DOI: 10.1002/ejoc.200500819

Preparation and Chiroptical Studies of Dendritic Alkaloid Derivatives

Uwe Hahn,[a] Astrid Kaufmann,[a] Martin Nieger,[b] Ondřej Julínek,[c] Marie Urbanova,[c] and Fritz Vögtle*[a]

Keywords: Alkaloids / Chirality / Circular dichroism / Dendrimers

A series of dendritic substituted alkaloids, deriving from quinine or atropine and Fréchet-type dendrons up to generation three, have been prepared. Enantioseparation of the dendronized atropine ammonium salts was achieved by HPLC on chiral stationary phases. Investigation of the chiroptical properties of the series of dendrimers by circular dichroism spectroscopy revealed an influence of the chiral core on the dendritic part with regard to the intensities of the Cotton bands. The chirality was found to be dependent on its chiral elements and the generation of the formally achiral dendritic branch attached to the chiral core ("dendritic effect").

Introduction

Because of the high molecular weight and the well defined structure, dendrimers can be considered as useful tools to study phenomena on a macromolecular level.[1,2] Many examples have been reported demonstrating "dendritic effects" when single units are implemented into dendritic edifices.[3–9] Particularly chiroptical studies[10–12] of chiral dendritic structures have received attention mainly based on their potential application in fields such as asymmetric catalysis,[13,14] or stereoselective recognition.[15] These examples mainly focus on substances from the pool of optically active natural compounds as chiral moieties like amino acids or carbohydrates. But not only stereogenic centres have been incorporated into dendrimers, also other types of chiral elements have been employed in structural investigations of chirality.[16] Recently, we have reported on dendrophanes[17] and dendroknots[18] bearing either a planar chiral [2.2]paracyclophane or a topologically chiral knot[19] moiety in the core. Such chiral nanoscopic structures exhibit dendritic effects with respect to their circular dichroism spectra. Along with increasing size of the dendritic part attached to the chiral subunit the amplitudes of the Cotton effects turned out to intensify in both series of dendritic molecules. These results suggest that a single chiral subunit could impart conformational orders in a more distant conformational flexible part of the molecule thus enhancing the intensity of the Cotton bands by circular dichroism induction from the centre to the periphery.

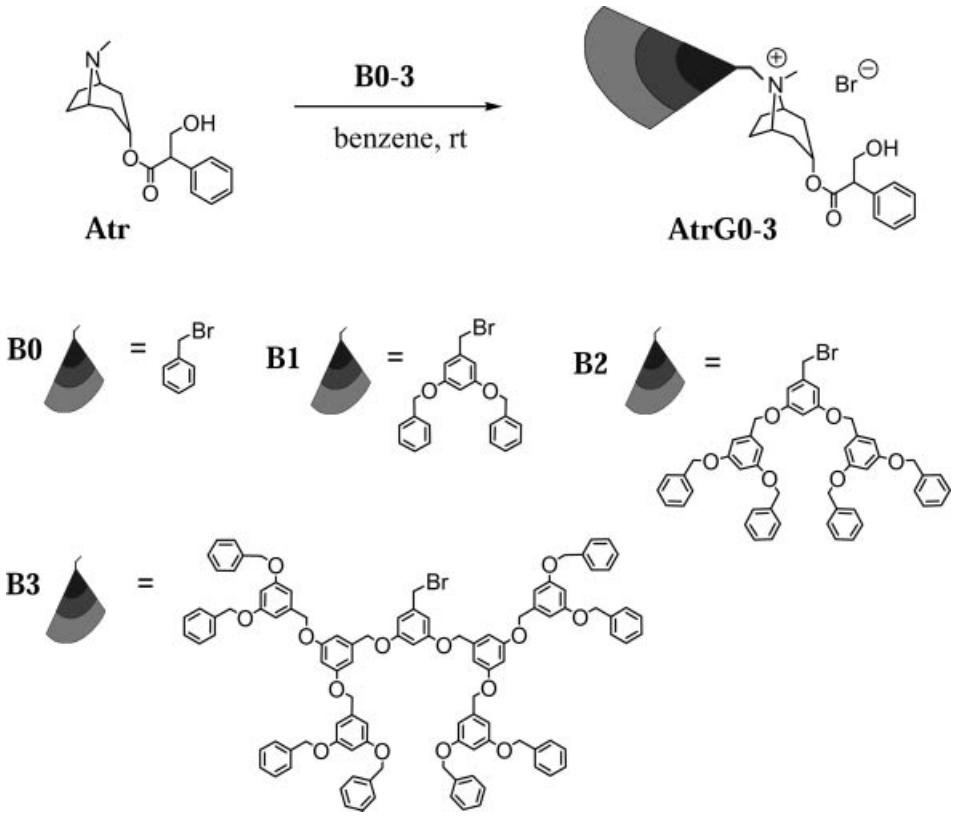
In continuation of our investigations in the field of chiral phenomena, we here report on new chiral dendrimers based on the alkaloids quinine and atropine as chiral core entities. In contrast to the representatives mentioned above, the series of compounds presented here focus on stereogenic centres. This is particularly interesting as stereogenic centres can be regarded as the simplest and at the same time well known chiral units, even if the chosen alkaloids atropine and quinine contain several stereocentres. Studies of the chiroptical properties of these systems by circular dichroism spectroscopy resulted in enhanced Cotton bands along with increasing size of the inherently achiral dendritic polybenzyl ether branches attached to the chiral core. For a series of quinine derivatives vibrational circular dichroism spectroscopy investigations were carried out demonstrating a dendritic effect along with growing size of the dendritic branch.

[a] Kekulé-Institut für Organische Chemie und Biochemie der Rheinischen Friedrich-Wilhelms-Universität Bonn,
Gerhard-Domagk-Strasse 1, 53121 Bonn, Germany
Fax: +49-228-73-5662
E-mail: voegtle@uni-bonn.de
[b] Institut für Anorganische Chemie der Rheinischen Friedrich-Wilhelms-Universität Bonn,
Gerhard-Domagk-Strasse 1, 53121 Bonn, Germany
[c] Department of Physics and Measurements and Department of Analytical Chemistry, Institute of Chemical Technology, Prague,
Technicka 5, 16628 Praha, Czech Republic
E-mail: marie.urbanova@vscht.cz

Results and Discussion

Preparation of Dendronized Alkaloids

The dendritic substituted atropine derivatives **AtrG0**–**3** have been prepared by *N*-substitution of the tropane part of the atropine structure by polybenzyl ether dendrons of the 0th to the 3rd generation. Thus, reaction of atropine (**Atr**) with the corresponding dendritic Fréchet-type bromides[20] **B0**–**3** in benzene afforded the series of *N*-arylmethyl-substituted atropine ammonium salts (Scheme 1). The compounds **AtrG0** and **AtrG1** substituted with a ben-



Scheme 1. Preparation of dendritic substituted atropine derivatives **AtrG0**–**3**.

zyl unit or first-generation Fréchet-type dendron precipitated as colourless solids which were only filtered off and washed with small amounts of benzene. Enantioseparation of the obtained racemates was achieved by HPLC on chiral stationary phases (CSP). Due to the solubility enhancing dendritic branches, no precipitates were observed for **AtrG2** and **AtrG3** substituted by dendritic wedges of the second or third generation. Therefore, purification was realized by HPLC along with enantioseparation on chiral stationary material. All compounds have been characterized by ^{1}H and ^{13}C NMR spectroscopy as well as by FAB mass spectrometry and elementary analysis. The structures of **AtrG0** and **AtrG1** were additionally confirmed by X-ray crystal analysis[21] (Figure 1).

The dendritic quinine derivatives **QuiG0**–**3** were prepared by quaternisation of the nitrogen of the quinuclidine moiety. The chemoselective reactions of the different dendritic Fréchet-type bromides[20] **B0**–**3** and the commercially available enantiopure (–)-quinine (**Qui**) were performed in benzene (Scheme 2). In case of the lower generations the salts precipitated as solids, which were filtered and washed with small amounts of benzene. Due to the increased lipophilicity, the products of the second and third generation **QuiG2** and **QuiG3** were soluble in benzene and have been purified by preparative size exclusion chromatography. All structures could be readily deduced from ^{1}H, ^{13}C NMR, FAB mass spectra and by elementary analysis.

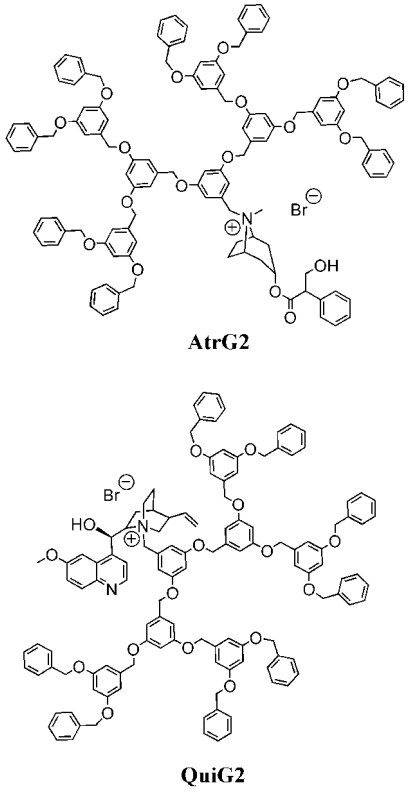
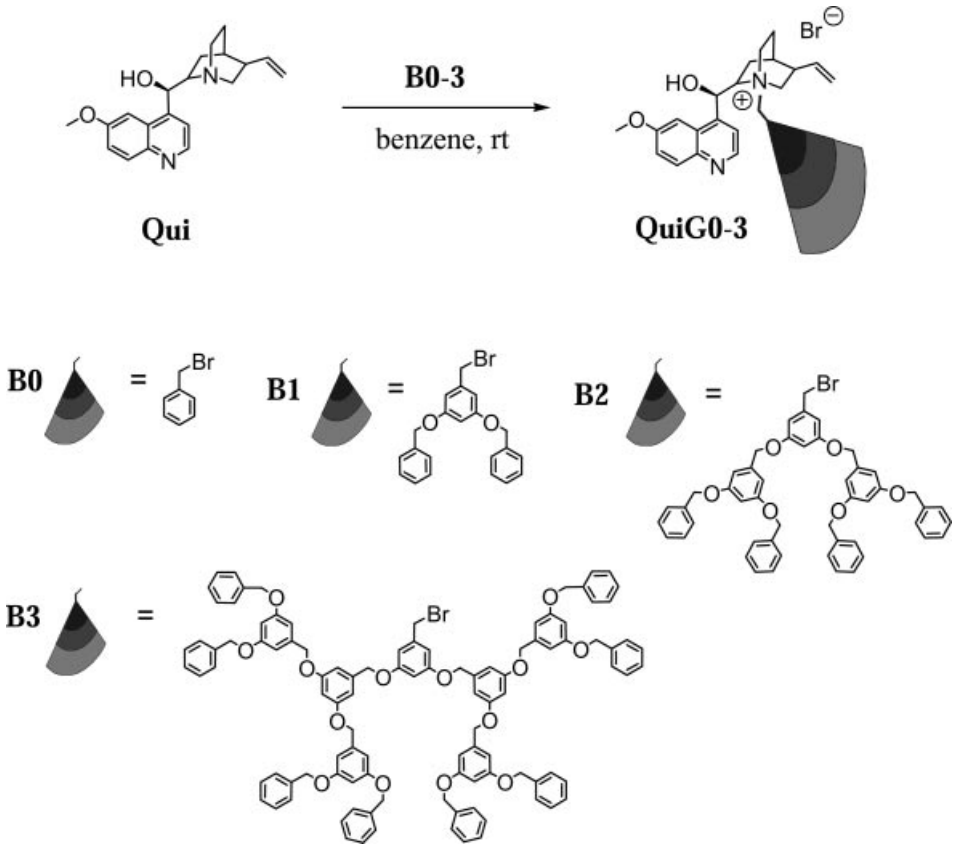


Figure 1. Dendronized alkaloids **AtrG2** and **QuiG2**.



Scheme 2. Preparation of dendritic substituted quinine derivatives **QuiG0**–**3**.

Enantioseparation and Chiroptical Properties

The enantioseparation of the racemic atropine derivatives **AtrG0**–**3** was performed by HPLC on a "Chiralcel OD" column [cellulosetris(3,5-dimethylphenyl)carbamate] [22] with *n*-hexane/methanol/ethanol (75:15:10) as eluent. In all cases enantioresolutions with baseline separation could be achieved with separation factors in the range of 1.24 to 1.66. The optical rotation values $[\alpha]_D^{20}$ of **AtrG0**–**3** showed decreasing values with growing size of the dendritic wedge. The dilution of the optical activity by attaching inherently achiral wedges to a chiral core is in agreement with previous findings in literature.[23]

The Cotton bands for each pair of enantiomers of dendritic atropine ammonium salts **AtrG0**–**2** are near to identical mirror images over the entire spectra in all cases (Figure 2, a). The third-generation compound **AtrG3** could not be solved in solvents for CD spectroscopy, which hampered any detailed chiroptical investigation. The CD spectra of **AtrG0**–**2** in the range of 190–300 nm show four distinct peaks in the aromatic region (Table 1) and the intensities of the molar CD increase with growing size of the dendritic substituent ("dendritic effect"). For such increased circular dichroism effects a CD signal is induced onto the achiral branches by placing them in a chiral environment.[24] As the number of chromophoric groups, namely the benzene and the dimethoxybenzene units, within the different generations increases, also an increased overall extinction coefficient is obtained for both series of enantiomers. The slightly shifted maximum in case of the higher generations at 220 nm might be explained by an overlap of the carbonyl absorption of the atropine moiety and the more intense absorption of the increasing number of chromophores of the polybenzyl ether dendrons.

A study of the chiroptical properties of the dendritic quinine samples **QuiG0**–**2** showed similar effects as found for the atropine derivatives. The values of the optical activity $[\alpha]_D^{20}$ decrease when going to higher generation substituted compounds, which is in agreement with literature statements.[23] The circular dichroism spectra of **QuiG0**–**2** in the range of 190–300 nm shows four distinct extrema in the aromatic region (part b of Figure 2, Table 2). On extension of the size of the dendritic branch attached to the chiral core increased Cotton bands were observed, thus leading to a dendritic effect. As discussed for **AtrG0**–**3**, the chiral core unit induces a CD signal on the dendritic polybenzyl ether branches and due to the increased number of chromophores for the various generations an enhanced signal was found.[24] Due to the low solubility in appropriate solvents for CD spectroscopy, it was not possible to record a CD spectrum for the third-generation compound **QuiG3**.

In addition, the dendronized quinine derivatives **QuiG0**–**2** were studied by vibrational circular dichroism (VCD) spectroscopy (Figure 3). Clear VCD pattern marked as 1–6

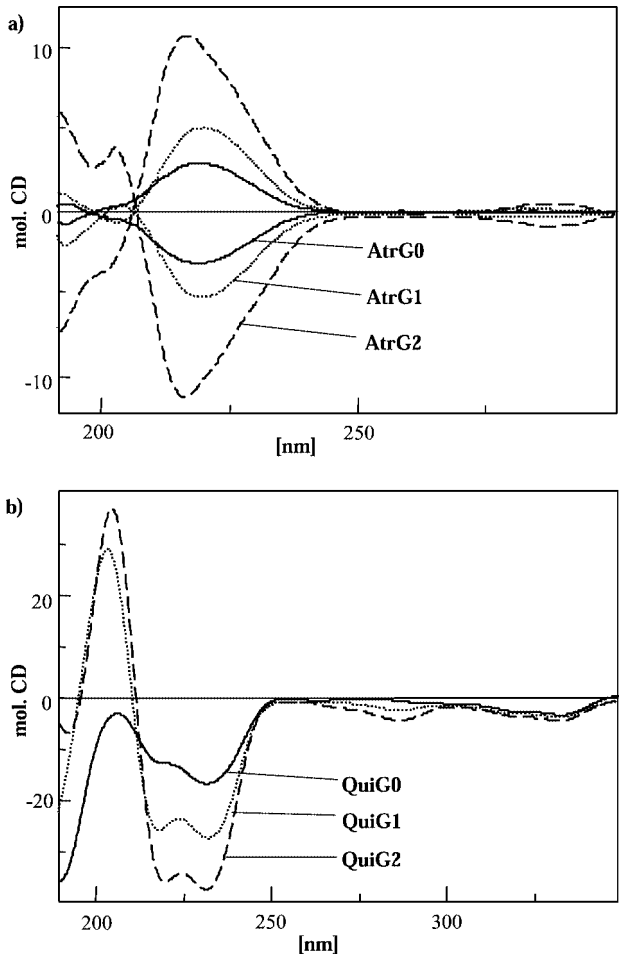


Figure 2. CD spectra of a) **AtrG0–2** and b) **QuiG0–2**.

Table 1. Location [nm] and intensity [M^{-1} cm^{-1}] of the CD bands of **AtrG0–2**.

Compound	192 nm	206 nm	221 nm	290 nm
AtrG0	1	1	3	0
AtrG1	2	1	5	1
AtrG2	7	4	11	2

Table 2. Location [nm] and intensity [M^{-1} cm^{-1}] of the CD bands of **QuiG0–2**.

Compound	205 nm	218 nm	232 nm	287 nm
QuiG0	–3	–12	–16	0
QuiG1	+	–24	–27	–2
QuiG2	+	–36	–38	–4

is observed for **QuiG0** which is in agreement with the chiral structure of the quinine moiety. Assignment of the VCD and corresponding IR absorption pattern is given in Table 3.[25] Apart from these signals, five peaks labeled 7–11 intensify in absorption along with the generation of the dendritic substituted quinine. Three of these bands, labeled 7, 10, and 11, can be assigned to C=C (1590 cm^{-1}), arom. O–R (1300–1340 cm^{-1}), and C–O–C (1160 cm^{-1}) vibrations and show a progressively enhanced VCD most likely originating from the increasing number of benzene and dimethoxybenzene units, which increases along with the generation of the dendritic substituent. The aromatic vibrations originating from the dendritic branches (signal 7) overlaps the absorption of the aromatic vibrations deriving from the quinine moiety (signal 1). The corresponding VCD signal from the quinine subunit is negative while the signal of the dendritic branches is stronger and positive, thus leading to positive VCD signals for **QuiG0–2** in this region. Because of intrinsic sensitivity relations of VCD to structure localized in molecules the observed "dendritic effect" is more due to the benzene and C–O–C groups rather than connected to the CH_2 subunits of the dendritic branches. Dendrimer **QuiG3** of the third generation has also been studied and an enhanced VCD absorption signal in comparison to the second generation derivative was observed. But due to a required concentration about ten times lower than for the **QuiG0** or **QuiG1**, the noise level increased and therefore the spectrum of **QuiG3** was not included in Figure 3.

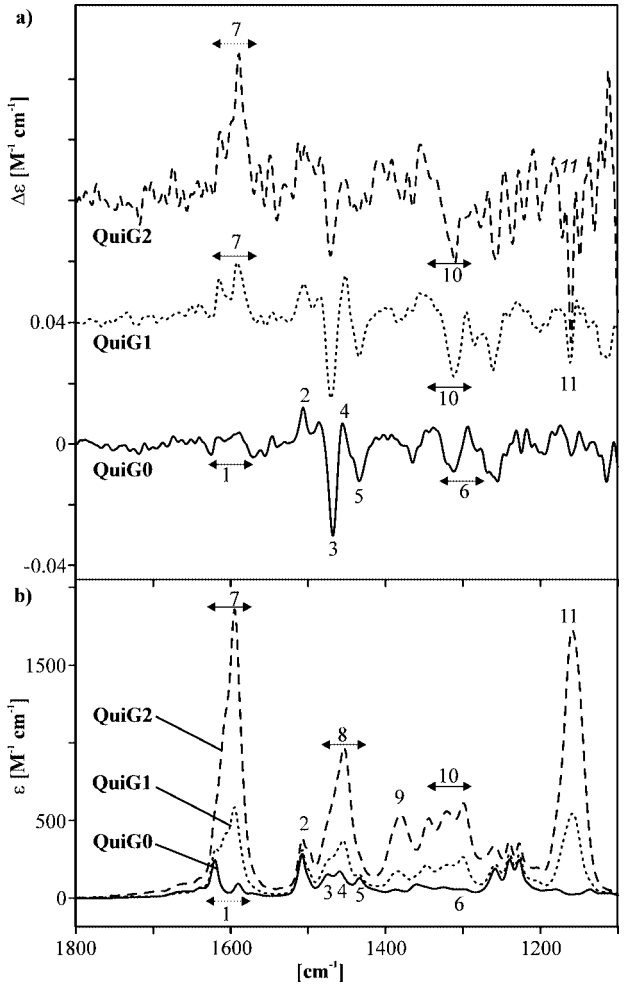


Figure 3. VCD a) and IR absorption b) spectra of **QuiG0–2**.

Table 3. Assignment of VCD and IR absorption signals to characteristic vibrations.

Pattern	ν [cm^{-1}]	Peak assignment
1	1590–1620	C=C, C=N ring[a]
2	1507	quinoline[a]
3–**5**	1433–1474	quinuclidine ring and asymmetric CH_3[a]
6	1300	quinuclidine ring and asymmetric CH_3[a]
7	1595	dimethoxybenzene[b]
8	1453	scissoring CH_2[b]
9	1380	CH_2 overlapped by CH_3[b]
10	1300–1344	arom. O–R[b]
11	1158	C–O–C[b]

[a] Band assigned to quinine moiety. [b] Band assigned to dendritic branch subunit.

Conclusions

New derivatives of the alkaloids atropine and quinine with dendritic polybenzyl ether units as substituents up to the 3rd generation were prepared. For the enantiomers of these dendritic substituted tropan- or chinchona-derived alkaloids an effect similar to dendrophanes[17] and dendroknots,[18] respectively, was observed. In contrast to the latter chiral stuctures, in the present cases the focus was put on stereogenic centres, which can be regarded as simple chiral units although the dendritic substituted quinine and atropine ammonium salts contain five stereocentres. For all different series of dendrimers an increasing induced circular dichroism effect was proved by enhanced Cotton band intensities in their corresponding CD spectra. To place the inherently achiral dendritic branches in a chiral environment induces a CD signal from the core to the peripheral units. This effect was found to be more pronounced for the higher generations as the number of chromophores within the generations increases. For the series of dendritic quinine compounds studies by VCD spectroscopy also revealed a dendritic effect along with growing size of the dendritic wedge, most likely caused by the increasing number of chromophores.

A possible explanation for this apparently more often to be expected phenomenon of induced circular dichroism effects for dendronized chiral molecules could be the chirally induced formation of propeller-like arrangements of the benzene rings within the dendritic wedges. In such microdomains one sense of rotation (clockwise or anticlockwise) could be favoured and lead to progressively increased Cotton band intensities. Theoretical calculations might help to explain the observed results in a more detailed way, but in the present situation calculations of such chiral architectures with large flexible dendritic wedges remain difficult.

Experimental Section

General Remarks: All reagents were used as purchased from commercial sources without further purification. Dendritic bromides **B0**–**3** were prepared according to previously described literature.[20] Solvents were dried using standard techniques prior to use. All reactions were performed in standard glassware under argon atmosphere. Melting points were determined on a Reichert Thermovar microscope and are uncorrected. NMR spectra were recorded using an AM 400 MHz Bruker instrument with solvent signal as reference. Mass spectra (FAB) were performed on a Concept 1H from Kratos Analytical Ltd., Manchester, Great Britain. Microanalyses were performed at the Kekulé-Institut für Organische Chemie und Biochemie, Bonn. UV spectra were taken on a Perkin–Elmer UV/Vis spectrometer Lambda 18. Rotational values have been recorded on a JASCO polarimeter. CD spectra were recorded on a J-810 Spectrometer from JASCO, Labor- und Datentechnik GmbH, Groß-Umstadt, Germany.

Vibrational Circular Dichroism (VCD) Measurements: Spectra were recorded in [D$_6$]DMSO and scanned using a pathlength of 50 μm. A Fourier transformed infrared spectrometer IFS-66/S equipped with a VCD/IRRAS module PMA 37 (Bruker, Germany) was used for the VCD and IR absorption measurements as described elsewhere.[26] VCD spectra were obtained as an average of 6 blocks of 3380 scans and measured with spectral resolution of 4 cm^{-1} and a zero filling factor of 4. The vibrational spectra presented are expressed in molar absorptivity ε (M^{-1}·cm^{-1}).

Enantioseparation by HPLC: The enantioseparation of the dendronized atropine derivatives **AtrG0**–**3** was performed at 25 °C on a line consisting of an analytical pump model 590 (Waters), a Rheodyne injector 7125 and a LCD 2084 UV detector (ECOM). The chiral resolution of all samples was carried out on a commercially available Chiralcel® OD column[22] (length 250 mm, i.d. 10 mm), with *n*-hexane/methanol/ethanol mixture (75:15:10) as eluent at a flow rate of 4.0 mL/min.

X-ray Crystallographic Analysis:[21] The crystal data for compound **AtrG0** were determined with a Nonius KappaCCD Diffractometer with Mo-K_α (λ = 0.71073 Å) radiation. $C_{24}H_{30}BrNO_3$-0.5*i*Pr_2O-0.5H_2O, M_r 520.5, colorless crystals, crystal size 0.40 × 0.20 × 0.15 mm, monoclinic, *C*2/c (No.15), a = 13.8422(3), b = 26.3511(7), c = 13.6295(4) Å, β = 96.485(1), V = 4939.6(2) Å^3, Z = 8, $D_{calcd.}$ = 1.400 g· cm^{-3}, μ = 1.698 mm^{-1}, T = 123(2) K, F(000) = 2192. 20638 reflections up to $2\theta_{max}$ = 50° were measured, 4352 of which were independent and used for all calculations. The structure was solved by direct methods and refined to F_2 anisotropically; the H atoms were refined with a riding model [H(O) free]. The final quality coefficient $wR_2(F^2)$ for all data was 0.1069, with a conventional $R(F)$ value of 0.0400 for 289 parameters and 1 restraint. An empirical absorption correction was applied.

The crystal data for compound **AtrG1** were determined with a Nonius KappaCCD Diffractometer with Mo-K_α (λ = 0.71073 Å) radiation. $C_{38}H_{42}BrNO_5$, M_r 672.6, colorless crystals, crystal size 0.12 × 0.09 × 0.06 mm, monoclinic, $P2_1/n$ (No.14), a = 20.2413(3), b = 9.9433(2), c = 33.0027(6) Å, β = 100.979(1), V = 6520.7(2) Å^3, Z = 8, $D_{calcd.}$ = 1.370 g· cm^{-3}, μ = 1.306 mm^{-1}, T = 123(2) K, F(000) = 2816. 78627 reflections up to $2\theta_{max}$ = 50° were measured, 11405 of which were independent and used for all calculations. The structure was solved by direct methods and refined to F_2 anisotropically; the H atoms were refined with a riding model [H(O) free]. The final quality coefficient $wR_2(F^2)$ for all data was 0.0724, with a conventional $R(F)$ value of 0.0284 for 817 parameters and 2 restraints. An empirical absorption correction was applied.

General Procedure for Dendronized Atropines AtrG0–3: A solution of atropine (**Atr**, 1 equiv.) and the corresponding dendritic benzyl bromide[20] **B0**–**3** (1 equiv.) in dry benzene (10 mL) was stirred at room temp. for 3 d. Purification was achieved as outlined in the following text.

AtrG0: This compound was prepared from **Atr** (289.4 mg, 1 mmol) and **B0** (0.12 mL, 1 mmol). The arising solid was filtered, washed

three times with small amounts of benzene and dried in vacuo to yield **AtrG0** (332.2 mg, 72%) as a colourless solid. M.p. 203 °C. $[\alpha]_D^{20}$ = +/–28 (*c* = 1, DMSO). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ (ppm) 1.70 (d, *J* = 17 Hz, 1 H; CH_2), 1.87 (d, *J* = 17 Hz, 1 H; CH_2), 1.95 (dd, *J* = 10 Hz, *J* = 11 Hz, 1 H; CH_2), 2.22 (dd, *J* = 11 Hz, *J* = 11 Hz, 1 H; CH_2), 2.40–2.60 (m, 4 H, CH_2), 2.93 (s, 3 H, CH_3), 3.70 (m, 1 H, CH_2), 3.76–3.89 (m, 3 H, CH), 3.99 (m, 1 H, CH_2), 4.47 (s, 2 H, NCH_2), 5.00 (d, *J* = 5 Hz, 1 H; CH), 7.27–7.41 (m, 5 H, arom. H), 7.47–7.58 (m, 5 H, arom. H). ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ (ppm) 24.3, 24.5, 31.7, 31.8 (CH_2), 39.8 (CH_3), 54.1 (CH), 62.8 (NCH_2), 62.9 (CH_2OH), 63.4 (CHO), 64.8, 64.9 (CHN), 127.4, 128.0, 128.2, 128.6, 128.9, 130.1, 132.9, 136.0 (arom. C), 171.2 (CO). MS (FAB, NBA): *m*/*z* (%) = 380.2 (100) $[M - Br^-]^+$. $C_{24}H_{30}BrNO_3$: C 62.61, H 6.57, Br 17.36, N 3.04; found: C 62.57, H 6.54, Br 17.30, N 3.01.

AtrG1: This compound was prepared from **Atr** (144.7 mg, 0.5 mmol) and **B1** (191.6 mg, 0.5 mmol). The arising solid was filtered, washed three times with small amounts of benzene and dried in vacuo to yield **AtrG1** (170.8 mg, 51%) as a colourless solid. M.p. 193 °C. $[\alpha]_D^{20}$ = +/–24 (*c* = 1, DMSO). ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ (ppm) 1.63 (d, *J* = 17 Hz, 1 H; CH_2), 1.82 (d, *J* = 17 Hz, 1 H; CH_2), 1.90 (dd, *J* = 10 Hz, *J* = 11 Hz, 1 H; CH_2), 2.18 (dd, *J* = 11 Hz, *J* = 11 Hz, 1 H; CH_2), 2.30–2.57 (m, 4 H, CH_2), 2.88 (s, 3 H, CH_3), 3.62–3.76 (m, 3 H, CH_2, NCH), 3.83 (m, 1 H, CH), 3.99 (m, 1 H, CH_2), 4.32 (s, 2 H, NCH_2), 4.98 (d, *J* = 5 Hz, 1 H; CHO), 5.13 (s, 4 H, OCH_2), 6.71 (d, *J* = 2 Hz, 2 H; arom. H), 6.85 (s, 1 H, arom. H), 7.27–7.46 (m, 15 H, arom. H). ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ (ppm) 24.4, 24.6, 31.8, 31.9 (CH_2), 40.3 (CH_3), 54.2 (CH_2), 63.1 (NCH_2), 63.2 (CH_2OH), 63.7, 65.2, 65.4 (CH), 69.7 (OCH_2), 103.7, 112.2, 127.7, 128.0, 128.2, 128.3, 128.7, 128.9, 130.0, 136.3, 136.9, 159.6 (arom. C), 171.5 (CO). MS (FAB, NBA): *m*/*z* (%) = 592.4 (100) $[M - Br^-]^+$. $C_{38}H_{42}BrNO_5$: C 67.85, H 6.29, Br 11.88, N 2.08; found: C 67.78, H 6.24, Br 11.81, N 2.05.

AtrG2: This compound was prepared from **Atr** (144.7 mg, 0.5 mmol) and **B2** (403.4 mg, 0.5 mmol). The solvent was evaporated and purification was achieved along with enantioseparation by HPLC on chiral stationary material to yield **AtrG2** (436.1 mg, 80%) as a colourless solid. M.p. 81 °C. $[\alpha]_D^{20}$ = +/–21 (*c* = 1, DMSO). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.61 (d, *J* = 17 Hz, 1 H; CH_2), 1.82 (d, *J* = 17 Hz, 1 H; CH_2), 1.88 (dd, *J* = 11 Hz, *J* = 11 Hz, 1 H; CH_2), 2.19 (dd, *J* = 11 Hz, *J* = 11 Hz, 1 H; CH_2), 2.34–2.54 (m, 4 H, CH_2), 2.95 (s, 3 H, CH_3), 3.71 (m, 1 H, CH_2), 3.78–3.87 (m, 3 H, CH), 4.03 (m, 1 H, CH_2), 4.42 (s, 2 H, NCH_2), 4.88 (s, 4 H, OCH_2), 4.92 (s, 8 H, OCH_2), 5.01 (d, *J* = 5 Hz, 1 H; CH), 6.43 (m, 2 H, arom. H), 6.53 (s, 1 H, arom. H), 6.60 (m, 6 H, arom. H), 7.10–7.33 (m, 25 H, arom. H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 25.1, 25.5, 32.6, 32.7 (CH_2), 40.7 (CH_3), 54.6 (CH), 63.3 (CH_2), 63.4 (CH_2OH), 64.2, 65.4, 65.5 (CH), 70.4 (OCH_2), 101.9, 104.6, 106.7, 112.2, 127.8, 127.9, 128.3, 128.4, 128.6, 128.7, 128.9, 129.3, 135.4, 137.0, 139.2, 160.2, 160.4 (arom. C), 172.1 (CO). MS (FAB, NBA): *m*/*z* (%) = 1016.5 (100) $[M - Br^-]^+$. $C_{66}H_{66}BrNO_9$: C 72.25, H 6.06, Br 7.28, N 1.28; found: C 72.19, H 6.02, Br 7.24, N 1.25.

AtrG3: This compound was prepared from **Atr** (28.9 mg, 0.10 mmol) and **B3** (166.0 mg, 0.10 mmol). The solvent was evaporated and purification was achieved along with enantioseparation by HPLC on chiral stationary material to yield **AtrG3** (148.6 mg, 76%) as a colourless amporphous product. $[\alpha]_D^{20}$ = +/–14 (*c* = 1, DMSO). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.67 (d, *J* = 17 Hz, 1 H; CH_2), 1.79 (d, *J* = 17 Hz, 1 H; CH_2), 1.88 (m, 2 H, CH_2), 2.20–2.48 (m, 4 H, CH_2), 2.95 (s, 3 H, CH_3), 3.20 (br. s, 1 H; OH), 3.81 (m, 2 H, CH_2, CH), 3.96 (m, 2 H, CH), 4.12 (m, 1 H, CH_2), 4.63 (d, *J* = 13 Hz, 1 H; NCH_2), 4.67 (d, *J* = 13 Hz, 1 H; NCH_2), 4.92–5.03 (m, 28 H, OCH_2), 5.05 (d, *J* = 5 Hz, 1 H; CH), 6.35–6.40 (m, 7 H, arom. H), 6.48 (d, *J* = 2 Hz, 2 H; arom. H), 6.53 (d, *J* = 2 Hz, 4 H; arom. H), 6.51 (d, *J* = 2 Hz, 8 H; arom. H), 7.17–7.28 (m, 45 H, arom. H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 24.8, 25.3, 32.3, 32.9 (CH_2), 40.3 (CH_3), 54.3 (CH), 63.0 (NCH_2), 63.1 (CH_2OH), 64.1, 65.1, 65.2 (CH), 69.8, 70.1, 70.2 (OCH_2), 101.6, 101.8, 104.3, 106.5, 112.0, 127.6, 127.7, 128.1, 128.2, 128.4, 128.5, 128.7, 129.1, 135.2, 136.8, 139.0, 139.3, 159.9, 160.1, 160.2 (arom. C), 171.7 (CO). MS (FAB, NBA): *m*/*z* (%) = 1216.5 (24) $[M - Br^-]^+$. $C_{122}H_{114}BrNO_{17}$: C 75.29, H 5.90, Br 4.11, N 0.72; found: C 75.09, H 5.82, Br 4.04, N 0.70.

General Procedure for Dendronized Quinines QuiG0–3: A solution of (–)-quinine (**Qui**, 1 equiv.) and the appropriate dendritic benzyl bromide[20] **B0**–**3** (1 equiv.) in dry benzene (10 mL) was stirred at room temp. for 3 d. Purification was achieved as outlined in the following text.

QuiG0: This compound was prepared from **Qui** (648.8 mg, 2 mmol) and **B0** (0.24 mL, 2 mmol). The arising solid was filtered, washed with small amounts of benzene and dried in vacuo to yield **QuiG0** (779.4 mg, 79%) as a colourless solid. M.p. 170 °C (decomp.). $[\alpha]_D^{20}$ = –278 (*c* = 1, DMSO). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ (ppm) 1.49 (dd, *J* = 13 Hz, *J* = 11 Hz, 1 H; CH_2), 1.64 (dd, *J* = 12 Hz, *J* = 11 Hz, 1 H; CH_2), 1.93 (s, 1 H, CH), 2.22 (m, 2 H, CH_2), 2.48 (dd, *J* = 7 Hz, *J* = 7 Hz, 1 H; CH), 3.02 (m, 1 H, CH_2), 3.39 (m, 2 H, CH_2), 3.81 (dd, *J* = 10 Hz, *J* = 7 Hz, 1 H; CH), 3.89 (s, 3 H, CH_3), 4.68 (d, *J* = 12 Hz, 1 H; CH_2), 4.86 (dd, *J* = 12 Hz, *J* = 11 Hz, 1 H; CH_2), 4.91 (d, *J* = 11 Hz, 1 H; CH_2), 5.02 (d, *J* = 17 Hz, 1 H; CH_2), 5.53 (ddd, *J* = 17 Hz, *J* = 11 Hz, *J* = 7 Hz, 1 H; CH), 6.02 (d, *J* = 12 Hz, 1 H; CH_2), 6.40 (d, *J* = 7 Hz, 1 H; arom. H), 6.61 (d, *J* = 7 Hz, 1 H; arom. H), 7.20–7.38 (m, 4 H, arom. H), 7.62 (d, *J* = 4 Hz, 1 H; arom. H), 7.70 (d, *J* = 7 Hz, 2 H; arom. H), 7.91 (d, *J* = 10 Hz, 1 H; arom. H), 8.64 (d, *J* = 4 Hz, 1 H; arom. H). ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ (ppm) 21.5, 24.7 (CH_2), 26.7, 38.0 (CH), 51.0 (NCH_2), 56.3 (CH_3), 60.9, 63.6 (NCH_2), 63.7 (NCH), 69.8 (CHOH), 101.9, 118.0, 120.4, 121.0, 126.0, 128.2, 129.2, 130.5, 132.0, 133.7, 136.2, 142.1, 144.3, 147.5, 158.0 (arom. C, allyl. C). MS (FAB, NBA): *m*/*z* (%) = 415.2 (100) $[M - Br^-]^+$. $C_{27}H_{31}BrN_2O_2$: C 65.45, H 6.31, Br 16.13, N 5.65; found: C 65.41, H 6.29, Br 16.10, N 5.60.

QuiG1: This compound was prepared from **Qui** (324,4 mg, 1 mmol) and **B1** (383.3 mg, 1 mmol). The arising solid was filtered, washed with small amounts of benzene and dried in vacuo to yield **QuiG1** (381.8 mg, 54%) as a yellowish solid. M.p. 189 °C (decomp.). $[\alpha]_D^{20}$ = –183 (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.36 (dd, *J* = 13 Hz, *J* = 11 Hz, 1 H; CH_2), 1.49 (dd, *J* = 12 Hz, *J* = 11 Hz, 1 H; CH_2), 1.87 (s, 1 H, CH), 2.12 (m, 2 H, CH_2), 2.35 (dd, *J* = 7 Hz, *J* = 7 Hz, 1 H; CH), 2.82 (m, 1 H, CH_2), 3.28 (m, 2 H, CH_2), 3.71 (dd, *J* = 10 Hz, *J* = 7 Hz, 1 H; CH), 3.81 (s, 3 H, CH_3), 4.66 (d, *J* = 12 Hz, 1 H; CH_2), 4.72 (dd, *J* = 12 Hz, *J* = 11 Hz, 1 H; CH_2), 4.90 (d, *J* = 11 Hz, 1 H; CH_2), 4.93 (s, 4 H, OCH_2), 4.98 (d, *J* = 17 Hz, 1 H; CH_2), 5.47 (ddd, *J* = 17 Hz, *J* = 11 Hz, *J* = 7 Hz, 1 H; CH), 5.85 (d, *J* = 12 Hz, 1 H; CH_2), 6.41 (d, *J* = 7 Hz, 1 H; CH), 6.52 (m, 2 H, arom. H), 6.92 (s, 2 H, arom. H), 7.15–7.30 (m, 7 H, arom. H), 7.35 (d, *J* = 7 Hz, 4 H; arom. H), 7.60 (d, *J* = 4 Hz, 1 H; arom. H), 7.90 (d, *J* = 10 Hz, 1 H; arom. H), 8.60 (d, *J* = 4 Hz, 1 H; arom. H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.8, 24.9 (CH_2), 26.6, 38.0 (CH), 51.2 (NCH_2), 56.4 (CH_3), 61.2, 63.4 (NCH_2), 64.2 (NCH), 69.4 (CHOH), 70.2 (OCH_2), 101.9, 104.5, 112.6, 118.0, 120.4, 121.0, 126.1, 127.8, 128.0, 128.4, 128.5, 132.1, 136.3, 136.4, 142.9, 144.3, 147.5, 158.1, 159.8 (arom. C, allyl. C). MS (FAB, NBA): *m*/*z* (%) = 627.2 (100) $[M - Br^-]^+$.

$C_{41}H_{43}BrN_2O_4$: C 69.58, H 6.12, Br 11.29, N 3.96; found: C 69.48, H 6.06, Br 11.28, N 3.94.

QuiG2: This compound was prepared from **Qui** (162.2 mg, 0.5 mmol) and **B2** (403.9 mg, 0.5 mmol). The solvent was evaporated and the residue purified by gel permeation chromatography (Biorad, Biobeads SX-1, CH_2Cl_2) to yield **QuiG2** (434.8 mg, 77%) as a yellowish amorphous product. $[\alpha]_D^{20} = -129$ (c = 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.27 (dd, J = 13 Hz, J = 11 Hz, 1 H; CH_2), 1.41 (dd, J = 12 Hz, J = 11 Hz, 1 H; CH_2), 1.80 (s, 1 H, CH), 2.06 (m, 2 H, CH_2), 2.31 (dd, J = 7 Hz, J = 7 Hz, 1 H; CH), 2.70 (m, 1 H, CH_2), 3.31 (m, 2 H, CH_2), 3.62 (dd, J = 10 Hz, J = 7 Hz, 1 H; CH), 3.75 (s, 3 H, CH_3), 4.56 (d, J = 12 Hz, 1 H; CH_2), 4.68 (dd, J = 12 Hz, J = 11 Hz, 1 H; CH_2), 4.87–5.02 (m, 14 H, CH_2), 5.40 (ddd, J = 17 Hz, J = 11 Hz, J = 7 Hz, 1 H; CH), 5.95 (d, J = 12 Hz, 1 H; CH_2), 6.41 (d, J = 7 Hz, 1 H; CH), 6.51 (m, 4 H, arom. H), 6.68 (d, J = 2 Hz, 4 H; arom. H), 6.92 (s, 4 H, arom. H), 7.16–7.36 (m, 19 H, arom. H), 7.61 (d, J = 4 Hz, 1 H; arom. H), 7.90 (d, J = 9 Hz, 1 H; arom. H), 8.60 (d, J = 4 Hz, 1 H; arom. H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 24.9 (CH_2), 26.5, 37.9 (CH), 51.2 (NCH_2), 56.4 (CH_3), 61.4, 63.6 (NCH_2), 64.2 (NCH), 69.5 (CHOH), 70.1, 70.2 (OCH_2), 101.8, 104.6, 106.6, 112.7, 118.1, 120.6, 120.8, 125.9, 127.7, 128.1, 128.4, 128.4, 128.7, 132.2, 136.3, 136.9, 139.1, 143.0, 144.3, 147.7, 158.1, 159.8, 160.2 (arom. C, allyl. C). MS (FAB, NBA): m/z (%) = 1051.5 (100) $[M - Br^-]^+$. $C_{69}H_{67}BrN_2O_8$: C 73.20, H 5.96, Br 7.06, N 2.47; found: C 73.11, H 5.93, Br 7.04, N 2.43.

QuiG3: This compound was prepared from **Qui** (32.4 mg, 0.10 mmol) and **B3** (166.0 mg, 0.10 mmol). The solvent was evaporated and the residue purified by gel permeation chromatography (Biorad, Biobeads SX-1, CH_2Cl_2) to yield **QuiG3** (164.2 mg, 83%) as a yellowish amorphous product. $[\alpha]_D^{20} = -73$ (c = 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.38 (dd, 1 H, J = 13 Hz, J = 11 Hz; CH_2), 1.41 (dd, J = 12 Hz, J = 11 Hz, 1 H; CH_2), 1.97 (s, 1 H, CH), 2.15 (m, 2 H, CH_2), 2.41 (m, 1 H, CH), 2.72 (m, 1 H, CH_2), 3.42 (m, 2 H, CH_2), 3.71 (dd, J = 11 Hz, J = 7 Hz, 1 H; CH), 3.89 (s, 3 H, CH_3), 4.53 (d, J = 12 Hz, 1 H; CH_2), 4.70 (dd, J = 12 Hz, J = 11 Hz, 1 H; CH_2), 4.95–5.11 (m, 30 H, CH_2), 5.40 (ddd, J = 17 Hz, J = 11 Hz, J = 7 Hz, 1 H; CH), 6.11 (d, J = 12 Hz, 1 H; CH_2), 6.30 (d, J = 7 Hz, 1 H; CH), 6.41–6.48 (m, 7 H, arom. H), 6.52 (d, J = 2 Hz, 2 H; arom. H), 6.58–6.61 (m, 4 H, arom. H), 6.68 (m, 8 H, arom. H), 7.24–7.41 (m, 43 H, arom. H), 7.98 (s, 1 H, arom. H), 8.76 (d, J = 5 Hz, 1 H; arom. H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.8, 24.9 (CH_2), 26.4, 37.9 (CH), 51.0 (CH_2), 56.3 (CH_3), 61.4, 63.6 (NCH_2), 63.9 (NCH), 69.8 (CHOH), 70.0, 70.1, 70.2 (OCH_2), 102.0, 102.3, 104.9, 106.8, 106.9, 107.0, 113.1, 118.4, 120.9, 121.2, 126.2, 128.0, 128.5, 128.8, 129.0, 132.6, 136.7, 137.2, 139.5, 139.7, 143.3, 144.7, 148.1, 158.5, 160.1, 160.4, 160.6 (arom. C, allyl. C). MS (FAB, NBA): m/z (%) = 1900.6 (23) $[M - Br^-]^+$. $C_{125}H_{115}BrN_2O_{16}$: C 75.78, H 5.85, Br 4.03, N 1.41; found: C 75.68, H 5.78, Br 3.99, N 1.39.

Acknowledgments

We are very grateful to Prof. Dr. S. Grimme, University of Münster, for DFT calculations and fruitful discussions and to Dr. G. Pawlitzki and A. Yoneva for technical assistance. VCD measurements were supported by a grant (MSM6046137307) from the Ministry of Education, Youth and Sports of the Czech Republic. The Deutscher Akademischer Austauschdienst (DAAD) is gratefully acknowledged for financial support within the exchange program with the University of Jyväskylä, Finland.

[1] a) G. R. Newkome, C. N. Moorefield, F. Vögtle, *Dendrimers and Dendrons: Concepts, Syntheses, Applications*, Wiley-VCH: Weinheim, **2001**; b) G. R. Newkome, C. N. Moorefield, F. Vögtle, *Dendritic Molecules: Concepts, Syntheses, Perspectives*, Wiley-VCH, Weinheim, **1996**; c) J. M. J. Fréchet, D. A. Tomalia, *Dendrimers and other Dendritic Polymers*, Wiley: Chichester, **2002**.

[2] L. Brunsveld, E. W. Meijer, A. E. Rowan, R. J. M. Nolte, *Top. Stereochem.* **2003**, *24*, 373–423.

[3] C. A. Schalley, C. Verhaelen, F.-G. Klärner, U. Hahn, F. Vögtle, *Angew. Chem.* **2005**, *117*, 481–485; *Angew. Chem. Int. Ed.* **2005**, *44*, 477–480.

[4] E. Delort, T. Darbre, J.-L. Reymond, *J. Am. Chem. Soc.* **2004**, *126*, 15642–15643.

[5] M.-S. Choi, T. Aida, H. Luo, Y. Araki, O. Ito, *Angew. Chem.* **2003**, *115*, 4194–4197; *Angew. Chem. Int. Ed.* **2003**, *42*, 4060–4063.

[6] D. L. Stone, D. K. Smith, P. T. McGrail, *J. Am. Chem. Soc.* **2002**, *124*, 856–864.

[7] A. W. Kleij, R. A. Gossage, R. J. M. K. Gebbink, N. Brinkmann, E. J. Reijerse, U. Kragl, M. Lutz, A. L. Spek, G. van Koten, *J. Am. Chem. Soc.* **2000**, *122*, 12112–12124.

[8] A. W. Kleij, R. A. Gossage, J. T. B. H. Jastrzebski, J. Boersma, G. van Koten, *Angew. Chem.* **2000**, *112*, 179–181; *Angew. Chem. Int. Ed.* **2000**, *39*, 176–178.

[9] J. Guittard, J.-C. Blais, D. Astruc, C. Valerio, E. Alonso, J. Ruiz, J.-L. Fillaut, *Pure Appl. Chem.* **1998**, *70*, 809–818.

[10] a) H. W. I. Peerlings, E. W. Meijer, *Chem. Eur. J.* **1997**, *3*, 1563–1570; b) H. W. I. Peerlings, M. P. Struijk, E. W. Meijer, *Chirality* **1998**, *10*, 46–52; c) L. Brunsveld, A. P. H. J. Schenning, M. A. C. Broeren, H. M. Janssen, J. A. J. M. Vekemans, E. W. Meijer, *Chem. Lett.* **2000**, 292–293.

[11] a) P. Murer, D. Seebach, *Helv. Chim. Acta* **1998**, *81*, 603–631; b) D. Seebach, P. B. Rheiner, G. Greiveldinger, T. Butz, H. Sellner, *Top. Curr. Chem.* **1998**, *197*, 125–164; c) S. Allenmark, *Chirality* **2003**, *15*, 409–422; d) C. W. Thomas, Y. Tor, *Chirality* **1998**, *10*, 53–59.

[12] a) B. Romagnoli, W. Hayes, *J. Mater. Chem.* **2002**, *12*, 767–799; b) B. Romagnoli, I. van Baal, D. W. Price, L. M. Harwood, W. Hayes, *Eur. J. Org. Chem.* **2004**, 4148–4157; c) S. Cicchi, A. Goti, C. Rosini, A. Brandi, *Eur. J. Org. Chem.* **1998**, 2591–2597; d) M. F. Ottaviani, F. Furini, A. Casini, N. J. Turro, S. Jokusch, D. A. Tomalia, L. Messori, *Macromolecules* **2000**, *33*, 7842–7851.

[13] a) R. van Heerbeek, P. C. J. Kamer, P. W. N. M. van Leeuwen, J. N. H. Reek, *Chem. Rev.* **2002**, *102*, 3717–3756; b) R. Kreiter, A. W. Kleij, R. J. M. Klein Gebbink, G. van Koten, *Top. Curr. Chem.* **2001**, *217*, 163–199; c) J. W. J. Knapen, A. W. van der Made, J. C. de Wilde, P. W. N. M. van Leeuwen, P. Wijkens, D. M. Grove, G. van Koten, *Nature* **1994**, *372*, 659–663.

[14] a) A. W. Bosman, H. M. Jansen, E. W. Meijer, *Chem. Rev.* **1999**, *99*, 1665–1688; b) D. Astruc, F. Chardac, *Chem. Rev.* **2001**, *101*, 2991–3024.

[15] a) L. Pu, *Chem. Rev.* **2004**, *104*, 1687–1716; b) V. J. Pugh, Q. S. Hu, L. Pu, *Angew. Chem.* **2000**, *112*, 3784–3787; *Angew. Chem. Int. Ed.* **2000**, *39*, 3638–3641; c) M. H. Xu, J. Lin, Q. S. Hu, L. Pu, *J. Am. Chem. Soc.* **2002**, *124*, 14239–14246; d) X. F. Mei, C. Wolf, *J. Am. Chem. Soc.* **2004**, *126*, 14736–14737; e) D. K. Smith, A. Zingg, F. Diederich, *Helv. Chim. Acta* **1999**, *82*, 1225–1241; f) D. K. Smith, F. Diederich, *Chem. Commun.* **1998**, 2501–2502; g) V. J. Pugh, Q. S. Hu, X. Zuo, F. D. Lewis, L. Pu, *J. Org. Chem.* **2001**, *66*, 6136–6140.

[16] For example see: a) S. R. Wyatt, Q.-S. Hu, X.-L. Yan, W. D. Bare, L. Pu, *Macromolecules* **2001**, *34*, 7983–7988; b) H. W. I. Peerlings, E. W. Meijer, *Eur. J. Org. Chem.* **1998**, *4*, 573–577; c) J. Yuan, G. Deng, Q. Fan, M. Liu, *Thin Solid Films* **2004**, *466*, 295–302; d) Y.-M. Chen, C.-F. Chen, F. Xi, *Chirality* **1998**, *10*, 661–666; e) V. Lellek, I. Stibor, *J. Mater. Chem.* **2000**, *10*, 1061–

1073; f) P. Gandhi, B. Huang, J. C. Gallucci, J. R. Parquette, *Org. Lett.* **2001**, *3*, 3129–3132; g) J. Issberner, M. Böhme, S. Grimme, M. Nieger, W. Paulus, F. Vögtle, *Tetrahedron: Asymmetry* **1996**, *7*, 2223–2232.
[17] C. Reuter, G. Pawlitzki, U. Wörsdörfer, M. Plevoets, A. Mohry, T. Kubota, Y. Okamoto, F. Vögtle, *Eur. J. Org. Chem.* **2000**, 3059–3067.
[18] a) J. Recker, W. M. Müller, U. Müller, T. Kubota, Y. Okamoto, M. Nieger, F. Vögtle, *Chem. Eur. J.* **2002**, *8*, 4434–4442; b) O. Lukin, T. Kubota, Y. Okamoto, A. Kaufmann, F. Vögtle, *Chem. Eur. J.* **2004**, *10*, 2804–2810.
[19] O. Lukin, F. Vögtle, *Angew. Chem.* **2005**, *117*, 1480–1501; *Angew. Chem. Int. Ed.* **2005**, *44*, 1456–1477.
[20] a) C. J. Hawker, J. M. J. Fréchet, *J. Am. Chem. Soc.* **1990**, *112*, 7638–7647; b) C. J. Hawker, J. M. J. Fréchet, *J. Chem. Soc., Chem. Commun.* **1990**, 1010–1013.
[21] CCDC-255624 (for **AtrG0**) and CCDC-255625 (for **AtrG1**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[22] Y. Okamoto, E. Yashima, *Angew. Chem.* **1998**, *110*, 1072–1095; *Angew. Chem. Int. Ed.* **1998**, *37*, 1020–1043.
[23] For example see: a) P. B. Rheiner, D. Seebach, *Chem. Eur. J.* **1999**, *5*, 3221–3226; b) G. Guillena, R. Kreiter, R. van de Coevering, R. J. M. Klein Gebbink, G. van Koten, P. Mazón, R. Chinchilla, C. Nájera, *Tetrahedron: Asymmetry* **2003**, *14*, 3705–3712; c) C. Rosini, S. Superchi, H. W. I. Peerlings, E. W. Meijer, *Eur. J. Org. Chem.* **2000**, 61–71.
[24] We have not made a deeper evaluation of the different rotation values or Cotton band intensities as this might not lead to more exact insight in mechanisms of "chirality transfer" or conformational changes. We suggest theoretical calculations to be more helpful in order to obtain more detailed information on conformational equilibria and corresponding circular dichroism induction, which will hopefully be available in the future. A "linearity" of effects or division of rotatory angles by the amount of benzene units for different dendritic generations seems to be rather formalistic.[23b] In order to ease future comparisons and calculations with similar systems, we have kept the concentration of the chiral subunits atropine and quinine constant in all cases.
[25] Assignment of the IR bands of **QuiG0**–**2** was done by consultation of characteristic frequency tables and by comparison with spectra of structurally related compounds.
[26] M. Urbanová, V. Setnička, K. Volka, *Chirality* **2000**, *12*, 199–203.

Received: October 19, 2005
Published Online: December 21, 2005

