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Synthesis of concave receptors derived from diphenylglycoluril

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Abstract. Improved synthetic methods are described for the synthesis of concave receptor molecules. These receptors consist of a diphenylglycoluril unit, flanked by two aromatic moieties. The most versatile synthetic method consists of Lewis-acid-catalyzed reaction of a tetrakis(chloromethyl) derivative of diphenylglycoluril with the appropriate benzene or naphthalene derivative.

Introduction

Natural receptors and enzymes are macromolecules consisting of linear chains of amino acids folded in such a way that a cavity or cleft is formed. In order to achieve this well-defined structure, a specific folding pattern is followed by the macromolecule, directed by hydrogen bonding, hydrophobic forces and other non-covalent interactions. When mimicking natural receptors it has become common practice to use rigid building blocks to ensure a well-defined geometry. This approach is more convenient than relying on non-covalent interactions in flexible molecules which are much harder to control. For several reasons, the benzene ring and other aromatic molecules are frequently used as building blocks to construct synthetic receptors. Aromatic groups are rigid and therefore useful as structural units. They are easy to functionalize, allowing for modification and extension of the receptor molecule. Aromatic moieties offer a versatile way of introducing binding interactions, *viz.* with aromatic guests via $\pi-\pi$ interactions[1] and with guests containing charged groups such as the ammonium group via ion-induced dipole interactions[2]. In the last few years a new class of synthetic receptors for aromatic guests has emerged[3], for which the name "molecular tweezer"[3c] or "molecular clip"[4] has been coined. In these receptors, the guest is sandwiched between two π-stacking aromatic surfaces, which play a dominant role in the binding of the guest.

In previous papers we reported on molecular clips derived from diphenylglycoluril [a], *e.g.* **2a-c**[4b]. Molecules **2a-c** contain a cleft which is formed by the glycoluril framework and two xylylene walls (Figure 1). We have shown that this cleft binds guests and that the xylylene walls assist in the binding process. Crown-ether derivatives of **2b** also bind benzenediols[4e] and, in addition, alkali salts[4b,c] and diammonium salts[4b,c]. The synthetic method we used to prepare **2a-c** is shown in Scheme 1. Reaction of the cyclic ether **1a** to give the required product demanded long reaction times and afforded only moderate yields with substituted benzenes other than 1,4-benzenediol. Consequently, the possibilities to vary the aromatic walls of the cleft were quite limited. Therefore we decided to investigate the procedure for assembling molecular clefts from **1a** and aromatic molecules in more detail. The results are presented here. They have been used to prepare the new receptors **2–7**. The binding properties of these receptors have been described elsewhere[5,6].

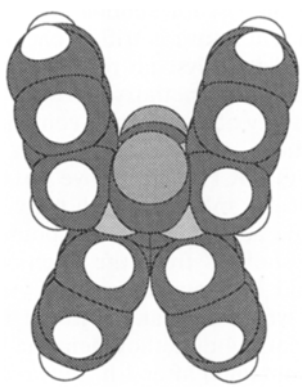
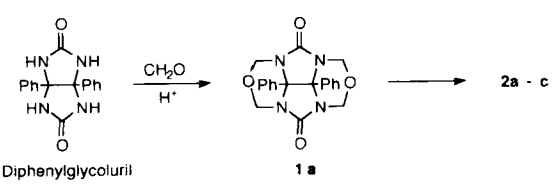


Fig. 1.



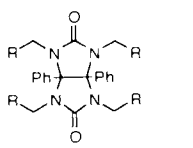
Scheme 1.

[a] *Chem. Abstr.* name: tetrahydro-3a,6a-diphenylimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione.

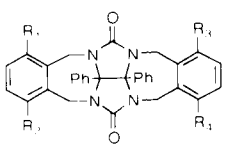
Results and discussion

The coupling of **1a** and other tetramethylene derivatives of diphenylglycoluril (*vide infra*) with aromatic compounds belongs to a type of reaction called amidoalkylation or, in this particular case, ureidoalkylation. This type of reaction has been reviewed by *Zaugg*[7]. The reactive species is a carbonium-imonium ion which is generated in an acid-catalyzed reaction. It acts as an electrophile towards the aromatic nucleus of the reactant[8]. Our original method of synthesizing **2b** involved refluxing **1a** with an excess of 1,4-benzenediol in 1,2-dichloroethane in the presence of 4-toluenesulfonic acid as a catalyst. In this article we will discuss some alternative procedures for increasing the reactivity of the system. Because of its synthetic convenience, we first tried to perform the synthesis of compounds **2** in concentrated sulfuric acid. This method, which is referred to as the Tscherniac–Einhorn reaction, could not be used to prepare **2b**, because of the excessive degradation of 1,4-benzenediol, as indicated by a blackening and tarring of the reaction mixture. Compound **2c**, however, could be obtained by this procedure in 94% yield, simply by stirring **1a** in concentrated sulfuric acid with a five-fold excess of 1,4-dimethoxybenzene at room temperature for 16 h. When 1,4-xylene and **1a** were stirred under the same conditions reaction took place, but no single product could be isolated. The reaction mixtures gave NMR spectra with very broad peaks, suggesting that a polymerization reaction had taken place.

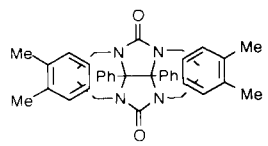
Another acidic catalyst for amidoalkylation that has been described in the literature is trifluoroacetic acid (TFA) in $CHCl_3$[9]. With this catalyst no reaction could be induced between **1a** and 1,4-dimethoxybenzene. In order to increase the reactivity of the starting compound we replaced the relatively stable cyclic ether group in **1a** by the better leaving group -$OCOCH_3$. Derivative **1b**, was prepared by heating **1a** in acetic anhydride with trifluoroacetic acid or 4-toluenesulfonic acid at 70°C. Compound **1b** is a stable solid which crystallizes from the reaction mixture upon cooling. It could be isolated in 95% yield. When compound **1b** was synthesized and, without isolation, heated with an excess of 1,4-dimethoxybenzene at 95°C, a 94% yield of **2c** was obtained after 1 h. This result confirms the increased reactivity of **1b** as compared to **1a**. The same procedure was applied to obtain multigram quantities of **2f** and **2g** from **1a** and **8a** or **8b**, respectively. Compounds **2f** and **2g** had previously been synthesized by an alkylation



1b R = OAc
1c R = Cl



2a R_{1-4} = H
2b R_{1-4} = OH
2c R_{1-4} = OMe
2d $R_1 = R_4$ = OAc $R_2 = R_3$ = OMe and $R_1 = R_3$ = OAc $R_2 = R_4$ = OMe
2e R_{1-4} = Me
2f R_{1-4} = OCH_2CH_2Cl
2g R_{1-4} = $(OCH_2CH_2)_2Cl$



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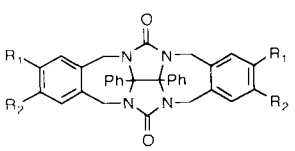
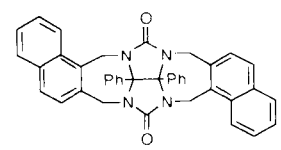
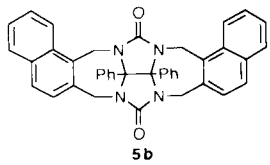


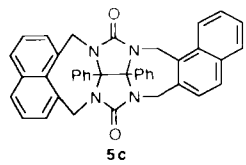
4a $R_1 = R_2$ = OMe
4b R_1, R_2 = $(OCH_2CH_2)_4O$



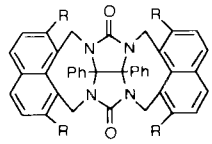
5a



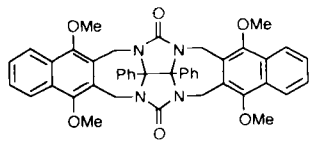
5b



5c



6a R = OH
6b R = OAc



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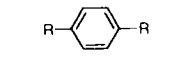
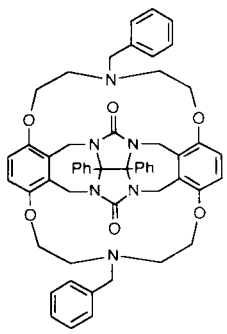
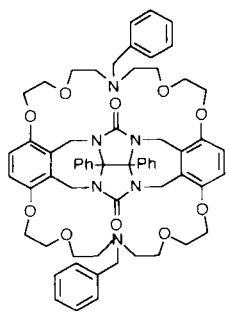


8a R = OCH_2CH_2Cl
8b R = $(OCH_2CH_2)_2Cl$



9a



9b

reaction of **2b** and subsequent chromatographic separation of the product from the complex reaction mixture. With the new procedure, **2f** and **2g** are obtained in a pure state without chromatographic separation in 88% and 65% yield, respectively. The side products remain in solution after precipitation of the product with MeOH. Compounds **2f** and **2g** are used as intermediates in the synthesis of **9a** and **9b**. These receptors can now be obtained in 64% and 58% overall yield starting from **1a**[5,6].

The procedure using **1b** and TFA/acetic acid (or **1a** and TFA/acetic acid without isolation of **1b**) was moderately efficient for the coupling with 4-methoxyphenol. A mixture of O-acylated derivatives **2d** was isolated in 61% yield. The presence of two isomers was confirmed by the ^{1}H-NMR spectrum of the product mixture, which showed two different acetyl groups and two different methoxy groups. The methylene groups connecting the diphenylglycoluril moiety with the aromatic cavity walls gave rise to a characteristic AB pattern, J 15.8 Hz, in the spectra of compounds **2a-c**. In **2d**, however, each of the two isomers has two chemically non-equivalent methylene groups. Consequently, the ^{1}H-NMR spectrum shows four AB patterns. With several other aromatic compounds the procedure using TFA/acetic acid did not work. With benzene no reaction took place at all. With dibenzo-18-crown-6 the only product that could be isolated was 4,4′-diacetyl-benzo-18-crown-6.

An alternative route to receptor molecules **2–7** is via the tetrachloro derivative **1c**, which we expected to be even more reactive towards aromatic compounds than the tetraacetoxy derivative **1b**, especially in combination with Lewis-acid catalysts. The synthesis of bis(chloromethyl) derivatives of compounds similar to glycoluril has been described in the literature[10].

If compound **1a** was refluxed in neat $SOCl_2$, it was partially converted into **1c**, but a small amount of **1a**

always remained present. After trying many variations on this reaction, we finally resorted to the use of **1b** as the starting compound. Compound **1c** could be prepared by stirring **1b** overnight at room temperature with $SOCl_2$ in CH_2Cl_2 solution (isolated yield 90%). The tetrachloro derivative turned out to be very moisture-sensitive.

Reaction of **1c** in 1,2-dichloroethane in the presence of a Lewis acid catalyst ($TiCl_4$, $SnCl_4$ or $AlCl_3$) proceeded smoothly with alkoxybenzenes such as 1,4-dimethoxybenzene, 1,2-dimethoxybenzene and benzo-15-crown-5. In the latter two cases, only the isomer with the methylene bridges at the 4,5 positions was formed (**4a** and **4b**, respectively). The C_{2v} symmetry, characteristic of this isomer, is apparent from the ^{1}H-NMR spectra of these compounds, which show one AB pattern for the methylene protons and one signal for the aromatic cavity wall protons. Reaction of **1c** with benzene ran very well in pure refluxing benzene with $AlCl_3$ as a catalyst. After one hour, **2a** could be isolated in quantitative yield.

Refluxing **1c** with neat 1,2- and 1,4-xylene in the presence of $SnCl_4$ as a catalyst yielded **3** and **2e** in 71% and 78% yield, respectively. In the former case, a mixture of isomers was obtained. About 30% of the xylylene moieties were connected with the glycoluril framework at the 3,4 positions (with two different ^{1}H-NMR shift values for the methyl groups), and the other 70% at the 4,5 position (with one ^{1}H-NMR shift value for the methyl groups), resulting in a mixture of isomers that could not be separated by chromatography or recrystallization. With naphthalene a mixture of isomers was formed (combined yield 56%) from which three components could be isolated. Two diastereomers, **5a** and **5b**, were obtained with the methylene groups at the 1,2 positions of the naphthalene moieties, and one isomer, **5c**[10], in which one naphthalene moiety was coupled at the 1,2 position and the other naphthalene moiety at the 1,8 positions. The isomer with only one carbonyl carbon signal at 158.0 ppm in the ^{13}C-NMR spectrum was assigned structure **5a**, which has C_2 symmetry. The isomer which displayed different NMR shifts for all methylene protons and all carbon atoms was assigned structure **5c**. The remaining isomer was given structure **5b**. That none of the cavity walls in **5c** is connected at 2,3 positions is inferred from the absence of signals from 1,4 protons of the naphthalene moieties in the aromatic region of the ^{1}h-NMR spectrum. With 2,7-dihydroxynaphthalene the only product is the 1,8-methylene isomer **6a**. This compound was converted to the tetraacetoxy derivative **6b** for characterization. With 1,4-dimethoxynaphthalene the reaction product was compound **7** (93% yield)[6].

In order to enlarge the aromatic surfaces of our receptors further we tried to perform a Lewis-acid-catalyzed reaction of **1c** with coronene and pyrene. Unfortunately, we were not able to isolate any coupled product, presumably because coronene and pyrene from very insoluble complexes with the Lewis acid catalyst.

Conclusions

Of the methods we have studied to attach aromatic molecules to the framework of diphenylglycoluril, the method that makes use of the tetrachloromethyl compound **1c** in combination with Lewis acids is the most versatile one. The moderate-to-high yields and short reaction times allow us to prepare a wide variety of molecular receptors based on diphenylglycoluril.

For the synthesis of **2f** and **2g**, the reaction in acetic anhydride is especially useful because it is compatible with the presence of haloalkyl groups and the work-up is extremely simple.

Table I Synthesis of receptor molecules.

Starting compounds	Method [a]	Product	Yield (%)
1c, benzene	C [b]	**2a**	>99
1a, 1,4-benzenediol	[c]	**2b**	75
1a, 1,4-dimethoxybenzene	A	**2c**	94
1a, 1,4-dimethoxybenzene	B	**2c**	96
1a, 4-methoxyphenol	B	**2d**	61 [d]
1c, 1,4-xylene	C [e]	**2e**	78
1a, **8a**	B	**2f**	88
1a, **8b**	B	**2g**	65
1c, 1,2-xylene	C	**3**	71 [d]
1c, 1,2-dimethoxybenzene	C	**4a**	40
1c, benzo-15-crown-5	C	**4b**	92
1c, naphthalene	C [e]	**5a–c**	56 [d]
1c, 2,7-dihydroxynaphthalene	C	**6a**	64
1c, 1,4-dimethoxynaphthalene	C	**7**	93

[a] See experimental section. [b] $AlCl_3$ was used as catalyst. [c] See ref. 4b. [d] Yield of all isomers. [e] $TiCl_4$ was used as a catalyst.

Experimental

For column chromatography Merck silica gel (60H) was used. 1,2-Dichloroethane was dried over 4Å molecular sieves prior to use. Benzene was distilled from sodium. Other chemicals were of reagent grade and were used without further purification unless stated otherwise.

1,4-Dimethoxynaphthalene[11], **1a**[4b], and **2b**[4b] were synthesized according to known procedures. **1a** was recrystallized from acetic acid before use.

1,3,4,6-Tetrakis(acetoxymethyl)tetrahydro-3a,6a-diphenylimidazo[4,5-d]imidazole-2,5(1H,3H)-dione (**1b**)

Compound **1a** (5.01 g, 13.25 mmol) and 4-toluenesulfonic acid (0.5 g, 2.63 mmol) in 20 ml of acetic anhydride were heated at 110°C for 3 h. After cooling 20 ml of diethyl ether was added and the product was filtered off, washed with ether and dried under vacuum. Yield 7.32 g (95%) of **1b**. ^{1}H NMR ($CDCl_3$) δ 7.18–6.75 (m, 10 H, ArH), 5.71 and 5.24 (2d, 8 H, NC*H*HOAc, *J* 12 Hz), 2.02 (s, 12 H, $COCH_3$). FAB-MS (3-nitrobenzyl alcohol) *m / z* 583 $(M+H)^+$. Anal. calcd for $C_{28}H_{30}N_4O_{10}\cdot 0.5\ H_2O$: C 56.80, H 5.36, N 9.46; found: C 56.91, H 5.22, N 9.31%; m.p. > 330°C (dec.).

1,3,4,6-Tetrakis(chloromethyl)tetrahydro-3a,6a-diphenylimidazo[4,5-d]imidazole-2,5(1H,3H)-dione (**1c**)

A mixture of 10 ml of CH_2Cl_2, 10 ml (137 mmol) of $SOCl_2$, and 7.32 g (12.6 mmol) of **1b** was stirred for 16 h. Diethyl ether (10 ml) was added and the product was filtered off, washed with ether and dried under vacuum. Yield 5.52 g (90%) of **1c**. ^{1}H NMR ($CDCl_3$) δ 7.31–6.87 (m, 10 H, ArH), 5.42 and 5.27 (2d, 8 H, NC*H*HCl, *J* 11.2 Hz). FAB-MS (3-nitrobenzyl alcohol) *m / z* 489 $(M+H)^+$, 453 $(M-Cl)^+$. Due to the instability of the compound no satisfactory analysis could be obtained.

General procedures for the synthesis of compounds **2–7**

Method A. *n* mmol of **1a** and 5*n* mmol of the appropriate benzene derivative were dissolved in 8*n* ml of concd. H_2SO_4 and stirred for 16 h at room temperature. The reaction mixture was poured onto ice and made basic with NaOH. The product was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*.

Method B. *n* mmol **1a** was dissolved in a mixture of *n* ml of acetic anhydride and *n* ml of trifluoroacetic acid. After heating for 30 min at 95°C, 2.2*n* mmol of the appropriate benzene derivative was added and the reaction mixture was heated for another 30 min. After cooling 4*n* ml of methanol was cautiously added and the resulting precipitate was filtered, washed with diethyl ether and dried *in vacuo*.

Method C. *n* mmol **1c**, 2.2*n* mmol of the appropriate benzene or naphthalene compound, and 8*n* mmol of catalyst ($AlCl_3$, $SnCl_4$, or $TiCl_4$) were refluxed under nitrogen in 1,2-dichloroethane. After the reaction had been completed 5*n* ml of 6N aqueous HCl was added and the mixture was refluxed again for 30 min. CH_2Cl_2 was added and the organic layer was washed with aqueous HCl, water and dried with $MgSO_4$. After filtering the solution, the solvent was removed by evaporation at reduced pressure.

5,7,12,13b,13c,14-Hexahydro-13b,13c-diphenyl-6H,13H-5a,6a,12a,13a-tetraazabenz[5,6]azuleno[2,1,8-ija]benz[f]azulene-6,13-dione (**2a**). Method C. Compound **1c** (0.930 g, 1.9 mmol) and $AlCl_3$ (1.6 g, 12 mmol) were refluxed in 8 ml of dry benzene (90 mmol) for 4 h under nitrogen. After this period 20 ml of 6 N aqueous HCl was added and the mixture was refluxed for another 30 min. After cooling, the product was extracted with CH_2Cl_2, the organic layer was washed with water, dried over $MgSO_4$, and concentrated. Yield 0.949 g (> 99%) of **2a**. Spectral data were in agreement with previously reported values[4b]. ^1H NMR ($CDCl_3$) δ 7.16 (m, 18 H, ArH), 4.77 and 4.15 (2d, 8 H, NC*H*HAr, *J* 15.8 Hz). FAB-MS (3-nitrobenzyl alcohol) *m/z* 499 $(M+H)^+$. Anal. calcd. for $C_{32}H_{26}N_4O_2$: C 77.09, H 5.26, N 11.24; found: C 77.07, H 5.16, N 11.12%; m.p. > 330°C.

5,7,12,13b,13c,14-Hexahydro-1,4,8,11-tetramethoxy-13b,13c-diphenyl-6H,13H-5a,6a,12a,13a-tetraazabenz[5,6]azuleno[2,1,8-ija]benz[f]azulene-6,13-dione (**2c**). Method A. Compound **1a** (0.21 g, 0.55 mmol) and 1,4-dimethoxybenzene (0.38 g, 2.75 mmol) yielded 0.32 g (94%) of pure **2c**. Method B. Compound **1a** (0.378 g, 1 mmol) and 1,4-dimethoxybenzene (0.303 g, 2.2 mmol) yielded 0.592 g (96%) of **2c**. Spectral data were in agreement with previously reported values[4b]. ^1H NMR ($CDCl_3$) δ 7.06 (s, 10 H, ArH), 6.45 (s, 4 H, ArH), 5.57 and 3.72 (2d, 8 H, NC*H*HAr, *J* 15.8 Hz), 3.68 (s, 12 H, OCH_3). FAB-MS (3-nitrobenzyl alcohol) *m/z* 619 $(M+H)^+$. Anal. calcd for $C_{36}H_{34}N_4O_6$: C 69.89, H 5.54, N 9.06; found: C 69.95, H 5.52, N 9.05%.

5,7,12,13b,13c,14-Hexahydro-1,8-diacetoxy-4,11-dimethoxy-13b,13c-di-phenyl-6H,13H-5a,6a,12a,13a-tetraazabenz[5,6]azuleno[2,1,8-ija]-benz[f]azulene-6,13-dione and *5,7,12,13b,13c,14-hexahydro-1,11,-diacetoxy-4,8-dimethoxy-13b,13c-diphenyl-6H,13H-5a,6a,12a,13a-tetra-azabenz-[5,6]azuleno[2,1,8-ija]benz[f]azulene-6,13-dione* (**2d**). Method B. Compound **1a** (3 g, 7.9 mmol) and 4-methoxyphenol (2.17 g, 17.5 mmol) yielded 3.3 g (61%) of **2d** as a mixture of diastereomers. ^1H NMR ($CDCl_3$) δ 7.07–7.01 (m, 10 H, ArH), 6.84 and 6.73 (2d, 4 H, ArH, *J* 8.8 Hz), 5.64, 5.02, 3.86 and 3.79 (4d, 8 H, NC*H*HAr, *J* 16 Hz) 3.80 (s, 6 H, OCH_3), 2.36 (s, 6 H, $OCOCH_3$). FAB-MS (3-nitrobenzyl alcohol) *m/z* 675 $(M+H)^+$. Anal. calcd. for $C_{38}H_{34}N_4O_8 \cdot 0.5\ H_2O$: C 66.76, H 5.16, N 8.19; found: C 66.78, H 5.01, N 8.15%.

5,7,12,13b,13c,14-Hexahydro-1,4,8,11-tetramethyl-13b,13c-diphenyl-6H,13H-5a,6a,12a,13a-tetraazabenz[5,6]azuleno[2,1,8-ija]benz[f]azulene-6,13-dione (**2e**). Method C. Compound **1c** (4.45 g, 9.1 mmol), 50 ml (0.4 mol) of dry 1,4-xylene and 5 ml (45.5 mmol) of $TiCl_4$ in 50 ml of 1,2-dichloroethane. Reaction time was 1.5 h. Yield 3.94 g (78%) of **2e**. ^1H NMR ($CDCl_3$) δ 7.11 (s, 10 H, ArH), 6.85 (s, 4 H, ArH), 5.07 and 3.87 (2d, 8 H, NC*H*HAr, *J* 15.8 Hz), 2.47 (s, 12 H, CH_3). FAB-MS (3-nitrobenzyl alcohol) *m/z* 555 $(M+H)^+$. Anal. calcd. for $C_{36}H_{34}N_4O_2$: C 77.95, H 6.18, N 10.10; found: C 77.87. H 6.07, N 10.00%; m.p. > 330°C.

5,7,12,13b,13c,14-Hexahydro-1,4,8,11-tetrakis(2-chloroethoxy)-13b,-13c-diphenyl-6H,13H-5a,6a,12a,13a-tetraazabenz[5,6]azuleno-[2,1,8-ija]benz[f]azulene-6,13-dione (**2f**). Method B. From compounds **1a** (1.6 g, 4.51 mmol) and **8a** (3.16 g, 13.5 mmol). Yield 3.2 g (88%). Spectral data were in agreement with previously reported values[4c]. ^1H NMR ($CDCl_3$) δ 7.05 (s, 10 H, ArH), 6.45 (s, 4 H, ArH), 5.55 (d, 4 H, NC*H*HAr, *J* 15.8 Hz) 4.2–3.45 (m, 20 H, OCH_2CH_2Cl, NC*H*HAr). FAB-MS (3-nitrobenzyl alcohol) *m/z* 811 $(M+H)^+$.

5,7,12,13b,13c,14-Hexahydro-1,4,8,11-tetrakis[2-(2-chloroethoxy)-ethoxy]-13b,13c-diphenyl-6H,13H-5a,6a,12a,13a-tetraazabenz[5,6]-azuleno[2,1,8-ija]benz[f]azulene-6,13-dione (**2g**). Method B. From compounds **1a** (1.5 g, 3.97 mmol) and **8b** (3.9 g, 7.3 mmol). Yield 2.55 g (65%). Spectral data were in agreement with previously reported values[4c]. ^1H NMR ($CDCl_3$) δ 6.95 (s, 10 H, ArH), 6.55 (s, 4 H, ArH), 5.45 (d, 4 H, NC*H*HAr, *J* 15.8 Hz) 4.1–3.6 (m, 36 H, $OCH_2CH_2OCH_2CH_2Cl$, NC*H*HAr). FAB-MS (3-nitrobenzyl alcohol) *m/z* 987 $(M+H)^+$. Anal. calcd. for $C_{56}H_{58}N_4O_{10}Cl_2$: C 61.77, H 5.37, N 5.15; found: C 61.58, H 5.45, N 5.30%.

5,7,12,13b,13c,14-Hexahydro-2,3,9,10-tetramethyl-13b,13c-diphenyl-6H,13H-5a,6a,12a,13a-tetraazabenz[5,6]azuleno[2,1,8-ija]benz[f]-azulene-6,13-dione and its isomers (**3**). Method C. From compound **1c** (0.212 g, 0.43 mmol), 20 ml of freshly distilled 1,2-xylene (163 mmol) and 0.4 ml (3.4 mmol) of $SnCl_4$. The mixture was refluxed for 16 h. After column chromatography ($CHCl_3$) 0.170 g (71%) of a mixture of isomers was obtained, which could not be separated further. ^1H NMR ($CDCl_3$) δ 7.10 (s, 10 H, ArH), 7.02 and 6.95 (s, 4 H, ArH), 5.23 and 3.90 (2d, 0.3×4 H, NC*H*HAr, *J* 15.8 Hz) 4.75 and 4.11 (2d, 0.7×4 H, NC*H*HAr, *J* 15.8 Hz) 2.42 and 2.22 (2s, 0.15×12 H, CH_3) 2.14 (s, 0.7×12 H, CH_3). FAB-MS (3-nitrobenzyl alcohol) *m/z* 555 $(M+H)^+$. Anal. calcd. for $C_{36}H_{34}N_4O_2$: C 77.95, H 6.18, N 10.10, found: C 77.65, H 6.03 N 9.88%.

5,7,12,13b,13c,14-Hexahydro-2,3,9,10-tetramethoxy-13b,13c-diphenyl-6H,13H-5a,6a,12a,13a-tetraazabenz[5,6]azuleno[2,1,8-ija]benz[f]azulene-6,13-dione (**4a**). Method C. From compound **1c** (0.50 g, 1.02 mmol), 1,2-dimethoxybenzene (0.30 g, 2.17 mmol), and $SnCl_4$ (1 ml, 8 mmol) in 10 ml of 1,2-dichloroethane. Reaction time was 1 h. Yield 0.246 g (40%) of **4a**. ^1H NMR ($CDCl_3$) δ 7.10 (s, 10 H, ArH), 6.80 (s, 4 H, ArH), 4.73 and 4.13 (d, 8 H, NC*H*HAr, *J* 15.8 Hz), 3.49 (s, 12 H, OCH_3). FAB-MS (3-nitrobenzyl alcohol) *m/z* 619 $(M+H)^+$. Anal. calcd. for $C_{36}H_{34}N_4O_6H_2O$: C 67.91. H 5.70, N 8.80; found: C 67.84, H 5.36, N 8.75%; m.p. 260°C.

2,3,5,6,8,9,11,12,15,17,20,21,23,24,26,27,29,30,33,34b,34c,35-Docosahydro-34b,34c-diphenyl-16H,34H-1,4,7,10,13,19,22,25,28,31-decaoxa-15a,16a,33a,34a-tetraazacyclopentadeca[4',5']benz[1',2':5,6]-azuleno[2,1,8-ija]cyclopentadeca[4,5]benz[1,2-f]azulene-16-34-dione (**4b**). Method C. From compound **1c** (0.25 g, 0.51 mmol), benzo-15-crown-5 (0.29 g, 1.08 mmol) and 0.5 ml (4 mmol) of $SnCl_4$ in 10 ml of 1,2-dichloroethane. Reaction time was 30 min. The product was purified by column chromatography ($CHCl_3$/MeOH/triethylamine, 94:5:1 v/v). Yield 0.413 (92%). ^1H NMR ($CDCl_3$) δ 7.06 (s, 10 H, ArH), 6.80 (s, 4 H, ArH), 4.69 (d, 4 H, NC*H*HAr, *J* 15.8 Hz), 4.27–3.58 (m, 36 H, OC*H*HCH$_2$, NC*H*HAr). FAB-MS (3-nitrobenzyl alcohol) *m/z* 879 $(M+H)^+$, 901 $(M+Na)^+$. Anal. calcd. for $C_{48}H_{54}N_4O_{12} \cdot CH_2Cl_2$: C 61.06, H 5.86, N 5.81; found: C 61.11, H 5.73, N 6.02%.

Reaction of **1c** *with naphthalene* (**5a–c**)

Method C. From compound **1c** (0.365 g, 0.75 mmol), naphthalene (0.256 g, 2.0 mmol) and 0.4 ml (3.65 mmol) of $TiCl_4$. The mixture was refluxed for 16 h. After column chromatography ($CHCl_3$/MeOH, 97:3 v/v) 251 mg (56%) of a mixture of at least four isomers was obtained. From this mixture three pure isomers could be obtained by column chromatography ($CHCl_3$/hexane 9:1 v/v), in order of elution:

7,9,16,17b,17c,18-Hexahydro-17b,17c-diphenyl-8H,17H-7a,8a,16a,17a-tetraazanaphth[1',2':5,6]azuleno[2,1,8-ija]napht[1,2-f]azulene-8,17-dione (**5a**). ^1H NMR ($CDCl_3$) δ 8.38 (d, 2 H, Napht H-4, *J* 8.7 Hz), 7.63–7.1 (m, 20 H, NaphtH, ArH), 5.79, 4.86, 4.33 and 4.15 (4d, 8 H, NC*H*HAr, *J* 16.2 Hz). ^{13}C NMR ($CDCl_3$): δ 158.0 (C=O), 135.4, 134.3, 133.2, 133.0, 131.6, 138.8, 128.72, 128.66, 128.4, 128.3, 128.2, 128.0, 127.8, 126.5, 125.3, 123.8 (C-Napht and C-Ph); 85.5 (Ph*C*N); 46.1, 38.8 (Napht*C*H$_2$N), FAB-MS (3-nitrobenzyl alcohol) *m/z* 599 $(M+H)^+$. Anal. calcd. for $C_{40}H_{30}N_4O_2$: C 80.25, H 5.05, N 9.36; found: C 79.67, H 4.91, N 9.12%.

7,9,16,17b,17c,18-Hexahydro-17b,17c-diphenyl-8H,17H-7a,8a,16a,17a-tetraazanaphth[5,6:7',8']azuleno[2,1,8-ija]naphth[1,2-f]azulene-8,17-dione (**5b**) ^1H NMR ($CDCl_3$) δ 8.36 (d, 2 H, Napht H-4, *J* 8.7 Hz), 7.63-7.1 (m, 20 H, NaphtH, PhH), 5.75, 4.93, 4,35 and 4.18 (4d, 8H, NC*H*HAr, *J* 16.2 Hz), FAB-MS (3-nitrobenzyl alcohol) *m/z* 599 $(M+H)^+$ (not enough material could be obtained for elemental analysis).

Compound **5c**. ^1H NMR ($CDCl_3$) δ 8.30 (d, 1 H, Napht H-4, *J* 8.7 Hz), 7.65–7.1 (m, 20 H, NaphtH, ArH), 5.74, 4.93, 4.90, 4.86, 4.58, 4.53, 4.27 and 4.09 (8d, 8 H, NC*H*HAr, *J* 16.2 Hz). ^{13}C NMR ($CDCl_3$): δ 157.65 and 157.25 (C=O), 135.86, 135.38, 134.78, 133,68, 133.54, 133.37, 132.91, 131.56, 131.03, 130.86, 130.74, 130.53, 130,10, 128.88, 128.71, 128.60, 128.39, 128.25, 128.17, 127.88, 127.69, 126,49, 125.27, 124.70, 123.82 (C-Napht and C-Ar); 85.32 and 84.01 (Ph*C*N); 48.09, 47.57, 45.76, 38.53 (Napht*C*H$_2$N). FAB-MS (3-nitrobenzyl alcohol) *m/z* 599 $(M+H)^+$. Anal. calcd. for $C_{40}H_{30}N_4O_2$: C 80.25, H 5.05, N 9.36; found: C 79.96, H 5.18, N 9.26%.

17b,17c-Dihydro-1,6,10,15-tetrahydroxy-17b,17c-diphenyl-7H,8H,9H,16H,17H,18H-7a,8a,16a,17a-tetraazapentaleno[1'',6'':5,6,7:3'',4'',:5',6',7']dicycloocta[1,2,3-de:1',2',3''-d'e']dinaphthalene-8,17-dione (**6a**). Method C. From compound **1c** (2.48 g, 5.08 mmol), 2,7-naphthalenediol (3.2 g, 20 mmol) and 5.5 ml (44 mmol) of $SnCl_4$. The mixture was refluxed for 30 min. After refluxing with aqueous HCl the product was isolated from the reaction mixture by filtration and was washed with MeOH. The product was purified by recrystallization from DMSO. Yield 2.1 g (64%) of colorless needles. FAB-MS (3-nitrobenzyl alcohol) *m/z* 663 $(M+H)^+$. Anal. calcd. for

$C_{40}H_{30}N_4O_6 \cdot 0.5H_2O$: C 71.53, H 4.65, N 8.34; found: C 71.53, H 4.63, N 8.37%; m.p. > 330°C. For further characterization compound **6a** was converted into compound **6b** (see below).

17b,17c-Dihydro-1,6,10,15-tetraacetoxy-17b,17c-diphenyl-7H,8H,9H,16H,17H,18H-7a,8a,16a,17a-tetraazapentaleno[1'',6'':5,6,7;3'',4'':5',6',7']dicycloocta[1,2,3-de:1',2',3'-d'e']dinaphthalene-8,17-dione (**6b**). Compound **6a** (0.781 g, 1.18 mmol) was heated at 100°C in 15 ml of acetic anhydride with 1 ml of pyridine. After 1 h, the solvent was evaporated, and the residue was purified by column chromatography ($CHCl_3$/MeOH, 97:3 v/v). Yield 0.431 g (44%) of **6b**. ^{1}H NMR ($CDCl_3$); the compound exists as a mixture of three conformers in solution[12]. The signals of the most abundant conformer, that with two-non-equivalent naphthyl groups, are given here. δ 7.84, 7.30, 7.34 and 6.94 (4 d, 8 H, Napht-H, *J* 8.7 Hz), 7.05–6.30 (m, 10 H, ArH), 5.65, 5.49, 4.87 and 4.19 (4d, 8 H, NC*H*HAr, *J* 15.8 Hz) 2.55 and 2.51 (2s, 12 H, OAc). ^{13}C NMR ($CDCl_3$): δ 169.72 (Acetyl C=O), 158.16 (urea C=O), 149.92, 148.82 (Napht C-2,7) 134.55, 134.03, 132.05, 131.92, 131.36, 130.30, 130.08, 128.83, 128.65, 128.18, 126.70, 126.61, 125.53, 122.29, 122.05, 121.71, 121.12 (Napht-C and Ph-C), 84.52, 83.61 (Ph*C*N), 39.89, 37.08 (Napht CH_2N), 21.56, 21.28 (acetyl CH_3). FAB-MS (3-nitrobenzyl alcohol) *m/z* 831 $(M+H)^+$. Anal. calcd. for $C_{48}H_{38}N_4O_{10} \cdot 0.5\ H_2O$: C 68.65, H 4.68, N 6.67; found: C 68.56, H 4.61, N 6.57%

6,8,15,16b,16c,17-Hexahydro-5,9,14,18-tetramethoxy-16b,16c-diphenyl-7H,16H-6a,7a,15a,16a-tetraazanaphtho[5,6]azuleno[2,1,8-ija]naphtho[f]-azulene-7,16-dione (**7**). Method C. From compound **1c** (0.480 g, 0.98 mmol), 1,4-dimethoxynaphthalene (0.340 g, 2.15 mmol) and 1.0 ml (8 mmol) of $SnCl_4$. The mixture was refluxed for 1 h. After column chromatography ($CHCl_3$/MeOH, 99:1 v/v) 0.602 g (93%) of pure **7** was obtained. ^{1}H NMR ($CDCl_3$) δ 7.92 (m, 4 H, Napht H-5,8), 7.42 (m, 4 H, Napht H-6,7), 7.15 (s, 10 H, ArH), 5.76 (d, 4 H, NC*H*HAr, *J* 15.8 Hz) 3.96 (d, 4 H, NC*H*HAr, *J* 15.8 Hz) 4.04 (s, 12 H, OCH_3). FAB-MS (3-nitrobenzyl alcohol) *m/z* 719 $(M+H)^+$. Anal. calcd. for $C_{44}H_{38}N_4O_6$: C 73.52, H 5.33, N 7.79; found: C 72.34, H 5.31, N 7.92%.

1,4-Bis(2-chloroethoxy)benzene (**8a**). A degassed suspension of 1.1 g (10 mmol) of 1,4-benzenediol and 1.2 g (21.4 mmol) of powdered KOH in 20 ml of 1,2-dichloroethane was refluxed for 16 h with 4 g of Aliquat as a phase-transfer catalyst. The reaction mixture was washed twice with water and concentrated *in vacuo*. After column chromatography ($CHCl_3$/hexane, 3:2 v/v) 1.04 g (44%) of **8a** was obtained. ^{1}H NMR ($CDCl_3$) δ 6.79 (s, 4 H, ArH), 4.16 (t, 4 H, OCH_2CH_2), 3.74 (t, 4 H, CH_2CH_2Cl).

1,4-Bis[2-(2-chloroethoxy)ethoxy)]benzene (**8b**). To a suspension of 1.07 g (44.4 mmol) of NaH in 50 ml of dry degassed DMF, 2.0 g (18.2 mmol) of 1,4-benzenediol and 9.86 g (35.4 mmol) of 1-[[2-(2-chloroethoxy)ethyl]sulfonyl]-4-methylbenzene[4c] were added. The suspension was stirred at room temperature for 20 h and poured into 250 ml of 1 *N* aqueous HCl. The aqueous suspension was extracted twice with 100 ml of $CHCl_3$. The combined organic layers were washed twice with a saturated solution of $NaHCO_3$ and concentrated *in vacuo*. After column chromatography (ethyl-acetate/hexane, 1:3 v/v) of the residue, 4.79 g (84%) of **8b** was obtained. ^{1}H NMR ($CDCl_3$) δ 6.83 (s, 4 H, ArH), 4.17–3.60 (m, 16 H, CH_2).

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