Catalytic Dendrophanes as Enzyme Mimics: Synthesis, Binding Properties, Micropolarity Effect, and Catalytic Activity of Dendritic Thiazolio-cyclophanes

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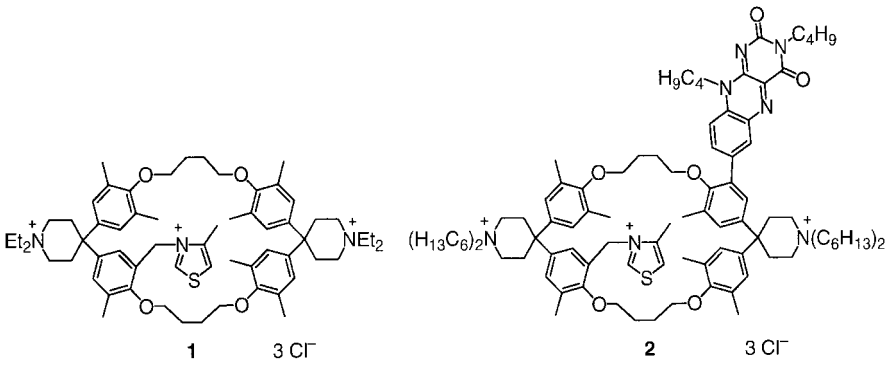
Catalytic dendrophanes **9** and **10** were prepared as functional mimics of the thiamine-diphosphate-dependent enzyme pyruvate oxidase, and studied as catalysts in the oxidation of naphthalene-2-carbaldehyde (**4**) to methyl naphthalene-2-carboxylate (**8**) (*Scheme 1*). They are composed of a thiazolio-cyclophane initiator core with four generation-2 (*G-2*) poly(etheramide) dendrons attached. The two dendrophanes were synthesized by a convergent growth strategy by coupling dendrons **11** and **12**, respectively (*Scheme 2*), with (chloromethyl)-cyclophane **42** (*Scheme 5*) and subsequent conversion with 4-methylthiazole (*Scheme 7*). The X-ray crystal structures of cyclophane precursors **30** (*Scheme 3*), **37**, and **38** (*Scheme 5*) on the way to dendrophanes were determined (*Fig. 1*). The crystal-structure analysis of the benzene clathrate of **37** revealed the formation of channel-like stacks by the cyclophane which incorporate its morpholinomethyl side chain and the enclathrated benzene molecule (*Fig. 2*). The interactions of the enclathrated benzene molecule with the phenyl rings of the two adjacent cyclophane molecules in the stack closely resemble those between neighboring benzene molecules in crystalline benzene (*Fig. 3*). The characterization by MALDI-TOF-MS (*Fig. 4*) and ^{1}H- and ^{13}C-NMR spectroscopy (*Fig. 5*) proved the monodispersity of the *G-2* dendrophanes **9** and **10** with molecular weights up to 11500 Da (for **10**). ^{1}H-NMR and fluorescence binding titrations in H_2O and aqueous MeOH showed that **9** and **10** form stable 1:1 complexes with naphthalene-2-carbaldehyde (**4**) and 6-(*p*-toluidino)naphthalene-2-sulfonate (**48**, TNS) (*Tables 1* and *2*). The evaluation of the fluorescence-emission maxima of bound TNS revealed that the dendritic branching creates a microenvironment of distinctly reduced polarity at the cyclophane core by limiting its exposure to bulk solvent. Initial rate studies for the oxidation of naphthalene-2-carbaldehyde to methyl naphthalene-2-carboxylate in basic aqueous MeOH in the presence of flavin derivative **6** revealed only a weak catalytic activity of dendrophanes **9** and **10** (*Table 3*), despite the favorable micropolarity at the cyclophane active site. The low catalytic activity in the interior of the macromolecules was explained by steric hindrance of reaction transition states by the dendritic branches.

1. Introduction. – In the past, chemists have developed a variety of low-molecular-weight model systems to mimic mechanisms of enzymatic catalysis [1]. These models typically provide a recognition site for the substrate and one or more functional groups known to be involved in the catalytic pathway. The creation of a favorable micro-environment at the active site, however, which is believed to play an important role in the catalytic mechanism of many enzymatic reactions, is difficult to achieve with low-molecular-weight models.

Dendrimer technology [2] provides a unique tool for creating synthetic models of globular proteins with deeply buried recognition or catalytic sites of distinct micro-polarity [3]. Studies of dendritic mimics of globular electron-transfer heme proteins revealed a strong microenvironmental effect on the redox potentials of metallopor-

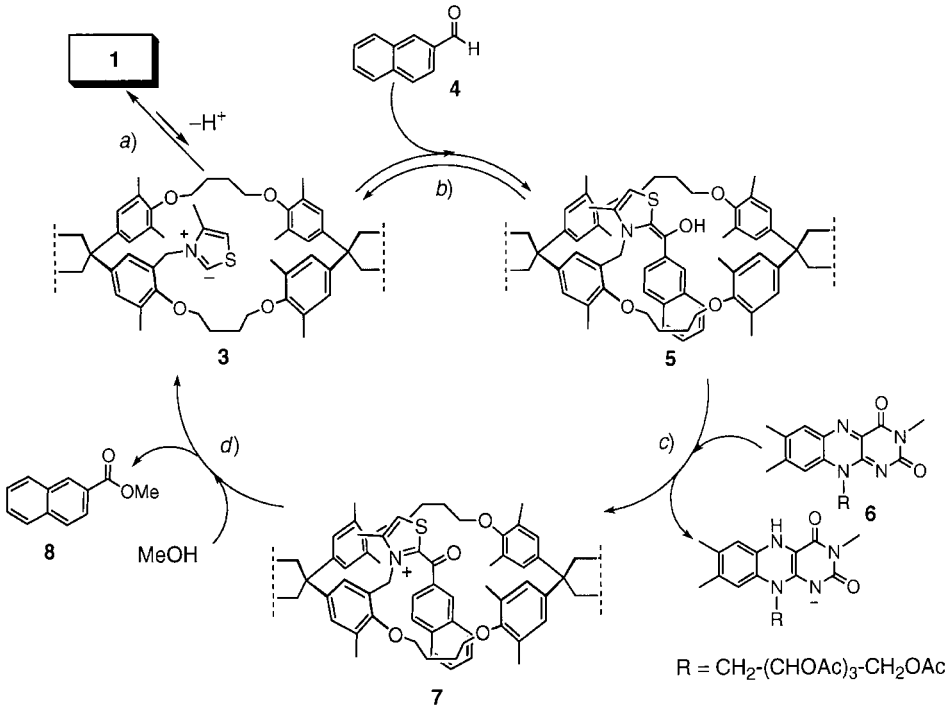
phyrins located at the core of the macromolecules [4]. Receptor sites have been embedded into dendritic shells [5][6], and *dendr*itic cyc*lophanes* (*dendrophanes*) were shown to complex arenes [7] or steroids [7b][8] in aqueous solutions at cyclophane recognition sites of reduced micropolarity. Catalytic sites have also been introduced inside dendrimers [9]; however, with increasing dendritic generation, steric hindrance by the branches in most cases has been found to decelerate the catalyzed reaction.

We had pursued in the past the mimicry of the mode of action of thiamine-diphosphate(ThDP)-dependent enzymes [10]. Simple thiazolium ions behave as functional analogs of the ThDP cofactor [11], and we prepared a variety of thiazolio-cyclophanes such as **1** and **2**, containing binding sites for aromatic substrates, as model systems for the enzymes transketolase [12] and pyruvate oxidase [13][14] (for thiazolio-cyclodextrins, see [15]). Thiazolio-cyclophane **1** catalyzes the oxidation of aromatic aldehydes to the corresponding carboxylic esters in the presence of an oxidizing agent such as a flavin derivative. The mechanism of this multistep process (*Scheme 1*) mimics the mode of action of pyruvate oxidase, which catalyzes the oxidative decarboxylation of pyruvate to acetyl phosphate [14][16]. In basic MeOH solution, **1** is in equilibrium with the thiazolium ylide **3** (*Scheme 1*, step *a*) which reacts with a bound aromatic aldehyde such as naphthalene-2-carbaldehyde (**4**) to yield the active aldehyde **5** (step *b*). In the presence of flavin derivative **6**, the active aldehyde intermediate is oxidized to the 2-acylthiazolium ion **7** (step *c*). Methyl ester **8** is formed in a rapid reaction of **7** with the solvent (MeOH), and the catalytically active thiazolium ylide is regenerated (step *d*). With the biscoenzyme-cyclophane **2**, the oxidation step also proceeds intramolecularly, and **2** is one of the most active artificial enzymes known to date [17].



The transition states in the usually rate-determining steps leading to the intermediate active aldehydes in ThDP- and thiazolium-ion-mediated catalysis are of reduced polarity compared to the corresponding ground-state substrates and intermediates. Therefore, a solvent or an enzymatic microenvironment of reduced polarity should lead to a large rate acceleration. Thus, the decarboxylation of pyruvate was found to be 10^6 times faster in EtOH than in H_2O [18]. It can be assumed that a large contribution to catalysis by ThDP-dependent enzymes is derived from the presence of a microenvironment at the active site with a distinctively reduced polarity compared to the surrounding aqueous solution.

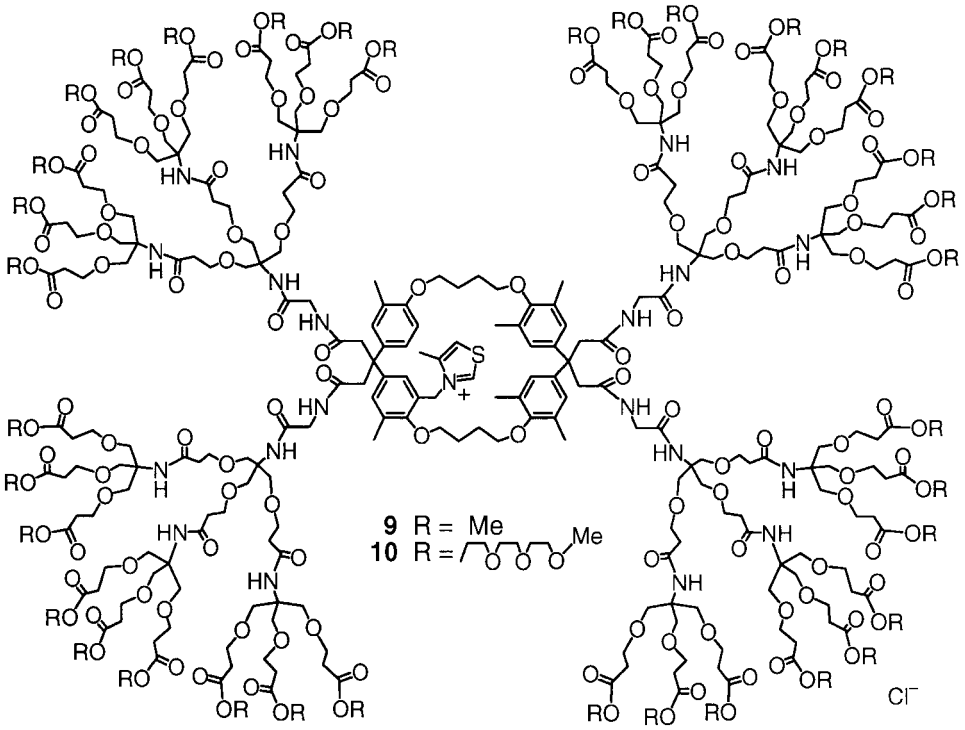
Scheme 1. *Catalytic Cycle for the Oxidation of Naphthalene-2-carbaldehyde* (**4**) *to Methyl Naphthalene-2-carboxylate* (**8**) *Catalyzed by Thiazolio-cyclophane* **1**



We hoped to reproduce such microenvironmental effects on catalysis by inserting a thiazolium-cyclophane into the core of globular dendrimers to form *catalytic dendrophanes*. This objective seemed particularly attractive since host-guest exchange kinetics in dendrophane complexes was found to be fast, with first-order decomplexation rate constants $k_{decompl.}$ around $10^3\ s^{-1}$ [7b], making a rate-limiting product release from the macromolecular catalyst therefore quite unlikely.

In this paper, we describe the synthesis and characterization of the first catalytic dendrophanes **9** and **10** with a thiazolio-cyclophane incorporated into globular dendritic shells bearing different surface groups. The binding properties of these enzyme mimics, an evaluation of the micropolarity at their active sites, and an investigation of their catalytic ability are presented.

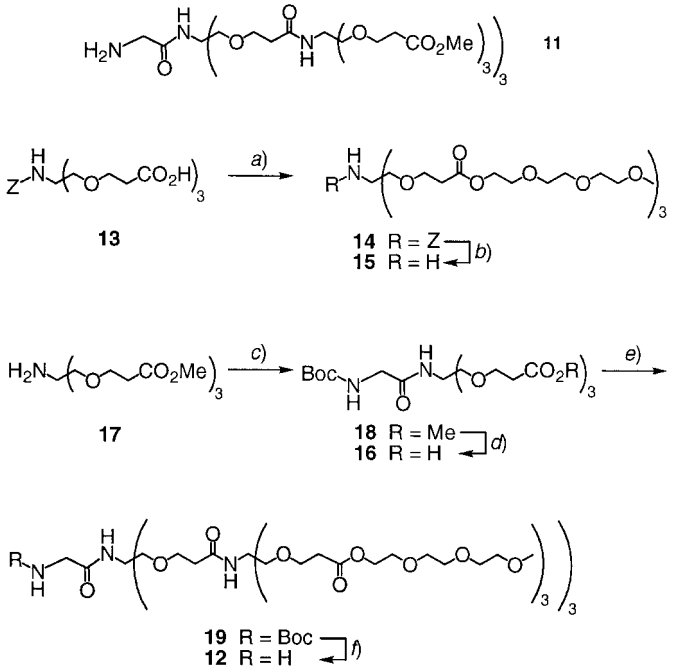
2. Results and Discussion. – 2.1. *Synthesis of Generation-2 Dendrons.* The *G-2* (generation 2) dendron **11**, which was required for the formation of target compound **9**, had previously been prepared during the synthesis of fullerene dendrimers [19] (*Scheme 2*). In the construction of *G-2* dendron **12** for incorporation into target compound **10**, monomer **13** [19] was transformed *via* the tris(acyl halide) into the tris(triethyleneglycol monomethyl ether) **14**, which was subsequently deprotected to give the free amine **15**. Coupling of triacid **16**, which was obtained in two steps from the *Newkome* monomer **17** [20] *via* Boc-protected (Boc = *tert*-butoxycarbonyl) amine **18**,



with **15** led to **19**, which was finally deprotected to yield the water-soluble *G-2* dendron **12**. Both dendrons **11** and **12** contain a glycine spacer between the bulky poly(ether-amide) wedge and the primary amine focal point to decrease the steric hindrance in the subsequent convergent dendrophane synthesis. In the convergent synthesis of fullerene dendrimers, the introduction of such a spacer proved to be essential for a successful coupling of bulky dendrons to the functionalized carbon spheres [19].

2.2. *Convergent Synthesis of* G-2 *Dendrophanes: Model Studies.* The two cyclophane-tetraalkanoic acids **20** and **21**, containing spacers of different length between the macrocyclic skeleton and the reactive COOH groups, were used as initiator cores to test the convergent synthesis of dendrophanes. We expected that the longer spacers in **21** would alleviate steric hindrance by the macrocyclic skeleton during the coupling of the bulky dendrons to the four COOH residues. The synthesis of **20** with the shorter spacers was readily achieved by hydrolysis of the known tetraester **22** (*Scheme 3*) [21]. The overall synthesis of **21** was longer and started from diphenol **23** [22], which was protected with (*t*-Bu)Me_2SiCl to give the bis(silyl ether) **24** (*Scheme 3*). Reduction of the ester groups with $LiAlH_4$ afforded diol **25** which was transformed into bis(methanesulfonate) **26**. Nucleophilic substitution with KCN under *Finkelstein* conditions (in the presence of KI) was accompanied by silyl-ether cleavage and yielded dinitrile **27**, which was converted into diester **28** with H_2SO_4 in EtOH. Alkylation with 1,4-dichlorobutane provided dichloride **29**, and cyclization with diphenol **28** afforded cyclophane **30** which was characterized by X-ray crystallography (*Sect. 2.4*). Ester hydrolysis finally led to cyclophane-tetrapropanoic acid **21**.

Scheme 2. *The Known Dendron* **11** [19] *and Synthesis of the New Dendron* **12**

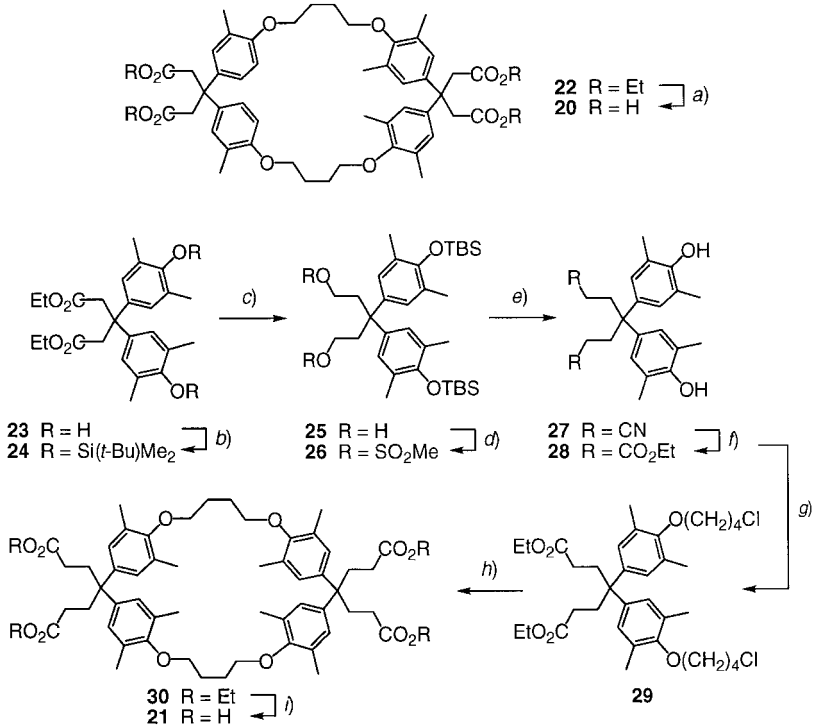


a) $SOCl_2$, CH_2Cl_2, r.t.; then $Me(OCH_2CH_2)_3OH$, CH_2Cl_2, r.t.; 76%. *b*) H_2, Pd/C, EtOH, r.t.; 87%. *c*) *t*-$BuOCONHCH_2CO_2H$, BtOH (= 1-hydroxy-1*H*-benzotriazole), EDC (= *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride), Et_3N, THF, r.t.; 87%. *d*) 2N NaOH, MeOH, r.t.; 85%. *e*) **15**, BtOH, DCC (= *N*,*N*′-dicyclohexylcarbodiimide), THF, r.t.; 60%. *f*) CF_3COOH, CH_2Cl_2, r.t.; 85%.

The two cyclophane-tetraalkanoic acids **20** and **21** were subsequently coupled (DCC, BtOH) with *G-2* dendron **11** (*Scheme 4*). The conversion of **20** with the smaller $-CH_2-$ spacers between the COOH groups and the sterically demanding macrocyclic skeleton afforded dendrophane **31** in 41% yield, whereas, under the same conditions, cyclophane **21** with the larger $-CH_2CH_2-$ spacers gave dendrophane **32** in 58% yield. All spectral data (matrix-assisted laser-desorption-ionization mass spectra (MALDI-TOF-MS), as well as ^1H- and ^{13}C-NMR spectra) were in full agreement with the constitution assigned to **31** and **32**, and also demonstrated the high purity of the two dendrophanes. Thus, the mass spectrum of **32** showed only one signal at *m*/*z* 6774, which can be assigned to the Na^+ complex of the molecular ion (calculated for $^{13}C_4{}^{12}C_{302}H_{488}N_{20}NaO_{144}$: 6774). Although the coupling yield obtained in the reaction of **21** with the less sterically congested propionic-acid side chains was, expectedly, somewhat higher, we decided to pursue the synthesis of catalytic dendrophanes *via* cyclophane-tetraacetates (such as **20**), which are synthetically much more readily accessible than cyclophane-tetrapropionates (such as **21**).

2.3. *Synthesis of Functionalized Cyclophane Initiator Cores.* As a construction strategy, we planned to introduce the thiazolium ring in **9** and **10** in the last step of the synthesis by reacting the corresponding dendrophanes bearing a halomethyl function-

Scheme 3. *Synthesis of the Cyclophane Initiator Cores* **20** *and* **21**

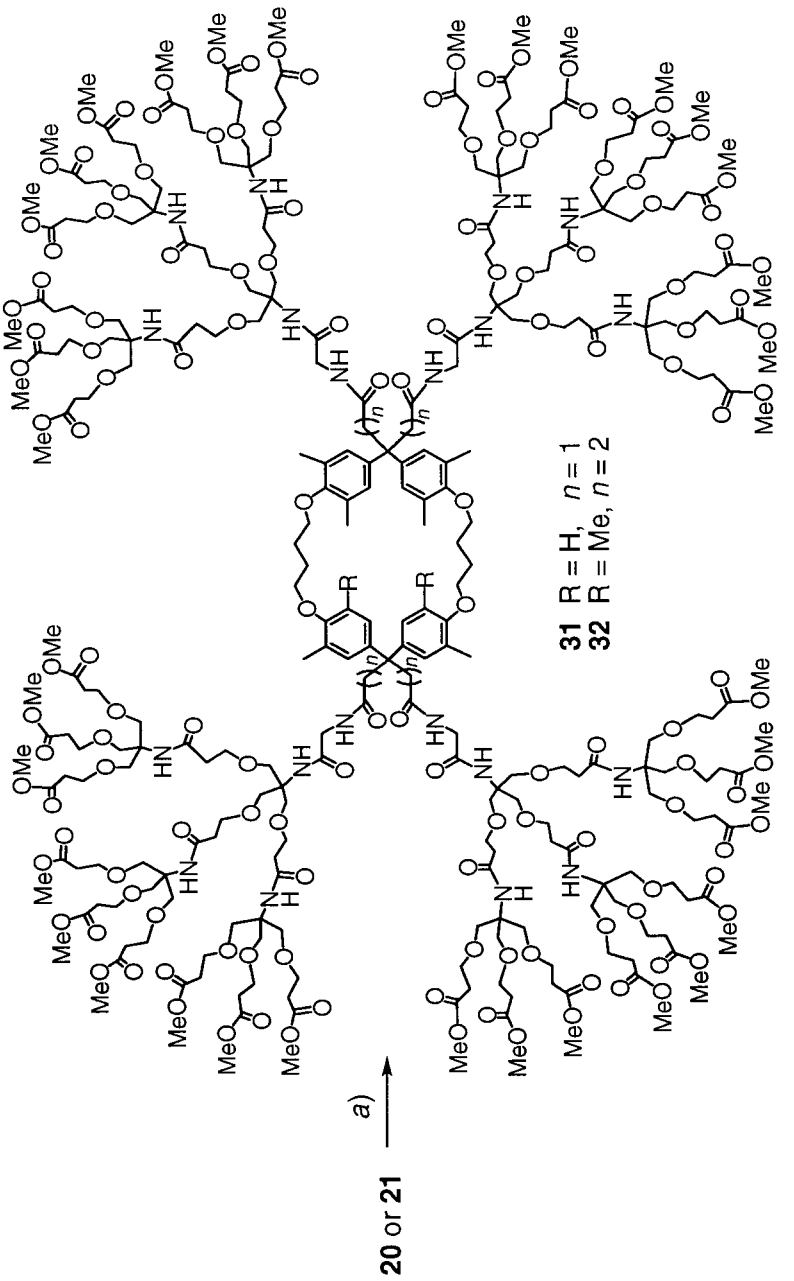


a) 2N NaOH, MeOH, r.t. → 60°; quant. *b*) (*t*-Bu)Me_2SiCl, imidazole, DMF, r.t. → 50°; 88%. *c*) $LiAlH_4$, Et_2O, −5° → 34°; 86%. *d*) $MeSO_2Cl$, Et_3N, CH_2Cl_2, −5°; 95%. *e*) KCN, KI, Me_2SO, 100°; 73%. *f*) H_2SO_4, EtOH, 78°; 82%. *g*) $Cl(CH_2)_4Cl$, Cs_2CO_3, K_2CO_3, DMF, 80°; 60%. *h*) **28**, Cs_2CO_3, K_2CO_3, DMF, PhMe, 80°; 20%. *i*) 2N NaOH, MeOH, THF, r.t. → 60°; quant.

ality with 4-methylthiazole. Since dendrophane **20** contains two reactive positions *ortho* to phenolic OH groups, direct haloalkylation, such as chloromethylation (*Blanc* reaction) with a large excess of HCHO and HCl [13b][14] would, at best, yield an almost certainly inseparable mixture of mono- and disubstituted products and starting material. Therefore, we decided to undertake a suitable monofunctionalization early in the synthesis when product separation is less problematic.

Following this strategy, diphenol **33** [21] was subjected to a *Mannich* reaction with paraformaldehyde (1.1 equiv.) and morpholine (*Scheme 5*) [23]. The mixture of starting material and mono- (**34**) and bis(morpholinomethyl) (**35**) derivatives was readily separated *via* formation of the hydrochloride salts of the aminomethylated compounds. When the crude product mixture, consisting of starting material and hydrochloride salts, was suspended in CH_2Cl_2/H_2O, only the starting material was dissolved in the organic layer. The dihydrochloride salt **35** · 2 HCl dissolved in the aqueous phase, whereas the salt of mono(aminomethylated) product, **34** · HCl, was not soluble in either one of these solvents and was recovered as a white precipitate in 43% yield. Alkylation of **34** with 1-bromo-4-chlorobutane gave dichloride **36**, which was

Scheme 4. *Synthesis of* G-2 *Dendrophanes* **31** *and* **32**

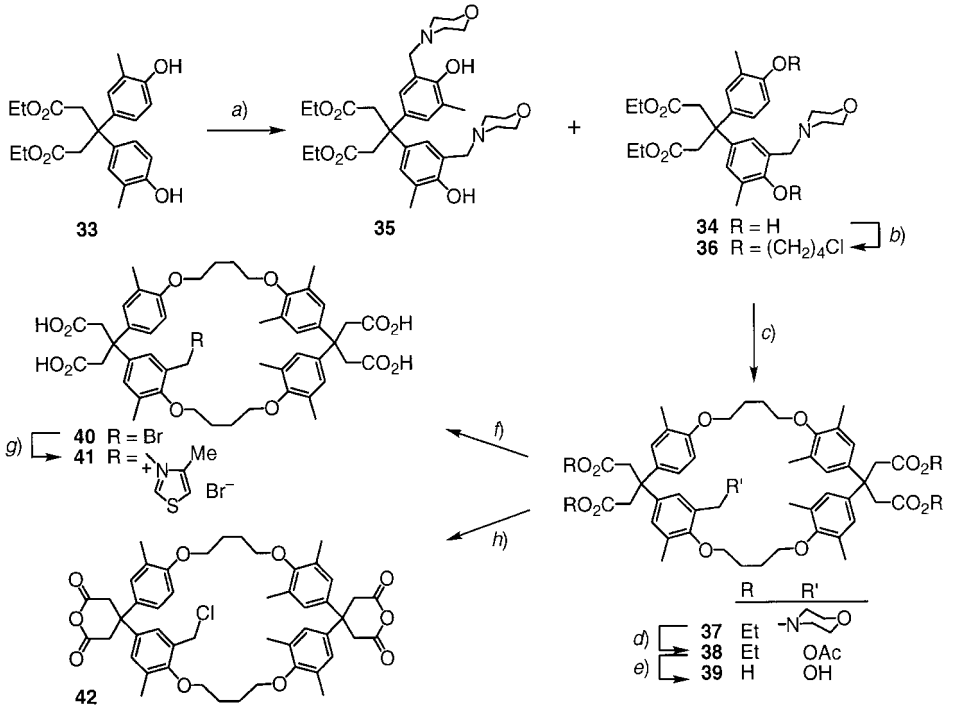


a) **11**, BtOH, DCC, THF, 0° → r.t.; 41% (**31**), 58% (**32**).

cyclized with **23** to give cyclophane **37**. Addition of *p*-xylene (8 mol-% relative to the solvent MeCN) significantly increased the yield of the macrocycle from 20 to 49%. This cosolvent presumably acts as a template by binding into the macrocyclic cavity that is forming in the transition state of the second, ring-closing alkylation step [24]. The (morpholinomethyl)-cyclophane **37** was converted with Ac_2O into the $AcOCH_2$ derivative **38**; both macrocycles were characterized by X-ray crystallography (*Sect. 2.4*). Tetraacetic acid **39**, containing the desired CH_2OH group, was obtained by basic hydrolysis (2N NaOH/MeOH/THF) of the five carboxylic-ester residues present in **38**. The benzyl-alcohol functionality seemed compatible with the formation of the dendrophanes, and we also expected its subsequent conversion into the halomethyl (and ultimately the thiazoliomethyl) group to proceed smoothly. Possible conditions for these final steps in the synthesis of the catalytic dendrophanes **9** and **10** were first explored with cyclophane **39**.

Treatment of **39** with HBr in AcOH yielded bromomethyl derivative **40** in 86% yield, and conversion with 4-methylthiazole in MeCN afforded thiazolio-cyclophane **41** in 62% yield (*Scheme 5*). However, both **40** and **41** were quite unstable and the former decomposed within 24 h, even in a degassed solution at 0°. Therefore, we decided to

Scheme 5. *Synthesis of Functionalized Cyclophanes*



a) Morpholine, HCHO, EtOH, 78°; 43% (**34**), 23% (**35**). *b*) $Br(CH_2)_4Cl$, Cs_2CO_3, K_2CO_3, MeCN, 80°; 68%. *c*) **23**, Cs_2CO_3, K_2CO_3, MeCN, *p*-xylene, 80°; 49%. *d*) Ac_2O, 140°; 70%. *e*) 2N NaOH, MeOH, THF, r.t.; 89%. *f*) HBr/AcOH, CH_2Cl_2, r.t.; 86%. *g*) 4-Methylthiazole, MeCN, r.t.; 62%. *h*) Me_3SiCl, Et_3N, $CHCl_3$, DMF, 50°, then $SOCl_2$, r.t.; 94%.

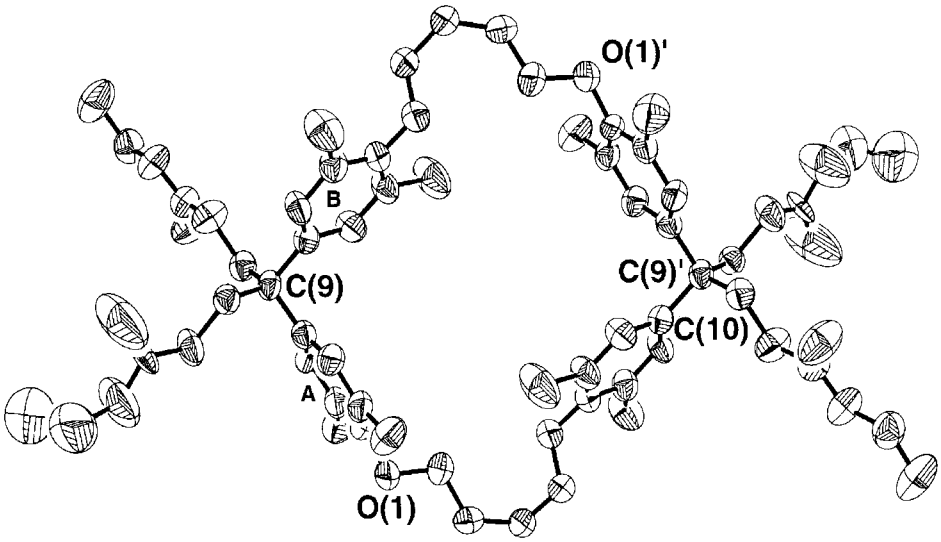
pursue the formation of a chloromethylated derivative. Although the reaction of **39** with HCl in different solvents afforded (chloromethyl)-cyclophane, we were unable to isolate it in pure form by precipitation or chromatography. On the other hand, reaction of **39** with $SOCl_2$ in the presence of Me_3SiCl and Et_3N yielded (chloromethyl)-cyclophane tetraacetic dianhydride **42** (94%) which was isolated as a stable compound by recrystallization from AcOEt.

2.4. *X-Ray Crystal Structures of Cyclophanes* **30**, **37**, *and* **38** [25]. The ORTEP representations of the three X-ray crystal structures (*Fig. 1*) show that the flexible ethyl-ester side chains in all three cyclophanes are partially disordered, which is the reason that the crystal structures are of only moderate quality (see *Exper. Part*). Furthermore, in the structure of **38**, the $AcOCH_2$ group and three Me substituents at the phenyl rings are also disordered and appear each at two positions related by a center of inversion (*Fig. 1,c*). Since rotation of the phenyl rings is restricted in the crystal, the positions of substituents on these rings are fixed with respect to the plane of the macrocycle encompassing O(1), C(9), O(1′), and C(9′). These 'frozen' rotamers of **38** are randomly distributed in the crystal lattice; thus, the crystal structure shows a superimposition of all of these rotamers to a centrosymmetric macrocycle. For cyclophane **37**, two of the possible conformers are found at defined positions in the crystal lattice.

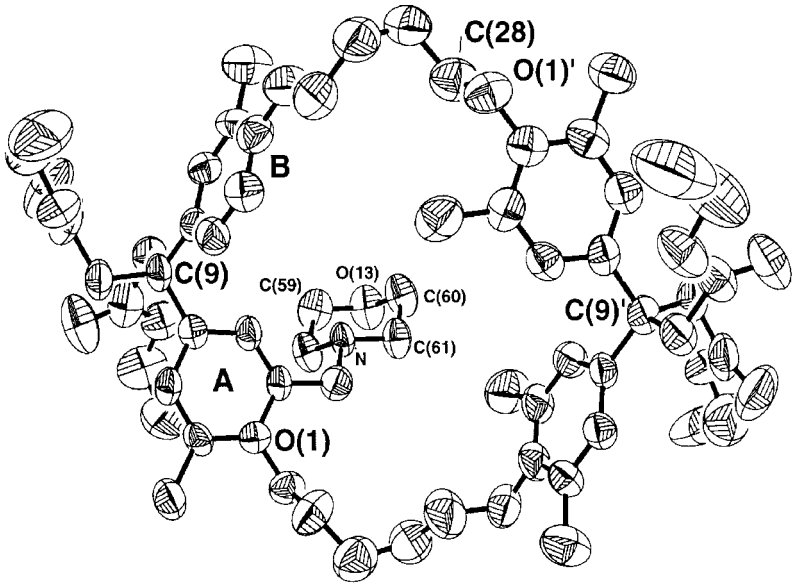
All three cyclophanes adopt conformations in the form of an open, rectangular molecular box which is best described by the atoms O(1), C(9), O(1′), and C(9′) at its four corners. With distances of the edges of 5.7(1) Å (O(1)···C(9)) and 9.4(2) Å (C(9)···O(1′)), the cavity dimensions are very similar in the three compounds. Opposite phenyl rings in all three macrocycles adopt a parallel orientation, except for the plane of the (morpholinomethyl)-substituted A-ring of cyclophane **37** which is tilted with respect to the plane of the opposite phenyl ring by 14°. The planes of the phenyl rings in all three structures differ from the perpendicular position relative to the macrocyclic plane encompassing O(1), O(1′), C(9), and C(9′) by torsional angles between 35° and 40°. The overall structures of **30** and **38** resemble each other closely, whereas the bulky morpholine moiety in **37** and the enclathration of a benzene molecule impose a different conformation of the cyclophane.

Owing to the restricted rotation of the differently substituted A- and B-rings, two diastereoisomeric pairs of enantiomers could theoretically be present in the crystal packing of cyclophane **37** which features planar chirality. However, only one pair of enantiomers, besides the enclathrated benzene molecule, displaying the morpholino-methyl group on the A-ring and the Me group on the B-ring on the same side of the cyclophane plane, is found in the elementary cell of the crystal structure of **37**. The enantiomers form channel-like stacks of head-to-head dimers (*Fig. 2,a*) in which the morpholine and enclathrated benzene rings are located between the cyclophane cavities. The interactions between adjacent morpholine units in a stack and between one morpholine moiety and the adjacent cyclophane are depicted in *Fig. 2,b*. A weak, H-bonding-type contact exists between the morpholine N-atom and the CH_2 group of the second morpholine ring (distance N···C(61) = 3.7 Å, angle N···H−C(61) = 132°), as well as between the morpholine O-atom and a CH_2O group in the $-O(CH_2)_4O-$ bridge of the adjacent cyclophane (distance O(13)···C(28) = 3.6 Å, angle O(13)···H−C(28) = 160°). Additionally, the CH_2 groups in α-positions to the

a)



b)



(*Fig. 1*)

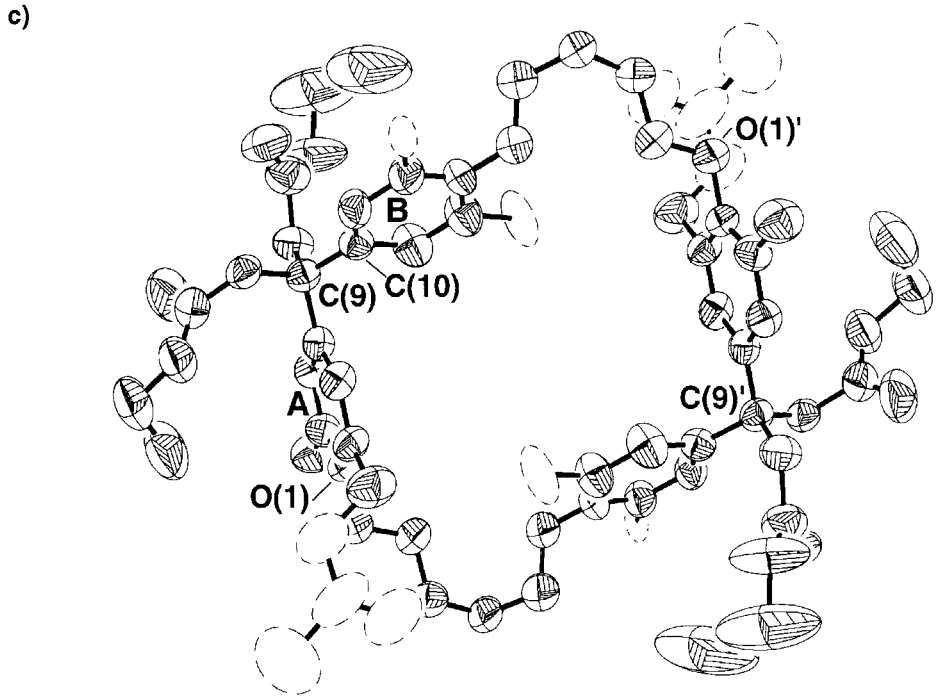


Fig. 1. *ORTEP Plots of the X-ray crystal structures of cyclophanes* **30** (*a*), **37** (*b*), *and* **38** (*c*). Thermal ellipsoids are shown at the 50% probability level.

morpholine O-atom show C–H$\cdots\pi$ interactions with the A- and B-rings of the adjacent cyclophane, with distances of 3.8 Å between the aliphatic C-atoms and the centers of these rings.

The alternating benzene rings and morpholine moieties in the channel-type stacks of **37** (*Fig. 2,a*) form a chain-like motif with the shortest distance C(benzene)–O(morpholine) of 3.9 Å. Each benzene molecule undergoes edge-to-face interactions with the eight neighboring phenyl rings of two cyclophanes, with a shortest center-to-center distance between interacting rings of *ca.* 5.0 Å. Interestingly, this pattern of aromatic interactions is closely similar to that observed in the orthorhombic crystal structure (space group *Pbca*) of benzene. This is evidenced by the least-squares superimposition of the two X-ray crystal structures (*Fig. 3*) [26][1]).

2.5. *Synthesis and Characterization of Catalytic Dendrophanes* **9** *and* **10**. The coupling of (hydroxymethyl)-cyclophane **39** with *G-1* dendron **17** (DCC/BtOH) afforded *G-1* dendrophane **43** in 37% yield (*Scheme 6*). Hydrolysis of the methyl-ester surface groups (1N NaOH/MeOH) provided dodecaacid **44**, an attractive precursor for a variety of water-soluble catalytic dendrophanes such as artificial hydrolases. Coupling of **39** with *G-2* dendron **11**, containing a glycine spacer at the focal point to prevent

[1]) We thank Prof. Dr. *G. Klebe*, University of Marburg, for performing the superimposition of the two structures, as described in [26].

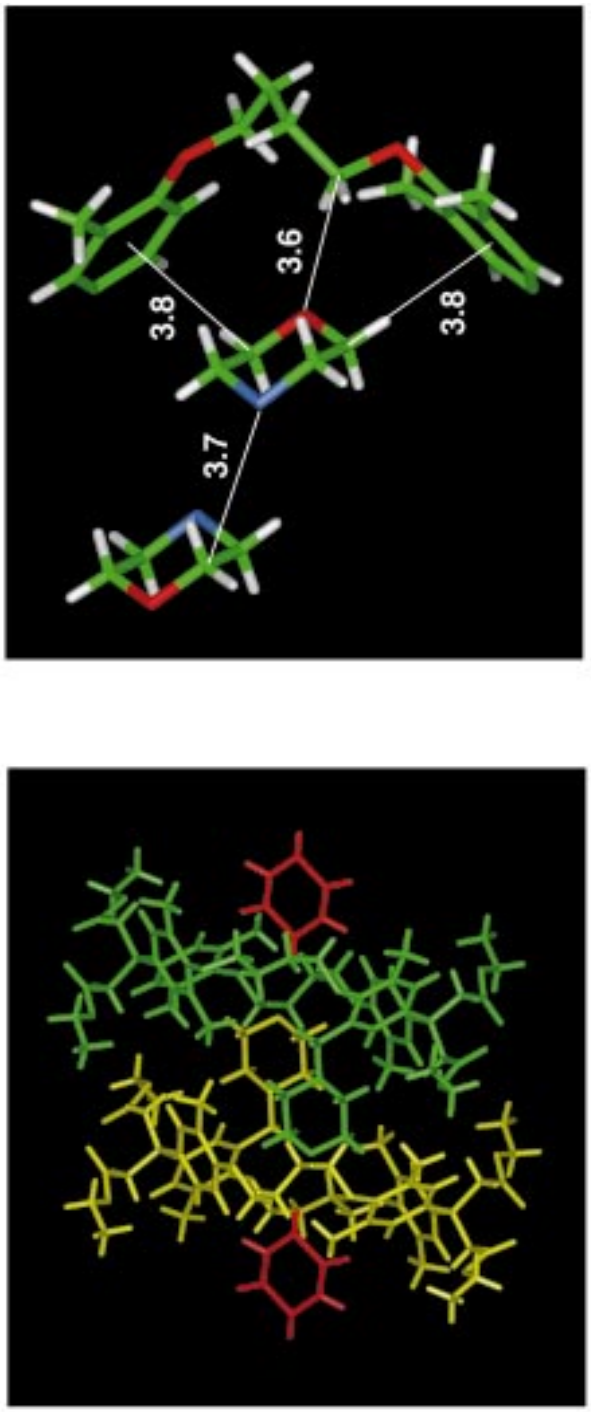


Fig. 2. Left: *Enantiomers of cyclophane* **37** (yellow and green) *forming channel-like stacks of head-to-head dimers in which the morpholine rings and enclathrated benzene* (red) *are located between cyclophane cavities.* Right: *Contacts between two morpholine rings in the stacks of* **37** *and between one morpholine ring and an adjacent cyclophane* (shown only as a fragment) *in the stacks of* **37**.

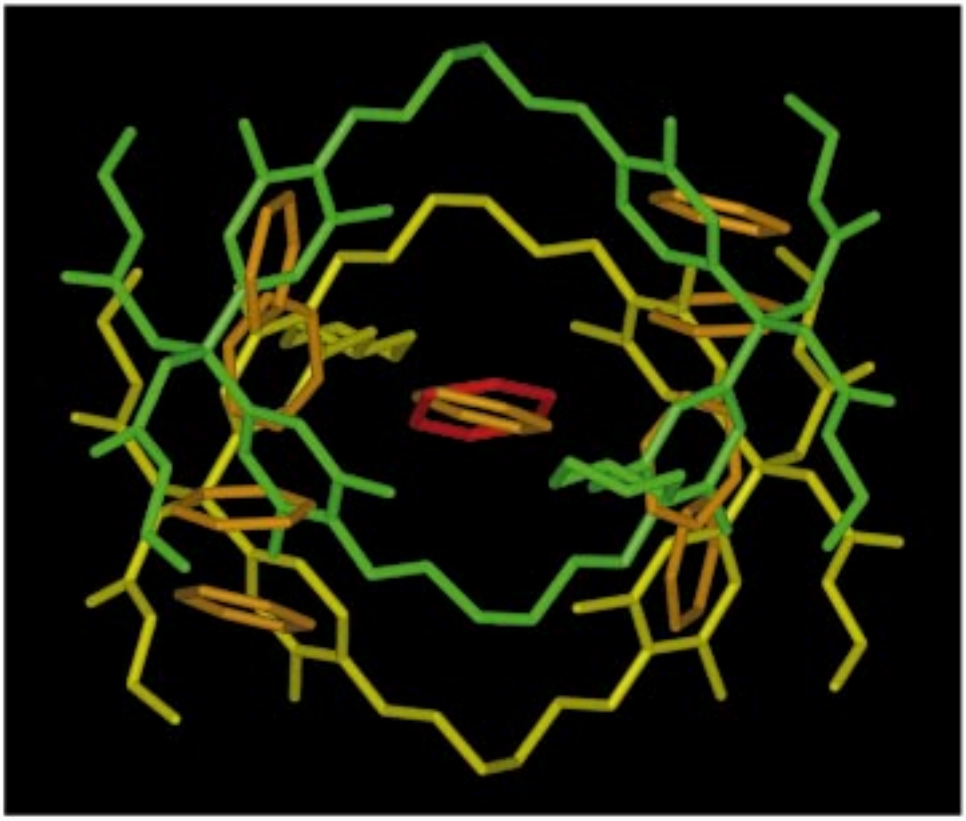
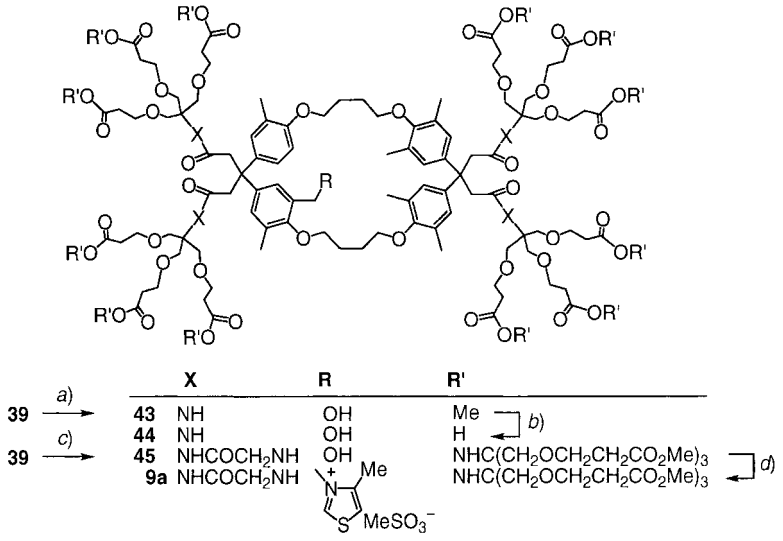


Fig. 3. *Superimposition of parts of the X-ray crystal structure of cyclophane* **37** (two adjacent macrocycles are shown in yellow and green together with enclathrated benzene in red) *and the X-ray crystal structure of orthorhombic benzene* (golden-yellow)

steric hindrance during amide-bond formation, gave *G-2* dendrophane **45** in an improved yield of 48%. The conversion of **45** with $MeSO_2Cl$ and Et_3N in $CDCl_3$ was monitored by ^{1}H-NMR spectroscopy, which indicated disappearance of the CH_2OH resonance at 4.59 ppm and appearance of the CH_2OSO_2Me signal at 5.14 ppm. Spectroscopic analysis, however, also showed that the methanesulfonate is not stable and decomposes slowly in solution over a period of 3 h at room temperature. Therefore, 4-methylthiazole was added after the mesylation reaction had proceeded for 90 min, and both ^{1}H-NMR and mass spectra provided evidence for the formation of target compound **9a**. The catalytic dendrophane, however, could not be completely purified by gel-permeation chromatography (GPC) or other procedures, and a monodisperse pure sample was not obtained by this route.

As expected, the coupling of (bromomethyl)-cyclophane **40** or (thiazoliomethyl)-cyclophane **41** with *G-2* dendron **11** did not lead to isolable amounts of the corresponding dendrophanes, presumably due to the instability of these functionalized macrocycles under the reaction and workup conditions. However, the coupling of (chloromethyl)-cyclophane **42** with **11** in the presence of the coupling reagent *O*-

Scheme 6. *Synthetic Approaches to Functionalized Dendrophanes*



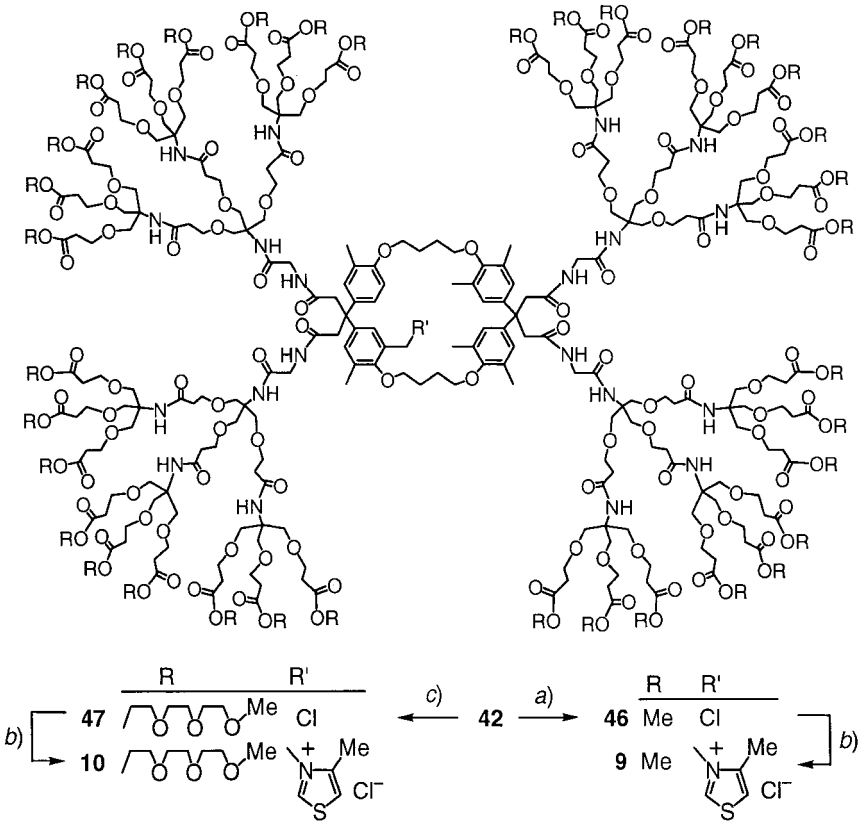
a) **17**, BtOH, DCC, THF, r.t. → 55°; 37%. *b*) 1N NaOH, MeOH, r.t.; 94%. *c*) **11**, BtOH, DCC, THF, 0° → r.t.; 48%. *d*) $MeSO_2Cl$, Et_3N, $CDCl_3$, r.t., then 4-methylthiazole, r.t.

(benzo-1*H*-triazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU) [27] and Et_3N afforded *G-2* (chloromethyl)-dendrophane **46** in 48% yield (*Scheme 7*). Conversion of **46** with 4-methylthiazole subsequently gave the monodisperse (thiazoliomethyl)-cyclophane **9** in 85% yield.

The coupling of *G-2* dendron **12**, containing triethyleneglycol monomethyl ether (TME) surface groups, with cyclophane **42** proved to be difficult. Apparently, the larger dendron (as compared to **11**), with a molecular mass >2600 Da, causes severe steric congestion in the transition state of the peptide-coupling reaction. Furthermore, the TME surface groups seem to favor the aggregation of the resulting dendrophanes, which decreases the efficiency of GPC purification. With a large excess of dendritic wedge (4 equiv. per anhydride function) and a more powerful coupling reagent (*O*-(7-aza-1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU)), the aza analog of HBTU [28], it was possible to isolate the water-soluble (chloromethyl)-dendrophane **47** in 56% yield (*Scheme 7*). Subsequent reaction with 4-methylthiazole afforded the target compound **10** in 50% yield, the moderate yield being largely due to the difficult GPC purification.

The ^1H- and ^{13}C-NMR as well as the MALDI-TOF mass spectra are in full agreement with the structures proposed for **9** and **10**. The MALDI-TOF-MS of **9** displays the base peak at *m*/*z* 6778.6 which corresponds to the most intense isotope of the calculated molecular-ion cluster $[M - Cl]^+$ (calculated for $^{13}C_4{}^{12}C_{301}H_{482}N_{21}O_{144}S^+$: 6779). A second intense signal at *m*/*z* 6799.5 corresponds to the Na^+ complex $[M - HCl + Na]^+$. Similarly, the spectrum of **10** features a peak from the molecular ion cluster $[M - Cl]^+$ as the base peak at *m*/*z* 11533 (calculated for $^{13}C_5{}^{12}C_{516}H_{914}N_{21}O_{252}S^+$: 11536) (*Fig. 4*). The almost complete absence of ions at lower masses provides proof

Scheme 7. *Synthesis of the Catalytic Dendrophanes* **9** *and* **10**



a) **11**, THF, r.t., then HBTU, Et_3N, 0° → r.t.; 48%. *b*) 4-methylthiazole, 50°; 85% (**9**), 50% (**10**). *c*) **12**, HATU, Et_3N, THF, 0° → r.t.; 56%.

for the monodispersity of the dendrophane, as well as for its stability under the mass spectrometric conditions.

The ^{1}H-NMR spectra (500 MHz, $CDCl_3$) of **9** and **10** feature the characteristic resonances of the thiazoliomethyl moiety; in the spectrum of **10**, they appear at 9.71 (H−C(2)), 7.81 (H−C(5)), and 5.41 (CH_2) ppm. The two C_s-symmetrical thiazoliodendrophanes contain two nonequivalent sets of dendrons, and, therefore, two sets of dendron resonances were expected to be present in the ^{13}C-NMR spectra. Two sets of signals are indeed observed in the spectra of **9** and **10** for some of the dendron C-atoms, in particular for C=O groups. Thus, the ^{13}C-NMR spectrum (125 MHz, $CDCl_3$) of **9** (*Fig. 5*) features a splitting of the resonances assigned to the quaternary C-atoms C(6,6′) and C(11,11′), and to three C=O groups, while all other dendron resonances are not duplicated. The C=O region clearly displays two signals for C(12,12′) and C(14,14′), respectively. Interestingly, only one resonance appears for C(7,7′) whereas, for C(2,2′) at the periphery of the dendrophane, two signals are recorded. This observation could be taken as evidence for a possible back-folding of the surface groups

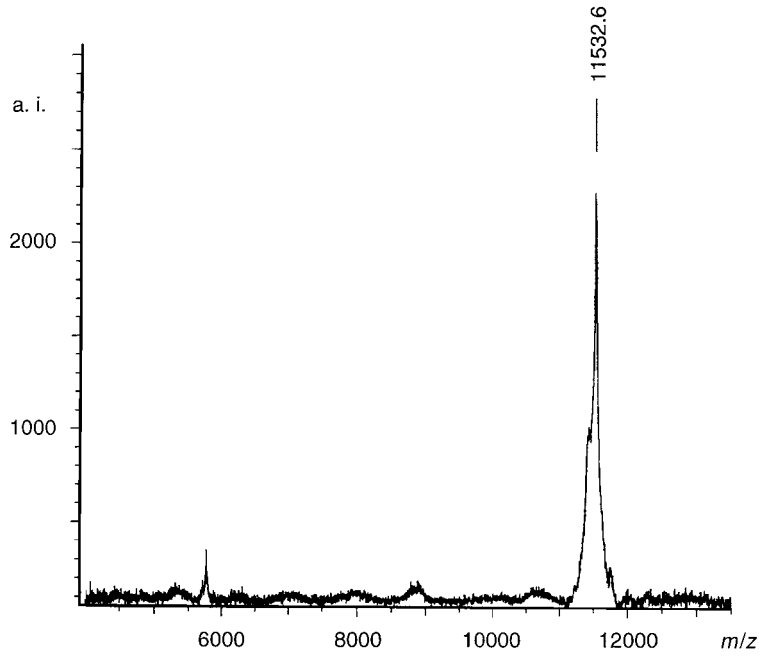


Fig. 4. *MALDI-TOF-MS* (matrix: 2,4,6-trihydroxyacetophenone, THA) *of the thiazolio-dendrophane* **10**

into the interior of the dendrophane [29]. Although weak, most of the cyclophane core signals are observed. Thus, the aliphatic region of the spectrum features five Aryl-*Me* resonances and eight signals for the two $-O(CH_2)_4O-$ bridges in the cyclophane besides the CH_2 resonance of the thiazoliomethyl residue (at 65.74 ppm). Moreover, 22 out of 27 expected resonances of aromatic C-atoms are visible between 110 and 160 ppm.

2.6. *Binding Properties of the Thiazolio-dendrophanes: Reduced Micropolarity at the Active Site.* Computer models of **9** and **10** suggested that the dendritic branches would provide substantial coverage of the cyclophane binding sites at the dendrophane cores [30]. In previous complexation studies with structurally related dendrophanes [7], we had observed that the dendritic shell around the cyclophane core did not significantly affect the substrate affinity to the recognition site. This was confirmed in the binding studies with **9** and **10**. The complexation properties of dendrophanes **9** and **10** were first investigated by 300-MHz or 500-MHz ^{1}H-NMR titrations at 300 K in D_2O/CD_3OD mixtures (*Table 1*). Titrations with naphthalene-2-carbaldehyde (**4**) or sodium 6-(*p*-toluidino)naphthalene-2-sulfonate (TNS; **48**) as guest molecules at constant host concentration were evaluated by nonlinear least-squares curve fitting [31].

The *singlet* of the CH_2 group of the thiazoliomethyl moiety was the only signal in the complex ^{1}H-NMR spectra which was not masked by signal overlap and could be observed throughout the entire titrations. At saturation binding, this resonance shows complexation-induced upfield shifts of up to 0.40 ppm (*Table 1*). Both **9** and **10** form 1:1 complexes with the two guests, and it can be assumed [7] that the guests are

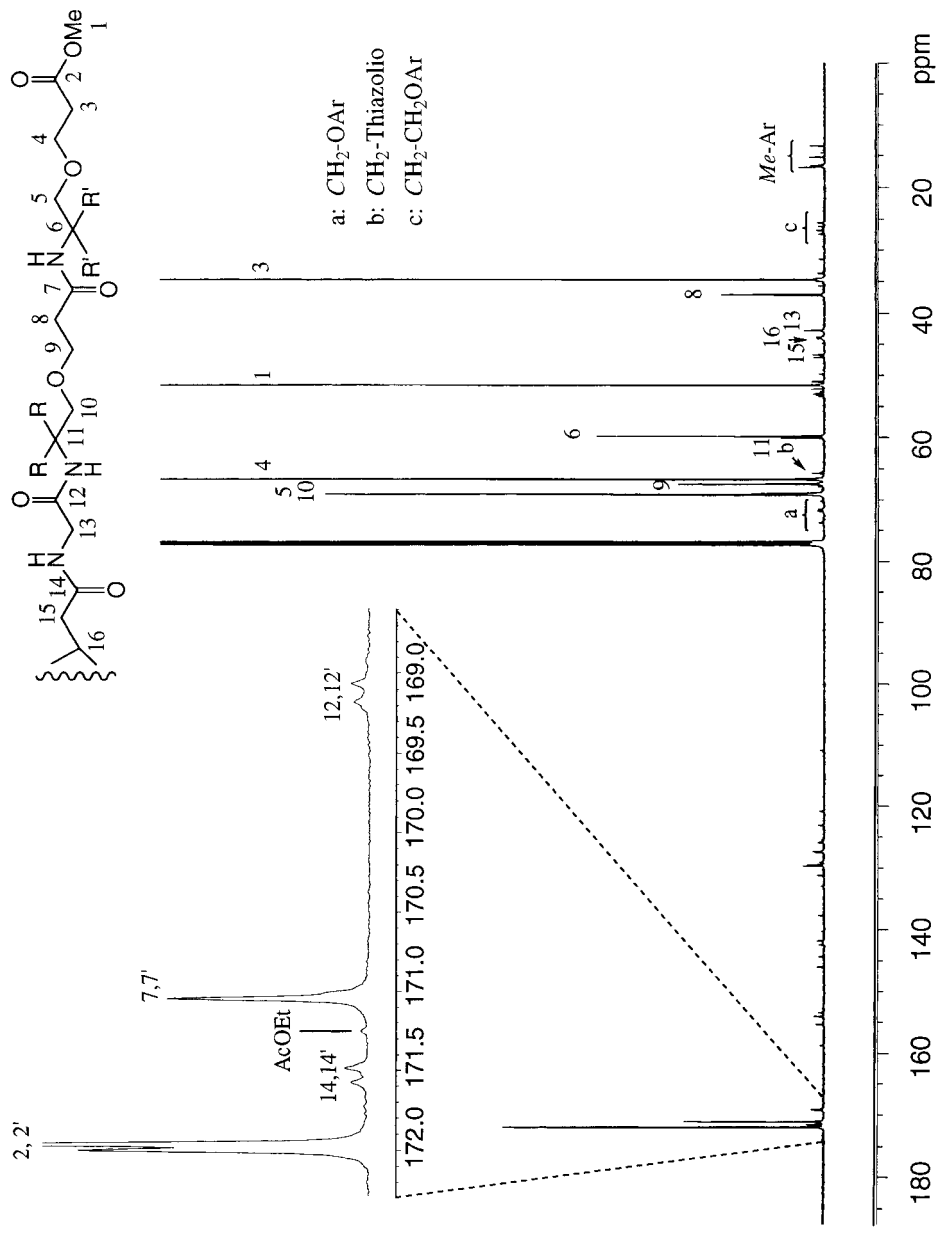


Fig. 5. *^{13}C-NMR Spectrum* (125 MHz, $CDCl_3$) *of the thiazolio-dendrophane* **9**

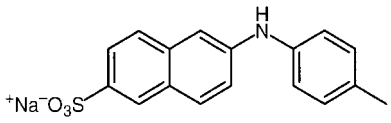


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Table 1. *Association Constants* (K_a) *and Complexation Free Enthalpies* (ΔG^0) *from* ^{1}*H-NMR Titrations at Constant Host Concentration for 1:1 Complexes of Dendrophanes* **9** *and* **10**, *and Cyclophane* **1** *with Guests* **4** *and* **48** *in* D_2O/CD_3OD *Mixtures* ($T = 300$ K). The complexation-induced changes in chemical shift calculated for saturation binding ($\Delta\delta_{sat}$) and the measured maximum upfield shifts ($\Delta\delta_{max}$) of the CH_2 resonance of the thiazoliomethyl moiety, which was monitored during the titration, are also given.

Host[a])	Guest[b])	Solvent D_2O/CD_3OD	K_a[c]) [l mol^{-1}]	ΔG^0 [kcal mol^{-1}]	$\Delta\delta_{sat}$ ($\Delta\delta_{max}$) [ppm]
9	**4**	2:3	300	−3.4	−0.04 (0.03)
1	**4**	2:3	380	−3.5	−0.17 (0.11)
9	**48**	2:3	600	−3.8	−0.37 (0.30)
10	**48**	1:1	900	−4.1	−0.36 (0.30)

[a]) Host concentration: 0.5–1.0 mM. [b]) Guest concentration: 0.2–8.0 mM. [c]) Uncertainty in K_a: ±15%.

incorporated into the well-defined cyclophane binding site at the dendritic cores, with apolar interactions and hydrophobic desolvation providing the major driving forces for association. The affinity of **9** for naphthalene-2-carbaldehyde (**4**) is similar to that measured for the corresponding complex of thiazolio-cyclophane **1**, which contains a similar binding site. This comparison indicates that the affinity of the cyclophane recognition site at the core is not altered by the surrounding dendritic branches.

The complexation of the fluorescent probe TNS (**48**) [7][32] was also investigated by fluorescence titrations ($T = 303$ K) with varying host concentration (*Table 2*). The complexation-induced change in the emission of **48** was monitored over a wavelength range between $\lambda_{em} = 420$ and 450 nm ($\lambda_{exc} = 360$ nm), and subsequently analyzed by the multi-wavelength nonlinear least-squares curve-fitting procedure implemented in the program 'SPECFIT' [33]. The complexation free enthalpies for the 1:1 complex between **48** and dendrophane **10** in H_2O/MeOH 1:1, which were determined by both ^{1}H-NMR ($\Delta G^0 = -4.1$ kcal mol^{-1}; *Table 1*) and fluorescence ($\Delta G^0 = -4.4$ kcal mol^{-1}; *Table 2*) titrations, were found to be in good agreement. A particularly strong complexation between receptor **10** and TNS was expected and observed in pure H_2O ($\Delta G^0 = -6.3$ kcal mol^{-1}; *Table 2*) where the driving forces for apolar association are the strongest [34].

The emission maximum and intensity of the fluorescent probe TNS (**48**) are strongly dependent on the polarity of the environment. Thus, the emission maximum shifts from *ca.* 500 nm in H_2O, to 443 nm in MeOH, and 429 nm in EtOH [32]. Again, the investigations with **9** and **10** confirm earlier findings with dendrophanes [7] that the dendritic branching has a profound effect on the polarity of the cyclophane binding site at the core. The dendritic shell prevents the exposure of this site to bulk solvent and creates a microenvironment of distinctly reduced polarity. Thus, the maximum of the intense emission of TNS (**48**) in the complex with **10** in H_2O appears at 429 nm, which suggests that the micropolarity at the cyclophane core corresponds to that of bulk

Table 2. *Association Constants* (K_a) *and Complexation Free Enthalpies* (ΔG^0) *from Fluorescence Titrations for 1:1 Complexes of Dendrophanes* **9** *or* **10** *with TNS* (**48**) *in* H_2O*/MeOH 1:1 and in Pure* H_2O ($T = 303$ K). Also given are the emission maxima (λ_{max}) of **48** in the various complexes.

Host	Solvent H_2O/MeOH	K_a [a]) [l mol^{-1}]	ΔG^0 [kcal mol^{-1}]	λ_{max} [nm]
10	1:1	1500	−4.4	424
9	1:1	2000	−4.5	436
10	1:0	37000	−6.3	429

[a]) Uncertainty in K_a: ±15%. Initial guest concentration [**48**] = $1 \cdot 10^{-5}$ M.

EtOH (*Table 2*). A comparison between the two dendrophanes **9** and **10** could only be executed in H_2O/MeOH 1:1 due to the insolubility of **9** in pure H_2O. The emission data of TNS (**48**) bound to the two receptors in the mixed solvent clearly show that the TME-functionalized branches in dendrophane **10** (λ_{max}(**48**) = 424 nm) are much more effective in reducing the polarity at the dendritic core than are the methyl-ester branches in **9** (λ_{max}(**48**) = 436 nm). This could be attributed to the larger dimensions of the TME-functionalized dendritic shell, which should provide a better and, possibly, more densely packed coverage of the cyclophane site.

2.7. *Catalytic Activity of the Thiazolio-dendrophanes* **9** *and* **10**. For the determination of the initial rate of the oxidation of naphthalene-2-carbaldehyde (**4**) to methyl naphthalene-2-carboxylate (**8**) catalyzed by the dendrophanes **9** and **10**, a degassed solution of substrate and flavin derivative **6** (*Scheme 1*) in MeOH containing Et_3N or 0.05M phosphate buffer (pH 7.5) was treated with a solution of the dendrophane in MeOH. The course of the reaction was followed by monitoring the decrease in absorbance of the visible flavin chromophore **6** ($\lambda = 448$ nm, $\varepsilon = 10000$ l mol^{-1} cm^{-1}) upon reduction to the colorless dihydroflavin derivative (end absorbance $A_{448} \approx 0$) as a function of the reaction time. Since the reaction of the formed 2-acylthiazolium ion (*Scheme 1*) with MeOH is very fast under basic conditions [35], the rate of disappearance of the oxidized form of the flavin derivative can be equated to the rate of formation of methyl naphthalene-2-carboxylate (**8**). The initial rates of the reaction were obtained by a least-squares linear-regression analysis of the linear part of the absorption *vs.* time curve. To evaluate the effects of the dendritic shell, the catalytic performance of **9** and **10** in the oxidation of **4** was compared under identical conditions to that of thiazolio-cyclophane **1** [13], a suitable model system for the active cyclophane core in the dendrophanes (*Table 3*). In all experiments, a large excess of substrate **4** was used. Therefore, the initial reaction rate v can be compared in a first approximation with the maximum initial rate v_{max} under substrate-saturation conditions, leading to v/[thiazolio catalyst] $\approx v_{max}$/[thiazolio catalyst] = k_{cat}. Saturation kinetics had previously been demonstrated for the oxidation of **4** catalyzed by thiazolio-cyclophane **1**.

The highest initial rate v/[catalyst] was measured with thiazolio-cyclophane **1** in MeOH containing Et_3N (*Table 3*). Under these conditions, dendrophanes **9** and **10** failed to show measurable catalytic activity. In MeOH/0.05M phosphate buffer (pH 7.5) 4:1, the activity of **1** decreased by a factor of three. In this solvent, the thiazolio-dendrophanes displayed weak catalytic activity. The initial rates in the presence of dendrophanes were 160 (**9**) and 50 times (**10**) lower than in the reaction catalyzed by **1**.

Table 3. *Initial Rates v/[Catalyst]* [s^{-1}] *of the Oxidation of Naphthalene-2-carbaldehyde* (**4**) *Catalyzed by the Thiazolio Derivatives* ***1***, **9**, *and* **10** (*c* between 0.5 and 1.0 mM) *in the Presence of Flavin Derivative* **6** (*c* = 0.25 mM) *at 303 K*

Solvent	Catalyst **1**[a)]	Catalyst **9**[b)]	Catalyst **10**[b)]
MeOH[c)]	$1.0 \cdot 10^{-2}$	–	–
MeOH/H_2O[d)] 4:1	$3.2 \cdot 10^{-3}$	$2.0 \cdot 10^{-5}$	$6.1 \cdot 10^{-5}$
MeOH/H_2O[d)] 3:2	$4.6 \cdot 10^{-4}$	–	$\sim 1.1 \cdot 10^{-5}$

[a)] [**4**] = 10 mM. [b)] [**4**] = 30 mM. [c)] Contains 0.05M Et_3N. [d)] 0.05M Aqueous phosphate buffer (pH 7.5).

In MeOH/0.05M phosphate buffer (pH 7.5) 3:2, the values for the initial rates dropped by an additional factor of 7 in the presence of **1** and by a factor of 5 in the presence of **10**. In this solvent, dendrophane **9** did not exhibit any measurable catalytic activity.

Why do dendrophanes **9** and **10** feature such low catalytic activity despite offering an active site with good binding activity and a favorable micropolarity? In the reaction of **1**, formation of the active aldehyde **5** is rate-determining and formation of methyl naphthalene-2-carboxylate is zero-order with respect to the oxidizing agent [13]. In the reactions catalyzed by the thiazolio-dendrophanes **9** and **10**, the decrease in flavin absorption as a function of reaction time could be fitted equally well to zero- and first-order rate laws. An unambiguous determination of the reaction order with respect to the oxidizing agent was not possible since the low initial rates in the presence of **9** and **10** were close to the detection limit of the method applied, and the period of linear decay in flavin absorption was quite short. We, therefore, propose that one of the reasons for the low catalytic activity of **9** and **10** may be that the intermolecular electron transfer from the active aldehyde intermediate to the flavin derivative became rate-determining due to the presence of the sterically shielding dendritic branches[2]). It also cannot be excluded that steric hindrance by the dendritic branches of **9** and **10** may unfavorably affect other transition states in the multistep catalytic cycle (*Scheme 1*) and, thereby, mask any favorable contributions from the reduced micropolarity inside the dendrophanes. Thus, this investigation seems to add yet another example to the list of reactions which display lower rates when catalyzed in the interior of dendrimers as a result of the steric hindrance by the dendritic branching [2c,d][3][9].

3. Conclusions. – The convergent synthesis of monodisperse dendrophanes with interior functionalized binding sites was achieved by coupling *G-2* poly(ether-amide) dendrons to cyclophane initiator cores. The versatility of the synthetic strategy was demonstrated with the preparation of (hydroxymethyl)- (**43**–**45**, *Scheme 6*), (chloromethyl)- (**46** and **47**, *Scheme 7*), and (thiazoliomethyl)-dendrophanes (**9** and **10**, *Scheme 7*). The characterization by ^{1}H- and ^{13}C-NMR spectroscopy, and MALDI-TOF-MS proved the monodispersity of these *G-2* dendrophanes with molecular weights up to 11500 Da.

[2]) Even with thiazolio-cyclophanes, the oxidation step can become rate-limiting under certain conditions [13][14]. Therefore, bis-coenzyme-cyclophane **2**, with the flavin derivative in close proximity to the active aldehyde intermediate, is a better catalyst than **1** in the presence of added flavin derivative.

The thiazolio-dendrophanes **9** and **10** were investigated as mimics for the ThDP-dependent enzyme pyruvate oxidase. ^{1}H-NMR and fluorescence binding titrations in H_2O and H_2O/MeOH showed that the receptors form stable 1:1 complexes with naphthalene-2-carbaldehyde (**4**) and TNS (**48**). The association strength is not affected by the dendritic branches which, on the other hand, create a microenvironment of distinctly reduced polarity at the cyclophane core by preventing the access of bulk solvent. Such reduced micropolarity was expected to enhance the thiazolium-ion- and flavin-mediated multistep catalytic oxidation of **4** which involves transition states that are less polar than the corresponding ground-state substrates and intermediates. Initial rate studies, however, revealed that the dendrophanes **9** and **10** are inferior to thiazolio-cyclophane **1** as catalysts for the oxidation reaction, presumably because of the unfavorable steric hindrance of the dendritic shells in the reaction transition states. In particular, the intermolecular electron transfer from the active aldehyde intermediate **5** to flavin **6** under formation of acylthiazolium intermediate **7** (*Scheme 1*) might be strongly affected by the dendritic branches, which could prevent the two reacting partners from approaching each other closely. Thus, this study suggests that the interior of densely packed dendrimers might not be a good environment for catalysis, due to steric interference of the dendritic branches. Other investigations have led to similar conclusions [3][9]. Although at first view, **9** and **10** mimic enzymes to a large extent by featuring a functionalized binding site and a dendritic shell to create a particular micropolarity at this site, the models suffer from the lack of secondary structure within the dendritic branches. The protein shell around an enzyme-active site not only ensures a correct positioning of the catalytic residues at that site and modulates its polarity, but also keeps the site open and free of steric hindrance for the reaction of the correct substrate. This is achieved through peptide backbone H-bonding under formation of β-pleated sheet, helix, and loop motifs [36]. Thus, one of the future challenges in the design of dendrimers and dendrophanes with interior catalytic sites is the implementation of defined secondary-structural motifs within the branches. Such secondary structure would also enhance the crystallinity of the usually oily macromolecules and enable their (highly desirable) structural characterization by X-ray crystallography.

Finally in this work, X-ray crystallographic studies on various cyclophanes (**30**, **37**, and **38**) provided another nice example [26] for the preference of an enclathrated benzene guest molecule to interact with the phenyl rings of surrounding host molecules in a way similar to the interactions seen between neighboring benzene rings in crystalline benzene.

Experimental Part

General. All reactions were carried out under Ar. Solvents and reagents were reagent-grade commercials and were used without further purification. Compounds **1** [13], **6** [37], **22** [21], and **23** [22] were prepared according to published procedures. THF and Et_2O were freshly distilled from sodium benzophenone ketyl; CH_2Cl_2 from CaH_2 under N_2. MeCN was stored over molecular sieves (3 Å). 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: glass sheets covered with SiO_2 *60* F_{254} from *Merck*, visualization by UV light. Prep. GPC: Biobeads (*Biorad SX-1*) in MePh without applying pressure. The collected fractions were analyzed by anal. GPC: *Merck* system with *Hitachi* refractive-index detector *L-7490*, UV detector *L-7400*, column oven *L-7360*, and pump *L-7100* on two TSKgel columns (*G 2500 HR*, 7.8 mm i.d. × 30 cm) with THF (HPLC standard) as eluent and a flow rate of 1 ml min^{-1}. Isolated products were dried for 24 h at 0.05 Torr prior to

spectral and anal. characterization. M.p.: *Büchi Smp-20* apparatus; uncorrected. UV/VIS (λ_{max} [nm] (ε [l mol^{-1} cm^{-1}])): *Varian Cary 5*. Fluorescence (λ_{max} [nm]): *Spex 212 Fluorolog*. 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* (%)). ES: *VG-TRIBRID* instrument (70 eV); FAB: *VG ZAB2-SEQ* spectrometer with 3-nitrobenzyl alcohol (NOBA) as matrix; MALDI-TOF: *Bruker-REFLEX* spectrometer with 2,5-dihydroxybenzoic acid (DHB), α-cyano-4-hydroxycinnamic acid (CCA), 3-(indol-3-yl)acrylic acid (IAA), diammonium citrate (citrate), 2-(4-hydroxyphenylazo)benzoic acid (HABA), 2,4,6-trihydroxyacetophenone (THA), and anthracene-1,8,9-triol (dithranol) as matrices. Elemental analyses were performed by the Mikrolabor at the Laboratorium für Organische Chemie, ETH-Zürich.

^{1}H-NMR Binding Titrations. They were carried out on a *Bruker 500* or a *Varian 300* NMR spectrometer thermostated to 300(1) K. For the titration, aliquots of a stock soln. (containing the host (c = 0.5–1.0 mM) and guest (c = 8.0–13.0 mM)) were added to a soln. of constant host concentration (c = 0.5–1.0 mM, 0.6 ml) in the NMR tube using a *Gilson Pipetman* (100, 200 or 1000 µl). Quant. binding data (K_a, ΔG^0, $\Delta\delta_{sat}$) were obtained by nonlinear least-squares curve-fitting of the experimental titration data [31].

Fluorescence Binding Titrations. Quant. binding data (K_a, ΔG^0) were determined by a global nonlinear least-squares curve-fitting [33][38] of the fluorescence emission data in the range between λ = 420 to 450 nm (λ_{exc} = 360 nm). The initial guest concentration was $1 \cdot 10^{-5}$ M, and the concentration of the host varied between $2.25 \cdot 10^{-6}$ and $1.5 \cdot 10^{-4}$ M by adding a stock soln. of host ($4.5 \cdot 10^{-4}$ M) in portions *via* microsyringe to the septum-capped fluorescence cuvette. After each addition, a fluorescence emission spectrum was recorded.

Kinetic Studies. Initial rates were determined in a UV cuvette (length: 0.40 cm) thermostated at 303(1) K. The solvents for the preparation of the stock solns. (H_2O and MeOH) were degassed by 3 freeze-pump-thaw cycles. The solns. of **4** and **6** in MeOH/0.05M phosphate buffer (pH 7.5) or MeOH/Et_3N (50 mM) were purged with Ar and further degassed in an ultrasound bath before the cuvette was placed into the UV/VIS spectrometer. A soln. of the thiazolium catalyst in MeOH was added, the resulting mixture ([**6**] = 0.25 mM; [thiazolium catalyst] = 0.5–1.0 mM; [**4**] = 10–50 mM) was shaken, and the decrease in flavin absorption at λ = 448 nm was monitored as a function of the reaction time. Initial rates were calculated by a standard regression analysis of the linear part of the absorption *vs.* time curve. They were reproduced at least 3 times.

Benzyl N-*Tris{[(2-([2-[2-(2-methoxyethoxy)ethoxy]ethoxy}carbonyl)ethoxy]methyl}methyl)carbamate* (**14**). A soln. of **13** [19] (2.00 g, 4.25 mmol) in CH_2Cl_2 (10 ml) and $SOCl_2$ (3 ml, 41.35 mmol) was stirred for 120 min at r.t. After evaporation to dryness, the residue was dried for 60 min at r.t./0.05 Torr, then dissolved in a soln. of triethyleneglycol monomethyl ether (6.97 g, 42.50 mmol) in CH_2Cl_2 (20 ml). After stirring for 150 min at r.t., CH_2Cl_2 (100 ml) was added, and the mixture was washed with sat. aq. $NaHCO_3$ soln. and H_2O. The org. layer was dried ($MgSO_4$), and the solvent was evaporated. The resulting residue was purified by GPC to give **14** (2.90 g, 76%). Yellow oil. IR (neat): 1731 (C=O). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.36–7.30 (*m*, 5 H); 5.27 (*s*, 1 H); 5.03 (*s*, 2 H); 4.22 (*t*, *J* = 4.8, 6 H); 3.70–3.61 (*m*, 36 H); 3.53 (*t*, *J* = 5.2, 6 H); 3.37 (*s*, 9 H); 2.56 (*t*, *J* = 6.2, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 171.01; 154.66; 136.34; 128.03; 127.55; 124.66; 71.52; 70.15; 68.95; 68.66; 66.31; 65.71; 63.20; 58.60; 58.31; 34.41. FAB-MS: 910 (100, M^+), 866 (50, [M – CO_2]$^+$), 776 (65, [M – $ArCH_2CO_2$]$^+$). Anal. calc. for $C_{42}H_{71}NO_{20}$ (910.03): C 55.43, H 7.86, N 1.54; found: C 55.18, H 7.98, N 1.66.

Tris{[2-([2-[2-(2-methoxyethoxy)ethoxy]ethoxy}carbonyl)ethoxy]methyl}methylamine (**15**). A suspension of **14** (1.75 g, 1.92 mmol) and Pd/C (0.20 g, 10%) in EtOH (10 ml) was stirred under H_2 (1 bar) for 120 min. The resulting mixture was filtered (*Celite*) and purified by CC (SiO_2; AcOEt/MeOH 93:7) to give **15** (1.30 g, 87%). Slightly yellow oil. IR (neat): 1737 (C=O). ^{1}H-NMR (200 MHz, $CDCl_3$): 4.25 (*t*, *J* = 5.0, 6 H); 3.73–3.63 (*m*, 30 H); 3.59–3.55 (*m*, 6 H); 3.39 (*s*, 9 H); 3.31 (*s*, 6 H); 2.60 (*t*, *J* = 6.2, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 171.07; 72.44; 71.52; 70.15; 68.69; 66.31; 63.17; 58.60; 55.49; 34.41. FAB-MS: 776 (100, MH^+). Anal. calc. for $C_{34}H_{65}NO_{18}$ (775.88): C 52.63, H 8.44, N 1.81; found: C 52.34, H 8.37, N 1.90.

tert-*Butyl* N-*({[([Tris{[2-(methoxycarbonyl)ethoxy]methyl}methyl)amino]carbonyl}methyl)carbamate* (**18**). A soln. of Boc-glycine (2.43 g, 13.85 mmol), **17** (3.50 g, 9.24 mmol), BtOH (1.88 g, 13.85 mmol), and EDC (2.66 g, 13.85 mmol) in THF (50 ml) was treated at r.t. with Et_3N (1.40 g, 13.85 mmol). The suspension was stirred for 2 d, filtered, washed with sat. aq. $NaHCO_3$ soln., and dried ($MgSO_4$). CC (SiO_2; CH_2Cl_2/MeOH 97:3) yielded pure **18** (4.30 g, 87%). Colorless oil. IR (neat): 1734, 1678 (C=O). ^{1}H-NMR (200 MHz, $CDCl_3$): 6.34 (*s*, 1 H); 5.29 (*s*, 1 H); 3.78 (*d*, *J* = 5.4, 2 H); 3.74–3.68 (*m*, 21 H); 2.56 (*t*, *J* = 6.3, 6 H); 1.46 (*s*, 9 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 169.75; 167.02; 153.50; 77.13; 66.56; 64.24; 57.26; 49.13; 41.87; 32.12; 25.74. FAB-MS: 537 (100, M^+), 437 (50, [M – CO_2CMe_3]$^+$). Anal. calc. for $C_{23}H_{40}N_2O_{12}$ (536.58): C 51.48, H 7.51, N 5.22; found: C 51.59, H 7.40, N 5.03.

tert-*Butyl* N-*{[({Tris[(2-carboxyethoxy)methyl]methyl}amino)carbonyl]methyl}carbamate* (**16**). To **18** (2.00 g, 3.73 mmol) in MeOH (25 ml), 2N NaOH (20 ml, 40.00 mmol) was added dropwise and the soln. was

stirred for 16 h at r.t. The mixture was washed with CH_2Cl_2 (30 ml), acidified with AcOH, and extracted twice with AcOEt (50 ml). The combined org. layers were dried ($MgSO_4$), filtered, and evaporated to dryness to give **16** (1.55 g, 85%). Colorless oil. IR (neat): 1718, 1658 (C=O). ^{1}H-NMR (200 MHz, CD_3OD): 7.07 (*s*, 1 H); 3.71–3.64 (*m*, 14 H); 2.53 (*t*, *J* = 6.2, 6 H); 1.45 (*s*, 9 H). ^{13}C-NMR (50 MHz, CD_3OD): 178.53; 175.23; 161.48; 83.80; 73.14; 71.20; 64.38; 48.06; 38.75; 31.74. FAB-MS: 495 (11, M^+), 395 (60, $[M - CO_2CMe_3]^+$).

tert-*Butyl* N-*{[({Tris[(2-{[(tris{[2-({2-[2-(2-methoxyethoxy)ethoxy]ethoxy}carbonyl)ethoxy]methyl}methyl)-amino]carbonyl}ethoxy)methyl]methyl}amino)carbonyl]methyl}carbamate* (**19**). DCC (0.80 g, 3.87 mmol) was added to a soln. of **16** (0.43 g. 0.87 mmol), **15** (3.0 g, 3.87 mmol), and BtOH (0.52 g, 3.87 mmol) in THF (15 ml). The suspension was stirred at r.t. for 3 d, filtered, washed with sat. aq. $NaHCO_3$ soln., and dried ($MgSO_4$). The solvent was evaporated *in vacuo*, and the residue was purified by GPC and CC (SiO_2; CH_2Cl_2/MeOH/NEt_3 95 : 4.5 : 0.5) to give **19** (1.40 g, 60%). Colorless oil. IR (neat): 1736, 1670 (C=O). ^{1}H-NMR (200 MHz, $CDCl_3$): 6.76 (*s*, 1 H); 6.13 (*s*, 3 H); 5.57 (*t*, *J* = 5.2, 1 H); 4.21 (*t*, *J* = 4.8, 18 H); 3.73–3.60 (*m*, 122 H); 3.55–3.50 (*m*, 18 H); 3.35 (*s*, 27 H); 2.51 (*t*, *J* = 6.2, 18 H); 2.38 (*t*, *J* = 6.2, 6 H); 1.45 (*s*, 9 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 169.21; 168.74; 167.05; 153.50; 76.81; 69.51; 68.12; 66.72; 66.70; 66.13; 64.28; 61.20; 57.39; 56.56; 41.80; 34.63; 32.28; 25.80. MALDI-TOF-MS (THA/citrate): 2792 (100, $[M + Na]^+$; calc. for $^{13}C_1{}^{12}C_{121}H_{223}N_5O_{63}Na^+$: 2790), 2771 (40, M^+), 2671 (80 $[M - CO_2CMe_3]^+$).

2-Amino-N-*{tris[(2-{[(tris{[2-({2-[2-(2-methoxyethoxy)ethoxy]ethoxy}carbonyl)ethoxy]methyl}methyl)-amino]carbonyl}ethoxy)methyl]methyl}acetamide* (**12**). CF_3COOH (1 ml) was added to a stirred soln. of **19** (0.45 g, 0.162 mmol) in CH_2Cl_2 (5 ml) at r.t. After 60 min, CH_2Cl_2 (100 ml) was added and the resulting soln. was washed with H_2O (3 ×). The org. layer was dried ($MgSO_4$), the solvent evaporated, and the residue purified by CC (SiO_2; CH_2Cl_2/MeOH/NEt_3 94 : 5 : 1) to give **12** (0.37 g, 85%). Colorless oil. IR (neat): 1736, 1674 (C=O). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.59 (*s*, 1 H); 6.22 (*s*, 3 H); 4.24 (*t*, *J* = 4.7, 18 H); 3.84 (*s*, 2 H); 3.72–3.62 (*m*, 120 H); 3.57–3.52 (*m*, 18 H); 3.38 (*s*, 27 H); 2.57 (*t*, *J* = 6.2, 18 H); 2.40 (*t*, *J* = 6.2, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 169.28; 168.99; 163.59; 69.39; 68.02; 67.96; 66.59; 65.10; 64.21; 61.10; 57.36; 56.47; 38.66; 34.37; 32.22. MALDI-TOF-MS (THA/citrate): 2693 (20, $[M + Na]^+$), 2669 (100, MH^+; calc. for $^{13}C_1{}^{12}C_{116}H_{215}N_5O_{61}H^+$: 2668).

5,14,20,29,32,37-Hexamethyl-7,12,22,27-tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta-1(30),3,5,13,13,15,18,20,28,31,33,35,37-dodecaene-2,2,17,17-tetraacetic acid (**20**). A suspension of **22** [21] (1.0 g, 1.07 mmol) in MeOH (25 ml) and 2N NaOH (15 ml, 30 mmol) was stirred for 15 h at 60°. The mixture was washed with AcOEt (50 ml), acidified with conc. aq. HCl soln., and extracted with AcOEt (3 × 75 ml). The combined org. layers were dried ($MgSO_4$) and evaporated to yield **20** (0.9 g, 100%). White powder. M.p. > 250°. IR (KBr): 2948 (O–H), 1711 (C=O). ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 11.82 (*s*, 4 H); 6.83–6.69 (*m*, 10 H); 3.99 (br. *t*, 4 H); 3.75 (br. *t*, 4 H); 3.36 (*s*, 4 H); 3.31 (*s*, 4 H); 2.02 (*s*, 6 H); 1.88 (*s*, 12 H); 1.84 (br. *s*, 8 H). ^{13}C-NMR (50 MHz, CD_3OD): 177.51; 177.38; 158.53; 157.60; 145.38; 142.31; 142.02; 133.10; 132.85; 131.10; 128.81; 128.56; 113.45; 75.20; 70.56; 48.47; 48.12; 44.97; 30.12; 28.37; 18.97; 18.88. FAB-MS: 825 (100, MH^+). Anal. calc. for $C_{48}H_{56}O_{12}$ · MeOH (857.02): C 68.67, H 7.06; found: C 68.74, H 7.05.

*Diethyl 3,3-Bis{4-[(*tert-*butyl)dimethylsilyloxy]-3,5-dimethylphenyl}pentanedioate* (**24**). (*t*-Bu)Me_2SiCl (5.13 g, 34.98 mmol) was slowly added to a soln. of **23** [22] (6.08 g, 14.21 mmol) and imidazole (4.80 g, 70.59 mmol) in DMF (60 ml) at r.t. After 5 h, a white precipitate formed, which was redissolved by heating to 40–50° for 10 h. Sat. aq. NaCl soln. (200 ml) was added, and the mixture was extracted with hexane (2 ×) and hexane/CH_2Cl_2 3 : 1. The combined org. layers were washed with sat. aq. NaCl soln., dried ($MgSO_4$), and filtered. Evaporation and recrystallization (MeOH) afforded **24** (8.16 g, 88%). White crystals. M.p. 113–115°. IR (KBr): 1733 (C=O). ^{1}H-NMR (200 MHz, $CDCl_3$): 6.70 (*s*, 4 H); 3.84 (*q*, *J* = 7.3, 4 H); 3.43 (*s*, 4 H); 2.13 (*s*, 12 H); 1.00 (*s*, 18 H); 0.96 (*t*, *J* = 7.2, 6 H); 0.16 (*s*, 12 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 171.57; 149.94; 138.80; 127.50; 127.16; 59.43; 45.42; 42.18; 25.82; 18.48; 17.75; 13.73; –3.27. EI-MS: 656 (15, M^+), 569 (100, $[M - CH_2CO_2Et]^+$). Anal. calc. for $C_{37}H_{60}O_6Si_2$ (657.05): C 67.64, H 9.20; found: C 67.85, H 9.29.

*3,3-Bis{4-[(*tert-*butyl)dimethylsilyloxy]-3,5-dimethylphenyl}pentane-1,5-diol* (**25**). A soln. of $LiAlH_4$ (1N) in Et_2O (26.30 ml, 26.30 mmol) was added at –5° under vigorous stirring to **24** (15.70 g, 23.93 mmol) in Et_2O (100 ml). The yellow mixture was stirred for 2 h at –5°, 1 h at r.t., and 2 h at reflux. The reaction was quenched at 0° by first adding MeOH and subsequently sat. aq. K^+/Na^+-tartrate soln. The resulting precipitate was filtered and carefully washed with CH_2Cl_2. The filtrate was dried ($MgSO_4$) and evaporated to provide **25** (11.70 g, 86%). White crystals. An anal. sample was obtained by recrystallization from benzene/pentane. M.p. 134–138°. IR (KBr): 3300 (OH). ^{1}H-NMR (200 MHz, $CDCl_3$): 6.75 (*s*, 4 H); 3.45 (*t*, *J* = 6.7, 4 H); 2.34 (*t*, *J* = 6.7, 4 H); 2.14 (*s*, 12 H); 1.02 (*s*, 18 H); 0.16 (*s*, 12 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 149.73; 140.27; 127.55; 127.49; 59.58; 45.62; 40.44; 25.86; 18.50; 17.84; –3.22. EI-MS: 572 (5, M^+), 554 (5, $[M - H_2O]^+$), 527 (5, $[M - C_2H_4OH]^+$); 73 (100). Anal. calc. for $C_{33}H_{56}O_4Si_2$ (572.97): C 69.18, H 9.85; found: C 69.23, H 9.97.

*3,3-Bis[4-[(*tert*-butyl)dimethylsilyloxy]-3,5-dimethylphenyl]pentane-1,5-diyl Bis(methanesulfonate)* (**26**). $MeSO_2Cl$ (1.70 ml, 21.89 mmol) was slowly added to a soln. of **25** (3.14 g, 5.49 mmol) and Et_3N (6.20 ml, 45.20 mmol) in CH_2Cl_2 (20 ml) at $-5°$. The yellow suspension was stirred for 3 h at $-5°$, then poured on ice and diluted with CH_2Cl_2 (100 ml). The org. layer was separated, washed with sat. aq. NH_4Cl soln., sat. aq. $NaHCO_3$ soln., and sat. aq. NaCl soln. Drying ($MgSO_4$) and plug filtration (SiO_2; CH_2Cl_2/AcOEt 95:5) yielded **26** (3.78 g, 95%) as a yellow oil which slowly crystallized. White crystals. M.p. 91–93°. ^{1}H-NMR (200 MHz, $CDCl_3$): 6.73 (*s*, 4 H); 4.00 (*t*, *J* = 7.0, 4 H); 2.94 (*s*, 6 H); 2.53 (*t*, *J* = 7.0, 4 H); 2.17 (*s*, 12 H); 1.03 (*s*, 18 H); 0.19 (*s*, 12 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 150.99; 138.80; 128.64; 127.85; 67.92; 45.75; 37.61; 37.44; 26.34; 18.98; 18.33; −2.70. EI-MS: 728 (4, M^+), 605 (24, $[M - C_2H_4OSO_2Me]^+$), 509 (35, $[M - C_2H_4OSO_2Me - HOSO_2Me]^+$); 73 (100). Anal. calc. for $C_{35}H_{60}O_8S_2Si_2$ (729.16): C 57.65, H 8.29, S 8.80; found: C 57.85, H 8.33, S 8.64.

4,4-Bis(4-hydroxy-3,5-dimethylphenyl)heptanedinitrile (**27**). A mixture of **26** (5.38 g, 7.39 mmol), KCN (4.80 g, 73.85 mmol), and KI (0.60 g, 3.61 mmol) in Me_2SO (100 ml) was stirred for 5 h at 100°. The brown soln. was poured on ice, and the mixture was extracted with benzene/Et_2O 1:1 and Et_2O. The combined org. layers were washed with sat. aq. NaCl soln., 1N HCl, sat. aq. $NaHCO_3$ soln., 1N HCl, and sat. aq. NaCl soln., dried ($MgSO_4$), and evaporated *in vacuo*. Recrystallization from benzene/pentane yielded pure **27** (1.32 g, 50%). The residue obtained by evaporation of the mother liquor was purified by CC (SiO_2; CH_2Cl_2) to give additional **27** (0.61 g; total yield 73%). Pale-yellow crystals. M.p. 205°. IR (KBr): 2251 (CN). ^{1}H-NMR (200 MHz, $CDCl_3$): 6.67 (*s*, 4 H); 2.35 (*t*, *J* = 7.2, 4 H); 2.20 (*s*, 12 H); 1.97 (*t*, *J* = 7.2, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 151.41; 136.00; 127.95; 123.44; 120.08; 47.84; 34.35; 16.39; 13.08. EI-MS: 362 (12, M^+), 308 (100, $[M - 2\,HCN]^+$). Anal. calc. for $C_{23}H_{26}N_2O_2 \cdot 0.5\,Et_2O$ (399.54): C 75.16, H 7.82, N 7.01; found: C 75.49, H 7.70, N 6.80.

Diethyl 4,4-Bis(4-hydroxy-3,5-dimethylphenyl)heptanedioate (**28**). H_2SO_4 (4.50 ml, 84.00 mmol) was added dropwise to a soln. of **27** (2.15 g, 5.94 mmol) in EtOH (50 ml). The mixture was heated for 75 h under reflux and subsequently poured on ice. The resulting suspension was extracted with Et_2O (100 ml), the org. layer was washed with H_2O and 10% aq. $NaHCO_3$ soln., dried ($MgSO_4$), and evaporated. CC (SiO_2; CH_2Cl_2/AcOEt 98:2) gave **28** (2.20 g, 82%). White crystals. M.p. 136–138°. IR (neat): 1715 (C=O). ^{1}H-NMR (200 MHz, $CDCl_3$): 6.75 (*s*, 4 H); 4.06 (*q*, *J* = 7.2, 4 H); 2.28 (*t*, *J* = 9.7, 4 H); 2.16 (*s*, 12 H); 1.97 (*t*, *J* = 9.7, 4 H); 1.21 (*t*, *J* = 7.2, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 173.82; 149.90; 138.34; 127.60; 122.00; 60.09; 46.39; 32.14; 29.33; 15.91; 13.89. EI-MS: 456 (9, M^+), 411 (6, $[M - EtO]^+$), 355 (100, $[M - EtO_2CC_2H_4]^+$). Anal. calc. for $C_{27}H_{36}O_6$ (456.58): C 71.03, H 7.95; found: C 71.29, H 8.24.

Diethyl 4,4-Bis[4-(4-chlorobutoxy)-3,5-dimethylphenyl]heptanedioate (**29**). 1,4-Dichlorobutane (7.10 ml, 63.62 mmol) was added to a suspension of **28** (1.45 g, 3.18 mmol), K_2CO_3 (1.32 g, 9.55 mmol), and Cs_2CO_3 (3.11 g, 9.55 mmol) in dry DMF (16.5 ml) at 80°. The brown mixture was stirred for 24 h at this temp., filtered over *Celite*, and evaporated to dryness. CC (SiO_2; hexane/AcOEt 9:1 → 8:2) gave **29** (1.22 g, 60%) as a colorless oil that slowly crystallized. White crystals. M.p. 55°. IR (neat): 1732 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 6.76 (*s*, 4 H); 4.06 (*q*, *J* = 6.9, 4 H); 3.78 (*t*, *J* = 6.3, 4 H); 3.64 (*t*, *J* = 6.6, 4 H); 2.28 (*t*, *J* = 7.5, 4 H); 2.20 (*s*, 12 H); 2.04 (*t*, *J* = 7.5, 4 H); 1.95 (*m*, 8 H); 1.21 (*t*, *J* = 6.9, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 173.92; 153.81; 141.99; 129.93; 128.14; 71.06; 60.38; 47.06; 44.99; 32.38; 29.67; 29.59; 27.86; 16.60; 14.20. FAB-MS: 636 (5, $[M - H]^+$), 591 (10, $[M - OEt]^+$), 535 (100, $[M - EtO_2CC_2H_4]^+$).

Tetraethyl 5,14,20,29,32,33,36,37-Octamethyl-7,12,22,27-tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta-1(30),3,5,13,15,18,20,28,31,33,35,37-dodecaene-2,2,17,17-tetrapropionate (**30**). A soln. of **29** (0.80 g, 1.25 mmol) and **28** (0.57 g, 1.25 mmol) in dry DMF (50 ml) and toluene (5 ml) was added over a period of 3 h to a suspension of Cs_2CO_3 (1.22 g, 3.75 mmol) and K_2CO_3 (0.52 g, 3.75 mmol) in dry DMF (150 ml) at 80°. The mixture was stirred at this temp. for 24 h, cooled to r.t., and filtered over *Celite*. CC (SiO_2; hexane/AcOEt 4:1) and recrystallization (hexane/CH_2Cl_2/PhH) yielded **30** (0.25 g, 20%). White crystals. M.p. 240°. IR (KBr): 1736 (C=O). ^{1}H-NMR (500 MHz, $CDCl_3$): 6.69 (*s*, 8 H); 4.06 (*q*, *J* = 7.1, 8 H); 3.85 (*t*, *J* = 5.8, 8 H); 2.28 (*t*, *J* = 8.0, 8 H); 2.13 (*s*, 24 H); 2.00–1.95 (*m*, 16 H); 1.21 (*t*, *J* = 7.1, 12 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 173.88; 153.67; 142.16; 129.85; 127.86; 72.15; 60.29; 46.67; 31.53; 29.44; 27.01; 16.64; 14.12. FAB-MS: 1021 (10, M^+), 975 (42, $[M - OEt]^+$), 919 (100, $[M - EtO_2CC_2H_4]^+$). Anal. calc. for $C_{62}H_{84}O_{12} \cdot 0.5\,H_2O$ (1030.36): C 72.27, H 8.32; found: C 72.30, H 8.54. X-Ray analysis: see *Fig. 1,a*.

5,14,20,29,32,33,36,37-Octamethyl-7,12,22,27-tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta-1(30),3,5,13,15,18,20,28,31,33,35,37-dodecaene-2,2,17,17-tetrapropionic Acid (**21**). 2N NaOH (0.50 ml, 1 mmol) was added to a soln. of **30** (79 mg, 0.0774 mmol) in MeOH/THF 1:1 (2 ml) at r.t. The suspension was heated for 6 h to 60°, diluted with H_2O (25 ml), and washed twice with CH_2Cl_2 (25 ml). The aq. layer was separated, acidified with conc. aq. HCl soln., and extracted with AcOEt (3 × 25 ml). The combined org. layers were dried ($MgSO_4$) and evaporated to give **21** (75 mg, 100%). White powder. M.p. > 250°. IR (KBr): 3431 (O–H), 1724 (C=O).

^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 6.73 (*s*, 8 H); 3.77 (br. *t*, 8 H); 2.20 (br. *t*, 8 H); 2.07 (*s*, 24 H); 1.84–1.50 (*m*, 16 H). ^{13}C-NMR (50 MHz, $(CD_3)_2SO$): 174.04; 152.99; 141.79; 128.96; 127.02; 71.11; 45.98; 30.77; 28.65; 25.75; 16.05. FAB-MS: 909 (100, M^+), 891 (59, $[M - H_2O]^+$), 836 (53, $[M - C_2H_4CO_2H]^+$).

5,14,20,29,32,37-Hexamethyl-7,12,22,27-tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta-1(30),3,5,13,-15,18,20,28,31,33,35,37-dodecaene-2,2,17,17-tetrayl-N,N′,N″,N‴-*tetrakis{[({tris[(2-{[(tris{[2-(methoxycarbonyl)-ethoxy]methyl}methyl)amino]carbonyl}ethoxy)methyl]methyl}amino)carbonyl]methyl}-2,2,17,17-tetrakis(acetamide)* (**31**). DCC (42 mg, 0.203 mmol) was added to a soln. of **20** (28 mg, 0.0338 mmol), **11** (300 mg, 0.203 mmol), and BtOH (27 mg, 0.203 mmol) in THF (5 ml) at 0°. The suspension was allowed to warm to r.t. over a period of 8 h and was stirred at this temp. for 3 d. After filtration and evaporation, the residue was taken up in toluene. Filtration afforded a soln. which was washed with H_2O, dried ($MgSO_4$), and evaporated to dryness. GPC and CC (SiO_2; CH_2Cl_2/MeOH 97:3 → 90:10) yielded **31** (100 mg, 41%). Colorless oil. IR (neat): 1738, 1664 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 6.77 (*s*, 4 H); 6.62 (*s*, 4 H); 6.61–6.52 (*m*, 6 H); 6.21 (*s*, 12 H); 3.97 (br. *t*, 4 H); 3.74–3.58 (*m*, 312 H); 3.20 (br. *s*, 8 H); 2.52 (*t*, *J* = 6.3, 72 H); 2.34 (*t*, *J* = 6.3, 24 H); 2.08 (*s*, 12 H); 2.00 (*s*, 6 H); 1.92 (br. *s*, 8 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.40; 171.99; 171.93; 171.46; 169.53, 169.35; 155.23; 154.42; 142.14; 139.22; 129.85; 129.40; 127.71; 125.79; 123.78; 110.81; 77.40; 71.67; 69.23; 67.63; 66.87; 60.20; 59.91; 51.74; 46.95; 46.79; 44.48; 42.92; 37.23; 34.77; 26.68; 25.45; 16.83; 16.62. MALDI-TOF-MS (CCA): 6690 (100, $[M + Na]^+$; calc. for $^{13}C_4{}^{12}C_{296}H_{476}O_{144}N_{20} \cdot Na^+$: 6690), 3769 (20), 1684 (30).

5,14,20,29,32,33,36,37-Octamethyl-7,12,22,27-tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta-1(30),3,5,13,15,18,20,28,31,33,35,37-dodecaene-2,2,17,17-tetrayl-N,N′,N″,N‴-*tetrakis{[({tris[(2-{[(tris-{[2-(methoxycarbonyl)ethoxy]methyl}methyl)amino]carbonyl}ethoxy)methyl]methyl}amino)carbonyl]methyl}-2,2,17,17-tetrakis(propionamide)* (**32**). DCC (63 mg, 0.304 mmol) was added to a soln. of **21** (46 mg, 0.0506 mmol), **11** (450 mg, 0.304 mmol), and BtOH (41 mg, 0.304 mmol) in dry THF (10 ml) at 0°. The suspension was allowed to warm to r.t. over a period of 8 h and was stirred for 3 d at this temp. After filtration and evaporation, the residue was taken up in toluene. Filtration afforded a soln. which was washed with H_2O, dried ($MgSO_4$), and evaporated to dryness. Purification by GPC and CC (SiO_2; CH_2Cl_2/MeOH 97:3 → 90:10) gave **32** (200 mg, 58%). Colorless oil. IR (neat): 1732, 1667 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 6.73 (*s*, 4 H); 6.64 (*s*, 8 H); 6.28 (br. *t*, 4 H); 6.13 (*s*, 12 H); 3.85 (*d*, *J* = 3.6, 8 H); 3.80 (br. *s*, 8 H); 3.72–3.57 (*m*, 300 H); 2.51 (*t*, *J* = 6.3, 72 H); 2.35 (*t*, *J* = 6.3, 24 H); 2.26 (br. *m*, 8 H); 2.08 (*s*, 24 H); 1.93 (br. *s*, 8 H); 1.90–1.82 (br. *m*, 8 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 173.25; 172.40; 171.38; 169.08; 153.74; 143.07; 130.04; 128.05; 72.37; 69.23; 67.64; 66.85; 60.23; 59.88; 51.74; 46.69; 42.75; 37.21; 34.75; 31.87; 31.00; 27.36; 16.62. MALDI-TOF-MS (dithranol): 6774 (100, $[M + Na]^+$; calc. for $^{13}C_4{}^{12}C_{302}H_{488}N_{20}O_{144} \cdot Na^+$: 6774).

Diethyl 3-(4-Hydroxy-3-methylphenyl)-3-{4-hydroxy-3-methyl-5-[(morpholin-4-yl)methyl]phenyl}pentane-1,5-dicarboxylate (**34**) *and Diethyl 3,3-Bis{4-hydroxy-3-methyl-5-[(morpholin-4-yl)methyl]phenyl}pentane-1,5-dicarboxylate* (**35**). A soln. of **33** [21] (5.00 g, 12.49 mmol) in EtOH (20 ml) was added at r.t. to a suspension of morpholine (1.44 g, 16.60 mmol) and paraformaldehyde (0.41 g, 13.73 mmol) in EtOH (5 ml), and the mixture was stirred for 20 h under reflux. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2 (100 ml). Half conc. aq. HCl soln. (50 ml) was added, and the suspension was stirred for 30 min at r.t. The white precipitate was filtered off and taken up in sat. aq. $NaHCO_3$ soln. The resulting aq. mixture was extracted with CH_2Cl_2 (3 × 100 ml), the combined org. layers were dried ($MgSO_4$) and evaporated to provide **34** (2.70 g, 43%). The aq. layer of the filtrate was neutralized with 5N NaOH and extracted with CH_2Cl_2 (3 ×). The combined org. layers were separated, dried ($MgSO_4$), and evaporated to afford **35** (1.70 g, 23%). The org. layer of the filtrate was dried ($MgSO_4$) and evaporated to give residual **33** (1.10 g, 22%).

Data of **34**: Colorless oil. IR (neat): 3421 (O–H), 1726 (C=O). ^{1}H-NMR (200 MHz, $CDCl_3$): 6.87–6.76 (*m*, 3 H); 6.59–6.52 (*m*, 2 H); 3.87 (*q*, *J* = 7.1, 4 H); 3.74 (br. *t*, *J* = 4.4, 4 H); 3.60 (*s*, 2 H); 3.42 (*s*, 4 H); 2.50 (br. *s*, 4 H); 2.15 (*s*, 6 H); 0.99 (*t*, *J* = 7.1, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 171.89; 153.80; 152.40; 138.37; 136.91; 129,89; 129.19; 126.05; 125.45; 124.08; 123.04; 119.07; 114.27; 66.81; 62.08; 59.99; 52.81; 45.70; 42.85; 16.05; 15.89; 13.96. EI-MS: 499 (75, M^+), 412 (100, $[M -$ morpholine$]^+$). Anal. calc. for $C_{28}H_{37}NO_7$ (499.60): C 67.32, H 7.46, N 2.80; found: C 67.17, H 7.54, N 2.69.

Data of **35**: Colorless oil. IR (neat): 3421 (O–H), 1728 (C=O). ^{1}H-NMR (200 MHz, $CDCl_3$): 6.77 (*d*, *J* = 1.6, 2 H); 6.55 (*d*, *J* = 1.6, 2 H); 3.83 (*q*, *J* = 7.2, 4 H); 3.72 (br. *t*, *J* = 4.2, 8 H); 3.58 (*s*, 4 H); 3.38 (*s*, 4 H); 2.50 (br. *s*, 8 H); 2.13 (*s*, 6 H); 0.96 (*t*, *J* = 7.2, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 171.73; 153.80; 136.91; 129.19; 125.48; 123.99; 119.04; 66.81; 62.15; 59.83; 52.81; 45.67; 42.81; 15.89; 13.99. EI-MS: 598 (100, M^+), 511 (70, $[M -$ morpholine$]^+$). Anal. calc. for $C_{33}H_{46}N_2O_8 \cdot 0.5\ CH_2Cl_2$ (641.21): C 62.75, H 7.39, N 4.37; found: C 62.97, H 7.32, N 3.94.

Diethyl 3-[4-(4-Chlorobutoxy)-3-methylphenyl]-3-{4-(4-chlorobutoxy)-3-methyl-5-[(morpholin-4-yl)methyl]phenyl}pentane-1,5-dicarboxylate (**36**). 1-Bromo-4-chlorobutane (23.71 g, 138.30 mmol) was slowly added

to a suspension of **34** (3.45 g, 6.91 mmol), K_2CO_3 (2.87 g, 20.74 mmol), and Cs_2CO_3 (6.76 g, 20.74 mmol) in MeCN (50 ml) at 80°. The mixture was stirred at this temp. for 8 h, then cooled to r.t., and filtered over *Celite*. Evaporation and CC (SiO_2; hexane/AcOEt 6:4) yielded **36** (3.20 g, 68%). Colorless oil. IR (neat): 1728 (C=O). ^{1}H-NMR (200 MHz, $CDCl_3$): 6.91 (*dd*, *J* = 8.4, 2.3, 1 H); 6.89 (br. *s*, 2 H); 6.84 (*d*, *J* = 2.3, 1 H); 6.67 (*d*, *J* = 8.4, 1 H); 3.96 (br. *t*, *J* = 5.4, 2 H); 3.92–3.80 (*m*, 6 H); 3.67–3.57 (*m*, 8 H); 3.45 (*s*, 4 H); 3.42 (*s*, 2 H); 2.36 (br. *t*, *J* = 4.4, 4 H); 2.22 (*s*, 3 H); 2.12 (*s*, 3 H); 2.00–1.94 (*m*, 8 H); 0.98 (*t*, *J* = 7.1, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 169.24; 152.99; 152.29; 139.25; 135.79; 127.79; 127.54; 127.25; 126.74; 126.08; 123.47; 123.22; 107.51; 69.83; 64.59; 57.90; 57.39; 55.17; 51.04; 43.45; 42.41; 42.28; 40.11; 27.01; 25.30; 24.26; 14.00; 11.68; 11.43. FAB-MS: 680 (100, M^+). HR-FAB-MS: 678.2985 ($[M-H]^+$, $C_{36}H_{51}Cl_2NO_7^+$; calc.: 678.2963).

Tetraethyl 5,14,20,29,33,36-Hexamethyl-32-[(morpholin-4-yl)methyl]-7,12,22,27-tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta-1(30),3,5,13,15,18,20,28,31,33,35,37-dodecaene-2,2,17,17-tetraacetate (**37**). A soln. of **23** (3.92 g, 9.15 mmol) and **36** (5.65 g, 8.32 mmol) in MeCN (300 ml) and *p*-xylene (50 ml) was added slowly over a period of 8 h to a suspension of K_2CO_3 (2.30 g, 16.64 mmol) and Cs_2CO_3 (16.27 g, 49.92 mmol) in MeCN (1000 ml) and *p*-xylene (200 ml) at 80°. The mixture was stirred at this temp. for 20 h, then cooled to r.t., and filtered over *Celite*. Evaporation and CC (SiO_2; hexane/AcOEt 6:4) afforded **37** (4.18 g, 49%). M.p. 126–128° (AcOEt/benzene/hexane). IR (KBr): 1728 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 6.90–6.70 (*m*, 5 H); 6.64 (*s*, 4 H); 4.01 (br. *t*, *J* = 6.0, 2 H); 3.92–3.78 (*m*, 14 H); 3.59 (br. *t*, 4 H); 3.45 (*s*, 4 H); 3.43 (*s*, 4 H); 3.37 (*s*, 2 H); 2.31 (br. *t*, 4 H); 2.17 (*s*, 3 H); 2.16 (*s*, 3 H); 2.12 (*s*, 6 H); 2.10 (*s*, 6 H); 1.98–1.92 (*m*, 8 H); 0.99–0.91 (*m*, 12 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.99; 171.91; 155.42; 154.69; 154.55; 154.26; 141.98; 141.90; 141.65; 138.61; 130.38; 129.86; 129.63; 129.42; 127.89; 127.84; 125.99; 125.95; 110.77; 73.42; 72.30; 72.00; 67.56; 67.09; 59.99; 59.96; 57.63; 53.57; 45.67; 45.64; 42.13; 42.00; 26.97; 26.90; 26.82; 25.45; 16.83; 16.79; 16.70; 16.53; 13.99; 13.95. FAB-MS: 1036 (100, M^+). Anal. calc. for $C_{61}H_{81}O_{13}N$ (1036.31): C 70.70, H 7.88, N 1.35; found: C 70.76, H 7.72, N 1.43. X-Ray analysis: see *Fig. 1,b*.

Tetraethyl 5-(Acetoxymethyl)-14,20,29,32,33,36-hexamethyl-7,12,22,27-tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]-octatriaconta-1(30),3,5,13,15,18,20,28,31,33,35,37-dodecaene-2,2,17,17-tetraacetate (**38**). A soln. of **37** (0.40 g, 0.39 mmol) in Ac_2O (10 ml) was stirred for 3 d at 140°. Evaporation provided a residue which was partitioned between sat. aq. $NaHCO_3$ soln. (40 ml) and CH_2Cl_2 (40 ml). The org. layer was separated, washed with H_2O, dried ($MgSO_4$), and evaporated. CC (SiO_2; hexane/AcOEt 6:4) yielded **38** (0.27 g, 70%). Colorless oil. M.p. 78–82° (AcOEt/PhH/hexane). IR (KBr): 1732 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 6.93 (*d*, *J* = 2.7, 2 H); 6.82–6.78 (*m*, 3 H); 6.66 (*s*, 4 H); 5.01 (*s*, 2 H); 4.02 (br. *t*, 2 H); 3.90–3.78 (*m*, 14 H); 3.45 (*s*, 4 H); 3.43 (*s*, 4 H); 2.11 (*s*, 6 H); 2.10 (*s*, 9 H); 2.02 (*s*, 3 H); 1.99–1.93 (*m*, 8 H); 1.94 (*s*, 3 H); 1.00–0.90 (*m*, 12 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.98; 171.83; 171.07; 155.52; 154.54; 154.44; 154.24; 142.60; 141.85; 141.67; 138.26; 131.21; 130.62; 129.91 (2 peaks); 129.85 (2 peaks); 129.64; 128.13 (2 peaks); 127.84; 127.05; 126.09; 125.97; 110.79; 73.73; 72.21; 71.90; 67.48; 62.03; 60.04; 59.94; 45.72; 45.67; 42.15; 41.99; 26.84; 26.78 (2 peaks); 25.39; 20.99; 16.78; 16.75; 16.62; 16.54; 13.95. FAB-MS: 1009 (100, M^+). Anal. calc. for $C_{59}H_{76}O_{14}$ (1009.24): C 70.22, H 7.59; found: C 70.21, H 7.47. X-Ray analysis: see *Fig. 1,c*.

5-(Hydroxymethyl)-14,20,29,32,33,36-hexamethyl-7,12,22,27-tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta-1(30),3,5,13,15,18,20,28,31,33,35,37-dodecaene-2,2,17,17-tetraacetic Acid (**39**). 2N NaOH soln. (10 ml) was added to a soln. of **38** (90 mg, 0.09 mmol) in MeOH/THF 1:1 (10 ml). The mixture was stirred at r.t. for 30 h, then washed with AcOEt. The aq. layer was acidified with conc. aq. HCl soln. and extracted with AcOEt (2×). The combined org. layers were separated, dried ($MgSO_4$), and evaporated. Recrystallization from CH_2Cl_2/MeOH/hexane yielded **39** (68 mg, 89%). White powder. M.p. 183–186°. IR (KBr): 1715 (C=O). ^{1}H-NMR (200 MHz, CD_3OD): 7.11–6.70 (*m*, 9 H); 4.56 (*s*, 2 H); 4.06 (br. *t*, 2 H); 3.94–3.80 (*m*, 6 H); 3.51 (*s*, 4 H); 3.46 (*s*, 4 H); 2.13 (*s*, 6 H); 2.08 (*s*, 9 H); 1.99 (*s*, 3 H); 2.01–1.92 (*m*, 8 H). ^{13}C-NMR (50 MHz, CD_3OD): 174.16; 155.28; 154.17; 154.04; 153.22; 142.84; 142.23 (2 peaks); 138.80; 133.03; 129.82; 129.60 (2 peaks); 129.50; 127.73 (2 peaks); 125.57 (2 peaks); 125.28; 110.36; 72.91; 71.80; 71.64; 67.16; 59.13; 44.94; 41.26; 26.47; 26.22; 26.13; 25.01; 15.55; 15.45 (2 peaks); 15.36. FAB-MS: 854 (100, M^+). Anal. calc. for $C_{49}H_{58}O_{13}\cdot$ MeOH (887.04): C 67.70, H 7.05; found: C 67.84; H 7.05.

5-(Bromomethyl)-14,20,29,32,33,36-hexamethyl-7,12,22,27-tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta-1(30),3,5,13,15,18,20,28,31,33,35,37-dodecaene-2,2,17,17-tetraacetic Acid (**40**). A soln. of HBr in AcOH (33%, 1 ml) was added to **39** (50 mg, 0.059 mmol) in CH_2Cl_2 (1 ml), and the mixture was stirred for 10 h at r.t. After addition of H_2O (30 ml), the mixture was extracted with AcOEt, and the org. layer was dried ($MgSO_4$). Evaporation and reprecipitation from AcOEt/hexane (3×) gave **40** (46 mg, 86%). White powder. M.p. 135° (dec.). IR (KBr): 1710, 1630 (C=O). ^{1}H-NMR (200 MHz, CD_3OD): 7.30–6.70 (*m*, 9 H); 4.53 (*s*, 2 H); 4.15–3.76 (br. *m*, 8 H); 3.62–3.50 (*m*, 8 H); 2.11–2.00 (*m*, 18 H); 2.01–1.96 (*m*, 8 H). ^{13}C-NMR (50 MHz, CD_3OD): 175.74; 175.57; 156.86; 155.75; 155.72; 155.34; 145.05; 143.92; 143.73; 140.03; 132.31; 132.03; 131.19; 130.96;

130.20; 129.33; 127.40; 127.26; 112.26; 74.03; 73.65; 73.01; 68.60; 46.48; 43.13; 42.86; 29.58; 27.88 (2 peaks); 27.67; 26.50; 17.35; 17.09; 16.96. FAB-MS: 918 (100, M^+).

5,14,20,29,33,36-Hexamethyl-32-[(4-methyl-3-thiazolio)methyl]-7,12,22,27-tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta-1(30),3,5,13,15,18,20,28,31,33,35,37-dodecaene-2,2,17,17-tetraacetic Acid Bromide (**41**). 4-Methylthiazole (2 ml) was added to a soln. of **40** (35 mg, 0.0381 mmol) in MeCN (1 ml), and the mixture was stirred for 12 h at r.t. The solvent was evaporated, and the residue was purified by precipitation from MeCN/Et_2O to afford **41** (24 mg, 62%). Pale-yellow powder. M.p. 167°. IR (KBr): 1715 (C=O). ^{1}H-NMR (300 MHz, CD_3OD): 9.61 (*d*, *J* = 2.7, 1 H); 7.70 (br. *s*, 1 H); 7.08 (br. *d*, 1 H); 6.90–6.87 (*m*, 2 H); 6.80 (*s*, 3 H); 6.78 (*s*, 2 H); 6.72 (*d*, *J* = 8.7, 1 H); 5.61 (*s*, 2 H); 4.02 (br. *s*, 4 H); 3.88 (br. *t*, 2 H); 3.74 (*t*, *J* = 6.0, 2 H); 3.55–3.41 (*m*, 8 H); 2.40 (*s*, 3 H); 2.19 (*s*, 3 H); 2.13 (*s*, 6 H); 2.08 (*s*, 6 H); 1.94 (*s*, 3 H); 1.99–1.89 (*m*, 8 H). ^{13}C-NMR (50 MHz, CD_3OD): 174.07; 173.72; 155.53; 154.14; 153.75; 146.93; 144.11; 142.55; 142.33; 138.70; 132.58; 131.41; 129.76 (2 peaks); 129.66 (2 peaks); 129.41; 127.57 (2 peaks); 127.50 (2 peaks); 127.38; 125.63; 123.95; 121.25; 110.27; 73.48; 71.96; 71.54; 67.45; 52.75; 45.10; 44.72; 41.45; 40.88; 26.69; 26.57; 25.93; 25.26; 15.62; 15.52; 15.39; 12.09. FAB-MS: 937 (100, $[M - Br]^+$). HR-FAB-MS: 936.3984 ($[M - Br]^+$, $C_{53}H_{62}NO_{12}S^+$; calc.: 936.3992).

5-(Chloromethyl)-14,20,29,32,33,36-hexamethyl-7,12,22,27-tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta-1(30),3,5,13,15,18,20,28,31,33,35,37-dodecaene-2,2,17,17-tetracarboxylic Acid Dianhydride (**42**). DMF was added dropwise to a suspension of **39** (160 mg, 0.187 mmol) in $CHCl_3$ (20 ml) until a clear soln. was obtained. Me_3SiCl (152 mg, 1.41 mmol) and Et_3N (76 mg, 0.75 mmol) were added, and the mixture was stirred for 3 h at 50°, then for 10 h at r.t. $SOCl_2$ (3 ml) was added, and the yellowish soln. was stirred for additional 3 h at r.t. and then quenched with H_2O (10 ml). The mixture was extracted with AcOEt (50 ml), and the org. layer was separated and dried ($MgSO_4$). Evaporation and recrystallization (AcOEt/hexane) afforded **42** (148 mg, 94%). White powder. M.p. 145° (dec.). IR (KBr): 1806, 1763 (cyclic anhydride), 1630 (C=O). ^{1}H-NMR (200 MHz, $CDCl_3$): 6.98 (*d*, *J* = 2.8, 1 H); 6.90–6.85 (*m*, 3 H); 6.74 (*s*, 3 H); 6.70 (*s*, 2 H); 4.49 (*s*, 2 H); 4.05 (br. *t*, 2 H); 3.96–3.78 (*m*, 6 H); 3.47 (*d*, J_{AB} = 16.6, 2 H); 3.39 (*s*, 4 H); 3.38 (*d*, J_{AB} = 16.6, 2 H); 2.18–2.00 (*m*, 18 H); 2.03–1.96 (*m*, 8 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 163.40; 163.15; 153.98; 153.09; 152.87; 152.55; 136.68; 135.60; 135.47; 131.38; 130.01; 129.12 (2 peaks); 129.00 (2 peaks); 126.90 (2 peaks); 125.50; 125.35; 123.79 (2 peaks); 123.70 (2 peaks); 123.41; 122.17; 109.19; 71.39; 70.08; 69.48; 64.85; 40.34; 40.12; 40.02; 38.56; 24.57; 24.34; 24.03; 22.98; 14.38; 14.31; 14.25. FAB-MS: 837 (100, MH^+) HR-FAB-MS: 837.3396 (MH^+; calc.: 837.3405).

5-(Hydroxymethyl)-14,20,29,32,33,36-hexamethyl-7,12,22,27-tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta-1(30),3,5,13,15,18,20,28,31,33,35,37-dodecaene-2,2,17,17-tetrayl-N,N′,N″,N‴*-tetrakis(tris{[2-(methoxycarbonyl)ethoxy]methyl}methyl)-2,2,17,17-tetrakis(acetamide)* (**43**). DCC (193 mg, 0.937 mmol) was added to soln. of **39** (100 mg, 0.117 mmol), **17** (888 mg, 2.343 mmol), and BtOH (127 mg, 0.941 mmol) in THF (10 ml). After stirring for 2 d at 55°, the mixture was filtered, and the filtrate was washed with H_2O and dried ($MgSO_4$). Evaporation and GPC provided **43** (100 mg, 37%). Colorless oil. IR (neat): 1737, 1661 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 6.93–6.57 (*m*, 9 H); 6.44 (*s*, 2 H); 6.39 (*s*, 2 H); 4.50 (*s*, 2 H); 3.97 (br. *s*, 2 H); 3.87–3.77 (*m*, 6 H); 3.63 (*s*, 36 H); 3.55 (*t*, *J* = 6.4, 24 H); 3.41 (*s*, 24 H); 3.15–2.97 (br. *m*, 8 H); 2.47 (*t*, *J* = 6.4, 24 H); 2.07–1.97 (*m*, 18 H); 1.91 (br. *s*, 8 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.28; 172.20; 171.80; 155.43; 154.54; 154.23; 153.58; 142.94; 142.31; 142.16; 138.76; 133.57; 130.07; 129.78 (2 peaks); 129.61; 127.96 (2 peaks); 126.14; 126.01; 125.82; 110.77; 73.27; 72.13; 71.64; 68.92; 67.19; 66.74; 60.99; 59.70; 59.64; 51.63; 47.16; 47.05; 45.55; 45.42; 34.75; 26.89; 26.75; 26.62; 25.27; 16.75; 16.52. MALDI-TOF-MS (dithranol): 2322 ($[M + Na]^+$; calc. for $^{13}C_2{}^{12}C_{111}H_{166}N_4O_{45}Na^+$: 2323). Anal. calc. for $C_{113}H_{116}N_4O_{45}\cdot 2\,CH_2Cl_2$ (2470.45): C 55.91, H 6.94, N 2.27; found: C 55.60, H 7.05, N 2.01.

5-(Hydroxymethyl)-14,20,29,32,33,36-hexamethyl-7,12,22,27-tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta-1(30),3,5,13,15,18,20,28,31,33,35,37-dodecaene-2,2,17,17-tetrayl-N,N′,N″,N‴*-tetrakis{tris[(2-carboxyethoxy)methyl]methyl}-2,2,17,17-tetrakis(acetamide)* (**44**). 1N NaOH (1 ml, 1 mmol) was added to a soln. of **43** (75 mg, 0.0326 mmol) in MeOH (1 ml). The mixture was stirred for 35 h at r.t., then diluted with H_2O (10 ml), washed with CH_2Cl_2 (20 ml), acidified with conc. aq. HCl soln., and extracted with AcOEt (50 ml). The org. layer was separated, dried ($MgSO_4$), and evaporated to yield **44** (65 mg, 94%). Colorless oil. IR (neat): 1707, 1644 (C=O). ^{1}H-NMR (200 MHz, CD_3COCD_3): 6.97–6.82 (*m*, 9 H); 4.58 (*s*, 2 H); 4.13 (br. *s*, 2 H); 3.98–3.82 (*m*, 6 H); 3.63 (*t*, *J* = 6.0, 24 H); 3.53 (*s*, 24 H); 3.45–3.24 (br. *m*, 8 H); 2.54 (*t*, *J* = 6.0, 24 H); 2.22–2.06 (*m*, 18 H); 1.97 (br. *s*, 8 H). ^{13}C-NMR (75 MHz, CD_3COCD_3): 174.29; 174.13; 172.77; 155.56; 154.67 (2 peaks); 153.47; 141.53; 140.96; 140.61; 137.38; 133.73; 129.66 (2 peaks); 129.44; 129.22; 128.71; 127.95 (2 peaks); 127.63; 125.76; 125.09; 110.78; 72.50; 71.89; 71.32; 66.97; 68.43; 66.59; 61.16; 60.97; 58.97; 47.67; 47.55; 43.99; 33.99; 26.19; 25.91; 24.60; 16.09; 15.93; 15.81; 15.71. FAB-MS: 2133 (100, MH^+; calc. for $^{13}C_2{}^{12}C_{99}H_{142}N_4O_{45}$: 2133).

5-(Hydroxymethyl)-14,20,29,32,33,36-hexamethyl-7,12,22,27-tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta-1(30),3,5,13,15,18,20,28,31,33,35,37-dodecaene-2,2,17,17-tetrayl-N,N′,N″,N‴*-tetrakis[[([tris[(2-[[(tris-*

{[2-(methoxycarbonyl)ethoxy]methyl}methyl)amino]carbonyl}ethoxy)methyl]methyl}amino)carbonyl]methyl}-2,2,17,17-tetrakis(acetamide) (**45**). DCC (29 mg, 0.141 mmol) was added to a soln. of **39** (20 mg, 0.0234 mmol), **11** (208 mg, 0.141 mmol), and BtOH (19 mg, 0.141 mmol) in THF (3 ml) at 0°. The resulting suspension was allowed to warm to r.t. over a period of 8 h, stirred for 3 d at this temp., and filtered. The filtrate was diluted with toluene and filtered again. The resulting soln. was washed with H_2O and dried ($MgSO_4$). Evaporation and GPC followed by CC (SiO_2; CH_2Cl_2/MeOH 94 : 6 → 90 : 10) yielded **45** (75 mg, 48%). Colorless oil. IR (neat): 1738, 1668 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 7.38 (br. *s*, 4 H); 7.04–6.53 (*m*, 13 H); 6.22 (*s*, 3 H); 6.21 (*s*, 9 H); 4.55 (*s*, 2 H); 3.96 (br. *s*, 8 H); 3.85–3.48 (*m*, 308 H); 3.26–3.12 (br. *m*, 8 H); 2.53 (*t*, *J* = 6.3, 72 H); 2.34 (*t*, *J* = 6.3, 24 H); 2.19 (*s*, 6 H); 2.09 (*s*, 12 H); 1.92 (br. *s*, 8 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 171.97; 171.65; 171.49; 171.09; 171.04; 170.97; 169.10; 169.07; 154.98; 154.06; 153.72; 153.07; 142.31; 142.00; 141.82; 138.38; 133.69; 129.83; 129.58 (fourfold intensity); 128.95; 128.15; 127.37 (double intensity); 125.86; 125.45; 125.22; 110.63; 71.85; 71.51; 69.08; 68.94; 68.63; 67.47; 66.70; 60.31; 60.06; 59.76; 51.56; 46.93; 46.73; 44.34; 44.09; 42.79; 37.13; 34.66; 26.93; 26.69; 26.61; 25.43; 16.76; 16.67; 16.55; 16.53. MALDI-TOF-MS (dithranol): 6720 (100, $[M + Na]^+$; calc. for $^{13}C_4{}^{12}C_{297}H_{478}N_{20}O_{145}Na^+$: 6720).

5-(Chloromethyl)-14,20,29,32,33,36-hexamethyl-7,12,22,27-tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta-1(30),3,5,13,15,18,20,28,31,33,35,37-dodecaene-2,2,17,17-tetrayl-N,N′,N″,N‴*-tetrakis{[({tris[(2-{[(tris{[2-(methoxycarbonyl)ethoxy]methyl}methyl)amino]carbonyl}ethoxy)methyl]methyl}amino)carbonyl]methyl}-2,2,17,17-tetrakis(acetamide)* (**46**). A soln. of **42** (18 mg, 0.0215 mmol) and **11** (191 mg, 0.129 mmol) in THF (1 ml) was stirred for 90 min at r.t., then cooled to 0°, and treated with HBTU (19 mg, 0.0498 mmol) and Et_3N (5 mg, 0,0495 mmol). The suspension was stirred at this temp. for 90 min, then allowed to warm to r.t. over a period of 3 h. Evaporation and purification by GPC and CC (SiO_2; CH_2Cl_2/MeOH 95 : 5 → 92 : 8) gave **46** (70 mg, 48%). Colorless oil. IR (neat): 1736, 1664 (C=O). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.40 (br. *s*, 4 H); 6.95–6.56 (*m*, 13 H); 6.24 (*s*, 12 H); 4.52 (*s*, 2 H); 4.06–3.32 (*m*, 316 H); 3.23 (br. *s*, 8 H); 2.56 (*t*, *J* = 6.3, 72 H); 2.37 (*t*, *J* = 6.0, 24 H); 2.15–2.06 (*m*, 18 H); 2.04–1.92 (br. *m*, 8 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 169.75; 169.37; 169.15; 168.83; 166.86; 152.74; 151.76; 151.56; 151.41; 140.87; 139.66; 135.85; 128.71; 128.30; 127.35; 127.28; 126.65; 125.09; 123.73; 123.25; 108.52; 71.00; 69.54; 69.00; 61.16; 66.69; 65.07; 64.31; 57.67; 57.36; 49.17; 44.44; 44.34; 41.71; 40.37; 39.20; 34.66; 32.22; 24.31 (2 ×); 24.03; 22.98; 14.28; 14.06. MALDI-TOF-MS (dithranol): 6737 ($[M + Na]^+$; calc. for $^{13}C_3{}^{12}C_{298}H_{477}N_{20}O_{144}Cl \cdot Na^+$: 6738).

5,14,20,29,33,36-Hexamethyl-32-[(4-methyl-3-thiazolio)methyl]-7,12,22,27-tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta-1(30),3,5,13,15,18,20,28,31,33,35,37-dodecaene-2,2,17,17-tetrayl-N,N′,N″,N‴*-tetrakis{[({tris[(2-{[(tris{[2-(methoxycarbonyl)ethoxy]methyl}methyl)amino]carbonyl}ethoxy)methyl]methyl}amino)carbonyl]methyl}-2,2,17,17-tetrakis(acetamide) Chloride* (**9**). A soln. of **46** (90 mg, 0.0134 mmol) in 4-methylthiazole (1 ml) was stirred for 24 h at 50°. Evaporation to dryness and purification by GPC provided **9** (78 mg, 87%). Pale-yellow oil. IR (neat): 1738, 1670 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 9.60 (br. *d*, 1 H); 7.80 (br. *d*, 1 H); 7.49 (br. *s*, 4 H); 6.96–6.55 (*m*, 13 H); 6.22–6.20 (*m*, 12 H); 5.39 (*s*, 2 H); 3.92–3.43 (*m*, 316 H); 3.21 (br. *s*, 8 H); 2.54 (*t*, *J* = 6.3, 72 H); 2.40–2.32 (*m*, 24 H); 2.17–2.05 (*m*, 21 H); 1.95 (br. *s*, 8 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 172.00; 171.96; 171.58; 171.49; 171.04; 169.18; 169.06; 158.71; 155.30; 154.01; 153.40; 145.99; 144.28; 142.38; 141.80; 137.59; 132.97; 131.20; 130.30; 129.60; 129.40; 129.06; 127.47; 127.26; 125.90; 125.72; 123.03; 120.81; 110.81; 73.71; 71.75; 71.58; 71.50; 69.07; 68.93; 67.46; 66.69; 65.74; 60.08; 60.06; 59.75; 59.71; 51.55; 47.06; 46.71; 44.10; 43.86; 42.79; 37.11; 37.05; 34.64; 27.34; 26.74; 26.06; 25.56; 16.86; 16.82; 16.71; 16.50; 15.17; 13.44. MALDI-TOF-MS (dithranol): 6779 ($[M - Cl]^+$; calc. for $^{13}C_4{}^{12}C_{301}H_{482}N_{21}O_{144}S^+$: 6779).

5-(Chloromethyl)-14,20,29,32,33,36-hexamethyl-7,12,22,27-tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta-1(30),3,5,13,15,18,20,28,31,33,35,37-dodecaene-2,2,17,17-tetrayl-N,N′,N″,N‴*-tetrakis{[({tris[(2-{[(tris{[2-({2-[2-(2-methoxy-ethoxy)ethoxy]ethoxy}carbonyl)ethoxy]methyl}methyl)amino]carbonyl}ethoxy)methyl]methyl}amino)carbonyl]methyl}-2,2,17,17-tetrakis(acetamide)* (**47**). HATU (68 mg, 0.179 mmol) and Et_3N (24 mg, 0.238 mmol) were added to a stirred soln. of **42** (25 mg, 0.030 mmol) and **12** (638 mg, 0.239 mmol) in THF (2 ml) at 0°. The suspension was stirred for 90 min at this temp. and was then allowed to warm to r.t. over a period of 4 h. After 20 h, the solvent was evaporated and the residue was purified by GPC to give **47** (190 mg, 56%). Colorless oil. IR (neat): 1734, 1663 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 7.19 (br. *s*, 4 H); 6.91–6.47 (*m*, 13 H); 6.22 (*s*, 12 H); 4.49 (*s*, 2 H); 4.21 (*t*, *J* = 4.8, 72 H); 3.68 (*t*, *J* = 4.9, 72 H); 3.66–3.60 (*m*, 424 H); 3.53 (*t*, *J* = 4.5, 72 H); 3.36 (*s*, 108 H); 3.19 (br. *s*, 8 H); 2.55 (*t*, *J* = 6.5, 72 H); 2.35 (*t*, *J* = 6.4, 24 H); 2.12–2.03 (*m*, 18 H); 1.93 (br. *s*, 8 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.80; 171.44; 169.27; 155.39; 154.24; 142.33; 138.48; 131.39; 130.94; 129.99; 129.66; 129.13; 128.76; 127.70; 126.37; 125.89; 111.26; 72.01; 70.62; 69.26; 66.82; 63.71; 60.23; 59.98; 59.07; 46.87; 46.27; 44.13; 42.83; 37.07; 34.82; 29.72; 28.42; 26.78; 25.58; 16.81. MALDI-TOF-MS (HABA): 11494 ($[M + Na]^+$; calc. for $^{13}C_5{}^{12}C_{512}H_{909}N_{20}O_{252}Cl \cdot Na^+$: 11496).

5,14,20,29,33,36-Hexamethyl-32-{[4-methyl-3-thiazolio]methyl}-7,12,22,27-tetraoxapentacyclo[26.2.2.2^{3,6}.2^{13,16}.2^{18,21}]octatriaconta-1(30),3,5,13,15,18,20,28,31,33,35,37-dodecaene-2,2,17,17-tetrayl-N,N′,N″,N‴-tetrakis{[({tris-[(2-{[(tris{[2-({2-[2-(2-methoxy}ethoxy)ethoxy]carbonyl}ethoxy]methyl}methyl)amino]carbonyl}ethoxy)methyl]methyl}amino)carbonyl]methyl}-2,2,17,17-tetrakis(acetamide) Chloride (**10**). A soln. of **47** (160 mg, 0.0139 mmol) in 4-methylthiazole (2 ml) was stirred for 24 h at 50°. After evaporation of the excess of 4-methylthiazole, the resulting residue was purified by GPC to give **10** (80 mg, 50%). Yellow oil. IR (neat): 1736, 1671 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 9.71 (*s*, 1 H); 7.81 (*s*, 1 H); 6.98–6.40 (*m*, 13 H); 6.20 (*s*, 12 H); 5.41 (*s*, 2 H); 4.20 (*t*, *J* = 4.8, 72 H); 3.66–3.60 (*m*, 496 H); 3.53 (*t*, *J* = 4.5, 72 H); 3.35 (*s*, 108 H); 3.19 (br. *s*, 8 H); 2.54 (*t*, *J* = 6.3, 72 H); 2.35 (br. *t*, 24 H); 2.18–2.02 (*m*, 21 H); 1.92 (br. *s*, 8 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 171.41; 171.38; 170.97; 168.95; 168.90; 158.79; 155.3; 154.0; 153.37; 145.90; 144.28; 142.41; 141.90; 137.64; 131.23; 130.79; 129.63; 129.44; 127.6; 127.2; 125.80; 123.04; 121.36; 111.02; 71.82; 70.47; 70.44; 69.06; 68.97; 68.39; 67.43; 66.63; 63.52; 60.23; 59.80; 59.78; 58.91; 47.00; 46.60; 44.07; 43.76; 42.66; 36.93; 34.69; 27.29; 26.62; 26.60; 25.60; 16.85; 16.77; 16.58; 13.77. MALDI-TOF-MS (THA): 11533 ($[M - Cl]^+$; calc. for $^{13}C_5{}^{12}C_{516}H_{914}N_{21}O_{252}S^+$: 11536).

X-Ray Crystal-Structure Analyses. The X-ray measurements were carried out on a *Picker-Stoe* diffractometer with CuK_α radiation using ω scans, $\lambda = 1.54178$ Å. Data were collected at $T = 293$ K. Further details of the crystal structure analyses are available on request from the Director of the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB12EZ (UK), on quoting the full journal citation and deposition numbers (CCDC).

Compound **30** ($C_{62}H_{86}O_{12}$, M_r 1023.37): triclinic space group $P\bar{1}$, $\rho_{calc.} = 1.144$ g/cm^{-3}, $Z = 1$, $a = 10.990(7)$, $b = 11.870(7)$, $c = 11.982(7)$ Å, $\alpha = 72.96(5)$, $\beta = 83.61(5)$, $\gamma = 86.79(5)°$, $V = 1485(2)$ Å^3. Single crystals were obtained by diffusion of hexane into a soln. of **30** in CH_2Cl_2/benzene. The structure was solved by direct methods and refined by full-matrix least-squares analysis (SHELXTL PLUS; heavy atoms anisotropic, H-atoms isotropic, whereby H-atom positions are based on stereochemical considerations) to give $R(1) = 0.0765$ and $R_w(2) = 0.1931$ for 338 variables and 2775 observed reflections with $I > 2\sigma(I)$ and $1.79 \leq \theta \leq 20.00$. Deposition-No. CCDC-113987.

Compound **37**·0.5 C_6H_6 ($C_{64}H_{84}NO_{13}$, M_r 1075.32): triclinic space group $P\bar{1}$, $\rho_{calc.} = 1.164$ g/cm^{-3}, $Z = 2$, $a = 14.010(10)$, $b = 14.437(11)$, $c = 16.570(11)$ Å, $\alpha = 91.82(6)$, $\beta = 113.70(5)$, $\gamma = 90.24(6)°$, $V = 3067(4)$ Å^3. Single crystals were obtained by recrystallization from AcOEt/benzene/hexane. The structure was solved by direct methods and refined by full-matrix least-squares analysis (SHELXTL PLUS; heavy atoms anisotropic, H-atoms isotropic, whereby H-atom positions are based on stereochemical considerations) to give $R(1) = 0.0684$ and $R_w(2) = 0.1824$ for 703 variables, 9 restraints, and 5755 observed reflections with $I > 2\sigma(I)$ and $1.59 \leq \theta \leq 20.04$. Deposition-No. CCDC-113988.

Compound **38** ($C_{23.20}H_{25.6}O_{5.60}$, M_r 394.04): monoclinic space group $P2(1)/c$, $\rho_{calc.} = 1.141$ g/cm^{-3}, $Z = 2$, $a = 9.035(3)$, $b = 19.250(6)$, $c = 17.071(5)$ Å, $\beta = 105.06(2)$, $V = 2867(2)$ Å^3. Single crystals were obtained by recrystallization from AcOEt/benzene/hexane. The structure was solved by direct methods and refined by full-matrix least-squares analysis (SHELXTL PLUS; heavy atoms anisotropic, H-atoms isotropic, whereby H-atom positions are based on stereochemical considerations) to give $R(1) = 0.0908$ and $R_w(2) = 0.2797$ for 350 variables and 2900 observed reflections with $I > 2\sigma(I)$ and $1.63 \leq \theta \leq 20.04$. Deposition-No. CCDC-113989.

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