tetrachloride; 80 °C (±0.5°). Reaction 3: **6** (5 g, 32.5 mmol), neat liquid; 180 °C (±0.5). **6** (3 g, 19.5 mmol), KSF montmorillonite (0.15 g and 0.3 g), 15 mL of anhydrous CCl_4; 77 °C (±0.5°).

Samples were heated in a 50-mL Pyrex flask under nitrogen atmosphere in an oil bath equipped with a thermostat.

Microwave Heating. The apparatus has already been described.[7a] It includes the following: a magnetron from a commercial microwave oven (2.45 GHz; adjustable power within the range 20–800 W), and a wave guide (monomode T_{01}) including (i) a circulator and a water load to absorb the reflected waves, (ii) a directional coupler (47,83 dB) connected to a power meter (Hewlett-Packard 438) through two sensors to measure the incident and reflected powers, and (iii) an E. H. tuner to minimize the reflected power.

The reactor, a quartz tube (25-mm internal diameter) fitted with a reflux condenser, temperature probe, and a septum for sampling are introduced in a cavity at a $\lambda/4$ distance of the short circuit located at the end of the wave guide.

Temperature measurement was carried out with a Luxtron optical fiber thermometer (755 Multichannel FLuoroptic Thermometer).

The reaction conditions under microwave irradiation were as follows: same amounts of reagents as conventional heating and absorbed power: reaction 1, from 270 to 150 W, 170 °C (±2°), reaction 2, from 141 to 23 W, 80 °C (±2°), reaction 3, neat cintronellal from 138 to 50 W, 180 °C (±2°), 5‰ KSF clay, from 301 to 247 W, 77 °C (±1°), and 10% KSF clay, from 278 to 223 W, 77 °C (±1°).

Analysis. The reaction mixtures were analyzed by ^{1}H NMR on Bruker AC 80 or AC 200 apparatus. Samples of isopulegols containing variable amounts of various diastereoisomers **7a–d** ((−)-isopulegol (**7a**), (+)-neoisopulegol (**7b**), (+)-isoisopulegol (**7c**), (+)-neoisoisopulegol (**7d**)) were prepared according to the methods previously described.[16,17]

These isomers were identified by ^{1}H NMR at 200 MHz, in particular from the proton CHO signals.[16,17] The reactions without catalyst (Figure 3a,b) led to the isomer ratios **7a**/**7b**/**7c** = 71/16/12 (trace of **7d**). In the case of KSF montmorillonite catalysis the ratios obtained were **7a**/**7b**/**7c** = 57/35/7 (trace of **7d**). These ratios have been found to be independent of the heating mode.

Adducts **4** and **5** were chromatographed on a silica column with hexane–ethyl acetate (9:1) as eluent and identified by comparison of the ^{1}H NMR with authentic samples.[14e] In the case of diethyl 2-hydroxy-2-(2-decenyl)propane-1,3-dioate (**4**) the trans isomer ($CY_2CH_2C{=}C$, δ = 2.70 ppm, J = 7.5 Hz; CH=CH, 2 m, δ = 5.36 and 5.52 ppm, J = 15.3 Hz) is the major isomer (74%); the cis isomer ($CY_2CH_2C{=}C$, δ = 2.79, J = 7.5 Hz) is the minor one, regardless of the heating mode.

Acknowledgment. This work was supported by the Centre National de la Recherche Scientifique, Electricité de France, and the Région Midi-Pyrénées.

Mesitylene-Derived 1,3-Alternate [1.1.1.1]Metacyclophanes

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Received July 27, 1992

Synthetic procedures to conformationally immobile 1,3-alternate [1.1.1.1]metacyclophanes based on mesitylene units are described. Coupling of mesitol (**19**) with bis(chloromethyl)mesitol (**20**) and bis(chloromethyl)mesitylene (**21**) in nitroethane in the presence of $SnCl_4$ affords metacyclophanes **6** and **7–10**, respectively, possessing extra-annular hydroxyl groups. Metacyclophanes **12** and **14**, which hold one or two pairs of carboxyl groups in the distal positions, have been obtained from the appropriate distal diol **8** and tetrol **6** by treatment with *tert*-butyl bromoacetate followed by basic hydrolysis. Functionalized molecular frameworks, such as **15** and **18**, have been also prepared in high yield by direct methods. The ^{1}H NMR spectral characteristics of 1,3-alternate metacyclophanes synthesized are briefly discussed. The structures of mono-, tri-, and tetrahydroxy metacyclophanes **10**, **7**, and **6**, respectively, have been determined by X-ray crystallography. All three macrocycles have very similar 1,3-alternate–biconic conformations with approximate $\bar{4}2m$ symmetry. Molecules **10** and **7** are isomorphous, and the lone hydroxyl group in **10** and the three hydroxyl groups in **7** are disordered over four possible sites. A toluene of solvation is docked against the molecular cavity in both **10** and **7**. Compound **6** has crystallographic 2-fold symmetry and what would have been voids in the crystal lattice are occupied by disordered solvent molecules.

Introduction

During the last decade there has been growing interest in the search for new conformationally preorganized building blocks from which specific hosts with desired properties can be designed by appropriate functionalization. In this respect readily available calix[4]arenes **1** and calix[4]resorcinarenes **2** (Chart I), containing a cavity adorned with intra- or extra-annular hydroxyl groups, respectively, have been the focus of considerable attention.[1] A further interest in calix[4]arenes relies on the fact that upon functionalization these macrocycles may adopt four extreme conformations, i.e. cone, partial cone, 1,2-alternate, and 1,3-alternate, thus providing additional shapes for selective molecular recognition.

The 1,3-alternate conformation of *p-tert*-butylcalix[4]arene has been shown to be appropriate to afford molecular receptors presenting new and peculiar inherent symmetries. Examples of doubly-crowned calix[4]arenes **3**[2,3] and double calixcrown **4**,[3,4] showing special shapes associated with the 1,3-alternate calix[4]arene moieties connected by

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‡ Department of Chemistry and Biochemistry, University of Guelph.

(1) For recent reviews on calixarenes and related compounds, see: Gutsche, C. D. *Calixarenes*; Monographs in Supramolecular Chemistry; Stoddart, J. F., Ed.; Royal Society of Chemistry: Cambridge, 1989. *Calixarenes, a Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer: Dordrecht, 1990.

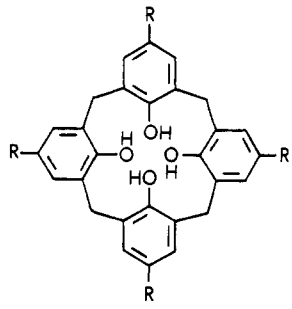
(2) Ghidini, E.; Ugozzoli, F.; Ungaro, R.; Harkema, S.; El-Fadl, A. A.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1990**, *112*, 6979.

(3) Asfari, Z.; Bressot, C.; Weiss, J.; Pappalardo, S.; Vicens, J. *Pure Appl. Chem.*, in press.

(4) Asfari, Z.; Abidi, R.; Arnaud, F.; Vicens, J. *J. Inclusion Phenom.* **1992**, *13*, 163.

0022-3263/92/1957-7102$03.00/0

Chart I



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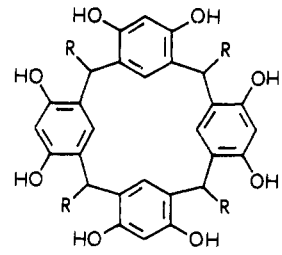

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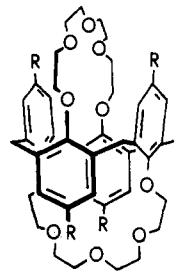

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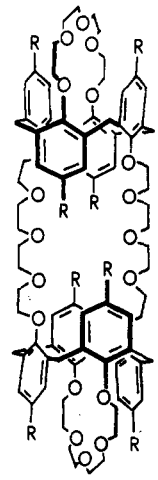
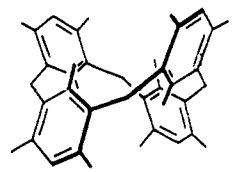


4



5

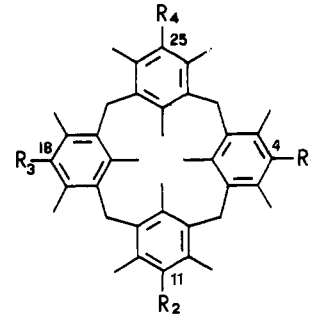
polyethereal bridging chains, have been recently reported in the literature. The yields of receptors of this type could be considerably improved if one could dispose of suitably functionalized shaping components in a prefixed 1,3-alternate conformation.

In order to tackle this problem, we resorted to metacyclophane skeleton **5**,[5] based on mesitylene units, which has been shown to exist in a fixed 1,3-alternate conformation in the temperature range −60 to 150 °C.[6] A further point of interest in the use of **5** as a molecular armature resides in its tendency to generate clathrate inclusion compounds with a variety of organic molecules in the solid state,[7] a property which may confer additional binding potential to the receptors derivable from **5** toward hydrophobic guests.

In this paper we report the synthesis, structural characterization, and host properties of the five possible mesitylene-derived 1,3-alternate [1.1.1.1]metacyclophanes **6–10**, possessing extra-annular hydroxyl groups (Chart II).

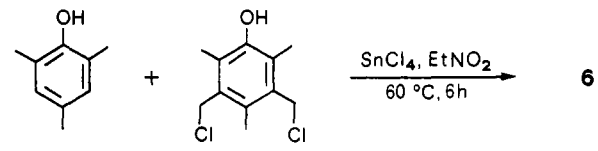
(5) (a) Ballard, J. L.; Kay, W. B.; Kropa, E. L. *J. Paint Technol.* **1966**, *38*, 251. (b) Bottino, F.; Montaudo, G.; Maravigna, P. *Ann. Chim. (Rome)* **1967**, *57*, 972. (c) Wu, T.-T.; Speas, J. R. *J. Org. Chem.* **1987**, *52*, 2330.
(6) Pappalardo, S.; Bottino, F.; Ronsisvalle, G. *Phosphorus Sulfur* **1984**, *19*, 327.
(7) Pappalardo, S. Unpublished results.

Chart II

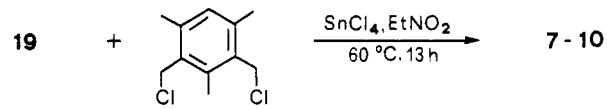


Compd	R_1	R_2	R_3	R_4
5	H	H	H	H
6	OH	OH	OH	OH
7	OH	OH	OH	H
8	OH	H	OH	H
9	OH	OH	H	H
10	OH	H	H	H
11	$OCH_2CO_2Bu^t$	H	$OCH_2CO_2Bu^t$	H
12	OCH_2CO_2H	H	OCH_2CO_2H	H
13	$OCH_2CO_2Bu^t$	$OCH_2CO_2Bu^t$	$OCH_2CO_2Bu^t$	$OCH_2CO_2Bu^t$
14	OCH_2CO_2H	OCH_2CO_2H	OCH_2CO_2H	OCH_2CO_2H
15	CH_2Cl	CH_2Cl	CH_2Cl	CH_2Cl
16	CH_2OAc	CH_2OAc	CH_2OAc	CH_2OAc
17	CH_2OH	CH_2OH	CH_2OH	CH_2OH
18	CHO	CHO	CHO	CHO

Scheme I



19 20



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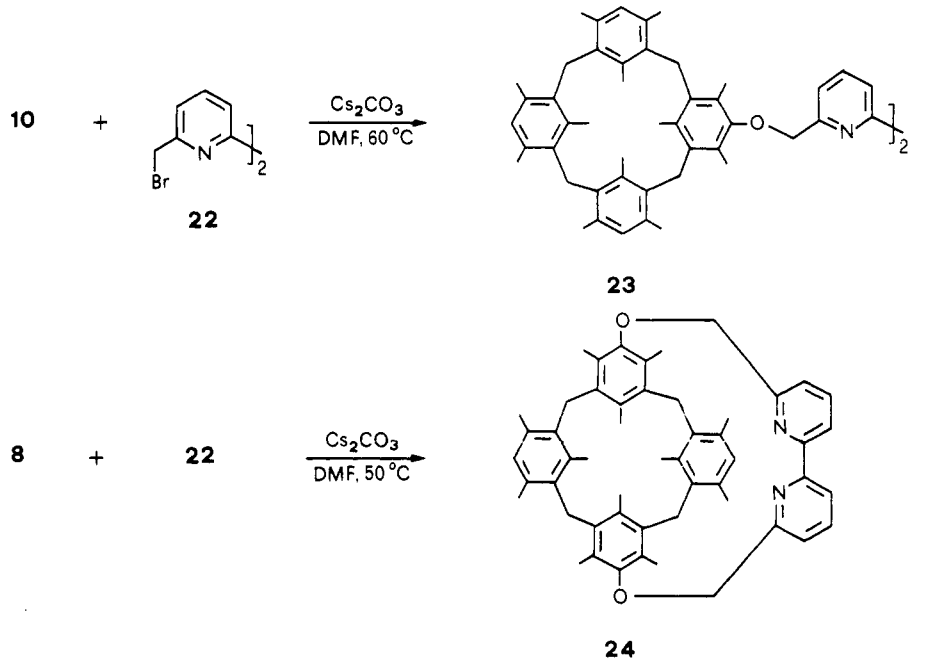
These compounds can be regarded as hybrids of the formaldehyde–resorcinol-based macrocycles and standard calix[4]arenes. Functionalization of **8** and **6** has been realized to afford derivatives **12** and **14** endowed with one or two pairs of distal carboxyl groups, respectively. Functionalized molecular frameworks, such as **15** and **18**, have been also prepared in high yield by direct methods.

Results and Discussion

Syntheses. Tetrahydroxymetacyclophane **6** was obtained in two steps from mesitol (**19**), as illustrated in Scheme I. Chloromethylation of **19** with $ClCH_2OCH_3$ in CH_2Cl_2 at 0 °C in the presence of $SnCl_4$ produced the known[8] 3,5-bis(chloromethyl)-2,4,6-trimethylphenol (**20**)

(8) (a) Wegler, R.; Regel, E. *Makromol. Chem.* **1952**, *9*, 1. (b) Morris, M. R.; Waring, A. J. *J. Chem. Soc. C* **1971**, 3266.

Scheme II



(65%), which was coupled with **19** (1 equiv) in nitroethane ($EtNO_2$) at 60 °C for 6 h to provide tetrol **6** (66%).

The syntheses of macrocyclic compounds usually make use of special techniques like high-dilution conditions, template effects, or principle of rigid groups. Although the condensation of **19** with **20** to give **6** requires three intermolecular steps in addition to the crucial intramolecular ring-closure step, no high-dilution conditions were needed.[9] Furthermore, the crude product separated out from the reaction medium and could be easily purified by recrystallization.

Much more intriguing is the synthesis that has led to the other four metacyclophanes bearing one to three hydroxyl groups at the outer periphery. When equimolar quantities of bis(chloromethyl)mesitylene (**21**) and **19** were reacted in $EtNO_2$ in presence of $SnCl_4$ (catalytic amounts) at 60 °C for 13 h (Scheme I), a copious precipitate was obtained. TLC analysis showed the presence of several components, which could be eventually separated by careful column chromatography (SiO_2, a gradient of AcOEt in cyclohexane as the eluent). The eluted fractions gave in the order the hydrocarbon macrocycle **5** (ca. 1%) as the fastest moving component, followed by monohydroxy compound **10** (9%), proximal dihydroxy metacyclophane **9** (8%), the expected distal dihydroxy metacyclophane **8** (28%) as the major component, and trihydroxy metacyclophane **7** (3%).

The obtention of macrocycles other than **8** can be explained if one takes into account that the formation of C–C bonds in Friedel–Crafts condensations is reversible,[10] and under the acidic reaction medium (catalyst, evolved HCl) protodealkylation processes with scission of the methylene bridge(s) and subsequent recombination(s) are likely to occur.[11-13]

Owing to a fixed 1,3-alternate conformation, proximal regioisomer **9** has no plane of symmetry and is inherently chiral. To the best of our knowledge, this is a rare example of atropisomeric inherently chiral calix[4]arene-like macrocycle in the 1,3-alternate conformation. Previous examples of inherently chiral calix[4]arenes reported in the literature refer to cone,[14] partial cone,[15] and 1,2-alternate[16] calix[4]arene conformers.

In order to test the reactivity of the sterically crowded extra-annular hydroxyl group in these systems, monohydroxy compound **10** was subjected to 6,6′-bis(bromomethyl)-2,2′-bipyridine (**22**) (0.5 equiv) in anhydrous *N*,*N*-dimethylformamide (DMF) at 60 °C in the presence of Cs_2CO_3 (Scheme II). The reaction proceeded smoothly, and bis-ether **23** could be isolated in 67% yield, thus ruling out possible steric hindrance effects of the two ortho-positioned methyl groups.

The distinction between regioisomers **8** and **9** was apparent from their ^1H NMR patterns (see below) and from chemical evidence. Molecular models suggested that **22** should be a suitable bridging reagent for diol **8** and too short for **9**. Indeed, we found that slow addition of a solution of **22** in DMF to a solution of **8** in DMF in the presence of Cs_2CO_3 resulted in the formation of intra-bridged metacyclophane **24** in 49% isolated yield (Scheme II), confirming that in **8** the two hydroxyl groups lie on the same side with respect to the plane containing the bridging methylenes.

When **8** was reacted with 2.2 equiv of *tert*-butyl bromoacetate with K_2CO_3 as a base in DMF, diester **11** was isolated in 80% yield. Basic hydrolysis of **11** in refluxing dioxane–H_2O, followed by acidification furnished diacid **12** (90%), bearing two opposite carboxyl groups. By using

(9) For tetramerization reactions followed by ring closure without high dilution conditions, see for example: Dahan, E.; Biali, S. E. *J. Org. Chem.* **1989**, *54*, 6003 and references cited therein.

(10) Norman, R. O. C.; Taylor, R. *Electrophilic Substitution in Benzenoid Compounds*; Elsevier: Amsterdam, 1965.

(11) Högberg, A. G. S. *J. Am. Chem. Soc.* **1980**, *102*, 6046.

(12) Böhmer, V.; Marschollek, F.; Zetta, L. *J. Org. Chem.* **1987**, *52*, 3200.

(13) de Mendoza, J.; Nieto, P. M.; Prados, P.; Sánchez, C. *Tetrahedron Lett.* **1990**, *46*, 671.

(14) Shinkai, S.; Arimura, T.; Kawabata, H.; Murakami, H.; Araki, K.; Iwamoto, K.; Matsuda, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1734. Böhmer, V.; Wolff, A.; Vogt, W. *Ibid.* **1990**, 968. Iwamoto, K.; Yanagi, A.; Arimura, T.; Matsuda, T.; Shinkai, S. *Chem. Lett.* **1990**, 1901. Iwamoto, K.; Yanagi, A.; Araki, K.; Shinkai, S. *Ibid.* **1991**, 473. Pappalardo, S.; Giunta, L.; Foti, M.; Ferguson, G.; Gallagher, J. F.; Kaitner, B. *J. Org. Chem.* **1992**, *57*, 2611.

(15) Pappalardo, S.; Caccamese, S.; Giunta, L. *Tetrahedron Lett.* **1991**, *32*, 7747.

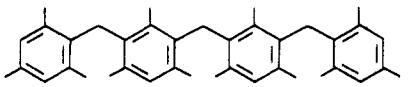
(16) Iki, H.; Kikuchi, T.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 669.

the above sequence, tetrol **6** was converted into tetraester **13** (70%), which upon hydrolysis provided tetraacid **14** (86%), whose tetrasodium salt is water-soluble. This compound is potentially useful for host–guest complexation studies in aqueous solution.[17]

Functionalized building blocks can be easily derived from metacyclophane **5** by direct methods. Chloromethylation of **5** with $ClCH_2OCH_3/SnCl_4$ in CS_2 at −15 °C gave tetrakis(chloromethyl) derivative **15** in high yield. Treatment of **15** with excess anhydrous CH_3COONa in CH_3COOH produced tetraacetate **16** (93%), which was converted to tetrakis(hydroxymethyl)metacyclophane **17** (95%) with anhydrous K_2CO_3 in boiling EtOH–dioxane. The Gross formylation (Cl_2CHOCH_3–$SnCl_4$) of **5** in CH_2Cl_2 at 0 °C gave tetraformyl derivative **18** in 59% yield.

1,3-Alternate metacyclophanes derived from mesitylene are high-melting crystalline materials (mp > 300 °C). Mostly they dissolve in chlorinated solvents, except the tetrasubstituted compounds possessing polar groups (OH, CHO, CH_2OH), which are soluble in aprotic dipolar solvents, such as dimethyl sulfoxide (DMSO) and DMF. Elemental analyses and ^1H NMR spectra suggest for some of these molecules the presence of included guest solvent in the crystals. For instance, hydroxyl-containing metacyclophanes **7**–**10** form stable crystalline 2:1 (host to guest) adducts with toluene, while tetrol **6** and tetraaldehyde **18** enclathrate DMF or DMSO, respectively, in a different ratio.

^1H NMR Spectral Features. The 1,3-alternate conformation of metacyclophanes **5**–**18** is substantiated by an upfield resonance for the intra-annular methyl groups (δ = 1.12 ± 0.07 ppm in $CDCl_3$ and 1.08 ± 0.07 in DMSO-d_6), which are strongly shielded ($\Delta\delta$ = 1.0 ppm) by the flanking mesitylene subunits with respect to the pertinent methyl groups in the linear model 3,3′-bis(2,4,6-trimethylbenzyl)dimesitylmethane (**25**).[6] In intrabridged compound



25

24 a pair of intra-annular methyl groups is further shielded at higher field (δ = 0.77 ppm) because of capping with the 2,2′-bipyridyl unit. Noteworthy, the ^1H NMR spectra are not affected by the temperature, indicating that the 1,3-alternate conformation is locked in the range investigated (25–80 °C, $CDCl_3$).

1,3-Alternate conformers exhibit distinctive ^1H NMR spectral patterns of the bridging methylenes arising from conformation and from the substitution pattern at the *extra* positions. The methylene protons show up as a singlet in symmetrically tetrasubstituted compounds (D_{2d} symmetry), and as one pair of doublets (J = 16.8–17.0 Hz) and one singlet in the ratio 1:1 in mono- and trisubstituted derivatives (C_s symmetry). In distally disubstituted metacyclophanes the $ArCH_2Ar$ groups appear as one pair of doublets (J = 17.0–17.5 Hz) (C_{2v} symmetry), while in the chiral proximally disubstituted derivative **9** they give rise to one pair of doublets (J = 17.0 Hz) and two singlets (C_2 symmetry). The OH groups in **6**–**10** resonate as sharp singlet(s) at δ = 4.47–4.50 ppm, indicating a weak (if any) intermolecular hydrogen bonding among hydroxyls.

Structure Descriptions. Although the crystals of **10**, **7**, and **6** only diffracted relatively poorly (see Experimental Section), we were able to obtain sufficient data to allow us to determine the details of their conformation unequivocally. All three molecules adopt a 1,3-alternate–biconic conformation with approximate $\bar{4}2m$ symmetry in the solid state (Figures 1, 2, and 3a). Molecules **10** and **7** occur as their toluene solvates (Figure 3b) and are isomorphous in the crystalline state and their space group requires no molecular symmetry; the space group for molecule **6** requires it to have 2-fold crystallographic symmetry.

In **10** the molecule (Figures 1 and 3a) is disordered in such a way that the unique OH group is distributed over four possible sites with occupancies of 0.50, 0.34, 0.09, and 0.07 for each site; in **7** the three hdyroxyl groups are distributed in a similar fashion with occupancies of 0.89, 0.87, 0.69, and 0.57 for each site. The overall 1,3-alternate conformation adopted by these metacyclophanes has been previously observed in solution for either flexible[18] and inflexible[19] tetrasubstituted calix[4]arenes by ^1H and ^{13}C NMR spectroscopy. The crystal structure of a structurally related 1,3-alternate calix[4]arene with mixed ligating

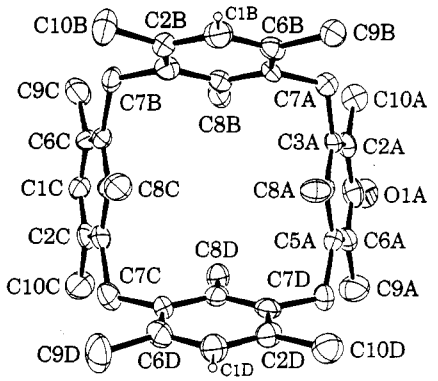


Figure 1. A view of the metacyclophane **10** showing the conformation and our numbering scheme. For clarity, only the major site of the disordered hydroxyl hydrogen atom (O1A) is shown; the hydrogen atoms are omitted except the three disordered aromatic hydrogens on C1B, C1C, and C1D. The non-hydrogen atoms are drawn as thermal ellipsoids at the 35% probability level. The view of isomorphous molecule **7** is very similar to this with the three hydroxyl oxygens disordered over the four possible sites.

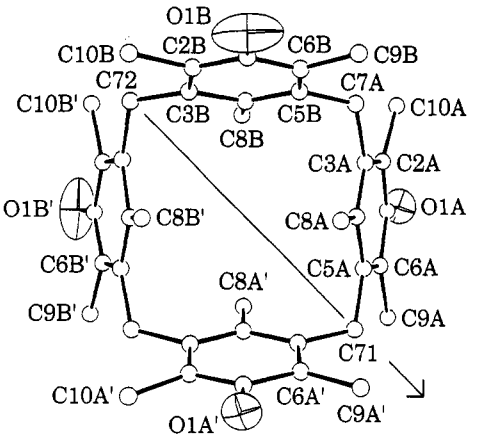


Figure 2. A view of the metacyclophane **6** showing the conformation and our numbering scheme. For clarity, carbon atoms are shown as spheres of an arbitrary size; hydrogen atoms are omitted. The oxygen atoms are drawn as thermal ellipsoids at the 50% probability level. The direction of the 2-fold crystallographic symmetry axis is also shown.

(17) Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 362.

(18) Groenen, L. C.; van Loon, J.-D.; Verboom, W.; Harkema, S.; Casnati, A.; Ungaro, R.; Pochini, A.; Ugozzoli, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1991**, *113*, 2385.

(19) Jaime, C.; de Mendoza, J.; Prados, P., Nieto, P. M.; Sánchez, C. *J. Org. Chem.* **1991**, *56*, 3372.

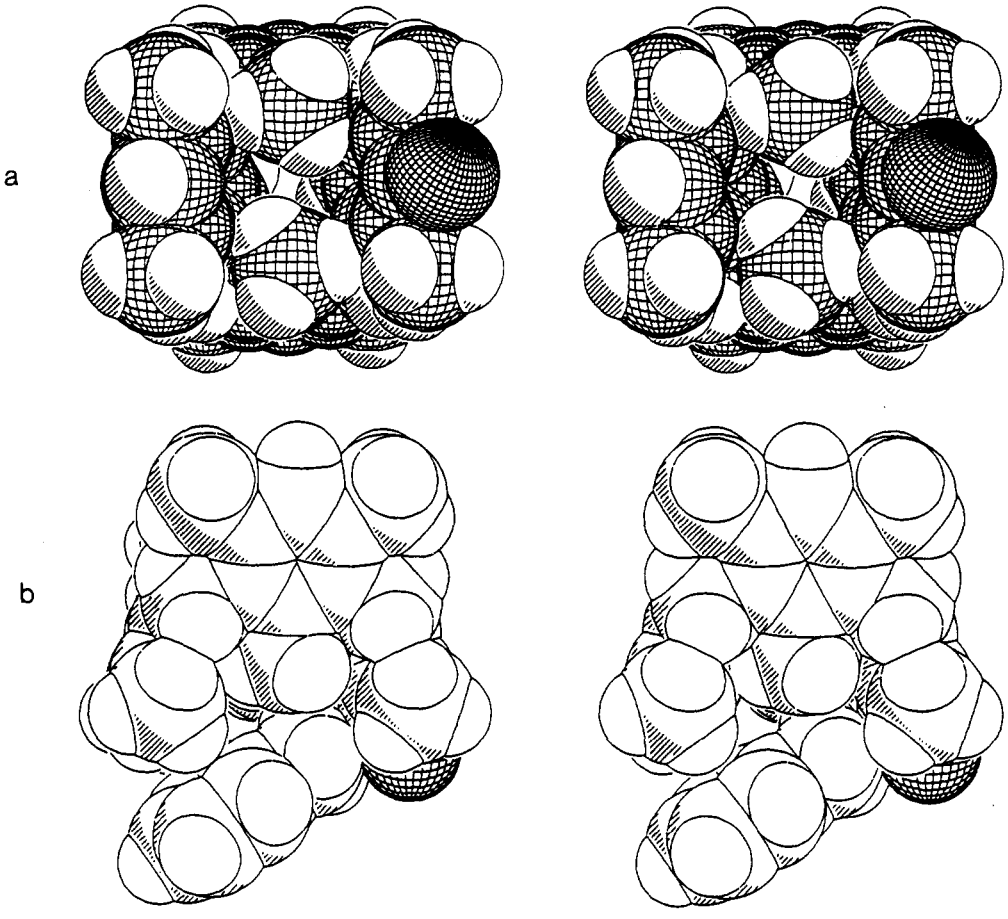


Figure 3. Two stereoviews of molecule **10** with the atoms depicted as their van der Waals spheres showing (a, top) the metacyclophane cavity and (b, bottom) the toluene molecule nestled against the cavity. Only one set of hydrogen atoms on the methyl group is shown.

Table I. Interplanar Angles Defining the Molecular Conformations for Molecules 10, 7, and 6

planes	10	7	6[a]
CH_2 plane/ring A	107.9 (2)	108.5 (2)	108.7 (4)
CH_2 plane/ring B	-105.8 (2)	-105.5 (2)	-109.7 (4)
CH_2 plane/ring C	110.9 (2)	109.3 (2)	[108.7 (4)]
CH_2 plane/ring D	-110.8 (2)	-109.2 (2)	[-109.7 (4)]
ring A/ring C	38.8 (2)	37.9 (2)	38.4 (4)
ring B/ring D	-36.1 (2)	-35.2 (2)	-38.3 (4)

[a] In molecule **6** because of the crystallographic symmetry there are only two unique interplanar angles involving the CH_2 plane. The aromatic rings and the inter-ring interplanar angles are between rings A and B′ and between B and A′ (where A′ and B′ are the rings related by the 2-fold symmetry axis shown in Figure 2).

groups at the lower rim has been reported very recently.[20]

The conformations in **10**, **7**, and **6** are defined by the angles which the aromatic rings make with the plane of the carbon atoms of the CH_2 moieties which link them as shown in Table I (mean interplanar angle 109°), the rings being tilted so that the methyl groups C(9x) and C(10x) (x = A, B, C, D, Figure 1), are directed *away* from the ring cavity. In each case, pairs of opposite rings are tilted away from each other with mean interplanar angles 37° (Table I). This leads to a fairly open biconic conformation as shown in Figure 1. The molecules have two cavities roughly defined for molecules **10** and **7** by carbon atoms C9A, C10A, C9C, C10C, with C8B, C8D as the base on one side of the molecule and C9B, C10B, C9D, C10D on the perimeter and C8A, C8C as the base on the other side; for molecule **6** the corresponding cavities are defined by C9A, C10A, C9B′, C10B′ on the perimeter and C8A′ and C8B as the base on one side of the molecule and by C9B, C10B, C9A′, C10A′ on the perimeter and C8A, C8B′ as the base on the other side.

In the crystal lattice of both **10** and **7** a toluene of solvation (Figure 3b) tries to fill the cavity containing the major OH site (with the toluene methyl group adjacent to the hydroxyl oxygen), but as it is really too large to fit in the cavity completely, it lies across the molecular cavity with its methyl group immediately adjacent to a site of the principal OH group with C7S···O1A 3.05 (1) Å in **10** and C7S···O1A 3.55 Å in **7**. The toluene molecular plane is oriented at an angle of -35.8 (7)° to the methylene carbon plane and at 73.0 (7)° to the plane through aromatic ring (A) in **10**; the corresponding values in **7** are -43.5 (2)° and 71.5 (2)°, respectively. Total enclathration of small solvent molecules within the calix cavity is well known, e.g. acetonitrile in tetraethyl *p-tert*-butylcalix[4]arenetetracarbonate.[21] In the case of molecule **6** there is no toluene of solvation partially enclathrated in the cavity but in what would have been a void in the crystal lattice between metacyclophane molecules there is a highly disordered solvent system (with crystallographic 32 site symmetry), which we were unable to identify as a chemically sensible moiety.

The shortest intermolecular contact (consistent with it being an intermolecular O–H···O hyrogen bond) in the crystal structure in **10** is between O1A and O1B′ of a neighboring molecule at 2.96 (1) Å; the corresponding distance in **7** is 2.93 (1) Å. In **10** because of the disorder,

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we were unable to locate the hydroxyl hydrogen. In the trihydroxymetacyclophane **7**, the hydroxyl hydrogens attached to the two major hydroxyl sites were located and the hydrogen bond involves O1A···H–O1B′ (HO1B′···O1A 1.96 Å); the hydroxyl hydrogen on O1A is not involved in the hydrogen bonding process, but is directed toward an adjacent methyl group. The hydrogen atoms attached to minor sites O1C and O1D could not be located in the final difference maps. In molecule **6** the shortest intermolecular contact (corresponding to an O–H···O hydrogen bond) is between O1A and O1A′ of a neighboring molecule at 2.73 (1) Å; again the lack of data did not allow us to locate these hydroxyl hydrogens.

Conclusions

The synthetic procedures here described provide a practical route to mesitylene-based 1,3-alternate [1.1.1.1]metacyclophanes that hold pairs of functional groups in the distal positions. Remarkably, the ring-closure reactions applied afford a single stereoisomer of the molecule. The rigid concave surfaces are maintained by conformational costraints intrinsic to the architecture of these building blocks. X-ray analysis has been used to elucidate the overall conformation and geometry of the voids available for guest accommodation. Further amplification of these structures and their potential as shaping components in supramolecular chemistry remain for future studies.

Experimental Section

General Comments. Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Unless otherwise noted, ^{1}H NMR spectra were obtained in $CDCl_3$ with Me_4Si as the internal standard and recorded at 250 MHz. EI MS were taken at 18 eV. For FAB (+) mass spectra, 3-nitrobenzyl alcohol was used as a matrix. Compounds **5**,[5b] **21**,[22] and **22**[23] were prepared by literature procedures.

3,5-Bis(chloromethyl)-2,4,6-trimethylphenol (20). To a chilled and stirred solution of **19** (4.08 g, 30 mmol) and $ClCH_2OCH_3$ (4.6 mL, 60 mmol) in CH_2Cl_2 (50 mL) was added dropwise anhydrous $SnCl_4$ (7 mL, 60 mmol) while the temperature was kept below 10 °C. Addition of half of the $SnCl_4$ produced a precipitate that slowly dissolved on further addition of catalyst. The mixture was stirred at 0 °C for 2 h and overnight at rt. HCl (2 N, 50 mL) was then added, and the resulting mixture was stirred for 10 min. The organic layer was separated from the water layer, washed (5% $NaHCO_3$, then H_2O), and dried (Na_2SO_4). Evaporation of the solvent left a brown residue, which was dissolved in $CHCl_3$ and passed through a short SiO_2 column, eluting with cyclohexane–AcOEt (4:1, v/v). The eluate was concentrated to give a yellowish solid, which on recrystallization from cyclohexane afforded **20** (4.5 g, 65%) as colorless needles: mp 130–133 °C (lit.[8b] mp 132 °C); MS m/z 234 (26), 232 (42, M^+), 199 (39), 197 [95, $(M - Cl)^+$], 162 [100, $(M - 2Cl)^+$].

3,5,7,10,12,14,17,19,21,24,26,28-Dodecamethyl[1.1.1.1]metacyclophane-4,11,18,25-tetrol (6).[24] To a stirred solution of **19** (2.04 g, 15 mmol) and **20** (3.48 g, 15 mmol) in $EtNO_2$ (100 mL) containing a few drops of anhydrous $SnCl_4$ was heated in an oil bath at 60 °C for 6 h under a vigorous N_2 stream. The reaction mixture became dark purple almost at once while a precipitate started to form after a few minutes. The mixture was allowed to stir overnight at rt. The solid was collected by filtration and washed with small portions of cold $EtNO_2$ until the washings were colorless. The light pink product on recrystallization from aqueous DMF gave **6** (2.93 g, 66%) as colorless crystals: mp > 300 °C; ^{1}H NMR δ 1.11 (s, int Me, 12 H), 2.30 (s, ext Me, 24 H), 3.94 (s, $ArCH_2Ar$, 8 H), and 4.50 (s, OH, 4 H); MS m/z 592 (100, M^+). Anal. Calcd for $C_{40}H_{48}O_4 \cdot 2DMF \cdot 1.5H_2O$: C, 74.86; H, 8.88; N, 3.80. Found: C, 74.57; H, 8.75; N, 3.98.

Coupling of 19 with 21. Metacyclophanes 7–10. Equimolar amounts of **19** and **20** (10 mmol) in $EtNO_2$ (60 mL) containing a few drops of anhydrous $SnCl_4$ were heated with stirring at 60 °C for 13 h under N_2. From the purple reaction mixture a precipitate started to form after 1 h. Usual workup gave a solid, which was chromatographed (column, SiO_2) eluting with a gradient of AcOEt in cyclohexane to afford the following fractions.

Fractions A gave a crystalline product (26 mg) identical in all respects to an authentic sample of macrocycle **5**.

Fraction B provided **3,5,7,10,12,14,17,19,21,24,26,28-dodecamethyl[1.1.1.1]metacyclophan-4-ol (10)** (245 mg, 9%) as white prisms: mp > 300 °C (toluene); R_f = 0.56 (cyclohexane–AcOEt 4:1); ^{1}H NMR δ 1.16, 1.17 (s, int Me, 12 H), 2.29, 2.33 (s, ext. Me, 24 H), 3.86 and 3.97 (AB q, J = 16.8 Hz, $ArCH_2Ar$, 4 H), 3.87 (s, $ArCH_2Ar$, 4 H), 4.48 (s, OH, 1 H), 6.79 (s, ArH, 2 H), and 6.81 (s, ArH, 1 H); MS m/z 544 (100, M^+). Anal. Calcd for $C_{40}H_{48}O \cdot 1/2C_7H_8$: C, 88.42; H, 8.87. Found: C, 88.20; H, 9.13.

Fraction C yielded **(±)-3,5,7,10,12,14,17,19,21,24,26,28-dodecamethyl[1.1.1.1]metacyclophane-4,11-diol (9)** (224 mg, 8%) as white crystals: mp > 300 °C (toluene); R_f = 0.41 (cyclohexane–AcOEt 4:1); ^{1}H NMR δ 1.15 (s, int Me, 12 H), 2.29, 2.34 (s, ext Me, 24 H), 3.85 and 3.97 (AB q, J = 17.0 Hz, $ArCH_2Ar$, 4 H), 3.87, 3.95 (s, $ArCH_2Ar$, 4 H), 4.48 (s, OH, 2 H), and 6.81 (s, ArH, 2 H); MS m/z 560 (100, M^+). Anal. Calcd for $C_{40}H_{48}O_2 \cdot 1/2C_7H_8$: C, 86.09; H, 8.64. Found: C, 86.62; H, 8.97.

Fraction D afforded **3,5,7,10,12,14,17,19,21,24,26,28-dodecamethyl[1.1.1.1]metacyclophane-4,18-diol (8)** (0.73 g, 26%) as white prisms: mp > 300 °C (toluene); R_f = 0.32 (cyclohexane–AcOEt 4:1); ^{1}H NMR δ 1.14, 1.16 (s, int Me, 12 H), 2.30, 2.33 (s, ext Me, 24 H), 3.85 and 3.97 (AB q, J = 17.0 Hz, $ArCH_2Ar$, 8 H), 4.49 (s, OH, 2 H), and 6.79 (s, ArH, 2 H); MS m/z 560 (100, M^+). Anal. Calcd for $C_{40}H_{48}O_2 \cdot 1/2C_7H_8$: C, 86.09; H, 8.64. Found: C, 86.53; H, 8.98.

Fraction E gave **3,5,7,10,12,14,17,19,21,24,26,28-dodecamethyl[1.1.1.1]metacyclophane-4,11,18-triol (7)** (86 mg, 3%): mp > 300 °C (toluene); R_f = 0.21 (cyclohexane–AcOEt 4:1); ^{1}H NMR δ 1.13, 1.14 (s, int Me, 12 H), 2.30, 2.31, 2.34 (s, ext Me, 24 H), 3.85 and 3.97 (AB q, J = 17.0 Hz, $ArCH_2Ar$, 4 H), 3.95 (s, $ArCH_2Ar$, 4 H), 4.47 (s, OH, 1 H), 4.49 (s, OH, 2 H), and 6.81 (s, ArH, 1 H); MS m/z 576 (68, M^+), 547 [100, $(M - CHO)^+$]. Anal. Calcd for $C_{40}H_{48}O_3 \cdot 1/2C_7H_8$: C, 83.88; H, 8.41. Found: C, 83.77; H, 8.62.

Bis-Ether 23. To a warm solution (60 °C) of macrocycle **10** (68 mg, 0.125 mmol) and **22** (22 mg, 0.065 mmol) in anhydrous DMF (10 mL) was added Cs_2CO_3 (0.3 g). The mixture was stirred at 60 °C under N_2 for 3 h. After cooling, the reaction mixture was filtered, and the filtrate was concentrated under vacuum. The residue was dissolved in $CHCl_3$, washed with water, and dried (Na_2SO_4). The solvent was evaporated to give a solid, which was chromatographed (column, SiO_2, eluent $CHCl_3$) to afford bis-ether **23** (55 mg, 67%) as a white powder: mp > 300 °C; ^{1}H NMR δ 1.17 (s, int Me, 12 H), 1.18 (s, int Me, 6 H), 1.20 (s, int Me, 6 H), 2.34 (s, ext Me, 24 H), 2.37 (s, ext Me, 12 H), 2.40 (s, ext Me, 12 H), 3.92 (m, $ArCH_2Ar$, 16 H), 4.93 (s, OCH_2, 4 H), 6.80 (s, ArH, 2 H), 6.85 (s, ArH, 4 H), 7.67 (d, J = 7.8 Hz, 5-PyH, 2 H), 7.85 (t, J = 7.8 Hz, 4-PyH, 2 H), and 8.33 (d, J = 7.8 Hz, 3-PyH, 2 H); FAB (+) MS m/z 1269 (100, MH^+). Anal. Calcd for $C_{92}H_{104}N_2O_2$: C, 87.02; H, 8.25; N, 2.21. Found: C, 86.81; H, 8.13; N, 2.04.

Intrabridged Metacyclophane 24. A solution of dihydroxy derivative **8** (0.14 g, 0.25 mmol) and **22** (0.085 g, 0.25 mmol) in dry DMF (50 mL) was added dropwise during 20 h to a stirred suspension of Cs_2CO_3 (1.5 g) in dry DMF (50 mL) at 50 °C under N_2. The mixture was kept at 50 °C for additional 4 h and allowed to stir at rt for 2 days. Usual workup gave a solid residue, which was chromatographed (column, SiO_2, eluent cyclohexane-AcOEt 3:1) to afford cage compound **24** (90 mg, 49%) as a white powder: mp > 300 °C; ^{1}H NMR δ 0.77, 1.02 (s, int Me, 12 H), 2.21, 2.27 (s, ext Me, 24 H), 3.74 and 3.84 (AB q, J = 17.3 Hz, $ArCH_2Ar$, 8 H), 5.26 (s, OCH_2, 4 H), 6.73 (s, ArH, 2 H), 7.68 (dd, J = 7.3, 1.6 Hz, 5-PyH, 2 H), 7.78 (t, J = 7.3 Hz, 4-PyH, 2 H), and 8.02 (dd, J = 7.3, 1.6 Hz, 3-PyH, 2 H); MS m/z 740 (27, M^+), 560 (31), 184 (100, $C_{12}H_{12}N_2$). Anal. Calcd for $C_{52}H_{56}N_2O_2 \cdot 0.7CHCl_3$: C,

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76.76; H, 6.93; N, 3.40. Found: C, 76.53; H, 7.18; N, 3.43.

4,18-Bis[[(*tert*-butyloxy)carbonyl]methoxy]-3,5,7,10,12,14,17,19,21,24,26,28-dodecamethyl[1.1.1.1]metacyclophane (11). A stirred slurry of 8 (1.69 g, 3 mmol), *tert*-butyl bromoacetate (1.33 g, 6.8 mmol), and anhydrous K_2CO_3 in dry DMF (50 mL) was heated at 60 °C under N_2 for 24 h. The solvent was evaporated under vacuum to give a solid, which was triturated with MeOH (10 mL), collected by filtration, washed with water, and dried to afford 11 (1.8 g, 80%) as a white powder: mp 222–224 °C; ^{1}H NMR δ 1.09, 1.14 (s, int Me, 12 H), 1.55 (s, *t*-Bu, 18 H), 2.32, 2.35 (s, ext Me, 24 H), 3.84 and 3.93 (AB q, J = 17.5 Hz, $ArCH_2Ar$, 8 H), 4.18 (s, OCH_2, 4 H), and 6.78 (s, ArH, 2 H); MS m/z 732 [5.3, $(M - 56)^+$], 676 [100, $(M - 2 \times 56)^+$]. Anal. Calcd for $C_{52}H_{68}O_6$: C, 79.15; H, 8.69. Found: C, 79.15; H, 8.77.

4,18-Bis(carboxymethyl)-3,5,7,10,12,14,17,19,21,24,26,28-dodecamethyl[1.1.1.1]metacyclophane (12). To a stirred solution of diester 11 (0.2 g, 0.25 mmol) in hot dioxane (10 mL) was added a solution of NaOH (0.2 g) in EtOH–H_2O (1:1 v/v, 10 mL). The mixture was refluxed for 24 h and the solvent was evaporated. The residue was acidified with dilute HCl, extracted with AcOEt, washed with water, and dried (Na_2SO_4). Concentration of the extract to a small volume and precipitation from petroleum ether afforded diacid 12 (0.15 g, 90%) as a white powder: mp > 300 °C; ^{1}H NMR δ 1.09, 1.15 (s, int Me, 12 H), 2.33, 2.35 (s, ext Me, 24 H), 3.85 and 3.93 (AB q, J = 17.2 Hz, 8 H), 4.44 (s, OCH_2, 4 H), and 6.79 (s, ArH, 2 H); MS m/z 676 (4, M^+), 560 (100). Anal. Calcd for $C_{44}H_{52}O_6 \cdot 1.5H_2O$: C, 75.08; H, 7.88. Found: C, 75.15; H, 7.61.

4,11,18,25-Tetrakis[[(*tert*-butyloxy)carbonyl]methoxy]-3,5,7,10,12,14,17,19,21,24,26,28-dodecamethyl[1.1.1.1]metacyclophane (13). To a warm (50 °C) solution of 6 (0.5 g, 0.84 mmol) in anhydrous DMF (20 mL) was added *t*-butyl bromoacetate (1.31 g, 6.6 mmol) and K_2CO_3 (1.4 g). The reaction mixture was stirred at 50 °C under N_2 for 3 days. The inorganic salts were filtered off, and the filtrate was concentrated under vacuum. The residue was triturated with MeOH, collected by filtration, washed with water and dried. Recrystallization from acetonitrile afforded tetraester 13 (0.73 g, 70%) as white shining prisms, mp 220–221 °C; ^{1}H NMR δ 1.05 (s, int Me, 12 H), 1.55 (s, *t*Bu, 36 H), 2.33 (s, ext Me, 24 H), 3.89 (s, $ArCH_2Ar$, 8 H), and 4.17 (s, OCH_2, 8 H); FAB (+) MS, m/z 1049 (100, MH^+). Anal. Calcd for $C_{64}H_{88}O_{12}$: C, 73.25; H, 8.45. Found: C, 73.46; H, 8.61.

4,11,18,25-Tetrakis(carboxymethoxy)-3,5,7,10,12,14,17,19,21,24,26,28-dodecamethyl[1.1.1.1]metacyclophane (14). To a stirred solution of 13 (0.33 g, 0.31 mmol) in hot dioxane (10 mL) was added a solution of NaOH (0.47 g) in EtOH–H_2O (1:1 v/v, 10 mL). After about 45 min reflux, a white solid deposited on the walls of the flask. At this point, a small volume of water was added until all the solid dissolved. This solution was refluxed with stirring for a total of 20 h. After cooling, the mixture was acidified with HCl, and the precipitate obtained was extracted with AcOEt, washed twice with water, and dried (Na_2SO_4). Evaporation of the solvent gave tetracid 14 (0.22 g, 86%) as a white powder: mp > 300 °C; ^{1}H NMR (DMSO-d_6) δ 1.01 (s, int Me, 12 H), 2.23 (s, ext Me, 24 H), 3.81 (s, $ArCH_2Ar$, 8 H), and 4.12 (s, OCH_2, 8 H); FAB (+) MS m/z 825 (100, M^+). Anal. Calcd for $C_{48}H_{56}O_{12} \cdot H_2O$: C, 68.39; H, 6.93. Found: C, 68.20; H, 7.14.

4,11,18,25-Tetrakis(chloromethyl)-3,5,7,10,12,14,17,19,21,24,26,28-dodecamethyl[1.1.1.1]metacyclophane (15). To a stirred slurry of 5 (2.64 g, 5 mmol) in CS_2 (40 mL), cooled at −15 °C, was added $ClCH_2OCH_3$ (4.1 g, 50 mmol) followed by dropwise addition of a solution of anhydrous $SnCl_4$ (1.3 g, 5 mmol) in CS_2 (10 mL). The mixture was kept at −15 °C for 1 h and stirred overnight at room temperature. After the mixture was poured into acidulated water, the organic layer was separated and the water layer was extracted with CS_2 (2 × 10 mL). The combined organic extract was washed (5% $NaHCO_3$ and then water) and dried over anhydrous $CaCl_2$. Evaporation of the solvent left a solid, which was triturated with Et_2O (20 mL) and filtered to afford 2 (3.06 g, 85%) as a white powder: mp > 300 °C; ^{1}H NMR δ 1.09 (s, int Me, 12 H), 2.46 (s, ext Me, 24 H), 4.02 (s, $ArCH_2Ar$, 8 H), and 4.72 (s, CH_2Cl, 8 H); MS m/z 724 (2.9), 722 (4.9), 720 (3.2, M^+), 36 (100). Anal. Calcd for $C_{44}H_{52}Cl_4$: C, 73.12; H, 7.25. Found: C, 72.87; H, 7.16.

4,11,18,25-Tetrakis(acetoxymethyl)-3,5,7,10,12,14,17,19,21,24,26,28-dodecamethyl[1.1.1.1]metacyclophane (16). A mixture of 15 (0.36 g, 0.5 mmol) and anhydrous AcONa (1.5 g, 18 mmol) in AcOH (15 mL) was refluxed with stirring for 20 h. After cooling, the mixture was diluted with water and the resulting precipitate was collected by filtration, thoroughly washed with water, and dried (0.38 g, 93%): mp > 300 °C; ^{1}H NMR δ 1.14 (s, int Me, 12 H), 2.07 (s, MeCO, 12 H), 2.39 (s, ext Me, 24 H), 4.03 (s, $ArCH_2Ar$, 8 H), and 5.23 (s, CH_2OAc, 8 H); MS m/z 816 (4, M^+), 180 (100). Anal. Calcd for $C_{52}H_{64}O_8$: C, 76.44; H, 7.89. Found: C, 76.03; H, 7.78.

3,5,7,10,12,14,17,19,21,24,26,28-Dodecamethyl[1.1.1.1]metacyclophane-4,11,18,25-tetramethanol (17). A slurry of 16 (0.327 g, 0.4 mmol) and anhydrous K_2CO_3 (1.2 g) in abs EtOH–dioxane (2:1 v/v, 30 mL) was refluxed with stirring for 24 h. After evaporation of the solvent, the residue was refluxed in water (20 mL) for 0.5 h, filtered, and dried to give tetrol 17 as a white powder (0.24 g, 93%): mp > 300 °C; ^{1}H NMR (80 MHz, DMSO-d_6) δ 1.06 (s, int Me, 12 H), 2.37 (s, ext Me, 24 H), 3.91 (s, $ArCH_2Ar$, 8 H), 4.51 (bs, CH_2OH, 8 H), and 4.61 (m, CH_2OH 4 H); MS m/z 648 (100, M^+). Anal. Calcd for $C_{44}H_{56}O_4 \cdot H_2O$; C, 79.23; H, 8.77. Found: C, 78.99; H; 8.66.

4,11,18,25-Tetraformyl-3,5,7,10,12,14,17,19,21,24,26,28-dodecamethyl[1.1.1.1]metacyclophane (18). To a chilled and stirred slurry of 5 (1.77 g, 3.35 mmol) and Cl_2CHOCH_3 (2.45 mL, 26.8 mmol) in CH_2Cl_2 (30 mL) was added dropwise a solution of $SnCl_4$ (1.57 mL, 13.4 mmol) in CH_2Cl_2 (10 mL). After the addition was complete, an orange solution was obtained. The reaction mixture was stirred overnight, and the precipitate obtained was collected by filtration, washed with acidulated water and EtOH, and dried. Recrystallization from DMSO afforded the tetraaldehyde 18 (1.27 g, 59%) as light yellow microcrystals: mp > 300 °C; ^{1}H NMR (DMSO-d_6) δ 1.15 (s, int Me, 12 H), 2.41, (s, ext Me, 24 H), 3.98 (bs, $ArCH_2Ar$, 8 H), and 10.54 (s, CHO, 4 H); MS, m/z 640 (3.7, M^+), 612 [10, $(M - CO)^+$], 584 [34, $(M - 2CO)^+$], 556 (51, $(M - 3CO)^+$], 528 [100, $(M - 4CO)^+$]. Anal. Calcd for $C_{44}H_{48}O_4 \cdot 1.2(CH_3)_2SO \cdot H_2O$: C, 74.05; H, 7.66; S, 5.11. Found: C, 74.39; H, 7.71; S, 5.26.

Structural Analyses for Metacyclophanes 10, 7, and 6. Details of the X-ray experimental conditions, cell data, data collection, and refinement for compounds 10, 7, and 6 are summarized in Table SI (see supplementary material available paragraph).[25] In molecules 10 and 7, all non-hydrogen atoms were located in an E maps which gave early indication of hydroxyl disorder. A toluene of solvation was also observed, nestled up to the cup of the calix. In the refinement, all non-hydrogen atoms were allowed anisotropic motion except for O1C and O1D (the *minor* oxygen atom sites), which were refined isotropically with a fixed U of 5.0 Å^2. In the final refinement cycles for 10 all four oxygen atom sites O1x (x = A, B, C, D) were constrained geometrically (C–O 1.36 Å) to the relevant C1x carbon with fixed occupancies (obtained previously from difference maps and initial isotropic refinement), the aromatic rings were constrained to be rigid hexagons (C–C 1.395 Å) and hydrogen atoms were positioned on geometric grounds (C–H 0.95 Å) and included as riding atoms in the structure factor calculations; no such costraints were used with molecule 7. The methyl hydrogens appeared to be disordered over two orientations and these were allowed for. The hydroxyl hydrogen could not be located for 10. In 7 two hydroxyl hydrogens (O1A and O1B) were visible in difference maps but the hydrogens of the minor sites (O1C and O1D) could not be located. In compound 6 to check on the Laue symmetry and optimize our chances of getting sufficient accurate data to allow solution of the structure, we collected data over three equivalent sections of reciprocal space and averaged them. The conditions governing diffraction (hkl only present if $-h + k + l = 3n$; $h\bar{h}0l$ only present if $l = 3n$ together with the observed $\bar{3}m$ Laue symmetry, allowed the space group to be either $R32$, $R3c$, or $R\bar{3}c$. The E statistics indicated space group $R\bar{3}c$, which was confirmed by the analysis. Structure solution and refinement were comparable to those for molecule 7. Difference maps revealed that while there was no toluene of solvation adjacent to a calix cup, there was a potential solvent volume in the lattice situated about a site with 32 crys-

(25) The authors have deposited atomic coordinates for structures 6, 7, and 10 with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge, Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

tallographic symmetry. Careful electron-density studies around this site showed five small density peaks, but nothing which would make any chemical sense. We opted for treating these peaks as part of a highly disordered solvent system and assigned them as carbon atoms with occupancy factors appropriate to their peak heights. The figures were prepared with the aid of ORTEPII[26] and PLUTON.[27]

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Acknowledgment. We thank J. Phillips and G. B. Williams for assistance with the data collection of molecule 10. S.P. thanks M.U.R.S.T. for partial support of this work. G.F. thanks NSERC Canada for Grants in Aid of Research.

Supplementary Material Available: Table SI listing details of data collection, structure solution, and refinement for molecules 10, 7, and 6 (1 page). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Concerning Attempts To Synthesize *out*-Bicyclo[4.4.4]tetradec-1-ene Derivatives

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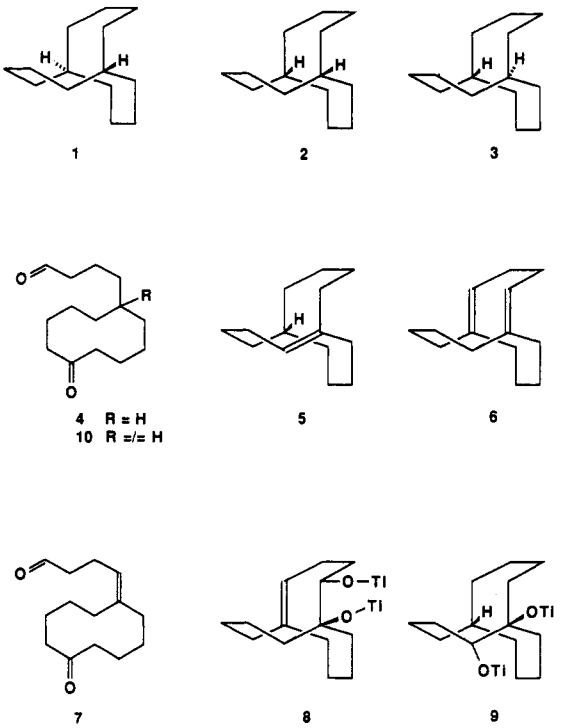
Received May 5, 1992

The keto aldehydes 4-[6-oxo-1-(tetrahydropyranyloxy)cyclodecyl]butanal (17), (*E*)-4-(6-oxocyclodec-1-enyl)butanal (24), and 4-(6-oxocyclodecylidene)butanal (7) have been synthesized. No bicyclo[4.4.4]tetradecadienes were found in the products from the zero-valent titanium reductive cyclization of compound 24. Instead, products arising from transannular reactions of the cyclodecyl ring system were isolated. 1,6-Divinylbicyclo[4.4.0]decane (32) was obtained from the reductive cyclization of keto enal 7. The most plausible route for its formation is through a Cope rearrangement of a bicyclo[4.4.4]tetradecene derivative, suggesting that an *out*-bicyclo[4.4.4]tetradecenylbistitanium pinacolate 8 intervened.

The strain inherent in bicyclo[4.4.4]tetradecane (1) was first suggested in a report[1] in 1974 and given a value derived from MM1 calculations. Further calculations have given rise to the suggestion[2,3] that potentially there are three different isomers of bicyclo[4.4.4]tetradecane, the in,out-isomer 2, the out,out-isomer 1, and the in,in-isomer 3, and that they are increasingly strained, in the order given. Calculations have also given rise to the suggestion[3] that the strain energies inherent in the corresponding bridgehead alkene derivatives are reduced over that of any of the saturated derivatives in this system. The term *hyperstable olefin* has been attached to such alkenes.

Conceptually, one could construct the bicyclo[4.4.4]-tetradecane skeleton by an intramolecular coupling reaction of an intermediate cyclodecyl derivative. In this context, the zero-valent titanium (Ti(0)) coupling reaction[4] of a keto aldehyde such as 4 is appealing since it offers a route to the saturated derivative by way of the bridgehead alkene derivative. The success of this approach to bicyclo[4.4.4]tetradecanes was clearly demonstrated by the synthesis of the in,out-isomer 2, via the in-alkene 5, by McMurry and Hodge.[5] With a more convergent approach than that first reported, it might be possible to delay introduction of the bridgehead hydrogens until after the cyclization had been effected. That is, it might be possible to synthesize a bicyclo[4.4.4]tetradecadiene such as 6.[6]



Reduction of such a diene would be expected to give the out,out-isomer 1. it is worth pointing out that the initial step, in the cyclization of a precursor such as 7, would give an out-alkene 8. The calculated strain[6b] energy for an out-alkene (182 kJ mol^{-1}) is lower than that calculated for an in,out-alkane (198 kJ mol^{-1}). An in,out-alkane intermediate 9 must form in the step leading to the in-alkene 5.

An alternative ploy, which might allow the synthesis of an out,out-derivative, is to put a substituent larger than hydrogen at the pro-bridgehead position in an intermediate

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(2) Alder, R. W. *Acc. Chem. Res.* **1983**, *16*, 321.
(3) Maier, W. F.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1981**, *103*, 1891.
(4) For a recent review see: McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513.
(5) McMurry, J. E.; Hodge, C. N. *J. Am. Chem. Soc.* **1984**, *106*, 6450.
(6) The strain energies associated with, at least, four of the five possible bridgehead dienes have been calculated and shown to be less, or comparable to, that calculated for the in-alkene 5: (a) Alder, R. W.; Arrowsmith, R. J.; Bryce, M. R.; Eastment, P.; Orpen, A. G. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1519. (b) McEwen, A. B.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1986**, *108*, 3951.

0022-3263/92/1957-7109$03.00/0