Dendroclefts: Optically Active Dendritic Receptors for the Selective Recognition and Chiroptical Sensing of Monosaccharide Guests

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The enantiomerically pure dendritic receptors with cleft-type recognition sites (dendroclefts) of generation zero ((−)-**G0**), one ((−)-**G1**), and two ((−)-**G2**) (*Fig. 1*) were prepared for the complexation of monosaccharides *via* H-bonding. They incorporate a rigid, optically active 9,9′-spirobi[9*H*-fluorene] core bearing 2,6-bis(carbonylamino)pyridine moieties as H-bonding sites in the 2,2′-positions. The dendritic shells in (−)-**G1** and (−)-**G2** are made out of a novel type of dendritic wedges of the first (**8**; *Scheme 2*) and second (**13**; *Scheme 3*) generations, which contain only donor O-atoms and are attached to the H-bonding edges of the core *via* glycine spacers (*Scheme 4*). The formation of stable 1:1 complexes (association constants K_a between 100 and 600 M^{-1}, $T = 298$ K; *Table 2*) between the three receptors and pyranosides in $CHCl_3$ was confirmed by ^{1}H-NMR and CD binding titrations as well as by *Job* plot analyses. The degree of dendritic branching was found to exert a profound effect on the stereoselectivity of the recognition processes. The binding enantioselectivity decreases with increasing degree of branching, whereas the diastereoselectivity increases. The ^{1}H-NMR analysis showed that the N−H···O H-bonds between the amide NH groups around the core and the sugar O-atoms become weakened with increasing dendritic generation, presumably due to steric factors and competition from intramolecular H-bonding between these amide groups and the O-atoms of the dendritic shell. The chiroptical properties of the dendroclefts respond to guest binding in a stereoselective manner. Whereas large differential changes are seen in the circular dichroism (CD) spectra of (−)-**G0** and (−)-**G1** upon complexation of the enantiomeric monosaccharides (*Figs. 3* and *4*), the CD spectra of the higher-generation derivative (−)-**G2** respond to a lesser extent to guest complexation (*Fig. 5*). This is indicative of a different binding geometry, more remote from the core chromophore. With their higher masses, the dendroclefts (−)-**G1** and (−)-**G2** are readily recycled from host-guest solutions by gel-permeation chromatography. The strong CD sensory response and the easy recyclability suggest applications of chiral dendroclefts as sensors for biologically important molecules.

1. Introduction. – During the last five years, emphasis in dendrimer research [1] has been placed on the development of functional derivatives [2]. In particular, a number of dendritic biological mimics have been reported, in which aspects of enzyme behavior are modeled in a conceptually novel manner by the presence of a branched superstructure [3].

Recently, attention has begun to be focussed on using branched architectures as receptors in molecular-recognition processes [4]. Dendrimers have been used extensively for nonspecific encapsulation processes within their three-dimensional superstructures [5]. Specific binding sites have, however, also been built into dendritic systems. Dendritic surfaces capable of multiple molecular-recognition events can exhibit enhanced binding or sensory effects [6]. At the other structural extreme, dendrimers containing a single, well-defined binding site buried deeply within the dendritic architecture have been of great interest. They have been used for the

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construction of well-defined, high-molecular-weight, dendritic supramolecular aggregates [7], and also to investigate the effect of the branched environment on small-molecule recognition [8]. Many biological-recognition events involving enzymes and other protein receptors take place in an environment which is carefully controlled by the surrounding layers of polypeptide shell, and it is hoped that dendritically shielded binding sites will mimic such specific microenvironmental effects [9].

Here, we report the synthesis of a series of novel dendritic cleft-type receptors (*dendroclefts*) of generations zero ((−)-**G0**), one ((−)-**G1**), and two ((−)-**G2**), which contain as initiator core a rigid, optically active 9,9′-spirobi[9*H*-fluorene] moiety bearing 2,6-bis(carbonylamino)pyridine moieties in the 2,2′-positions (*Fig. 1*) (for a preliminary communication of parts of this study, see [10]; see also [4b]). This pre-organized H-bonding cleft is suitable for the molecular complexation of monosaccharide guests *via* H-bonding in non-competitive solvents [11]. The novel type of dendritic wedges attached to the core *via* glycine spacers possess terminal triethyleneglycol-monomethyl-ether groups, which provide excellent solubility in a wide range of solvents including H_2O. More importantly, these branches lack H-bond-donor sites, which reduces their capability to compete with the core for the binding of monosaccharide guests.

This study describes the first examples of chiral molecular recognition within a dendritic superstructure (for a review on chiral dendrimers, see [12]). The three novel dendroclefts form 1:1 host-guest complexes with monosaccharides (for general discussions on the larger number of molecular receptors synthesized for carbohydrate recognition, see [13]), and we show that the enantio- and diastereoselectivity of the recognition events is strongly dependent on the dendritic generation. The dendroclefts can be considered as crude structural mimics of bacterial sugar-binding and sugar-transporting proteins, which possess a H-bonding recognition site deeply buried in a hydrophobic microenvironment [14].

In addition, we present the chiroptical properties of the novel receptors and describe their remarkable sensory response to monosaccharides. Our results indicate a highly enantio- and diastereoselective response to different monosaccharide guests. Furthermore, the circular dichroism (CD) spectra exhibit interesting dependencies on the dendritic generation of the receptors, an observation which sheds further light on the nature of chiral recognition in dendritically shielded environments. CD Spectroscopy has been previously used to monitor molecular complexation by synthetic hosts (for a discussion of the use of CD spectroscopy to monitor molecular recognition events, see [15]), but it has less frequently been used to probe H-bonding mediated complexation [16]. The development of sensors for biologically important substrates is an area of intense current activity [17], and a number of fluorescent sensors which undergo formation of cyclic boronate esters with saccharides have been reported [18], including a dendritic system [6a]. Chiral saccharides have also been shown to induce a detectable circular dichroism upon formation of a cyclic boronate ester with achiral bis-boronic acids [19].

2. Results and Discussion. – 2.1. *Synthesis of the Dendroclefts.* The synthesis of the dendritic receptors was targeted by the convergent approach [20], and started from the

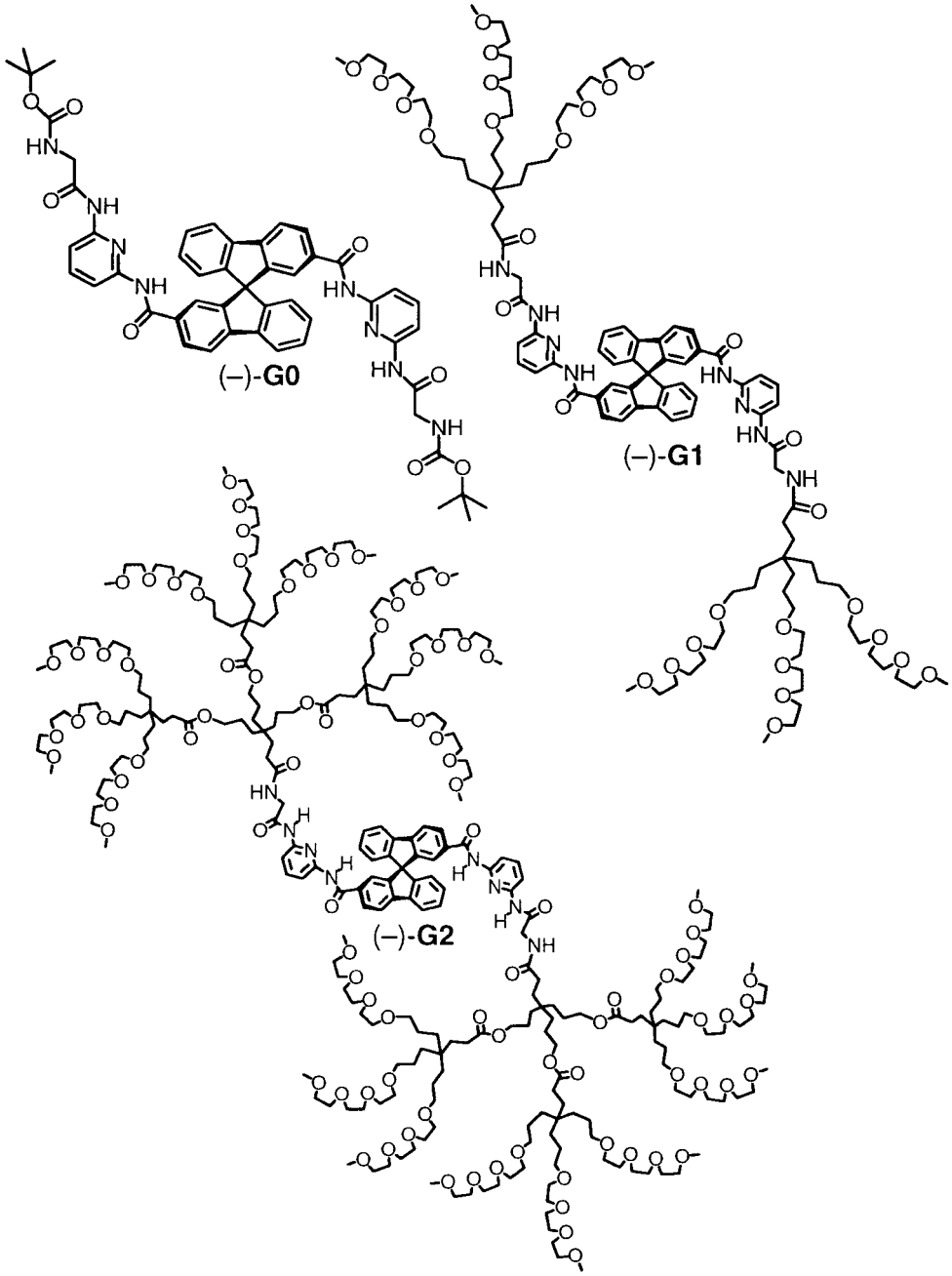
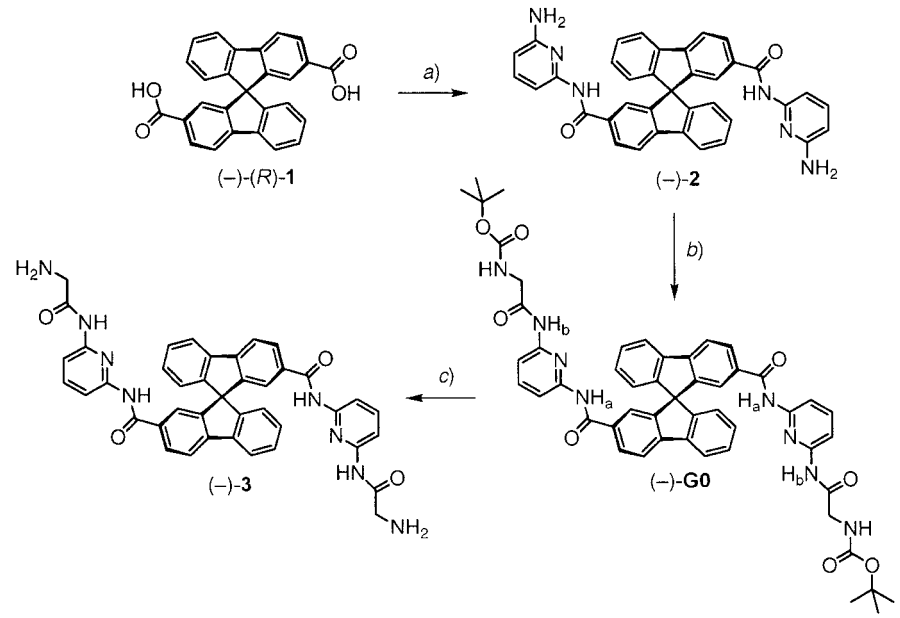


Fig. 1. *Dendritic cleft-type receptors (dendroclefts) of generations zero* ((–)-**G0**), *one* ((–)-**G1**), *and two* ((–)-**G2**)

known dicarboxylic acid (−)-(*R*)-**1** [21] (the spirobifluorene cleft is (*R*)-configured in all compounds reported in this paper; for the absolute configuration, see [22]). Conversion with $SOCl_2$/pyridine to the corresponding bis(acyl chloride), followed by reaction with pyridine-2,6-diamine afforded diamide (−)-**2** (*Scheme 1*). Direct attachment of dendritic branches to (−)-**2** *via* peptide-bond formation was not successful, presumably due to the sterically and electronically attenuated nucleophilicity of the NH_2 groups attached to the pyridine rings. Therefore, glycine spacers were attached to the core: diamine (−)-**2** was reacted with Boc-protected (Boc = (*tert*-butoxy)carbonyl) glycine using HATU (= *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate) [23] as coupling reagent to yield the generation zero derivative (−)-**G0**. Removal of the Boc groups with CF_3COOH led to (−)-**3** as the core for the preparation of the dendroclefts of generation one and two.

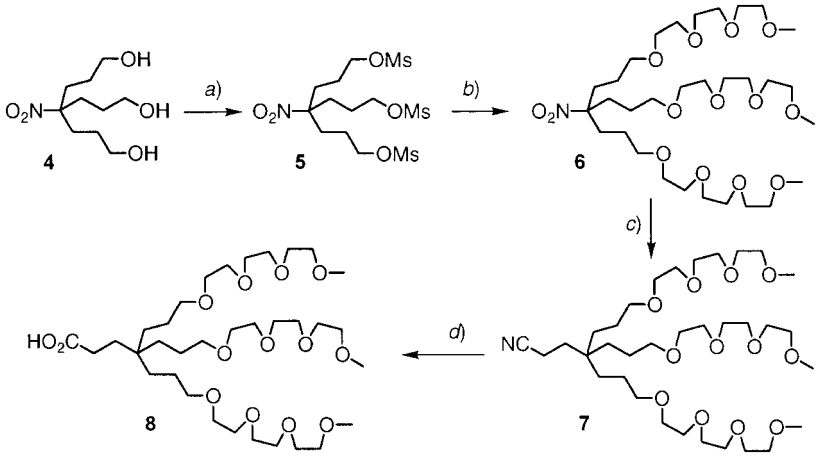
Scheme 1. *Synthesis of the Receptor* (−)-**G0** *and the Dendritic Core* (−)-**3**



a) $SOCl_2$, pyridine, 2 h, r.t., then pyridine-2,6-diamine, Et_3N, THF, 12 h, r.t.; 85%. *b*) *N*-[(*tert*-butoxy)carbonyl]glycine, HATU, Et_3N, THF, 2–7 d, Δ, 81%. *c*) CF_3COOH, CH_2Cl_2, 30 min, r.t.; 87%.

The synthesis of the novel dendritic wedges started with nitromethanetris[propanol] (**4**) which was converted to the tris-mesylate **5** (*Scheme 2*). *Williamson* ether synthesis with triethyleneglycol monomethyl ether (NaH/THF) provided **6**, which was transformed by loss of the NO_2 group and radical addition to acrylonitrile (Bu_3SnH, α,α′-azobis[isobutyronitrile] (AIBN)) [24][25] into nitrile **7**. The crude material was hydrolyzed (H_2O_2/KOH) to yield the first generation dendritic wedge **8**. It is noteworthy that, in spite of the excellent H_2O-solubility of compounds **6**–**8**, they can all be extracted from H_2O into CH_2Cl_2, which greatly facilitates their handling and purification.

Scheme 2. *Synthesis of the Dendritic Wedge* **8**



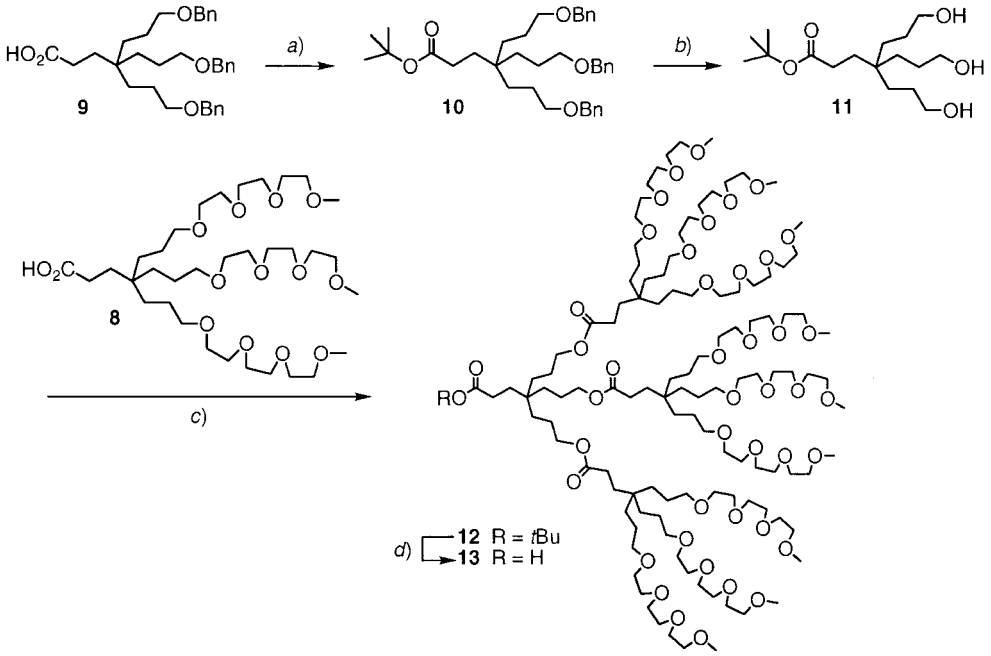
a) $MeSO_2Cl$, Et_3N, THF, 12 h, r.t.; 71%. *b*) $Me(OCH_2CH_2)_3OH$, NaH, THF, 4–12 h, 60°; 45%. *c*) Bu_3SnH, acrylonitrile, AIBN, PhMe, 1 h, 110°. *d*) H_2O_2, KOH, EtOH/H_2O, 21 h, Δ; 40% (steps *c* and *d*).

For the synthesis of the second generation dendritic wedge, carboxylic acid **9** [25] was protected as the *tert*-butyl ester *via* an anhydride intermediate (*Yamaguchi* conditions) [26] (*Scheme 3*). The $PhCH_2$ (Bn) protecting groups in **10** were subsequently removed hydrogenolytically, yielding iterator **11**. Transformation of the generation one dendritic wedge **8** into the corresponding acyl chloride, followed by coupling to iterator **11**, yielded ester **12** which was purified by preparative gel-permeation chromatography (GPC, *Biobeads SX-1*, CH_2Cl_2). Finally, cleavage of the *tert*-butyl ester gave the desired second-generation dendritic wedge **13**.

For the preparation of the novel dendroclefts (−)-**G1** and (−)-**G2**, the wedges **8** and **13**, respectively, were converted to the corresponding acyl chlorides and subsequently coupled to the diamino core (−)-**3** (*Scheme 4*). The products were easily purified *via* preparative GPC and fully characterized.

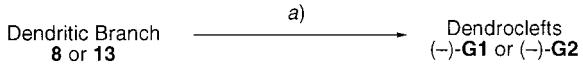
2.2. *Physical Properties of the Novel Dendroclefts.* The matrix-assisted laser-desorption-ionization time-of-flight (MALDI-TOF) mass spectra of the new dendritic receptors displayed the molecular ions as the parent ions ((−)-**G1**: *m/z* 2068.8 (calculated for $^{13}C_2{}^{12}C_{107}H_{164}N_8O_{30}$: 2067.1); (−)-**G2**: *m/z* 5287.0 (calculated for $^{13}C_4{}^{12}C_{267}H_{476}N_8O_{90}$: 5287.2)), with a notable absence of any significant fragment ions. The ^{1}H-NMR spectra showed all expected resonances, including the low-intensity peaks for the protons of the buried 9,9′-spirobi[9*H*-fluorene] cleft. With nuclear *Overhauser* effect (NOE) difference spectroscopy, the two amide protons $N-H_a$ and $N-H_b$ (for the labeling, see compound (−)-**G0** in *Scheme 1*) could be clearly distinguished. The positions of these resonances in $CDCl_3$ were strongly dependent on dendritic generation (*Table 1*), being shifted downfield with increasing dendritic functionalization. This is probably due to increasingly efficient intramolecular H-bonding to O-atoms of the dendritic shell. The more accessible proton $N-H_b$ was particularly strongly affected by the first generation of branching, with the second

Scheme 3. *Synthesis of the Dendritic Wedge* **13**



a) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 2 h, r.t., then *t*-BuOH, 4-(dimethylamino)pyridine (DMAP), PhH, 12 h, r.t.; 64%. *b*) H_2, Pd/C, EtOH, 12 h, r.t.; 99%. *c*) **8**, $(COCl)_2$, CH_2Cl_2, 12 h, r.t., then **11**, Et_3N, THF, 3 h, r.t.; 59%. *d*) CF_3COOH, CH_2Cl_2, 2 h, r.t., 93%.

Scheme 4. *Synthesis of the Dendrocleft Receptors* (−)-**G1** *and* (−)-**G2**



a) $(COCl)_2$, CH_2Cl_2, 12 h, r.t., then (−)-**3**, Et_3N, THF, 1 h, r.t.; 75% ((−)-**G1**), 60% ((−)-**G2**).

generation having little additional effect. Proton $N-H_a$, however, is more deeply buried within the cleft and is affected equally by both first and second generations of dendritic branching, in other words, more branching was required to alter its more deeply buried environment.

The chirality of dendritic superstructures has been an issue of considerable interest [12][27a]. One method which has often been used to monitor dendritic chirality is the measurement of the molar optical rotations ($[M]_D^{298}$). For the three dendroclefts (−)-**G0**, (−)-**G1**, and (−)-**G2**, these values were all quite similar (*Table 1*), indicating that the axial chirality of the core is the principal contributor to molar rotation and that it is unaffected by dendritic functionalization. This is in contrast to the results of *Peerlings* and *Meijer* who used a (*S*)-1,1′-binaphthalene-2,2′-diol derivative as an axially chiral dendritic core and observed that the molar optical rotation increased with increasing dendritic functionalization [27b]. The two chiral clefts differ profoundly in their conformational flexibility: whereas the spirobifluorene moiety is rigid, the 1,1′-

Table 1. *Selected Physical Properties of the Dendroclefts*

Compound	$\delta(NH_a)$ [a] [ppm]	$\delta(NH_b)$ [a] [ppm]	$[M]_D^{298}$ [b] [°]	λ_{max} [c] [nm]	$\lvert I_{max}/I_{min} \rvert$ [c]
(−)-**G0**	8.12	8.18	−1215	296	0.715
(−)-**G1**	8.35	8.61	−1025	295	0.668
(−)-**G2**	8.50	8.66	−1495	293	0.596

[a]) Determined from 500-MHz ^{1}H-NMR spectra at 298 K in $CDCl_3$. [b]) Polarimetry in $CDCl_3$ ($c = 0.03$ mM). [c]) Determined from CD spectra in CH_2Cl_2 as shown in *Fig. 2*. In the spectrum of (−)-**G0**, I_{max} appears at 296 nm and I_{min} at 332 nm.

binaphthalene moiety is flexible, and the dihedral angle about its chirality axis could readily change as a function of the dendritic generation [22]. This difference could well explain the observed differences in the variation of the molar optical rotation with increasing dendritic generation.

The novel receptors have intense circular dichroism (CD) spectra and exhibit exciton chirality coupling which originates from the spirobifluorene core (*Fig. 2*). Interestingly, unlike the molar optical-rotation values, the chiroptical properties of the spirobifluorene core are systematically affected by the presence of dendritic branching (*Table 1*). In particular, the peak maximum of the positive CD band shifts to shorter wavelength, and the relative intensity of the major positive (I_{max}) and negative (I_{min}) bands decreases with increasing dendritic generation. These variations could be due either to H-bonding between the O-atoms in the shell and the amide H-atoms in the diamidopyridine moieties attached to the core, or to a change in torsional angle between fluorene and adjacent pyridine planes caused by the dendritic branching. In

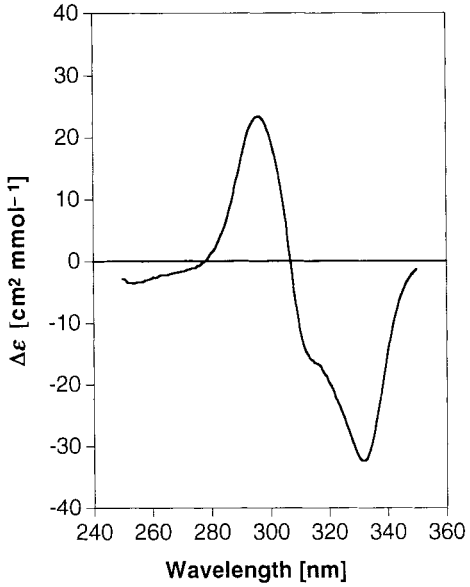
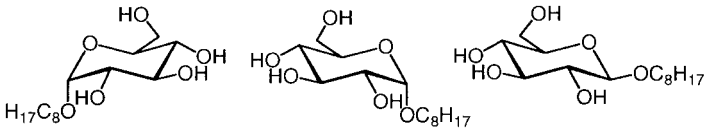


Fig. 2. *CD Spectrum of* (−)-**G0** ($c = 0.032$ mM) *in dry* $CHCl_3$

either case, this example clearly illustrates the power of CD measurements, which are able to record subtle aspects of dendritic behavior that simple measurements of optical rotations can miss.

2.3. *^{1}H-NMR Binding Studies with 1-*O*-Octyl Glucopyranosides.* ^{1}H-NMR Binding titrations with the dendroclefts ($c = 0.5$ mM) and the monosaccharide guests **14**–**16** ($c = 0.5$ to 10.0 mM) were performed at 298 K in $CDCl_3$ that had been deacidified with anhydrous K_2CO_3 and stored over activated powdered molecular sieves (4 Å). The 1 : 1 stoichiometry of the formed complexes was confirmed by *Job* plot analyses. H-Bonding between the O-atoms of the sugar and the NH groups of the receptor represent major host-guest interactions in all complexes, as evidenced by the large complexation-induced downfield shifts (up to 1.2 ppm at saturation binding) of the NH resonances in the pyridine-2,6-dicarboxamide moieties. It is assumed that H-bonds between the pyridine N-atoms and the sugar OH groups also contribute to the stability of the associations (for pyridines as H-bond acceptors in sugar-recognition processes, see [28]). The downfield shifts of the NH protons were used to calculate association constants K_a [M^{-1}] and binding free enthalpies ΔG° [kJ mol^{-1}] using a nonlinear least-squares curve-fitting approach (*Table 2*) [29]. The stability constants for the complexes formed by all three cleft-type receptors are of similar magnitude (K_a between 100 and 600 M^{-1}) with octyl β-D-glucoside undergoing the most stable association in each case. Apparently, the dendritic shell in (−)-**G1** and (−)-**G2** does not prevent the sugar molecules from penetrating the receptor and interacting with the core H-bonding sites.



Octyl α-L-glucoside **14** Octyl α-D-glucoside **15** Octyl β-D-glucoside **16**

The presence of dendritic branching subtly alters the selectivity of these novel receptors. The core receptor (−)-**G0**, which has no dendritic branching, exhibits a high enantioselectivity for octyl α-D-glucoside (**15**) over octyl α-L-glucoside (**14**), whilst the dendritically functionalized receptors (−)-**G1** and (−)-**G2** do not. Conversely, whilst (−)-**G0** shows little diastereoselectivity for octyl β-D-glucoside over octyl α-D-glucoside, the novel dendroclefts exhibit a marked diastereoselectivity which increases with dendritic generation (*Table 2*). This use of dendritic branching to modulate the stereoselectivity of a molecular recognition process is unprecedented (for diastereoselectivities in dendritic-growth processes, see [30]). It is believed that this switch in selectivity stems from interactions between the ether O-atoms in the dendritically functionalized systems with the bound sugar substrate. A comparison between the complexation-induced downfield shifts ($\Delta\delta_{sat}$) of the amide protons NH_a in the dendroclefts and the unfunctionalized core supports this hypothesis. The $\Delta\delta_{sat}$ values caused by the sugar complexation are smaller for the dendroclefts (−)-**G1** and, in particular, (−)-**G2** than for (−)-**G0** (*Table 2*), which indicates a weakening of the N–H$\cdots$O H-bonding interactions between sugar and 2,6-bis(carbonylamido)pyridine groups with increasing dendritic generation. This weakening could be caused by both

Table 2. *Association Constants* (K_a) *and Complexation Free Enthalpies* (ΔG°) *from* ^{1}*H-NMR Titrations at Constant Receptor Concentration for 1:1 Complexes of Dendroclefts (−)-***G0**, *(−)-***G1**, *and (−)-***G2** *with Pyranosides* **14**–**16** *in* $CDCl_3$ ($T = 298$ K). The enantioselectivity[a]) and diastereoselectivity[b]) of the binding processes, as well as the complexation-induced changes in chemical shift of protons NH_a and NH_b (see *Scheme 1*), calculated for saturation binding, $\Delta\delta_{sat}$, are also given.

Receptor	Pyranoside	K_a[c]) [M^{-1}]	ΔG° [kJ mol^{-1}]	Enantio-selectivity [kJ mol^{-1}]	Diastereo-selectivity [kJ mol^{-1}]	$\Delta\delta_{sat}$ NH_a [ppm]	$\Delta\delta_{sat}$[d]) NH_b [ppm]
(−)-**G0**	**14**	100	−11.4			1.18	
(−)-**G0**	**15**	425	−15.0	3.6	0.7	1.05	
(−)-**G0**	**16**	570	−15.7			0.89	
(−)-**G1**	**14**	160	−12.6			0.92	0.90
(−)-**G1**	**15**	225	−13.4	0.8	1.4	1.06	1.02
(−)-**G1**	**16**	390	−14.8			0.83	0.66
(−)-**G2**	**14**	170	−12.7			0.51	0.46
(−)-**G2**	**15**	205	−13.2	0.5	2.3	0.56	0.50
(−)-**G2**	**16**	530	−15.5			0.38	0.27

[a]) Difference in stability $\Delta(\Delta G^\circ)$ between complexes formed by enantiomeric guests. [b]) Difference in stability $\Delta(\Delta G^\circ)$ between complexes formed by diastereoisomeric guests. [c]) Uncertainty in K_a estimated as ±10%. For the complexes of (−)-**G1** and (−)-**G2**, the downfield shifting signals of both NH_a and NH_b were monitored and evaluated; K_a values quoted are averages over multiple runs and from titration data involving both protons, which are in very good agreement. [d]) The NH protons of the peptide bond between glycine linkers and dendritic wedges are not undergoing significant H-bonding to the sugar substrates; maximum observed $\Delta\delta$ values in titrations were 0.20 ((−)-**G0**), 0.12 ((−)-**G1**), and 0.05 ppm ((−)-**G2**); due to marked broadening and the small $\Delta\delta$ values, these resonances were not evaluated.

steric factors and competitive intramolecular H-bonding between the amide NH groups and the O-atoms in the dendritic branches (see *Sect. 2.2*). However, the overall binding strength does not change markedly upon changing from (−)-**G0**, to (−)-**G1**, and to (−)-**G2** (*Table 2*). Therefore, it is proposed that, with increasing dendritic generation, the weakening N−H···O H-bonding interactions at the core are increasingly compensated by O···H−O H-bonding interactions between the O-atoms in the dendritic shell and the sugar OH groups.

2.4. *Circular Dichroism Binding Studies.* Binding studies were also performed by monitoring complexation-induced changes in the intense CD spectra of the three receptors. The CD titrations were performed at 298 K with [receptor] = 0.03 mM and [sugar] = 0.5–10.0 mM in $CHCl_3$ that was deacidified with K_2CO_3 and stored over activated powdered molecular sieves (4 Å).

The receptors exhibited dramatic CD responses to the addition of the monosaccharides. *Fig. 3* illustrates spectra recorded during addition of **15** to a solution of (−)-**G0**. As is evident, there are three major spectral changes: *i*) a new negative band develops at $\lambda = 280$ nm, *ii*) the positive CD band at $\lambda = 296$ nm shifts bathochromically and increases in intensity, and *iii*) the negative CD band at $\lambda = 332$ nm decreases in intensity. Interestingly, the chiroptical response is enantioselective. The addition of **14** (the enantiomer of **15**) to the solution of (−)-**G0** invokes similar changes at $\lambda = 280$ and 296 nm, although smaller in magnitude (*Fig. 4*). At $\lambda = 332$ nm, however, the response is markedly different. Monosaccharide **14** caused essentially no perturbation at this wavelength and, instead, caused a considerable change in the CD spectrum around 315 nm. The response elicited by glucopyranoside **16** was intermediate between the

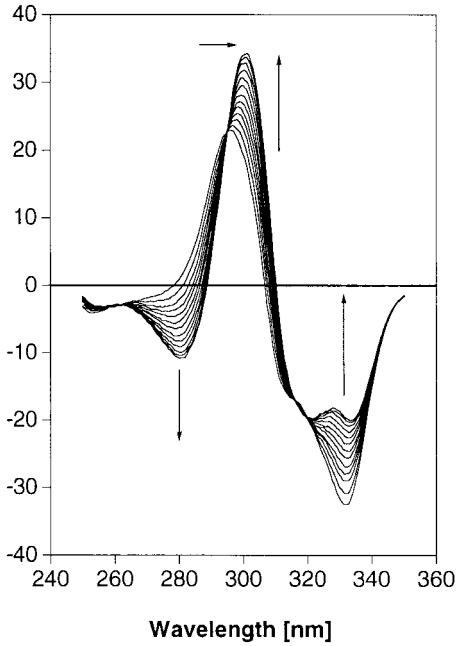


Fig. 3. *Changes in the CD spectrum of* (−)-**G0** ($c = 0.032$ mM) *in* $CHCl_3$ *upon addition of octyl* α-D-*glucoside* **15** ($c = 0.00$, 0.43, 0.85, 1.26, 1.66, 2.17, 2.67, 3.38, 4.07, 4.92, 5.93, 6.86, and 7.73 mM)

extremes of the two enantiomers. The core receptor (−)-**G0** is, therefore, capable of binding and chiroptically sensing saccharide guests in an enantioselective manner.

CD Titrations were also performed with the dendroclefts (−)-**G1** and (−)-**G2**. Both receptors exhibited chiroptical monosaccharide sensing, having the same trends in stereoselective response as (−)-**G0**. The magnitude of response of (−)-**G1** was similar to that of (−)-**G0**, but the magnitude or response of (−)-**G2** was considerably muted (*Fig. 5*). It is, therefore, clear that (−)-**G2** exhibits different chiroptical sensing properties than (−)-**G0** and (−)-**G1**, and, as the core recognition site is the same in each case, this is consistent with the dendritic branching changing the way in which the receptor binds and interacts with monosaccharide guests. Thus, the CD titration data correlate well with the ^{1}H-NMR results, which exhibited smaller complexation-induced downfield shifts for the NH protons near the core in titrations with (−)-**G2** than with (−)-**G0** or (−)-**G1** (*Table 2*), indicative of different binding modes. It is suggested that guests in the complexes of (−)-**G2**, on time average, are bound less closely to the spirobifluorene cleft and, therefore, induce smaller changes in the chiroptical properties of the core chromophore.

Binding constants were also elucidated from the CD spectral data with the global fit program *Specfit V. 2.09* [31]. Although the data showed a fair correlation with the ^{1}H-NMR results, it is not perfect. The CD binding studies are performed at much lower host concentration, and the effect of any residual H_2O (< 1 mM) in the solvent, which can affect monosaccharide binding strength, will play a more important role [32].

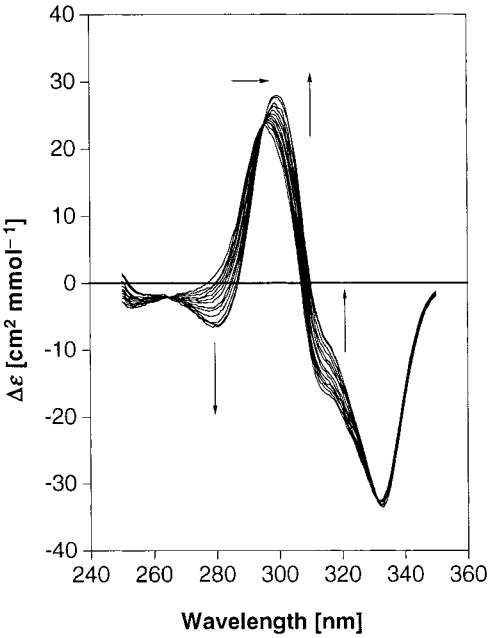


Fig. 4. *Changes in the CD spectrum of* (−)-**G0** ($c = 0.032$ mM) *in* $CHCl_3$ *upon addition of octyl* α-L-*glucoside* **14** ($c = 0.00$, 0.42, 0.83, 1.23, 1.62, 2.12, 2.61, 3.31, 3.98, 4.82, 5.80, 6.71, and 7.56 mM)

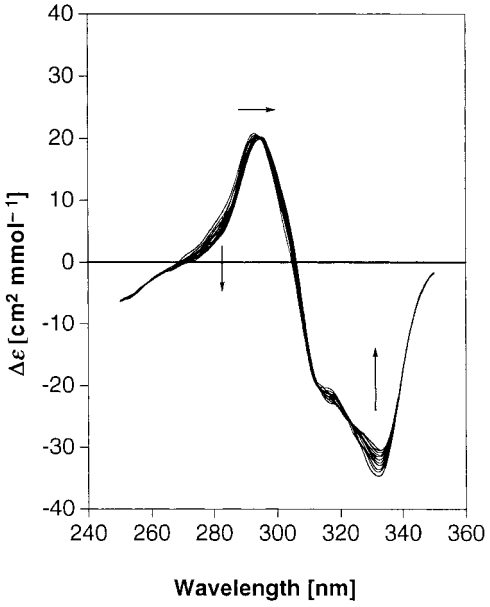


Fig. 5. *Changes in the CD spectrum of* (−)-**G2** ($c = 0.031$ mM) *in* $CHCl_3$ *upon addition of octyl* α-D-*glucoside* **15** ($c = 0.00$, 0.34, 0.67, 1.00, 1.32, 1.64, 2.04, 2.24, 3.18, 3.92, 4.62, and 5.98 mM)

One particularly noteworthy feature of both (−)-**G1** and (−)-**G2** is that, after being used in sugar-sensing experiments, they are easily recycled. This is a direct consequence of their higher molecular masses. Simple filtration through a plug of *Sephadex LH-20* gel with MeOH as the eluent allows full recovery of pure dendritic material, with the smaller monosaccharide guest being retained on the plug. Recyclability is an important aspect of sensor design, and clearly even a relatively small dendritic system such as (−)-**G1**, which couples sensitive stereoselective response and ease of recyclability, indicates the potential of dendritic systems for applications in this area.

3. Conclusions. – Enantiomerically pure dendritic cleft receptors (*dendroclefts*) featuring a chiral 9,9′-spiro[9*H*-bifluorene] core with two 2,6-bis(carbonylamino)pyridine H-bonding centers and novel dendritic branches that lack H-bond-donor sites were prepared for the recognition of 1-*O*-octyl glucopyranosides in the noncompetitive solvent $CDCl_3$. They are the first dendritic receptors which recognize carbohydrate substrates by noncovalent bonding interactions and feature unprecedented stereoselectivity in molecular-recognition processes within dendritic superstructures. The formation of stable 1:1 complexes with octyl glucopyranosides (K_a between 100 and 600 M^{-1}, $T = 298$ K) was shown in ^{1}H-NMR and CD binding titrations, as well as by *Job* plot analyses. The major host-guest bonding interactions are N−H···O H-bonds between the amide NH groups at the core and the O-atoms of the monosaccharides and presumably also N···H−O H-bonds between the pyridine N-atoms and the HO groups of the guests. The stereoselectivity of the recognition processes is profoundly altered by the degree of dendritic branching. Whereas the enantioselectivity drops sharply with increasing dendritic generation from the core receptor ((−)-**G0**) to the generation one ((−)-**G1**) and two ((−)-**G2**) dendroclefts, the diastereoselectivity increases markedly in the same direction. The analysis of complexation-induced changes in chemical shift suggests that, with increasing dendritic generation, the N−H···O host-guest H-bonding becomes weakened, and it is proposed that these interactions are increasingly replaced by O···H−O H-bonds between the ether O-atoms of the dendritic branches and the sugar OH groups.

The CD spectra of the novel receptors respond to the bound guests, reporting on complexation in an unambiguous and stereoselective manner. By modulating binding geometry, strength, and selectivity, the degree of dendritic branching also has a direct impact on the magnitude of the CD sensory response. Both ^{1}H-NMR and chiroptical data suggest that guests in the complexes of the higher generation dendrocleft (−)-**G2** bind, on time average, less closely to the spirobifluorene core, thereby inducing fewer changes in the chiroptical properties of this chromophore. The measured guest-selective chiroptical effects clearly illustrate the potential of dendritic receptors to act as readily recyclable sensors for biologically important substrates, and this study, therefore, expands the potential application range of dendritic technology.

Experimental Part

General. All reactions were carried out under Ar. Solvents and reagents were reagent-grade commercials and were used without further purification. Compounds **9** [25] and **14** [33] were prepared according to published procedures. THF was freshly distilled from sodium benzophenone ketyl; CH_2Cl_2 from CaH_2 under N_2 and stored

over molecular sieves (3 Å). Et_3N was distilled from KOH and stored over KOH pellets. Evaporation *in vacuo* was conducted at H_2O aspirator pressure. Column chromatography (CC): SiO_2 *60* (230–400 mesh, 0.040–0.063 mm) from *Fluka*. TLC: *Polygram SIL G/UV$_{254}$* from *Macherey-Nagel*; visualization by UV light or Ce/Mo stain. Prep. GPC: *Biobeads* (*Biorad SX-1*) without pressure. Anal. GPC: at 40° on *Shodex* size-exclusion chromatography columns with a *Merck L-7360* column oven and driven by a *Merck L-7100* pump. Product detection was performed with either a *Merck L-7400* UV/VIS detector or a *Merck L-7490* refractive-index detector. Data was displayed and processed with a *Merck-Hitachi D-2500 chromato-integrator*. Isolated products were dried for 24 h at 0.1 Torr prior to spectral and anal. characterization. M.p.: *Büchi Smp-20* apparatus; uncorrected. IR Spectra [cm^{-1}]: *Perkin-Elmer 1600-FTIR*. NMR Spectra: *Bruker AMX 500* and *Varian Gemini 300* or *200* at 296–300 K, with solvent peak as reference. MS (*m/z* (%)): FAB: *VG ZAB2-SEQ* spectrometer with 3-nitrobenzyl alcohol (NOBA) as matrix; MALDI-TOF: *Bruker-REFLEX* spectrometer with 2,4,6-trihydroxyacetophenone/diammonium citrate as matrix and detecting in the positive-ion mode. Elemental analyses were performed by the Mikrolabor at the Laboratorium für Organische Chemie, ETH-Zürich.

Binding Studies. ^{1}H-NMR Titrations were performed at 298 K with [dendrocleft] = 0.5 mM and [sugar] = 0.5–10.0 mM in $CDCl_3$ deacidified with anhydrous K_2CO_3 and stored over activated powdered molecular sieves (4 Å). Nonlinear least-squares curve-fitting analysis of the data yielded quantitative binding data (K_a, ΔG°, $\Delta\delta_{sat}$) [29]. CD Titrations were also performed at 298 K with [dendrocleft] = 0.02 mM and [sugar] = 0.5–10.0 mM in $CHCl_3$ dried and stored as described. Global curve-fitting analysis [32] yielded K_a and ΔG° values for the 1:1 complexes formed.

*(−)-*N,N′*-Bis(6-aminopyridin-2-yl)-9,9′-spirobi[9*H*-fluorene]-2,2′-dicarboxamide* ((−)-**2**). To (−)-(*R*)-**1** (0.74 g, 1.83 mmol) in $SOCl_2$ (15 ml), pyridine (5 drops) was added, and the mixture was heated to reflux for 2 h. After evaporation *in vacuo*, the formed acyl halide was dried at 10^{-1} Torr/r.t. for 4 h and dissolved in THF (100 ml). This soln. was added dropwise over 20 min to pyridine-2,6-diamine (1.92 g, 17.6 mmol) and Et_3N (0.50 g, 4.96 mmol) in THF (10 ml). After stirring for 12 h and evaporation *in vacuo*, CC (SiO_2, CH_2Cl_2/MeOH/Et_3N 95:4.5:0.5), followed by recrystallization (CH_2Cl_2/hexane), yielded (−)-**2** (0.91 g, 85%). Pale-yellow solid. M.p. 190° (dec.). $[\alpha]_D^{298} = -197.2$ ($c = 0.294$, Me_2CO). IR (KBr): 3349, 1667, 1615, 1575, 1529, 1455, 1302, 1246, 790, 748. ^{1}H-NMR (200 MHz, $CDCl_3$): 8.04 (*s*, 2 H); 8.00–7.75 (*m*, 6 H); 7.57 (*d*, $J = 8.4$, 2 H); 7.40 (*t*, $J = 7.9$, 4 H); 7.19 (*s*, 2 H); 7.13 (*t*, $J = 7.5$, 2 H); 6.71 (*d*, $J = 7.5$, 2 H); 6.19 (*d*, $J = 8.0$, 2 H); 4.20 (br. *s*, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 165.0; 157.0; 149.8; 148.7; 148.4; 145.7; 140.5; 140.0; 133.8; 129.1; 128.3; 127.9; 124.1; 122.6; 121.0; 120.5; 104.5; 103.6; 65.70. FAB-MS: 587 (100, MH^+), 478 (33), 307 (22), 154 (16). Anal. calc. for $C_{37}H_{26}N_6O_2 \cdot 0.5\ H_2O$ (595.6): C 74.61, H 4.57, N 14.11; found: C 74.61, H 4.59, N 13.86.

*(−)-*N,N′*-Bis[6-(2-{[(*tert*-butoxy)carbonyl]amino}acetamido)pyridin-2-yl]-9,9′-spirobi[9*H*-fluorene]-2,2′-dicarboxamide* ((−)-**G0**). To (−)-**2** (0.240 g, 0.41 mmol), N-[(*tert*-butoxy)carbonyl]glycine (0.234 g, 1.34 mmol), and Et_3N (0.280 g, 2.77 mmol) in THF (5 ml) at 0°, HATU (0.500 g, 1.31 mmol) was added, and the mixture was stirred for 2–7 d at reflux. The completion of the reaction was monitored by TLC (SiO_2; AcOEt/CH_2Cl_2 75:25). Evaporation *in vacuo*, CC (SiO_2, AcOEt/CH_2Cl_2/Et_3N 75:24.5:0.5), and recrystallization (CH_2Cl_2/hexane) afforded (−)-**G0** (0.301 g, 81%). White powder. M.p. 219° (dec.). $[\alpha]_D^{298} = -134.9$ ($c = 0.340$, THF). IR (KBr): 3393–3300, 2975, 1685, 1585, 1508, 1449, 1299, 1245, 1156, 800, 750. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.18 (br. *s*, 2 H); 8.12 (br. *s*, 2 H); 7.96–7.89 (*m*, 8 H); 7.80 (*d*, $J = 8.1$, 2 H); 7.65 (*t*, $J = 8.1$, 2 H); 7.41 (*t*, $J = 7.5$, 2 H); 7.24 (*s*, 2 H); 7.16 (*t*, $J = 7.5$, 2 H); 6.72 (*d*, $J = 7.5$, 2 H); 5.18 (br. *s*, 2 H); 3.92–3.85 (br. *m*, 4 H); 1.38 (*s*, 18 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 168.5; 165.7; 156.4; 149.8; 149.1; 148.9; 148.5; 145.9; 140.5; 133.6; 129.3; 128.4; 127.9; 124.2; 123.0; 121.0; 120.4; 110.3; 109.9; 80.62; 65.72; 45.87; 28.18. FAB-MS: 902 (40, MH^+), 901 (62, M^+), 702 (53), 701 (100, $[M - 2\ Me_3COCO + 2\ H]^+$), 504 (33), 478 (66), 387 (37), 313 (38), 154 (59), 136 (65). Anal. calc. for $C_{51}H_{48}N_8O_8$ (901.0): C 67.99, H 5.37, N 12.44; found: C 67.95, H 5.56, N 12.17.

*(−)-*N,N′*-Bis[6-(2-aminoacetamido)pyridin-2-yl]-9,9′-spirobi[9*H*-fluorene]-2,2′-dicarboxamide* ((−)-**3**). A soln. of (−)-**G0** (0.10 g, 0.11 mmol) in CH_2Cl_2 (5 ml) and CF_3COOH (1 ml) was stirred for 30 min, then evaporated to dryness and partitioned between 5% aq. KOH soln. (20 ml) and CH_2Cl_2 (100 ml)/THF (10 ml). The org. layer was dried ($MgSO_4$) and evaporated to dryness yielding (−)-**3** (0.068 g, 87%), which was used in the construction of the dendroclefts without further purification. Poorly soluble white powder. $[\alpha]_D^{298} = -166.3$ ($c = 0.177$, THF). IR (KBr): 3300–3420, 1670, 1592, 1583, 1512, 1448, 1302, 1243, 1155, 801, 750. ^{1}H-NMR (200 MHz, $CDCl_3$): 9.35 (*s*, 2 H); 8.38 (*s*, 2 H); 8.01–7.59 (*m*, 12 H); 7.32–7.26 (*m*, 4 H); 7.08 (*t*, $J = 7.5$, 2 H); 6.61 (*d*, $J = 7.5$, 2 H); 3.25 (*s*, 4 H); 1.35 (br. *s*, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 171.4; 165.2; 149.8; 149.3; 148.9; 148.5; 146.1; 140.9; 140.5; 133.7; 129.4; 128.5; 128.1; 124.2; 122.7; 121.2; 120.6; 109.8; 109.5; 65.8; 45.1. FAB-MS: 740 (17, MK^+), 723 (69, MNa^+), 701 (100, MH^+), 670 (16, $[M - CH_2NH_2]^+$), 504 (18), 478 (33), 289 (35).

Nitromethanetriyl Tris[(trimethylene)(methanesulfonate)] (**5**). To **4** (5.14 g, 21.85 mmol) and Et_3N (9.93 g, 98.37 mmol) in THF (150 ml), $MeSO_2Cl$ (8.26 g, 72.1 mmol) was added dropwise at 0° over 15 min. After stirring at r.t. for 12 h, the soln. was washed with H_2O, 10% aq. HCl soln., sat. aq. $NaHCO_3$ soln., and sat. aq. NaCl soln. Drying (Na_2CO_3), evaporation *in vacuo*, CC (SiO_2; AcOEt/hexane 67:33), followed by recrystallization (AcOEt/acetone), furnished **5** (7.27 g, 71%). White, waxy solid. IR ($CHCl_3$): 2967, 2344, 2254, 1788, 1540, 1454, 1358, 1350, 1177, 971, 907, 700, 649. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.22 (*t*, *J* = 6.1, 6 H); 3.02 (*s*, 9 H); 2.00–2.12 (*m*, 6 H); 1.60–1.77 (*m*, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 92.7; 68.8; 37.5; 31.4; 23.7. FAB-MS: 470 (5, MH^+), 423 (6, $[M-NO_2]^+$), 327 (34), 307 (36), 289 (26), 231 (100), 154 (97), 137 (73). Anal. calc. for $C_{13}H_{27}NO_{11}S_3$ (469.5): C 33.25, H 5.80, N 2.98, S 20.49; found: C 33.19, H 5.65, N 3.00, S 20.62.

Tris(3-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propyl)(nitro)methane (**6**). NaH (50% suspension in mineral oil, 0.95 g, 19.8 mmol) was washed with hexane (3×), dried *in vacuo*, and suspended in THF (20 ml). Triethyleneglycol monomethyl ether (2.31 g, 14.1 mmol) in THF (10 ml) was added dropwise, and the mixture was stirred for 2 h at r.t. A soln. of **5** (2.00 g, 4.26 mmol) in THF (10 ml) was added by syringe, and the mixture was heated to 60° for 4–12 h. Upon completion of the reaction (TLC), the mixture was cooled to r.t. and poured into ice-cold sat. aq. NH_4Cl soln. (15 ml). After extraction with CH_2Cl_2 (4 × 50 ml), the combined org. extracts were dried ($MgSO_4$) and evaporated *in vacuo*. CC (SiO_2; CH_2Cl_2/MeOH/Et_3N 95:4:1) gave **6** (1.275 g, 45%). Pale-yellow oil. IR (neat): 2923, 2871, 1533, 1451, 1353, 1297, 1246, 1194, 1117, 1030, 851. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.64–3.49 (*m*, 36 H); 3.40 (*t*, *J* = 6.4, 6 H); 3.34 (*s*, 9 H); 1.96–1.88 (*m*, 6 H); 1.52–1.40 (*m*, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 94.1; 71.8; 70.6; 70.1; 58.9; 32.1; 23.9. FAB-MS: 696 (17, MNa^+), 674 (18, MH^+), 671 (24), 627 (100 $[M-NO_2]^+$), 508 (28), 479 (18), 135 (41). Anal. calc. for $C_{31}H_{63}NO_{14}$ (673.8): C 55.26, H 9.42, N 2.08; found: C 55.19, H 9.39, N 2.08.

7-{2-[2-(2-Methoxyethoxy)ethoxy]ethoxy}-4,4-bis(3-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propyl)heptanenitrile (**7**). A mixture of **6** (1.33 g, 1.98 mmol), acrylonitrile (1.21 g, 22.8 mmol), Bu_3SnH (1.84g, 6.34 mmol), and AIBN (0.35 g, 2.13 mmol) in toluene (25 ml) was heated at 110° for 1 h. After cooling, AcOEt (100 ml) was added, and the solid residue was removed by filtration. The soln. was concentrated, and MeCN (150 ml) was added. The resulting soln. was washed with hexane (2 × 150 ml), and the MeCN phase was evaporated to dryness. Purification by CC (SiO_2; CH_2Cl_2/MeOH/Et_3N 95:4:1) yielded **7** (1.14 g, 85%), contaminated with a minor by-product, but of sufficient purity for use in the next conversion. Small quantities of anal. pure oily material were also obtained from the column. IR (neat): 2933, 2869, 1458, 1350, 1300, 1244, 1199, 1112, 1033, 944, 852. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.68–3.48 (*m*, 36 H); 3.38–3.30 (*m*, 15 H); 2.19 (*t*, *J* = 8.1, 2 H); 1.62–1.37 (*m*, 8 H); 1.30–1.10 (*m*, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 126.0; 69.5; 69.4; 69.2; 68.2; 68.1; 67.8; 67.6; 56.6; 34.3; 29.4; 27.1; 24.2; 20.8. FAB-MS: 683 (100, MH^+), 630 (15), 518 (31), 147 (34), 103 (67). Anal. calc. for $C_{34}H_{67}NO_{12}$ (681.9): C 59.89, H 9.90, N 2.05; found: C 59.63, H 9.72, N 1.94.

7-{2-[2-(2-Methoxyethoxy)ethoxy]ethoxy}-4,4-bis(3-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}propyl)heptanoic Acid (**8**). Partially purified **7** (1.14 g) was dissolved in EtOH (60 ml), and a soln. of KOH (2.61 g, 45.8 mmol) in H_2O (6 ml) was added. A 1:1 mixture of H_2O_2 (30%, 4.4 ml) and H_2O (4.4 ml) was then added in two portions at 10 min intervals. The mixture was heated to 60° for 3 h and to reflux for 18 h. After evaporation of the EtOH *in vacuo* (*Caution:* do not reduce solns. of peroxide to dryness), H_2O (150 ml) was added and the mixture was extracted with CH_2Cl_2 (3 × 50 ml). The aq. soln. was acidified to pH 1 by careful addition of 10% aq. HCl soln., and the product was extracted with CH_2Cl_2 (4 × 100 ml). The combined org. extracts were dried ($MgSO_4$) and evaporated to dryness. CC (SiO_2; CH_2Cl_2/MeOH/CF_3COOH 95:4.5:0.5 afforded **8** (0.55 g, 40% starting from **6**). Colorless oil. IR ($CHCl_3$): 2866, 1727, 1455, 1350, 1133, 1111, 911, 622. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.64–3.51 (*m*, 36 H); 3.34–3.32 (*m*, 15 H); 2.26–2.18 (*m*, 2 H); 1.57–1.41 (*m*, 8 H); 1.31–1.15 (*m*, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 177.7; 71.8; 70.5; 70.4; 70.0; 58.9; 36.4; 32.0; 30.7; 28.25; 23.20. FAB-MS: 724 (60, MNa^+), 701 (95, M^+). Anal. calc. for $C_{34}H_{68}O_{14}$ (700.9): C 58.26, H 9.78; found: C 58.22, H 9.70.

tert-*Butyl 7-(Benzyloxy)-4,4-bis[3-(benzyloxy)propyl]heptanoate* (**10**). To **9** (2 g, 3.75 mmol) and Et_3N (0.379 g, 3.75 mmol) in THF (3 ml), 2,4,6-trichlorobenzoyl chloride (0.912 g, 3.75 mmol) in THF (5 ml) was added by syringe. The mixture was stirred until precipitation of $HNEt_3^+Cl^-$ was complete (2 h), filtered, and the solvent was removed under high vacuum (10^{-1} Torr, 4 h). The anhydride intermediate thus formed was dissolved together with *t*-BuOH (0.555 g, 7.5 mmol) in benzene, and DMAP (1.831 g, 15 mmol) in PhH (4 ml) was added. The mixture was stirred overnight, then diluted with Et_2O (100 ml), and washed with 3% aq. HCl soln., H_2O, and sat. aq. $NaHCO_3$ soln. (50 ml of each). Drying (Na_2CO_3), evaporation to dryness, and CC (SiO_2; hexane/AcOEt 8:2) provided **10** (0.132 g, 64%). Colorless oil. IR ($CHCl_3$): 2945, 2862, 1719, 1495, 1454, 1367, 1155, 1093. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.33–7.30 (*m*, 15 H); 4.49 (*s*, 6 H); 3.43 (*t*, *J* = 6.6, 6 H); 2.16–2.05 (*m*, 2 H); 1.60–1.46 (*m*, 8 H); 1.44 (*s*, 9 H); 1.40–1.37 (*m*, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 173.4; 138.6; 128.2;

127.5; 127.4; 79.9; 72.8; 71.0; 36.3; 32.4; 31.2; 29.7; 28.0; 23.38. FAB-MS: 587 (9, $[M-H]^+$), 533 (24, $[M-Me_3C+2H]^+$), 271 (33), 181 (100), 91 (84). Anal. calc. for $C_{38}H_{52}O_5$ (588.8): C 77.51, H 8.90; found: C 77.39, H 8.78.

tert-*Butyl 7-Hydroxy-4,4-bis(3-hydroxypropyl)heptanoate* (**11**). To **10** (6.25 g, 10.6 mmol) in EtOH (50 ml), Pd/C (10%, 1.51 g) was added, and the mixture was stirred vigorously overnight under H_2. Filtration through *Celite*, evaporation *in vacuo*, and rigorous drying (10^{-1} Torr/r.t., 48 h) afforded **11** (3.38 g, 99%). Highly viscous oil. IR ($CHCl_3$): 3625, 3410, 2942, 2873, 1717, 1456, 1368, 1162, 1054. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.58 (br. *t*, 6 H); 2.58 (br. *s*, 3 H); 2.15–2.07 (*m*, 2 H); 1.59–1.55 (*m*, 8 H); 1.41 (*s*, 9 H); 1.22–1.19 (*m*, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 174.1; 80.4; 63.1; 36.1; 32.0; 31.2; 29.8; 27.9; 26.1. FAB-MS: 341 (54, *M*Na$^+$), 319 (28, *M*H$^+$), 263 (100), 245 (77). Anal. calc. for $C_{17}H_{34}O_5$ (318.4): C 64.12, H 10.76; found: C 64.38, H 10.72.

tert-*Butyl 7-{[7-{2-[2-(2-Methoxyethoxy)ethoxy]ethoxy}-4,4-bis(3-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}-propyl)heptanoyl]oxy}-4,4-bis(3-{[7-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}-4,4-bis(3-{2-[2-(2-methoxyethoxy)-ethoxy]ethoxy}propyl)heptanoyl]oxy}propyl)heptanoate* (**12**). To **8** (0.297 g, 0.42 mmol) in dry CH_2Cl_2 (10 ml), oxalyl chloride (0.6 g, 4.72 mmol) was added by syringe, and the mixture was stirred for 12 h. After evaporation *in vacuo*, the crude acyl halide was dried in high vacuum (10^{-1} Torr/r.t., 4 h) and dissolved in THF (5 ml). A soln. of **11** (0.036 g, 0.11 mmol) and Et_3N (0.040 g, 0.40 mmol) in THF (5 ml) was added dropwise, and the progress of the reaction was monitored by anal. GPC. After typically less than 3 h, the mixture was evaporated to dryness, and the product was purified by prep. GPC (2×) eluting with CH_2Cl_2 and monitoring the fraction collection by anal. GPC to give **12** (0.159 g, 59%). Colorless oil. IR ($CHCl_3$): 3568, 2867, 1739, 1458, 1350, 1250, 1110, 851. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.94–3.90 (*m*, 6 H); 3.61–3.47 (*m*, 108 H); 3.37–3.31 (*m*, 18 H); 3.33 (*s*, 27 H); 2.16–2.08 (*m*, 8 H); 1.44–1.39 (*m*, 28 H); 1.26–1.13 (*m*, 28 H); 1.39 (*s*, 9 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 173.7; 172.8; 80.0; 71.8; 71.7; 70.4 (3×); 70.2; 69.9; 64.9; 58.7; 36.1 (2×); 32.0 (2×); 30.8; 29.5; 28.3; 27.8; 23.1; 22.2; 14.9. MALDI-TOF-MS: 2390.4 (100%, *M*Na$^+$; $^{13}C_2{}^{12}C_{117}H_{232}O_{44}Na$ gives 2390.5). Anal. calc. for $C_{119}H_{232}O_{44}$ (2367.1): C 60.38; H 9.88; found: C 60.31, H 9.77.

7-{[7-{2-[2-(2-Methoxyethoxy)ethoxy]ethoxy}-4,4-bis(3-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}pro-pyl)heptanoyl]oxy}-4,4-bis(3-{[7-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}-4,4-bis(3-{2-[2-(2-methoxyethoxy)-ethoxy]ethoxy}propyl)heptanoyl]oxy}propyl)heptanoic Acid (**13**). A soln. of **12** (0.144 g, 0.067 mmol) in CH_2Cl_2 (2 ml) and CF_3COOH (2 ml) was stirred for 2 h and then evaporated *in vacuo*. The product was dissolved in 3% aq. HCl soln. (35 ml) and extracted with CH_2Cl_2 (4 × 50 ml). The combined org. layers were dried ($MgSO_4$) and evaporated to dryness, yielding pure **13** (0.144 g, 93%). Colorless oil. IR ($CHCl_3$): 3500 (br.), 2868, 1733, 1458, 1350, 1248, 1112, 851. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.96–3.90 (*m*, 6 H); 3.61–3.47 (*m*, 108 H); 3.37–3.31 (*m*, 18 H); 3.33 (*s*, 27 H); 2.19–2.08 (*m*, 8 H); 1.55–1.39 (*m*, 28 H); 1.23–1.13 (*m*, 28 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 174.9; 174.0; 71.9; 71.8; 70.5 (2×); 70.4; 70.3; 70.0; 64.5; 58.8; 36.2; 36.1; 32.1; 31.8; 31.0; 30.3; 28.4; 27.6; 23.2; 22.3. MALDI-TOF-MS: 2333.9 (100%, M^+, $^{13}C_1{}^{12}C_{114}H_{224}O_{44}Na$; calc. 2333.5). Anal. calc. for $C_{115}H_{224}O_{44}$ (2311.01): C 59.77, H 9.77; found: C 59.91, H 9.51.

*(−)-*N,N′*-Bis(6-{2-[7-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}-4,4-bis(3-{2-[2-(2-methoxyethoxy)ethoxy]-ethoxy}propyl)heptanamido]acetamido}pyridin-2-yl)-9,9′-spirobi[9*H*-fluorene]-2,2′-dicarboxamide* ((−)-**G1**). To **8** (0.105 g, 0.15 mmol) in CH_2Cl_2 (10 ml), oxalyl chloride (0.26 ml, 3.0 mmol) was added dropwise. After the evolution of CO ceased, the soln. was stirred for a further 1 h, then evaporated *in vacuo*. After drying at 10^{-1} Torr/r.t. (4 h), the formed bis(acyl halide) was dissolved in THF (3 ml) and a soln. of (−)-**3** (0.045 g, 0.065 mmol) and Et_3N (0.020 g, 0.20 mmol) in THF (5 ml) was added. After 1 h, the reaction was completed (anal. GPC control) and the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 ml), and this soln. was washed with sat. aq. $NaHCO_3$ soln. (50 ml), dried (Na_2CO_3), and evaporated to dryness. Purification by prep. GPC (2 columns, CH_2Cl_2), monitoring the fraction collection by anal. GPC, yielded (−)-**G1** (0.99 g, 75%). Extremely viscous oil. $[\alpha]_D^{298} = -50.2$ ($c = 0.379$, THF). IR (neat): 3292 (br.), 2920, 2870, 1670, 1584, 1522, 1447, 1299, 1242, 1105, 803, 752. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.61 (br. *s*, 2 H); 8.35 (br. *s*, 2 H); 8.00–7.80 (*m*, 10 H); 7.63 (*t*, $J = 8.4$, 2 H); 7.42 (*t*, $J = 8.1$, 2 H); 7.32 (*s*, 2 H); 7.18 (*t*, $J = 7.6$, 2 H); 6.73 (*d*, $J = 7.6$, 2 H); 3.66–3.50 (*m*, 72 H); 3.37 (*t*, $J = 6.4$, 12 H); 3.30 (*s*, 18 H); 3.30–3.20 (*m*, 4 H); 2.16 (br. *m*, 4 H); 1.53 (br. *m*, 4 H); 1.44 (br. *m*, 12 H); 1.17 (br. *m*, 12 H) (2 NH protons not detected due to broadening). ^{13}C-NMR (125 MHz, $CDCl_3$): 175.0; 168.1; 165.3; 149.8; 149.3; 148.8; 148.4; 145.9; 140.5; 133.6; 129.2; 128.3; 127.9; 124.2; 123.2; 121.0; 120.4; 109.9; 109.7; 71.88; 71.86; 71.83; 70.57; 70.55; 70.49; 70.43; 70.01; 65.8; 58.9; 44.6; 36.6; 32.1; 31.5; 30.1; 23.3. MALDI-TOF-MS: 2068.8 (100%, M^+, $^{13}C_2{}^{12}C_{107}H_{164}N_8O_{30}$; calc. 2067.1). Anal. calc. for $C_{109}H_{164}N_8O_{30} \cdot CH_2Cl_2$ (2151.5): C 61.41, H 7.78, N 5.21; found: C 61.17, H 7.23, N 5.04.

*(−)-*N,N′*-Bis(6-{2-[7-{[7-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}-4,4-bis(3-{2-[2-(2-methoxyethoxy)ethoxy]-ethoxy}propyl)heptanoyl]oxy}-4,4-bis(3-{[7-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}-4,4-bis(3-{2-[2-(2-methoxy-*

*ethoxy)ethoxy]ethoxy}propyl)heptanoyl]oxy}propyl)heptanamido]acetamido}pyridin-2-yl)-9,9′-spirobi[9*H*-fluorene]-2,2′-dicarboxamide* ((−)-**G2**). The preparation from **13** (180 mg, 0.078 mmol) and (−)-**3** (20 mg, 0.029 mmol) *via* the bis(acyl chloride) followed exactly the protocol for the synthesis of (−)-**G1**. Purification by prep. GPC (one column eluted with THF, a second one eluted with CH_2Cl_2) afforded (−)-**G2** (92 mg, 60%). Sticky colorless gum. $[\alpha]_D^{298} = -28.3$ ($c = 0.381$, THF). IR (neat) 3500 (br.), 3316 (br.), 2910, 2868, 1731, 1674, 1585, 1522, 1449, 1351, 1300, 1244, 1109, 853, 804, 753. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.66 (br. *s*, 2 H); 8.50 (br. *s*, 2 H); 8.00-7.85 (*m*, 8 H); 7.81 (br. *d*, $J = 8.1$, 2 H); 7.64 (*t*, $J = 8.1$, 2 H); 7.43 (*t*, $J = 7.5$, 2 H); 7.28 (*s*, 2 H); 7.17 (*t*, $J = 7.5$, 2 H); 6.83 (br. *s*, 2 H); 6.73 (*d*, $J = 7.7$, 2 H); 4.00 (*t*, $J = 6.6$, 12 H); 3.68–3.60 (*m*, 144 H); 3.56–3.52 (*m*, 72 H); 3.40–3.35 (*m*, 94 H); 2.19–2.13 (br. *m*, 16 H); 1.65–1.35 (br. *m*, 64 H); 1.30–1.10 (br. *m*, 48 H). ^{13}C-NMR ($CDCl_3$): 174.0; 173.8; 167.8; 165.2; 149.9; 149.4; 148.8; 148.5; 145.9; 140.5; 133.7; 129.2; 128.4; 127.7; 124.2; 123.3; 121.1; 120.4; 109.8; 109.6; 72.0; 71.9; 70.58; 70.55; 70.47; 70.14; 65.8; 64.8; 59.0; 44.1; 36.5; 36.3; 32.2; 31.6; 31.2; 30.1; 28.61; 23.4; 22.5. MALDI-TOF-MS: 5287.0 (100%, M^+, $^{13}C_4{}^{12}C_{267}H_{476}N_8O_{90}$; calc. 5286.7). Anal. calc. for $C_{271}H_{476}N_8O_{90} \cdot 2.5\ CH_2Cl_2$ (5499.1): C 59.74, H 8.82; found: C 59.76, H 8.61.

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REFERENCES

[1] a) D. A. Tomalia, A. M. Naylor, W. A. Goddard III, *Angew. Chem.* **1990**, *102*, 119; *ibid., Int. Ed.* **1990**, *29*, 138; b) G. R. Newkome, C. N. Moorefield, F. Vögtle, 'Dendritic Molecules: Concepts, Syntheses, Perspectives', VCH, Weinheim, 1996; c) O. A. Matthews, A. N. Shipway, J. F. Stoddart, *Prog. Polym. Sci.* **1998**, *23*, 1; d) H.-F. Chow, T. K.-K. Mong, M. F. Nongrum, C.-W. Wan, *Tetrahedron* **1998**, *54*, 8543.

[2] M. Fischer, F. Vögtle, *Angew. Chem.* **1999**, *111*, 934; *ibid., Int. Ed.* **1999**, *38*, 885.

[3] a) D. K. Smith, F. Diederich, *Chem. Eur. J.* **1998**, *4*, 1353; b) T. Habicher, F. Diederich, *Helv. Chim. Acta*, in press.

[4] a) F. Zeng, S. C. Zimmerman, *Chem. Rev.* **1997**, *97*, 1681; b) D. K. Smith, F. Diederich, A. Zingg, in 'Supramolecular Science: Where It Is and Where It Is Going', Eds. R. Ungaro, E. Dalcanale, Kluwer, Dordrecht, 1999, pp. 261–272; c) V. V. Narayanan, G. R. Newkome, *Top. Curr. Chem.* **1998**, *197*, 19.

[5] a) J. F. G. A. Jansen, E. M. M. de Brabander-van den Berg, E. W. Meijer, *Science (Washington, D.C.)* **1994**, *266*, 1226; b) G. R. Newkome, C. N. Moorefield, G. R. Baker, M. J. Saunders, S. H. Grossman, *Angew. Chem.* **1991**, *103*, 1207; *ibid., Int. Ed.* **1991**, *30*, 1178; c) A. I. Cooper, J. D. Londono, G. Wignall, J. B. McClain, E. T. Samulski, J. S. Lin, A. Dobrynin, M. Rubinstein, A. L. C. Burke, J. M. J. Fréchet, J. M. DeSimone, *Nature (London)* **1997**, *389*, 368.

[6] a) T. D. James, H. Shinmori, M. Takeuchi, S. Shinkai, *Chem. Commun.* **1996**, 705; b) C. Valério, J.-L. Fillaut, J. Ruiz, J. Guittard, J.-C. Blais, D. Astruc, *J. Am. Chem. Soc.* **1997**, *119*, 2588; c) R. Roy, *Curr. Opin. Struct. Biol.* **1996**, *6*, 692.

[7] a) S. C. Zimmerman, F. Zeng, D. E. C. Reichert, S. V. Kolotuchin, *Science (Washington, D.C.)* **1996**, *271*, 1095; b) B. Kenda, F. Diederich, *Angew. Chem.* **1998**, *110*, 3357; *ibid., Int. Ed.* **1998**, *37*, 3154; c) G. R. Newkome, L. A. Godinez, C. N. Moorefield, *Chem. Commun.* **1998**, 1821.

[8] a) S. Mattei, P. Wallimann, B. Kenda, W. Amrein, F. Diederich, *Helv. Chim. Acta* **1997**, *80*, 2391; b) J. P. Collman, L. Fu, A. Zingg, F. Diederich, *Chem. Commun.* **1997**, 193; c) S. C. Zimmerman, Y. Wang, P. Bharathi, J. S. Moore, *J. Am. Chem. Soc.* **1998**, *120*, 2172.

[9] P. J. Dandliker, F. Diederich, A. Zingg, J.-P. Gisselbrecht, M. Gross, A. Louati, E. Sanford, *Helv. Chim. Acta* **1997**, *80*, 1773.

[10] D. K. Smith, F. Diederich, *Chem. Commun.* **1998**, 2501.

[11] J. Cuntze, L. Owens, V. Alcázar, P. Seiler, F. Diederich, *Helv. Chim. Acta* **1995**, *78*, 367.

[12] D. Seebach, P. B. Rheiner, G. Greiveldinger, T. Butz, H. Sellner, *Top. Curr. Chem.* **1998**, *197*, 125.

[13] a) A. Bähr, A. S. Droz, M. Püntener, U. Neidlein, S. Anderson, P. Seiler, F. Diederich, *Helv. Chim. Acta* **1998**, *81*, 1931; b) A. P. Davis, R. S. Wareham, *Angew. Chem.*, in press.

[14] a) F. A. Quiocho, *Pure Appl. Chem.* **1989**, *61*, 1293; b) H. Lis, N. Sharon, *Chem. Rev.* **1998**, *98*, 637.

[15] J. E. Forman, R. E. Barrans, D. A. Dougherty, *J. Am. Chem. Soc.* **1995**, *117*, 9213.

[16] T. Mizutani, T. Murakami, N. Matsumi, T. Kurahashi, H. Ogoshi, *J. Chem. Soc., Chem. Commun.* **1995**, 1257.

[17] A. W. Czarnik, *Chem. Biol.* **1995**, *2*, 423.

[18] a) T. D. James, K. R. A. S. Sandanayake, S. Shinkai, *Angew. Chem.* **1996**, *108*, 2038; *ibid., Int. Ed.* **1996**, *35*, 1911; b) T. D. James, K. R. A. S. Sandanayake, S. Shinkai, *Nature (London)* **1995**, *374*, 345.
[19] a) M. Takeuchi, H. Kijima, I. Hamachi, S. Shinkai, *Bull. Chem. Soc. Jpn.* **1997**, *70*, 699; b) M. Takeuchi, T. Imada, S. Shinkai, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1117.
[20] C. J. Hawker, J. M. J. Fréchet, *J. Am. Chem. Soc.* **1990**, *112*, 7638.
[21] a) G. Haas, V. Prelog, *Helv. Chim. Acta* **1969**, *52*, 1202; b) V. Prelog, D. Bedekovic, *Helv. Chim. Acta* **1979**, *62*, 2285.
[22] P. Lustenberger, E. Martinborough, T. Mordasini Denti, F. Diederich, *J. Chem. Soc., Perkin Trans. 2* **1998**, 747.
[23] a) L. A. Carpino, *J. Am. Chem. Soc.* **1993**, *115*, 4397; b) J. M. Bofill, F. Albericio, *J. Chem. Res. (S)* **1996**, 302.
[24] N. Ono, H. Miyake, A. Kamimura, I. Hamamoto, R. Tamura, A. Kaji, *Tetrahedron* **1985**, *41*, 4013.
[25] G. R. Newkome, S. Arai, F. R. Fronczek, C. N. Moorefield, X. Lin, C. D. Weis, *J. Org. Chem.* **1993**, *58*, 898.
[26] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
[27] a) H. W. I. Peerlings, E. W. Meijer, *Chem. Eur. J.* **1997**, *3*, 1563; b) H. W. I. Peerlings, E. W. Meijer, *Eur. J. Org. Chem.* **1998**, 573.
[28] a) M. Inouye, T. Miyake, M. Furusyo, H. Nakazumi, *J. Am. Chem. Soc.* **1995**, *117*, 12416; b) C.-Y. Huang, L. A. Cabell, E. V. Anslyn, *J. Am. Chem. Soc.* **1994**, *116*, 2778; c) M. Inouye, K. Takahashi, H. Nakazumi, *J. Am. Chem. Soc.* **1999**, *121*, 341.
[29] B. Peterson, Associate V. 1.6, Ph. D. Dissertation, University of California at Los Angeles, 1994.
[30] P. K. Murer, J.-M. Lapierre, G. Greiveldinger, D. Seebach, *Helv. Chim. Acta*, **1997**, *80*, 1648.
[31] R. A. Binstead, A. D. Zuberbühler, *Specfit Global Analysis, V. 2.09*, Spectrum Software Associates 1993.
[32] a) R. P. Bonar-Law, J. K. M. Sanders, *J. Am. Chem. Soc.* **1995**, *117*, 259; b) T. Mizutani, T. Kurahashi, T. Murakami, N. Matsumi, H. Ogoshi, *J. Am. Chem. Soc.* **1997**, *119*, 8991.
[33] G. M. Brown, P. Dubreuil, F. M. Ichhaporia, J. E. Desnoyers, *Can. J. Chem.* **1970**, *48*, 2525.

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