

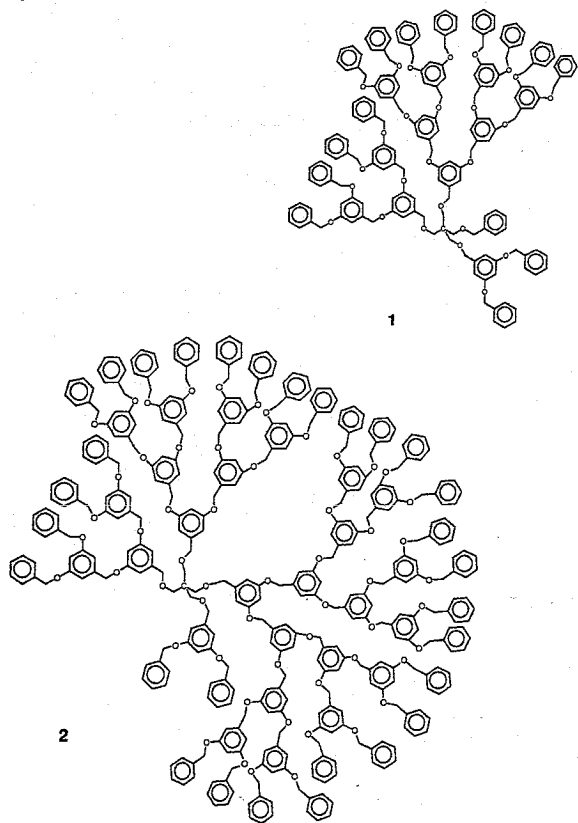
Cryptochirality and Dendrimers

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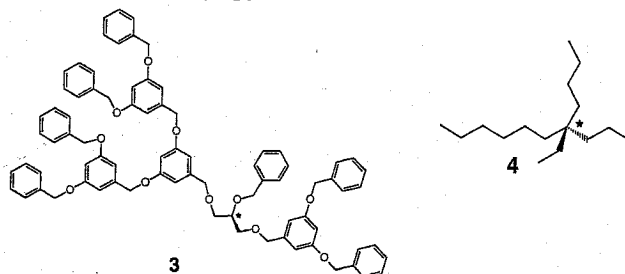
Introduction

Structural chirality in dendritic structures is generally regarded as a contradiction in terms. On the one hand, most dendritic macromolecules known today are based upon highly symmetrical architectures, that emanate from a central core¹. On the other hand, structural chirality is, in our opinion, characterized by any form of geometrical asymmetry. Hence, studying chiral dendrimers and therefore introducing both symmetry and asymmetry into a molecule is not obvious. However, already from the pioneering days of dendrimer research, it has been shown that chirality can be introduced at various levels. Some chiral dendrimers have been reported that are based upon chiral endgroups², chiral cores³, chiral building blocks⁴ and even combinations thereof⁵. These investigations led recently to the disclosure of intriguing chiral recognition effects⁵ and unconventional chiroptical properties of densely packed dendritic highly curved surfaces⁶. Although, many of these stereochemical studies with chiral dendrimers aim at cooperative supramolecular chiral effects, they are not classified within the scope of structural chirality in a more fundamental way. We have recently introduced the concept of a chiral dendrimer, owing its chirality to the fact that four dendritic wedges of different generations are attached to a central carbon core⁷.



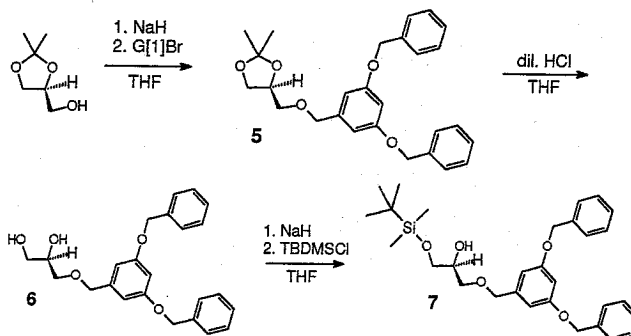
Molecules 1 and 2 were prepared in their racemic form, making use of a stepwise modification of the four alcohol functionalities of

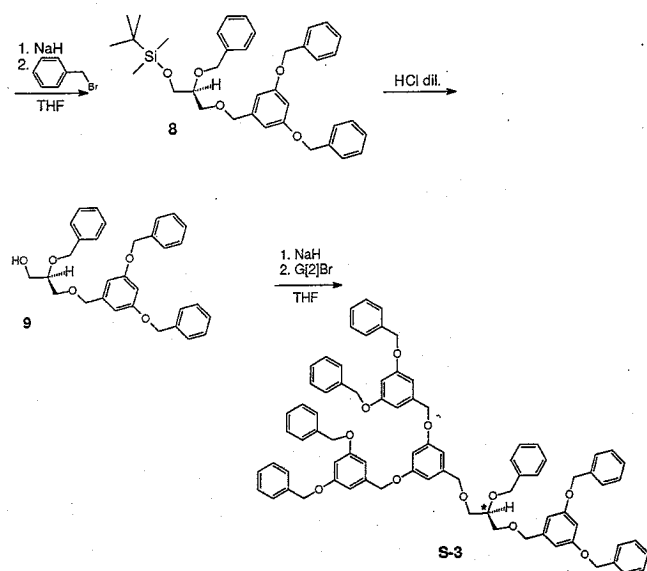
pentaerythritol with Fréchet type dendritic wedges⁸ in a convergent synthetic route. Neither 1 nor 2 could be resolved into the corresponding enantiomers, hampering any detailed chiroptical study. Therefore, chiral dendrimer 3 has been designed to study this type of chiral dendrimers, that can be obtained by using a chiral triol derivative, S-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol (S-solketal), as a starting material. The chirality in this dendrimer 3 stems from the fact that now the two primary alcohols of glycerol are substituted with Fréchet type dendritic wedges of different generation. In this preprint, we present the synthesis and characterization of the first enantiomerically pure cryptochiral⁹ dendrimer, being the macromolecular, dendritic analogue of the well-known textbook example, 5-ethyl-5-propyl-undecane 4¹⁰.



Synthesis

Enantiomerically pure S-solketal is used as starting material for both enantiomers of 3, while the Fréchet type dendritic wedges⁸ are used as building blocks. The synthetic scheme for S-3 is depicted in scheme 1. The route is designed with the aim to have no racemization of the chiral core to occur during synthesis as an enantiomerically pure chiral dendrimer is required. First the primary alcohol of S-solketal is coupled with the first generation of bromide ([G-1]-Br) to give 5 in 96 % yield. Hydrolysis of the ketal under acidic conditions to 6, followed by a selective protection of the newly generated primary alcohol over the secondary one with TBDMSCl yielded 7 in 54 % yield. Etherification of the secondary alcohol with benzylbromide ([G-0]-Br) to 8, followed by acid catalyzed deprotection of the TBDMS protecting group gave 9. The final step in the synthesis of chiral dendrimer S-3 was a Williamson coupling of 9 with the second generation of bromide ([G-2]-Br). Dendrimer S-3 was purified by using column chromatography. The same reaction route from S-solketal was used to prepare R-3 by changing the sequence of attachment of the [G-1] and [G-2] in the described synthesis. All spectroscopic data of the new products are in full agreement with the structures assigned. A number of reference experiments were performed to show that racemization during the synthesis is highly unlikely.





Scheme 1. Synthetic route to chiral dendrimer S-3.

Chiroptical properties

All chiral molecules, except for S-3 and R-3, synthesized in this study showed optical activity in solution. The chiral dendrimer showed an $[\alpha]_D^{20} = 0.00 \pm 0.01$ ($c=11$, chloroform), while its precursor alcohol 9 exhibits an $[\alpha]_D^{20} = +9.6$ ($c = 0.86$, dichloromethane). Ultraviolet (UV), circular dichroism (CD) 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 are found for S-3. A typical example of a CD spectrum, with saturation at the low energy side, is shown in figure 1.

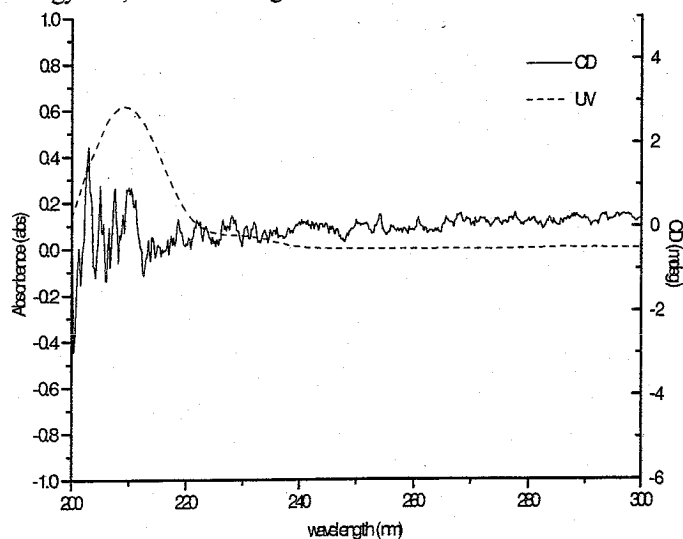


Figure 1. UV and circular dichroism (CD) of chiral dendrimer S-3 in hexane.

Discussion and outlook

The synthetic scheme for S-3 and R-3 is straightforward, the yields are high, and no indications for racemization are found. Due to the

lack of any detectable optical activity in either S-3 or R-3, these low-generation dendrimers are called cryptochiral⁹. The two different substituents to the glycerol core, attached via the primary alcohol functionalities, differ on the one hand significantly in size, but on the other hand, they have a closely related molecular structure. Therefore, the cryptochirality is proposed to be the result of significant conformational freedom of the different substituents. This explanation is also used to describe the cryptochirality of 4¹⁰. Whether, the structural chirality of S-3 is detectable is still unclear, because the conformational freedom will probably also lead to a vanishing enantiomeric difference in the geometry of S-3 and R-3. These new results are consistent with the failures to resolve dendrimers 1 and 2 into their corresponding enantiomers. In order to obtain measurable structural chirality with dendrimers, we will turn our attention towards the highest generation analogues of 1 and 2, in which a densely packed surface is expected to freeze in a mesoscopic chiral object.

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