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Synthesis of Inherently Chiral Azacalix[4]arenes and Diazadioxacalix[4]arenes

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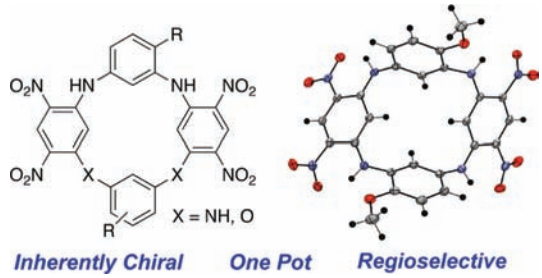
ABSTRACT



Described are nucleophilic aromatic substitution reactions for the synthesis of inherently chiral azacalix[4]arenes and diazadioxacalix[4]arenes comprised of two or three different aromatic monomers. A variety of functional groups are tolerated at the 2-, 4-, and 5-positions on the nucleophilic-component monomers; reactions are run under ambient atmosphere; and the macrocycles are constructed without isolation of intermediate linear species.

Advances in heteracalixarene synthesis continue to spur active investigation of these compounds as platforms for molecular design and molecular recognition.[1] Our laboratory[2] and others[3] have previously shown that nucleophilic aromatic substitution (S_NAr) reactions are highly efficient for the synthesis of oxacalix[4]arene macrocycles by the condensation of diphenols with a variety of electron-deficient aromatic 1,3-dihalides. The high substrate scope provides access to macrocycles that incorporate two different aromatic monomers (two-component macrocycles) bearing a range of functionality. Azacalix[4]arenes, in contrast, are more difficult to prepare in high yield and are most commonly accessed via metal-catalyzed C−N coupling reactions.[4]

(1) (a) König, B.; Fonseca, M. H. *Eur. J. Inorg. Chem.* **2000**, 2303–2310. (b) Vystotsky, M.; Saadioui, M.; Böhmer, V. *Calixarenes 2001*; Kluwer Academic Publishers: Dordrecht, Netherlands, 2001; pp 250−265. (c) Morohashi, N.; Narumi, F.; Iki, N.; Hattori, T.; Miyano, S. *Chem. Rev.* **2006**, *106*, 5291–5316. (d) Wang, M.-X. *Chem. Commun.* **2008**, 4541–4551. (e) Maes, W.; Dehaen, W. *Chem. Soc. Rev.* **2008**, *37*, 2393–2402. (f) Tsue, H.; Ishibashi, K.; Tamura, R. *Top. Heterocycl. Chem.* **2008**, *17*, 73–96.

(2) (a) Katz, J. L.; Feldman, M. B.; Conry, R. R. *Org. Lett.* **2005**, *7*, 91–94. (b) Katz, J. L.; Geller, B. J.; Conry, R. R. *Org. Lett.* **2006**, *8*, 2755–2758. (c) Katz, J. L.; Geller, B. J.; Foster, P. D. *Chem. Commun.* **2007**, 1026–1028. (d) Wackerly, J. W.; Meyer, J. M.; Crannell, W. C.; King, S. B.; Katz, J. L. *Macromolecules* **2009**, 8181–8186.

(3) (a) Lehmann, F. P. A. *Tetrahedron* **1974**, *30*, 727–733. (b) Gilbert, E. E. *J. Heterocycl. Chem.* **1974**, *11*, 899–904. (c) Wang, M.-X.; Yang, H.-B. *J. Am. Chem. Soc.* **2004**, *126*, 15412–15422. (d) Hao, E.; Fronczek, F. R.; Vicente, M. G. H. *J. Org. Chem.* **2006**, *71*, 1233–1236. (e) Yang, F.; Yan, L.; Ma, K.; Yang, L.; Li, J.; Chen, L.; You, J. *Eur. J. Org. Chem.* **2006**, 1109–1112. (f) Maes, W.; Van Rossom, W.; Van Hecke, K.; Van Meervelt, L.; Dehaen, W. *Org. Lett.* **2006**, *8*, 4161–4164. (g) Konishi, H.; Mita, T.; Morikawa, O.; Kobayashi, K. *Tetrahedron Lett.* **2007**, *48*, 3029–3032. (h) Li, M.; Ma, M.-L.; Li, X.-Y.; Wen, K. *Tetrahedron* **2009**, *65*, 4639–4643. (i) Hu, S.-Z.; Chen, C.-F. *Chem. Commun.* **2010**, *46*, 4199–4201. See also **1d**,**e** and references cited therein.

(4) (a) Ito, A.; Ono, Y.; Tanaka, K. *New J. Chem.* **1998**, *22*, 779–781. (b) Ito, A.; Ono, Y.; Tanaka, K. *J. Org. Chem.* **1999**, *64*, 8236–8241. (c) Selby, T. D.; Blackstock, S. C. *Org. Lett.* **1999**, *1*, 2053–2055. (d) Hauck, S. I.; Lakshmi, K. V.; Harwig, J. F. *Org. Lett.* **1999**, *1*, 2057–2060. (e) Miyazaki, Y.; Kanbara, T.; Yamamoto, T. *Tetrahedron Lett.* **2002**, *43*, 7945–7948. (f) Wang, M.-X.; Zhang, X.-H.; Zheng, Q.-Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 838–842. (g) Suzuki, Y.; Yanagi, T.; Kanbara, T.; Yamamoto, T. *Synlett* **2005**, 263–266. (h) Fukushima, W.; Kanbara, T.; Yamamoto, T. *Synlett* **2005**, 2931–2934. (i) Tsue, H.; Ishibashi, K.; Takahashi, H.; Tamura, R. *Org. Lett.* **2005**, *7*, 2165–2168. (j) Vale, M.; Pink, M.; Rajca, S.; Rajca, A. *J. Org. Chem.* **2008**, *73*, 27–35. (k) Tsue, H.; Matsui, K.; Ishibashi, K.; Takahashi, H.; Tokita, S.; Ono, K.; Tamura, R. *J. Org. Chem.* **2008**, *73*, 7748–7755.

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Relatively few S_NAr-based ring formations of either azacalix[4]arenes or diazadioxacalix[4]arenes have been reported. Yields are often modest, and preformation and isolation of linear precursors is frequently required.[5]

Calix[4]arenes lacking planes of symmetry through opposing arenes are inherently chiral;[6] in systems that lack structural rigidity, rotation through the annulus leads to enantiomerization. In principle, inherently chiral heteracalix[4]arenes are accessible by S_NAr methods, simply by cyclizing an aromatic monomer lacking an internal plane of symmetry between reactive nucleophilic or electrophilic sites. However, regioselectivity in such a cyclization has not been achieved except by multistep fragment coupling.[7] In this letter, we describe a general strategy for the one-pot synthesis of inherently chiral[8] three-component azacalix[4]arenes and diazadioxacalix[4]arenes. Furthermore, adaptation of the method provides an entry into two-component azacalix[4]arenes, and we report that cyclizations using 4-substituted 1,3-diaminobenzenes are highly selective for the inherently chiral *anti*-regioisomer.

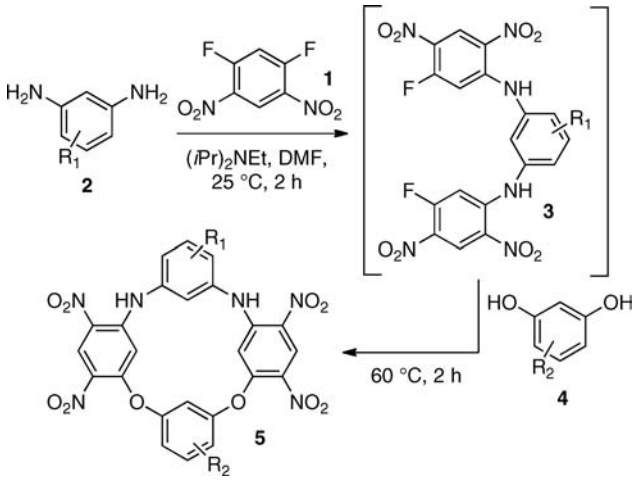
We initially investigated the formation of linear 1:2 adducts formed from condensation of 1,5-difluoro-2,4-dinitrobenzene **1** and 1,3-diaminobenzenes **2** using exact stoichiometric ratios (Table 1). Using air-dried glassware under ambient atmosphere, reaction of 4-methoxy-substituted diamine **2a** with electrophile **1** (1:2 stoichiometric ratio, DMF, $(i\text{Pr})_2$NEt, 25 °C, 2 h) cleanly provided the corresponding linear 1:2 adduct (trimer) **3a** (R = 4-OCH_3). The reaction remained homogeneous throughout, indicating that control of speciation is likely due to the strong deactivating ability of the amino substituent upon initial addition, suppressing displacement of the second fluorine atoms on the electrophilic rings.

In situ generated trimer **3a** was cyclized simply by addition of 1 equiv of resorcinol **4a** and subsequent heating to 60 °C for 2 h. ^{1}H NMR analysis revealed high selectivity for formation of diazadioxacalix[4]arene **5a** over other linear and cyclic oligomeric products (see Figure 2 and the Supporting Information), and **5a** was isolated in 72% yield following chromatographic purification. Homogenous reaction conditions were also maintained during the cyclization step; solubility does not drive product selectivity, maximizing the potential generality of the process.

The scope of this three-component macrocyclization procedure is summarized in Table 1. 4-Methoxy diamine **2a** cyclized equally well with electron-rich and electron-poor diphenols: condensation with 5-carbomethoxy-substitued **4a** (entry 1) and 5-methyl-substituted **4b** (entry 2) furnished diazadioxacalix[4]arenes **5a** and **5b** in 72% and 70% yield, respectively. Both 4-methyl- and 4-aminophenyl-substituted diamines **2b** and **2c** reacted analogously, furnishing three-component macrocycles **5c**−**5e** in 67−69% isolated yields (entries 3−5). Electron-withdrawing groups, however, were not tolerated at the 4-position on the 1,3-diamine coupling partner. No significant formation of heteracalix[4]arenes was observed with either 4-chloro- or 4-nitro-1,3-phenylenediamine under analogous reaction conditions.

4-Hexyl resorcinol **4c** also furnished good yields of inherently chiral diazadioxacalix[4]arenes when paired with internally symmetric diamine **2d**, and macrocycle **5f** was isolated in 68% yield (Table 1, entry 6). Resorcinol **4c** also cyclized with diamine **2e**, which bears a methyl group in the 2-position (entry 7, 71% yield). 2-Substitution could also be introduced on diphenol **4**. The in situ generated trimer

Table 1. Synthetic Scope of Diazadioxacalix[4]arenes **5**[a]



entry	diamine **2**	diphenol **4**	product (yield)[b]
1	**2a** (R_1 = 4-OCH_3)	**4a** (R_2 = 5-CO_2Me)	**5a** (72%)[c]
2	**2a** (R_1 = 4-OCH_3)	**4b** (R_2 = 5-CH_3)	**5b** (70%)[c]
3	**2b** (R_1 = 4-CH_3)	**4a** (R_2 = 5-CO_2Me)	**5c** (68%)
4	**2c** (R_1 = 4-NHPh)	**4a** (R_2 = 5-CO_2Me)	**5d** (67%)
5	**2c** (R_1 = 4-NHPh)	**4b** (R_2 = 5-CH_3)	**5e** (69%)
6	**2d** (R_1 = 5-CO_2Me)	**4c** (R_2 = 4-*n*-hexyl)	**5f** (68%)
7	**2e** (R_1 = 2-CH_3)	**4c** (R_2 = 4-*n*-hexyl)	**5g** (71%)[d]
8	**2c** (R_1 = 4-NHPh)	**4d** (R_2 = 2-OH, 5-CO_2Et)	**5h** (66%)

[a] 1.0 equiv of diamine **2**, 2.0 equiv of **1**, 4.7 equiv of $(i\text{Pr})_2$NEt; then 1.0 equiv of diphenol **4**. [b] Isolated yield after chromatographic purification. [c] 7.0 equiv of $(i\text{Pr})_2$NEt. [d] Trimer formation run at 40 °C for 2 h, cyclization at 70 °C for 2 h.

(5) (a) Liu, S.-Q.; Wang, D.-X.; Zheng, Q.-Y.; Wang, M.-X. *Chem. Commun.* **2007**, *37*, 3856–3858. (b) Touil, M.; Lachkar, M.; Siri, O. *Tetrahedron Lett.* **2008**, *49*, 7250–7252. (c) Konishi, H.; Hashimoto, S.; Sakakibara, T.; Matsubara, S.; Yasukawa, Y.; Morikawa, O.; Kobayashi, K. *Tetrahedron Lett.* **2009**, *50*, 620–623. (d) Clayden, J.; Rowbottom, S. J. M.; Ebenezer, W. J.; Hutchings, M. G. *Tetrahedron Lett.* **2009**, *50*, 3923–3925. (e) Tanaka, H.; Wada, A.; Shiro, M.; Hioki, K.; Morisaki, D.; Kunishima, M. *Heterocycles* **2009**, *79*, 609–616. (f) Clayden, J.; Rowbottom, S. J. M.; Hutchings, M. G.; Ebenezer, W. J. *Tetrahedron Lett.* **2009**, *65*, 4871–4880. (g) Xue, M.; Chen, C.-F. *Org. Lett.* **2009**, *11*, 5294–5297. (h) Touil, M.; Haddoub, R.; Touil, M.; Raimundo, J.-M.; Siri, O. *Org. Lett.* **2010**, *12*, 2722–2725. (i) Wang, L.-X.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *J. Org. Chem.* **2010**, *75*, 741–747.

(6) (a) Böhmer, V.; Kraft, D.; Tabatabai, M. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, *19*, 17–39. (b) Cort, A. D.; Mandolini, L.; Pasquini, C.; Schiaffino, L. *New. J. Chem.* **2004**, *28*, 1198–1199.

(7) (a) Hou, B.-Y.; Wang, D.-X.; Yang, H.-B.; Zheng, Q.-Y.; Wang, M.-X. *J. Org. Chem.* **2007**, *72*, 5218–5226. (b) Hou, B.-Y.; Zheng, Q.-Y.; Wang, M.-X. *Tetrahedron* **2007**, *63*, 10801–10808. (c) Van Rossom, W.; Kishore, L.; Robeyns, K.; Van Meervelt, L.; Dehaen, W.; Maes, W. *Eur. J. Org. Chem.* **2010**, 4122–4129.

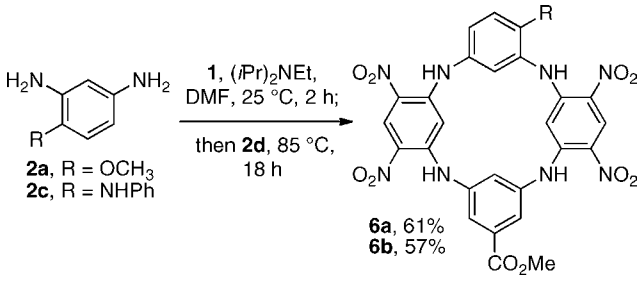
(8) The term "inherently chiral" is used to identify macrocycles that lack internal planes of symmetry due to asymmetrically disposed substituents. The inherently chiral heteracalix[4]arenes described in this letter undergo enantiomerization at ambient temperature. Future work will address post-cyclization derivativization to furnish resolvable enantiomers.

derived from diamine **2c** reacted with ethyl gallate **4d** selectively across the *meta*-disposed phenols, providing macrocycle **5h** in 66% yield, which bears a lower-rim hydroxyl group (entry 8).

Consistent with the observations of Siri,[5b] formation of diazadioxacalix[4]arenes **5** was optimal at unusually high reaction concentrations (approximately 0.40 M with respect to diamine **2**). The lack of oligomeric mixtures observed in single-step oxacalix[4]arene formation reactions is attributed to reversible C−O bond formation leading to thermodynamic product distributions.[1d,e,2d] Analogous C−N bond cleavage is unlikely, and we have not observed C−N bond cleavage under our macrocyclization conditions: product distributions reflect kinetic mixtures. Thus, there exists a strong kinetic bias for diazadioxacalix[4]arene formation over oligomerization for the sequence leading to macrocycles **5**. Intramolecular hydrogen bonding between the bridging diaryl amines and adjacent nitro groups has been proposed as a conformational constraint in similar systems.[5b] The observed kinetic bias for heteracalix[4]arene formation is also consistent with our electrophile-dependent conformational model for oxacalixarene versus poly(*meta*-phenylene oxide) formation[2d]> and that electrophiles such as **1** bearing sterically bulky groups in the 2- and 4-positions are sufficient to gear linear oligomers into favorable conformations for cyclization.

We next sought to adapt our three-component coupling procedure to accommodate nitrogen atoms at all four bridging positions. In situ generated trimer **3a** reacted with diaminobenzene **2d** at 85 °C over 18 h and furnished inherently chiral azacalix[4]arene **6a** in 61% yield after chromatographic purification (Scheme 1). Analogously, trimer formation using

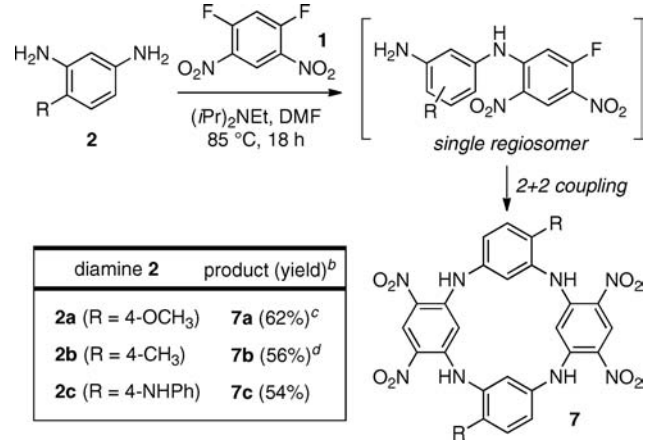
Scheme 1. Synthesized Three-Component Azacalix[4]arenes **6**



diamine **2c**, followed by cyclization with **2d**, formed three-component azacalix[4]arene **6b** in 57% isolated yield. Thus, by simply modulating temperature to match substrate nucleophilicity, a variety of inherently chiral three-component azacalix[4]arenes and diazadioxacalix[4]arenes are readily accessed in a single reaction vessel, without the need for inert atmosphere, and using exact stoichiometric quantities of the aromatic monomers.

The ability of diaminobenzene **2d** to successfully displace the fluorine atoms on trimers **3** suggested that an analogous procedure would also furnish two-component azacalix[4]arenes. Reaction of equimolar quantities of diaminobenzene **2a** and 1,5-difluoro-2,4-dinitrobenzene **1** at 85 °C (DMF, (*i*Pr)$_2$NEt, 18 h) produced a single major product azacalix[4]arene macrocycle, and isomerically pure *anti*-azacalix[4]arene **7a** was isolated in 62% yield (Scheme 2). No *syn*-azacalix[4]arene regioisomer

Scheme 2. *Anti*-Selective Synthesis of Azacalix[4]arenes **7**[a]



diamine **2**	product (yield)[b]
2a (R = 4-OCH$_3$)	**7a** (62%)[c]
2b (R = 4-CH$_3$)	**7b** (56%)[d]
2c (R = 4-NHPh)	**7c** (54%)

[a] 1.0 equiv of diamine **2**, 1.0 equiv of **1**, 4.7 equiv of (*i*Pr)$_2$NEt. [b] Isolated yield after chromatographic purification. [c] 7.0 equiv of (*i*Pr)$_2$NEt. [d] 90 °C reaction temperature.

was detectable, and the remainder of the material consisted of higher oligomers (see Supporting Information). The structure of **7a** was confirmed by X-ray crystallography (Figure 1), which also revealed substantial gearing of the

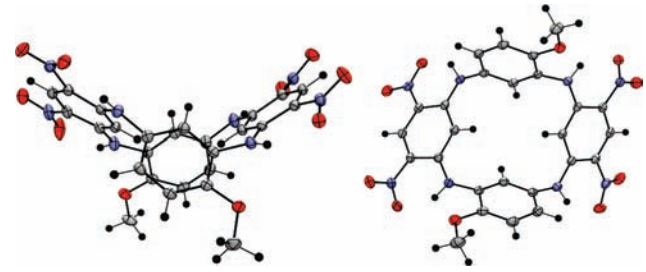


Figure 1. X-ray crystal structure of **7a** (thermal ellipsoids at the 30% probability level; oxygen = red, nitrogen = blue, carbon = gray, hydrogen = black).

aromatic framework (27° average dihedral angle between opposing aromatic rings). Equally selective formation of the inherently chiral *anti*-regioisomer was observed in cyclizations using diamines **2b** or **2c**, furnishing azacalix[4]arenes **7b** and **7c** in 56% and 54% isolated yield, respectively.

4-Substituted nucleophiles have not previously found general utility for the construction of heteracalix[4]arenes, presumably due to the problematic formation of regioisomeric mixtures. Regioselective monoarylation of both diamines **2a** and **2b**, however, is well precedented in the literature.[9] The high *anti*-regioselectivity obtained in the synthesis of azacalix[4]arenes **7** is consistent with formation

of a single regioisomeric dimer in the initial linear coupling step (Scheme 2). Subsequent coupling of dimers (2 + 2 pathway), under conditions of kinetic product control, then furnishes macrocycles with *anti*-regiochemistry. Supporting this mechanism, selectivity was not observed in the formation of diazadioxacalix[4]arenes **5** (3 + 1 pathway) using two different 4-substituted nucleophiles: attempted coupling of diamine **2c**, diphenol **4c**, and electrophile **1** under the reaction conditions described in Table 1 led to the formation of a mixture of regioisomers.

It has been documented that azacalix[4]arenes similar to **6** and **7** have low solubility in organic solvents and that this can complicate purification and lower obtained product yields.[5b,c,h] All heteracalixarenes described above are isolated via precipitation of reaction mixtures (by addition of aqueous acid), followed by chromatographic purification. In many cases, ^{1}H NMR analysis of the precipitated reaction residues revealed nominally "pure" products without discrete single contaminants present in >5% quantity. We suspected that higher oligomers accounted for the remaining mass balance for reactions leading to macrocycles **5**−**7** but that these impurities were difficult to identify and quantify by ^{1}H NMR. GPC analysis performed on the unpurified reaction residues of **5a** and **7a** indeed revealed significant quantities of oligomers, which were removed upon chromatographic purification (see Figure 2 and the Supporting Information). Thus, our reported yields appear to accurately reflect the kinetic cyclization selectivity versus oligomerization inherent under the reaction conditions. Furthermore, we urge caution in identifying heteracalixarenes as analytically pure without GPC verification when obtained by precipitation methods under conditions of kinetic product control, as significant quantities of oligomeric contaminants can be difficult to detect by NMR.

In conclusion, we have described one-pot methods for the construction of inherently chiral azacalix[4]arenes and diazadioxacalix[4]arenes comprised of either two or three different aromatic monomers. In addition, we have shown that single-step azacalix[4]arene formation using 4-substituted 1,3-diaminobenzenes can proceed with high selectivity for the inherently chiral *anti*-regioisomer. Investigations to expand substrate scope, and to structurally rigidify the synthesized macrocycles to permit resolution of enantiomers, are ongoing and will be reported in due course.

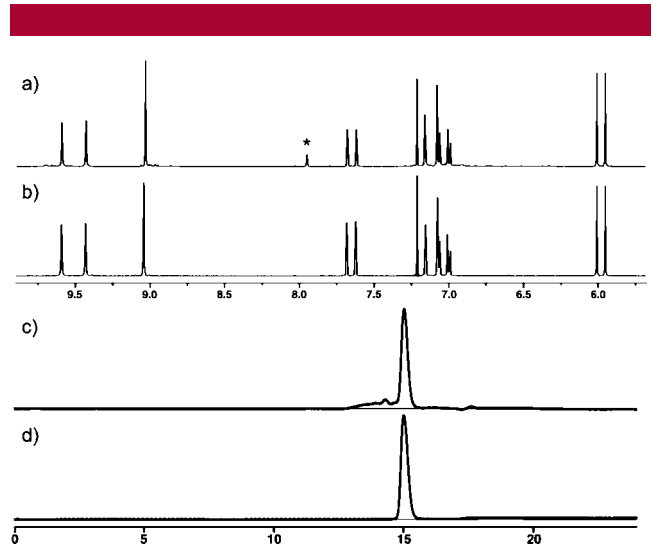


Figure 2. Partial ^{1}H NMR spectra (10.0−5.7 ppm range) and GPC chromatograms of heteracalixarene **5a** (from Table 1, entry 1) before and after chromatographic purification. (a) ^{1}H NMR spectrum of unpurified **5a** (* denotes residual DMF resonance). (b) ^{1}H NMR spectrum of purified **5a**. (c) GPC chromatogram of unpurified **5a**. (d) GPC chromatogram of purified **5a**. GPC baselines are shown with a gray line below chromatogram peaks.

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Supporting Information Available: Experimental procedures and characterization data for compounds **3a**, **5a**−**h**, **6a**−**b**, and **7a**−**c** and X-ray crystallographic data for compound **7a** (CIF format). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) (a) Chang, J.-Y.; Lin, C.-F.; Pan, W.-Y.; Bacherikov, V. A.; Chou, T.-C.; Chen, C.-H.; Dong, H.; Cheng, S.-Y.; Tsai, T.-J.; Lin, Y.-W.; Chen, K.-T.; Chen, L.-T.; Su, T.-L. *Bioorg. Med. Chem.* **2003**, *11*, 4959–4969. (b) Bacherikov, V. A.; Chang, J.-Y.; Lin, Y.-W.; Chen, C.-H.; Pan, W.-Y.; Dong, H.; Lee, R.-Z.; Chou, T.-C.; Su, T.-L. *Bioorg. Med. Chem.* **2005**, *13*, 6513–6520. (c) Su, T.-L.; Lin, Y.-W.; Chou, T.-C.; Zhang, X.; Bacherikov, V. A.; Chen, C.-H.; Liu, L. F.; Tsai, T.-J. *J. Med. Chem.* **2006**, *49*, 3710–3718. (d) Touil, M.; Raimundo, J.-M.; Lachkar, M.; Marsal, P.; Siri, O. *Tetrahedron* **2010**, *66*, 4377–4382.