Synthesis of a Novel Benzocyclotrimer with One Rigid and One Flexible Electron-Rich Cavity

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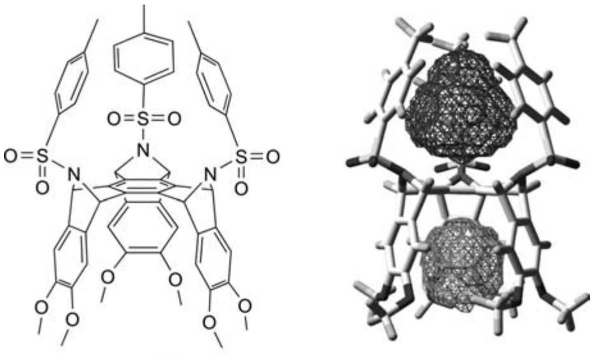
The straightforward synthesis of a novel benzocyclotrimer is herein presented. The *syn*-product is characterized by an electron-rich rigid aromatic cavity and a flexible electron-rich aromatic pocket. The molecule is a potential scaffold for supramolecular applications.

Introduction. – Supramolecular applications in chemistry [1] have attracted the interest of a large number of scientists, since the first applications described by *D. J. Cram*, *J.-M. Lehn*, and *C. J. Pedersen* since 1987 [2]. The prerequisite for the supramolecular phenomenon is the electronic and steric reciprocity between the host and the guest partners. In order to form supramolecules with high selectivity, the synthesis of hosts with specific shapes and finely tuned electronic surfaces is mandatory.

Benzocyclotrimers [3] are rigid molecules characterized by one or two cavities, which have been successfully employed in supramolecular chemistry [4]. Among them, benzocyclotrimers bearing aromatic rings are characterized by large stiff cavities. In this report, we describe the synthesis of the electron rich benzocyclotrimer *syn*-**1** displaying one rigid hemi-cavity in the lower part of the structure (*Fig. 1*). Furthermore, the three tolyl residues form one flexible cavity at the upper part of the central aromatic ring (*Fig. 1*).



syn-**1**

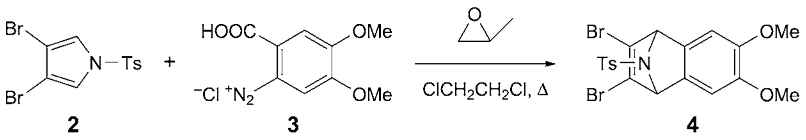
Fig. 1. *Benzocyclotrimer* syn-**1***, displaying the upper gated-cavity and the lower hemi-cavity*

Results and Discussion. – The starting material for the synthesis of the benzocyclotrimer *syn*-**1** was 3,4-dibromo-*N*-tosylpyrrole **2**, which can be obtained from commercially available 1-(4-tolylsulfonyl)pyrrole [5]. Pyrrole **2** reacted in a [4 + 2] cycloaddition with the benzyne derived from the decomposition of the 2-diazonium-4,5-dimethoxy benzoate zwitterion **3**, acting as the dienophile[1]) (*Scheme 1*). The benzyne intermediate was at first obtained *in situ*, by the action of isopentylnitrite in CH_2Cl_2/acetone in the presence of the pyrrole, for safety reason. The yields of the cycloadduct were disappointingly low (about 20% after chromatography). For this reason, it was decided to isolate the diazonium salt by precipitation as chloride, which turned out to be stable when moistened with Et_2O and stored for a short time in a refrigerator [7]. The diazonium chloride was conveniently converted into the benzyne form in the presence of pyrrole **2**, by the action of propylene oxide [7]. Several experiments allowed to optimize the amount and rate of the addition of the hydrogen chloride scavenger. Indeed, the rapid addition of 1 equiv. of propylene oxide led to the formation of the cycloadduct in modest yield (20% yield of isolated product). The addition of the scavenger in such an amount to completely consume the suspended diazonium chloride (nearly two equiv.), led to an increase in the yield of the cycloadduct (36%). Finally, 2.1 equiv. of scavenger was added at a slower rate (27 mmol/h), to obtain the cycloadduct in a yield of 53% of isolated product **4** (*Scheme 1*).

Stannylation of the dibromide **4** was attempted at first by metalation with butyllithium to obtain compound **5** and transmetalation with trimethyltin chloride, furnishing the desired stannane **6** in low yields (about 20%), accompanied by non negligible amounts of a tin free compound (*Scheme 2*). Characterization (^{1}H- and ^{13}C-NMR, HMQC, HMBC, COSY, NOESY) of this product allowed the assessment of structure **9** to this compound. An obvious hypothesis for its formation is that at first the addition of the lithiated intermediate **5** to a second molecule of **4** takes place to form **7**. The ring-opening of the aza-bridge, with simultaneous formation of a C=C bond in the saturated ring, is favoured by the release in strain in **8**. A further gain in energy is obtained by the elimination of a molecule of Ts-NLiBr (a compound analogous to chloramine-T) and complete aromatization of the naphthyl moiety (*Scheme 2*).

In order to minimize this side product, the lithiation reaction was performed at – 90° for a shorter time (3–4 min) before quenching with trimethyltin chloride. Owing to this precaution, a nearly quantitative yield of trimethyltin derivative **6** was obtained.

Scheme 1. *Synthesis of the Bicycle* **4**, via *Cycloaddition Reaction of Pyrrole* **2** *with the Aryne from Diazonium Salt* **3**



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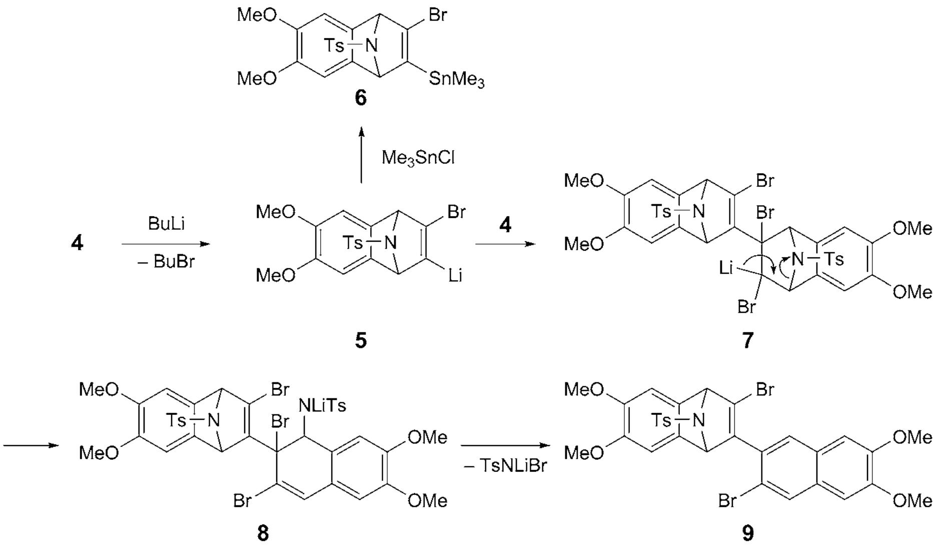
[1]) This compound is commercially available, but it is more convenient to prepare it from the less expensive methyl ester, according to [6].

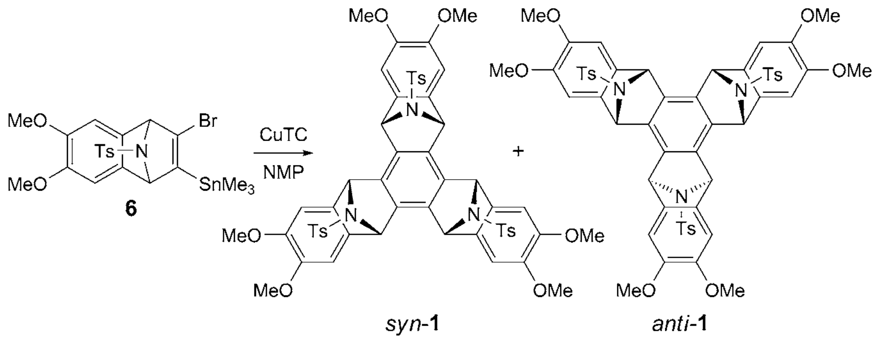
Scheme 2. *Stannylation of* **4** *and Mechanistic Hypothesis for the Formation of By-Product* **9**



The cyclotrimerization of **6** was accomplished with freshly prepared copper(I) 2-thiophenecarboxylate (CuTC) in dry NMP [8] (*Scheme 3*).

The isolation and purification of the benzocyclotrimers was accomplished by flash-chromatograpy and trituration with AcOEt in order to remove some residual NMP. The *syn*- and *anti*-diastereoisomers were obtained in 68% overall yield and in a 1:2.2 ratio. Attempts of demethylation of the phenolic moieties with boron tribromide in CH_2Cl_2 at low temperature [9] invariably caused opening of the aza-bridge and aromatization of the products, as witnessed by the disappearance of the signals resonating at 5.70 ppm, concomitantly with the appearance of a set of signals at 8.95 ppm.

Scheme 3. *Cyclotrimerization of* vic-*Bromostannane* **6**



Conclusions. – In conclusion, a straightforward synthesis of a new benzocyclotrimer, characterized by two cavities, has been presented. Equilibrium geometry and electronic structure of this compound have been investigated by means of DFT calculations (see *General* in *Exper. Part*). In the most stable structure (*syn*-**1**-**A**), depicted in *Fig. 2*, the relative positions of the tosyl groups do not allow the definition of the gated-cavity sketched in *Fig. 1.* An equilibrium geometry (*syn*-**1**-**B**) having such a cavity has been obtained by introducing three C–C constrains among the tosyl-Me groups, each one of 4.5 Å (see *Fig. 2*). This value allows the inter-atomic distances among the Me fragments to be slightly higher than the sums of the *Van der Waals* radii, as observable in the inset of *Fig. 2*. The *Gibbs* energy difference between *syn*-**1**-**A** and *syn*-**1**-**B** is quite low, about 5.3 kcal/mol, this suggesting the facile formation of the gated-cavity.

The minimum electron density values inside the rigid hemi-cavity and the gated-cavity in *syn*-**1**-**B** are below 10^{-3} electron bohr^{-3}, as observable in the slice reported in

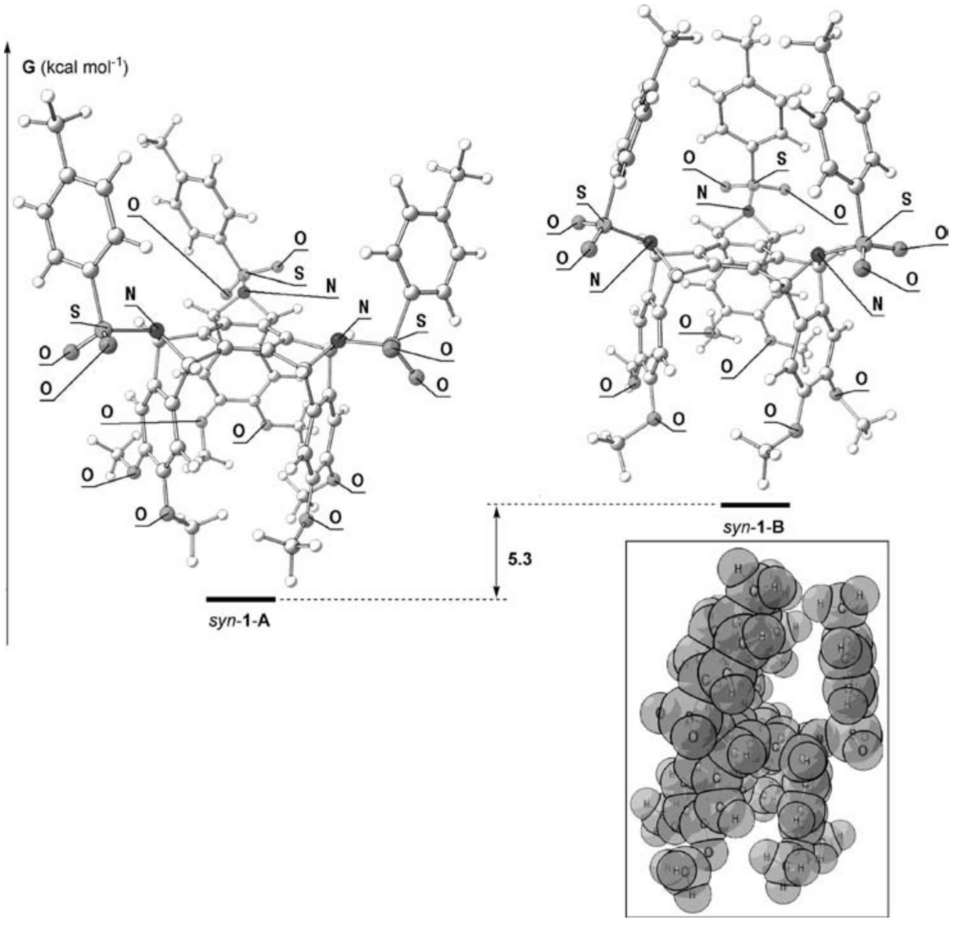


Fig. 2. Syn-**1**-**A** *and* syn-**1**-**B** *geometries and relative* Gibbs *energies.* Inset: *syn*-**1**-**B**, *Van der Waals* spheres

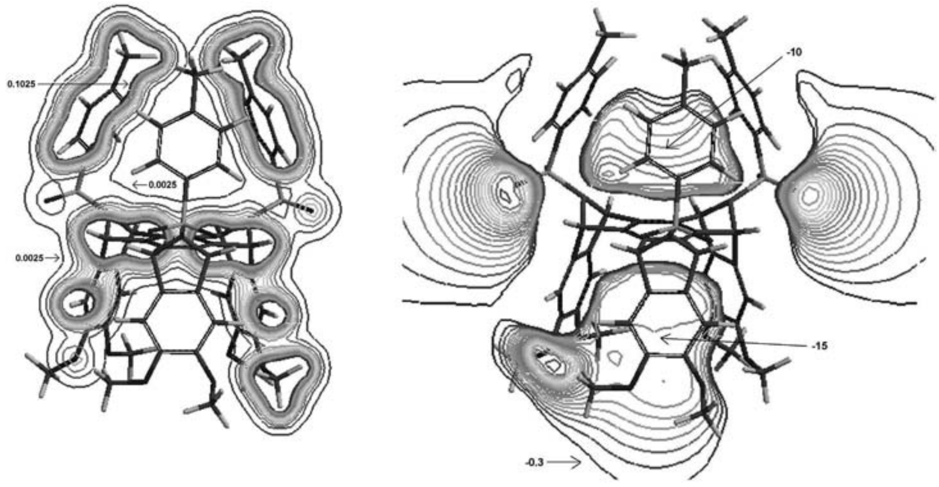


Fig. 3. *Electron density* (left, electrons/Bohr^3) *and electrostatic potential maps* (right, kcal/mol) *for* syn-**1**-**B**, *slices taken perpendicular to the central aromatic ring*

Fig. 3, taken perpendicular to the central aromatic ring. Greater differences between the two cavities arise from the analysis of the electrostatic potential maps (see *Fig. 3*). The value of electrostatic interaction energy for a charge inside the rigid hemi-cavity is around -15 kcal/mol, while less interaction is expected in the other cavity, where the electrostatic interaction energy at the centre amounts to about -10 kcal/mol. The volume of the hemi-cavity and the volume included between the tosyl groups were estimated to be about 34 and 64 Å^3, respectively.

The authors wish to thank Università Ca' Foscari Venezia and MIUR (Rome) within PRIN national framework.

Experimental Part

General. Solvents were dried over standard drying agents and freshly distilled prior to use. The reagents were purchased from *Aldrich* and *Acros*, and were used without further purification unless otherwise stated. All moisture-sensitive reactions were carried out under Ar. Flash chromatography separations: silica gel (*Machery-Nagel 60 M*, 0.04–0.063 mm or 0.063–0.2 mm). IR Spectra: *PerkinElmer Spectrum One* spectrophotometer with NaCl optics. ^{1}H- and ^{13}C-NMR (300 and 75 MHz, resp.) spectra: *Bruker Avance 300* instrument with TMS as internal standard in $CDCl_3$, except where defined otherwise; *J* values in Hz. Computational details: all the ground-state geometry optimizations have been carried out *in vacuo* using the hybrid DFT functional EDF 2 [10] in combination with the split-valence double-ζ polarized basis set 6-31G(d,p) [11]. The 'restricted' formalism has been used in all calculations. No symmetry constrains have been applied, while geometry constrains have been introduced in selected cases [12]. The software used is Spartan '08^2) [13]. Cartesian coordinates of *syn*-**1**-**A** and *syn*-**1**-**B** are collected in a separated .xyz file. The volumes of the cavities were calculated with the program DeepView/Swiss PdbViewer 4.0.4 by using a 1-N molecular probe on the minimized structure *syn*-**1**-**B**.

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^{2}) Except for molecular mechanics and semi-empirical models, the calculation methods used in Spartan have been documented in [13b].

*3,4-Dibromo-1-tosyl-1*H*-pyrrole* (*=3,4-Dibromo-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole*; **2**). A soln. of Br_2 (7.4 ml, 140 mmol) in glacial AcOH (80 ml) was added dropwise in 30 min to a soln. of 1-tosyl-1*H*-pyrrole [5] (13.50 g, 60 mmol) in glacial AcOH (200 ml), and the mixture was maintained at 120° for 1.5 h. The resulting dark soln. was poured onto H_2O and ice (1 l), and the pH was adjusted to neutral with aq. sat. $NaHCO_3$. The resulting solid material was filtered and dissolved in CH_2Cl_2, dried over Na_2SO_4, and decolorized with charcoal. The soln. was filtered over a *Celite* pad, concentrated at reduced pressure. The resulting solid material was crystallized from hot ^{i}PrOH to afford 5.76 g of tan crystals (25% yield). M.p. 135–137°. ^{1}H-NMR: 7.76 (*d*, $J=8.5$, 2 H); 7.34 (*d*, $J=8.5$, 2 H); 7.17 (*s*, 2 H); 2.43 (*s*, 3 H).

2-Carboxy-4,5-dimethoxybenzenediazonium Chloride (**3**). Aq. HCl (37%, 5 ml) and isopentylnitrite (10.4 ml, 124.32 mmol) were sequentially added to an ice cooled soln. of 2-amino-4,5-dimethoxybenzoic acid [6][7] (10.00 g, 50.60 mmol) in EtOH (80 ml). The mixture was maintained under vigorous stirring, until the solid appeared completely dispersed in the soln. (30 min). Et_2O (50 ml) was added in order to complete the precipitation of the salt, which was washed with small amounts of cold Et_2O (2 × 10 ml) and partially dried by suction in the funnel (CAUTION! Dry diazonium salts are explosive!), to obtain 11.30 g of tan solid material (91% yield). ^{1}H-NMR ((D_6)DMSO): 8.66 (*s*, 1 H); 7.73 (*s*, 1 H); 4.10 (*s*, 3 H); 3.93 (*s*, 3 H).

2,3-Dibromo-1,4-dihydro-6,7-dimethoxy-9-tosyl-1,4-epiminonaphthalene (*=2,3-Dibromo-1,4-dihydro-6,7-dimethoxy-9-[(4-methylphenyl)sulfonyl]-1,4-epiminonaphthalene*; **4**). Propylene oxide (3.46 ml, 95.83 mmol) was added *via* a syringe-pump during 3.5 h to a slurry of **3** (11.16 g, 45.63 mmol) and **2** (8.61 g, 22.71 mmol) in 1,2-dichloroethane (100 ml) maintained at 100°. Heating was maintained until N_2 evolution ceased (nearly 4.5 h). The resulting soln. was diluted with CH_2Cl_2, washed with aq sat. $NaHCO_3$ (3 × 50 ml), dried over Na_2SO_4, decolorized with charcoal, and concentrated at reduced pressure. The resulting dark oil was crystallized from Et_2O to obtain a first crop of tan crystals (3.76 g). M.p. 168–173°. Mother liquors were concentrated and purified by flash-chromatography (eluent CH_2Cl_2) and crystallized from Et_2O what gave a second crop of colorless crystals (2.46 g; overall yield 53%). M.p. 170–174°. IR (KBr): 1482, 1345, 1160, 1071, 707, 576. ^{1}H-NMR: 7.59 (*d*, $J=8.4$, 2 H); 7.24 (*d*, $J=8.4$, 2 H); 6.93 (*s*, 2 H); 5.31 (*s*, 2 H); 3.83 (*s*, 6 H); 2.40 (*s*, 3 H). ^{13}C-NMR: 146.6; 143.9; 137.5; 134.9; 133.6; 129.8; 128.5; 107.4; 74.3; 56.5; 21.5. Anal. calc. for $C_{19}H_{17}Br_2NO_4S$: C 44.29, H 3.33; found: C 44.25, H 3.39.

2-Bromo-1,4-dihydro-6,7-dimethoxy-9-tosyl-3-(trimethylstannyl)-1,4-epiminonaphthalene (*=2-Bromo-1,4-dihydro-6,7-dimethoxy-9-[(4-methylphenyl)sulfonyl]-3-(trimethylstannanyl)-1,4-epiminonaphthalene*; **6**). A soln. of butyl lithium in hexane (2.5M, 2.1 ml, 5.15 mmol) was added to a soln. of **4** (2.20 g, 4.29 mmol) in dry THF (14 ml) maintained at −90° under Ar. After 3 min, trimethyltin chloride (1.03 g, 5.15 mmol) was added in one portion and the temp. was left to rise to r.t. in 4 h. The mixture was diluted in CH_2Cl_2, washed with H_2O (3 × 20 ml), dried over Na_2SO_4, and concentrated at reduced pressure to afford 2.41 g (94% yield) of crystalline material. M.p. 63°. IR (KBr): 1479, 1339, 1158, 1071, 693, 573. ^{1}H-NMR: 7.48 (*d*, $J=8.1$, 2 H); 7.14 (*d*, $J=8.1$, 2 H); 6.83 (*s*, 2 H); 6.65 (*s*, 2 H); 5.45 (*s*, 1 H); 5.17 (*s*, 1 H); 3.78 (*s*, 3 H); 3.76 (*s*, 3 H); 2.35 (*s*, 3 H); 0.13 (*s*, 9 H). ^{13}C-NMR: 152.8; 146.5; 145.8; 145.5; 143.3; 139.4; 138.7; 135.5; 129.4; 128.5; 107.8; 106.8; 74.5; 74.2; 56.5; 56.3; 21.4; −9.1. Anal. calc. for $C_{22}H_{26}BrNO_4SSn$: C 44.10, H 4.37; found: C 43.97, H 4.33.

2-Bromo-3-(3-bromo-6,7-dimethoxynaphthalen-2-yl)-1,4-dihydro-6,7-dimethoxy-9-tosyl-1,4-epiminonaphthalene (*=2-Bromo-3-(3-bromo-6,7-dimethoxynaphthalen-2-yl)-1,4-dihydro-6,7-dimethoxy-9-[(4-methylphenyl)sulfonyl]-1,4-epiminonaphthalene*; **9**). Compound **9** was obtained in 34% yield, when the previous reaction was performed at −78° and waiting 30 min before quenching with trimethyltin chloride. M.p. 140–144°. IR (KBr): 2993, 1503, 1254, 1173, 1057, 698, 580. ^{1}H-NMR: 7.92 (*s*, 1 H); 7.51 (*d*, $J=8.3$, 2 H); 7.23 (*s*, 1 H); 7.09 (*d*, $J=8.3$, 2 H); 6.99 (*s*, 1 H); 6.97 (*s*, 1 H); 6.87 (*s*, 1 H); 6.71 (*s*, 1 H); 5.75 (*d*, $J=1.7$, 1 H); 5.37 (*d*, $J=1.7$, 1 H); 3.98 (*s*, 3 H); 3.95 (*s*, 3 H); 3.82 (*s*, 3 H); 3.72 (*s*, 3 H); 2.35 (*s*, 3 H). ^{13}C-NMR: 151.6; 150.9; 150.2; 146.4; 146.3; 143.3; 139.0; 138.4; 135.2; 132.5; 130.4; 130.0; 129.1; 128.7; 128.6; 128.4; 127.6; 117.2; 108.6; 107.6; 106.3; 105.2; 74.3; 72.9; 56.4; 56.3; 56.0; 55.9; 21.4. Anal. calc. for $C_{31}H_{27}Br_2NO_6S$: C 53.08, H 3.88; found: C 53.20, H 3.85.

Cyclotrimerization of **6** *with CuTC.* Copper(I) 2-thiophenecarboxylate (CuTC) (405 mg, 2.36 mmol) was added to a soln. of **6** (940 mg, 1.57 mmol) in dry NMP (4.0 ml) maintained at −20°

under Ar. The mixture was left to rise to r.t. in 18 h, diluted with CH_2Cl_2 (100 ml) and 10% aq. NH_3 (50 ml) and vigorously stirred for 1 h. Layers were separated and the org. phase was washed with 10% aq. NH_3 (3 × 20 ml), dried over Na_2SO_4, and concentrated at reduced pressure. The residue was purified by flash-chromatography (eluent AcOEt/cyclohexane with a gradient from 4:1 to pure AcOEt). First eluate: anti-*5,6,11,12,17,18-hexahydro-2,3,8,9,14,15-hexamethoxy-19,20,21-tritosyl-5,18:6,11:12,17-triepiminotrinaphthylene* (*anti*-**1**) was triturated with AcOEt to eliminate residual NMP to afford 262 mg of tan solid material (47% yield). M.p. 94°. IR (KBr): 1485, 1337, 1295, 1158, 1068, 693, 567. ^{1}H-NMR: 7.11 (*d*, $J = 8.3$, 4 H); 6.96 (*s*, 2 H); 6.93 (*d*, $J = 8.3$, 2 H); 6.75 (*s*, 2 H); 6.63 (*d*, $J = 8.1$, 4 H); 6.53 (*s*, 2 H); 6.06 (*d*, $J = 8.1$, 2 H); 5.80 (*s*, 2 H); 5.71 (*s*, 2 H); 5.62 (*s*, 2 H); 3.85 (*s*, 6 H); 3.67 (*s*, 6 H); 3.64 (*s*, 6 H); 2.18 (*s*, 6 H); 1.82 (*s*, 3 H). ^{13}C-NMR: 147.4; 147.2; 146.9; 143.4; 142.6; 138.0; 137.8 (2 overlapping C); 134.1; 133.9; 133.8; 133.7; 133.6; 129.3; 128.6; 127.5; 127.4; 107.0; 106.7; 106.4; 66.4; 66.2; 65.8; 56.5; 56.3; 56.2; 21.2; 20.7. Anal. calc. for $C_{57}H_{51}N_3O_{12}S_3$: C 64.21, H 4.82; found: C 64.39, H 4.89.

Second eluate: syn-*5,6,11,12,17,18-hexahydro-2,3,8,9,14,15-hexamethoxy-19,20,21-tritosyl-5,18:6,11:12,17-triepiminotrinaphthylene* (*syn*-**1**) was triturated with AcOEt to eliminate residual NMP to afford 117 mg of tan solid material (21% yield). M.p. 90°. IR (KBr): 1331, 1295, 1163, 1074, 693, 579. ^{1}H-NMR: 7.43 (*d*, $J = 7.9$, 6 H); 7.09 (*d*, $J = 7.9$, 6 H); 6.44 (*s*, 6 H); 3.55 (*s*, 18 H); 2.34 (*s*, 9 H). ^{13}C-NMR: 147.3; 143.6; 137.9; 134.7; 133.6; 129.5; 128.0; 106.5; 66.3; 56.1; 21.3. Anal. calc. for $C_{57}H_{51}N_3O_{12}S_3$: C 64.21, H 4.82; found: C 63.86, H 4.90.

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Received January 21, 2015