76. Large Water-Soluble Cyclophanes with Convergent Intracavity Functionality

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New tricyclic spacers, readily available through fourfold *Mannich* reaction of substituted dibenzyl ketones, were introduced into a series of ten H_2O-soluble cyclophanes with spacious preorganized cavity binding sites. These spacers provide H_2O-solubility with amine or crown-ether functionality remote from the cyclophane cavity while directing functional groups such as keto or OH groups in a precise geometrical array inside the cavity. The cyclophanes were designed to include organic substrates *via* a combination of apolar and specific polar functional-group interactions. The X-ray crystal-structure analysis of the tritopic receptor **18** with one potential neutral-molecule and two cation-binding sites showed a large rectangular open cavity with dimensions of roughly 9 × 14 Å and a spacing of 9.7 Å between the O-atoms of two convergent C=O groups. Despite the binding-site preorganization, cyclophanes incorporating two of the new spacers did not show any substrate binding in aqueous solutions. The failure of these systems to function as receptors is mainly due to steric hindrance to important cyclophane aromatic ring-guest interactions. Also, the favorable solvation of the intracavity functionality may prevent the formation of complexes. Hybrid receptors constructed from the novel spacers and diphenylmethane units were found to bind flat aromatic substrates as well as bulky [4.2]paracyclophanes. The observed large differences in stability ($\Delta\Delta G° > 2$ kcal mol^{-1}) of the complexes formed by three structurally closely related hybrid receptors with convergent C=O, OH, or CH_2 groups and 6-hydroxynaphthalene-2-carbonitrile as guest can be explained by a strong solvation effect of the convergent functional groups on apolar inclusion complexation.

1. Introduction. – Large cyclophanes with preorganized cavities form stable inclusion complexes with apolar solutes in aqueous and organic solutions [1–6]. These host-guest associations are stabilized mainly through dispersion forces, solvophobic interactions, and aromatic-aromatic interactions [7]. The structural diversity of the cyclophane hosts, which were developed over the past decade, is quite impressive [8–28]. Concurrently, receptors featuring convergent functional-group arrays were constructed for the selective complexation of complementary substrates through multiple H-bonding [29–31]. With one exception [32], the latter complexes are stable only in solvents such as $CHCl_3$, benzene, or tetrahydrofuran (THF) since these solvents do not compete efficiently for the H-bond donor and acceptor sites of the interacting solutes. The inefficiency of neutral-molecule complexation by synthetic H-bonding receptors in more bio-relevant aqueous environments currently prevents their use for drug delivery, drug detoxification, and biosensoring. Therefore, we have initiated a program to develop novel complexing agents which combine the features of the H-bonding receptors and H_2O-soluble cyclophanes to form molecular complexes with high specificity in aqueous environments [33]. While these complexes should be stabilized mainly through strong apolar and solvophobic forces, high guest selectivity would be established through oriented H-bonding interactions. In this paper, we describe the synthesis, structural characterization, and binding

properties of a new series of H_2O-soluble cyclophanes featuring C=O or OH residues converging in a precise geometrical array into large apolar binding cavities [6] [8] [11] [34].

2. Results and Discussion. – 2.1. *Exploration of New Spacers for Water-Soluble Cyclophanes with Convergent Functional Groups.* A cyclic unit built up from a 1,3-diarylpropan-2-one core structure was chosen as a readily accessible rigid spacer for incorporation into recptors (*Fig. 1*). By linking two such building blocks into a cyclophane, a preorganized cavity with convergent ketone functionality forms. The ready transformation of the ketone to other functionality and the incorporation of a variety of polar H_2O-solubility-providing groups remote from the cavity [1] [2] should allow the preparation of a rich diversity of receptors.

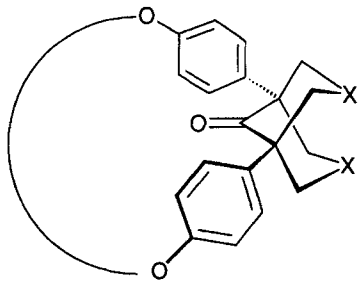
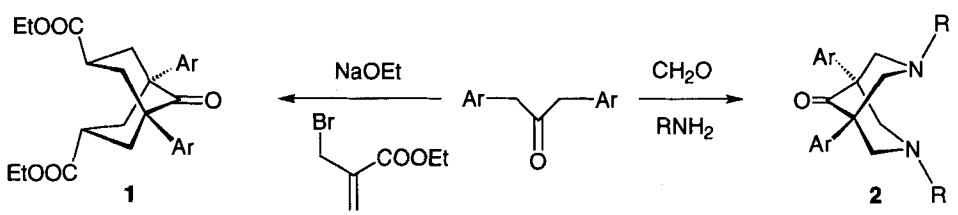


Fig. 1. *Receptor design.* X = H_2O-solubility-providing group.

In a first attempt to generate the desired spacers, treatment of 1,3-diphenylpropan-2-one with 2 equiv. of ethyl 2-(bromomethyl)acrylate under basic conditions gave the bicyclic ester **1** as an oil in low yield (*Scheme 1*) [35]. However, attempts to generate substituted derivatives of **1** suitable for incorporation into macrocycles were discouraging, and an alternative design was considered.

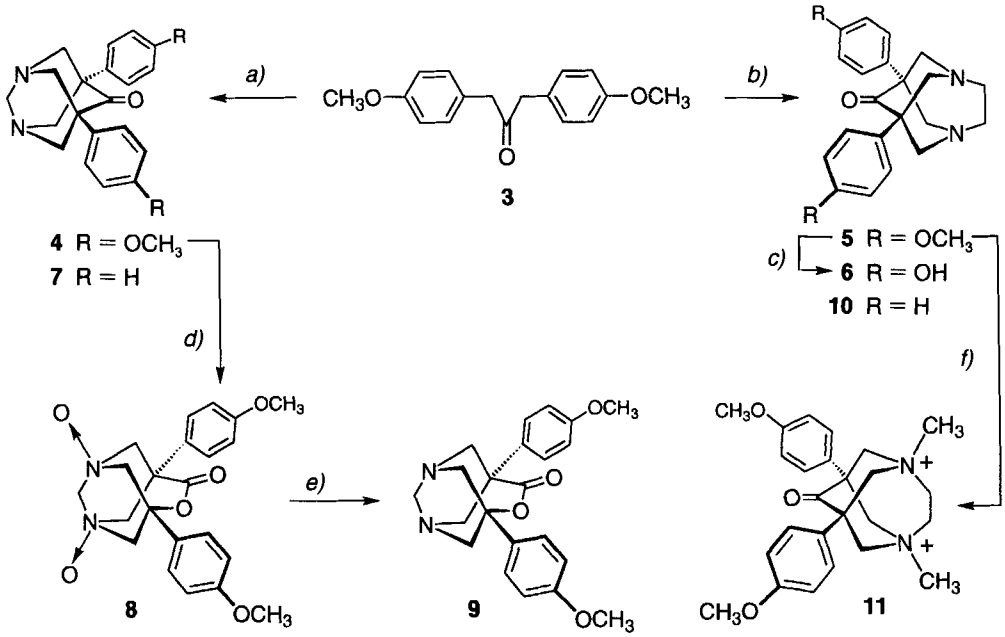
Scheme 1. *Possible Synthetic Approaches to Spacers for Cyclophane Hosts with Convergent Functional Groups*



The *Mannich* reaction of various 1,3-diarylpropan-2-ones with ammonia or primary amines affords crystalline products of fourfold condensations in high yields (see **2**, *Scheme 1*) [36]. Due to their ease of preparation and purification (they usually crystallize from the reaction mixture), these condensation products were chosen as building blocks for the planned receptors. Reaction of 1,3-bis(4-methoxyphenyl)propan-2-one (**3**) with formaldehyde and ammonia or ethylene-1,2-diamine afforded **4** and **5**, respectively (*Scheme 2*). Treatment of **5** with HI in refluxing AcOH afforded the corresponding bis(phenol) cyclization component **6**.

Methods for the introduction of H_2O-solubilizing groups were evaluated. The reaction of **7** with an excess of 3-chloroperbenzoic acid (3-$ClC_6H_4CO_3H$) was reported to give a H_2O-soluble bis(*N*-oxide) derivative [37]. However, treatment of **4** with an excess of

Scheme 2. *Synthetis of Spacers* **4** *and* **6** *and Exploration of* H_2O*-soluble Derivatives*



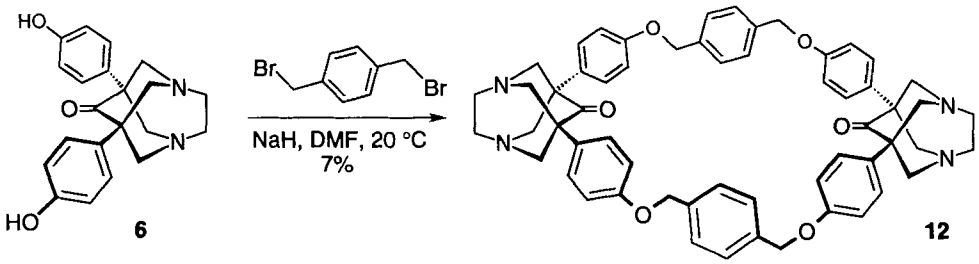
a) NH_4OAc, CH_2O, abs. EtOH, reflux, 5 h; 72%. *b*) $H_2NCH_2CH_2NH_2$, AcOH, CH_2O, abs. EtOH, reflux, 5 h; 61%. *c*) 47% aq. HI soln. AcOH, reflux, 42 h; 88%. *d*) 3-$ClC_6H_4CO_3H$, CH_2Cl_2, 20°, 14 h. *e*) PPh_3, $CHCl_3$, reflux, 4 h; 64% (steps *d* and *e*). *f*) MeI, DMF, 20°, 48 h.

3-$ClC_6H_4CO_3H$ cleanly gave the ring-expanded bis(*N*-oxide) **8** and, after reaction with PPh_3, the diaminolactone **9** (*Scheme 2*). Even the reaction with 2 equiv. of 3-$ClC_6H_4CO_3H$ at low temperatures afforded a mixture of ring-expanded and non-ring-expanded *N*-oxides. Apparently, the electron-donating aryl MeO groups in **4** stabilize the transition state for the *Baeyer-Villiger* reaction relative to that for *N*-oxide formation, and, for this reason, the use of *N*-oxides as solubilizing functionality in receptors built from **4** or **5** was abandoned.

The reaction of **7** and **10** with an excess of MeI in refluxing acetone gives the corresponding mono-quaternary ammonium salts, which precipitate directly from the reaction mixture [36f]. It is probable that the precipitation of the mono-quaternary salts prevented further reaction to give the bis-alkylated products. Treament of **5** with an excess of MeI in dimethylformamide (DMF) at 20° indeed gave a homogeneous solution from which the bis-quaternary salt **11** was isolated as evidenced by its ^{1}H-NMR spectrum in $(CD_3)_2SO$ (*s* at 3.53 ppm (2 MeN) and characteristic downfield shifts (as compared to the spectrum of **5**) of the resonances of CH_2NCH_2). Additionally, **5** was soluble in 2M HCl at concentrations less than $5 \cdot 10^{-3}$ mol l^{-1}. The incorporation of the corresponding diphenol **6** into a suitable macrocyclic structure, followed by permethylation or protonation, was, therefore, expected to provide H_2O-soluble compounds for evaluation as receptors.

2.2. *A Cyclophane Incorporating Ethylene-1,2-diamine-Bridged Tricyclic Units.* The macrocyclic compound **12** was chosen as the initial synthetic target. The *p*-xylylene (= phen-1,4-ylenebis(methyl)) residues in the bridges between the two spacers were

Scheme 3. *Synthesis of Cyclophane* **12**



chosen to maximize the apolar character of the cavity to provide a large hydrophobic driving force for the complexation of organic molecules [10]. High-dilution cyclization of **6** with 1,4-bis(bromomethyl)benzene gave the target compound **12** in low yield (*Scheme 3*). The poor cyclization yield (7%) is due not only to the usual formation of oligomeric and polymeric by-products, but also, presumably, to competitive alkylation of the phenoxide and tertiary-amine nucleophiles of **6** by the reactive alkyl halide.

Macrocycle **12** was surprisingly insoluble in acidic aqueous solutions. Reactions with an excess of MeI afforded the expected tetra-quaternary salt as evidenced by its ^{1}H-NMR spectrum ($(CD_3)_2SO$). However, the salt decomposed in the presence of protic solvents to give a complex mixture, presumably through a *retro-Mannich* or *Hoffman*-elimination process. As a result of these problems, alternative receptor designs were evaluated.

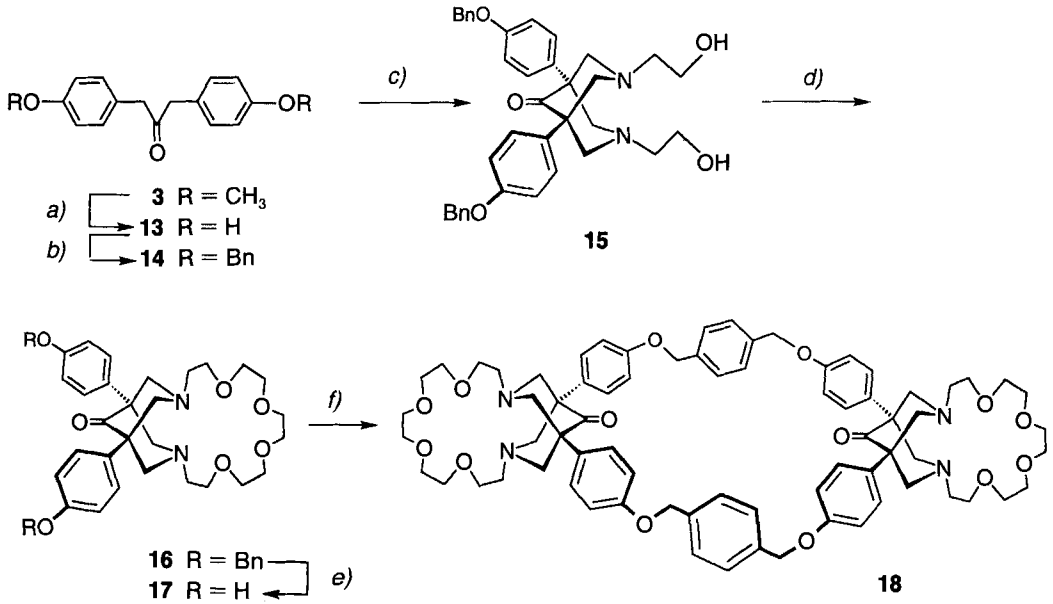
2.3. *Tritopic Cyclophane Receptors with One Apolar-Substrate and Two Cation Binding Sites.* We attributed the poor solubility of **12** in part to the high degree of structural rigidity of the novel spacer. To reduce this rigidity, tricyclic spacers with flexible crown-ether residues were incorporated into the cyclophanes. For the preparation of these spacers, ketone **3** was first transformed into the benzyl-protected derivative **14** *via* the demethylated **13** (*Scheme 4*). Subsequent *Mannich* reaction between **14** and 2-aminoethanol followed by cyclization of resulting diol **15** with triethylene glycol ditosylate gave the protected tricyclic building block **16**. Debenzylation afforded the bis(phenol) cyclization precursor **17** which was reacted with 1,4-bis(chloromethyl)benzene to give cyclophane **18**.

Crystallization of **18** from $CHCl_3$ yielded crystals suitable for X-ray analysis[1]). In the crystal, **18** adopts a spacious preorganized rectangular cavity with dimensions of roughly 9 × 14 Å and with a distance of 9.7 Å between the O-atoms of the two convergent C=O groups. The interior of this large cavity is solvated by a pool of highly disordered $CHCl_3$ molecules which, except for two (*Fig. 2a*), cannot be located. The crystals were not stable in the absence of the solvent and, for X-ray diffraction, were mounted in a capillary with solvent. The O···O distance of 11.3 Å between the aromatic-ether O-atoms of the tricyclic unit is very similar to that between the O-atoms in naphthyl(phenyl)methane spacers which were previously used to shape efficient large apolar binding sites [38]. Thus, all structural data suggest that the cavity of **18** should be suitably sized for the inclusion of large organic molecules such as steroids.

Cyclophane **18** was soluble in 1.5M DCl in D_2O/CD_3OD 6:4 at concentrations less than $5 \cdot 10^{-4}$ M. Unfortunately, broad signals were observed in the ^{1}H-NMR spectra of **18**, indicative of aggregation, even when diluted to $1 \cdot 10^{-4}$ M. Therefore, the evaluation of

[1]) Details of the X-ray crystal structure were given in the preliminary communication [33].

Scheme 4. *Synthesis of Cyclophane* **18**



a) HBr, AcOH, reflux, 4 h; 95%. *b*) $PhCH_2Br$, K_2CO_3, acetone, reflux, 12 h; 87%. *c*) $HOCH_2CH_2NH_2$, AcOH, CH_2O, abs. EtOH, reflux, 5 h; 37%. *d*) $TosO(CH_2CH_2O)_3Tos$, NaH, THF, reflux, 20 h; 63%. *e*) $NH_4(HCOO)$, 10% Pd/C, acetone, reflux, 2 h; 73%. *f*) *p*-$ClCH_2C_6H_4CH_2Cl$, Cs_2CO_3, MeCN, reflux, 1 d; 14%.

host-guest binding studies would be complicated by the presence of aggregates, and further modification of the receptor design was carried out.

To enhance the H_2O-solubility of the receptor, polar carboxylic acid groups were appended at the xylylene bridges. For this purpose, the bis(chloromethyl) derivative **20** was prepared from diester **19** and subsequently cyclized with **17** to give cyclophane **21** and, after hydrolysis, the desired tetra-acid **22** which was isolated as tris(hydrochloride salt) (*Scheme 5*).

The macrocyclic tetra-acid **22** was soluble in D_2O containing 0.01M Na_2CO_3, and the onset of aggregation as observed by ^{1}H-NMR occurred at [**22**] = $2 \cdot 10^{-4}$ M. Disappointingly, ^{1}H-NMR spectra of mixtures with [**22**] = $2–5 \cdot 10^{-4}$ M and suitably sized potential guests including hydrocortisone, taurodeoxycholic acid, brucine methiodide, and 2′,3′-*trans*-dihydroxy[4.2]paracyclophane (c = $1–5 \cdot 10^{-4}$ M) in 0.01M Na_2CO_3 in D_2O exhibited no chemical-shift changes relative to spectra of the individual components. The unexpected failure to observe complexation with **22** at this point was tentatively explained by steric hindrance of the bulky solvated carboxylate groups on the cavity periphery. Alternatively, the substituted xylene units could turn into the cavity, therefore filling any potential binding site.

The *p*-xylylene bridges were subsequently replaced by flexible butanediyl chains which serve as bridges between diphenylmethane and naphthyl(phenyl)methane units in a large variety of efficient cyclophane hosts [1] [2] [38]. The dichloride **23** was prepared by alkylation of **17** with an excess of 1,4-dichlorobutane, and cyclization of **17** with **23** afforded the target compound **24** (*Scheme 6*).

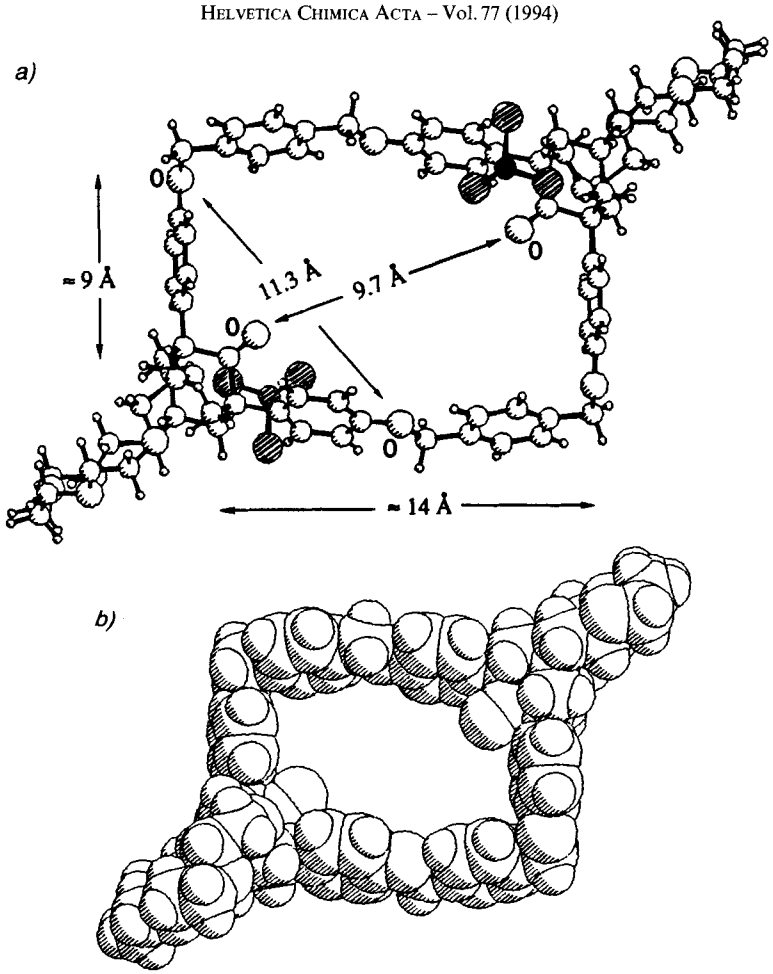
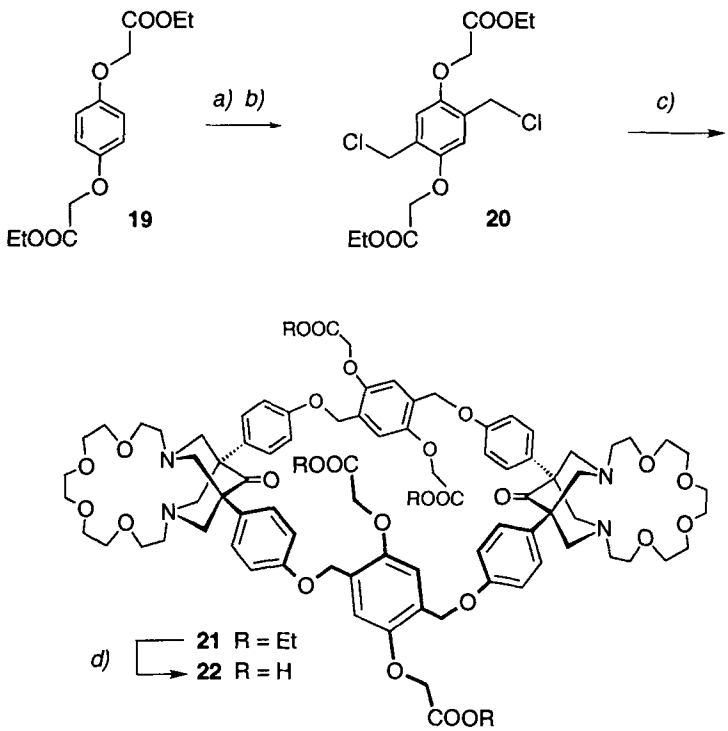


Fig. 2. a) *X-Ray crystal structure of cyclophane* **18** *showing selected interatomic distances and the two localized* $CHCl_3$ *molecules.* b) *Space-filling representation of the X-ray crystal structure of* **18**

Cyclophane **24** was soluble in 1.5M DCl in D_2O/CD_3OD 6:4, and aggregation occurred at [**24**] > $5 \cdot 10^{-4}$ M. No evidence for complex formation between **24** and hydrocortisone, cholic acid, or adamantane-1-acetic acid was observed in qualitative ^{1}H-NMR binding studies in the above solvent below the critical aggregation concentration. The inability of **24** to form inclusion complexes with suitably sized molecules, despite the high degree of preorganization of the cavity (*Fig. 2* and CPK model examinations), was explained by the efficient solvation of the intracavity functionality. However, at this point, it also became increasingly clear, that the convergent functional groups themselves were preventing crucial binding interactions by sterically blocking contacts between the aromatic rings of the cyclophane and the substrate. The blocking of the accessibility of the macrocyclic aromatic rings for interactions with cavity-bound substrates is clearly visible in the X-ray crystal structure show in *Fig. 2*.

The intracavity functionality was modified by reduction of **24** to the bis(diol) **25** which was obtained as a mixture of *meso*- and (±)-forms with significantly different ^{1}H-NMR

Scheme 5. *Synthesis of Cyclophane* **22**



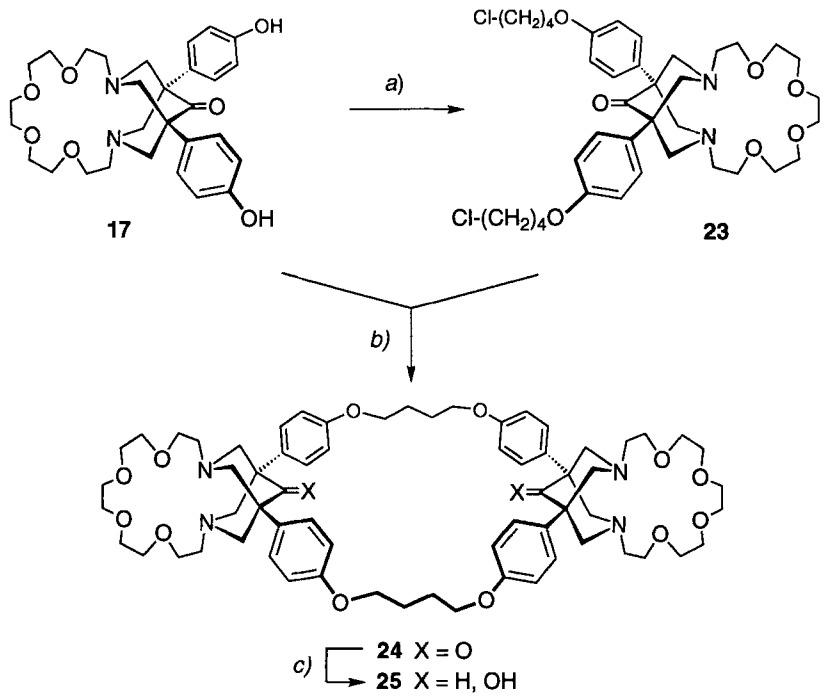
a) Conc. aq. HCl, 37% aq. CH_2O, 20°, 6 d. *b*) $SOCl_2$, THF, reflux, 3 h, then abs. EtOH, pyridine, CH_2Cl_2, 20°, 14 h; 65% (steps *a* and *b*). *c*) **17** (1 equiv.), Cs_2CO_3, MeCN, reflux, 1 d; 13%. *d*) $LiOH \cdot H_2O$, THF, H_2O, 20°, 2 d, then 1N aq. HCl; 80%.

spectra (*Scheme 6*). The aggregation properties of **25** were significantly more favorable than those of **24**. No aggregation was observed at $[\mathbf{25}] = 3 \cdot 10^{-3}$ M in 1.5M DCl in D_2O/CD_3OD 6:4. The OH groups increase the hydrophilic nature of the compound, and, as expected from the results obtained with **24**, the bis(diol) **25** did not show any significant binding capability.

2.4. *Hybrid Receptors Incorporating a Diphenylmethane Spacer Show Cavity Inclusion Complexation.* The synthesis of the first hybrid receptor involved the cyclization of bis(phenol) **17** with the known dichloride **26** [39] to the macrocyclic amide **27** (*Scheme 7*). Hydrolysis of the amide group, followed by *Eschweiler-Clarke* methylation gave the target compound **28**.

Cyclophane **28** was soluble in 3M DCl in D_2O/CD_3OD 8:2 and did not show any aggregation up to $c = 7 \cdot 10^{-3}$ M. In qualitative ^{1}H-NMR binding studies, no evidence for complex formation with hydrocortisone or adamantane-1-acetic acid was observed. However, substituted naphthalenes formed axial cavity inclusion complexes with **28**. The association constant for complexation of 2-hydroxynaphthalene-6-carbonitrile was determined in a ^{1}H-NMR binding titration [40] as $K_a = 1101\,mol^{-1}$ (293 K). This promising result induced a more detailed study of complexation in related hybrid receptors with various intracavity functionality.

Scheme 6. *Synthesis of Cyclophanes* **24** *and* **25**

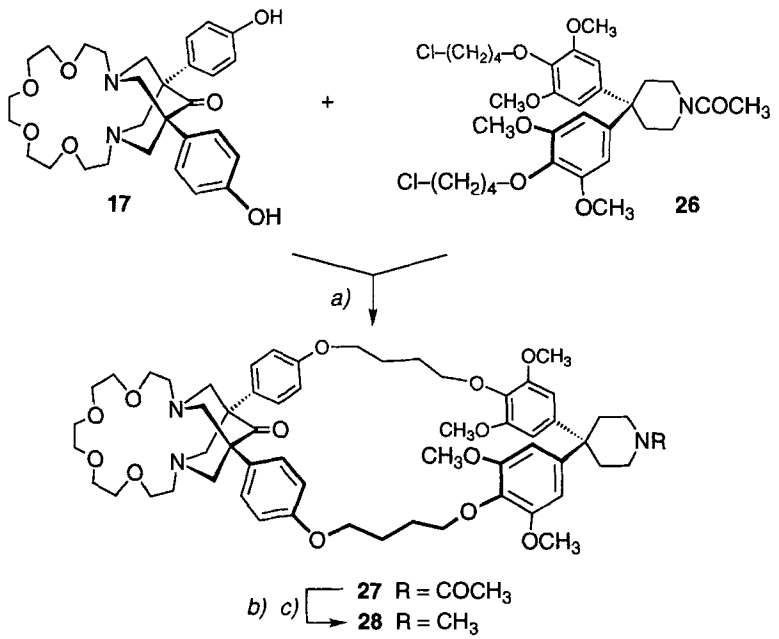


a) $Cl(CH_2)_4Cl$, NaH, DMF, 20°, 3 h; 99%. *b*) Cs_2CO_3, DMF, 75–80°, 3 d; 18%. *c*) $LiAlH_4$, THF, 20°, 3 h; 68%.

For the synthesis of these receptors, the crown unit of **28** was replaced by the tricyclic aminal unit derived from **4** (*Scheme 2*). Since the cyclic aminal is unstable to the hydrolysis of an acetamido group (as in **27** → **28**, *Scheme 7*), it was necessary to prepare the carbamate-protected diphenylmethane unit **32** following the sequence **29** [41] → **30** → **31** → **32** (*Scheme 8*). *Mannich* reaction of ketone **14** (*Scheme 4*) with NH_3 gave the tricyclic system **33**. Reductive removal of the benzyl protecting groups could be effected either before or after *Wolff-Kishner* reduction to **34**, affording bis(phenols) **35** and **36**, respectively. Strictly anhydrous conditions were necessary for the success of the *Wolff-Kishner* reaction. In the presence of H_2O, the reaction yielded an inseparable mixture of **34** and the corresponding alcohol. The alcohol is presumably produced *via* one-electron reduction of the ketone by hydroxide ion [42]. Additionally, examination of the ^{1}H-NMR spectrum of the crude *Wolff-Kishner* reaction mixture indicated that partial aminal hydrolysis occurred to give the corresponding bis(secondary amine) as major by-product. To simplify the purification of **34**, the crude reaction mixture was treated with formaldehyde, followed by crystallization to afford **34** as the only product in good yield. With the bis(phenols) **35** and **36** in hand, cyclization with dichloride **32** was carried out to give the macrocycles **37** and **39**, respectively. The macrocyclic ketone **37** was reduced to give the alcohol **38**. Deprotection under acidic conditions yielded the desired hybrid receptors **40**–**42**.

The hybrid receptors **40**–**42** were soluble in 0.8M DCl in D_2O/CD_3OD 6:4 at $c \leqslant 2 \cdot 10^{-3}$ M with no indication of aggregation. Qualitative ^{1}H-NMR complexation

Scheme 7. *Synthesis of Cyclophane* **28**

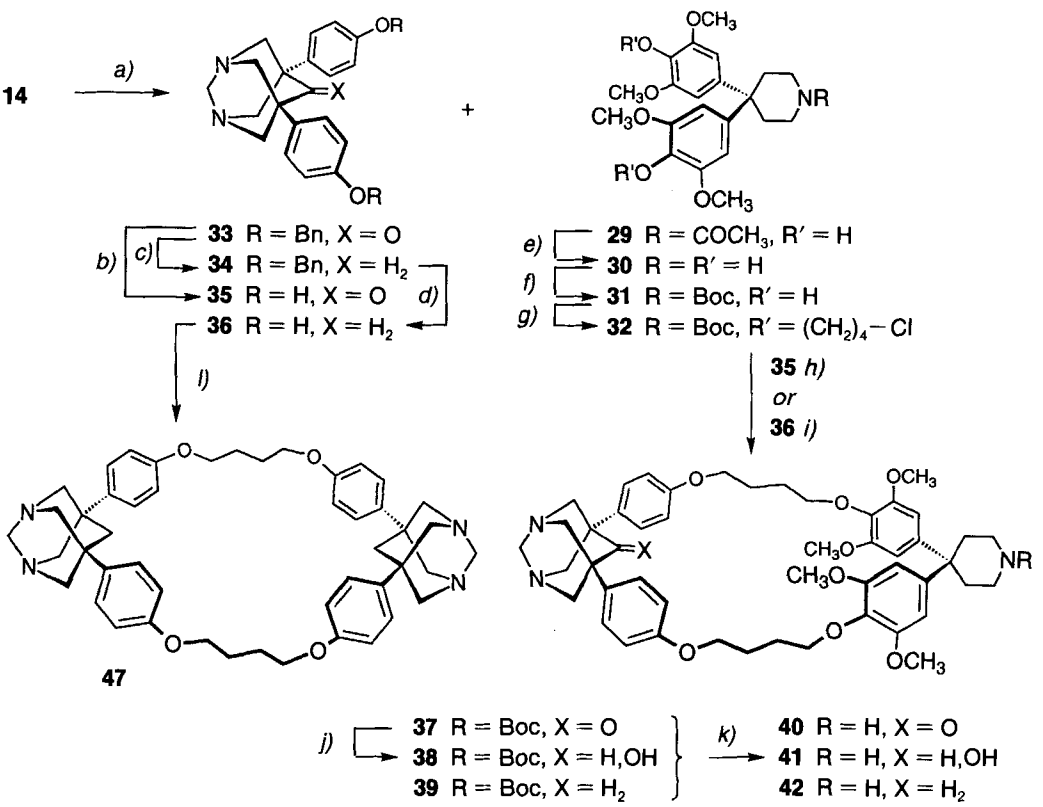


a) Cs_2CO_3, DMF, 75–80°, 1 d; 17%. *b*) KOH, $MeOCH_2CH_2OH$, reflux, 36 h. *c*) 37% aq. CH_2O soln., 88% aq. HCOOH soln., H_2O, 110°, 1 d; 46% (steps *b* and *c*).

studies at one concentration ($[H]_o = [G]_o \approx 1 \cdot 10^{-3}$ M) showed evidence for inclusion of naphthalene derivatives by hosts (H) **40** and **42**. Complexation of larger guests (G) such as steroids, paracyclophanes, and adamantane derivatives by the functionalized receptors **40** and **41** was not observed. However, the apolar host **42** was capable of inclusion of paracyclophanes such as **43** and adamantane-1-acetic acid, but not steroids. Full binding titrations were executed in which either host or guest concentration was kept constant, and the results are shown in *Table 1*. Proton resonances evaluated in the titrations were either those of the aromatic H-atoms of naphthalene guests or the $ArOCH_2$ bridge H-atoms of the host. In addition, the resonances of the intracavity H-atoms $ArCCH_2CAr$ of **42** shifted significantly upon inclusion complexation. Although excellent nonlinear least-squares fits to the experimental data points were obtained in each case, the thermodynamic data should be considered approximations, since the degree of saturation binding observed in the titrations was limited by solubility and reached only values between *ca.* 30 and 60% (see *Table 2, Exper. Part*).

The following conclusions can be drawn: *i*) The inclusion of the bulky paracyclophane guest **43** confirms that the tricyclic spacer in **42** forms a spacious preorganized cavity binding site as suggested by the X-ray structure analysis of **18** (*Fig. 2*). *ii*) The naphthalene guests **44–46** are preferentially included axially in the narrow diphenylmethane region of the binding site and undergo aromatic-aromatic interactions with the two trialkoxybenzene rings of **40** and **42** [39]. The aromatic rings of the tricyclic spacer are sterically prevented from interacting with the naphthalene rings and, in addition, shape a region of the cavity which is too wide for a tight incorporation of these flat substrates.

Scheme 8. *Synthesis of the Hybrid-Cyclophanes* **40–42** *and Macrocycle* **47**



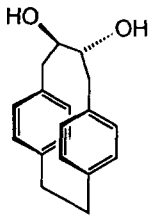
a) CH_2O, NH_4OAc, abs. EtOH, reflux, 3 d; 78%. *b*) $NH_4(HCOO)$, 10% Pd/C, THF, reflux, 1.5 h; 88%. *c*) $NH_2NH_2 \cdot H_2O$, anh. NaOAc, $HO(CH_2CH_2O)_2H$, reflux, 2 d, then 37% aq. CH_2O, MeOH, reflux, 4 h; 99%. *d*) $NH_4(HCOO)$, 10% Pd/C, DMF, 50°, 1.5 h; 88%. *e*) Conc. aq. HCl soln., MeOH, reflux, 1 d; 100%. *f*) $(Boc)_2O$, CH_2Cl_2, Et_3N, 20°, 15 min. *g*) $Cl(CH_2)_4Cl$, K_2CO_3, acetone, reflux, 3 d; 76% (steps *f* and *g*). *h*) Cs_2CO_3, DMF, 50–55°, 6 d; 13%. *i*) Cs_2CO_3, DMF, 50°, 4 d; 13%. *j*) $LiAlH_4$, THF, 20°, 1.5 h; 82%. *k*) CF_3COOH, CH_2Cl_2, 20°, 1 h; 86% (**40**), 74% (**41**), 52% (**42**). *l*) $Cl(CH_2)_4Cl$, DMF, 55°, 7 d; 6%.

This is demonstrated by the differential complexation-induced shifts of the $ArOCH_2$ protons at both spacers. At [**44**] = 9 mM and [**42**] = 0.5 mM, the OCH_2 protons at the diphenylmethane unit are shifted upfield by 0.34 ppm, whereas the OCH_2 protons at the tricyclic spacer were only shifted by 0.07 ppm. Naphthalene complexation in the hybrid cyclophanes is almost entirely due to favorable interactions of the guests with the diphenylmethane unit. *iii*) Host **42** with no intracavity functional group is by far the best receptor. Ketone **40** forms weaker complexes, whereas the hydroxy derivative **41** does not exhibit any significant binding. The observed differences in stability between the complexes of 6-hydroxynaphthalene-2-carbonitrile (**44**) ($\Delta\Delta G^\circ \geqslant 2$ kcal mol^{-1}) reflect specific desolvation effects [2] [7] [39]. In the cavities of **40** and **41**, incorporation of an apolar naphthalene residue leads to the energetically unfavorable desolvation of the strongly solvated intracavity functional group. *iv*) There is no complexation with guests bearing appropriate functional groups to H-bond specifically with the intracavity functionality of

Table 1. *Association Constants* K_a [l mol^{-1}] and *Binding Free Energies* $-\Delta G°$ [kcal mol^{-1}] *for 1:1 Inclusion Complexes Determined by 500-MHz ^{1}H-NMR Titrations at 293 K in 0.8 M DCl in D_2O/CD_3OD 6:4*

Host	Guest	K_a [l mol^{-1}]	$-\Delta G°$ [kcal mol^{-1}]
28	**44**	110	2.7[a])
40	**44**	40	2.2
41	**44**	$\ll$ 10	$\ll$ 1.3
42	**44**	210	3.1
42	**45**	80	2.6
42	**46**	50	2.3
42	**43**	120	2.8[b])

[a]) In 3M DCl in D_2O/CD_3OD 8:2.
[b]) In 0.8M DCl in D_2O/CD_3OD 1:1.



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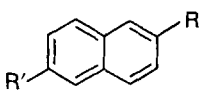

44 R = OH, R′ = CN
45 R = OH, R′ = MeO
46 R = R′ = SO_3H

40 and **41**. Apparently, there is no energy gained by replacing the solvation shells of these groups by H-bonds to a bound substrate.

2.5. *Steric Hindrance of the Interactions between Substrate and Aromatic Rings in a Large Apolar Cyclophane Prevents Complexation.* Although the above analysis strongly suggests that the diphenylmethane unit is largely responsible for substrate binding in the hybrid receptors, the performance of the tricyclic spacer in **42** encouraged the preparation of **47** (*Scheme 8*) through reaction of bis(phenol) **36** with 1,4-dichlorobutane in the presence of Cs_2CO_3 under high-dilution conditions. Macrocycle **47** was expected to form a spacious apolar cavity for the complexation of large lipophilic guests. Binding studies were performed in 1.5M DCl in D_2O/CD_3CN 6:4 at [**47**] $\leq 7 \cdot 10^{-4}$ M. No evidence for complexation was observed with adamantane-1-acetic acid, testosterone, or 6-hydroxy-naphthalene-2-carbonitrile (**44**). We take this as additional evidence for the crucial role of the aromatic rings in cyclophane inclusion complexation. The spatial orientation of the aromatic rings attached to the spacers in **47** is unsuitable for favorable interactions with cavity-bound substrates. In sharp contrast, diphenylmethane spacers properly orient their aromatic rings for apolar and aromatic-aromatic host-guest interactions in [*n*.1.*n*.1]paracyclophanes which, as a result, are among the best binders of organic molecules known [1] [2].

3. Conclusions. – In this study, several cyclophane receptors with polar functional groups converging into spacious preorganized apolar binding sites were prepared to complex organic molecules *via* the simultaneous use of favorable polar and apolar interactions. Novel tricyclic spacers were introduced which direct carbonyl and alcohol functionalities inside the cavity while locating H_2O-solubility-providing groups outside the potential recognition site. In binding studies with appropriate guests, no evidence for inclusion complex formation was obtained. The failure of the receptors to function as planned is mainly due to important cyclophane aromatic ring-guest interactions being prevented by steric hindrance. An efficient solvation of the intracavity functionality may be another factor in preventing the formation of complexes.

Hybrid receptors were constructed from the novel tricyclic spacers and the well-studied diphenylmethane units. An interesting trend based on differential solvation requirements of intracavity functional groups was observed in the complexation of 6-hydroxynaphthalene-2-carbonitrile. An OH group was found to provide a much greater hindrance to binding than a ketone group. This reflects that the OH residue is associated with a larger ordered solvation network than the C=O group. The cavity of the alcohol is, therefore, more hydrophilic and less suitable for apolar complexation.

Although the compounds prepared in this work failed to function as planned by not showing efficient binding based on apolar interactions and specific intracavity functional-group interactions, their study produced valuable results. A better understanding of the effects of solvation on hydrophobic complexation was obtained. The molecular structure of **18** showed the largest preorganized cavity in a synthetic cyclophane observed by X-ray analysis. The rigid location of functional groups buried between two aryl units in the new tricyclic spacers invites the exploration of the chemistry of these groups and the stereoelectronic constraints resulting from their unique position. Thus, while the *Baeyer-Villiger* oxidation of **4** to lactone **8** proceeded cleanly, the *Beckmann* rearrangement leading to the corresponding lactame was unsuccessful. The preparation of novel catalytic cyclophanes [40] [43] based on the tricyclic building blocks of this study may be possible. These units should direct catalytic groups such as transition-metal-coordinated phosphines inside the cavity rather than towards its periphery. Work on such systems is in progress.

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Experimental Part

General. See [40] [43]. Steroids for binding studies were purchased from *Aldrich* and used as received. Paracyclophane **43** was kindly provided by Prof. *D. J. Cram*, UCLA. Evaporation and concentration *in vacuo* was done at H_2O-aspirator pressure, drying *in vacuo* at 10^{-2} Torr. Desorption-electron impact (DEI) mass spectra were recorded on a *VG-7070-EHF* instrument at UC Riverside.

^{1}H-NMR Complexation Studies. For the preparation of samples, see [40]. During the binding titrations, either host or guest concentration was varied (*Table 2*), and the changes in chemical shift of protons of the solute held at constant concentration were monitored and evaluated. The association constants K_a and binding free energies $-\Delta G°$ were calculated from the titration curves by a nonlinear least-squares treatment using a program written by *S. B. Ferguson* [44]. *Table 2* shows the maximum observed complexation-induced changes in chemical shifts $\Delta\delta$(obs), the calculated changes at saturation binding $\Delta\delta$(sat), and the degree of saturation reached during the titration.

1,3-Bis(4-methoxyphenyl)propan-2-one (**3**). A soln. of $MnCl_2 \cdot 4H_2O$ (379 g, 1.91 mol) in H_2O (250 ml) was added slowly with stirring to a soln. of (4-methoxyphenyl)acetic acid (313.5 g, 1.88 mol) in aq. Na_2CO_3 soln. (200 g, 1.88 mol). The resulting precipitate was collected and dried *in vacuo* at 80°: 415 g of an off-white powder. The solid was divided into two portions, each of which was pyrolyzed in a 500-ml round-bottom flask (distillation head, vacuum adapter). The flask and distillation head were heated to *ca.* 200–250° with a heating mantle and heating tape under a vacuum of *ca.* 0.5 Torr. The product distilled over and solidified to give a yellow mass which was recrystallized from abs. EtOH: 145 g (57%). M.p. 86–87° ([36b]: m.p. 84–86°). ^{1}H-NMR (200 MHz, $CDCl_3$): 3.46 (*s*, 4 H); 3.72 (*s*, 6 H); 6.78 (*d*, J = 9.1, 4 H); 6.99 (*d*, J = 9.1, 4 H).

5,7-Bis(4-methoxyphenyl)-1,3-diazatricyclo[3.3.1.1^{3,7}]decan-6-one (**4**). A mixture of **3** (10.2 g, 0.037 mol), NH_4OAc (57 g, 0.74 mol), and paraformaldehyde (5.2 g, 0.17 mol) in abs. EtOH (110 ml) was heated to reflux for 5 h. After cooling, the formed precipitate was collected and washed with abs. EtOH. Drying *in vacuo* afforded **4** (9.9 g, 72%). White solid. M.p. 219–220°. IR ($CDCl_3$): 1702 (C=O). ^{1}H-NMR (360 MHz, $CDCl_3$): 3.76, 3.82 (2*d*, J = 12.6, 8 H); 3.80 (*s*, 6 H); 4.26 (*s*, 2 H); 6.91 (*d*, J = 8.9, 4 H); 7.12 (*d*, J = 8.9, 4 H). DEI-MS: 364 (34, M^+), 133 (100, $MeOC_6H_4CCH_2^+$). Anal. calc. for $C_{22}H_{24}N_2O_3$ (364.45): C 72.51, H 6.64, N 7.69; found: C 72.37, H 6.74, N 7.66.

Table 2. *Selected Examples of ^{1}H-NMR-Titration-Binding Data* (500 MHz, 293 K)

Run	*Concentration* [mM][a])	Protons observed[b])	$\Delta\delta$ (obs)[c])	$\Delta\delta$ (sat)[d])	% sat.[e])
1)	**[44]** = 1.00	H–C(5)	0.82	2.19	37
	$[\mathbf{28}]_{max}$ = 5.38	H–C(1)	0.58	1.67	35
2)	**[40]** = 0.50	OCH_2[f])	0.29	1.09	27
	$[\mathbf{44}]_{max}$ = 8.90				
3)	**[42]** = 0.52	$ArCCH_2CAr$	0.37	0.60	62
	$[\mathbf{44}]_{max}$ = 8.94	OCH_2[f])	0.34	0.54	63
4)	**[42]** = 0.55	$ArCCH_2CAr$	0.29	0.74	39
	$[\mathbf{45}]_{max}$ = 9.37	OCH_2[f])	0.19	0.42	45
5)	**[42]** = 0.54	$ArCCH_2CAr$	0.16	0.43	37
	$[\mathbf{43}]_{max}$ = 5.11				

[a]) Highest concentration of titrant at which $\Delta\delta$(obs) was determined.
[b]) Proton shifts of the binding partner held at constant concentration are evaluated.
[c]) Maximum observed complexation-induced change in ^{1}H-NMR chemical shift.
[d]) Complexation-induced change in ^{1}H-NMR chemical shift calculated for saturation binding.
[e]) Percent of saturation binding reached during the titration.
[f]) Ether linkage at the diphenylmethane unit.

1,8-Bis(4-methoxyphenyl)-3,6-diazatricyclo[4.3.1.1^{3,8}]undecan-9-one (**5**). Ethylene-1,2-diamine (15.5 ml, 0.23 mmol) followed by AcOH (8.0 ml, 0.14 mmol) was added to a suspension of **3** (10.4 g, 38.4 mmol) and paraformaldehyde (13.6 g, 0.45 mmol) in abs. EtOH (1.5 l), and the mixture was refluxed for 5 h. The resultant dark reddish-brown soln. was concentrated to 100 ml and allowed to cool. The precipitate was collected, washed with cold abs. EtOH (100 ml), and dried *in vacuo* to give **5** as a fine white powder: 8.92 g (61%). M.p. 201–202° (EtOH). IR ($CDCl_3$): 1705 (C=O). ^{1}H-NMR (500 MHz, $CDCl_3$): 3.31 (*s*, 4 H); 3.43, 3.82 (2*d*, *J* = 14.1, 8 H); 3.80 (*s*, 6 H); 6.89 (*d*, *J* = 8.9, 4 H); 7.18 (*d*, *J* = 8.9, 4 H). EI-MS (70 eV): 378 (100, M^+). Anal. calc. for $C_{23}H_{26}N_2O_3$ (378.47): C 72.99, H 6.92, N 7.40; found: C 73.02, H 7.00, N 7.40.

1,8-Bis(4-methoxyphenyl)-3,6-dimethyl-9-oxo-3,6-diazoniabicyclo[4.3.1.1^{3,8}]undecane Diiodide (**11**·2I$^-$). To a soln. of **5** (5 mg) in DMF (1 ml) was added MeI (1 ml). The homogeneous soln. was stirred at 20° for 2 d, then concentrated to *ca.* 0.5 ml. Precipitation with Et_2O gave **11** as a yellow solid which was dried *in vacuo*. ^{1}H-NMR (360 MHz, $(CD_3)_2SO$): 3.53 (*s*, 6 H); 3.78 (*s*, 6 H); 4.42 (*s*, 4 H); 4.63, 4.85 (2*d*, *J* = 13.9, 8 H); 7.04 (*d*, *J* = 9.0, 4 H); 7.38 (*d*, *J* = 9.0, 4 H).

1,8-Bis(4-hydroxyphenyl)-3,6-diazatricyclo[4.3.1.1^{3,8}]undecan-9-one (**6**). A suspension of **5** (5.0 g, 13.2 mmol), 47% aq. HI soln. (10 ml, 69.0 mmol) and H_2O (10 ml) in AcOH (250 ml) was refluxed for 42 h, then concentrated *in vacuo* to near dryness. H_2O was added to bring the total volume to 100 ml, then conc. aq. NH_4OH soln. (*ca.* 50 ml) was added dropwise to give pH 7. Sodium metabisulfite (0.5 g) was added to the hot suspension which was stirred vigorously while it slowly cooled to 20°. The suspension was cooled to 0°, then filtered through a fritted-glass funnel. The solid was washed on the frit with H_2O (25 ml) and Et_2O (50 ml), then dried *in vacuo* at 90°: **6** (4.1 g, 88%) as a yellow-white powder. An anal. sample was obtained by recrystallization from benzene. M.p. 285° (dec.). IR (KBr): 1700 (C=O). ^{1}H-NMR (500 MHz, $(CD_3)_2CO$): 3.28 (*s*, 4 H); 3.42, 3.69 (2*d*, *J* = 13.8, 8 H); 6.78 (*d*, *J* = 9.1, 4 H); 7.12 (*d*, *J* = 9.1, 4 H). DEI-MS: 350 (100, M^+). Anal. calc. for $C_{21}H_{22}N_2O_3$ (350.42): C 71.98, H 6.33, N 7.99; found: C 71.65, H 6.02, N 7.79.

3,6-Bis(4-methoxyphenyl)-4-oxa-1,8-diazatricyclo[4.3.1.1^{3,8}]undecan-5-one (**9**). A soln. of 80% 3-chloroperbenzoic acid (0.99 g, 4.6 mmol) in CH_2Cl_2 (15 ml) was added dropwise to a stirred soln. of **4** (0.47 g, 1.3 mmol) in CH_2Cl_2 (90 ml) at 0° under Ar. The mixture was allowed to warm slowly to 20°, then stirred overnight, concentrated, and chromatographed (basic alumina (act. I, 10 g), $CHCl_3$→$CHCl_3$/MeOH 3:1). The isolated hygroscopic yellow oil was dissolved in warm $CHCl_3$ (10 ml) and diluted with Et_2O to 100 ml. The precipitated solid was dried *in vacuo*: crude **8**. Very hygroscopic white solid. ^{1}H-NMR (360 MHz, CD_3OD): 3.80, 3.83 (2*s*, 6 H); 4.04, 4.72 (2*d*, *J* = 12.3, 4 H); 4.15, 4.30 (2*d*, *J* = 13.8, 4 H); 4.72, 4.99 (2*d*, *J* = 11.1, 2 H); 6.95 (*d*, *J* = 9.5, 2 H); 7.01 (*d*, *J* = 9.5, 2 H); 7.19 (*d*, *J* = 9.5, 2 H); 7.67 (*d*, *J* = 9.5, 2 H). The solid was dissolved in $CHCl_3$ (100 ml), PPh_3 (0.86 g, 3.3 mmol) was added, and the mixture refluxed under Ar for 4 h. Evaporation give a thick oil which was triturated with Et_2O (20 ml) to afford a white solid. Recrystallization from abs. EtOH/$CHCl_3$ 95:5 gave colorless **9** (0.32 g, 64%). M.p. 211–213°. IR ($CDCl_3$): 1718 (C=O). ^{1}H-NMR (500 MHz, $CDCl_3$): 3.62, 3.88 (2*d*, *J* = 14.5, 4 H); 3.69, 4.11 (2*d*, *J* = 14.5, 4 H); 3.82 (*s*, 6 H); 4.19, 4.35 (2*d*, *J* = 13.3, 2 H); 6.93 (*d*, *J* = 9.2, 4 H); 7.12 (*d*, *J* = 9.2, 2 H); 7.50 (*d*, *J* = 9.2, 2 H). DEI-MS 380 (75, M^+), 133 (100, $MeOC_6H_4CCH_2^+$). Anal. calc. for $C_{22}H_{24}N_2O_4$ (380.45): C 69.46, H 6.36, N 7.36; found: C 69.60, H 6.47, N 7.43.

14, 21, 38, 45-Tetraoxa-4, 7, 28, 31-tetraazatridecacyclo[44.2.2.2^{10,13}.2^{16,19}.2^{22,25}.2^{34,37}.2^{40,43}.1^{2,7}.1^{2,9}.1^{4,9}.1^{26,31}.1^{26,33}.1^{28,33}]hexahexaconta-10,12,16,18,22,24,34,36,40,42,46,48,49,51,53,58,60,62-octadecaene-56,65-dione (**12**). Bis-(phenol) **6** (0.82 g, 2.34 mmol) was added under Ar to NaH (60% dispersion; 1.37 g, 0.034 mmol) in dry DMF (700 ml). A soln. of 1,4-(bromomethyl)benzene (0.77 g, 2.92 mmol) in DMF (50 ml) was added to the stirred mixture *via* syringe pump over 40 h. After stirring for 1 d, AcOH (1 ml) was added, the solvent evaporated, and the residue extracted with $CHCl_3$/MeOH 4:1 (200 ml) and filtered. Silica gel (5 g) was added to the soln. and the solvent evaporated. Chromatography of the adsorbed material (SiO_2 (300 ml), $CH_2Cl_2 \rightarrow CH_2Cl_2$/MeOH 97:3) gave an impure yellow-white solid which was dissolved in a small amount of hot $CHCl_3$ and precipitated with abs. EtOH: **12** (70 mg, 7%). Colorless powder. M.p. *ca.* 300° (dec.) IR ($CDCl_3$): 1704 (C=O). ^{1}H-NMR (500 MHz, $CDCl_3$): 3.31 (*s*, 8 H); 3.40, 3.80 (2*d*, *J* = 13.5, 16 H); 5.11 (*s*, 8 H); 6.84 (*d*, *J* = 8.9, 8 H); 7.05 (*d*, *J* = 8.9, 8 H); 7.32 (*s*, 8 H). FAB-MS: 905 (100, $[M + H]^+$). Anal. calc. for $C_{58}H_{56}N_4O_6$ (905.12): C 76.97, H 6.24, N 6.19; found: C 77.03, H 6.28, N 6.16.

Reaction with MeI: A homogenous soln. of **12** (20 mg) and MeI (6 ml) in DMF (4 ml) was stirred at 20° in the dark for 7 h and concentrated to *ca.* 1 ml. Precipitation with Et_2O gave **12**·4 MeI as a yellow solid which was dried *in vacuo*. ^{1}H-NMR (360 MHz, $(CD_3)_2SO$): 3.52 (*s*, 12 H); 4.44 (*s*, 8 H); 4.59, 4.85 (2*d*, *J* = 13.9, 16 H); 5.20 (*s*, 8 H); 7.04 (*d*, *J* = 9.1, 8 H); 7.27 (*d*, *J* = 9.1, 8 H); 7.39 (*s*, 8 H). The ^{1}H-NMR of a soln. of **12**·4 MeI in D_2O/CD_3OD 1:1 (solubility 3 mg/ml) indicated extensive decomposition.

1,3-Bis(4-hydroxyphenyl)propan-2-one (**13**). A soln. of **3** (21.9 g, 0.081 mol) in 48% aq. HBr soln. (100 ml) and AcOH (250 ml) was refluxed for 4 h. The clear soln. was diluted to 1 l with H_2O and extracted with Et_2O (3 × 350 ml), the combined Et_2O layer washed with aq. sodium metabisulfite (2 × 500 ml) and sat. aq. NaCl soln. (500 ml), dried ($MgSO_4$) and evaporated **13** (18.6 g, 95%). Pink solid which gave a yellow-orange powder upon recrystallization from benzene. M.p. 150–152°. IR (KBr): 1710 (C=O). ^{1}H-NMR (500 MHz, $CDCl_3$): 3.61 (*s*, 4 H); 6.73 (*d*, *J* = 9.3, 4 H); 6.98 (*d*, *J* = 9.3, 4 H). DEI-MS: 242 (9, M^+), 107 (100, $HOC_6H_4CH_2^+$). Anal. calc. for $C_{15}H_{14}O_3$ (242.28): C 74.36, H 5.82; found: C 74.47, H 5.80.

1,3-Bis[4-(benzyloxy)phenyl]propan-2-one (**14**). To a soln. of **13** (10.0 g, 0.041 mol) in acetone (250 ml) was added benzyl bromide (11.0 ml, 0.093 mol) and anh. K_2CO_3 (20 g, 0.14 mol). After refluxing for 12 h, filtration through *Celite*, evaporation, and crystallization from abs. EtOH yielded **14** (15.1 g, 87%). Yellow crystalline solid. M.p. 119°. IR ($CDCl_3$): 1714 (C=O). ^{1}H-NMR (500 MHz, $CDCl_3$): 3.60 (*s*, 4 H); 5.00 (*s*, 4 H); 6.99 (*d*, *J* = 8.5, 4 H); 7.02 (*d*, *J* = 8.5, 4 H); 7.28–7.41 (*m*, 10 H). DEI-MS: 422 (100, M^+). Anal. calc. for $C_{29}H_{26}O_3$ (422.53): C 82.44, H 6.20; found: C 82.43, H 6.17.

3,7-Bis(2-hydroxyethyl)-1,5-bis[4-(benzyloxy)phenyl]-3,7-diazabicyclo[3.3.1]nonan-9-one (**15**). A mixture of **14** (5.02 g, 11.9 mmol), 2-aminoethanol (5.0 ml, 82.7 mmol), AcOH (4.0 ml, 69.9 mmol), and paraformaldehyde (4.34 g, 0.144 mol) in abs. EtOH (175 ml) was refluxed under Ar for 5 h. Evaporation of the EtOH yielded a thick red oil which was chromatographed (SiO_2 (500 ml), AcOEt → AcOEt/MeOH/Et_3N 92:4:4): 2.6 g (37%) of a yellow foam. IR ($CDCl_3$): 1724 (C=O). ^{1}H-NMR (360 MHz, $CDCl_3$): 2.74 (*t*, *J* = 5.8, 4 H); 3.18, 3.68 (2*d*, *J* = 12.5, 8 H); 3.74 (*t*, *J* = 5.8, 4 H); 5.07 (*s*, 4 H); 6.98 (*d*, *J* = 8.9, 4 H); 7.19 (*d*, *J* = 8.9, 4 H); 7.30–7.45 (*m*, 10 H). FAB-HR-MS: 593.3013 ($[M + H]^+$, $C_{37}H_{41}N_2O_5^+$, calc. 593.3015).

1,20-Bis[4-(benzyloxy)phenyl]-6,9,12,15-tetraoxa-3,18-diazatricyclo[16.3.1.1^{3,20}]tricosan-21-one (**16**). A suspension of **15** (2.05 g, 3.46 mmol) and NaH (80% dispersion; 0.30 g, 10.0 mmol) in dry THF (700 ml) was refluxed under Ar for 30 min. A soln. of TosO(CH_2CH_2O)Tos [45] (1.75 g, 3.82 mmol) in THF (300 ml) was added and reflux continued for 20 h. After addition of AcOH (1 ml), the mixture was evaporated and the orange residue extracted with warm $CHCl_3$ (300 ml). Filtration through *Celite*, concentration, and chromatography (SiO_2 (300 ml), AcOEt → AcOEt/MeOH/Et_3N 96:2:2) afforded **16** (1.53 g, 63%). Yellow-orange oil which foamed in *in vacuo*. IR ($CDCl_3$): 1724 (C=O). ^{1}H-NMR (360 MHz, $CDCl_3$): 2.83 (*t*, *J* = 5.8, 4 H); 3.11 (*d*, *J* = 12.5, 4 H); 3.5–3.8 (*m*, 20 H); 5.04 (*s*, 4 H); 6.92 (*d*, *J* = 9.1, 4 H); 7.20 (*d*, *J* = 9.1, 4 H); 7.29–7.45 (*m*, 10 H). FAB-HR-MS: 707.3696 ($[M + H]^+$, $C_{43}H_{51}N_2O_7^+$, calc. 707.3696).

1,20-Bis(4-hydroxyphenyl)-6,9,12,15-tetraoxa-3,18-diazatricyclo[16.3.1.1^{3,20}]tricosan-21-one (**17**). A mixture of **16** (1.52 g, 2.15 mmol), $NH_4(HCOO)$ (2.33 g, 36.9 mmol) and, 10% Pd/C (0.63 g) in acetone (50 ml) was refluxed under Ar for 2 h, filtered through *Celite*, and evaporated to give a yellow oil. Chromatography (SiO_2 (150 ml), AcOEt/MeOH/Et_3N 90:5:5) yielded **17** (0.82 g, 73%). Waxy yellow solid. IR (KBr): 1724 (C=O). ^{1}H-NMR (360 MHz, $CDCl_3$): 2.82 (*t*, obscured by H_2O, 4 H); 3.03 (*d*, *J* = 11.1, 4 H); 3.48–3.79 (*m*, 20 H); 6.74 (*d*, *J* = 8.8, 4 H); 7.09 (*d*, *J* = 8.8, 4 H). DEI-HR-MS: 526.2656 (M^+, $C_{29}H_{38}N_2O_7^+$, calc. 526.2679).

7,10,13,16,26,33,43,46,49,52,62,69-Dodecaoxa-4,19,40,55-tetraazatridecacylo[68.2.2.2^{22,25}.2^{28,31}.2^{34,37}.2^{58,61}.2^{64,67}.1^{2,19}.1^{2,21}.1^{4,21}.1^{38,55}.1^{38,57}.1^{40,57}]nonaconta-22, 24, 28, 30, 34, 36, 58, 60, 64, 66, 70, 72, 73, 75, 77, 82, 84, 86-octadecaene-80,89-dione (**18**). A mixture of **17** (0.40 g, 0.76 mmol), 1,4-(bromomethyl)benzene (0.135 g, 0.77 mmol), and Cs_2CO_3 (1.35 g, 4.1 mmol) in dry MeCN (800 ml) was refluxed under Ar for 1 d, then filtered, evaporated, and chromatographed (SiO_2 (300 ml), AcOEt → AcOEt/MeOH/Et_3N 96:2:2). Crystallization from

abs. EtOH/$CHCl_3$ 9:1 afforded **18** (66 mg, 14%). White crystalline solid. M.p. 251°. IR ($CDCl_3$): 1725 (C=O). ^{1}H-NMR (500 MHz, $CDCl_3$): 2.82 (*t*, $J \approx 5.0$, 8 H); 3.10 (*d*, $J = 11.1$, 8 H); 3.53 (*s*, 8 H); 3.62, 3.65 (2*t*, $J = 5.4$, 16 H); 3.71 (*d*, $J = 11.1$, 8 H); 3.74 (*t*, $J = 5.0$, 8 H); 5.08 (*s*, 8 H); 6.82 (*d*, $J = 8.9$, 8 H); 7.08 (*d*, $J = 8.9$, 8 H); 7.29 (*s*, 8 H). FAB-HR-MS: 1257.6406 ($[M + H]^+$, $C_{74}H_{89}N_4O_{14}^+$, calc. 1257.6375). Anal. calc. for $C_{74}H_{88}N_4O_{14}$ (1257.55): C 70.67, H 7.06, N 4.46; found: C 70.74, H 6.95, N 4.42.

Diethyl 2,2'-(Phen-1,4-ylenedioxy)bis(acetate) (**19**). A mixture of hydroquinone (5 g, 0.046 mol), ethyl bromoacetate (15 ml, 0.135 mol), and anh. K_2CO_3 (25 g, 0.18 mol) in acetone (20 ml) was refluxed for 2 d, then filtered through *Celite*, and evaporated. The crude residue was dissolved in Et_2O (300 ml) and washed with 1N aq. NaOH (200 ml), the aq. layer extracted with Et_2O (100 ml), the combined org. layer dried (Na_2SO_4) and evaporated, and the yellow solid crystallized from abs. EtOH: **19** (4.69 g, 37%). White solid. M.p. 71–72° ([46]: m.p. 70–71°). ^{1}H-NMR (360 MHz, $CDCl_3$): 1.30 (*t*, $J = 7.2$, 6 H); 4.27 (*q*, $J = 7.2$, 4 H); 6.86 (*s*, 4 H).

Diethyl 2,2'-[2,5-Bis(chloromethyl)phen-1,4-ylenedioxy]bis(acetate) (**20**). A suspension of **19** (2.66 g, 9.42 mmol) and 37% aq. CH_2O soln. (20 ml, 0.27 mol) in conc. aq. HCl soln. (250 ml) was stirred at 20° for 6 d, then diluted with H_2O (500 ml). The formed precipitate was isolated by filtration and dried *in vacuo*: 2.82 g of colorless crude diacid. ^{1}H-NMR (360 MHz, $(CD_3)_2SO$): 4.72 (*s*, 8 H); 7.09 (*s*, 2 H). The diacid was dissolved in THF (100 ml) and refluxed together with $SOCl_2$ (20 ml) under Ar for 3 h. Evaporation gave crude bis(acyl chloride) as a pink solid which was refluxed together with abs. EtOH (6 ml) and dry pyridine (3 ml) in CH_2Cl_2 (100 ml) at 20° overnight. The mixture was washed with 0.5N aq. NaOH (100 ml), 0.5N aq. HCl (100 ml), and H_2O (150 ml), dried (Na_2SO_4), and evaporated and the yellow solid recrystallized from hexanes/CH_2Cl_2 10:1: colorless **20** (2.35 g, 65%). M.p.124–127°. IR ($CDCl_3$): 1755 (C=O). ^{1}H-NMR (360 MHz, $CDCl_3$): 1.30 (*t*, $J = 7.1$, 6 H); 4.27 (*q*, $J = 7.1$, 4 H); 4.67, 4.70 (2*s*, 8 H); 6.89 (*s*, 2 H). EI-MS (70 eV): 378 (100, M^+). Anal. calc. for $C_{16}H_{20}Cl_2O_6$ (379.24): C 50.67, H 5.32; found: C 50.80, H 5.24.

Tetraethyl 2,2',2'',2'''-[80,89-Dioxo-7,10,13,16,26,33,43,46,49,52,62,69-dodecaoxa-4,19,40,55-tetraazatridecacyclo[68.2.2.2^{22,25}.2^{28,31}.2^{34,37}.2^{58,61}.2^{64,67}.1^{2,19}.1^{2,21}.1^{4,21}.1^{38,55}.1^{38,57}.1^{40,57}]nonaconta-22,24,28,30,34,36,58,60,64,66,70,72,73,75,77,82,84,86-octadecaene-29,65,75,84-tetrayloxy]tetrakis(acetate) (**21**). A mixture of **17** (0.40 g, 0.76 mmol), Cs_2CO_3 (1.8 g, 5.5 mmol), and **20** (0.29 g, 0.76 mmol) in MeCN (800 ml) was refluxed for 1 d, filtered, and evaporated. The residue was chromatographed twice (SiO_2 (50 ml), AcOEt→AcOEt/MeOH/Et_3N 95:2.5:2.5, then SiO_2 (50 ml), AcOEt/Me_2CO/Et_3N 88:10:2) and recrystallized from i-PrOH: colorless **21** (85 mg, 13%). M.p. 179–181°. IR ($CDCl_3$): 1750, 1731 (C=O). ^{1}H-NMR (500 MHz, $CDCl_3$): 1.21 (*t*, $J = 7.2$, 12 H); 2.82 (*t*, $J \approx 4$, 8 H); 3.07 (*d*, $J = 10.7$, 8 H); 3.53 (*s*, 8 H); 3.64 (*m*, 16 H); 3.71 (*d*, $J = 10.7$, 8 H); 3.74 (*t*, $J \approx 4$, 8 H); 4.15 (*q*, $J = 7.2$, 8 H); 4.53 (*s*, 8 H); 5.16 (*s*, 8 H); 6.84 (*s*, 4 H); 6.86 (*d*, $J = 8.8$, 8 H); 7.07 (*d*, $J = 8.8$, 8 H). FAB-MS: 1666 ($[M + H]^+$). Anal. calc. for $C_{90}H_{112}N_4O_{26} \cdot 3H_2O$ (1719.95): C 62.85, H 6.92, N 3.26; found: C 63.08, H 6.66, N 3.07.

2,2',2'',2'''-[80,89-Dioxo-7,10,13,16,26,33,43,46,49,52,62,69-dodecaoxa-4,19,40,55-tetraazatridecacyclo[68.2.2.2^{22,25}.2^{28,31}.2^{34,37}.2^{58,61}.2^{64,67}.1^{2,19}.1^{2,21}.1^{4,21}.1^{38,55}.1^{38,57}.1^{40,57}]nonaconta-22,24,28,30,34,36,58,60,64,66,70,72,73,75,77,82,84,86-octadecaene-29,65,75,84-tetrayloxy]tetrakis(acetic Acid) (**22**). A soln. of **21** (26 mg, 0.016 mmol) in THF (2 ml) was added to a soln. of $LiOH \cdot H_2O$ (11 mg, 0.26 mmol) in H_2O (1 ml) and the mixture stirred vigorously for 2 d at 20°. Upon dilution with MeCN (10 ml), a white precipitate formed which was collected and dissolved in MeOH/H_2O 3:1 (1 ml). The soln. was acidified with 1N aq. HCl (1 ml) and evaporated to produce a colorless precipitate which was dried *in vacuo*: **22**·3 HCl (20 mg, 80%). M.p. 203–205° (dec.). IR (KBr): 1735 (C=O). ^{1}H-NMR (500 MHz, $(CD_3)_2SO$, 377 K): 3.14 (br. *t*, 8 H); 3.49 (*s*, 8 H); 3.61, 3.64 (2*m*, 16 H); 3.76 (*d*, $J = 10.7$, 8 H); 3.84 (br. *t*, 8 H); 4.08 (*d*, $J = 10.7$, 8 H); 4.58 (*s*, 8 H); 5.15 (*s*, 8 H); 6.95 (*d*, $J = 8.9$, 8 H); 6.98 (*s*, 4 H); 7.19 (*d*, $J = 8.9$, 8 H). FAB-MS: 1554 ($[M + H]^+$). Anal. calc. for $C_{82}H_{96}N_4O_{26} \cdot 3HCl$ (1663.07): C 59.22, H 6.00, N 3.37; found: C 59.25, H 5.63, N 3.41.

1,20-Bis[4-(4-chlorobutyloxy)phenyl]-6,9,12,15-tetraoxa-3,18-diazatricyclo[16.3.1.1^{3,20}]tricosan-21-one (**23**). To a soln. of **17** (0.305 g, 0.58 mmol) in DMF (30 ml) was added NaH (80% dispersion; 0.08 g, 2.7 mmol). After 15 min, 1,4-dichlorobutane (10 ml, 91 mmol) was added and the mixture stirred at 20° for 3 h. After addition of H_2O (3 ml), the soln. was evaporated, the residue suspended in AcOEt (100 ml) and washed with H_2O (100 ml), the aq. layer extracted with AcOEt (50 ml) and CH_2Cl_2 (50 ml), the combined org. layer dried (Na_2SO_4) and evaporated, and the residue dried *in vacuo*: **23** (0.41 g, 99%). Clear yellow oil. IR ($CDCl_3$): 1726 (C=O). ^{1}H-NMR (500 MHz, $CDCl_3$): 1.94 (*m*, 8 H); 2.84 (br. *t*, 4 H); 3.11 (*d*, $J = 10.7$, 4 H); 3.54 (*s*, 4 H); 3.61 (*t*, $J = 6.4$, 4 H); 3.63 (*m*, 8 H); 3.73 (*d*, $J = 10.7$, 4 H); 3.74 (br. *t*, 4 H); 3.98 (*t*, $J = 5.6$, 4 H); 6.83 (*d*, $J = 8.7$, 4 H); 7.19 (*d*, $J = 8.7$, 4 H). FAB-HR-MS: 707.3229 ($[M + H]^+$, $C_{37}H_{53}Cl_2N_2O_7^+$, calc. 707.3230).

7,10,13,16,26,31,41,44,47,50,60,65-Dodecaoxa-4,19,38,53-tetraazaundecacyclo[64.2.2.2^{22,25}.2^{32,35}.2^{56,59}.1^{2,19}.1^{2,21}.1^{4,21}.1^{36,53}.1^{36,55}.1^{38,55}]dooctaconta-22,24,32,34,56,58,66,68,69,71,76,78-dodecaene-74,81-dione (**24**). A soln. of **23** (0.335 g, 0.50 mmol), **17** (0.26 g, 0.49 mmol), and Cs_2CO_3 (0.85 g, 2.6 mmol) in DMF (500 ml) was heated to 75–80° under Ar for 3 d, then evaporated. The residue was extracted with CH_2Cl_2 and the insoluble material

removed by filtration through *Celite*. Chromatography (SiO_2 (200 ml), AcOEt→AcOEt/MeOH/Et_3N 97:1.5:1.5) afforded a yellow oil which was crystallized from abs. EtOH/CH_2Cl_2 10:1: colorless **24** (100 mg, 18%). M.p. 210–215° (dec.). IR (KBr): 1727 (C=O). ^{1}H-NMR (500 MHz, $CDCl_3$): 1.96 (*m*, 8 H); 2.83 (*t*, *J* = 4.8, 8 H); 3.08 (*d*, *J* = 10.9, 8 H); 3.54 (*s*, 8 H); 3.64 (*m*, 16 H); 3.71 (*d*, *J* = 10.9, 8 H); 3.75 (*t*, *J* = 4.8, 8 H); 4.02 (br. *t*, 8 H); 6.81 (*d*, *J* = 8.8, 8 H); 7.14 (*d*, *J* = 8.8, 8 H). FAB-MS: 1162 ([*M* + H]$^+$). Anal. calc. for $C_{66}H_{88}N_4O_{14}$ (1161.46): C 68.25, H 7.64, N 4.82; found: C 68.10, H 7.56, N 4.90.

7,10,13,16,26,31,41,44,47,50,60,65-Dodecaoxa-4,19,38,53-tetraazaundecacyclo[64.2.2.2^{22,25}.2^{32,35}.2^{56,59}.1^{2,19}.1^{2,21}.1^{4,21}.1^{36,53}.1^{36,55}.1^{38,55}]dooctaconta-22,24,32,34,56,58,66,68,69,71,76,78-dodecaene-74,81-diol (**25**). A mixture of **24** (51 mg, 0.044 mmol) and $LiAlH_4$ (39 mg, 1.1 mmol) in THF (10 ml) was stirred under Ar for 3 h, then quenched by the addition of 1N aq. NaOH (0.2 ml) and H_2O (0.5 ml). The solids were filtered off and rinsed with CH_2Cl_2. The org. soln. was chromatographed (neutral Al_2O_3 (act. I, 10 ml), $CHCl_3$→$CHCl_3$/MeOH 95:5) and the crude product dissolved in CH_2Cl_2 (5 ml). Upon addition of Et_2O (20 ml), a precipitate formed which was dried *in vacuo*: **25** (35 mg, 68%) as a colorless mixture of stereoisomers. M.p. 175–220° (dec.). ^{1}H-NMR (500 MHz, $CDCl_3$): 1.98 (*m*, 2 × 8 H); 2.80–4.17 (*m*, 2 × 64 H); 4.77 (*s*, 2 H); 4.79 (*s*, 2 H); 6.62 (*d*, *J* = 8.9, 8 H); 6.87 (*d*, *J* = 8.9, 8 H); 7.44 (*d*, *J* = 8.9, 8 H); 7.54 (*d*, *J* = 8.9, 8 H). FAB-MS: 1165 ([*M* + H]$^+$). Anal. calc. for $C_{66}H_{92}N_4O_{14}\cdot 5H_2O$ (1255.56): C 63.14, H 8.19, N 4.46; found: C 63.38, H 7.58, N 4.42.

1′-Acetyl-33,39,52,55-tetramethoxyspiro[7,10,13,16,26,31,41,46-octaoxa-4,19-diazaoctacyclo[45.2.2.2^{22,25}.2^{32,35}.2^{37,40}.1^{2,19}.1^{2,21}.1^{4,21}]hexaconta-22,24,32,34,37,39,47,49,50,52,54,56-dodecaene-36,4′-piperidin]-59-one (**27**). A mixture of **17** (0.236 g, 0.45 mmol), **26** [39] (0.275 g, 0.45 mmol), and Cs_2CO_3 (0.98 g, 3.0 mmol) in DMF (300 ml) was heated to 75–80° under Ar for 1 d, then filtered and evaporated. The residue was extracted exhaustively with CH_2Cl_2 and any insoluble material removed by filtration through *Celite*. Chromatography (SiO_2 (100 ml), CH_2Cl_2→CH_2Cl_2/MeOH 85:15) afforded a yellow-orange foam which was crystallized from MeOH/Et_2O 9:1: colorless **27** (83 mg, 17%). M.p. 129–130°. IR ($CDCl_3$): 1723 (C=O). ^{1}H-NMR (500 MHz, $CDCl_3$): 1.86, 1.94 (2*m*, 8 H); 2.08 (*s*, 3 H); 2.28 (br. *m*, 4 H); 2.85 (br. *t*, 4 H); 3.13 (2*d*, *J* = 7.4, 4 H); 3.49 (br. *m*, 4 H); 3.52 (*s*, 4 H); 3.62 (*s*, 12 H); 3.64 (br. *m*, 8 H); 3.75 (br. *m*, 8 H); 3.91 (*t*, *J* = 6.2, 4 H); 4.17 (*t*, *J* = 6.5, 4 H); 6.37 (*s*, 4 H); 6.84 (*d*, *J* = 8.9, 4 H); 7.10 (*d*, *J* = 8.9, 4 H). FAB-MS: 1067 ([*M* + H]$^+$). Anal. calc. for $C_{60}H_{79}N_3O_{14}$ (1066.31): C 67.59, H 7.47, N 3.94; found: C 67.81, H 7.34, N 3.98.

33,39,52,55-Tetramethoxy-1′-methylspiro[7,10,13,16,26,31,41,46-octaoxa-4,19-diazaoctacyclo[45.2.2.2^{22,25}.2^{32,35}.2^{37,40}.1^{2,19}.1^{2,21}.1^{4,21}]hexaconta-22,24,32,34,37,39,47,49,50,52,54,56-dodecaene-36,4′-piperidin]-59-one (**28**). A mixture of **27** (45 mg, 0.042 mmol) and KOH (44 mg, 0.79 mmol) in $MeOCH_2CH_2OH$ (3 ml) was refluxed for 1 d, then additional KOH (50 mg, 0.89 mmol) was added and reflux continued for 12 h. The mixture was diluted with CH_2Cl_2 (25 ml) and washed with H_2O (25 ml), the aq. layer extracted with CH_2Cl_2 (3 × 10 ml), and the combined org. layer washed with sat. aq. NaCl soln. (25 ml), dried (Na_2SO_4), and evaporated: crude secondary amine as a thick brown oil. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.75–2.09 (br. *m*, 8 H); 2.27 (br. *m*, 4 H); 2.85 (br. *m*, 8 H); 3.10 (br. *m*, 4 H); 3.59 (*s*, 12 H); 3.60–3.80 (*m*, 20 H); 3.93 (*t*, *J* = 6.2, 4 H); 4.19 (*t*, *J* = 6.5, 4 H); 6.40 (*s*, 4 H); 6.85 (*d*, *J* = 8.9, 4 H); 7.11 (*d*, *J* = 8.9, 4 H). FAB-MS: 1025 ([*M*$^+$ + H]).

The crude secondary amine was combined with 37% aq. CH_2O soln. (0.3 ml), 88% aq. HCOOH soln. (0.18 ml), and H_2O (1.5 ml) and the mixture warmed to 110° for 1 d. After evaporation, 0.5N aq. NaOH (20 ml) was added, followed by extraction with CH_2Cl_2 (2 × 30 ml). The org. soln. was dried (Na_2SO_4), evaporated, and chromatographed (SiO_2 (10 ml), AcOEt→AcOEt/MeOH/Et_3N 87:10:3): **28** (20 mg, 46%) as a white foam which was recrystallized from hexanes/CH_2Cl_2 8:2. M.p. 95–97°. IR ($CDCl_3$): 1718 (C=O). ^{1}H-NMR (500 MHz, $CDCl_3$): 1.86, 1.95 (2*m*, 8 H); 2.22 (*s*, 3 H); 2.33–2.50 (2*m*, 8 H); 2.85 (*t*, *J* = 4.8, 4 H); 3.12 (*d*, *J* = 10.5, 4 H); 3.52 (*s*, 4 H); 3.62 (*s*, 12 H); 3.60–3.69 (*m*, 16 H); 3.92 (*t*, *J* = 6.1, 4 H); 4.17 (*t*, *J* = 6.6, 4 H); 6.39 (*s*, 4 H); 6.85 (*d*, *J* = 8.7, 4 H); 7.10 (*d*, *J* = 8.7, 4 H). FAB-MS: 1039 ([*M* + H]$^+$). Anal. calc. for $C_{59}H_{79}N_3O_{13}$ (1038.30): C 68.25, H 7.67, N 4.05; found: C 68.05, H 7.46, N 4.18.

2,2′,6,6′-Tetramethoxy-4,4′-(piperidine-4,4-diyl)bis(phenol) (**30**). A suspension of **29** [41] (13.48 g, 31.2 mmol) in a mixture of MeOH (50 ml) and conc. aq. HCl soln. (20 ml) was refluxed for 1 d, then concentrated to 20 ml, neutralized with conc. aq. NH_4OH soln., and chilled overnight. The formed precipitate was collected, washed with ice-cold H_2O (10 ml), and dried *in vacuo*: **30** (12.15 g, 100%). Tan solid. M.p. 250–252°. ^{1}H-NMR (360 MHz, $(CD_3)_2SO$): 2.21 (br. *s*, 4 H); 2.69 (br. *s*, 4 H); 3.70 (*s*, 12 H); 6.50 (*s*, 4 H). EI-HR-MS (50 eV): 389.1846 (*M*$^+$, $C_{21}H_{27}NO_6^+$, calc. 389.1838).

1,1-Dimethylethyl 4,4′-Bis[3,5-dimethoxy-4-(4-chlorobutyloxy)phenyl]piperidine-1-carboxylate (**32**). To a stirred suspension of **30** (8.74 g, 22.5 mmol) in CH_2Cl_2 (500 ml) was added Et_3N (5.2 ml, 72 mmol) and di(*tert*-butyl) dicarbonate (6.4 ml, 28 mmol). The mixture was stirred at 20° for 15 min, washed with H_2O (500 ml), dried (Na_2SO_4), and evaporated: crude **31**. Pink foam. IR ($CDCl_3$): 1760 (C=O). ^{1}H-NMR (360 MHz, $CDCl_3$): 1.45 (*s*, 9 H); 2.27 (br. *s*, 4 H); 3.49 (br. *m*, 4 H); 3.81 (*s*, 12 H); 6.43 (*s*, 4 H). EI-HR-MS (50 eV): 489.2340 (*M*$^+$, $C_{26}H_{35}NO_8^+$, calc. 489.2362).

The crude **31** was combined with acetone (300 ml), 1,4-dichlorobutane (100 ml), and an excess of K_2CO_3 and the mixture refluxed for 3 d, then filtered through *Celite* and evaporated. Chromatography (SiO_2 (200 ml), CH_2Cl_2/MeOH 95:5) and drying *in vacuo* afforded **32** (11.5 g, 76%). IR ($CDCl_3$): 1760 (C=O). ^{1}H-NMR (200 MHz, $CDCl_3$): 1.46 (*s*, 9 H); 1.88, 2.00 (2*m*, 8 H); 2.29 (br. *s*, 4 H); 3.50 (br. *m*, 4 H); 3.65 (*t*, *J* = 6.5, 4 H); 3.76 (*s*, 12 H); 3.96 (*t*, *J* = 6.0, 4 H); 6.43 (*s*, 4 H). EI-HR-MS (50 eV): 669.2844 (M^+, $C_{34}H_{49}Cl_2NO_8^+$, calc. 669.2835).

5,7-Bis[4-(benzyloxy)phenyl]-1,3-diazatricyclo[3.3.1.1^{3,7}]decan-6-one (**33**). A mixture of **14** (9.78 g, 23.2 mmol), paraformaldehyde (3.4 g, 0.113 mol), and NH_4OAc (37.5 g, 0.486 mol) in abs. EtOH (150 ml) was refluxed for 3 h. The precipitate formed upon cooling was collected and rinsed with abs. EtOH until the rinse was colorless. The resulting white powder was dried *in vacuo*: **33** (9.34 g, 78%). M.p. 173°. IR ($CDCl_3$): 1702 (C=O). ^{1}H-NMR (500 MHz, $CDCl_3$): 3.75, 3.80 (2*d*, *J* = 12.4, 8 H); 4.25 (*s*, 2 H); 5.05 (*s*, 4 H); 6.79 (*d*, *J* = 8.9, 4 H); 7.09 (*d*, *J* = 8.9, 4 H); 7.31–7.43 (*m*, 10 H). EI-HR-MS (50 eV): 516.2434 (M^+, $C_{34}H_{32}N_2O_3^+$, calc. 516.2413). Anal. calc. for $C_{34}H_{32}N_2O_3$ (516.65): C 79.04, H 6.24, N 5.42; found: C 79.18, H 6.15, N 5.16.

5,7-Bis[4-(benzyloxy)phenyl]-1,3-diazatricyclo[3.3.1.1^{3,7}]decane (**34**). A suspension of **33** (4.18 g, 8.09 mmol), anh. NaOAc (3.61 g, 44.0 mmol), and $NH_2NH_2 \cdot H_2O$ (22 ml, 0.45 mol) in diethylene glycol (130 ml) was refluxed for 2 d, then diluted with H_2O (500 ml). The precipitate was collected and washed with H_2O (50 ml) and chilled MeOH (50 ml). The white solid was combined with MeOH (300 ml) and 37% aq. CH_2O soln. (15 ml) and the suspension refluxed for 4 h, concentrated to 80 ml, and cooled. The formed solid was filtered, washed with chilled MeOH, and dried *in vacuo*: **34** (4.05 g, 99%). Fine white powder. M.p. 245° (dec.). ^{1}H-NMR (500 MHz, $CDCl_3$): 2.40 (*s*, 2 H); 3.29, 3.51 (2*d*, *J* = 12.7, 8 H); 4.20 (*s*, 2 H); 5.06 (*s*, 4 H); 6.98 (*d*, *J* = 8.9, 4 H); 7.25 (*d*, *J* = 8.9, 4 H); 7.32–7.44 (*m*, 10 H). EI-HR-MS (50 eV): 502.2605 (M^+, $C_{34}H_{34}N_2O_2^+$, calc. 502.2620). Anal. calc. for $C_{34}H_{34}N_2O_2$ (502.66): C 81.24, H 6.82, N 5.57; found: C 80.93, H 7.00, N 5.61.

5,7-Bis(4-hydroxyphenyl)-1,3-diazatricyclo[3.3.1.1^{3,7}]decan-6-one (**35**). A mixture of **33** (1.07 g, 2.06 mmol), 10% Pd/C (0.55 g), and $NH_4(HCOO)$ (9.4 g, 150 mmol) in THF (200 ml) was refluxed for 1.5 h and filtered. The insoluble material was extracted with THF (300 ml) overnight in a *Soxhlet* apparatus to give a cloudy suspension. Addition of THF (100 ml) gave a clear soln. which was filtered through *Celite*, concentrated *in vacuo* to *ca.* 10 ml, and diluted with Et_2O: **35** (0.61 g, 88%) as a white precipitate. A sample for analysis was recrystallized from abs. EtOH. M.p. *ca.* 300°. IR ($CDCl_3$): 1692 (C=O). ^{1}H-NMR (500 MHz, $(CD_3)_2SO$): 3.55, 3.69 (2*d*, *J* = 13.5, 8 H); 4.08 (*s*, 2 H); 6.71 (*d*, *J* = 8.5, 4 H); 6.99 (*d*, *J* = 8.5, 4 H). EI-HR-MS (50 eV): 336.1458 (M^+, $C_{20}H_{20}N_2O_3^+$, calc. 336.1474). Anal. calc. for $C_{20}H_{20}N_2O_3$ (336.39): C 71.41, H 5.99, N 8.33; found: C 71.49, H 6.21, N 8.43.

5,7-Bis(4-hydroxyphenyl)-1,3-diazatricyclo[3.3.1.1^{3,7}]decane (**36**). A mixture of **34** (3.30 g, 6.56 mmol), 10% Pd/C (0.87 g), and $NH_4(HCOO)$ (3.79 g, 60 mmol) in DMF (350 ml) was stirred at 50° for 1.5 h and then filtered. The solids were extracted with MeOH in a *Soxhlet* apparatus for 3 d and the org. soln. filtered through *Celite*. Evaporation followed by crystallization from abs. EtOH yielded **36** (1.87 g, 88%). White powder. M.p. > 315° (dec.). ^{1}H-NMR (500 MHz, $(CD_3)_2SO$): 2.22 (*s*, 2 H); 3.06, 3.32 (2*d*, *J* = 12.5, 8 H); 4.02 (*s*, 2 H); 6.71 (*d*, *J* = 8.7, 4 H); 7.16 (*d*, *J* = 8.7, 4 H). EI-HR-MS (50 eV): 322.1686 (M^+, $C_{20}H_{22}N_2O_2^+$, calc. 322.1681). Anal. calc. for $C_{20}H_{22}N_2O_2 \cdot 0.25\ H_2O$ (326.91): C 73.48, H 6.94, N 8.57; found: C 73.29, H 6.67, N 8.61.

1,1-Dimethylethyl 20′,26′,39′,42′-Tetramethoxy-46′-oxospiro[piperidine-4,23′-[13,18,28,33]tetraoxa[4,6]diazaoctacyclo[32.2.2.2^{9,12}.2^{19,22}.2^{24,27}.1^{2,6}.1^{2,8}.1^{4,8}]heptatetraconta[9,11,19,21,24,26,34,36,37,39,41,43]dodecaene]-1-carboxylate (**37**). A mixture of **32** (0.993 g, 1.48 mmol), **35** (0.525 g, 1.56 mmol), and Cs_2CO_3 (2.25 g, 6.9 mmol) in DMF (1.5 l) was warmed to 50–55° for 6 d, then filtered, and evaporated. The residue was extracted with $CHCl_3$ (400 ml). The org. soln. was filtered through *Celite* and chromatographed on SiO_2 (250 ml, $CH_2Cl_2 \rightarrow CH_2Cl_2$/MeOH 98:2) to yield a thick yellow oil which was crystallized from Et_2O/CH_2Cl_2 9:1: **37** (0.19 g, 13%). White powder. M.p. 147°. IR ($CDCl_3$): 1699, 1682 (C=O). ^{1}H-NMR (500 MHz, $CDCl_3$): 1.44 (*s*, 9 H); 1.85, 1.96 (2*m*, 8 H); 2.24 (br. *s*, 4 H); 3.46 (br. *s*, 4 H); 3.64 (*s*, 12 H); 3.78 (br. *m*, 8 H); 3.89 (*t*, *J* = 6.5, 4 H); 4.21 (*t*, *J* = 6.8, 4 H); 4.26 (*s*, 2 H); 6.37 (*s*, 4 H); 6.91 (*d*, *J* = 8.8, 4 H); 7.00 (*d*, *J* = 8.8, 4 H). FAB-HR-MS: 933.4808 (M^+, $C_{54}H_{67}N_3O_{11}^+$, calc. 933.4775). Anal. calc. for $C_{54}H_{67}N_3O_{11}$ (934.15): C 69.43, H 7.23, N 4.50; found: C 69.60, H 7.05, N 4.13.

1,1-Dimethylethyl 20′,26′,39′,42′-Tetramethoxyspiro[piperidine-4,23′-[13,18,28,33]tetraoxa[4,6]diazaoctacyclo[32.2.2.2^{9,12}.2^{19,22}.2^{24,27}.1^{2,6}.1^{2,8}.1^{4,8}]heptatetraconta[9,11,19,21,24,26,34,36,37,39,41,43]dodecaene]-1-carboxylate (**39**). A mixture of **32** (0.445 g, 0.66 mmol), **36** (0.22 g, 0.68 mmol), and Cs_2CO_3 (0.95 g, 2.9 mmol) in DMF (700 ml) was warmed to 50° for 4 d. The mixture was filtered and evaporated and the residue extracted with $CHCl_3$. Filtration through *Celite* and chromatography (SiO_2 (150 ml), $CH_2Cl_2 \rightarrow CH_2Cl_2$/MeOH 1:1; then neutral Al_2O_3 (act. I, 20 ml), $CHCl_3 \rightarrow CHCl_3$/MeOH 97:3) gave **39** (85 mg, 13%). White foam. For analysis, a sample was recrystallized from $Et_2O/CHCl_3$ 95:5. M.p. 183°. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.44 (*s*, 9 H); 1.87, 1.98 (2*m*, 8 H); 2.16 (*s*, 2 H); 2.28 (br. *s*, 4 H); 3.34 (*d*, *J* = 12.8, 4 H); 3.48 (*m*, 8 H); 3.67 (*s*, 12 H); 3.91 (*t*, *J* = 5.8, 4 H); 4.18 (*s*, 2 H); 4.23 (*t*, *J* = 7.1, 4 H); 6.42 (*s*, 4 H); 6.92 (*d*, *J* = 8.8, 4 H); 7.14 (*d*, *J* = 8.8, 4 H). FAB-HR-MS: 920.5056

($[M + H]^+$, $C_{54}H_{70}N_3O_{11}^+$, calc. 920.5061). Anal. calc. for $C_{54}H_{69}N_3O_{10}$ (920.17): C 70.49, H 7.56, N 4.57; found: C 70.72, H 7.43, N 4.34.

1,1-Dimethylethyl 20′,26′,39′,42′-Tetramethoxy-46′-hydroxyspiro[piperidine-4,23′-[13,18,28,33]tetraoxa-[4,6]diazaoctacyclo[32.2.2.2.2^{9,12}.2^{19,22}.2^{24,27}.1^{2,6}.1^{2,8}.1^{4,8}]heptatetraconta[9,11,19,21,24,26,34,36,37,39,41,43]-dodecaene]-1-carboxylate (**38**). A mixture of **37** (63 mg, 0.067 mmol) and $LiAlH_4$ (20 mg, 0.52 mmol) in THF (10 ml) was stirred at 20° for 1.5 h, then quenched with 1N aq. NaOH (0.5 ml) and H_2O (0.5 ml). The solids were filtered off and washed with $CHCl_3$, the org. soln. dried (Na_2SO_4) and evaporated, and the clear oil triturated with Et_2O: **38** (52 mg, 82%). White powder. M.p. 139°. ^{1}H-NMR (360 MHz, $CDCl_3$): 1.43 (*s*, 9 H); 1.80–2.04 (2 br. *m*, 8 H); 2.28 (br. *s*, 4 H); 3.33 (*d*, *J* = 12.9, 4 H); 3.49 (br. *s*, 4 H); 3.58 (*d*, *J* = 12.9, 2 H); 3.68 (*s*, 12 H); 3.76 (*s*, 1 H); 3.83, 3.92 (2*m*, 4 H); 3.93 (*t*, *J* = 12.9, 2 H); 4.10 (*s*, 2 H); 4.13, 4.25 (2*m*, 4 H); 6.39 (*s*, 4 H); 6.92 (*d*, *J* = 8.9, 4 H); 7.17 (*d*, *J* = 8.9, 4 H). FAB-HR-MS: 936.5034 ($[M + H]^+$, $C_{54}H_{70}N_3O_{11}^+$, calc. 936.5010). Anal. calc. for $C_{54}H_{69}N_3O_{11} \cdot H_2O$ (954.18): C 67.97, H 7.50, N 4.40; found: C 68.13, H 7.26, N 4.53.

20′,26′,39′,42′-Tetramethoxyspiro[piperidine-4,23′-[13,18,28,33]-tetraoxa[4,6]diazaoctacyclo[32.2.2.2.2^{9,12}.2^{19,22}.2^{24,27}.1^{2,6}.1^{2,8}.1^{4,8}]heptatetraconta[9,11,19,21,24,26,34,36,37,39,41,43]dodecaen]-46′-one (**40**). A soln. of **37** (66 mg, 0.071 mmol) and CF_3COOH (1 ml) in CH_2Cl_2 (5 ml) was stirred at 20° for 1 h after which more CF_3COOH (1 ml) was added. After 15 min stirring, CH_2Cl_2 (10 ml) was added followed by H_2O (2 ml) and conc. aq. NH_4OH soln. (5 ml). The aq. phase was exhaustively extracted with CH_2Cl_2 and the combined org. layer dried (Na_2SO_4) and evaporated. Crystallization from cold MeOH yielded **40** (51 mg, 86%). White powder. M.p. 215° (dec.). IR ($CDCl_3$): 1699 (C=O). ^{1}H-NMR (360 MHz, $CDCl_3$): 1.86, 1.97 (2*m*, 8 H); 2.44 (br. *s*, 4 H); 3.07 (br. *s*, 4 H); 3.62 (*s*, 12 H); 3.77 (br. *m*, 8 H); 3.91 (*t*, *J* = 6.0, 4 H); 4.20 (*t*, *J* = 6.6, 4 H); 4.26 (*s*, 2 H); 6.36 (*s*, 4 H); 6.91 (*d*, *J* = 8.9, 4 H); 7.00 (*d*, *J* = 8.9, 4 H). FAB-HR-MS: 834.4346 ($[M + H]^+$, $C_{49}H_{60}N_3O_8^+$, calc. 834.4329).

20′,26′,39′,42′-Tetramethoxyspiro[piperidine-4,23′-[13,18,28,33]tetraoxa[4,6]diazaoctacyclo[32.2.2.2.2^{9,12}.2^{19,22}.2^{24,27}.1^{2,6}.1^{2,8}.1^{4,8}]heptatetraconta[9,11,19,21,24,26,34,36,37,39,41,43]dodecaen]-46′-ol (**41**). As described for **40**, from **38** (37 mg, 0.039 mmol). Crystallization from Et_2O/CH_2Cl_2 9:1 gave **41** (24 mg, 74%). White powder. M.p. 225° (dec.). ^{1}H-NMR (360 MHz, $CDCl_3$): 1.87, 1.98 (2*m*, 8 H); 2.39 (br. *m*, 4 H); 2.91 (br. *m*, 4 H); 3.36 (*d*, *J* = 12.9, 4 H); 3.58 (*d*, *J* = 12.9, 2 H); 3.69 (*s*, 12 H); 3.77 (*s*, 1 H); 3.84, 3.93 (2*m*, 4 H); 3.95 (*d*, *J* = 12.9, 2 H); 4.11 (*s*, 2 H); 4.16, 4.27 (2*m*, 4 H); 6.41 (*s*, 4 H); 6.92 (*d*, *J* = 8.9, 4 H); 7.18 (*d*, *J* = 8.9, 4 H). FAB-HR-MS: 836.4498 ($[M + H]^+$, $C_{49}H_{62}N_3O_8^+$, calc. 836.4486).

20′,26′,39′,42′-Tetramethoxyspiro[piperidine-4,23′-[13,18,28,33]tetraoxa[4,6]diazaoctacyclo[32.2.2.2.2^{9,12}.2^{19,22}.2^{24,27}.1^{2,6}.1.^{2,8}.1^{4,8}]heptatetraconta[9,11,19,21,24,26,34,36,37,39,41,43]dodecaene] (**42**). As described for **40**, from **39** (37 mg, 0.04 mmol). Crystallization from $Et_2O/CHCl_3$ 8:2 gave **42** (17 mg, 52%). White powder. M.p. 205–210° (dec.). ^{1}H-NMR (500 MHz, $CDCl_3$): 1.82, 1.91 (2*m*, 8 H); 2.11 (*s*, 2 H); 2.27 (br. *m*, 4 H); 2.89 (br. *m*, 4 H); 3.28, 3.43 (2*d*, *J* = 12.6, 8 H); 3.64 (*s*, 12 H); 3.86 (*t*, *J* = 6.0, 4 H); 4.12 (*s*, 2 H); 4.18 (*t*, *J* = 7.1, 4 H); 6.38 (*s*, 4 H); 6.87 (*d*, *J* = 8.8, 4 H); 7.08 (*d*, *J* = 8.8, 4 H). FAB-HR-MS: 820.4512 ($[M + H]^+$, $C_{49}H_{62}N_3O_8^+$, calc. 820.4537). Anal. calc. for $C_{49}H_{61}N_3O_8 \cdot H_2O$ (838.06): C 70.23, H 7.58, N 5.01; found: C 70.21, H 7.40, N 5.06.

13,18,34,39-Tetraoxa-4,6,25,27-tetraazaundecacyclo[38.2.2.2^{9,12}.2^{19,22}.2^{30,33}.1^{2,6}.1^{2,8}.1^{4,8}.1^{23,27}.1^{23,29}.1^{25,29}]hexapentaconta-9,11,19,21,30,32,40,42,43,45,50,52-dodecaene (**47**). A mixture of **36** (0.55 g, 1.71 mmol), 1,4-dichlorobutane (0.19 ml, 1.74 mmol), and Cs_2CO_3 (2.9 g, 8.9 mmol) in DMF (1.7 l) was warmed to 55° for 7 d, then filtered, and evaporated. The residue was extracted with CH_2Cl_2, filtered through *Celite*, and chromatographed (SiO_2 (50 ml), $CH_2Cl_2 \rightarrow CH_2Cl_2$/MeOH 75:25). The resultant oily solid was suspended in CH_2Cl_2 (30 ml) and washed with sat. aq. Na_2CO_3 soln. (10 ml). The aq. layer was extracted with CH_2Cl_2 (2 × 5 ml) and the combined org. layer dried (Na_2SO_4), concentrated to 2 ml, then diluted with hot abs. EtOH (3 ml), and chilled. The formed precipitate was washed with Et_2O: **47** (40 mg, 6%). White powder. M.p. 315–320° (dec.). ^{1}H-NMR (360 MHz, $CDCl_3$): 1.98 (br. *m*, 8 H); 2.33 (*s*, 4 H); 3.32, 3.50 (2*d*, *J* = 12.3, 16 H); 4.06 (br. *m*, 8 H); 4.19 (*s*, 4 H); 6.86 (*d*, *J* = 8.8, 8 H); 7.20 (*d*, *J* = 8.8, 8 H). FAB-MS: 753 (100, $[M + H]^+$). Anal. calc. for $C_{48}H_{56}N_4O_4 \cdot 2\ H_2O$ (789.04): C 73.07, H 7.66, N 7.10; found: C 72.98, H 7.25, N 7.10.

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