (dd, J = 8.1 and 0.8 Hz, 2H, BNH). ^{13}C-NMR ($CDCl_3$): δ 61.6 (CH_2Ar), 70.1 ($ArOCH_2Ph$), 105.6 (ArC-3,5), 115.1 (ArC-1), 118.6 (BNCH), 122.0 (BNC), 123.0 (BNCH), 125.5 (BNCH), 125.7 (BNCH), 127.0, 127.3, 128.2 (PhCH, BNCH), 128.5 (BNCH), 129.4 (2 x C, ArC-4, BNC), 134.3 (BNC), 137.2 (PhC-*ipso*), 155.1 (BNC), 158.3 (ArC-2,6). IR (KBr): ν 3031 (=C–H stretch), 2927 and 2868 (CH_2 stretch), 1595 and 1507 (C=C stretch), 1452 (CH_2 deformation), 1264 (CO stretch, arylalkyl ether). $[\alpha]_D^{20}$ = –53.3 (c = 0.90, CH_2Cl_2). MALDI-TOF-MS: Calc. for $C_{62}H_{50}O_6$: 889.4. Found: 915 $[M+Na]^+$, 931 $[M+K]^+$. Anal.: Calc. C, 83.57; H, 5.66. Found C, 83.53; H, 5.69.

S-2,2'-Bis[2,6-bis(3,5-dibenzyloxy-benzyloxy)benzyloxy]-1,1'-binaphthalene, 16

A vigorously stirred mixture of *S*-(–)-1,1'-bi-2-naphthol (141.5 mg, 0.494 mmol), **8** (821.7 mg, 1.02 mmol), 18-crown-6 (0.03 g, 0.1 mmol) and potassium carbonate (2.5 g, 18 mmol) in acetone (50 mL) was heated under reflux for 2 days. The reaction mixture was allowed to cool to room temperature and the salts were removed by filtration. The filtrate was concentrated *in vacuo* and subjected to column chromatography (30 g SiO_2, toluene, R_f = 0.2), which furnished pure **16** (0.52 g, 60%) as a slightly yellow foam. ^{1}H-NMR ($CDCl_3$): δ 4.38, 4.48 (2 x d, J = 12.6 Hz, 8H, $ArOCH_2Ar'$), 4.78, 4.83 (2 x d, J = 11.6 Hz, 16H, $Ar'OCH_2Ph$), 5.17, 5.19 (2 x d, J = 10.1 Hz, 4H, CH_2Ar), 6.10 (d, J = 8.4 Hz, 4H, ArH-3,5), 6.44 (d, J = 2.1 Hz, 8H, Ar'H-2,6), 6.54 (t, J = 2.2 Hz, 4H, Ar'H-4), 6.77 (m, 2H, BNH), 6.81 (t, J = 8.3 Hz, 2H, ArH-4), 6.91 (d, J = 8.5 Hz, 2H, BNH), 7.02 (m, 2H, BNH), 7.18–7.29 (m, 40H, PhH), 7.41 (d, J = 8.1 Hz, 2H, BNH), 7.48 (d, J = 9.0 Hz, 2H, BNH), 7.55 (d, J = 9.1 Hz, 2H, BNH). ^{13}C-NMR ($CDCl_3$): δ 61.1 (CH_2Ar), 69.8 ($ArOCH_2Ar'$, $Ar'OCH_2Ph$), 101.2 (Ar'C-4), 105.3 (Ar'C-2,6), 105.7 (ArC-3,5), 114.6 (ArC-1), 116.8 (BNCH), 121.1 (BNC), 122.9 (BNCH), 125.4 (BNCH), 125.6 (BNCH), 127.4, 127.7, 128.4 (PhCH, BNCH), 128.8 (BNCH), 129.2 (BNC), 129.6 (ArC-4), 134.2 (BNC), 136.8 (PhC-*ipso*), 140.0 (Ar'C-1), 155.0 (BNC), 158.1 (ArC-2,6), 159.9

(Ar'C-3,5). IR (KBr): ν 3061 and 3031 (=C–H stretch), 2927 and 2869 (CH_2 stretch), 1595 and 1497 (C=C stretch), 1451 (CH_2 deformation). $[\alpha]_D^{20} = -23.2$ (c = 1.74, CH_2Cl_2). MALDI-TOF-MS: Calc. for $C_{118}H_{98}O_{14}$: 1739.7. Found: 1763.6 $[M+Na]^+$, 1780.6 $[M+K]^+$. Anal.: Calc. C, 81.45; H, 5.68. Found C, 81.04; H, 5.77.

8.7 References

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9 Isocyanates and dendrimer synthesis

Summary

*A mild and convenient method for the synthesis and isolation of isocyanates, obtained from the reaction of primary amines with di-t-butyltricarbonate **(1)** is described. This method proved not only applicable for the quantitative formation of both aromatic and aliphatic isocyanates, but also rendered accessible isocyanates that cannot be synthesized using the conventional methods. Dendritic isocyanates were constructed by the reaction of **1** with all generations of poly(propylene imine) dendrimers. These compounds were reacted in situ with primary and secondary alcohols and amines to afford a variety of end group functionalized dendrimers, **11–14**. Also building block **8** could be synthesized when using **1**, which proved to be very useful for the construction of dendrimers in a one-pot synthetic procedure. The selectivity difference of the two isocyanate functionalities of this building block toward alcohols proved to be of crucial importance for the construction of the polycarbamate/urea based dendrimers **16–20**.*

9.1 Introduction

For the synthesis of aliphatic or aromatic isocyanates out of the corresponding primary amines, commonly phosgene or triphosgene is employed.[1] However, this involves relative drastic conditions, in view of the formation of gaseous hydrochloric acid, while phosgene is highly toxic. Other limitations arise in the construction of multifunctional isocyanates, especially when intramolecular reactions may occur, e.g. in the attempted synthesis of 1,3-propanediisocyanate starting from 1,3-diaminopropane, a six–membered urea ring is formed instead. These observations initiated many investigations toward new synthetic approaches for the construction of less hazardous, although sufficiently reactive phosgene analogs. A nice example, which is already commercially available is 1,1'-carbonyldiimidazole,[2] a compound that has even been proven useful in the synthesis of e.g. (hyperbranched) polymers[3] and dendrimers.[4] Recently, Knölker *et al.*[5] reported on the use of di-*t*-butyldicarbonate (BOC_2O) as a reagent in the synthesis of isocyanates. With this procedure aromatic as well as aliphatic primary amines can be converted into isocyanates in

high yields with BOC_2O when using 4-N,N-dimethylaminopyridine (DMAP) as the catalyst. Unfortunately, the method was limited to sterically hindered amines. This method is closely related to a report of Tarbell[6] on the *in situ* formation of some aromatic isocyanates by means of di-*t*-butyltricarbonate. The potential of this method was, however, by far not investigated to its full extent. In this chapter we report first on the use of tricarbonate **1** for the synthesis of isocyanates **2–10**, starting from the corresponding primary amines. Moreover, dendritic polycarbamate- and urea-based poly(propylene imine) dendrimers **11–14** could be obtained by a reaction of the *in situ* formed dendritic isocyanates with alcohols and amines. The utility of this method was illustrated in the reaction of enantiomerically pure isocyanate **3** with the primary amines of all generations of poly(propylene imine) dendrimers to yield urea-based structures **15a–15e**. Finally, a new and convenient method is introduced for the synthesis of polycarbamate/urea dendrimers **16–20** in a one-pot procedure based on the use of diisocyanate **8** as a building block.

9.2 Synthesis of isocyanates

For the construction and isolation of isocyanates on laboratory scale we employed di-*t*-butyltricarbonate **1** as the reagent in a reaction with primary amines. This compound has already been proven useful for the *in situ* formation of some aromatic isocyanates,[6] starting from primary amines. The synthesis of **1** was first reported in 1969[7] as a precursor of di-*t*-butyldicarbonate (BOC_2O). The Organic Syntheses procedure was followed and starts with the insertion of CO_2 in potassium-*t*-butoxide and subsequent reaction with phosgene (Figure 1). After crystallization from pentane, the desired tricarbonate **1** was obtained in 84% yield. When stored at room temperature compound **1** gradually decomposes to CO_2, isobutene and *t*-butanol.[7] Therefore, this compound is stored at, or preferably below, 4 °C to maintain its original quality. This compound was used as a reagent for the conversion of a variety of primary amines into isocyanates **2–10** (Table 1).

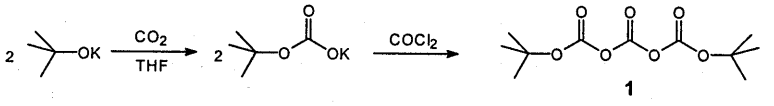
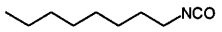
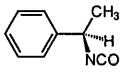
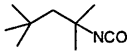
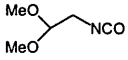
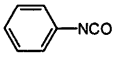
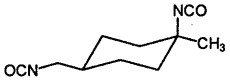
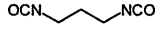
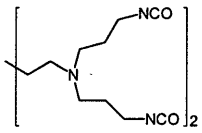


Figure 1. *Synthesis of di-t-butyltricarbonate 1.*

The conversion of the primary amines into the corresponding isocyanates (**2–10**) was performed in freshly distilled CH_2Cl_2, but reactions performed in e.g. THF or acetone also afforded the desired isocyanates in excellent yields. The reactions were performed on a 5–10 mmol scale by the addition of a solution of the amine in CH_2Cl_2 to a stirred solution of **1** in

CH_2Cl_2. An immediate evolution of CO_2 was observed during the addition. After stirring for 5 min at room temperature the solvent was removed *in vacuo* to yield the crude isocyanate that was purified either by bulb-to-bulb distillation (**2–9**) or by precipitation (**10**).

Table 1. *Observed and isolated yields for a number of selected isocyanates 2–10.*

	Isocyanate	Observed yield (%)[a]	Isolated yield (%)[a]
2		100	92
3		100	93
4		100	93
5	$MeO_2C(CH_2)_{10}NCO$	100	80
6		50[b]	85
7		95	87
8		100	98
9		60	48[c]
10		100	88[d]

[a]Average of at least two experiments.

[b]A 1:1 mixture of isocyanate (**6**) and *t*-butyl-dicarbonate adduct is formed. The latter decomposes during distillation to furnish isocyanate **6**.

[c]Also 6% of di-*t*-butyldicarbonate (BOC_2O) is present that could not be removed by distillation.

[d]Purification was performed by precipitation of the side-products in pentane. Estimated purity 97%.

As can be deduced from this table, the method is suitable for the synthesis of aliphatic isocyanates attached to a secondary (**2**), tertiary (**3**) or even a sterically hindered quaternary carbon atom (**4**), and affords the isocyanates in good to excellent yields. The base/acid sensitivity of this reaction was tested by reaction of primary amine-based compounds bearing also a methyl ester or an acid-sensitive dimethylacetal moiety. In high yields the corresponding isocyanates **5** and **6** could be isolated, respectively. The observed yield of the

dimethylacetal isocyanate **6** of 50% in the crude reaction mixture is caused by the fact that first a 1:1 mixture of the product and the corresponding *t*-butyldicarbonate adduct is formed. The latter decomposes during distillation into the desired isocyanate.

The use of this method for the synthesis of aromatic isocyanates is tested by a reaction of **1** with aniline and in high yields phenylisocyanate **7** could be isolated.[6] However, when using less nucleophilic amines such as 2- and 3-aminopyridine or melamine, no isocyanate could be obtained from the reaction mixture. The tricarbonate **1** was in all cases converted to BOC_2O, which also occurred in a reaction of **1** with pyridine or pyrrole. This is in agreement with literature data,[7] stating that a reaction of **1** with DABCO (a tertiary amine) is the standard procedure for the synthesis of BOC_2O.

This novel method was also tested for a number of diamines and even a tetraamine. In the case of *cis*-4-isocyanatomethyl-methyl-cyclohexaneisocyanate (IMCI)[8] **8**, the yields were excellent. For 1,3-propanediisocyanate **9** the isolated yield was only 48%, despite a higher yield in the crude reaction mixture. Unfortunately, a small amount of BOC_2O was formed during the reaction that could not be removed entirely by distillation. However, when using the conventional methods for isocyanate construction the desired 1,3-propanediisocyanate **9** can not be isolated at all, due to the formation of cyclic six-membered urea. A reaction of **1** with *trans*-1,2-diaminocyclohexane[9] afforded 70% of the desired diisocyanate, beside 30% of the ring-closed urea (Figure 2). Unfortunately, the desired diisocyanate could only be isolated in very low yields (< 20%) due to side-reactions during distillation, even when distillation was conducted at very low pressures and low temperatures (< 60 °C).

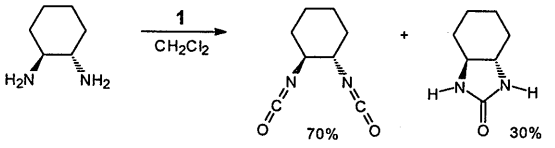


Figure 2. *Conversion of trans-1,2-diaminocyclohexane into the corresponding diisocyanate.*

A proposed reaction mechanism of primary amines with **1** is outlined in figure 3 and is in good agreement with the inititial literature data.[6]

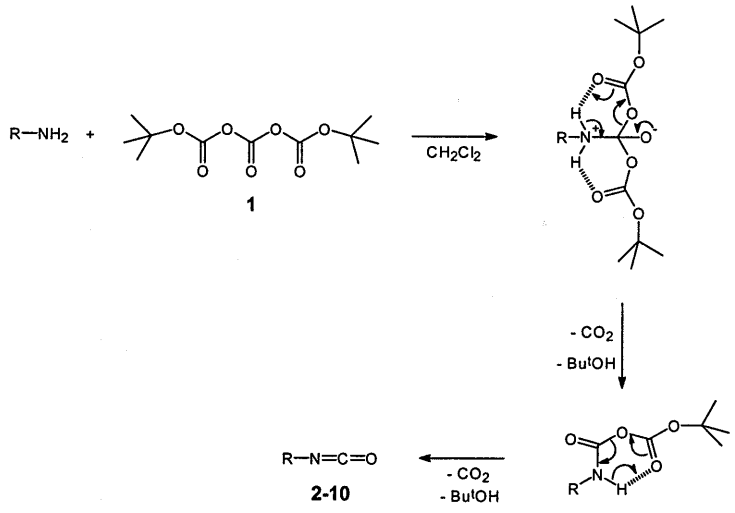
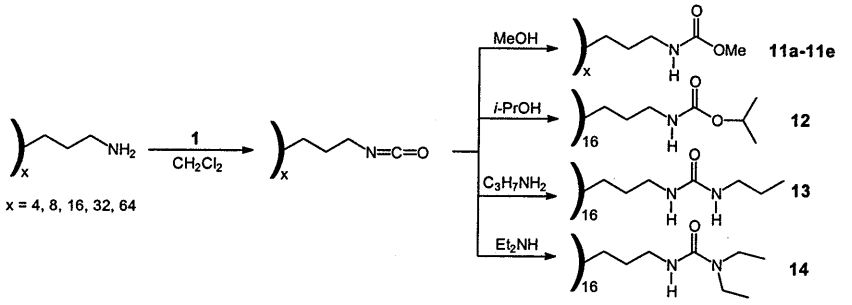


Figure 3. *A proposed reaction mechanism for the formation of isocyanates.*

First the nucleophilic amine interacts with the most electrophilic carbon atom of **1**. This complex readily transfers an amine proton to loose *t*-butylcarbonate, which spontaneously decomposes into CO_2 and *t*-butanol. This reaction furnishes the *t*-butyldicarbonate intermediate, which in turn, by intramolecular proton transfer, looses *t*-butylcarbonate, furnishing the desired isocyanate. In the specific case of dimethylacetal derivative **6** the second step only goes to completion when heated, i.e. during distillation. Unlike what is reported in the literature[5] the *t*-butanol formed during the reaction does not react with the isocyanate under these reaction conditions to lead to a BOC group.

The reaction is expected to go to completion within a couple of seconds and except for 1,2-diaminocyclohexane and **9** no urea-based side-products were observed. Therefore, the possibilities for the conversion of the primary amines of the poly(propylene imine) dendrimers[10] into the corresponding dendritic isocyanates were examined. Reaction of **1** with the first generation poly(propylene imine) dendrimer[10] yielded tetra-isocyanate **10**, besides some BOC_2O, as could be determined by ^{1}H-NMR, ^{13}C-NMR and IR spectroscopy. Since this molecule was not volatile enough for distillation, the complete purification was hampered. Therefore, a precipitation procedure with pentane was developed to remove the side-products from the reaction mixture. The desired isocyanate could be obtained in 88% yield with an estimated purity of 97%, as was deduced from ^{1}H- and ^{13}C-NMR spectroscopy. Higher generations of poly(propylene imine) dendrimers[10] were also reacted with the tricarbonate, to yield the multifunctional isocyanate dendrimers in excellent conversions. However, the isolation of the products proved to be very difficult as an insoluble material was obtained when the solvent was evaporated. In order to prove the formation of the dendritic isocyanates,

the *in situ* formed dendritic isocyanates were reacted with primary and secondary alcohols and amines to furnish structures **11–14** (Scheme 1), in yields of 70–100% (see experimental section). ^{13}C-NMR and IR spectroscopy proved to be very useful tools to analyze the products as, especially in the carbamate dendrimers **11–12**, there is a significant difference between signals belonging to a carbonyl from a carbamate and a urea functionality. The latter is expected to be present in defect structures. However, within the experimental error of these techniques no indications for inter- or intramolecular crosslinks were found.



Scheme 1. *Functionalization of the in situ formed dendritic isocyanates to yield structures 11–14.*

For a more detailed study on the nature of possible defects accompanying the reaction, ESI-MS was measured on the carbamate-functionalized dendrimer of the third generation, **11c** with 16 end groups, as for this compound the parent amine dendrimer contains almost no defects.[10c] The mass spectrum of **11c** (Figure 4) indicates the presence of the $[M+H]^+$ peak at *m/z* 2617 (Calculated mass for $C_{120}H_{240}N_{30}O_{32}$: 2614.9 Da). The peak at higher mass (2674) is related to a defect in the parent dendrimer. Other defects that can be ascribed to defects present in the parent dendrimer can be found at *m/z* 2559 (one end group missing), 2501 (two end groups missing) and 2444 (three end groups missing). Defect structures caused by the reaction with **1** are related to the intramolecular formation of a urea ring and can be found at *m/z* 2527 (one defect) and 2469 (one end group missing and one defect). The defects caused by the reaction are characterized by a mass loss of 90. The amount of defects caused by the conversion to the dendritic isocyanates can be estimated from the ESI-MS spectrum and is approximately 0.5% per end group.

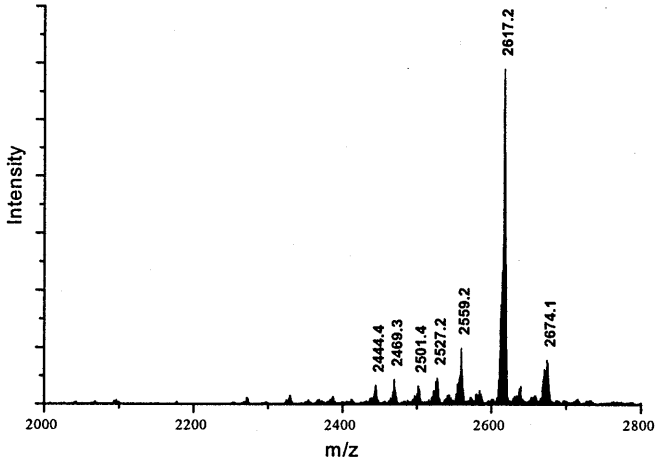


Figure 4. *ESI-MS spectrum of the third generation carbamate-funtionalized dendrimer 11c.*

These results lead to the conclusion that we are capable to convert the poly(propylene imine) dendrimers into dendritic isocyanates with an unexpected high precision. The ^{13}C-NMR and IR spectroscopical data suggest that it is even possible up to the largest generation of dendrimer, carrying 64 primary amine end groups. This paves the way to many possibilities for further functionalization with primary and secondary amines and alcohols (Scheme 1) using this convenient and mild method.

The utility of this method is presumably not limited to laboratory use only, but may as well have potential for applications in industry.

9.3 Chiral urea-based poly(propylene imine) dendrimers 15a–15e

Since the method for the synthesis of highly reactive isocyanates also opens up major possibilities in traditional dendrimer chemistry, we modified the peripheral primary amine end groups of the poly(propylene imine) dendrimers, as previously reported by Newkome,[11] with an enantiomerically pure isocyanate, *R*-α-methylbenzylisocyanate, **3**. Our goal was to test the reactivity of these isocyanates with the peripheral primary amine groups in the dendrimers and to test the ease of construction of these urea-based dendrimers **15a–15e** (Figure 5).

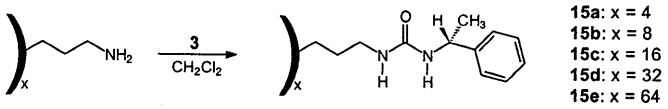


Figure 5. *Synthesis of chiral urea-based poly(propylene imine)dendrimers **15a–15e**.*

For this purpose all generations poly(propylene imine) dendrimers were brought into reaction with enantiomerically pure isocyanate **3** in CH_2Cl_2. The reaction was worked-up after 30 min by precipitation of the newly formed urea-based dendrimers in diethyl ether. This way dendrimers **15a–15e** were isolated in excellent yields. Characterization was performed by ^{1}H-NMR, ^{13}C-NMR and IR spectroscopy as well as by optical rotation. Considerable broadening was observed in ^{1}H-NMR, already for the first generation, but, this can be expected for these persistent hydrogen-bonded urea-based structures. ^{13}C-NMR spectroscopy in combination with IR spectroscopy was a nice tool to detect the presence of defects and incomplete functionalizations. The use of these techniques indicated that, within the error of the techniques used, no starting materials or unreacted primary amine functionalities were present. Also, the optical rotation was measured for all compounds obtained, but no anomalies were found as the obtained values were roughly constant for all generations at approximately $[\alpha]_D^{20} = +15$ (c = 1, $CHCl_3$).

Using this method, we have been able to employ the poly(propylene imine) dendrimers for fast functionalization with isocyanates to furnish urea-based dendrimers **15a–15e** in excellent yields when adopting a very simple work-up procedure.

9.4 Polycarbamate/urea dendrimers 16–20

9.4.1 Synthesis of diisocyanate building block 8

Most dendrimers are constructed in a procedure that makes use of a AB_2 or AB_3 building block, either by using the convergent or divergent route. A limited number of methods make use of other strategies.[12-13] Zimmerman *et al.*[13] reported for example on a very effective orthogonal coupling strategy based on the use of AB_2 and CD_2 building blocks. The major advantage of this novel approach is that the number of steps is decreased by obviating (de)protection or activation steps. The disadvantage, however, is related to the fact that for this strategy two building blocks have to be synthesized, instead of only one in the normal procedures.

Especially for the construction of divergently synthesized dendrimers, highly reactive species are required and very often amines are used for this purpose. However, surprisingly, almost no reports are known on the use of highly reactive isocyanates in dendrimer synthesis. Recently, Rannard *et al.*[4] reported on the use of a phosgene analog; 1,1'-carbonyldiimidazole. This compound was used in dendrimer construction, leading to structures based on the linkage between the branching units *via* carbonate, urethane, urea and even amide bonds, thus giving rise to a large number of possible structures.

In our approach we used diisocyanate **8** as a building block for the synthesis of polycarbamate/urea-based dendrimers **16–20**. Building block **8** is used at DSM and its utility in dendrimer construction was disclosed by Rolf van Benthem.[14] The elegance in the use of this building block lies in the reactivity difference of the two isocyanate moieties toward alcohols. When using zirconium(IV)acetylacetonate as the catalyst the selectivity amounts 100:1 for alcohols in favor of the isocyanate attached to the secondary carbon.[14] Both isocyanate groups are highly reactive toward secondary amines. This finding enabled Van Benthem to synthesize dendrimers in an orthogonal coupling procedure in which the use of protective groups is circumvented. Van Benthem synthesized dendrimers of the first up to the third generation, starting from the building block that consisted of a mixture of 4 isomers. The characterization was limited to GPC due to the different isomers present, but this technique gave a good idea on the utility of this new, fast and elegant method in dendrimer construction. In order to enable a good molecular characterization, one isomer had to be isolated from the mixture of 4 isomers.[8] For this purpose diamine precursor **22** was isolated in a 20% yield from the mixture of 4 isomers of 3(4)-aminomethyl-methyl-cyclohexanamine **21**,[8] by salt formation with *p*-nitrobenzoic acid in ethanol. Isocyanate **8** was obtained by a reaction of diamine **22** with tricarbonate **1** as described in paragraph 9.2 (Figure 6). The structure of **8** was determined by a modification with methylisocytosine and a comparison of the ^{13}C-NMR data with the crystal structure data obtained for this compound.[15]

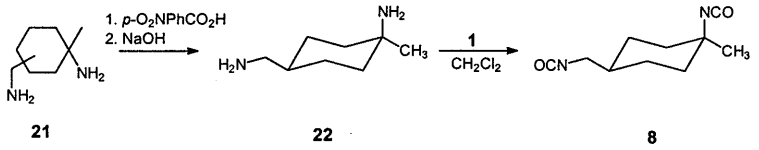
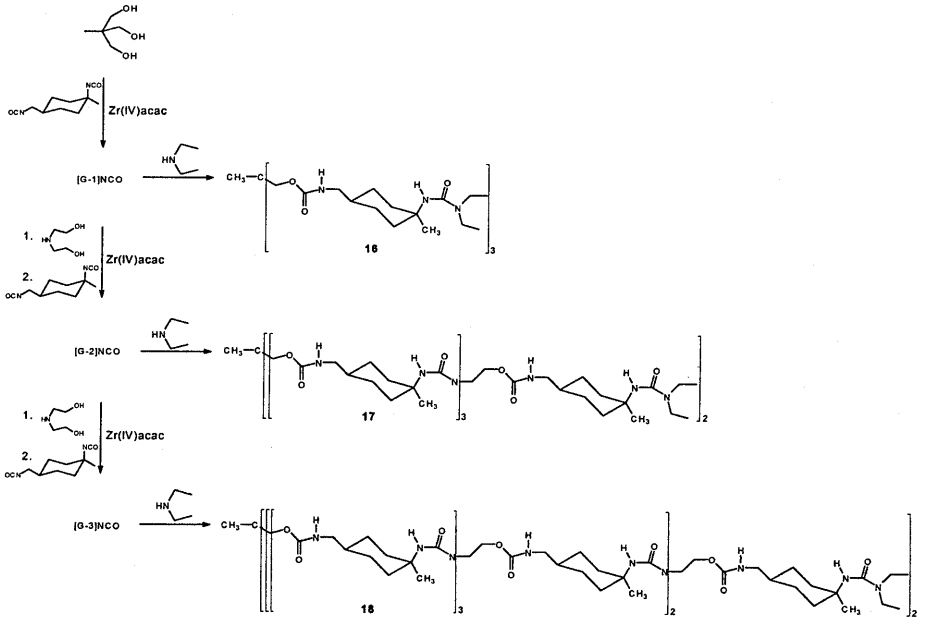


Figure 6. *Synthesis of di-isocyanate building block 8.*

9.4.2 Synthesis of polycarbamate/urea dendrimers 16–20

All dendrimers were constructed either starting from 1,1,1-tris(methylol)ethane (for structures **16–18**, Scheme 2) or 1,1'-ferrocenedimethanol (for compounds **19–20**, Scheme 3)[16]

as the core material. Diethanolamine was used as branch unit, **8** as building block, and diethylamine as end capper in chloroform as the solvent. Also THF was tested as the reaction solvent, but yielded much poorer results compared to chloroform. Zirconium(IV) acetylacetonate was used as the catalyst (1 mol% per reactive group), but the quantities were not optimized in these reactions.



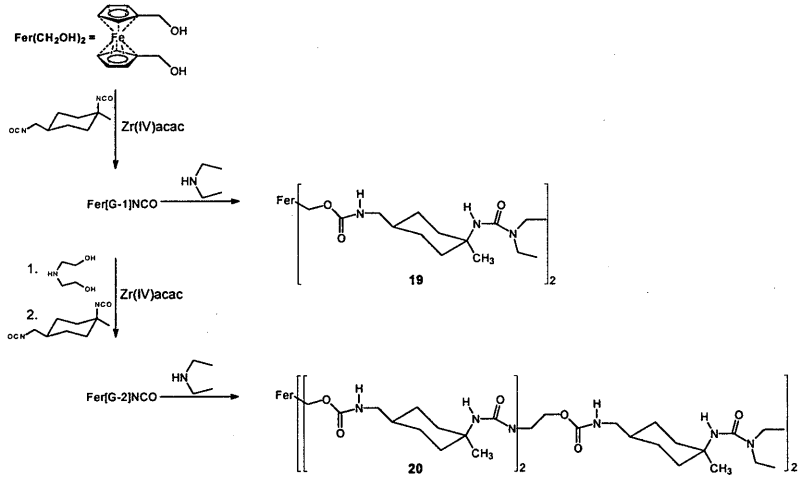
Scheme 2. *Synthesis of polycarbamate/urea-based dendrimers **16–18**.*

For the synthesis of the first generation dendrimer **16** the triol core was brought into reaction with **8** using zirconium(IV)acetylacetonate as the catalyst under reflux conditions for 8 h to yield precursor molecule [G-1]NCO. The reaction is expected to be much faster, however, when stoichiometric amounts of isocyanate are used, longer reaction times are required for the reaction to go to full conversion. Reaction of the remaining isocyanate functionality with diethylamine at room temperature (30 min) and subsequent evaporation of the solvent furnished first generation dendrimer **16** as a white foam.

The second generation dendrimer was synthesized by repeating the reaction sequence to intermediate [G-1]NCO as described above. Subsequently the isocyanate functionality was reacted with diethanolamine. This reaction was performed at room temperature for a period of 8 h. It is expected that the reaction only takes 30 min (analogous to end capping with diethylamine), however, again we employed stoichiometric amounts of reagent. After the addition a viscous syrup was gradually formed. Addition of **8** and a fresh portion of catalyst

to the reaction mixture, followed by heating under reflux for a period of 8 h resulted in the complete dissolution of the viscous material and led to the formation of precursor molecule [G-2]NCO. Reaction with diethylamine (30 min at room temperature) and subsequent evaporation of the solvent furnished dendrimer **17** as a white foam.

For the synthesis of the third generation dendrimer the reaction sequence is repeated up to precursor [G-2]NCO. Subsequently the isocyanate functionality is reacted with diethanolamine, which resulted in the formation of a highly viscous syrup. This again dissolved after the addition of **8**, a fresh portion of catalyst and heating of the reaction mixture to reflux for a period of 8 h. This afforded precursor molecule [G-3]NCO that was end-capped by a reaction with diethylamine (30 min at room temperature). Evaporation of the solvent furnished dendrimer **18** as a white foam.



Scheme 3. *Synthesis of ferrocene-functionalized dendrimers **19–20**.*

To illustrate the versatility of this new method in dendrimer construction, a ferrocene-based core was used, to furnish structures **19–20** in high yields and purities.[16] The synthesis of these compounds is very straightforward and analogous to that described for compounds **16–18**, with the difference that the reaction times required for the coupling of isocyanate **8** to the alcohol functionalities of the core or the branching unit were much longer. This may be caused by pollution of the zirconium catalyst with the iron from the ferrocene core. Compounds **19** and **20** were obtained in quantitative yields and could be isolated as yellow foams.

9.4.3 Characterization of polycarbamate/urea dendrimers 16–20

Dendrimers **16–20** could be fully characterized by NMR and IR spectroscopy and mass spectral analysis. ^{1}H-NMR only proved to be useful for the first generation dendrimer **16**. When measuring this compound at room temperature different conformations could be observed in a $CDCl_3$ solution. Therefore, elevated temperatures (50 ^{0}C) were employed, leading to well-resolved spectra. ^{13}C-NMR spectroscopy (Figure 7 and 8) proved to be a very powerful tool for the characterization of the newly formed dendrimers and was much more useful than ^{1}H-NMR spectroscopy. In ^{13}C-NMR spectroscopy compounds **16** and **17** reveal a set of well-resolved peaks, thus making full characterization possible. For **17** most signals of the two different IMCI-building blocks can be seen as a separate set of signals. For dendrimer **18** some defect structures can be observed in ^{13}C-NMR, especially in the region of the newly formed urethane and carbamate area at δ = 157–158 ppm. Strikingly, however, the absorptions from the triol core material can still be retrieved as a separate set of signals at 16.8, 38.9 and 66.3 ppm, while they only represent 1, 1 and 3 carbon atoms, respectively, out of 299 carbon atoms in total for the dendrimer.

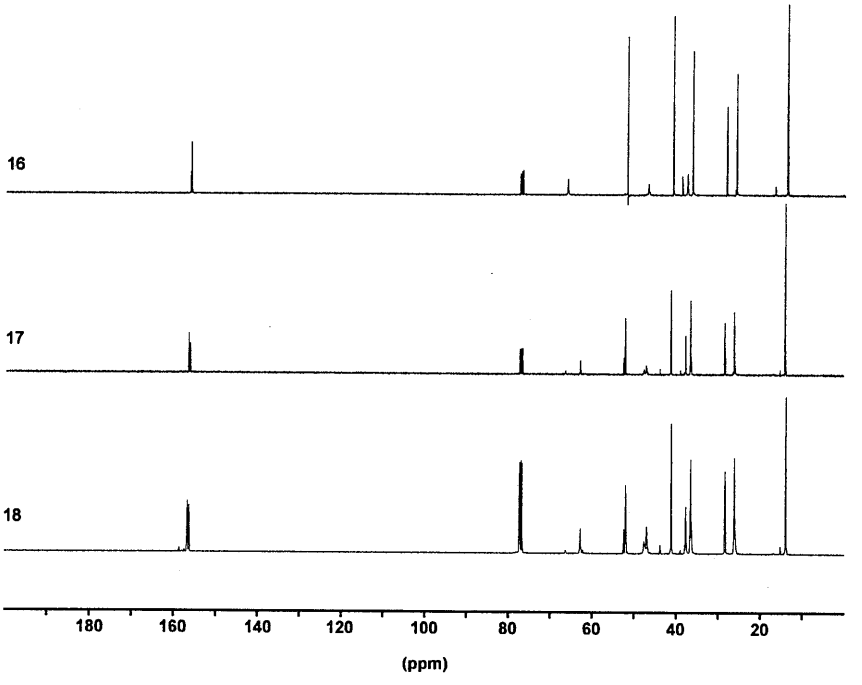


Figure 7. *^{13}C-NMR spectra ($CDCl_3$, 50 ^{0}C) of polycarbamate/urea-based dendrimers **16–18**.*

Similar spectra were obtained for the ferrocene-based structures **19–20** (Figure 8). The absorptions of the ferrocene core in the molecule resonate as a set of 4 signals at δ-values of

62, 69, 70 and 83 ppm. Also in this case for the second generation dendrimer **20**, most signals corresponding to the two different building blocks can be seen as a set of different signals in the spectrum.

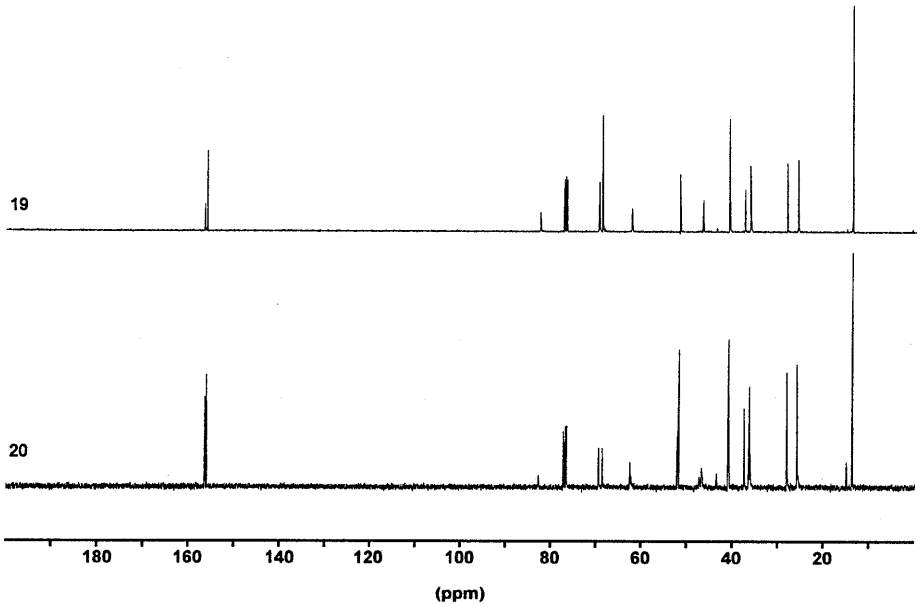


Figure 8. *^{13}C-NMR spectra ($CDCl_3$, 50 °C) of ferrocene-based dendrimers **19–20**.*

In compounds **17–20** also some diethylamine (at δ-values of 15.2 and 43.8 ppm in the ^{13}C-NMR spectrum) was present that could not be removed by evaporation, not even at low pressures and elevated temperatures. This type of encapsulation is a phenomenon that has been observed before for dendrimers having multiple hydrogen-bonding units present in the structure.[17] In IR spectroscopy in the solid state the newly found carbamate and urea C=O stretch vibrations are found at wavenumbers of 1710 and 1640 cm^{-1}, respectively. Mass spectrometry is a very powerful tool for studying this type of structures and for the characterization we used two different techniques: LSI-MS and ESI-MS. The latter has previously been reported very useful for the analysis of defects present in the poly(propylene imine) dendrimers.[10c] The results of the studies on structures **16–20** are listed in table 2.

Table 2. *LSI-MS and ESI-MS data of polycarbamate/urea dendrimers* ***16–20.***

Dendrimer	Molecular Formula	Calc. Mass	LSI-MS	ESI-MS
16	$C_{47}H_{87}N_9O_9$	921.7	923 $[M+H]^+$	923 $[M+H]^+$
			945 $[M+Na]^+$	945 $[M+Na]^+$
				961 $[M+K]^+$
17	$C_{131}H_{237}N_{27}O_{27}$	2621.8	2645 $[M+Na]^+$	2622 $[M]^+$
				2645 $[M+Na]^+$
18	$C_{299}H_{537}N_{63}O_{63}$	6022.2	6044 $[M+Na]^+$	–
19	$C_{40}H_{64}FeN_6O_6$	780.5	–	781 $[M]^+$
				804 $[M+Na]^+$
20	$C_{96}H_{164}FeN_{18}O_{18}$	1914.2	–	1915 $[M+H]^+$
				1936 $[M+Na]^+$

When using ESI-MS for the dendrimers of the first and second generation dendrimers, **16–17** and **19–20**, the molar masses could be nicely detected. However, this proved to be impossible for the third generation dendrimer **18**. When using LSI-MS for the first and second generation dendrimers **16** and **17**, the molar masses could be determined smoothly. Again the third generation **18** gave problems in analysis, but fortunately a very weak signal could be detected for the molar mass corresponding to $[M+Na]^+$. The fact that the mass determination for the third generation dendrimer proved to be so hard may well be caused by the fact that ionization of this structure is highly hampered by its hydrophobic character.

The versatility of this new synthetic method is exemplified in the synthesis of ferrocene-based[16] structures **19** and **20**. Besides analysis of these compounds by NMR, IR and mass spectral techniques also UV spectroscopy and CV measurements were conducted. In UV spectroscopy, measured in a CH_2Cl_2 solution λ_{max} values were found at 226–227 nm, showing no shift in absorption in either generation. The CV measurements were performed in a CH_2Cl_2 solution with Bu_4NPF_6 as an electrolyte at a scan speed of 100 mV/s (Figure 9). The processes of oxidation and reduction proved to be completely reversible. From these measurements no differences in oxidation potential can be observed as for both generations the oxidation potential was found at +0.58 V and did not shift.

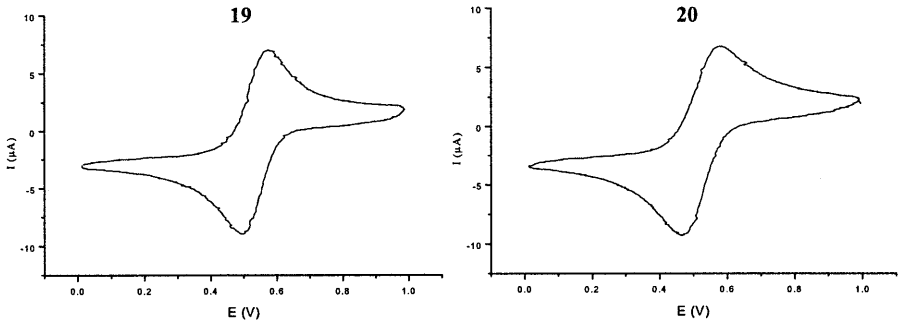


Figure 9. *CV measurements on ferrocene-based dendrimers 19–20.*

9.4.4 Outlook of the new synthetic strategy in dendrimer synthesis

In conclusion, we have presented a new synthetic approach to polycarbamate/urea dendrimers based on an AB–CD_2 coupling strategy. The elegance in this procedure lies in the fact that we don't have to employ activation or deprotection steps which makes it possible to construct dendrimers within a time span of 2–3 days, even for the largest dendrimers. For this purpose we simply make use of the reactivity difference between the two isocyanate functionalities in the AB building block **8**. These dendrimers could be fully characterized by ^{13}C-NMR, IR spectroscopy and mass spectrometry. The synthetic strategy necessitates only techniques as stirring, heating and accurate dosing, and there is no work-up required for the purification of the compounds. Since a wide variety of polyols, amines and aminoalcohols is commercially available this new procedure is not limited to the synthetic strategy followed, but allows for the incorporation of a large variety of functional molecules, either in the core, in the branching units or at the end groups.

9.5 Conclusion

We have introduced a mild and convenient method for the synthesis and isolation of isocyanates by the reaction of primary amines with di-*t*-butyltricarbonate **1**. This method paves the way for an easy construction of compounds, that were hitherto unknown or very hard to synthesize, even making dendritic isocyanates possible with up to 64 functional end groups. Possible defects present in functionalized dendritic isocyanates could be nicely analyzed by ^{13}C-NMR and IR spectroscopy as well as by ESI-MS for the carbamate

functionalized dendrimer of the third generation. This indicated that practically no defects are present in this structure. Applications of this method are foreseen both in industry and for laboratory use.

The utility of this method is exemplified first by the modification of the peripheral primary amines of the poly(propylene imine) dendrimers with chiral isocyanate **3**, to yield urea-based dendrimers **15a–15e** in quantitative yields by making use of a fast and convenient procedure.

Several strategies for the construction of dendrimers are known, but all methods have in common that high selectivities and reactivities are required in order to obtain these well-defined materials. In this context, surprisingly, only one example is known which rests on the use of highly reactive isocyanate derivatives.[4] The utility of isocyanates for the construction of divergently synthesized dendrimers is shown with asymmetric diisocyanate **8** as a building block. Due to the selectivity difference between the two reactive sites of **8** toward alcohols, dendrimers **16–20** could be constructed in a one-pot procedure, requiring only stirring, heating and accurate dosing. A dendrimer of up to the third generation with a molecular mass of over 6,000 Da could be synthesized in this way within a time span of 2–3 days, which is considerably shorter compared to the normal procedures. Analysis was performed by IR and ^{13}C-NMR spectroscopy and mass spectrometry. Usually, the possible structures of divergently synthesized dendrimers are highly limited due to the specific synthetic strategy followed. However, due to the availability of many polyols and aminoalcohols the strategy presented here opens up ample possibilities to obtain a large variety of dendrimeric structures, even bringing tailor-made structures within the realm of reality.

9.6 Experimental section

General

All solvents were of c.p. quality, except those used as a reaction solvent which were of p.a. quality. Melting points are uncorrected and were determined with a Jeneval microscope equipped with a Linkam hot stage. NMR spectra were run on a Bruker AM-400 spectrometer at frequencies of 400.1 MHz and 100.6 MHz for ^{1}H- and ^{13}C-nuclei, respectively. TMS was used as an internal standard and δ-values are given in ppm. The following abbreviations are used in the peak assignments of the dendrimers: core refers to the 1,1,1-tris(methylol)ethane or the 1,1'-ferrocenedimethanol unit, branch refers to the diethanolamine unit, ring refers to the *cis*-4-isocyanatomethyl-1-methylcyclohexan-isocyanate unit and end refers to the diethylamine unit. IR-spectra were taken on a Perkin Elmer 1600 series FT-IR and data are given in cm^{-1}. $[\alpha]_D^{20}$ Data were measured on a Jasco DIP-370 digital polarimeter. LSI-MS spectra were recorded at the University of Birmingham using a VG ZabSpec mass spectrometer, using a *p*-nitrobenzyl alcohol matrix. ESI-MS spectra were recorded on a Perkin Elmer-Sciex API 300 MS/MS mass spectrometer. UV measurements were performed on a Perkin

Elmer Lambda 3B spectrometer in CH_2Cl_2 as a solvent and data are given in nm. CV measurements were measured in CH_2Cl_2 with 0.1 M Bu_4NPF_6 as a supporting electrolyte using a Potentioscan Wenking POS73 potentiostat at a scan speed of 100 mV/s. A platinum disk was used as working electrode, the counter electrode was a platinum plate and a saturated calomel electrode (SCE) was used as reference electrode, internally calibrated vs. Fc/Fc^+ (0.43 V vs. SCE).

Di-*t*-butyltricarbonate, 1[7]

A stirred solution of potassium-*t*-butoxide (56.11 g, 0.500 mol) in freshly distilled THF (675 mL) was cooled on an ice/salt bath (0–5 °C) and carbon dioxide was bubbled through the mechanically stirred reaction mixture over a period of 1 h. During that time the solution became turbid and highly viscous. To the cooled solution phosgene (20% solution in toluene, 155 mL, 0.30 mol) was added dropwise over a period of 45 min. Argon was bubbled through the solution over a period of 45 min to remove most of the excess of phosgene. Pentane was added (600 mL), the salts were removed by filtration and the filtrate was concentrated *in vacuo* on a cold bath. Purification was accomplished by the addition of pentane (600 mL) and subsequent cooling to –10 °C. The formed crystals were filtered off and dried, to yield pure **1** (53.4 g, 81%) as a colorless crystalline solid. m.p. = 63–64 °C (lit.:[7] 62–63 °C). ^{1}H-NMR ($CDCl_3$): δ 1.58 (s, 18H, CH_3). ^{13}C-NMR ($CDCl_3$): δ 27.1 (CH_3), 87.2 ($C(CH_3)_3$), 143.2 ($CO_2CO_2CO_2$), 144.5 ($CO_2CO_2CO_2$). IR (KBr): ν 2986, 2944 (CH_3 stretch), 1865 and 1787 (C=O stretch).

General procedure for the formation of isocyanates 2–10

To a stirred solution of **1** (1.0–1.1 eq per primary amine group) in dry CH_2Cl_2 was added a solution of primary amine in dry CH_2Cl_2. During the addition carbon dioxide evoluted from the reaction mixture. Stirring was continued for 5 min, after which the solvent was evaporated and the residue was purified either by a bulb-to-bulb distillation (**2–9**) or by a precipitation procedure (**10**). The yields are listed in Table 1. Spectroscopic data for isocyanates **2–10** are listed below.

***n*-Octylisocyanate, 2**[18]

Bulb-to-bulb distillation at T_{oven} = 125 °C/29 mbar. ^{1}H-NMR ($CDCl_3$): δ 0.89 (t, J = 7.1 Hz, 3H, CH_3), 1.29–1.40 (m, 10H), 1.61 (qui, J = 6.9 Hz, 2H, CH_2CH_2NCO), 3.28 (t, J = 6.7 Hz, 2H, CH_2NCO). ^{13}C-NMR ($CDCl_3$): δ 14.0 (CH_3), 22.6, 26.5, 28.9, 29.1, 31.3, 31.7, 43.0 (CH_2), 122.0 (NCO). IR (KBr): ν 2928, 2857 (CH_2 stretch), 2275 (NCO stretch).

***R*-α-Methylbenzylisocyanate, 3**[18]

B.p. 78–79 °C/8.0 mbar. ^{1}H-NMR ($CDCl_3$): δ 1.55 (d, J = 6.7 Hz, 3H, CH_3), 4.71 (qua, J = 6.8 Hz, 1H, C*H), 7.25–7.36 (m, 5H, PhH). ^{13}C-NMR ($CDCl_3$): δ 25.9 (CH_3), 54.5 (C*H), 123.3 (NCO), 125.2, 127.7, 128.6 (PhCH), 142.4 (PhC-*ipso*). $[\alpha]_D^{20}$ = +14 (c = 2.5, $CHCl_3$). IR (KBr): ν 3066, 3032 (=C–H stretch, phenyl), 2982, 2932 (CH_3 stretch), 2274 (NCO stretch), 1604, 1494 (C=C stretch, phenyl).

t-Octylisocyanate, 4[5]

Bulb-to-bulb distillation at T_{oven} = 100 °C/95 mbar. ^{1}H-NMR ($CDCl_3$): δ 1.04 (s, 9H, $C(CH_3)_3$), 1.41 (s, 6H, $C(CH_3)_2$), 1.52 (s, 2H, CH_2). ^{13}C-NMR ($CDCl_3$): δ 31.1 ($C(CH_3)_3$), 31.6 ($C(CH_3)_3$), 32.8 ($C(CH_3)_2$), 55.2 (CH_2), 58.2 ($C(CH_3)_2$), 121.6 (NCO). IR (KBr): ν 2958 (CH_3 stretch), 2261 (NCO stretch).

Methyl 11-isocyanatoundecanoate, 5

Bulb-to-bulb distillation at T_{oven} = 150 °C/0.16 mbar. ^{1}H-NMR ($CDCl_3$): δ 1.29–1.39 (m, 12H), 1.62 (m, 4H), 2.30 (t, J = 7.4 Hz, 2H), 3.29 (t, J = 6.6 Hz, 2H), 3.66 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$): δ 24.8, 26.4, 28.8, 29.0, 29.2, 29.3, 31.2, 33.9, 42.9 (CH_2), 51.3 (CH_3), 121.9 (NCO), 174.1 (CO_2CH_3). IR (KBr): ν 2270 (NCO stretch), 1738 (C=O stretch, ester).

Isocyanato acetaldehyde dimethyl acetal, 6

Bulb-to-bulb distillation at T_{oven} = 90 °C/24 mbar. ^{1}H-NMR ($CDCl_3$): δ 3.31 (d, J = 5.3 Hz, 2H, CH_2), 3.42 (s, 6H, CH_3), 4.48 (t, J = 5.3 Hz, CH). ^{13}C-NMR ($CDCl_3$): δ 44.2 (CH_2), 53.9 (CH_3), 102.4 (CH), 124.9 (NCO). IR (KBr): ν 2263 (NCO stretch).

Phenylisocyanate, 7[6,18]

Bulb-to-bulb distillation at T_{oven} = 100 °C/39 mbar. ^{1}H-NMR ($CDCl_3$): δ 7.05–7.32 (m, 5H, PhH). ^{13}C-NMR ($CDCl_3$): δ 124.7, 125.7, 129.5, 133.4. IR (KBr): ν 2270 (NCO stretch).

***cis*-4-Isocyanatomethyl-1-methyl-cyclohexylisocyanate, 8[8]**

B.p. = 81 °C/0.03 mbar. ^{1}H-NMR ($CDCl_3$): δ 1.25–1.37 and 1.37–1.44 (m, 4H, CH_2-3,5), 1.38 (s, 3H, CH_3), 1.45–1.55 (m, 1H, CH), 1.67–1.72 and 1.79–1.85 (m, 4H, CH_2-2,6), 3.21 (d, J = 6.4 Hz, 2H, CH_2N). ^{13}C-NMR ($CDCl_3$): δ 25.9 (CH_2-3,5), 31.3 (CH_3), 38.0 (CH), 38.5 (CH_2-2,6), 48.2 (CH_2N), 57.9 (C-*ipso*). IR (KBr): ν 2935, 2860 (CH_2 stretch), 2254 (NCO stretch), 1447 (C–CH_3 and CH_2 deformation).

1,3-Diisocyanatopropane, 9

Bulb-to-bulb distillation at T_{oven} = 140 °C/17 mbar. ^{1}H-NMR ($CDCl_3$): δ 1.86 (quintet, J = 6.5 Hz, 2H, $CH_2CH_2CH_2$), 3.50 (t, J = 6.3 Hz, 4H, $CH_2CH_2CH_2$). ^{13}C-NMR ($CDCl_3$): δ 31.8 ($CH_2CH_2CH_2$), 39.8 ($CH_2CH_2CH_2$), 122.1 (NCO). IR (KBr): ν 2267 (NCO stretch).

N,N,N',N'-Tetrakis(3-isocyanatopropyl)-1,4-butanediamine, 10

^{1}H-NMR ($CDCl_3$): δ 1.40 (br, 4H, $NCH_2CH_2CH_2CH_2N$), 1.70 (quintet, J = 6.6 Hz, 8H, CH_2CH_2NCO), 2.37 (br, 4H, $NCH_2CH_2CH_2CH_2N$), 2.47 (t, J = 6.7 Hz, 8H, $NCH_2CH_2CH_2NCO$), 3.37 (t, J = 6.4 Hz, 8H, CH_2NCO). ^{13}C-NMR ($CDCl_3$): δ 24.7 ($NCH_2CH_2CH_2CH_2N$), 28.6 (CH_2CH_2NCO), 40.6 (CH_2CH_2NCO), 50.3 ($NCH_2CH_2CH_2NCO$), 53.6 ($NCH_2CH_2CH_2CH_2N$), 121.6 (NCO). IR (KBr): ν 2957 and 2813 (CH_2 stretch), 2284 (NCO stretch), 1470 (CH_2 deformation).

General procedure for the construction of carbamate and urea dendrimers 11–14

To a stirred solution of **1** (1.0 g, 3.8 mmol) in CH_2Cl_2 (30 mL) was added a solution of the poly(propylene imine) dendrimer (approx. 100 mg, 1 mmol of primary amine end group) in CH_2Cl_2 (10 mL). After stirring at room temperature for 5 min, methanol (**11**), 2-propanol (**12**), propylamine (**13**) or diethylamine (**14**) was added (about 2 mL). (In the specific case of **13** first a few drops of pyridine were added to the reaction mixture before adding the propylamine in order to neutralize the excess of **1**.) Stirring was continued for 15 min at room temperature. Subsequently the reaction mixture was filtered through cotton wool and concentrated *in vacuo*. The products were purified by precipitation from diethyl ether : hexane (1:1 for **11** and **14**; 1:10 for **12**) or $CHCl_3$: diethyl ether (1:5 for **13**). This furnished the products in high yields (70–100%).

[G-1] Methyl carbamate dendrimer 11a

^{13}C-NMR ($CDCl_3$, 50 °C): δ 25.0 ($NCH_2(CH_2)_2CH_2N$), 27.2 (CH_2CH_2NH), 40.1 (CH_2NH), 51.8 (CH_3), 52.3 ($NCH_2CH_2CH_2NH$), 54.1 ($NCH_2(CH_2)_2CH_2N$), 157.1 (C=O). IR (KBr): ν 3334 (NH stretch), 2947 (CH_2 and CH_3 stretch), 1708 (C=O stretch, carbamate), 1463 (CH_2 deformation).

[G-2] Methyl carbamate dendrimer 11b

^{13}C-NMR ($CDCl_3$, 50 °C): δ 24.6 ($NCH_2CH_2CH_2N$), 25.0 ($NCH_2(CH_2)_2CH_2N$), 27.0 (CH_2CH_2NH), 39.8 (CH_2NH), 51.6 (CH_3), 52.0, 52.1 (CH_2NCH_2), 54.1 ($NCH_2(CH_2)_2CH_2N$), 157.0 (C=O). IR (KBr): ν 3333 (NH stretch), 2947 (CH_2 and CH_3 stretch), 1706 (C=O stretch, carbamate), 1463 (CH_2 deformation).

[G-3] Methyl carbamate dendrimer 11c

^{13}C-NMR ($CDCl_3$, 50 °C): δ 24.6 ($NCH_2CH_2CH_2N$), 25.1 ($NCH_2(CH_2)_2CH_2N$), 27.1 (CH_2CH_2NH), 39.9 (CH_2NH), 51.6 (CH_3), 52.0, 52.1, 52.2, 52.4 (CH_2NCH_2), 54.3 ($NCH_2(CH_2)_2CH_2N$), 157.0 (C=O). IR (KBr): ν 3332 (NH stretch), 2948 (CH_2 and CH_3 stretch), 1707 (C=O stretch, carbamate), 1463 (CH_2 deformation).

[G-4] Methyl carbamate dendrimer 11d

^{13}C-NMR ($CDCl_3$, 50 °C): δ 24.5 ($NCH_2CH_2CH_2N$), 25.0 ($NCH_2(CH_2)_2CH_2N$), 27.1 (CH_2CH_2NH), 39.8 (CH_2NH), 51.6 (CH_3), 52.0, 52.1, 52.2, 52.4 (CH_2NCH_2), 54.2 ($NCH_2(CH_2)_2CH_2N$), 157.0 (C=O). IR (KBr): ν 3334 (NH stretch), 2948 (CH_2 and CH_3 stretch), 1710 (C=O stretch, carbamate), 1464 (CH_2 deformation).

[G-5] Methyl carbamate dendrimer 11e

^{13}C-NMR ($CDCl_3$, 50 °C): δ 24.6 (CH_2CH_2N), 27.1 (CH_2CH_2NH), 39.8 (CH_2NH), 51.6 (CH_3), 52.0, 52.1, 52.2, 52.5, 52.8 (CH_2NCH_2), 157.1 (C=O). IR (KBr): ν 3334 (NH stretch), 2947 (CH_2 and CH_3 stretch), 1705 (C=O stretch, carbamate), 1462 (CH_2 deformation).

[G-3] Isopropyl carbamate dendrimer 12

^{13}C-NMR ($CDCl_3$, 50 °C): δ 22.0 (CH_3), 24.5, 24.7 ($NCH_2CH_2CH_2N$), 25.0 ($NCH_2(CH_2)_2CH_2N$), 27.2 (CH_2CH_2NH), 39.6 (CH_2NH), 52.0, 52.1, 52.2, 52.4 (CH_2NCH_2), 54.3 ($NCH_2(CH_2)_2CH_2N$), 67.4 (CH), 156.3 (C=O). IR (KBr): ν 3332 (NH stretch), 2943 (CH_2 and CH_3 stretch), 1696 (C=O stretch, carbamate), 1463 (CH_2 deformation).

[G-3] Propyl urea dendrimer 13

^{13}C-NMR (CD_3OD, 50 °C): δ 12.0 (CH_3), 24.8 (CH_3CH_2), 25.5 ($NCH_2CH_2CH_2N$), 26.3 ($NCH_2(CH_2)_2CH_2N$), 29.0 (CH_2CH_2NH), 39.8, 43.2 (CH_2NH), 53.0, 53.7, 53.8 (CH_2NCH_2), 55.6 ($NCH_2(CH_2)_2CH_2N$), 161.6 (C=O). IR (KBr): ν 3417 (NH stretch), 2957 (CH_2 and CH_3 stretch), 1633 (C=O stretch,urea), 1462 (CH_2 deformation).

[G-3] Diethyl urea dendrimer 14

^{13}C-NMR ($CDCl_3$, 50 °C): δ 13.5 (CH_3), 23.9, 24.1 ($NCH_2CH_2CH_2N$), 24.7 ($NCH_2(CH_2)_2CH_2N$), 26.8 (CH_2CH_2NH), 39.5 (CH_2NH), 40.5 (CH_3CH_2N), 51.8, 52.1 (CH_2NCH_2), 53.9 ($NCH_2(CH_2)_2CH_2N$), 157.2 (C=O). IR (KBr): ν 3352 (NH stretch), 2933 (CH_2 and CH_3 stretch), 1626 (C=O stretch, urea), 1463 (CH_2 deformation).

General procedure for the coupling of 3 to the poly(propylene imine) dendrimers in the preparation of urea dendrimers 15a–15e

The poly(propylene imine) dendrimers (about 125 mg, approximately 1.2 mmol primary amine end groups) was dissolved in CH_2Cl_2 (3 mL). To the stirred reaction mixture a solution of **3** (1.05 eq per primary amine end group) in CH_2Cl_2 was added. After the addition was complete stirring was continued for 30 min at room temperature after which the product was precipitated by the addition of diethyl ether (12 mL). The solvent was decanted and the last traces of solvent were removed *in vacuo* yielding **15a–15e** as white foams in quantitative yields. When following this particular work-up procedure no starting materials could be detected. In ^{1}H-NMR the signals considerably broadened. Typical absorptions in ^{13}C-NMR ($CDCl_3$): δ 23.3 (CH_3), 24.3–27.6 ($CH_2CH_2CH_2N$), 37.9 (CH_2NH), 49.1 (C*H), 50.9–53.4 (CH_2NCH_2), 125.8, 126.6, 128.3 (PhCH), 145.1 (PhC-*ipso*), 158.7 (NHCONH). IR (KBr): ν 3345 (NH stretch), 2935 (CH_2 stretch), 1630 (C=O stretch, urea). $[\alpha]_D^{20}$ = +19 (**15a**), +16 (**15b**), +13 (**15c**), +14 (**15d**), +14 (**15e**) (c = 1.0, $CHCl_3$).

[G-1] dendrimer 16

A stirred mixture of 1,1,1-tris(methylol)ethane (60.2 mg, 0.50 mmol), **8** (291.5 mg, 1.50 mmol), and Zr(IV)acac$_4$ (1 mol% per end group) in $CHCl_3$ (10 mL) was heated under reflux for 2 days after which the mixture was allowed to cool to room temperature. Subsequently diethylamine (0.5 mL) was added after which stirring was continued for 30 min at room temperature. The solvent was removed by evaporation to yield **16** (quant.) as a white foam. ^{1}H-NMR ($CDCl_3$, 50 °C): δ 0.96 (s, 3H, CH_3 core), 1.08 and 1.25 (2 x pt, J = 13.5 Hz, 12H, CH_2-3,5 ring), 1.13 (t, J = 7.1 Hz, 18H, CH_3 end), 1.36 (s, 9H, CH_3 ring), 1.44 (m, 3H, CH ring), 1.58 and 2.23 (2 x d, J = 13.2 Hz, 12H, CH_2-2,6 ring), 3.02 (t, J = 6.1 Hz, 6H, CH_2N ring), 3.23 (quartet, J = 7.1 Hz, 12H, CH_2 end), 3.96 (s, 6H, CH_2 core), 4.02 (s, 3H, NH), 5.08 (br s, 3H, NH). ^{13}C-NMR ($CDCl_3$, 50 °C): δ 13.7 (CH_3 end), 16.6 (CH_3 core), 25.8 (CH_2-3,5 ring), 28.1 (CH_3 ring), 36.3 (CH_2-2,6 ring), 37.5 (CH ring), 38.7 (C-*ipso* core), 40.9

(CH_2 end), 46.8 (CH_2NH ring), 51.8 (C-*ipso* ring), 66.1 (CH_2 core), 156.1 and 156.2 (C=O). IR (KBr): ν 3314 (NH stretch), 2970 (CH_3 stretch), 2928 (CH_2 stretch), 1713 and 1634 (C=O stretch). *m/z*: Calc. for $C_{47}H_{87}N_9O_9$: 921.7. LSI-MS: 923 $[M+H]^+$, 945 $[M+Na]^+$; ESI-MS: 923 $[M+H]^+$, 945 $[M+Na]^+$, 961 $[M+K]^+$.

[G-2] dendrimer 17

A stirred mixture of 1,1,1-tris(methylol)ethane (60.1 mg, 0.50 mmol), **8** (291.9 mg, 1.50 mmol), and Zr(IV)acac$_4$ (1 mol% per end group) in $CHCl_3$ (10 mL) was heated under reflux overnight. The mixture was allowed to cool to room temperature after which diethanolamine (157.9 mg, 1.50 mmol) was added and stirring was continued for 8 h at room temperature. This resulted in the formation of a highly viscous oil that disappeared after the addition of a fresh portion of **8** (582.8 mg, 3.00 mmol) in $CHCl_3$ (10 mL) and some fresh catalyst (1 mol% per end group). This mixture was stirred and heated under reflux overnight after which the reaction mixture was again allowed to cool to room temperature. Diethylamine (1 mL) was added to the reaction mixture and stirring was continued for 30 min at room temperature. The solvent was removed by evaporation to furnish **17** (quant.) as a white foam. ^{13}C-NMR ($CDCl_3$, 50 °C): δ 13.9 (CH_3 end), 16.8 (CH_3 core), 25.9 and 26.1 (CH_2-3,5 ring), 28.2 and 28.4 (CH_3 ring), 36.3 and 36.5 (CH_2-2,6 ring), 37.7 (CH ring), 38.9 (C-*ipso* core), 41.2 (CH_2 end), 47.0 and 47.6 (CH_2NH ring and CH_2N branch), 52.0 and 52.4 (C-*ipso* ring), 62.8 (CH_2O branch), 66.4 (CH_2 core), 156.3 and 156.7 (C=O). IR (KBr): ν 3316 (NH stretch), 2967 (CH_3 stretch), 2928 (CH_2 stretch), 1712 and 1644 (C=O stretch). *m/z*: Calc. for $C_{131}H_{237}N_{27}O_{27}$: 2621.8. LSI-MS: 2645 $[M+Na]^+$; ESI-MS: 2622 $[M]^+$, 2645 $[M+Na]^+$.

[G-3] dendrimer 18

A stirred mixture of 1,1,1-tris(methylol)ethane (60.1 mg, 0.50 mmol), **8** (291.9 mg, 1.50 mmol), and Zr(IV)acac$_4$ (1 mol% per end group) in $CHCl_3$ (10 mL) was heated under reflux overnight. The mixture was allowed to cool to room temperature after which diethanolamine (157.9 mg, 1.50 mmol) was added and stirring was continued for 8 h at room temperature. This resulted in the formation of a highly viscous oil that disappeared after the addition of a fresh portion of **8** (582.8 mg, 3.00 mmol) in $CHCl_3$ (10 mL) and some fresh catalyst (1 mol% per end group). This mixture was stirred and heated under reflux overnight after which the reaction mixture was again allowed to cool to room temperature. A diethanolamine (315.2 mg, 3.00 mmol) solution in $CHCl_3$ (8 mL) was added and stirring was continued for 8 h at room temperature resulting in the formation of a highly viscous syrup that again dissolved after the addition of **8** (1.1631 g, 6.00 mmol) and a fresh portion of catalyst (1 mol% per end group). This mixture was stirred and heated under reflux overnight after which diethylamine (2 mL) was added to the reaction mixture and stirring was continued for 30 min at room temperature. The solvent was removed by evaporation to furnish **18** (quant.) as a white foam. ^{13}C-NMR ($CDCl_3$, 50 °C): δ 13.9 (CH_3 end), 16.8 (CH_3 core), 25.9, 26.1 and 26.2 (CH_2-3,5 ring), 28.1 and 28.3 (CH_3 ring), 36.3 and 36.5 (CH_2-2,6 ring), 37.6, 37.9 and 38.1 (CH ring), 38.9 (C-*ipso* core), 41.1 (CH_2 end), 47.0 and 47.6 (CH_2NH ring and CH_2N branch), 52.0 and 52.4 (C-*ipso* ring), 62.8 (CH_2O branch), 66.3 (CH_2 core), 156.3 and 156.6 (C=O). IR (KBr): ν 3308 (NH stretch), 2966 (CH_3 stretch), 2927 (CH_2 stretch), 1710 and 1644 (C=O stretch). *m/z*: Calc. for $C_{299}H_{537}N_{63}O_{63}$: 6022.2. Found: LSI-MS: 6044 $[M+Na]^+$.

[G-1] Ferrocene dendrimer 19

A stirred mixture of 1,1'-ferrocenedimethanol (62.0 mg, 0.25 mmol), **8** (98.0 mg, 0.50 mmol), and Zr(IV)acac$_4$ (1 mol% per end group) in $CHCl_3$ (10 mL) was heated under reflux for 1 day after which the mixture was allowed to cool to room temperature. Subsequently diethylamine (2 mL) was added after which stirring was continued for 30 min at room temperature. The solvent was removed by evaporation to yield **19** (quant.) as a yellow foam. ^{13}C-NMR ($CDCl_3$, 50 °C): δ 13.5 (CH_3 end), 25.8 (CH_2-3,5 ring), 28.2 (CH_3 ring), 36.2 (CH_2-2,6 ring), 37.5 (CH ring), 40.8 (CH_2 end), 46.7 (CH_2NH ring), 51.8 (C-*ipso* ring), 62.3 (CH_2 core), 68.8, 69.6, (CH core), 82.6 (C-*ipso* core), 156.0, 156.5 (C=O). IR (KBr): ν 3317 (NH stretch), 2925 (CH_3 and CH_2 stretch), 1704 and 1638 (C=O stretch). UV (CH_2Cl_2): λ 227. *m/z*: Calc. for $C_{40}H_{64}FeN_6O_6$: 780.5. ESI-MS: 780.9 $[M]^+$, 803.8 $[M+Na]^+$.

[G-2] Ferrocene dendrimer 20

A stirred mixture of 1,1'-ferrocenedimethanol (61.5 mg, 0.25 mmol), **8** (97.0 mg, 0.50 mmol), and Zr(IV)acac$_4$ (1 mol% per end group) in $CHCl_3$ (10 mL) was heated under reflux for 2 days. The mixture was allowed to cool to room temperature after which diethanolamine (52.5 mg, 0.50 mmol) was added and stirring was continued for 1 day at room temperature. A fresh portion of **8** (194.4 mg, 1.00 mmol) in $CHCl_3$ (10 mL) and some fresh catalyst (1 mol% per end group) were added. This mixture was stirred and heated under reflux for 3 days after which the reaction mixture was again allowed to cool to room temperature. Diethylamine (1 mL) was added to the reaction mixture and stirring was continued for 30 min at room temperature. The solvent was removed by evaporation to furnish **20** (quant.) as a yellow foam. ^{13}C-NMR ($CDCl_3$, 50 °C): δ 13.8 (CH_3 end), 25.7 and 25.9 (CH_2-3,5 ring), 28.0 and 28.2 (CH_3 ring), 36.1 and 36.3 (CH_2-2,6 ring), 37.4 and 37.5 (CH ring), 41.0 (CH_2 end), 46.8 and 47.4 (CH_2NH ring and CH_2N branch), 51.9 and 52.3 (C-*ipso* ring), 62.4 and 62.6 (CH_2O), 68.6, 69.5 (CH core), 82.9 (C-*ipso* core), 156.1, 156.5, 156.6 (C=O). IR (KBr): ν 3315 (NH stretch), 2926 (CH_3 and CH_2 stretch), 1707 and 1638 (C=O stretch). UV (CH_2Cl_2): λ 226. *m/z*: Calc. for $C_{96}H_{164}FeN_{18}O_{18}$: 1914.2. ESI-MS: 1914.5 $[M]^+$, 1936.4 $[M+Na]^+$.

***cis*-4-Aminomethyl-1-methyl-cyclohexanamine, 22**

To a stirred solution of the mixture of isomers, **21**[8] (35.7 g, 250 mmol) in ethanol (500 mL) *p*-nitrobenzoic acid (83.73 g, 500 mmol) was added and this mixture was stirred for 3 days at room temperature, after which the salts were isolated by filtration. The solid was dissolved in brine (400 mL) and NaOH was added (30 g, 0.75 mol). This solution was extracted with CH_2Cl_2 (3 x 200 mL). The organic layers were combined, filtered through cotton wool and concentrated *in vacuo* to yield the crude material, which was purified by distillation, to furnish pure **22** (7.32 g, 20%) as a colorless liquid. b.p. = 102–103 °C/12 mm Hg. ^{1}H-NMR ($CDCl_3$): 1.09 (s, 4H, NH_2), 1.11 (s, 3H, CH_3), 1.15–1.23 and 1.33–1.40 (m, 5H, CH and CH_2-3,5), 1.47–1.52 and 1.59–1.64 (m, 4H, CH_2-2,6), 2.56 (d, J = 5.8 Hz, 2H, CH_2NH_2). ^{13}C-NMR ($CDCl_3$): δ 25.6 (CH_2-3,5), 32.5 (CH_3), 38.9 (CH_2-2,6), 40.3 (CH), 47.7 (C-*ipso*), 48.0 (CH_2NH_2). IR (KBr): ν 3354 (NH stretch), 2920 (CH_2 stretch), 1573 (NH deformation), 1452 (C–CH_3 stretch).

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18. These compounds are commercially available.

Summary

This thesis describes the synthesis and characterization of chiral dendrimers. The combination of chirality and dendrimers is a contradictory one as we are combining the high symmetry of dendrimers with the asymmetry of chirality. However, chiral dendrimers can contribute to a better fundamental understanding of chirality in nanosized structures, but also to development of applications in areas like e.g. biology, catalysis and chiral clathration. A review on these topics is the subject of chapter 1.

In chapter 2 the modification of the peripheral primary amines of the poly(propylene imine) dendrimers with BOC-protected amino acids is described and these compounds have already been proven useful to encapsulate guest molecules: *the dendritic box*. Also the chiroptical features proved to be of much interest as the optical activity decreased upon going to higher generations of dendrimers. More insight into the chiroptical behavior of the chiral end group could be deduced from model studies, which revealed a strong solvent dependency on the chiroptical properties. This may well be caused by the presence of different conformations in different solvents. The influence of multiple hydrogen-bonding interactions in combination with dense packing of the surface end groups was investigated in more detail and proved to be of crucial relevance for the chiroptical properties of these nanosized architectures. The use of the N-*t*-BOC-L-phenylalanine end group largely contributed to a better understanding of packing phenomena in nanosized structures, and this chiral unit is even proposed as a useful probe to study interactions inside molecules.

In chapter 3 the chiral probe is used to study the effect of a homologous series of N,N'-alkylene diamides. Within this series of homologs large differences could be observed in solubility, NMR and IR spectroscopy and chiroptical properties. This can be explained in terms of inter- versus intramolecular hydrogen-bonding interactions, giving rise to the formation of ring structures of particular sizes in the case of intramolecular hydrogen bonding. Especially the pentamethylene derivative revealed deviating properties suggesting its strong preference to an intramolecular hydrogen-bonded conformation in chloroform.

In chapters 4 and 5 saccharide modified dendrimers are described that are very promising candidates for biological studies. In cooperation with the group of prof. Stoddart the poly(propylene imine) dendrimers were modified with carboxylic acid-functionalized saccharide units, based on galactose and lactose, as described in chapter 4. This leads to the formation of densely-packed sugar balls. Less densely-packed systems could be obtained by the introduction of a spacer between the dendrimer surface and the saccharide unit. The solubility behavior was strongly influenced by the spacer length employed, indicating that the interplay of hydrophilic and hydrophobic interactions is crucial for the properties of these systems. This is described in chapter 5.

In chapter 6 an enantiomerically pure chiral dendritic object is described built from enantiomerically pure *S*-(+)-solketal as a core molecule to which constitutionally different Fréchet-type dendritic wedges are attached. The obtained enantiomerically pure Fréchet-type dendritic dendrimers showed no detectable optical activity, and can therefore be referred to as cryptochiral. This lack of optical activity can be explained in terms of flexibility, which considerably reduces the difference between the constitutionally different wedges and by consequence does not allow expression of chirality.

In chapter 7 axially chiral dendrimers are described, built from enantiomerically pure *S*-(–)-1,1'-bi-2-naphthol and Fréchet-type dendritic wedges. On going to higher generations of dendrimers a marginal increase in molar rotation could be observed. This increase could be attributed to steric repulsion between the dendritic wedges, leading to a larger torsional angle between the naphthyl units, and therefore, a larger molar rotation. That the effect is small can be attributed to the high degree of flexibility in these dendritic wedges.

In chapter 8 the rigidification of dendritic wedges is described by the introduction of so-called backfolding wedges in which the substitution pattern of the Fréchet-type dendritic wedges is changed from 3,5-dibenzyloxy to 2,6-dibenzyloxy. As could be deduced from chiroptical studies on chiral molecules modified with these backfolding wedges indeed more rigidity was introduced. This guarantees the desired and intriguing packing, up to now only achievable at higher generations of dendrimers.

In the nineth and last chapter a new method for the synthesis of isocyanates and their use in dendrimer synthesis is described. The great potential of di-*t*-butyltricarbonate for the synthesis of isocyanates, starting from the corresponding primary amines is demonstrated. When using this method it even proved possible to synthesize isocyanates that are not accessible by the standard procedures. Furthermore, the primary amine end groups of all five generations of poly(propylene imine) dendrimers could be converted into the desired multi-isocyanates. In cooperation with DSM the utility of this method is exemplified in the construction of polycarbamate/urea based dendrimers, making use of an asymmetric bifunctional building block, that revealed a high regioselectivity in reactions with alcohols. This new method furnished polycarbamate/urea based dendrimers in a one-pot procedure, only necessitating stirring, heating and accurate dosing. Even the synthesis of the third generation dendrimer with a molecular weight of over 6,000 gave no real problems and could be performed within a time span of 2–3 days. Considering the fact that many polyols and aminoalcohols are available, numerous dendrimers become accessible, even bringing tailor-made dendrimers within the realm of reality.

Samenvatting

Dit proefschrift beschrijft de synthese en karakterisering van chirale dendrimeren. De combinatie van de sterk symmetrische dendrimeren met chiraliteit, en dus asymmetrie, lijkt tegenstrijdig. Deze chirale dendrimeren zijn zeer intrigerend en kunnen, naast een beter fundamenteel begrip van chiraliteit in nanostructuren, ook bijdragen aan mogelijk interessante toepassingen op het gebied van de biologie, van de asymmetrische katalyse, en van chirale insluiting, zoals staat beschreven in hoofdstuk 1.

In hoofdstuk 2 wordt de modificatie van de perifere primaire amines van de poly(propyleen imine) dendrimeren met BOC-beschermde aminozuren beschreven, wat al heeft geleid tot de ontdekking van het dendrimere doosje, waarin gastmoleculen kunnen worden opgesloten. Daarnaast bleken ook de chiroptische eigenschappen van dit dendrimere doosje uitermate interessant, aangezien de optische activiteit afneemt gaande naar hogere dendrimeergeneraties. Aan de hand van modelstudies kon worden aangetoond dat de chirale groep sterk gevoelig is voor de chemische omgeving waarin deze zich bevindt, wat waarschijnlijk berust op verschillende conformaties in verschillende oplosmiddelen. De invloed van meervoudige waterstofbruginteracties in combinatie met dichte pakking over het dendrimeeroppervlak werden nader onderzocht en bleken inderdaad van cruciaal belang voor de chiroptische eigenschappen van de chirale dendrimeren. Door gebruik te maken van de BOC-L-fenylalanine eindgroep konden we pakkingsfenomenen bestuderen in architecturen van nanometerdimensies, waarbij we de gevoelige chirale eindgroep zelfs als probe kunnen gebruiken om interacties binnenin moleculen te bestuderen.

In hoofdstuk 3 is deze chirale probe gebruikt in een homologe reeks van N,N'-alkylene diamides. In deze serie bleken er grote onderlinge verschillen te bestaan ten aanzien van de oplosbaarheid, NMR en IR spectroscopische en chiroptische eigenschappen, waarbij intramoleculair ringstructuren van een bepaalde omvang werden gevormd. Deze bleken bij voorkeur te worden gevormd indien werd uitgegaan van het pentamethyleen derivaat.

In de hoofdstukken 4 en 5 worden suikergemodificeerde dendrimeren beschreven, die interessant zijn vanuit biologisch oogpunt. In samenwerking met de groep van prof. Stoddart werden poly(propyleen imine) dendrimeren gebruikt, waarvan de perifere primaire aminegroepen werden gemodificeerd met carbonzuur gefunctionaliseerde suikermoleculen, op basis van galactose en lactose, zoals staat beschreven in hoofdstuk 4. Dit leidde tot de vorming van dicht gepakte suikerdendrimeren. Minder dicht gepakte systemen konden worden verkregen door een spacer tussen het dendrimeeroppervlak en het saccharide te introduceren, zoals staat beschreven in hoofdstuk 5. Bij toenemende spacerlengte bleek uit het oplosbaarheidsgedrag dat hydrofobe en hydrofiele interacties een belangrijke rol spelen.

In hoofdstuk 6 wordt een enantiomeerzuiver chiraal dendritisch object beschreven, dat is opgebouwd uit enantiomeer zuiver *S*-(+)-solketal als chiraal kernmateriaal, waaraan

constitutioneel verschillende Fréchet-type dendrimere wedges werden bevestigd. Deze verbindingen vertonen geen meetbare optische activiteit en kunnen derhalve worden aangemerkt als cryptochiraal. Dit kan worden verklaard in termen van flexibiliteit, waardoor het onderscheid tussen de constitutioneel verschillende wedges verwaarloosbaar klein wordt, niet leidend tot een detecteerbare optische rotatie.

In hoofdstuk 7 worden axiaal chirale dendrimeren beschreven, die zijn opgebouwd uit enantiomeerzuiver *S*-(–)-1,1'-bi-2-naftol en Fréchet-type dendrimere wedges. Gaande naar hogere dendrimeergeneraties kon een marginale toename in de molaire rotatie worden waargenomen. Deze toename wordt veroorzaakt door sterische repulsie tussen de wedges, die leidt tot een grotere torsiehoek tussen de naftyleenheden, resulterend in een grotere molaire rotatie. Dit effect is echter gering, wat een extra aanwijzing is voor de flexibiliteit in deze systemen.

In hoofdstuk 8 staat beschreven hoe meer rigiditeit kan worden geïntroduceerd door het ontwikkelen van de zgn. terugvouwdendrimeren, waarbij we het substitutiepatroon van de Fréchet-type dendrimeren hebben veranderd van 3,5-dibenzyloxy naar 2,6-dibenzyloxy. Dit bleek inderdaad uit chiroptische studies van chirale verbindingen, die gemodificeerd zijn deze terugvouwwedges. Dit laat toe om reeds bij zeer lage dendrimeergeneraties de gewenste en bovendien zeer intrigerende pakkingsfenomenen waar te nemen.

In het negende en laatste hoofdstuk wordt een nieuwe methode beschreven voor de synthese van isocyanaten, en hun gebruik in dendrimeersyntheses. Allereerst wordt een milde synthesemethode voor isocyanaten beschreven, bestaande uit een reactie van di-*t*-butyltricarbonaat met de overeenkomstige primaire amines. Het bleek met deze nieuwe methode zelfs mogelijk om isocyanaten te maken, die met de standaard synthesemethoden niet toegankelijk waren. Tevens konden de perifere primaire amine uiteinden van alle generaties poly(propyleen imine) dendrimeren met deze methode volledig worden omgezet in de overeenkomstige multi-isocyanaten. In samenwerking met DSM, zijn polycarbamaat–ureum dendrimeren ontwikkeld en gesynthetiseerd in een één-pots procedure, uitgaande van een niet-symmetrisch bifunctioneel isocyanaat, met een hoge regioselectiviteit ten aanzien van alcoholen. Zelfs de synthese van de derde generatie dendrimeer met een molgewicht van meer dan 6000 Da leverde geen problemen op en kon worden uitgevoerd in een tijdsbestek van slechts 2–3 dagen. De beschikbaarheid van vele polyolen en aminoalcoholen maakt talloze structuren toegankelijk en brengt de zgn. tailor-made dendrimeren dichterbij.

Curriculum vitae

Rob Peerlings werd op 29 september 1970 geboren te Weert. Na het behalen van zijn MAVO diploma (1986) aan de MAVO St. Oda in Budel en VWO diploma (1989) aan het Bisschoppelijk College in Weert, studeerde hij Scheikundige Technologie aan de Technische Universiteit Eindhoven. Het afstudeerwerk met als titel "Synthese en karakterisering van arylsystemen" werd verricht in de vakgroep Organische Chemie onder de begeleiding van dr.ir. L. Groenendaal en prof.dr. E.W. Meijer. In juni 1994 studeerde hij af, waarna hij per 1 juli 1994 begon als OIO in dezelfde vakgroep onder de leiding van prof.dr. E.W. Meijer. Het verrichte onderzoek in de periode van juli 1994 tot juli 1998 ligt ten grondslag aan dit proefschrift. Vanaf oktober 1998 zal hij werkzaam zijn bij Bayer in Leverkusen.

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