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Communications

The Tetramerization of 2,4-Dimethoxycinnamates. A Novel Route to Calixarenes

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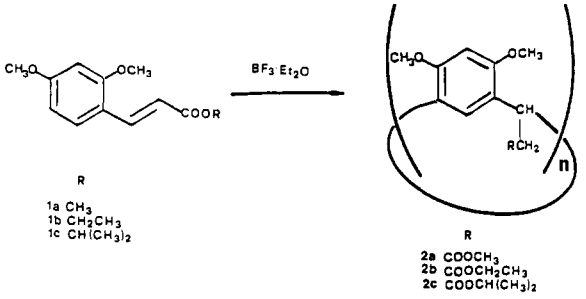
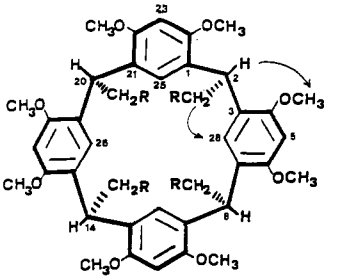
Summary: Treatment of (*E*)-2,4-dimethoxycinnamic acid methyl ester with BF_3·Et_2O in $CHCl_3$ at room temperature afforded in 75% yield two stereoisomeric *C*-alkylcalix[4]resorcinarenes, which were shown to be in the 1,2-alternate and flattened-cone configurations.

As reported previously,[1] treatment of (*E*)-3,4-dimethoxycinnamic acid methyl ester with BF_3·Et_2O (in the ratio 1:1.5) at room temperature affords aryltetralin lignans in high yield (90%).

Further studies reported here were undertaken in order to provide additional information as to the generality and the mechanism of the reaction. For this purpose the isomeric (*E*)-2,4-dimethoxycinnamic acid methyl ester (**1**)



was treated with BF_3·Et_2O under the above-noted conditions. However, the reaction proceeded to afford in 75% yield two unexpected products, which were assigned the general structure **2a** ($n = 4$). The two isomers were shown to be in the flattened-cone (**3**, 60%) and 1,2-alternate (**4**, 40%) configurations, respectively.[2]



3 R = $COOCH_3$

The ^1H NMR spectrum (Table I) of the more polar compound **3**, when compared with that of the starting material *1*, showed the disappearance of the ortho–meta coupled aromatic proton and of the olefinic bond. A one-proton triplet (δ 4.94) and a two-proton doublet (δ 2.84) suggested that the HC=CH group had been transformed into a saturated CH–CH_2 entity. In the APT-^{13}C NMR spectrum (Table I) the resonances of two quaternary carbons (δ 156.0 and 123.8) were significantly more intense than those of the protonated aromatic carbons, thereby requiring that *two* carbon atoms must be attributed to these signals.

Moreover, the signal of the aliphatic methine group in the ^{13}C NMR spectrum was at higher field than that of the

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(1) Botta, B.; Iacomacci, P.; Vinciguerra, V.; Delle Monache, G.; Gacs-Baitz, E.; Botta, M.; Misiti, D. *Chem. Pharm. Bull.* **1990**, *38*(12), 3238.

(2) Systematic names: **3**, *r*-2,*c*-8,*c*-14,*c*-20-tetra(carbomethoxymethyl)pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-4,6,10,12,16,18,22,24-octol, octamethyl ether; **4**, *r*-2,*c*-8,*t*-14,*t*-20-tetra(carbomethoxymethyl)pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-4,6,10,12,16,18,22,24-octol, octamethyl ether.

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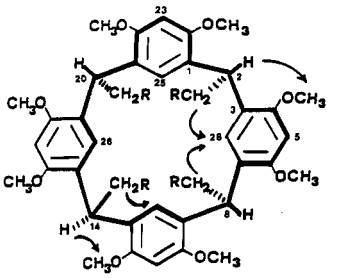
Table I. ^{13}C- and ^{1}H-NMR Spectra of *C*-Alkylcalix[4]resorcinarenes[a]

	4		3	
carbon	δ_C	δ_H	δ_C	δ_H
1, 3	124.33	-		
7, 9	123.85	-		
13, 16	123.53	-	123.76	-
19, 21	122.89	-		
2	30.41	5.45 (1, H, t; 8)		
8, 20	33.31 (×2)	5.06 (2 H, dd; 6, 10)	33.04	4.94 (1 H, t; 7)
14	29.38	5.09 (1 H, t; 8)		
4, 24	156.30	-		
6, 22	156.15	-		
10, 18	155.96	-	156.00	-
12, 16	155.86	-		
5, 23	96.54	6.41 (2 H, s)		
11, 17	95.81	6.40 (2 H, s)	96.19	6.32 (1 H, s)
26, 27	127.34	7.24 (2 H, s)		
25. 28	126.16	6.38 (2 H, s)	125.67	6.46 (1 H, s)
2-CH_2	40.65	2.86 (2 H, d; 8)		
8-, 20-CH_2	38.92 (×2)	2.96 (2 H, dd; 6, 15) 2.85 (2 H, dd; 10, 15)	38.42	2.84 (1 H, d; 7)
14-CH_2	39.74	2.35 (2 H, d; 8)		
CO	172.57 173.01 (×2) 172.49	- - -	172.80	-
COO*Me*	51.36 51.42 (×2) 51.12	3.53 (3 H, s) 3.57 (6 H, s) 3.43 (3 H, s)	51.36	3.57 (3 H, s)
OMe	56.29 56.05 55.79 55.74	3.85 (6 H, s) 3.83 (6 H, s) 3.78 (6 H, s) 3.66 (6 H, s)	55.83	3.65 (6 H, s)

[a] 300 MHz; in $CDCl_3$, TMS as internal reference. The carbon and proton resonances were correlated through a HETCOR experiment. In each set the carbon resonances may be interchanged, except those with approximately double intensity.

methylene group, indicating that this group was in turn substituted by two aromatic rings. In summary, a partial structure **2a** was formulated for compound **3**. The quasi-molecular peak at m/z 889 in the FAB MS spectrum of **3** was in agreement with the structure of a tetrameric macrocycle (n = 4 in **2a**), which can be described as a C-alkylated calix[4]resorcinarene.[3] The identity of the ^{1}H- and ^{13}C-NMR signals of the four monomeric units revealed a C_4 symmetry for the molecule. Since the CH and the CH_2 signals showed a mutual NOE effect (indicated by arrows in structure **3**) with those of the aromatic methoxy group and the low-field aromatic proton, respectively, the compound **3** was assigned a flattened-cone configuration with the substituents in a pseudoaxial and all-cis arrangement.

Compound **4** showed a very similar FAB-MS spectrum and thus was a calix[4]arene isomeric with **3**. The signals belonging to the aliphatic moiety exhibited a distribution of essentially 1:2:1 in the ^{1}H- and ^{13}C-NMR spectra (Table I); conversely, the resonances of the aromatic moiety



4 R = $COOCH_3$

showed a distribution of 2:2 in both the spectra. These findings are consistent with the existence of a symmetry plane passing through the C-2 and C-14 methine groups and perpendicular to the macrocyclic ring.[4]

Due to this plane each aromatic proton and carbon has a mirror counterpart, as listed in Table I, and their relative signals, in terms of intensity, reveal this situation. The same distribution characterizes the signals of the aliphatic chains at C-8 and C-20; that is, they reveal a double intensity signal attributed to a given carbon and its corresponding counterpart.

Irradiation of the aromatic proton signals at δ 7.24 (H-25, H-28) and at δ 6.41 (H-26, H-27) enhanced the methylene signals at δ 2.86 (2-CH_2) and at δ 2.35 (14-CH_2), respectively. These findings require the C-2 and the C-14 methylenes to be in a pseudoaxial position. Analogously, NOE measurements (arrows in structure **4**) established the proximity between the two equivalent methylenes and the H-25, H-28 aromatic protons, thus indicating the 8-CH_2 and the 20-CH_2 to be also in a pseudoaxial position. As a confirmation, irradiation of the H-14 signal caused the enhancement of the neighboring methoxy group resonance. In conclusion, the less polar product was assigned the structure **4** with a 1,2 alternate configuration and a cis–trans–cis (relative to C-2) arrangement.

Noteworthy is that with a longer time of reaction the percentage of the 1,2-alternate structure decreased, and after 48 h the flattened cone conformation constituted more than 90% in the reaction mixture. The same result was obtained in shorter time by increasing the temperature ($CHCl_3$ at reflux) or the ratio of $BF_3{\cdot}Et_2O$ (1:3 or 1:6), without change in the overall yield. Finally, when the reaction was run at room temperature with $BF_3{\cdot}Et_2O$ in a ratio of 1:1 and was stopped after 7 h, the dimeric compound **5** was obtained together with most of the starting material. The isolation of the intermediate **5** confirms that the first step of the reaction requires, in the substrate, the presence of a methoxy group in C-4 and a free position para to the second methoxy group, as previously reported from our study involving the dimerization of (*E*)-3,4-dimethoxycinnamic acid methyl ester.[1] The following steps of the reaction may therefore proceed by successive stepwise growth (dimer → trimer → tetramer) or by cyclooligomerization of **5**.[5] The actual mechanism still remains uncertain.

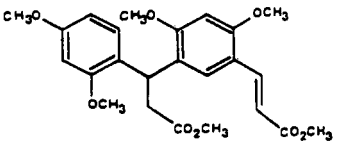


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Table II. Energies of MM2 (MODEL) Minimized Conformations of Calix[4]resorcinarenes

conformation	E (kcal)	conformation	E (kcal)
flattened cone (C_{2v})	86.7	flattened partial cone 2 (C_{2h})	89.1
flattened partial cone 1 (C_s)	87.6	1,2 alternate (C_{2h})	90.0
1,3 alternate (D_{2d})	87.8		

Table III. Energies of MM2 (MODEL) Minimized Conformations of C-(Carbomethoxymethyl)calix[4]resorcinarenes

conformation	E (kcal)	conformation	E (kcal)
flattened cone (C_{2v})	109.4	flattened partial cone 1 (C_s)	118.2
1,2 alternate (C_s)	111.6	flattened partial cone 2 (C_2h)	121.3
1,3 alternate (D_{2d})	116.1		

Since it was not possible to obtain suitable crystals of **3** and **4** for X-ray analysis, a molecular modeling study was undertaken in order to compare the 3D-structures with those suggested by the NMR results. A calix[4]resorcinarene with methylene bridges was manually input by the SKETCH mode of the program SYBIL[6] and minimized with the SYBIL MAXIMIN2 routine (TRIPOS force field) on a Silicon Graphics Personal Iris workstation. A random conformational search with a 10° stepwise increment of the eight nonaromatic rotatable C–C bonds was carried out on this molecule using the SEARCH module within SYBIL with an energy cutoff of 70 kcal/mol (default value). This calculation yielded 33 geometries, which converged after a MAXIMIN2 energy minimization to five conformations, resembling with some distortion the flattened cone, two kinds of flattened partial cone, the 1,3 alternate, and the 1,2 alternate conformations. Further minimization of these structures with the program MODEL[7] (MM2 force field) led to the first above-reported four conformations, with the symmetries C_{2v}, C_{2h}, C_s, and D_{2d}, respectively. The 1,2-alternate conformation was built up from the fifth structure, which showed a very high strain energy, by changing manually the coordinates of half of the molecules as to obtain a C_{2h} symmetry. The input structure was then minimized with the program MODEL. The energies of the final five MM2 minimized conformations are reported in Table II. The four aliphatic chain CH_2COOCH_3 were then added to each conformation; in the case of the 1,2 alternate conformation the substituents were drawn in cis–trans–cis configuration relative to C-2, in accordance with the ^1H NMR data, while in the remaining conformations the R groups were added in all-cis relative configuration. The five structures so obtained were minimized until convergence with MODEL and then submitted to a further random search on the side chains to find the preferred spatial orientation. The results of the molecular mechanics calculations on the five conformations of the calix[4]resorcinarene **2a** (n = 4) are summarized in Table III. The calculations predict the flattened cone conformation to be at the lowest energy in agreement with our results and the literature data.[4,8] The 1,2 alternate conformation with the cis–trans–cis configuration was also shown to have a low conformational energy, in agreement with the experimental results.

An all-cis configuration of the minimized 1,2 alternate conformation was built up by epimerization of C-14 atom by EPIMR command within MODEL. Notably, this stereoisomer minimized to a higher steric energy of 116.5 kcal/mol. In summary, the molecular modeling study confirmed the conformations and the configurations assigned on the basis of the NMR experiments.

Treatment with $BF_3{\cdot}Et_2O$ of other cinnamates (**1b** and **1c**), to be presented in a future detailed paper, gave compounds with general structures **2b** (n = 4) and **2c** (n = 4), respectively, thus affording evidence for the general versatility of the reaction.[9] The nonphenolic substrate, the low (room) temperature, and the good yields are the outstanding features of this approach to calixarenes.

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Registry No. **1a**, 66417-42-3; **1b**, 24393-63-3; **1c**, 140111-45-1; **3** (R = $COOCH_3$), 140111-46-2; **3** (R = $COOCH_2CH_3$), 140111-47-3; **3** (R = $COOCH(CH_3)_2$), 140111-48-4; **4** (R = $COOCH_3$), 140223-16-1; **4** (R = $COOCH_2CH_3$), 140223-17-2; **4** (R= $COOCH(CH_3)_2$), 140223-18-3; **5**, 140111-49-5.

Supplementary Material Available: Experimental details and data of **3–5**, including ^1H and ^{13}C NMR spectra (8 pages). 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.

(6) SYBIL (Version 5.4); Tripos Associates, Inc.: St. Louis, MO 63144.
(7) Steliou, K. MODEL (Version K.S.2.96); University of Montreal, Canada.
(8) Hogberg, A. G. S. *J. Org. Chem.* **1980**, *45*, 4498.
(9) On the other hand, 2,6-dimethoxycinnamic acid ethyl ester undergoes initial rearrangement to 2,4-dimethoxycinnamate (**1b**) and subsequent tetramerization to afford calixarenes with general structure **2b** (n = 4).

Stereocontrolled Synthesis of a C_1–C_{15} Segment for the Marine Macrolides Swinholide A and Scytophycin C: Use of a Vinylogous Mukaiyama Aldol Reaction

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Summary: The C_1–C_{15} segment (±)-**8** of swinholide A/scytophycin C was prepared in eight steps from (*E*)-4-chlorobut-3-en-2-one (**10**) in 19% overall yield with 87% diastereoselectivity. The C_7 stereocenter was controlled by the novel, vinylogous Mukaiyama aldol reaction, **16** + **18** → **19**, mediated by $BF_3{\cdot}OEt_2$. The related C_1–C_{13} segment (±)-**9** for misakinolide A was also prepared.

Swinholide A, a novel cytotoxic macrolide isolated from marine sponges of the genus *Theonella swinhoei*, was first

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