

Chiral dendrimers with backfolding wedges

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Dendritic wedges with a substitution pattern that forces the growth inwards are introduced and the use of this new building strategy is exemplified in the synthesis and chiroptical properties of a chiral dendrimer.

The first reports on the synthesis and properties of dendrimers¹ initiated many studies towards this new class of highly branched macromolecules. A wide variety of synthetic routes have led to the production of a large number of new dendritic structures, even leading to structures that are now commercially available.² The branching pattern of many, if not all, of these dendrimers is designed to facilitate the growth of each next generation outwards. As a result, dendrimers can be obtained that possess a highly packed periphery and cavities in the interior, making for example, encapsulation of guest molecules possible.³ Recently, however, it has been indicated that many of the structures studied so far have a rather flexible conformation, leading to an average density that is not different for interior and periphery. So far, conformational rigidity in these structures has only been found at higher generations of dendrimers.^{3–6} Restricted flexibility at lower generations, however, has not been observed before and is of interest for many applications foreseen for dendrimers, *e.g.* molecular recognition and catalysis.⁷ Also our search for an optically active chiral dendritic object, which owes its chirality to the presence of constitutionally different wedges attached to a central carbon atom, is hampered by this flexibility.⁸ Recently, the enantiomerically pure dendrimer (*S*)-**1** was described (Fig. 1); however, no detectable optical activity was observed.⁹ Here, we present the concept of backfolding wedges in the synthesis of dendrimers with restricted flexibility at lower generations. The effect of these wedges is exemplified in a chiroptical study based on the

modification of the Fréchet-type poly(benzylether) wedges by changing from a 3,5- to a 2,6-dibenzoyloxy substitution pattern.

2,6-Dihydroxybenzoic acid was used as a starting material for the synthesis of both desired backfolding dendritic wedges. The first generation was synthesized starting from a reaction of 2,6-dihydroxybenzoic acid with 3 equiv. of benzylbromide, yielding benzyl 2,6-dibenzoyloxybenzoate **2**, which was reduced by a reaction with LiAlH₄ to 2,6-dibenzoyloxybenzyl alcohol **3** (Scheme 1). Bromination of **3** was accomplished by a reaction with PBr₃, yielding 2,6-dibenzoyloxybenzyl bromide **4**, the first generation bromide backfolding dendrimer. For the synthesis of the second generation of bromide backfolding dendritic wedge, first 2,6-dihydroxybenzoic acid was converted into methyl 2,6-dihydroxybenzoate **5** *via* reaction with methyl iodide in DMF in the presence of NaHCO₃. In our first approach to backfolding, the normal Fréchet-type dendritic wedge of the first generation was brought into reaction with **5**, yielding **6**. After reduction to the corresponding benzyl alcohol **7**, the desired benzyl bromide **8** was obtained *via* reaction with PBr₃. The crystalline benzyl bromides **4** and **8** proved to be rather acid sensitive and compound **8** even decomposes on standing in a CHCl₃ solution.

The effect of the backfolding dendritic wedges was tested in the synthesis of (*S*)-**9**, the conformationally more rigid analogue of (*S*)-**1** (Fig. 1). The assigned conformational flexibility in (*S*)-**1** is based on the chiroptical study, as there is no detectable optical activity in terms of optical rotatory dispersion (ORD), circular dichroism (CD) or optical rotation,⁹ and therefore this compound can be referred to as being prochiral.¹⁰

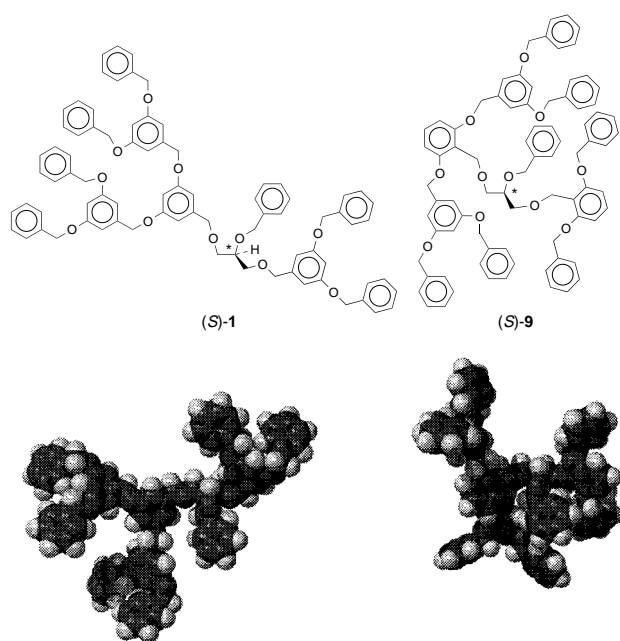
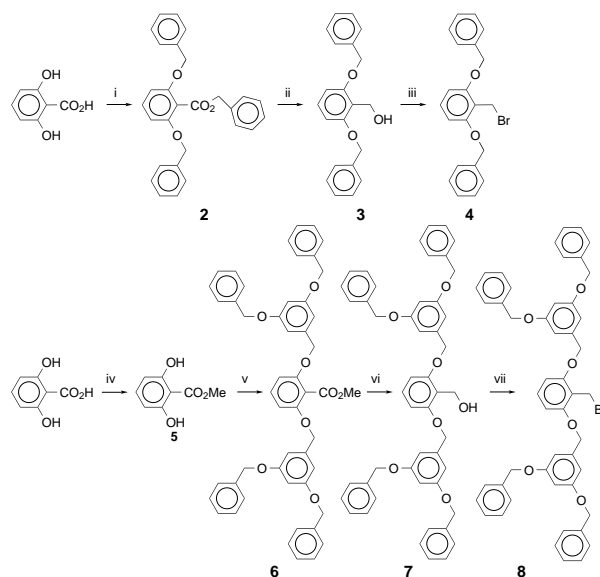
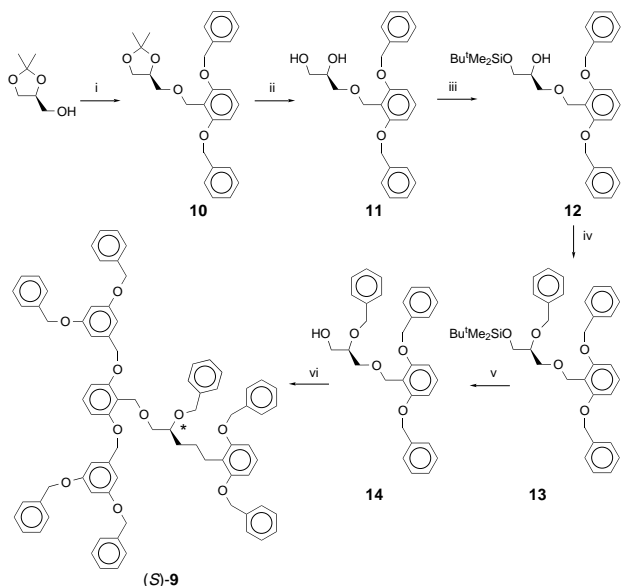


Fig. 1 Modelling study of (*S*)-**1** and (*S*)-**9**



Scheme 1 Reagents and conditions: i, BnBr, K₂CO₃, 18-crown-6, acetone; ii, LiAlH₄, Et₂O, 65% for two steps; iii, PBr₃, Et₂O, 96%; iv, MeI, NaHCO₃, DMF, 77%; v, [G-1]Br, K₂CO₃, 18-crown-6, acetone, 67%; vi, LiAlH₄, THF, 75%; vii, PBr₃, Et₂O–THF, 74%



Scheme 2 Reagents and conditions: i, 4, NaH, THF, 98%; ii, TsOH, MeOH, 75%; iii, NaH, Bu^tMe₂SiCl, THF, 54%; iv, NaH, BnBr, THF, 77%; v, Bu₄NF, THF, 77%; vi, 8, NaH, THF, 68%.

The synthetic approach to chiral dendrimer (*S*)-**9** is similar to the synthesis of (*S*)-**1**, with normal Fréchet-type wedges, as reported before.⁹ 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*)-2,2-dimethyl-1,3-dioxolane-4-methanol [$[\alpha]_D^{20}$] +15.2 (neat, 25 °C)] was used as a starting material for the synthesis of the backfolding dendrimer (*S*)-**9**. The free alcohol functionality was brought into reaction with the first generation of backfolding bromide **4**, yielding **10**. Deprotection of the acetal protecting group was performed under mild acidic conditions, making use of a catalytic amount of toluene-*p*-sulfonic acid in MeOH, leading to diol **11**, which could be obtained as a white crystalline solid. In order to differentiate between the two alcohol functionalities a bulky protecting group was introduced via a reaction with NaH and Bu^tMe₂SiCl. Only the desired monosubstituted product **12** and unreacted product **11** could be obtained after the reaction, which could be separated by washing with hexane (in which only the product dissolved). The free secondary alcohol functionality was reacted with benzyl bromide (the zeroth generation of dendrimer), yielding **13**. Subsequently, the Bu^tMe₂Si group was removed by reaction with Bu₄NF to yield precursor molecule **14**. In the final step the free primary alcohol functionality of **14** was reacted with the second generation of 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 using column chromatography. All spectroscopic data are in full agreement with the compounds obtained.†

Backfolding dendrimer (*S*)-**9** exhibited, in sharp contrast to (*S*)-**1**, an optical activity of [$[\alpha]_D^{20}$] +0.8 (*c* = 2.2, CH₂Cl₂). A more thorough study was performed using ORD, UV and CD measurements. For the CD measurements, distilled CH₂Cl₂ was used and spectra were measured at λ = 320–220 nm. A very weak signal was found at λ = 280 nm, at a temperature of 15 °C, indicative of an induced chiral effect. However, at more elevated temperatures (30 °C) this signal vanished, indicating that the conformational flexibility/rigidity can be triggered by temperature. The difference in chiroptical effects for (*S*)-**1** and (*S*)-**9** are proposed to be the result of more conformational rigidity in the latter.

In conclusion, we present the concept of a backfolding dendritic wedge by modifying the branching pattern of Fréchet-type dendritic wedges. The backfolding character of this new type of dendrimers is illustrated in chiral dendrimer (*S*)-**9**, which exhibits optical activity. The chiroptical properties show that when introducing these conceptually new wedges an overall conformationally more rigid structure is obtained. The use of this new type of wedge enables us create more conformational rigidity at low generations, which up to now was only possible at very high generations.

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Notes and References

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‡ Selected data for (*S*)-**9**: δ_{H} (CDCl₃) 3.58–3.69 (m, 4 H, C*HCH₂), 3.79 (q, *J* 5.5, 1 H, C*H), 4.51 and 4.67 (2*s, 4 H, CH₂OCH₂OAr), 4.71 and 4.73 (2d, *J* 10.3, C*HOCH₂Ph), 4.89 and 4.90 (2s, 8 H, ArOCH₂Ph, ArOCH₂Ar'), 4.91 (s, 8 H, Ar'OCH₂Ph), 6.44 and 6.48 (2d, *J* 8.4, 4 H, ArH-3,5), 6.51 (t, *J* 2.2, 2 H, Ar'H-4), 6.64 (d, *J* 2.2, 4 H, Ar'H-2,6), 7.03–7.35 (m, 37H, ArH-4 and PhH); δ_{C} (CDCl₃) 61.4, 69.8, 70.1, 70.9, 71.0, 71.8 (CH₂), 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'OCH₂PhC-*ipso*), 137.1 (ArOCH₂PhC-*ipso*), 139.1 (C*HOCH₂PhC-*ipso*), 139.7 (Ar'C-1), 158.4 (ArC-2,6), 159.9 (Ar'C-3,5); ν_{max} (KBr)/cm⁻¹ 3031 (=C-H), 2927 and 2872 (-CH₂-), 1596 and 1497 (C=C), 1452 (CH₂); 1115 (CH₂OCH₂). [$[\alpha]_D^{20}$] +0.8 (*c* 2.2, CH₂Cl₂). *m/z* 1233 (M + Na⁺), 1249 (M + K⁺), 1343 (M + Cs⁺).

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