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Calixradialenes: Calixarene Derivatives with Exocyclic Double Bonds

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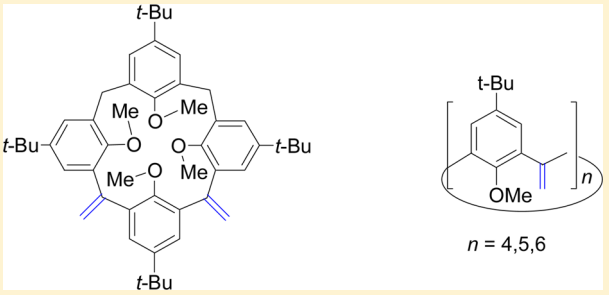
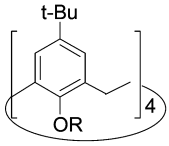
Supporting Information

ABSTRACT: Reaction of dioxocalix[4]arene **7** with MeLi followed by 2-fold elimination of water yielded calixarene **8** possessing exocyclic double bonds at two adjacent bridges. Calixarene **8** exists in tetrachloroethane-d_2 solution at rt, as a 2.3:1 mixture of the *1,3-alternate* and *partial cone* conformers. Keto[*n*]calixarenes (*n* = 5, 6) were prepared via hydrolysis of the bromocalixarenes **11** and **12**, followed by CrO_3 oxidation of the respective hydroxymethylene derivatives. Addition of MeLi to the ketocalix[*n*]arenes (*n* = 4, 5 and 6) followed by elimination of water yielded the corresponding calix[*n*]radialenes. Calix[5]- and calix[6]radialenes adopt in the crystal irregular alternate (i.e., noncone) conformations.

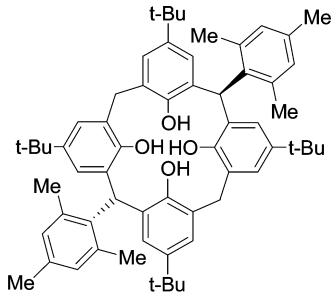


INTRODUCTION

The "classical" calix[*n*]arenes are [1^n] metacyclophane derivatives consisting of a cyclic array of phenol and methylene units.[1] Structural modifications of the methylene bridges of the calixarenes[2] (e.g., via incorporation of substituents,[3−7] or via oxidation to carbonyl groups)[8] may change the intrinsic conformational preferences of the calix scaffold. For example, whereas the parent tetrahydroxycalix[4]arene **1a** adopts a cone conformation, its distally substituted *trans* derivative **2** (with two methylene bridges monosubstituted by bulky mesityl rings) adopts the 1,2-alternate conformation,[9] while its ketocalixarene analogue **3** adopts a 1,3-alternate conformation both in the solid state and in solution.[10]



1a R = H
1b R = Me
1c R = Ac



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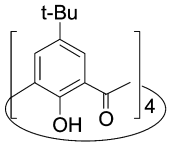

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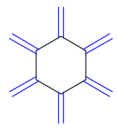
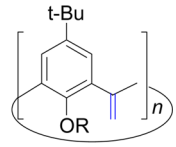
A structural modification of interest involves the incorporation of exocyclic[11] double bond functionalities to the bridges since these may serve as useful precursors for a wide array of organic transformations at the bridges. Such systems possessing several double bonds "radiating" from the center of the macrocycle can be viewed as the calixarene analogues of the [*n*]radialenes (Scheme 1)[12] and therefore can be dubbed "calixradialenes".[13] A noteworthy structural feature shared by both the ketocalixarenes and calixradialenes is the presence of cross conjugation between pairs of geminal rings.

Scheme 1



[6]radialene



calix[*n*]radialene

To the best of our knowledge, calixradialenes have not been reported in the chemical literature so far, but the preparation of a calix[4]arene possessing a single exocyclic double bond at a bridge has been reported by Fantini and co-workers.[14] This derivative (**5**) was prepared via monolithiation of tetramethoxycalixarene **1b**, reaction with diiodomethane of the lithiated derivative, and base-catalyzed elimination of the resulting alkylated product (Scheme 2).[14]

In this contribution we report the preparation of a calix[4]arene derivative with two exocyclic double bonds at adjacent bridges, and calix[*n*]arene derivatives (*n* = 4, 5, and 6) with exocyclic double bonds at all bridges.

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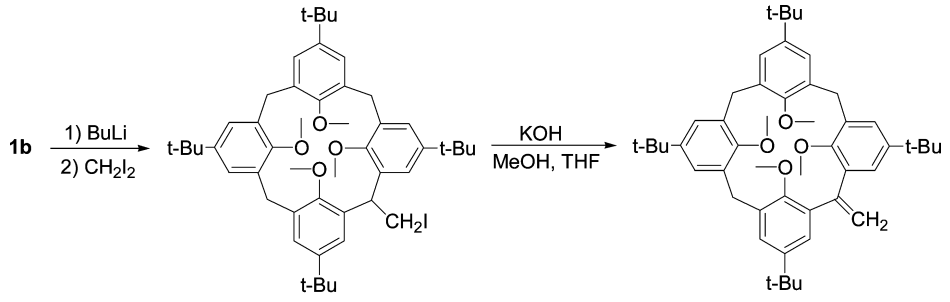
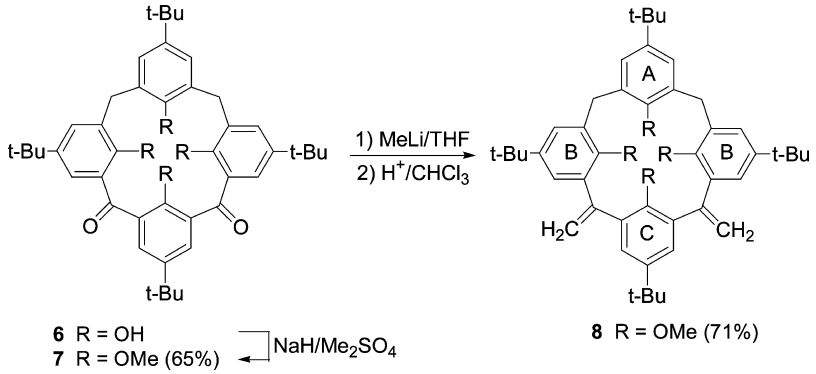
Scheme 2



Scheme 3



RESULTS AND DISCUSSION

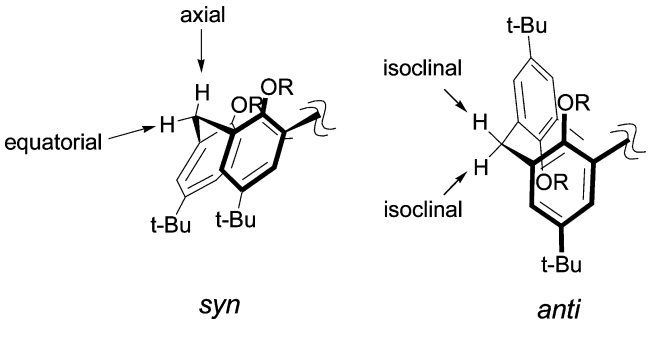
Incorporation of Exocyclic Double Bonds at Bridges of the Calix[4]arene Skeleton. The formal incorporation of exocyclic double bonds at bridges of a calixarene skeleton may be achieved in principle via a two-step process starting from a ketocalixarene derivative with the OH groups protected (e.g., by methyl groups). Addition of MeLi to the carbonyl groups of the ketocalixarene, followed by elimination of water, should result in a calixarene derivative with exocyclic methylene groups. The incorporation of exocyclic methylenes at all bridges by this route requires the availability of the appropriate ketocalixarene (with all bridges oxidized to carbonyl groups). The incorporation of methylenes at specific positions (e.g., at two adjacent bridges) requires either a regioselective addition of the organometallic reagent to some specific carbonyls of the protected ketocalixarene (leading to a derivative with both carbonyl and double bonds at the bridges), or alternatively, the synthetic availability of a calixarene in which only some specific bridges have been oxidized to carbonyl groups.

In the C−C bond-formation step, stereocenters are formed at the bridges. In the case of the reaction of PhLi with the tetramethyl ether of ketocalixarene **3**, all four possible isomers (*rccc*, *rcct*, *rctt*, and *rtct*) were detected in the NMR spectrum of the crude mixture, indicating that the reaction proceeds in nonstereoselective fashion.[15] From a preparative point of view, even if the addition of MeLi to the ketocalixarene proceeds in nonstereoselective fashion, this is most likely inconsequential since it could be expected that all the stereoisomers should afford after dehydration the same calixradialene derivative.

Calix[4]arene with Exocyclic Double Bonds at a Pair of Adjacent Bridges. The starting material for the preparation of the system was dioxocalixarene **6**, prepared as described previously via CrO_3 oxidation of the *partial cone* atropisomer of *p-tert*-butylcalix[4]arene tetraacetate,[16] followed by hydrolysis of the acetate groups.[17] Methylation of this derivative (NaH/dimethylsulfate) yielded its tetramethoxy derivative **7** in 65% yield (Scheme 3).

In contrast to the ^{1}H NMR spectrum of **6** where only a single conformer was detected at low temperature,[17] two patterns of signals in a ca. 6.6:1 ratio are observed in the ^{1}H NMR spectrum of **7** (in $CDCl_3$, rt), in agreement with the presence of two conformers. For the major conformer, the signals of the methylene protons (a pair of doublets) are well separated ($\Delta\delta$ = 1.04 ppm), while for the minor conformer the pair of doublets are closely spaced ($\Delta\delta$ = 0.21 ppm). In a *syn* conformation of a pair of geminal rings, the methylene proton located in an axial position is in proximity to a pair of oxygens and is deshielded relative to the equatorial proton. On the other hand, in an *anti* conformation, the pair of methylene protons are both located at isoclinal positions, and each proton is in proximity to an oxygen atom (Scheme 4). Depending on the symmetry of the macrocycle, pair of isoclinal protons on a given

Scheme 4



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methylene should possess identical or similar chemical shifts. On this basis, the signals of the well-separated pair of methylene protons of the major form suggests *syn* arrangements of pairs of geminal ring attached to a given methylene of **7**, while the closely spaced methylene signals of the minor form suggest *anti* arrangements of these pairs of geminal rings. Since, in addition, pairs of rings connected to a carbonyl in ketocalixarenes favor the *anti* over the *syn* arrangement,[4f,17] the major and minor conformers of **7** can be ascribed to a *partial cone* and *1,3-alternate* forms, respectively.

Reaction of 7 with MeLi. Reaction of **7** with MeLi/THF afforded the dialcohol derivative as a mixture of stereoisomers as shown by the ^{1}H NMR spectrum of the crude product. Without purification, this mixture was dehydrated by treatment with *p*-toluenesulfonic acid in $CHCl_3$ to yield **8**. The ^{1}H NMR spectrum of **8** displays a pattern of signals indicating the presence of conformers, but in contrast to **7**, the populations of the two major conformers are more similar (in 1,1,2,2-tetrachloroethane-d_2 at rt the population ratio is 2.3:1). Two pairs of doublets are observed for the methylene protons. These pairs differ in their chemical shift separations ($\Delta\delta$ = 1.05 and 0.17 ppm), but in contrast to **7**, the closely separated signals are those corresponding to the major (more populated) conformer (Figure 1).

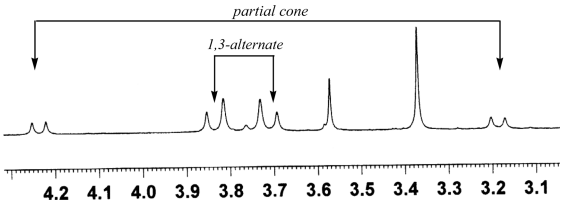
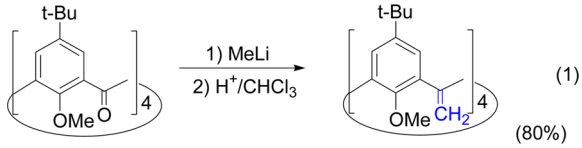


Figure 1. ^{1}H NMR spectrum (400 MHz, $C_2D_2Cl_4$, rt) of the methylene and low-field methoxy region of compound **8**. The closely spaced and well-separated pair of methylene doublets are assigned to *1,3-alternate* and *partial cone* conformations, respectively.

The vinyl protons of each conformer appeared as a pair of doublets and were more closely spaced for the major than for the minor conformer. Assuming that pairs of rings attached to an exocyclic double bond possess the same conformational preferences as those attached to a carbonyl group (i.e., favor an *anti* over a *syn* arrangement), the two conformers observed can be ascribed to the *1,3-alternate* (major conformer) and *partial cone* forms (minor conformer). The characterization of the major conformer as the *1,3-alternate* form is supported by a NOESY spectrum (in CD_2Cl_2). Since the two "B" rings (cf. Scheme 3) are related by mirror symmetry, the signals of these groups could be readily identified in the NMR spectrum by integration. NOE cross peaks are present between the methoxy signals at the two "B" rings and the aromatic protons signals (singlets) at rings A and C. These interactions, indicating steric proximity, suggest *anti* arrangement of pairs of geminal rings and are in agreement with the adoption in solution of a *1,3-alternate* conformation in which each methoxy group is in steric proximity to an aromatic proton at an adjacent ring. In addition to the NOE cross peaks, chemical exchange cross peaks between the two conformers are also observed, indicating mutual interconversion between the conformers.

Preparation of Calix[4]radialene. The starting material for the preparation of calix[4]radialene **10** was ketocalix[4]-arene **9**, which was synthesized as described previously[8a,17] via oxidation of the *1,3-alternate* atropisomer of *p-tert*-butylcalix-[4]arene tetraacetate with excess CrO_3, followed by hydrolysis of the acetate groups and methylation of the hydroxy groups.[18] Reaction of **9** with excess MeLi, followed by acid-catalyzed 4-fold elimination of water from the crude tetra-addition product yielded calix[4]radialene **10** (eq 1). Calix[4]arene **10** displays a simple ^{1}H NMR spectrum with single singlets for the *t*-Bu, methoxy, and aromatic protons, in addition to a singlet for the vinyl protons at δ = 5.28 ppm.



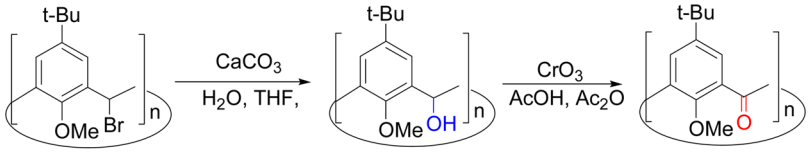
(1)

9 **10**

Hydrolysis of Pentabromocalix[5]Arene 11. Preliminary experiments indicated that reaction of *p-tert*-butylcalix[5]arene pentaacetate with CrO_3 only results in the oxidation of part of the methylene groups,[19] and therefore an alternative method was attempted for the preparation of the desired ketocalix[5]-arene **15**. The chosen approach consisted of a two-step sequence involving hydrolysis of the pentabromocalixarene **11** and oxidation of the resulting pentahydroxy derivative **13** (Scheme 5). Since the oxidation of a hydroxymethine bridge to a carbonyl group is more facile than the corresponding oxidation of a methylene group, a smooth oxidation of **13** to the ketocalix[5]arene was expected. An additional benefit of this route is that the lower-rim groups are already present in their desired protected form (i.e., as methoxy groups) in the resulting ketocalixarene obtained by this route.

The hydrolysis of **11** was attempted in a H_2O/THF mixture in the presence of K_2CO_3. In contrast to the analogous reaction of the larger calix[6]arene **12** (see below), the hydrolysis reaction of **11** was slow and required three days to complete. The ^{1}H NMR spectrum of the crude product of the hydrolysis reaction of **11** (in DMSO-d_6) displays several signals each for the *t*-Bu, methoxy, hydroxy, methine, and aromatic protons. This pattern can be interpreted as indicating that the product adopts several conformations which are "frozen" on the NMR time scale at room temperature, or as indicating that the hydrolysis reaction proceeded in nonstereoselective fashion,

Scheme 5



11: n = 5 *(all-cis)*
12: n = 6 *(all-cis)*

13: n = 5 (mixture of isomers)
14: n = 6 *(all-cis)*

15: n = 5
16: n = 6

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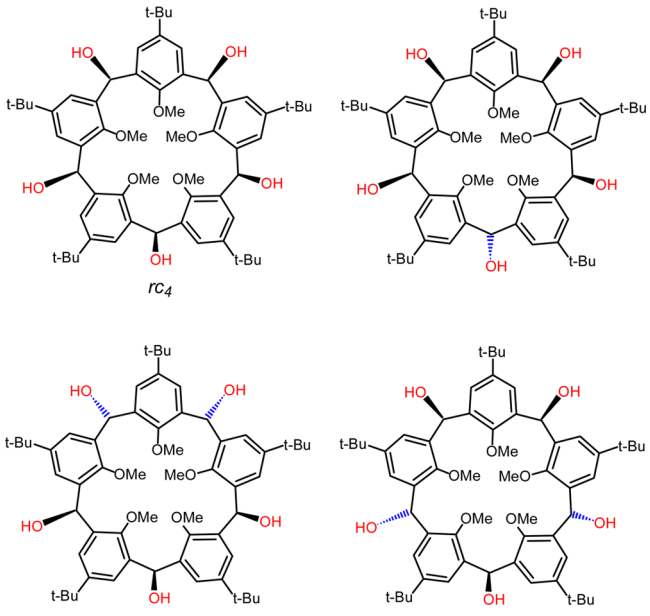
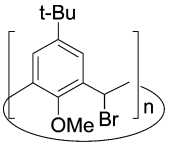
and several stereoisomeric forms of the product were formed. Heating a solution of **13** in DMSO-d_6 to 380 K did not result in a substantial change in the NMR spectrum. On this basis, it can be tentatively concluded that, precluding the presence of unusually high rotational barriers, the large number of NMR signals observed is due to the presence of a mixture of stereoisomers. In principle it could be possible that during the long reaction time required, either the starting material or the product isomerized under the reaction conditions and that this isomerization (and not a nonstereoselective process) is responsible for the mixture of isomers obtained. Examination of the crude reaction mixture by ^{1}H NMR at a shorter reaction time (after 18 h) revealed a mixture of unreacted starting material and products, with the ratio between the isomers of the product essentially identical to that observed after three days of reaction. On this basis, it seems likely that the obtained stereoisomeric mixture of products is the result of the nonstereoselective character of the reaction. We have previously found that alcoholysis reactions of **11** in the presence of 2-propanol or cyclohexanol yields the *all-cis* derivatives in stereoselective fashion, but mixtures of stereoisomers are obtained for the less bulky nucleophiles, methanol and ethanol. Similarly, for the bromocalix[4]arene analogue, **17**, reactions with small and reactive nucleophiles such as azide were nonstereoselective.[4b] It may be possible that the relative small size of water is at least partially responsible for the lack of stereoselectivity in the reaction of **11**.

Four isomers are possible for a pentahydroxy derivative **13** (Scheme 6). Under a time scale where all bond rotations are fast, the *all-cis* (i.e., the rc_4 form) possesses average C_{5v} symmetry, while the rest of the isomers possess average C_s symmetries. Eight strong signals could be clearly detected in the high-temperature ^{1}H NMR spectrum of the *tert*-butyl region of **13** (Figure 2). Since only the *rccc* form is expected to display a single *t*-Bu signal while the rest are expected to display three (in a 1:2:2 ratio), assuming some signal overlap, the presence of eight *t*-Bu signals could indicate the presence of either three or all four stereoisomeric forms.

Scheme 6



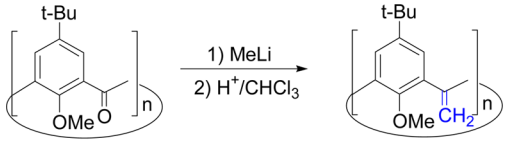


17: n = 4

To determine the number of stereoisomers present in the mixture of **13**, we conducted the acetylation of the OH groups at the bridges with acetic anhydride under acidic conditions. Our hope was that the number of acetyl signals in the resulting product will enable us to decide whether three or all four stereoisomeric forms are present. Surprisingly, inspection of the crude product by NMR indicated that the mixture of isomeric products now contains a major form (the symmetric *all-cis* form of the pentaacetate derivative **18**) (Scheme 7). Clearly under the reaction conditions there was a change in the configuration of the stereocenters at the bridges, a process that requires reversible cleavage of the C(bridge)−O bonds. It seems highly likely that the acidic conditions used for the acetylation reaction facilitate this reversible cleavage and that the *all-cis* product is the major stereoisomer in the mixture since it is the isomer most stable thermodynamically.

The *all-cis* isomer **18** was hydrolyzed under basic conditions (to avoid the possibility of isomerization during the reaction) to yield the pentahydroxy *all-cis* isomer **19** (Scheme 7) which was identified by its simple pattern of signals indicating a highly symmetric structure. The availability of **19** enabled us to unambiguously identify the NMR signals of the *all-cis* isomer in the spectrum of **13**. For example, in the NMR spectrum of **13** shown in Figure 2, the signal at ca. δ 1.16 ppm corresponds to the *t*-Bu group of the *all-cis* (rc_4) isomer **19**,[20] while the remaining seven signals necessarily correspond to the other stereoisomers. Since each of these remaining isomers should display at most three signals, and seven additional *t*-Bu signals are present, we can conclude that in the hydrolysis reaction all four stereoisomeric forms **13** are obtained. From the relative integration of the signals it could be estimated that in the mixture obtained the relative ratios of the *all-cis* and the three remaining forms is approximately 1:4:9:3. The *all-cis* form is therefore the less abundant component in the mixture of isomers obtained.

Preparation of calix[5]radialene. Pentahydroxycalix[5]arene **13** (a mixture of isomers) was used as starting material for the oxidation reaction. Reaction with CrO_3 proceeded readily and afforded the hitherto unknown ketocalix[5]arene **15** (Scheme 5). As observed for other ketocalixarene derivatives,[10,21] a characteristic feature of the ketocalix[5]arene **15** is the low-field chemical shift of the aromatic protons (δ 7.66 ppm) due to the deshielding effects of the carbonyl groups at the bridges. Conversion of **15** into calix[5]radialene **20** was conducted according to eq 2. In general the NMR spectrum of **20** is very similar to that of its lower homologue **10**.



(2)

15: n = 5
16: n = 6

20: n = 5 (32%)
21: n = 6 (36%)

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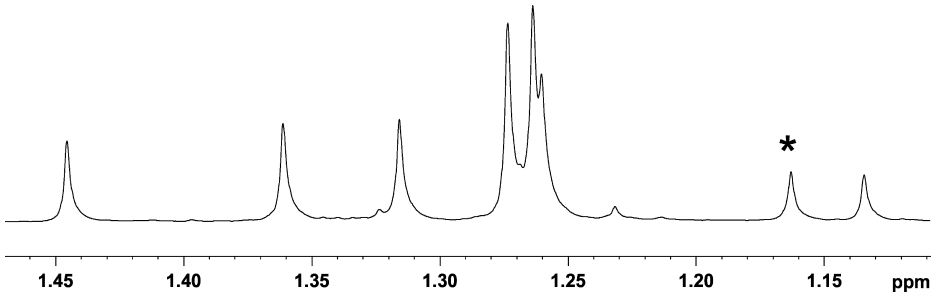
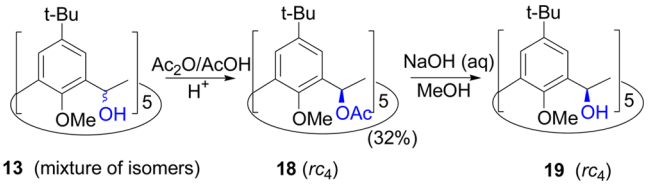


Figure 2. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, 380 K, *t*-Bu region) of the mixture of pentahydroxy derivatives **13** obtained from the hydrolysis of **11**. The starred signal at ca. δ 1.16 ppm corresponds to the *all-cis* (rc_4) isomer.

Scheme 7



13 (mixture of isomers) **18** (rc_4) **19** (rc_4)

A single crystal of calix[5]radialene **20** was grown from acetone. X-ray analysis of **20** indicated that the molecule crystallized without a solvent molecule, and that it adopts in the crystal an irregular "non-cone" conformation (Figure 4) where four contiguous rings are oriented in alternate fashion "up" and "down" and the fifth ring is nearly coplanar with the mean macrocyclic plane (cf. the aryl ring at the left in Figure 3). The torsional angles of the aryl rings with the exocyclic double bonds are within the range of 39.1° and 82.6°.

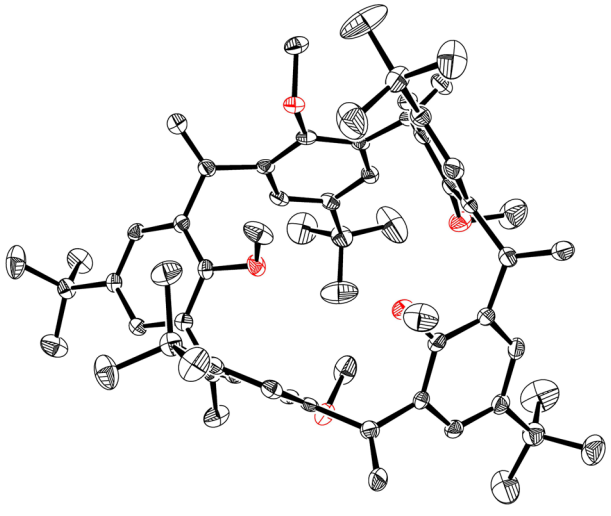


Figure 3. Crystal structure of calix[5]radialene **20**.

Preparation of Calix[6]radialene. Ketocalix[6]arene **16** was prepared previously via CrO_3 oxidation of *p-tert*-butylcalix[6]arene hexaacetate, hydrolysis of the acetate groups, and methylation of the OH groups.[21] The last step, required specific reaction conditions (Cs_2CO_3, dry dimethyl acetamide, MeI, 80 °C, and a pressure reactor) to minimize the formation of monoxanthone and dixanthone products. To avoid the use of a pressure reactor needed for the alkylation step, we decided to synthesize the product by the two-step sequence depicted in Scheme 5. Hexahydroxycalix[6]arene **14**, has been previously prepared by acetolysis of hexabromocalix[6]arene **12** followed by $LiAlH_4$ reduction of the acetate groups of the resulting product, but a shorter method could involve simple hydrolysis of **12**. Indeed, reflux of a mixture of **12**, THF/water, and $CaCO_3$ for 18 h afforded **14** (*all-cis*). The higher reactivity of **12** as compared to **11** (as evidenced by the shorter reaction time needed for the hydrolysis reaction) is most likely due to the larger ring size, which increases the conformational flexibility of the calix scaffold. As a result, conformations where there is conjugation of the pair of geminal rings with a developing cationic orbital are easier to attain, which increases the reactivity of the system.

CrO_3 oxidation of the hexahydroxy derivative proceeded readily and afforded ketocalix[6]arene **16**. Finally, addition of excess MeLi followed by acid-catalyzed 6-fold elimination of water yielded the calix[6]radialene **21** (eq 2). Calix[6]radialene **21** was crystallized from acetonitrile/THF and submitted to X-ray crystallography. The molecule adopts a conformation which can be described as a distorted "1,2,3-alternate" conformation with three adjacent rings oriented in one direction ("up") and the three adjacent rings remaining oriented in the opposite direction ("down") (Figure 4). The calix[6]radialene crystallyzed with a molecule of acetonitrile. The included solvent molecule directs its methyl group toward the calix cavity.

Similar to its homologues **10** and **20**, calix[6]radialene **21** displays in the ^{1}H NMR spectrum single signals for the *t*-Bu, methoxy, aromatic, and methylene groups. However, upon lowering the temperature in CD_2Cl_2 the signals broaden and

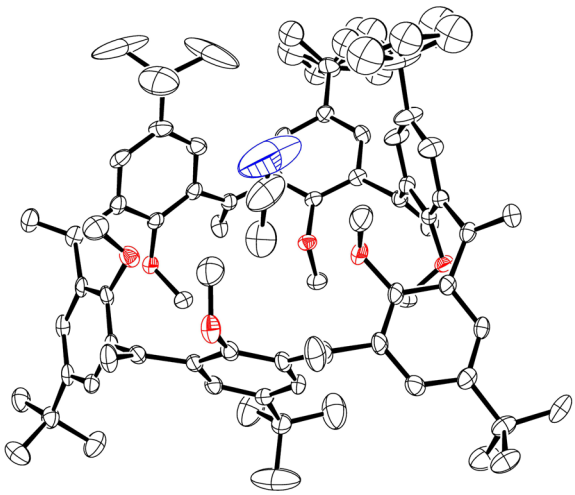


Figure 4. Molecular structure of calix[6]radialene **21**. The two *tert*-butyl groups on the top left of the structure are disordered.

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decoalesce. At 188 K, a very complex spectrum is observed with at least nine different signals for the methoxy groups (Figure S17, Supporting Information [SI]). This large number of signal most likely indicates the presence of two (or more) populated conformers since a single asymmetric conformation should display, at most, six methoxy signals. These conformers are most likely the result of the different possible "up" or "down" arrangements of the rings.

CONCLUSIONS

We have shown that calix[4]arene derivatives possessing at the bridges two exocyclic double bonds as well the calix[*n*]radialene (*n* = 4, 5, 6) derivatives can be synthesized via addition of MeLi to the corresponding ketocalixarenes, followed by elimination of water.

The approach presented for the introduction of double bonds at the bridges, and the one reported by Fantini and coworkers,[14] are complementary. Whereas the C−C bond-formation step in Fantini's approach involves lithiation of a methylene bridge and reaction with a nucleophile, our approach involves reversing the polarity of the carbon atom at the bridge via its oxidation to carbonyl, followed by a reaction with a nucleophile. Since reaction of **1b** with excess of an organolithium reagent usually results in the formation of the monoalkylated derivative, Fantini's approach should be the method of choice for the incorporation of a single double bond, whereas the present approach may be preferred if several exocyclic double bonds are desired in the target calixarene derivative.

EXPERIMENTAL SECTION

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetramethoxy-2,14-dioxocalix[4]arene (7). To a stirred solution of **6** (1 g, 1.48 mmol) in dry THF (75 mL) were added dry DMF (5 mL), NaH (60% dispersion in mineral oil, 2g) in small portions, followed by dimethyl sulfate (8 mL, 8.4 mmol). The mixture was heated at reflux overnight under an argon atmosphere and cooled to room temperature. After neutralization of the NaH (5 mL MeOH) and of the excess of dimethyl sulfate (5 mL conc. ammonium hydroxide), the solvents were evaporated, and the residue was dissolved in chloroform (40 mL). The solution was washed successively with brine, dil. HCl, and brine, was dried ($MgSO_4$) and evaporated. The residue was triturated with ethanol and filtered to yield 0.65 g (60%) of pure **7**, mp 235 °C (dec).

^{1}H NMR (400 MHz, $CDCl_3$) major conformer δ 7.71 (d, J = 2.4 Hz, 2H), 7.58 (d, J = 2.4 Hz, 2H), 7.39 (s, 2H), 6.58 (s, 2H), 4.41 (d, J = 12.8 Hz, 2H), 3.76 (s, 3H), 3.38 (s, 6H), 3.37 (partially overlapping d, J = 12.8 Hz, 2H), 1.85 (s, 3H), 1.37 (s, 18H), 1.33 (s, 9H), 0.93 (s, 9H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ197.9, 197.8, 196.7, 157.4, 155.8, 154.9. 151.8, 146.8, 146.5, 145.7, 145.0, 144.3, 143.9, 137.0, 136.1, 135.4, 134.5, 133.9, 133.0, 132.6, 132.5, 131.6, 131.2, 130.5, 130.4, 130.2, 126.3, 125.7, 125.3, 124.9, 63.0, 62.9, 62.8, 61.7, 60.9, 60.4, 59.3, 58.5, 58.4, 34.6, 34.57, 34.54, 34.4, 34.3, 33.9, 33.7, 31.5, 31.44, 31.41, 31.40, 31.30, 31.28, 31.00, 30.99 ppm. HRMS (ESI-QTOF) m/z 733.4474 (M + H$^+$), calcd for $C_{48}H_{61}O_6$: 733.4468.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetramethoxy-2,14-dimethylenecalix[4]arene (8). To a solution of **7** (2.0 g, 2.73 mmol) in dry THF (160 mL) at 0 °C was added 7.5 mL MeLi (1.6 M in diethyl ether, 12 mmol). The mixture was stirred under argon at 0 °C for 30 min and then at room temperature for an additional 2 h. The unreacted MeLi was quenched by addition of MeOH in small portions. After evaporation of the solvents, the residue was dissolved in chloroform and the solution washed with aq HCl (1 M) and brine and was then dried and evaporated. The crude methylation product was dissolved in chloroform (50 mL), *p*-toluenesulfonic acid (60 mg) was added, and the solution was heated to 60 °C for 2.5 h. The cooled solution was washed with aq $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated. The residue was triturated with cold ethanol and filtered to yield 1.4 g (71%) **8**, mp 240−242 °C.

^{1}H NMR (400 MHz, $C_2D_2Cl_4$, rt) (major conformer) δ 7.20 (s, 2H), 7.11 (d, J = 2.4 Hz, 2H), 7.09 (d, J = 2.4 Hz, 2H), 7.03 (s, 2H), 5.28 (d, J = 2.2 Hz, 2H), 5.24 (d, J = 2.2 Hz, 2H), 3.84 (d, J = 15.0 Hz, 2H), 3.71 (d, J = 15.0 Hz, 2H), 2.94 (s, 6H), 2.80 (s, 3H), 2.43 (s, 3H) 1.29 (s, 9H), 1.26 (s, 18H), 1.23 (s, 9H) (minor conformer) 7.24 (d, J = 2.4 Hz, 2H), 7.19 (s, 2H), 6.74 (s, 2H), 5.48 (d, J = 2.2 Hz, 2H), 5.12 (d, J = 2.2 Hz, 2H), 4.24 (d, J = 12.6 Hz, 2H), 3.19 (d, J = 12.6 Hz, 2H), 3.57 (s, 3H), 3.37 (s, 6H), 1.62 (s, 3H), 1.35 (s, 9H), 1.24 (s, 18H), 1.02 (s, 9H) ppm.

^{13}C NMR (125 MHz, CD_2Cl_2) δ 155.2, 154.9, 154.2, 154.1, 153.8, 152.5, 152.1, 151.8, 149.6, 149.4, 149.0, 148.7, 145.4, 145.3, 144.9, 144.6, 143.9, 143.7, 136.7, 136.4, 136.0, 135.9, 135.8, 134.8, 134.7, 134.0, 133.7, 133.4, 127.6, 127.3, 127.0, 126.7, 125.95, 125.89, 123.7, 125.2, 124.9, 124.8, 123.8, 117.9, 117.6, 116.9, 116.6, 60.2, 60.1, 59.2, 59.0, 58.7, 57.7, 38.2, 38.0, 37.1, 34.0, 33.9, 33.88, 33.82, 33.7, 33.6, 31.9, 31.3, 31.2, 31.18, 31.1, 30.0, 29.7, 29.3 ppm. HRMS (ESI-QTOF) m/z 746.5175 (M + NH_4^+), calcd for $C_{50}H_{68}NO_4$: 746.5148.

5,11,17,23-Tetra-*tert*-butyl-2,8,14,20-tetramethylene-25,26,27,28−tetramethoxycalix[4]arene (10). To a solution of **9** (0.5 g, 0.66 mmol) in 50 mL dry THF at 0 °C was added MeLi (3.4 mL, 1.17 M, 4 mmol). The mixture was stirred under an inert atmosphere for 2 h at room temperature and then quenched with dil HCl. After extraction with chloroform, the organic phase was dried (Na_2SO_4) and evaporated. The residue was dissolved in 30 mL toluene, and *p*-toluenesulfonic acid (25 mg) was added, After heating to reflux for 18 h, the solvent was evaporated and the residue treated with an aqueous solution of Na_2SO_4 and extracted with chloroform. The organic phase was evaporated and the residue recrystallized from chloroform/methanol to yield 0.4 g (0.53 mmol, 80%) calix[4]-radialene **10**, mp 295−305 °C.

^{1}H NMR (500 MHz, $CDCl_3$, rt) δ 7.26 (s, 8H), 5.28 (s, 8H), 2.88 (s, 12H), 1.32 (s, 36H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 149.1, 145.2, 135.8, 125.6, 177.5, 59.0, 34.1, 31.5 ppm. HRMS (ESI-QTOF) m/z 775.4695 (M + Na$^+$), calcd for $C_{52}H_{64}O_4Na^+$: 775.4702.

5,11,17,23,29-Penta-*tert*-butyl-2,8,14,20,26-pentahydroxy-31,32,33,34,35-pentamethoxycalix[5]arene (13) (mixture of stereoisomers). To a solution of pentabromocalix[5]arene **11** (8 g, 6.27 mmol) in 360 mL THF was added 48 mL water and 60 g $CaCO_3$, and the mixture was heated to reflux for 3 days. After cooling to rt, the solid was filtered, and the filtrate was evaporated to yield 5.3 g (88%) of the stereoisomeric mixture of pentahydroxy derivatives **13**, mp 350 °C (dec). The product was used without purification in the next oxidation step.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.68 (Ar, d (J = 2.4 Hz)), 7.63 (Ar, s), 7.49 (Ar, d (J = 2.4 Hz)), 7.43 (Ar, m), 7.34 (Ar, m), 7.30 (Ar, s), 7.24 (Ar, d (J = 2.4 Hz)), 7.19 (Ar, m), 7.16 (Ar, m), 6.91 (Ar, s), 6.67 (Ar, s), 6.27 (CH, d(J = 5.2 Hz)), 6.04 (CH, d (J = 5.2 Hz)), 5.85 (CH, m), 5.72 (CH, d (J = 5.6 Hz)), 5.69 (CH, d (J = 4.8 Hz)), 5.49 (OH, d (J = 4.8 Hz)), 5.42 (OH, m), 5.38 (OH, d (J = 4.8 Hz)) 5.35 (OH, d (J = 5.2 Hz)), 5.28 (OH, d (J = 6 Hz)), 3.55 (OMe, s), 3.48 (OMe, s), 3.26 (OMe, s), 2.72 (OMe, s), 2.47 (OMe, s), 2.22 (OMe, s), 2.11 (OMe, s), 1.40 (*t*-Bu, s), 1.35 (*t*-Bu, s), 1.27 (*t*-Bu, s), 1.25 (*t*-Bu, s), 1.19 (*t*-Bu, s), 1.10 (*t*-Bu, s), 1.05 (*t*-Bu, s) ppm ; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 154.5, 153.6, 153.4, 152.7, 152.4, 152.2, 151.9, 151.8, 145.3, 145.1, 145.0, 144.8, 144.7, 144.4, 140.1, 138.5, 138.12, 138.08, 138.0, 137.9, 137.8, 137.7, 137.3, 137.1, 128.9, 126.8, 126.5, 125.8, 125.2, 124.4, 124.1, 123.8, 123.4, 123.2, 69.1, 68.8, 67.9, 66.2, 64.5, 63.4, 63.3, 63.1, 62.9, 62.8, 62.5, 61.7, 61.3, 61.2, 60.8, 35.3, 35.1, 35.0, 34.9, 34.8, 34.7, 32.3, 32.24, 32.21, 32.1, 32.0, 31.9, 31.4, 26.1, 22.0 ppm. HRMS (ESI-QTOF) m/z 978.6113 (M + NH_4)$^+$, calcd for $C_{60}H_{84}NO_{10}$: 978.6095.

5,11,17,23,29-Penta-*tert*-butyl-31,32,33,34,35-pentamethoxy-2,8,14,20,26-pentaoxocalix[5]arene (15). To a mixture of **13** (5.2 g, 5.4 mmol), acetic anhydride (350 mL), and acetic acid (20 mL) was slowly added CrO_3 (10 g, 0.1 mol) and the mixture was heated to reflux for 3 h. After cooling to rt, chloroform (300 mL) was

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added to the green mixture, the organic phase was separated, and washed three times with 250 mL portions of 1 M HCl and with portions of water (200 mL) until the washings were colorless. The organic solution was concentrated to 20 mL by evaporation, and acetonitrile (50 mL) was added. After standing for several days at rt, crystals of pure **15** were formed that were collected by filtration (2.82 g, 55%), mp 338−339 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.66 (s, 10H), 3.08 (s, 15H), 1.31 (s, 45H) ppm ; ^{13}C NMR ($CDCl_3$, 100 MHz); δ 196.7, 155.5, 146.5, 134.2, 129.8, 63.4, 34.9, 31.5 ppm. HRMS (ESI-QTOF) m/z 968.5310 $(M + NH_4)^+$, calcd for $C_{60}H_{74}NO_{10}$: 968.5313.

5,11,17,23,29-Penta-*tert*-butyl-2,8,14,20,26-pentamethylene-31,32,33,34,35-pentamethoxycalix[5]arene (20). To a mixture of **15** (1.17 g, 1.23 mmol), NaH (0.3 g, 60% in mineral oil), and dry THF (100 mL) at 0 °C under argon, was slowly added during 7 min MeLi (9 mL, 3% solution in methyltetrahydrofuran/cumene, 10.53 mmol). After the addition was complete, the mixture was stirred for 30 min at 0 °C and for an additional 90 min at rt. After quenching the mixture with 60 mL MeOH, the solvents were evaporated, and the orange-red residue was dissolved in 160 mL chloroform. The solution was washed twice with 80 mL 1 N HCl and twice with water and the solvent evaporated. The orange residue was dissolved in chloroform (50 mL), and *p*-toluenesulfonic acid (50 mg) was added. After gentle reflux for 30 min, the solution was cooled, 50 mL of chloroform were added and the dark organic phase was washed twice with 20 mL of an aq saturated solution of $NaHCO_3$, and twice with water. After evaporation of the solvent, the residue was recrystallized from chloroform/acetonitrile (or chloroform/acetone) to yield 370 mg (32%) **20**, mp 269−270 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.21 (s, 10H), 5.37 (s, 10H), 2.92 (s, 15H), 1.26 (s, 45H) ppm ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.7, 147.7, 145.4, 135.9, 127.3, 119.0, 60.4, 34.5, 31.7 ppm. HRMS (ESI-QTOF) m/z 958.6357 $(M+NH_4)^+$, calcd for $C_{65}H_{84}NO_5$: 958.6350.

5,11,17,23,29-Penta-*tert*-butyl-31,32,33,34,35-pentamethoxy-2,8,14,20,26-pentaacetoxycalix[5]arene (*all-cis* isomer, 18). To a solution of **13** (1.1 g, 1.14 mmol) in acetic anhydride (80 mL) and glacial acetic acid (20 mL) were added four drops of conc. H_2SO_4, and the mixture was heated to reflux for 6 h. After cooling to rt, the mixture was poured into 100 mL of ice water. The solid that formed overnight was filtered and dissolved in 100 mL chloroform. The solution was washed consecutively with a sat. aq solution of $NaHCO_3$ and water, and the organic phase was concentrated to 10−20 mL. After addition of 50 mL methanol the solvents were allowed to slowly evaporate. The crystalline precipitate that initially formed over several days was filtered, yielding **18** (0.43 g), mp 334−335 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49 (s, 5H), 7.21 (s, 10H), 3.67 (s, 15H), 2.11 (s, 15H), 1.09 (s, 45H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.0, 153.1, 146.4, 133.4, 124.5, 66.7, 62.4, 34.7, 31.6, 21.6 ppm. HRMS (ESI-QTOF) m/z 1188.6634 M + $NH_4)^+$, calcd for $C_{70}H_{94}NO_{15}$:1188.6623.

5,11,17,23,29-Penta-*tert*-butyl-2,8,14,20,26-pentahydroxy-31,32,33,34,35-pentamethoxycalix[5]arene (*all-cis* isomer, 19). A mixture of **18** (0.2 g, 0.17 mmol), 2 M aq NaOH (30 mL), and methanol (30 mL) was heated to reflux for 6 h. After cooling to rt, conc HCl was added until pH = 1, and the white solid formed was filtered giving 0.15 g solid. Recrystallization from $CHCl_3$/MeOH afforded 0.12 g (73%) of pure **19**, mp 312−313 °C,

^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.30 (s, 10H), 6.27 (d, J = 4.8 Hz, 5H), 5.44 (d, J = 4.8 Hz, 5H)„ 3.56 (s, 15H), 1.10 (s, 45H) ppm ; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 152.7, 145.3, 137.9, 123.8, 63.3, 62.5, 34.9, 32.0 ppm. HRMS (ESI-QTOF) m/z 978.6095 [M + $NH_4)^+$, calcd for $C_{60}H_{84}NO_{10}$: 978.6095.

5,11,17,23,29,35-Hexa-*tert*-butyl-2,8,14,20,26,32-hexahydroxy-37,38,39,40,41,42-hexamethoxycalix[6]arene (14). A mixture of hexabromocalix[6]arene **12** (6.65 g, 4.35 mmol), 300 mL THF, 49 mL water, and 16.63 g $CaCO_3$ was refluxed for 18 h. After gravitational filtration of the carbonate salt, the filtrate was evaporated in vacuum to yield 4.6 g (92%) crude **25**. The spectroscopic properties of the product were identical to those previously reported.[4c] The product was used without purification in the next oxidation step, but if necessary it may be purified by recrystallization from methanol/chloroform.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-2,8,14,20,26,32-hexaoxocalix[6]arene (16). A mixture of powdered **14** (8 g, 6.94 mmol), 610 mL acetic anhydride, and 16 mL glacial acetic acid was heated to 70 °C, and then chromium trioxide (16.7 g, 0.166 mol) was added slowly. The mixture was heated to reflux for 3 h. After cooling to rt, chloroform (350 mL) was added, and the mixture was washed several times with aq HCl (0.05 M) until the washing become colorless. The organic phase was evaporated and the residue recrystallized from chloroform/ethanol to yield 3.8 g (48%) **16**. The spectroscopic properties of the product were identical to those previously reported.[21]

5,11,17,23,29,35-Hexa-*tert*-butyl-2,8,14,20,26,32-hexamethylene-37,38,39,40,41,42-hexamethoxycalix[6]arene (21). *(a) Preparation of the hexaalcohol intermediate (mixture of isomers).* To a stirred suspension of **15** (1.5 g, 1.3 mmol) in 130 mL dry THF cooled to 0 °C was slowly added MeLi (10 mL, 3% solution in 2-methyltetrahydrofuran/cumene, 11.7 mmol) over 8 min. After stirring for 30 min, the ice bath was removed and the mixture stirred at room temperature for 1.5 h. The mixture was quenched with methanol, and the solvents were evaporated. The orange-red residue was dissolved in 160 mL chloroform, and the solution was washed twice with 80 mL HCl 1 M (the color changed to yellow). The organic phase was washed again with water and evaporated, and the residue was recrystallized from chloroform/methanol to give 600 mg of the hexaalcohol intermediate, mp 350−351 °C. (b) *Elimination of water.* To 900 mg of the hexaalcohol intermediate dissolved in 190 mL toluene was added *p*-toluene sulfonic acid (200 mg), and the mixture was refluxed for 4 h. After cooling, the mixture was washed twice with 40 mL saturated sodium bicarbonate solution and once with water, and the organic phase was evaporated. The crude residue was dissolved in 80 mL chloroform, concentrated in vacuum, and crystallized from chloroform/methanol to give 800 mg of **21**, mp 242−243 °C. The overall yield for the sequence is 37%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (s, 12H), 5.53 (s, 12H), 2.96 (s, 18H), 1.22 (s, 54H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 153.0, 146.6, 145.6, 135.7, 127.5, 118.6, 59.7, 34.5, 31.7 ppm. HRMS (ESI-QTOF) m/z 1151.7099 (M + Na^+), calcd for $C_{78}H_{96}O_6Na$: 1151.7105.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C spectra of compounds **7**, **8**, **10**, **15**, **18**, **19**, and **20** and **21** and crystallographic data (cif files) for compounds **20** and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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