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Conformational Control in the Synthesis of Mixed Tetraethers of Calix[4]arene

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Abstract: A series of mixed tetraethers of calix[4]arene in which two distal substituents are methyl acetates and the other two are 1-alkenyl groups with 3-6 carbon atoms in the chain have been prepared by two routes which differ in the order in which the group (methyl acetate or alkenyl) were introduced. The final conformational outcome depends on which group was introduced first. Cone (major) and 1,3-alternate (minor) conformers resulted when the alkenyl groups were introduced first. When the order was reversed, only partial cone conformers were produced. Formation of cone/1,3-alternate conformers via one route and partial cone conformers by the alternative route may be explained on the basis of a template effect operating at the fourth alkylation stage and involving the sodium counterion of the base.

The expressions "lower rim through the annulus" and "upper rim through the annulus" describe the semi-rotational movement of the hydroxy groups or of the para aryl groups, respectively, through the central cavity of calixarenes. As a consequence, calix[4]arenes have access to four distinctive conformations: cone, partial cone, 1,2-alternate and 1,3-alternate.[1,2] Upper rim through the annulus motion is not possible with calix[4]arenes even when the para aryl substituent is as small as hydrogen, while the alternative lower rim motion can be restricted by the size of the substituents attached to the phenolic hydroxyl groups. The available evidence suggests that methoxy groups are too small to prevent rotation whereas ethoxy and propoxy groups are too large to pass through the annulus and, consequently, at room temperature, these latter derivatives exist in fixed, non-interconverting conformations.[3] However, at temperatures above 100°C interconversion of the tetra ethoxy conformations does occur.[4] Temperature dependent conformational interconversion has not been observed with the n-propyl ethers, though the substituent effect appears to be quite finely balanced since Puddephatt[5] and co-workers have recently observed a slow interconversion of the partial cone and 1,3-alternate conformers of the tetra-O-propargyl ether of calix[4]arene at room temperature.

The tetra-O-methyl ether exists in $CDCl_3$ solution at room temperature as a mixture of all four conformers interconverting rapidly on the NMR timescale with the partial cone as the key intermediate since each of the other three conformers can be reached by a single rotation of one of the aryl subunits of the partial cone.[6,7] The relative stabilities of the tetra-O-methyl calix[4]arene ethers are: partial cone (most stable) > 1,2-alternate > cone > 1,3-alternate.

Although it can be difficult to predict the conformation of calix[4]arenes alkylated with groups larger than methyl, there is now substantial evidence to indicate that factors such as the nature of the para substituents, the base and solvent used, and the reaction temperature, may all play a role. An important study in this area was made by Shinkai and co-workers[4] who investigated the effect of different bases on the tetra-O-alkylation of p-*tert*-

butylcalix[4]arene. Use of 1-bromopropane and sodium hydride resulted in cone and partial cone products in approximately equal amounts with a trace of the 1,3-alternate conformer. However, reaction with caesium carbonate as base produced partial cone and 1,3-alternate conformers in a 1:2 ratio. These authors concluded that while the cone conformer results when the metal cation, e.g. Na^+, can act as a template, the 1,3-alternate results when the cation cannot, e.g. when Cs^+ is used. The conformations of the partially alkylated intermediates may also influence the final outcome. A case in point is the alkylation of p-*tert*-butylcalix[4]arene using sodium hydride as the base in THF-DMF: in ethylation the conformation of the tetraalkylated product is determined at the fourth stage whereas that of 1-propylation is determined at the third stage.

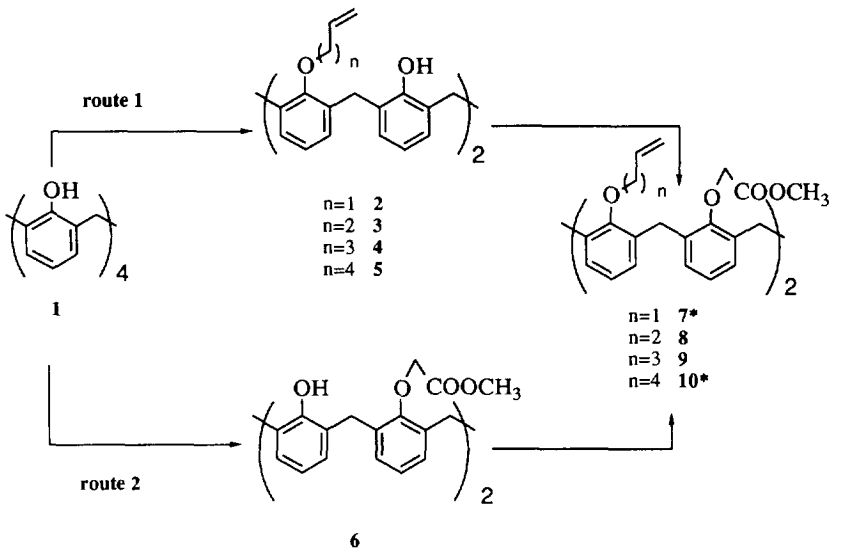
The study by Reinhoudt and co-workers[8] of the relative stabilities of conformers of both partially and fully alkylated calix[4]arenes indicates that the final outcome is the result of a balance of energies involving Van der Waals and bond energy on the one hand and electrostatic and hydrogen bond energy on the other. The conclusions arrived at from various computational studies agreed well with experimental observations in most cases.

During recent work on the synthesis of bridged, polyfunctional calix[4]arenes[9] we have uncovered an additional factor at play in the synthesis of tetraethers with two different substituents, namely the *order* in which the substituents are introduced. The target molecules were tetraethers, each with two distally disposed alkenyl groups and two methyl acetate groups on the lower rim (**Scheme 1**). Both these groups should be sufficiently bulky to prevent rotation through the annulus of the aryl subunit to which they are attached.

RESULTS AND DISCUSSION

Calix[4]arene **1** was transformed into a total of four tetraethers **7-10** (**Scheme 1**) via the two-step sequence of alkylation with the appropriate alkenyl bromide and potassium carbonate in acetone to form the disubstituted intermediates **2-5**, followed by a second alkylation using methyl bromoacetate and sodium hydride in THF (route 1). The synthesis of tetraethers **8** and **9** was repeated via the alternative sequence (route 2) of adding the methyl acetate residues first to form the disubstituted intermediate **6**, followed by, again with sodium hydride as the base in THF, the two alkenyl groups. All five disubstituted intermediates **2-6** were obtained in good yield (60-85 %), each in a stable cone conformation. The four tetraethers **7-10** were also obtained in good yield (70-80%), but the conformations of **8** and **9** were route dependent.

Compounds **7-10** (**Scheme 2**), when prepared by route 1, were obtained as mixtures of cone (major) and 1,3-alternate (minor) conformers with the exception of **8** which existed exclusively in the cone conformation. The individual conformers of **7**, **9** and **10** were separable by flash chromatography and their structures were assigned on the basis of their ^1H NMR spectra which also confirmed that they were conformationally frozen at ordinary temperatures. Both conformations of each compound displayed a single AB system for the hydrogen atoms of the methylene bridges and a single set of signals for each different group attached to the phenolic oxygen atoms. NOESY NMR experiments were used to corroborate the conformations of the 1,3-alternate isomers. For example, the spectra of **9** revealed an interaction (**Figure 1**) between each one of the hydrogens of the methylene bridge and the methylenes adjacent to the oxygen of the adjacent subunit. Furthermore there was also a noe interaction between the *meta* hydrogen atoms of each aryl subunit and the bridging methylene groups which, as previously, depended on their relative positions. These effects are indicative of the 1,3-alternate conformation.



Scheme 1: (*) only by route 1

Although several 1,3-alternate derivatized calix[4]arenes are known,[1,2] the majority have four identical substituents on the lower rim or are 1,3-bridged[10] or bis-crown[11] derivatives. Examples similar to those discussed here with two different substituents are much less common. Gutsche and co-workers[12] have provided an example in which cone or 1,3-alternate conformers are produced selectively in the benzylation of a calix[4]arene with different substituents on the upper rim. Here the 1,3-alternate conformer was obtained using caesium carbonate in DMF, though with four identical substituents on the lower rim.

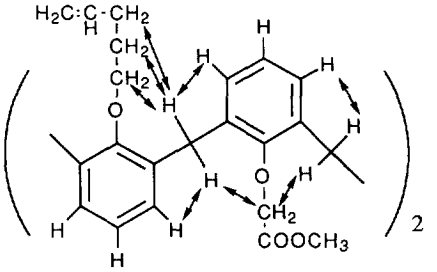
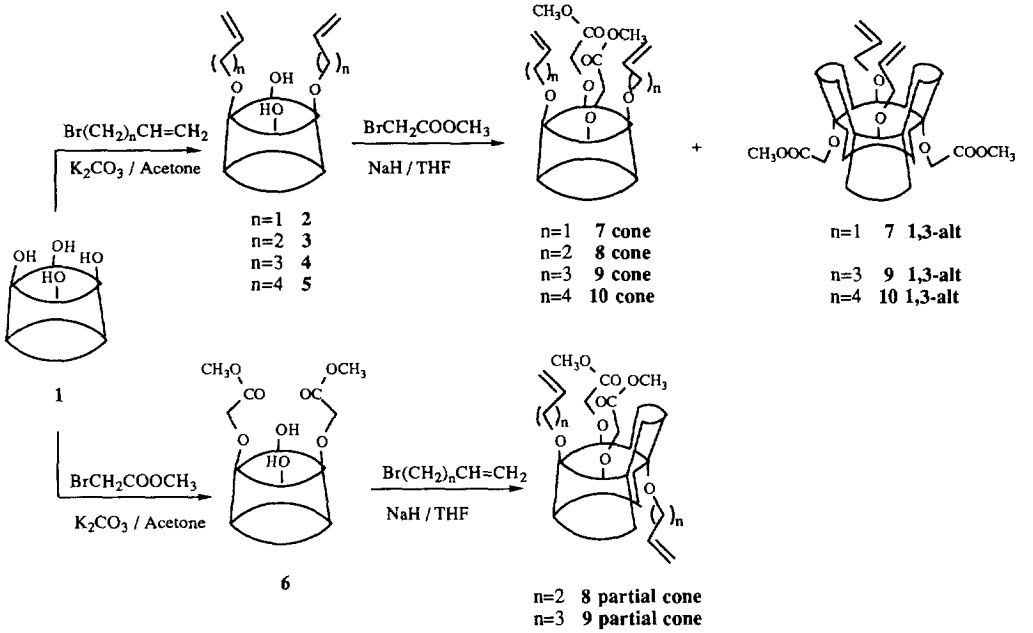


Figure 1

When tetraethers **8** and **9** were synthesised by route 2 only partial cone conformers were obtained with the lone inverted phenolic subunit carrying the alkenyl rather than the methyl acetate side chain. (**Scheme 2**). The ^{1}H NMR spectra of **8-pc** and **9-pc** exhibited two AB systems for the hydrogen atoms of the methylene bridges and two different set of signals for the two alkenyl chains indicating that they were non-equivalent.

The dependence of product conformation on the order in which the two different substituents are introduced can be interpreted with reference to **Scheme 3**. When route 1 was used the dialkylated intermediates **2-5** were all produced in stable cone conformations, but this fact does not preclude conformational inversion of one or both of the two remaining hydroxyl groups during further alkylation. For example, Gutsche and Reddy[13] have found that while the 1,3-(distal) dibenzyl ether of p-*tert*-butylcalix[4]arene is fixed in the cone conformation, on further

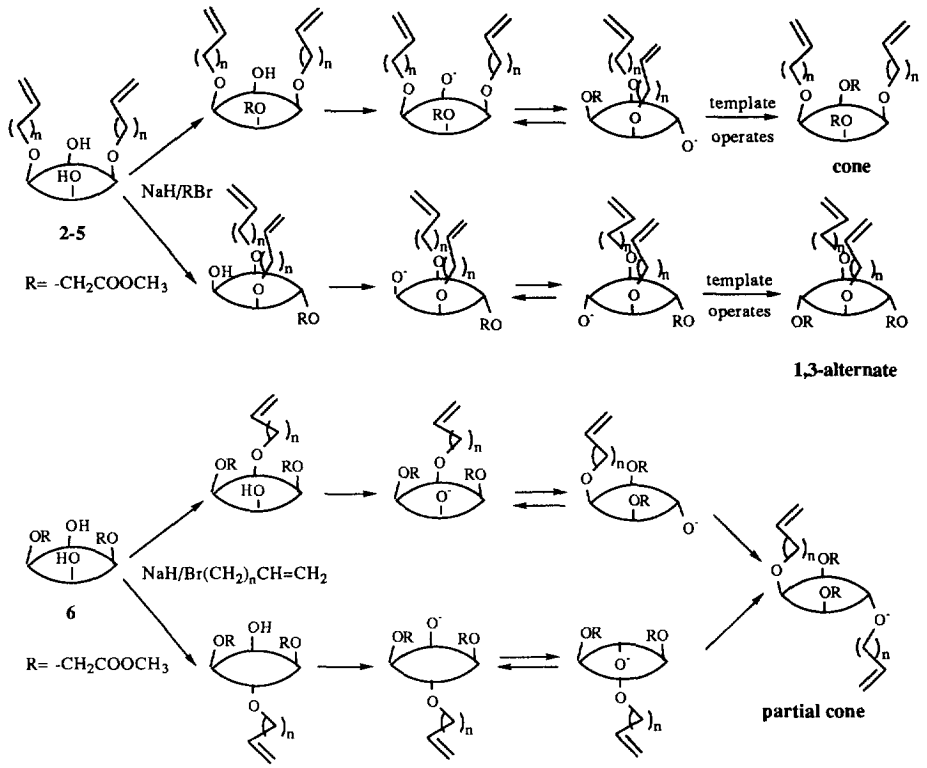
benzylation, non-interconverting cone and partial cone tetraethers resulted. In our study, dialkenyl ethers **2-5** yielded tetraethers **7-10**, respectively, which, with the exception of **8**, were mixtures of cone and 1,3-alternate conformers, the latter the result of inversion of both phenolic rings.



Scheme 2

Removal of the first proton in **2-5** by sodium hydride eliminates one stabilising intramolecular hydrogen bond and the resulting phenoxide subunit becomes conformationally mobile until trapped by an incoming alkyl acetate residue. The formation of **7**, **9** and **10** in both cone and 1,3-alternate conformations shows that trapping of the phenoxide subunits can occur at both extremes of rotation through the annulus with the location of the first alkyl acetate group directing the introducton of the second. This interpretation is supported by the fact that partial cone conformers, which would result if the second phenoxide group did not invert, were not among the products. That the first alkyl acetate residue directs the second onto the same face of the molecule in a *syn* fashion may be attributed to a template effect imposed by the sodium counterion through coordination to the ester carbonyl groups and the ethereal oxygen atoms. There is already much evidence for selective complexation of sodium ion by calix[4]arene alkyl ester derivatives.[14]

In route 2 where tetraethers **8** and **9** were obtained from diester diphenol **6** other factors come into play (**Scheme 3**). As with its disubstituted counterparts **2-5** above, this intermediate also exists in a stable cone conformation with a similar freedom to rotate one or both of its phenoxide subunits under the reaction conditions for further alkylation to form **8** and **9**. However, unlike the situation encountered in route 1, addition of the first alkenyl group to **6** does not enhance the binding environment around the sodium counterion to the extent that it directs the second alkenyl group into the *syn* geometry. Consequently, the fourth and final substituent enters into and fixes the preferred partial cone arrangement. Although simple ethers of calix[4]arene do bind sodium cation, extraction and stability constant measurements show that they are much weaker binders than alkyl acetate groups.[14]

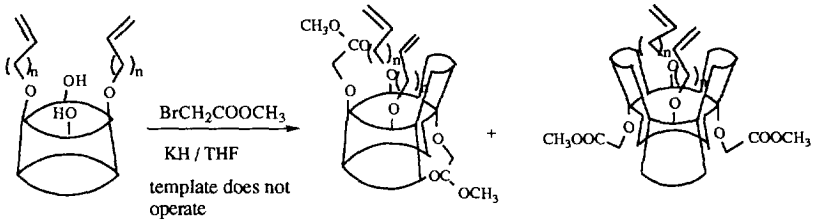


Scheme 3

To further demonstrate that a template effect does not play an important role in route 2 because of the indifferent complexing ability of simple alkyl ether podands, we conducted the complete alkylation of p-*tert*-butylcalix[4]arene using 5-bromopentene and sodium hydride in THF. The result was the formation of tetraether **11** as a 2:3 mixture of cone and partial cone conformers. This contrasts with the reaction of the same calixarene with ethyl bromoacetate, again with sodium hydride in THF, to form the tetraethyl acetate in the cone conformation exclusively.

To complete this study we repeated the synthesis of **8** and **9** from **3** and **4**, respectively, using potassium hydride as the base instead of sodium hydride. Although potassium cation is capable of complex formation with several calix[4]arene derivatives, thermodynamic studies show that potassium complexes are generally much less stable than the corresponding sodium complexes.[14] One might expect that with potassium hydride as the base there would have been less evidence of a template effect. In the event, the product obtained from **3** was **8** exclusively in the partial cone conformation with one methyl acetate residue inverted, designated partial cone' (**Scheme 4**). Similarly, the reaction of **4** to form **9** yielded the corresponding partial cone, (also with an ester residue inverted) with some of the 1,3-alternate conformer, but none of the cone conformer, indicative of a template effect, was obtained. The results suggest the absence of a template effect when potassium is the counterion. They also show, in conclusion, that the order in which the different substituents are attached to the calixarene plays an important role in the final conformational outcome. In fact the selection of either one way or

the other leads to different conformers. Thus by following different orders of substituent introduction it is possible to obtain different conformers of the same target calixarene. An example of this fact is compound **9** for which four of the five possible conformers could be isolated. This conclusion should facilitate the design and construction of multi-functional calix[4]arene with predetermined conformations. The new derivatives described here are being used in the construction of bridged calixarenes, which will be discussed in a later publication.



n=2 **3**
n=3 **4**

n=2 **8 partial cone'**
n=3 **9 partial cone'**

n=3 **9 1,3-alt**

Scheme 4

EXPERIMENTAL SECTION

Melting points were determined with an electrothermal melting point apparatus. ^{1}H NMR spectra were recorded with General Electric QE 300 (^{1}H 300 MHz) and General Electric omega 500 (^{1}H 500 MHz) instruments with Me_4Si as internal standard. Analytical TLC was performed on silica gel plates (SiO_2, Merck, 60 F_{254}), while silica gel 60 (SiO_2, Merck, flash chromatography) was used for preparative column chromatography. Microanalysis were carried out by the Service of Microanalysis of the School of Chemistry. Alkenyl bromides and methyl bromoacetate were acquired from Aldrich and used without further purification.

Route 1

Synthesis of 25,27-dialkenyl-26,28-dihydroxycalix[4]arenes **2-5.**

In a 2-neck round-bottom flask **1** (2.35 mmol) was dissolved in dry acetone (20 ml) and K_2CO_3 (4.7 mmol) added. The suspension was treated with the appropriate alkenyl bromide (allyl bromide for compound **2**, 4-bromobutene for compound **3**, 5-bromopentene for compound **4** and 6-bromohexene for compound **5**) (7 mmol). The mixture was refluxed under nitrogen until the reaction reached completion (the reaction was monitored by TLC). After cooling to room temperature, the reaction mixture was filtered and the inorganic solid obtained washed with an additional portion of acetone. The organic solvent was evaporated and the crude material recrystallised from dichloromethane-methanol to obtain the corresponding dialkenyl substituted calixarene as white crystals.

2 (85%), mp=105-106 °C. 300 MHz ^{1}H NMR ($CDCl_3$): δ 8.05 (s, OH, 2H), 7.08 (d, ArH, 4H), 6.90 (d, ArH, 4H), 6.75 (t, ArH, 2H), 6.68 (t, ArH, 2H), 6.25 (m, -CH=, 2H), 5.80 (d, =CH, 2H), 5.45 (d, =CH, 2H), 4.55 (d, OCH_2, 4H), 4.35 (d, $ArCH_2Ar$, 4H), 3.40 (d, $ArCH_2Ar$, 4H). FAB Mass: m/z=504.

3 (70%), mp=223-224 °C. 300 MHz ^{1}H NMR ($CDCl_3$): δ 8.05 (s, OH, 2H), 7.08 (d, ArH, 4H), 6.90 (d, ArH, 4H), 6.77 (t, ArH, 2H), 6.65 (t, ArH, 2H), 6.22 (m, -CH=, 2H), 5.30 (d, =CH, 2H), 5.20 (d, =CH, 2H), 4.32 (d, $ArCH_2Ar$, 4H), 4.08 (t, OCH_2, 4H), 3.40 (d, $ArCH_2Ar$, 4H), 2.80 (m, CH_2, 4H). FAB Mass: m/z=532.

4 (72%), mp=175-176 °C. 300 MHz ^{1}H NMR ($CDCl_3$): δ 8.25 (s, OH, 2H), 7.08 (d, ArH, 4H), 6.90 (d, ArH, 4H), 6.70 (t, ArH, 2H), 6.62 (t, ArH, 2H), 5.95 (m, -CH=, 2H), 5.20 (d, =CH, 2H), 5.05 (d, =CH, 2H), 4.35 (d, $ArCH_2Ar$, 4H), 4.05 (t, OCH_2, 4H), 3.40 (d, $ArCH_2Ar$, 4H), 2.55 (m, CH_2, 4H), 2.15 (m, CH_2, 4H). FAB Mass: m/z=560.

5 (60%), mp=107-108 °C 300 MHz ^{1}H NMR ($CDCl_3$): δ 8.18 (s, OH, 2H), 7.05 (d, ArH, 4H, J=7.5Hz), 6.90 (d, ArH, 4H, J=7.5Hz), 6.73 (t, ArH, 2H, J=9Hz), 6.64 (t, ArH, 2H, J=9Hz), 5.86 (m, -CH=, 2H), 5.91 (d, =CH, 2H, J=9Hz), 5.85 (d, =CH, 2H, J=8Hz), 4.30 (d, $ArCH_2Ar$, 4H, J=12Hz), 4.00 (t, OCH_2, 4H, J=9Hz), 3.39 (d, $ArCH_2Ar$, 4H, J=12Hz), 2.23 (m, CH_2, 4H), 1.85 (m, CH_2, 4H). FAB Mass: m/z=588.

*Synthesis of 25,27-dialkenyl-26,28-dimethoxycarbonylmethyleneoxy calix[4]arene derivatives **7**, **8**, **9**, **10** using NaH as base.*

In a 2-neck round-bottom flask, either **2**, **3**, **4** or **5** (0.94 mmol) was dissolved in dry THF (20ml). To this solution an excess of NaH (2.82 mmol) and methyl bromoacetate (2.25 mmol) were added. The mixture was refluxed under nitrogen until the reaction reached completion (the progress of the reaction was monitored by TLC). The mixture was cooled to room temperature and a few drops of water carefully added to destroy the excess of NaH. The solvent was evaporated and the crude material dissolved in CH_2Cl_2. The inorganic precipitate was separated by filtration and the organic solution washed with water and dried with $MgSO_4$. In the case of **7**, **9** and **10**, cone and 1,3-alternate conformers present in the crude material were separated by column chromatography (flash silica, hexane / ethylacetate rising polarity from 10% to 30%). In the case of **8** only the cone conformer was obtained and this was recrystallised from CH_2Cl_2 / MeOH.

7 (cone) (42.5%), mp=114-115 °C. 500 MHz ^{1}H NMR ($CDCl_3$): δ 6.78 (d, ArH, 4H, J=10Hz), 6.70 (t, ArH, 2H, J=7Hz), 6.49 (m, ArH, 6H), 6.42 (m, -CH=, 2H), 5.19 (dd, =CH, 2H, J=6Hz, J= 1Hz), 5.15 (dd, =CH, 2H, J= 6Hz, J=0.8Hz), 4.60 (d, O<u>CH$_2$</u>CH, 4H, J=6.5Hz), 4.55 (s, OCH_2CO, 4H), 4.53 (d, $ArCH_2Ar$, 4H, J=15Hz), 3.78 (s, OCH_3, 6H), 3.18 (d, $ArCH_2Ar$, 4H, J=15Hz). Anal.Calcd. for $C_{40}H_{40}O_8$: C, 74.05%, H, 6.21%. Found: C, 74.05%, H, 6.23%.

7 (1,3-alternate) (25.5%), mp=130-131 °C. 500 MHz ^{1}H NMR ($CDCl_3$): δ 7.11 (d, ArH, 4H, J=10Hz), 6.98 (d, ArH, 4H, J=10Hz), 6.79 (t, ArH, 2H, 12Hz), 6.69 (t, ArH, 2H, 10Hz), 5.73 (m, -CH=, 2H), 5.06 (dd, =CH, 2H, J= 25Hz, J=5Hz), 4.93 (dd, =CH, 2H, J=25Hz, J=4Hz), 4.17 (d, O<u>CH$_2$</u>CH, 4H, J=10Hz), 3.94 (d, $ArCH_2Ar$, 4H, J=25Hz), 3.72 (d, $ArCH_2Ar$, 4H, J=25Hz), 3.66 (s, OCH_3, 6H), 3.43 (s, OCH_2CO, 4H). Anal.Calcd. for $C_{40}H_{40}O_8$: C, 74.05%, H, 6.21%. Found: C, 74.34%, H, 6.21%.

8 (cone) (71%), mp=143-144 °C. 500 MHz ^{1}H NMR ($CDCl_3$): δ 6.77 (d, ArH, 4H, J=7Hz), 6.70 (t, ArH, 2H, J=1Hz), 6.50 (m, ArH, 6H), 5.92 (m, -CH=, 2H), 5.17 (dd, =CH, 2H, J=16Hz, J= 1Hz), 5.08 (dd, =CH, 2H, J= 10Hz, J=1Hz), 4.67 (d, OCH_2CO, 4H, J=6.5Hz), 4.63 (d, $ArCH_2Ar$, 4H, J=13Hz), 3.95 (t, O<u>CH$_2$</u>CH, 4H, J=7Hz), 3.77 (s, OCH_3, 6H), 3.21 (d, $ArCH_2Ar$, 4H, J=13Hz), 2.68 (m, CH_2, 4H). Anal.Calcd. for $C_{42}H_{44}O_8$: C, 74.53%, H, 6.55%. Found: C, 74.25%, H, 6.46%.

9 (cone) (60%), wax mp=44-45 °C. 300 MHz ^{1}H NMR ($CDCl_3$): δ 6.90 (d, ArH, 4H, J=7Hz), 6.80 (t, ArH, 2H, J=8Hz), 6.38 (m, ArH, 6H), 5.88 (m, -CH=, 2H), 5.07 (dd, =CH, 2H, J=19Hz, J= 1.5Hz), 4.99 (d, =CH, 2H, J= 10Hz), 4.75 (s, OCH_2CO, 4H), 4.66 (d, $ArCH_2Ar$, 4H, J=14Hz), 3.84 (t, O<u>CH$_2$</u>CH, 4H, J=7Hz), 3.74 (s, OCH_3, 6H), 3.22 (d, $ArCH_2Ar$, 4H, J=14Hz), 2.24 (m, CH_2, 4H), 1.99 (m, CH_2, 4H). Anal.Calcd. for $C_{44}H_{48}O_8$: C, 74.07%, H, 6.86%. Found: C, 74.01%, H, 6.85%.

9 (1,3-alternate) (22%), mp=90-91 °C. 300 MHz ^{1}H NMR ($CDCl_3$): δ 7.09 (d, ArH, 4H, J=7.5Hz), 7.04 (d, ArH, 4H, J=7.5Hz), 6.79 (t, ArH, 4H, 7Hz), 5.80 (m, -CH=, 2H), 5.03 (d, =CH, 2H, J= 6Hz), 4.98 (dd, =CH, 2H, J=6Hz, J=2Hz), 4.01 (d, $ArCH_2Ar$, 4H, J=16Hz), 3.82 (d, $ArCH_2Ar$, 4H, J=16Hz), 3.61 (s, OCH_3, 6H), 3.52 (t, $O\underline{CH_2}CH$, 4H, J=8Hz), 3.40 (s, OCH_2CO, 4H), 1.95 (m, CH_2, 4H), 1.34 (m, CH_2, 4H). Anal.Calcd. for $C_{44}H_{48}O_8$: C, 74.07%, H, 6.86%. Found: C, 73.80%, H, 6.85%.

10 (cone) (66.5%), wax mp=41-42 °C. 300 MHz ^{1}H NMR ($CDCl_3$): δ 6.92 (d, ArH, 4H, J=8Hz), 6.88 (t, ArH, 2H, J=6.8Hz), 6.36 (t, ArH, 2H, J=6Hz), 6.28 (d, ArH, 4H, J=6.8Hz), 5.84 (m, -CH=, 2H), 5.03 (d, =CH, 2H, J=17Hz), 4.96 (d, =CH, 2H, J= 10Hz), 4.76 (s, OCH_2CO, 4H), 4.67 (d, $ArCH_2Ar$, 4H, J=14Hz), 3.82 (t, $O\underline{CH_2}CH$, 4H, J=7Hz), 3.73 (s, OCH_3, 6H), 3.22 (d, $ArCH_2Ar$, 4H, J=14Hz), 2.15 (m, CH_2, 4H), 1.88 (m, CH_2, 4H), 1.58 (m, CH_2, 4H). Anal.Calcd. for $C_{46}H_{52}O_8$: C, 75.38%, H, 7.15%. Found: C, 75.12%, H, 7.10%.

10 (1,3-alternate) (12.5%), mp=93-94°C. 500 MHz ^{1}H NMR ($CDCl_3$): δ 7.09 (d, ArH, 4H, J=7.5Hz), 7.03 (d, ArH, 4H, J=7.5Hz), 6.78 (m, ArH, 4H), 5.84 (m, -CH=, 2H), 5.07 (d, =CH, 2H, J= 15Hz), 5.02 (d, =CH, 2H, J=15Hz), 3.99 (d, $ArCH_2Ar$, 4H, J=15Hz), 3.75 (d, $ArCH_2Ar$, 4H, J=15Hz), 3.62 (s, OCH_3, 6H), 3.52 (t, $O\underline{CH_2}CH$, 4H, J=7Hz), 3.43 (s, OCH_2CO, 4H), 2.04 (m, CH_2, 4H), 1.31 (m, CH_2, 8H). Anal.Calcd. for $C_{46}H_{52}O_8$: C, 75.38%, H, 7.15%. Found: C, 74.95%, H, 6.99%.

*Synthesis of 25,27-dialkenyl-26,28-dimethoxycarbonyl ethyleneoxy calix[4]arene derivatives **8, 9** using KH as base.*

The reaction was conducted in the same way as in the previous case but using either **3** or **4** as starting material and KH as base. In the case of compound **9**, both isomers were separated by column chromatography (flash silica, hexane-ethyl acetate raising polarity from 9:1 to 6:4).

8 (partial cone') (63%), mp=144-145 °C. 500 MHz ^{1}H NMR ($CDCl_3$): δ 7.22 (d, ArH, 2H, J=7.6Hz), 6.98 (m, ArH, 4H), 6.86 (t, ArH, 1H, J=5Hz), 6.80 (t, ArH, 1H, J=5Hz), 6.41 (t, ArH, 2H, J=7.5Hz), 6.17 (m, ArH, 2H), 5.86 (m, -CH=, 2H), 5.10 (dd, =CH, 2H, J=15.5, J= 1.6Hz), 5.03 (dd, =CH, 2H, J=9.3Hz, J=1.4Hz), 4.30 (s, OCH_2CO, 2H), 4.25 (d, $ArCH_2Ar$, 2H, J=13.9 Hz), 3.85 (s, OCH_2CO, 2H), 3.75 (s, OCH_3, 3H), 3.77-3.66 (m, $O\underline{CH_2}CH_2$, 4H), 3.69 (d, $ArCH_2Ar$, 2H, J=13.9 Hz), 3.60 (d, $ArCH_2Ar$, 2H, J=13.9 Hz), 3.53 (s, OCH_3, 3H), 3.07 (d, $ArCH_2Ar$, J= 13.9 Hz), 2.49 (m, CH_2, 4H). Anal.Calcd. for $C_{42}H_{44}O_8$: C, 74.53%, H, 6.55%. Found: C, 74.32%, H, 6.38%.

9 (partial cone') (46%), mp= 85-86 °C.:500 MHz ^{1}H NMR ($CDCl_3$): δ 7.28 (d, ArH, 2H, J=7.5Hz), 7.05 (m, ArH, 4H), 6.95 (t, ArH, 1H, J=7.2Hz), 6.88 (t, ArH, 1H, J=7.2Hz), 6.47 (t, ArH, 2H, J=7.5Hz), 6.25 (m, ArH, 2H), 5.88 (m, -CH=, 2H), 5.09 (dd, =CH, 2H, J=17, J= 1.7Hz), 5.01 (dd, =CH, 2H, J=8.3Hz, J=1.6Hz), 4.39 (s, OCH_2CO, 2H), 4.32 (d, $ArCH_2Ar$, 2H, J=13.9 Hz), 3.95 (s, OCH_2CO, 2H), 3.83 (s, OCH_3, 3H), 3.80-3.65 (m, 2 $O\underline{CH_2}CH_2$, 4H), 3.77 (d, $ArCH_2Ar$, 2H, J=10.7 Hz), 3.67 (d, $ArCH_2Ar$, 2H, J=10.7 Hz), 3.58 (s, OCH_3, 3H), 3.15 (d, $ArCH_2Ar$, J= 13.9 Hz), 2.26 (m, CH_2, 4H), 1.93 (m, CH_2, 4H). Anal.Calcd. for $C_{44}H_{48}O_8$: C, 74.07%, H, 6.86%. Found: C, 73.90%, H, 6.84%.

9 (1,3-alternate) (30%), mp=90-91 °C. Spectroscopical and analytical data stated before.

Route 2

*Synthesis of 25,27-dimethoxycarbonylmethyleneoxy-26,28-dihydroxy calix[4]arene **6**.*

1 (3.5 mmol) was refluxed with methyl bromoacetate (7.7 mmol) and anhydrous potassium carbonate (93.85 mmol) in dry acetone (20 ml), under nitrogen for 20 h. The reaction mixture was cooled and filtered through celite, which was washed with more acetone. The solvent was then evaporated and the resulting solid was recrystallised from CH_2Cl_2 / MeOH to yield **6**, (60%), mp= 207-208 °C. 300 MHz ^1H NMR ($CDCl_3$): δ 7.52 (s, OH, 2H), 7.03 (d, ArH, 4H, J=9Hz), 6.90 (d, ArH, 4H, J=9Hz), 6.73 (t, ArH, 2H, J=8Hz), 6.67 (t, ArH, 2H, J=8Hz), 4.73 (s, OCH_2, 4H), 4.47 (d, $ArCH_2Ar$, 4H, J=12Hz), 3.87 (s, OCH_3, 6H), 3.40 (d, $ArCH_2Ar$, 4H, J=12Hz). FAB Mass: M^+=568, M^++Na^+=591.

*Synthesis of 25,27-dialkenyl-26,28-dimethoxycarbonylmethyleneoxy calix[4]arene derivatives **8, 9**.*

Compound **6** (0.53 mmol) was stirred with an excess of NaH (2.6 mmol) in dry THF under nitrogen. To this mixture an excess of the corresponding alkenyl bromide (4-bromobutene or 5-bromopentene) (2 mmol) was added. The mixture was refluxed for 20 h. After that the reaction mixture was cooled and the excess of NaH destroyed by the careful addition of a few drops of water. The mixture was filtered and the inorganic solid was washed with chloroform. The organic solution was evaporated and the solid obtained was pumped under vacuum to remove excess alkenyl bromide. The crude material was redissolved in chloroform and washed with water. The organic phase was dried with $MgSO_4$ and evaporated to dryness. The solid obtained was purified by column chromatography (flash silica, hexane - ethyl acetate 10%) to obtain either **8 (partial cone)**, or **9 (partial cone)**.

8 (partial cone) (57%), mp=98-99 °C. 300 MHz ^1H NMR ($CDCl_3$): δ 7.38 (d, ArH, 2H, J=9Hz), 7.11 (d, ArH, 2H, J=9Hz), 6.94 (m, ArH, 4H), 6.49 (t, ArH, 2H, J=10Hz), 6.26 (d, ArH, 2H, J=9Hz), 5.92 (m, -CH=, 1H), 5.74 (m, -CH=, 1H), 5.23-4.94 (set of d, $=CH_2$, 4H), 4.43 (d, OCH_2CO, 2H, J=12Hz), 4.34 (d, OCH_2CO, 2H, J=12Hz), 4.11 (d, $ArCH_2Ar$, 2H, J=12Hz), 3.87-3.79 (m, 2H $ArCH_2Ar$ + 2H $O\underline{CH_2}CH$) 3.83 (s, OCH_3, 6H), 3.66 (d, $ArCH_2Ar$, 2H, J=12Hz), 3.45 (t, $O\underline{CH_2}CH$, 2H, J=9Hz), 3.09 (d, $ArCH_2Ar$, 2H, J=12Hz), 2.66 (m, CH_2, 2H), 2.17 (m, CH_2, 2H). Anal.Calcd. for $C_{42}H_{44}O_8$: C, 74.53%, H, 6.55%. Found: C, 74.03%, H, 6.60%.

9 (partial cone) (62%), mp=130-131 °C. 500 MHz ^1H NMR ($CDCl_3$): δ 7.38 (d, ArH, 2H, J=7.5 Hz), 7.09 (d, ArH, 2H, J=7.5Hz), 6.91 (m, ArH, 4H), 6.48 (t, ArH, 2H, J=7.5Hz), 6.26 (d, ArH, 2H, J=7.5Hz), 5.90 (m, -CH=, 2H), 5.13-4.94 (set of d, $=CH_2$, 4H), 4.40 (d, OCH_2CO, 2H, J=15Hz), 4.36 (d, OCH_2CO, 2H, J=15Hz), 4.12 (d, $ArCH_2Ar$, 2H, J=15Hz), 3.84-3.79 (m, 2H $ArCH_2Ar$ + 2H $O\underline{CH_2}CH$) 3.82 (s, OCH_3, 6H), 3.65 (d, $ArCH_2Ar$, 2H, J=15Hz), 3.42 (t, $O\underline{CH_2}CH$, 2H, J=8Hz), 3.10 (d, $ArCH_2Ar$, 2H, J=15Hz), 2.24 (m, CH_2, 2H), 2.02 (m, CH_2, 2H), 1.93 (m, CH_2, 2H), 1.53 (m, CH_2, 2H). Anal.Calcd. for $C_{44}H_{48}O_8$: C, 74.07%, H, 6.86%. Found: C, 73.45%, H, 6.84%.

*Synthesis of 25,26,27,28-tetrapent-1-enyl-p-tert-butylcalix[4]arene **11**.*

p-*Tert*-butylcalix[4]arene (0.5g, 0.77 mmol) was dissolved in 15 ml of a mixture of THF-DMF (10:1) with 5-bromopentene (0.52g, 3.38 mmol) and a excess of NaH (0.96g). The mixture was refluxed under nitrogen for 3 days. After cooling, an inorganic solid appeared which was filtered off. The solvent was removed in a evaporator and the residue obtained was dissolved in CH_2Cl_2, washed with water and dried with $MgSO_4$. After removing the solvent a yellow oil was obtained. A small amount of warm ethanol was added to precipitate out the product as a white solid (0.48g, 68%). This solid corresponded to the desired product in a mixture of cone and partial cone conformers (cone 36% : partial cone 64%). By silica preparative chromatography (hexane 96 : ethyl acetate 4) both isomers could be separated.

11 cone mp= 128-129 °C. 500 MHz ^{1}H NMR ($CDCl_3$): δ 6.77 (s,ArH, 8H), 5.89 (m, -CH=, 4H), 5.75 (2d, $=CH_2$, 8H, J=17Hz, J=2Hz), 4.38 (d, $ArCH_2Ar$, 4H, J=12Hz), 3.86 (t, OCH_2, 8H, J=8Hz), 3.12 (d, $ArCH_2Ar$, 4H, J=12Hz), 2.19-2.12 (m, CH_2, 16H), 1.08 (s, t-but, 36H). Anal. Calc. for $C_{64}H_{88}O_4$: C, 83.43%, H, 9.63%. Found C, 83.26%, H, 9.95%.

11 partial cone mp= 209-210 °C. 500 MHz ^{1}H NMR ($CDCl_3$): δ 7.20 (s,ArH, 2H), 7.08 (s,ArH, 2H), 6.84 (d,ArH, 2H, J=2Hz), 6.59 (d,ArH, 2H, J=2Hz), 5.85 (m, -CH=, 3H), 5.75 (m, -CH=, 3H), 5.07-4.98 (m, $=CH_2$, 8H), 4.08 (d, $ArCH_2Ar$, 2H, J=13Hz), 3.8-3.5 (m, $ArCH_2Ar$, 4H + OCH_2, 8H), 3.05 (d, $ArCH_2Ar$, 2H, J=13Hz), 2.18 (m, CH_2, 4H), 2.08 (m, CH_2, 2H), 1.94 (m, CH_2, 6H), 1.82 (m, CH_2, 2H), 1.65 (m, CH_2, 2H), 1.40 (s, t-but, 9H), 1.33 (s, t-but, 9H), 1.04 (s, t-but, 18H). Anal. Calc. for $C_{64}H_{88}O_4$: C, 83.43%, H, 9.63%. Found C, 83.06%, H, 9.99%.

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