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Odd-Numbered Oxacalix[*n*]arenes ($n = 5, 7$): Synthesis and Solid-State Structures

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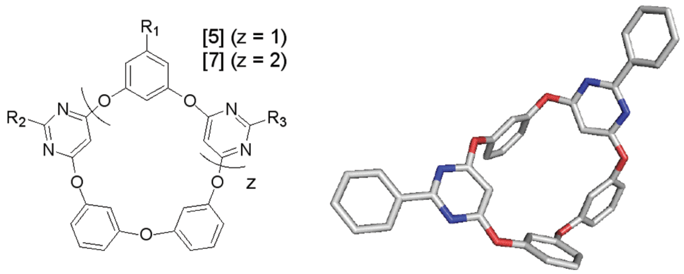
ABSTRACT



The critical synthetic access to odd-numbered calix[*n*]arenes has evidently resulted in less attention for these macrocycles, although specific molecular recognition phenomena have been observed for some of them. A straightforward fragment coupling approach has been designed, applying kinetically controlled nucleophilic aromatic substitution reaction conditions, affording odd-numbered oxacalix[*n*]arenes ($n = 5, 7$) selectively in high yields. The solid-state conformational behavior and the oxacalix[*n*]arene cavity size were explored by single-crystal X-ray diffraction studies.

Heteracalixarenes,[1−7] emerging members of the [1_n]metacyclophane family in which the classical methylene bridges are replaced by heteroatoms, currently rejuvenate conventional calixarene chemistry. The conformational behavior, size, and structure of the cavity of this novel generation of cyclooligomers may be fine-tuned by the bond lengths and bond angles of the bridging heteroatoms, enhancing their molecular recognition ability. Nowadays, straightforward protocols toward heteracalixarenes (mostly S-,[2] N-,[3,4] and O-bridged[5,6]) and postmacrocyclization functionalizations of these macrocycles are frequently appearing in the literature.

All procedures toward O-bridged heteracalixarenes[7] reported to date focus on the preparation of oxacalix[*n*]arenes, wherein *n* is an even number between 4 and 12, either directly starting from monomeric precursors or by means of a stepwise approach. The vast majority of oxacalix[*n*]-(het)arenes have been synthesized by nucleophilic aromatic substitution (S_NAr) reactions involving a nucleophilic *m*-dihydroxybenzene component and an electrophilic 1,3-dihalogenated (hetero)aromatic building block. Careful optimization of the S_NAr reaction conditions has usually afforded the oxacalix[4]arene predominantly over other cyclooligomers and noncyclic materials by thermodynamic control.[5,6] Recently, more kinetic conditions have been developed affording larger oxacalix[*n*]arenes ($n = 6, 8$) or poly(*m*-phenylene oxides) selectively in good yields.[6r,u]

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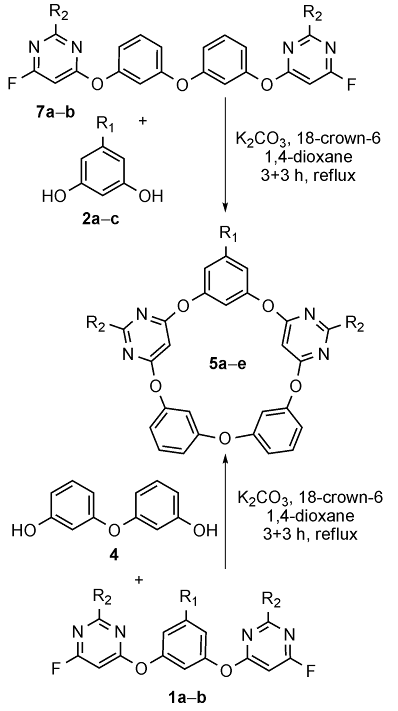
Calix[*n*]arenes with an odd number of aromatic units (*n* = 5, 7) are much less prominent as they are less readily obtained. As a consequence they have been considerably less studied, notwithstanding their specific host−guest properties imposed by the particular diameter and shape of the macrocycles.[8] Odd-numbered (homo)heteracalixarenes are also rare.[9,10] A few azacalix[*n*]arenes (*n* = 5, 7) and N,O-bridged calix[*n*]arenes have recently been prepared by stepwise strategies.[9b−e] To the best of our knowledge, however, no odd-numbered oxacalixarenes were reported until now. Of particular concern for the synthesis of enlarged oxacalix[*n*]arenes (*n* > 4) is the high thermodynamic stability, and hence preferential formation, of the cyclotetramer, which introduces the necessity of more kinetically controlled fragment coupling protocols.[5]

In earlier work our group optimized one-pot $\mathrm{S_NAr}$ procedures toward oxacalix[2]arene[2]pyrimidines starting from dihalopyrimidine precursors and resorcinol derivatives,[6f] and straightforward fragment coupling pathways ([3 + 3] and [3 + 5] $\mathrm{S_NAr}$ reactions) toward enlarged oxacalix[*n*]arenes (*n* = 6, 8).[6r] Upon simultaneous addition of the multiaryl building blocks under more kinetically controlled reaction conditions (K_2CO_3, 18-crown-6, 1,4-dioxane, high dilution, reflux), scrambling of the fragments was prevented to a large extent and the enlarged macrocycles were favored (over 70% yield).[6r] By a similar stepwise approach it should be possible to synthesize odd-numbered oxacalix[*m*]arene[*n*]pyrimidines, the "missing links" in the oxacalixarene series, and investigations toward their synthesis and conformational behavior were hence initialized.

Scheme 1. Synthesis of Oxacalix[3]arene[2]pyrimidines **5a−e**



First of all, a [2 + 3] fragment coupling approach toward oxacalix[5]arenes was envisaged (Scheme 1). For this purpose an electrophilic triaryl building block **1a** (R_1 = Me, R_2 = Ph) was prepared, combining orcinol (5-methyl-1,3-dihydroxybenzene, **2a**) and a slight excess (2.05 equiv) of 4,6-difluoro-2-phenylpyrimidine (**3a**) in acetone with K_2CO_3 base and 18-crown-6 (85% yield).[6r] The use of difluoropyrimidines over their dichloro analogues was preferred as a noticeable improvement of the selectivity was observed before for the synthesis of oxacalix[2]arene[2]pyrimidines.[6f,r] 3,3′-Oxydiphenol (**4**) was selected as the nucleophilic diaryl

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(4) Recent additions to the azacalixarene field: (a) Vale, M.; Pink, M.; Rajca, S.; Rajca, A. *J. Org. Chem.* **2008**, *73*, 27. (b) Touil, M.; Lachkar, M.; Siri, O. *Tetrahedron Lett.* **2008**, *49*, 7250. (c) Tsue, H.; Ishibashi, K.; Tokita, S.; Takahashi, H.; Matsui, K.; Tamura, R. *Chem.—Eur. J.* **2008**, *14*, 6125. (d) Lawson, K. V.; Barton, A. C.; Spence, J. D. *Org. Lett.* **2009**, *11*, 895. (e) Xue, M.; Chen, C.-F. *Org. Lett.* **2009**, *11*, 5294. (f) Yao, B.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *Chem. Commun.* **2009**, 2899. (g) Yao, B.; Wang, D.-X.; Gong, H.-Y.; Huang, Z.-T.; Wang, M.-X. *J. Org. Chem.* **2009**, *74*, 5361. (h) Clayden, J.; Rowbottom, S. J. M.; Ebenezer, W. J.; Hutchings, M. G. *Org. Biomol. Chem.* **2009**, *7*, 4871. (i) Zhang, E.-X.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *J. Org. Chem.* **2009**, *74*, 8595. (j) Wang, L.-X.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *J. Org. Chem.* **2010**, *75*, 741. (k) Katz, J. L.; Tschaen, B. A. *Org. Lett.* **2010**, *12*, 4300.

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(6) Recent additions to the oxacalixarene field: (a) Wang, M.; Yang, H. *J. Am. Chem. Soc.* **2004**, *126*, 15412. (b) Katz, J. L.; Feldman, M. B.; Conry, R. R. *Org. Lett.* **2005**, *7*, 91. (c) Hao, E.; Fronczek, F. R.; Vicente, M. G. H. *J. Org. Chem.* **2006**, *71*, 1233. (d) Yang, F.; Yan, L.; Ma, K.; Yang, L.; Li, J.; Chen, L.; You, J. *Eur. J. Org. Chem.* **2006**, 1109. (e) Katz, J. L.; Geller, B. J.; Conry, R. R. *Org. Lett.* **2006**, *8*, 2755. (f) Maes, W.; Van Rossom, W.; Van Hecke, K.; Van Meervelt, L.; Dehaen, W. *Org. Lett.* **2006**, *8*, 4161. (g) Csokai, V.; Kulik, B.; Bitter, I. *Supramol. Chem.* **2006**, *18*, 111. (h) Konishi, H.; Tanaka, K.; Teshima, Y.; Mita, T.; Morikawa, O.; Kobayashi, K. *Tetrahedron Lett.* **2006**, *47*, 4041. (i) Wang, Q.-Q.; Wang, D.-X.; Zheng, Q.-Y.; Wang, M.-X. *Org. Lett.* **2007**, *9*, 2847. (j) Zhang, C.; Chen, C.-F. *J. Org. Chem.* **2007**, *72*, 3880. (k) Van Rossom, W.; Maes, W.; Kishore, L.; Ovaere, M.; Van Meervelt, L.; Dehaen, W. *Org. Lett.* **2008**, *10*, 585. (l) Wang, D.-X.; Zheng, Q.-Y.; Wang, Q.-Q.; Wang, M.-X. *Angew. Chem., Int. Ed.* **2008**, *47*, 7485. (m) Ferrini, S.; Fusi, S.; Giorgi, G.; Ponticelli, F. *Eur. J. Org. Chem.* **2008**, 5407. (n) Konishi, H.; Mita, T.; Yasukawa, Y.; Morikawa, O.; Kobayashi, K. *Tetrahedron Lett.* **2008**, *49*, 6831. (o) Hou, B.-Y.; Zheng, Q.-Y.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *Chem. Commun.* **2008**, 4541. (p) Capici, C.; Garozzo, D.; Gattuso, G.; Messina, A.; Notti, A.; Parisi, M. F.; Pisagatti, I.; Pappalardo, S. *ARKIVOC* **2009**, *viii*, 199. (q) Li, M.; Ma, M.-L.; Li, X.-Y.; Wen, K. *Tetrahedron* **2009**, *65*, 4639. (r) Van Rossom, W.; Ovaere, M.; Van Meervelt, L.; Dehaen, W.; Maes, W. *Org. Lett.* **2009**, *11*, 1681. (s) Wu, L.; Jiao, L.; Lu, Q.; Hao, E.; Zhou, Y. *Spectrochim. Acta, Part A* **2009**, *73*, 353. (t) Ma, M.-L.; Li, X.-Y.; Wen, K. *J. Am. Chem. Soc.* **2009**, *131*, 8338. (u) Wackerly, J. W.; Meyer, J. M.; Crannell, W. C.; King, S. B.; Katz, J. L. *Macromolecules* **2009**, *42*, 8181. (v) Van Rossom, W.; Kundrát, O.; Ngo, T. H.; Lhoták, P.; Dehaen, W.; Maes, W. *Tetrahedron Lett.* **2010**, *51*, 2423. (w) Wang, Q.-Q.; Wang, D.-X.; Yang, H.-B.; Huang, Z.-T.; Wang, M.-X. *Chem.—Eur. J.* **2010**, *16*, 7265. (x) Hu, S.-Z.; Chen, C.-F. *Chem. Commun.* **2010**, *46*, 4199. (y) Van Rossom, W.; Kishore, L.; Robeyns, K.; Van Meervelt, L.; Dehaen, W.; Maes, W. *Eur. J. Org. Chem.* **2010**, 4122.

(7) We prefer the term heteracalixarenes to distinguish this class of heteroatom-bridged macrocycles from heterocalixarenes, the heterocyclic analogues of classical C-bridged calixarenes, e.g., calixpyrroles.

(8) Examples of odd-numbered (classical) calixarenes and their supramolecular applications: (a) Atwood, J. L.; Barbour, L. J.; Heaven, M. W.; Raston, C. L. *Chem. Commun.* **2003**, 2270. (b) Martino, M.; Neri, P. *Mini-Rev. Org. Chem.* **2004**, *1*, 219. (c) Garozzo, D.; Gattuso, G.; Notti, A.; Pappalardo, A.; Pappalardo, S.; Parisi, M. F.; Perez, M.; Pisagatti, I. *Angew. Chem., Int. Ed.* **2005**, *44*, 4892. (d) Makha, M.; McKinnon, J. J.; Sobolev, A. N.; Spackman, M. A.; Raston, C. L. *Chem.—Eur. J.* **2007**, *13*, 3907. (e) Dalgarno, S. J.; Tian, J.; Warren, J. E.; Clark, T. E.; Makha, M.; Raston, C. L.; Atwood, J. L. *Chem. Commun.* **2007**, 4848. (f) Gargiulli, C.; Gattuso, G.; Liotta, C.; Notti, A.; Parisi, M. F.; Pisagatti, I.; Pappalardo, S. *J. Org. Chem.* **2009**, *74*, 4350. (g) Gattuso, G.; Notti, A.; Parisi, M. F.; Pisagatti, I.; Amato, M. E.; Pappalardo, A.; Pappalardo, S. *Chem.—Eur. J.* **2010**, *16*, 2381.

precursor and could be synthesized by combining 3-methoxyphenol and 3-bromoanisol in a Cu-assisted coupling reaction and subsequent cleavage of the methyl groups with HBr in acetic acid.[11] Coupling of the two complementary fragments **1a** and **4** under the previously optimized S_NAr conditions afforded the first oxacalix[3]arene[2]pyrimidine **5a** (Scheme 1). After purification by column chromatography, **5a** was isolated in an acceptable yield of 57% (Table 1). In addition, 16% of the larger oxacalix[6]arene[4]pyrimidine **6a** was obtained.[12]

Table 1. Scope of Synthesized Oxacalix[*n*]arenes (*n* = 5, 7)

S_NAr	R_1	R_2	calix[5] (%)	calix[10] (%)
[2 + 3]	Me	Ph	**5a** (57)	**6a** (16)
[2 + 3]	Me	SMe	**5b** (41)	**6b** (17)
[1 + 4]	Me	Ph	**5a** (68)	**6a** (14)
[1 + 4]	Me	SMe	**5b** (64)	**6b** (9)
[1 + 4]	H	Ph	**5c** (74)	**6c** (13)
[1 + 4]	*t*-Bu	Ph	**5d** (75)	**6d**[a]
[1 + 4]	H	SMe	**5e** (50)	**6e**[a]

S_NAr	R_1	R_2	calix[7] (%)	calix[14] (%)
[2 + 5]	H	SMe	**12a** (73)	**13a** (8)
[2 + 5]	SMe	Ph	**12b** (59)	**13b** (14)
[3 + 4]	SMe	Ph	**12b** (66)	**13b** (11)

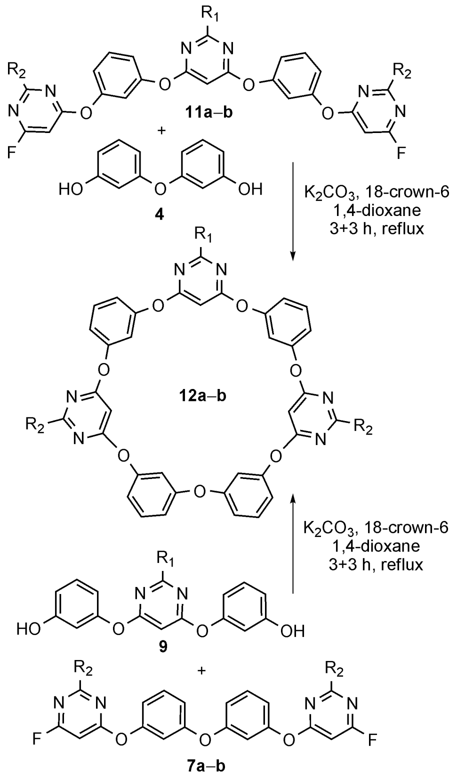
[a] Could not be isolated in pure form.

Combination of diaryl compound **4** with bispyrimidine triaryl precursor **1b** (R_1 = Me, R_2 = SMe) under the same [2 + 3] fragment coupling conditions afforded oxacalix[5]arene **5b** in 41% yield, together with 17% of oxacalix[10]arene **6b** (Scheme 1, Table 1). The use of a 2-methylsulfanylpyrimidine building block implements the possibility to perform substitution reactions, either by Liebeskind−Srogl or, after oxidation, S_NAr reactions. Such postmacrocyclization functionalization options are rather specific for oxacalix[*m*]arene[*n*]pyrimidines and highly interesting toward the preparation of a broad range of potential host molecules.[6k]

When attempting to improve the oxacalix[5]arene yield, a [4 + 1] fragment coupling strategy was also examined (Scheme 1). To obtain the appropriate linear precursors, diaryl building block **4** was now first reacted with an electrophilic 4,6-difluoropyrimidine (2.05 equiv) affording bispyrimidine tetraaryl fragments **7** (**7a**: R_2 = Ph, 95%, and **7b**: R_2 = SMe, 82%; Scheme 1). Upon reaction of tetraaryl precursor **7a** and orcinol (**2a**), an improved 68% yield was achieved for cyclopentamer **5a**, with an additional 14% of cyclodecamer **6a**. By combining **7a** with resorcinol (**2b**) or 5-*tert*-butyl-1,3-dihydroxybenzene (**2c**), the respective cyclopentamers **5c** (74%) and **5d** (75%) were also prepared in high yields. Coupling tetraaryl derivative **7b** with resorcinol afforded bis(methylsulfanyl)oxacalix[5]arene **5e** in 50% yield, whereas combination with orcinol gave a slightly higher yield (64% **5b**).

An alternative electrophilic diaryl compound, 6,6′-oxybis(4-fluoro-2-methylsulfanylpyrimidine) (**8**), was obtained as a side product during fluorination of 4,6-dichloro-2-methylsulfanylpyrimidine. Simultaneous addition of **8** and nucleophilic triaryl building block **9**[6r] (R_1 = SMe; see Scheme 2) under kinetic [3 + 2] fragment coupling conditions afforded pentaoxacalix[2]arene[3]pyrimidine **10** in 18% yield (see the structure in the Supporting Information). The rather low yield is most probably the result of the labile bispyrimidine oxygen bridge, which can be envisaged to cleave and promote scrambling more rapidly.

Scheme 2. Synthesis of Oxacalix[4]arene[3]pyrimidines **12a**,**b**



To expand the scope of odd-numbered oxacalix[*n*]arenes and study their molecular recognition features on a later stage, calix[7]arene macrocycles were also prepared. To this extent a [5 + 2] fragment coupling strategy applying the

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(9) Examples of odd-numbered heteracalixarenes (N-/S-/N,O-bridged): (a) Nakabayashi, S.; Fukushima, E.; Baba, R.; Katano, N.; Sugihara, Y.; Nakayama, J. *Electrochem. Commun.* **1999**, *1*, 550. (b) Liu, S.-Q.; Wang, D.-X.; Zheng, Q.-Y.; Wang, M.-X. *Chem. Commun.* **2007**, 3856. (c) Tsue, H.; Matsui, K.; Ishibashi, K.; Takahashi, H.; Tokita, S.; Ono, K.; Tamura, R. *J. Org. Chem.* **2008**, *73*, 7748. (d) Zhang, E.-X.; Wang, D.-X.; Zheng, Q.-Y.; Wang, M.-X. *Org. Lett.* **2008**, *10*, 2565. (e) Wu, J. C.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *Tetrahedron Lett.* **2009**, *50*, 7209.

(10) Examples of odd-numbered homoheteracalixarenes: (a) Shokova, E. A.; Kovalev, V. V. *Russ. J. Org. Chem.* **2004**, *40*, 607. (b) Ashram, M. *J. Inclusion Phenom. Macrocyclic Chem.* **2006**, *54*, 253. (c) Thomas, J.; Maes, W.; Robeyns, K.; Ovaere, M.; Van Meervelt, L.; Smet, M.; Dehaen, W. *Org. Lett.* **2009**, *11*, 3040. (d) Kaewtong, C.; Pulpoka, B. *J. Inclusion Phenom. Macrocyclic Chem.* **2009**, *65*, 129. (e) Chen, Y.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *J. Org. Chem.* **2010**, *75*, 3786.

(11) Yang, F.; Zhao, J.; Li, Y.; Zhang, S.; Shao, Y.; Shao, H.; Ma, T.; Gong, C. *Eur. Polym. J.* **2009**, *45*, 2053.

(12) Chromatographic purification of the oxacalix[5]arene from the oxacalix[10]arene congener is often not trivial.

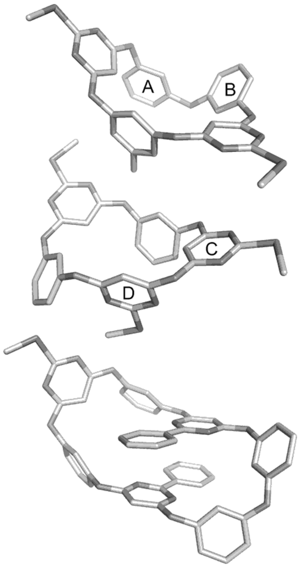

Figure 1. Single-crystal X-ray structures for oxacalix[5]arenes **5b** (top) and **10** (middle) and oxacalix[7]arene **12b** (bottom).

same kinetic S_NAr conditions was performed (Scheme 2), joining oxybisphenol (**4**) and trispyrimidine pentaaryl precursor **11a** ($R_1 = H$, $R_2 = SMe$).[6r] An encouragingly high yield of 73% was obtained for oxacalix[4]arene[3]pyrimidine **12a** in combination with 8% of oxacalix[8]arene[6]pyrimidine **13a** (Table 1). Such an enormous oxacalix[14]arene macrocycle has never been reported before (or at least not isolated in pure form and adequately characterized).[5,6] Upon combination of diaryl building block **4** and pentaaryl fragment **11b** ($R_1 = SMe$, $R_2 = Ph$) a somewhat lower yield (59%) was obtained for oxacalix[7]arene **12b**. As an alternative procedure, with the previous success in mind, a [4 + 3] coupling approach was also pursued (Scheme 2). Bispyrimidine tetraaryl precursor **7a** ($R_2 = Ph$) and nucleophilic triaryl derivative **9** ($R_1 = SMe$) were combined to obtain oxacalix[7]arene **12b** in 66% yield (11% [14] **13b**, Table 1).

Because of the wider dimension of their annulus, calix[5]arenes are more prone to conformational interconversions than calix[4]arenes. To elucidate the solid-state structure of some of the novel oxacalix[5]arenes, X-ray diffraction studies were undertaken.[13] Vapor diffusion of pentane into a $CHCl_3$ solution of **5b** resulted in suitable single crystals (Figure 1). A distorted 1,3-alternate conformation, which is dominant for oxacalix[4]arenes,[5,6] can still be recognized in the structure but the alternation is disrupted at the stage of the oxybisphenol part: ring B breaks the alternation order, whereas ring A adopts an almost parallel (twisted) position in respect to the orcinol ring. X-ray diffraction analysis of single crystals of **5c** showed a very similar "interrupted alternating" conformation (see the Supporting Information), whereas for oxacalix[5]arene **10** the alternation is disrupted at ring D of the bispyrimidine part (Figure 1).

In the same way the solid-state conformation of oxacalix[10]arene **6b** was analyzed, showing a stretched rectangular conformation (more details in the Supporting Information). A diffraction-quality single crystal of oxacalix[7]arene **12b** was also obtained (Figure 1, more details in the Supporting Information).[13,14]

In summary, the first odd-numbered oxacalix[*n*]arenes (*n* = 5, 7) have been synthesized through efficient fragment coupling approaches by using easily obtainable building blocks. Straightforward access to these provisionally underinvestigated macrocycles provides a springboard for further supramolecular research based on these novel cyclooligomers.

Acknowledgment. We thank the FWO for financial support and a postdoctoral fellowship to W.M., and the KU Leuven and the Ministerie voor Wetenschapsbeleid for continuing financial support.

Supporting Information Available: Experimental procedures and data, ^1H and ^{13}C NMR spectra for all novel building blocks and oxacalix[*n*]arenes, and X-ray structures for **5b**, **5c**, **6b**, and **12b** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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[13] The only single-crystal X-ray structures of enlarged oxacalix[*n*]arenes ([6]/[8]) have been reported in refs 6r and 6w although Katz reported similar structures at the Calix 2007 conference (Maryland, VS). The structures of two ortho-linked [1_6]oxacyclophanes were also recently reported: Ma, M.; Wang, H.; Li, X.; Liu, L.; Jin, H.; Wen, K. *Tetrahedron* **2009**, *65*, 300.

[14] Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre; deposition no. CCDC-798286 up to 798289. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK, by fax: +44(0)-1223−336033, or by e-mail: deposit@ccdc.cam.ac.uk.