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Structure and Equilibration Studies of Bis- and Tris(spirodienone) Derivatives of Medium-Sized Calixarenes

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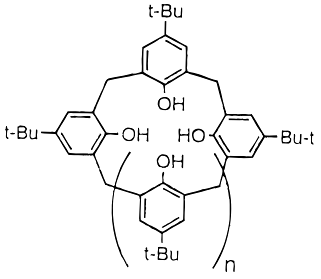
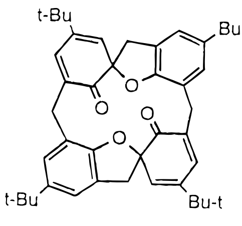
The isomerism of the tris(spirodienone) derivatives of *p-tert*-butylcalix[6]arene and bis(spirodienone) derivatives of *p-tert*-butylcalix[5]arene is analyzed. Oxidation of *p-tert*-butylcalix[6]arene with phenyltrimethylammonium tribromide/base afforded two chiral tris(spirodienone) calix[6]arene derivatives (**3** and **4**) which react with excess benzyne yielding the corresponding *all-exo* tris adducts **5** and **6**. The structural characterization of the tris(spirodienone) derivatives was achieved by 2D NMR methods and in the case of **3**, by X-ray crystallography. The main product **3** possess an alternant disposition of the ether and carbonyl functional groups and three spiro stereocenters of dissimilar configurations (*RRS*/*SSR*), while the disposition of the functional groups in **4** is nonalternant. Equilibration studies in toluene at 85 °C indicate that **3** is the thermodynamically most stable isomer. The tris adduct **5** exists in two nearly equally populated conformations which interconvert with a barrier of 12.1 ± 0.2 kcal mol^{-1}. A bis(spirodienone) derivative of *p-tert*-butylcalix[5]arene was synthesized by oxidation (K$_3$Fe(CN)$_6$/base) of the corresponding monospirodienone derivative. The product obtained is more likely the cycloenantiomeric pair which isomerizes in toluene solution to an isomeric mixture consisting mainly of a heterodirectional isomer of C_2 symmetry.

Introduction

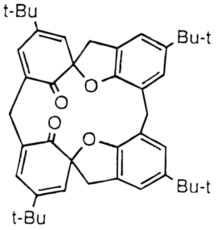
The calix[*n*]arenes are achiral synthetic macrocycles which are obtained by basic condensation of *p*-substituted phenols and formaldehyde.[1] Mild oxidation of *p-tert*-butylcalix[4]arene (**1a**) may result in the formation of mono- and bis(spirodienone) derivatives.[2−5] These compounds are of interest as synthetic intermediates for the preparation of selective functionalized and chemically modified calixarenes.[3,5] In addition, the polyspirodienone derivatives are of interest *per se* as potential ligands due to the presence of a cyclic array of ether and carbonyl functionalities and of spiro carbon stereocenters which may render the systems chiral. Three diastereomeric bis(spirodienone) calix[4]arene derivatives (**2A**, **2A′**, and **2B**) were isolated in the oxidation of **1a** and were structurally characterized by X-ray crystallography.[3a] These derivatives slowly mutually isomerize in solution, and the *meso* isomer **2A** is the thermodynamically more stable form in toluene at 80 °C. The mutual isomerization probably involves the homolytic cleavage of the spiro C−O bonds. Addition of excess benzyne to the bis(spirodienone) derivatives gives the corresponding *exo*-Diels−Alder bis adducts which are configurationally stable.[3a]



1a n=1
1b n=2
1c n=3



2A (*RS*)
2A' (*RR/SS*)



2B (*RS*)

The polyspirodienone derivatives of the larger calixarenes are of interest since they should possess larger cavities than those presented by the bis(spirodienone) calix[4]arene derivatives. The larger the number of phenol units in the macrocyclic array of the calixarenes, the larger the number of possible isomeric polyspirodienone derivatives. However, it could be expected that similarly to the bis(spirodienone) derivatives of **1a**, where **2A** is the isomer formed in excess, some isomers will be formed preferentially in the oxidation of the large ring calixarenes. In this paper we describe the preparation,

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[⊗] Abstract published in *Advance ACS Abstracts*, November 15, 1996.

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(2) For a review on calixarene spirodienone derivatives see: Aleksiuk, O.; Grynszpan, F.; Litwak, A. M.; Biali, S. E. *New J. Chem.* **1996**, *20*, 476. For a review on spirodienone derivatives of bis(naphthols) see: Ward, R. S. *Chem. Br.* **1973**, *9*, 44.

(3) (a) Litwak, A. M.; Grynszpan, F.; Aleksiuk, O.; Cohen, S.; Biali, S. E. *J. Org. Chem.* **1993**, *58*, 393. (b) Aleksiuk, O.; Grynszpan, F.; Biali, S. E. *J. Chem. Soc., Chem. Commun.* **1993**, 11. (c) Aleksiuk, O.; Grynszpan, F.; Biali, S. E. *J. Org. Chem.* **1993**, *58*, 1994. (d) Grynszpan, F.; Aleksiuk, O.; Biali, S. E. *J. Org. Chem.* **1994**, *59*, 2070. (e) Aleksiuk, O.; Grynszpan, F.; Biali, S. E. *J. Incl. Phenom.* **1994**, *19*, 237.

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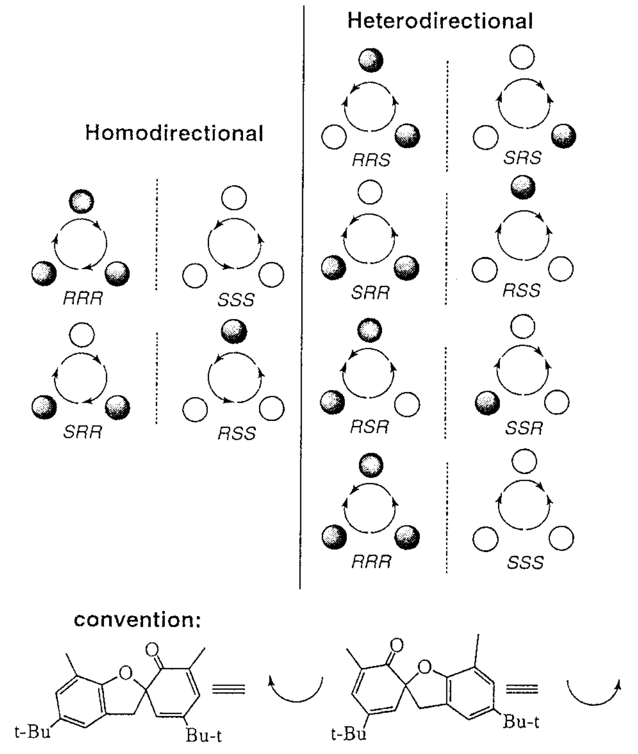


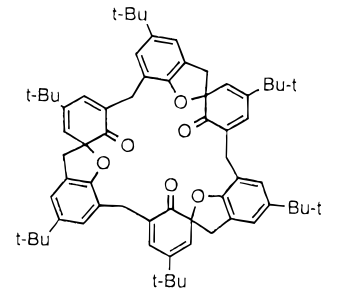
Figure 1. Schematic representation of the isomeric forms of the tris(spirodienone) calix[6]arene derivatives. Open/filled spheres represent the configuration (*R* or *S*) of the chiral carbons. The sense of the curved arrow (clockwise or counterclockwise) denotes the directionality of a given spirodienone moiety.

structural characterization, and equilibration studies of the polyspirodienone derivatives of *p*-*tert*-butylcalix[6]arene (**1c**) and *p*-*tert*-butylcalix[5]arene (**1b**).[6]

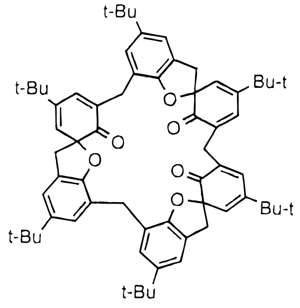
Results and Discussion

Tris(spirodienone) Derivatives of *p*-*tert*-Butylcalix[6]arene. Exhaustive oxidation of **1c** may result in the formation of systems containing three spirodienone subunits. In contrast to the bis(spirodienone) derivatives **2**, where both achiral and chiral isomer are possible, systems including an odd number of stereocenters are all chiral since no *meso* form is possible. The most convenient way to analyze the isomerism of the polyspirodienone calixarene derivatives is to envision the systems as possessing two independent stereogenic structural features: the spiro stereocenters (of either *R* or *S* configuration) and the directionality of each spirodienone subunit.[3a,7] Disregarding conformational isomerism, twelve isomeric forms (six enantiomeric pairs) should exist for the tris(spirodienone) derivatives. A schematic representation of the twelve isomeric forms is shown in Figure 1 where the two possible senses of direction of the spirodienone moiety are represented by a clockwise or counterclockwise arrow, and filled and empty spheres represent *R* and *S* configurations of the spiro stereocenters. Only one pair of enantiomers possess C_3 symmetry, while in the rest of the isomers the symmetry is lowered to C_1. A homodirectional[8] disposition of the three curved arrows represents an alternant arrangement of carbonyl and ether functionalities while an heterodirectional[8] disposition corresponds to a nonalternant arrangement of the carbonyl and ether groups.

Exhaustive Oxidation of *p*-*tert*-Butylcalix[6]arene. Reaction of a CH_2Cl_2 solution **1c** with an excess of phenyltrimethylammonium tribromide/aqueous NaOH resulted in a complex mixture of products. From that mixture we isolated two yellow tris(spirodienone) calix[6]arene derivatives (**3** and **4**) in 15% and 25% yield, respectively, and in addition, a side product. The separation of the mixture was carried out by column chromatography. Recrystallizations from different solvents were unsuccessful in purifying **4** beyond 95%. Tris(spirodienone) **4** (CI MS: *m*/*z* 967.7 (MH^+)) displayed in the ^1H NMR spectrum (400 MHz, $CDCl_3$, rt) three sharp and three broad t-Bu signals in the 0.88−1.29 ppm region, twelve doublets for the methylene protons in the 2.98−3.89 ppm region, three doublets for the vinyl signals at 5.81, 5.94, and 5.95 ppm, two broad signals at 6.17 and 6.79 ppm, and seven partially overlapping doublets in the 6.96−7.06 ppm region. The diastereotopicity of pairs of protons on the different methylene groups and the vinyl signals are all characteristic of the spirodienone calixarene derivatives.[3,5] The ^{13}C NMR (100.62 MHz, $CDCl_3$) spectrum displayed three carbonyl signals at 197.12, 197.56, and 199.01 ppm, and three signals at 82.21, 82.45, and 85.30 ppm which can be assigned to the spiro carbons. The patterns of the NMR spectra suggest the presence of three spirodienone moieties in a macrocycle of C_1 symmetry. Inspection of a solution of **4** in $CDCl_3$ which stood for seven days at room temperature indicated that, similarly to the bis(spirodienone) derivatives of **1a**, an isomerization process might be taking place (see below).



3



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The main tris(spirodienone) product (**3**, CI MS: *m*/*z* 967.7 (MH^+)) also isomerized in solution, making it difficult to isolate it as a pure material. This product displays in the ^1H NMR (400 MHz, $CDCl_3$, rt) spectrum three broad singlets at 0.93, 0.95, and 1.00 ppm integrating for three t-Bu groups, one sharp singlet integrating for two t-Bu groups at 1.25 ppm, one sharp t-Bu singlet at 1.26 ppm, six partially overlapping AB systems for the twelve methylene protons at the 2.90−4.00 ppm region, and six vinyl and six aromatic signals (Figure 2). The ^{13}C NMR spectrum displays three carbonyl signals at 196.93, 198.12, and 198.7 ppm and three spiro signals resonating at 82.49, 82.94, and 82.99 ppm, in agreement with a tris(spirodienone) structure of C_1 symmetry.

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(6) For a preliminary communication see: Grynszpan, F.; Biali, S. E. *J. Chem. Soc., Chem. Commun.* **1994**, 2545. Part of this work was presented in the XXth International Symposium on Macrocyclic Chemistry, Jerusalem, Israel, July 2−7, 1995, Abstract, p 3. Grynszpan, F.; Aleksiuk, O.; Biali, S. E. *Pure Appl. Chem.* **1996**, *68*, 1429.

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(8) Biali, S. E.; Buda, A. M.; Mislow, K. *J. Org. Chem.* **1988**, *53*, 1289.

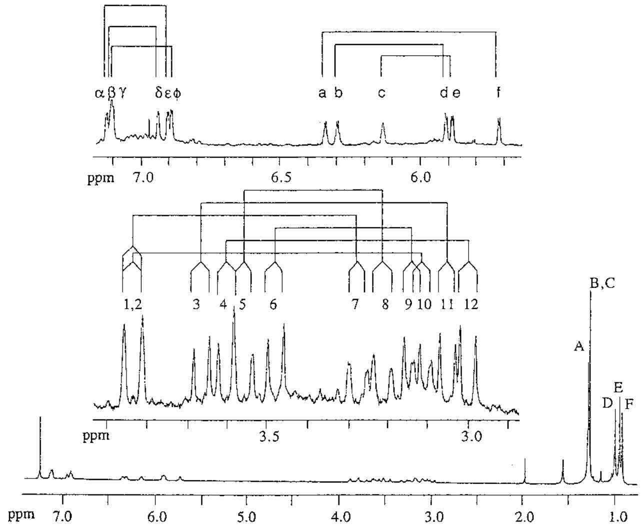
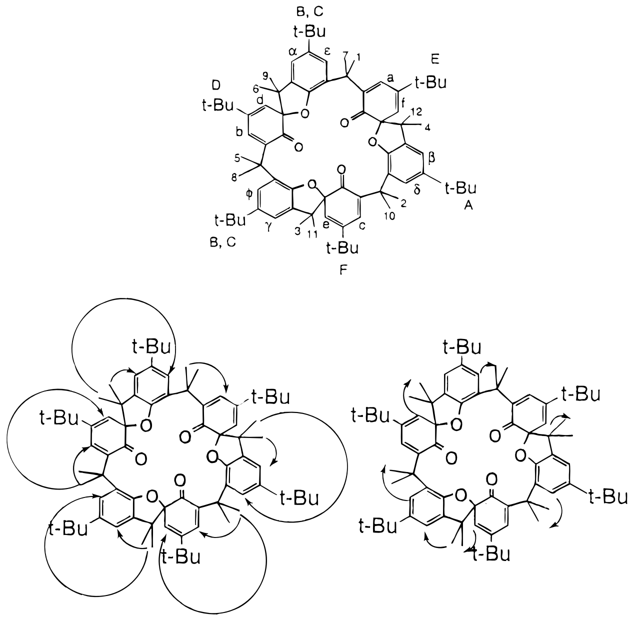


Figure 2. 200 MHz ^{1}H NMR of **3** in $CDCl_3$ at rt. Top and center: 400 MHz expansions of the aromatic-vinyl and methylene regions.



COSY correlations NOESY correlations

Figure 3. Bottom: Observed COSY and NOESY correlations of **3** (the arrows represent the observed correlations). Top: total assignment of the ^{1}H signals of **3** (cf. Figure 2).

The structure of **3** was deduced from the NMR data. Mutually coupled methylene signals as well as the long range coupled vinyl and aromatic proton pairs were identified by a 2D DQF COSY spectrum. NOE cross peaks between the t-Bu signals and vinyl signals revealed that the three broad t-Bu signals (D, E, and F, Figure 2) belong to the cyclohexadienone rings. In addition, several long-range coupling correlations and NOE interactions were detected between the methylene protons and the vinyl and aromatic signals. The total assignment of the signals and a selection of NOESY and COSY correlations are shown in Figure 3.

On the basis of their chemical shift, the aromatic and vinyl protons can be divided in two subgroups. In the case of the aromatic protons the downfield subgroup can be assigned to the protons adjacent to the dihydrofuran methylenes while in the case of the vinyl protons the upfield subgroup is the one which corresponds to the protons adjacent to those methylene protons.

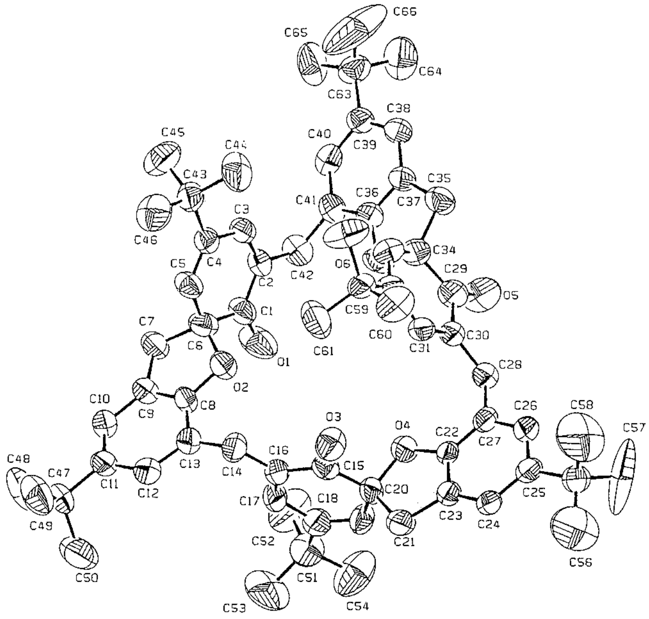


Figure 4. Numbering scheme of the molecular structure of the tris(spirodienone) derivative **3**.

The NOE interactions found between the aromatic and methylene protons (cf. Figure 3) indicate that there is an alternant arrangement of ether and carbonyl groups along the macrocycle. Since according to the NMR data the structure has C_1 symmetry, the three stereocenters must necessarily possess dissimilar configurations (*RRS*/*SSR*). Cooling down of a $CDCl_2F$[9] sample of **3** to 135 K resulted in some shifting and some broadening of the ^{1}H NMR signals but not in a decoalescence process, indicating that either the rotational barrier is lower than 7 kcal mol^{-1} or that the system exists in a single preferred conformation.

Crystal Structure of 3. Single crystals suitable for X-ray crystallography were grown from a CH_2Cl_2/MeCN solution. The molecule presented in the crystal three disordered t-Bu groups (those attached to the phenyl rings). In addition, disordered solvent molecules of MeCN, CH_2Cl_2, and H_2O were found in the unit cell which raised the *R* factor to 0.109. Although a detailed analysis of the solvent inclusion is unwarranted, the quality of the crystal structure is sufficient to corroborate the structural assignment based on the spectroscopic data and to analyze the conformation of the molecule in the crystal. The crystal structure unambiguously shows that the three spirodienone subunits are arranged in a homodirectional fashion, with the ether and carbonyl groups arranged alternantly along the macrocycle and the three chiral centers possessing dissimilar configurations (*RRS* or *SSR*). The numbering scheme and a stereoview of the molecular structure of **3** are shown in Figures 4 and 5.

In the crystal conformation of **3** the phenoxy rings are almost coplanar to the mean plane of the molecule, with the spiro oxygens pointing into the molecular cavity, whereas the dienone rings are almost perpendicular to the mean plane of the molecule. Similar conformations were observed in the crystal structures of the bis(spirodienone) calix[4]arene derivatives **2A**, **2B**, and **2A′**.

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[9] Siegel, J.; Anet, F. A. L. *J. Org. Chem.* **1988**, *53*, 2629.

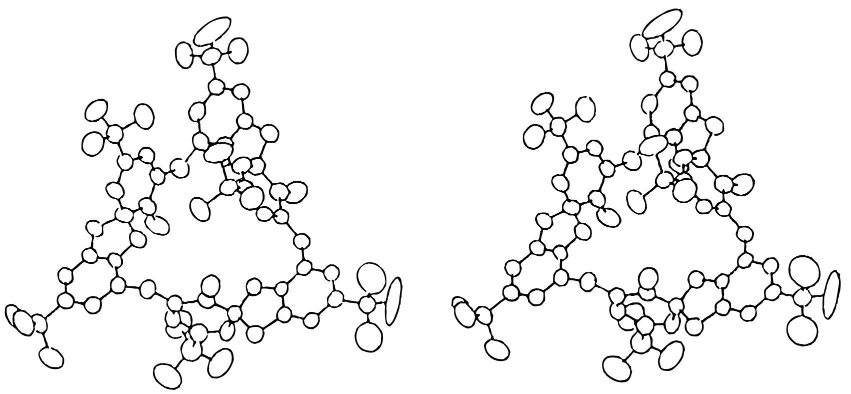


Figure 5. Stereoview of the crystal structure of **3**.

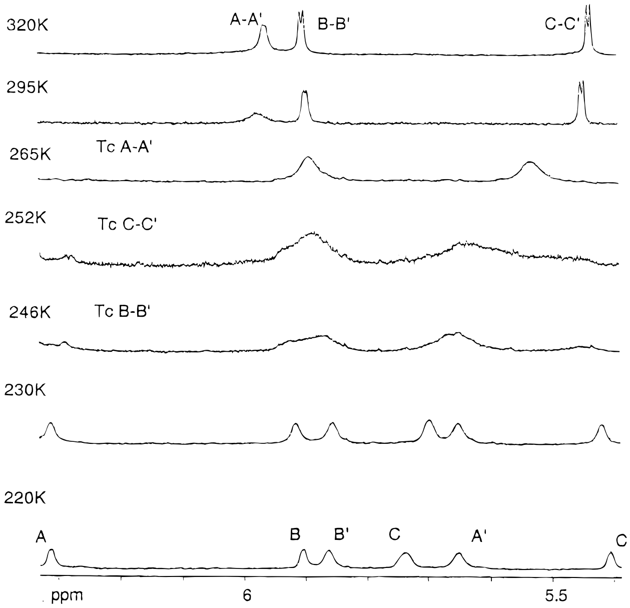
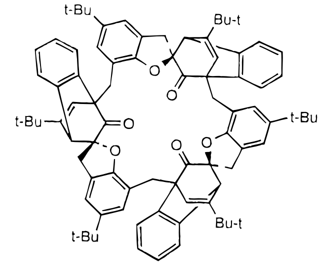


Figure 6. 400 MHz ^{1}H NMR spectrum of the vinyl region of **5** in $CDCl_3$ at different temperatures.

Two carbonyl groups are pointing to one side (i.e., both "up") while the remaining one is pointing to the opposite side ("down") of the mean plane of the molecule. Although the molecule is asymmetric, the crystal conformation resembles an equilateral triangle, in which the phenoxy rings and the dienone rings are located at its vertices and sides, respectively. The spiro C−O bonds are somewhat elongated (O(2)C(6): 1.462(8) Å, O(4)C(20): 1.481(7) Å, O(6)C(34): 1.466(7) Å) as observed in the crystal structures of the bis(spirodienone) derivatives in which these bond lengths are in the 1.47−1.49 Å range.[3a] The O···O nonbonded distances between the three ether oxygens are O(2) O(4): 5.39, O(2) O(6): 5.16, O(4) O(6): 5.51 Å. These oxygens delimit a cavity with a radius of ca. 1.33 Å,[10] which indicates that this derivative may be suitable for the ligation of a small cation such as Li^+.

Homodirectional Diels−Alder Tris Adducts. Since the Diels−Alder benzyne bis adducts of the bis(spirodienone) derivatives do not isomerize, it could be expected that the corresponding Diels−Alder tris adducts of the tris(spirodienone) derivatives will be configurationally stable. The reaction of **3** with an excess of benzyne generated *in situ* from benzenediazonium 2-carboxylate hydrochloride[11] yielded a product (**5**) which was isolated by preparative TLC (silica gel, eluent 1:1 CH_2Cl_2/CCl_4; R_f: 0.45). **5** displays in the ^{1}H NMR spectrum ($CDCl_3$, rt) some broad signals, which sharpen upon raising the temperature to 320 K. The spectrum displays five t-Bu signals in the 0.97−1.19 ppm region integrating for 54 protons, six AB systems integrating for twelve methylene protons in the 2.58−3.95 ppm range, and three allylic doublets at 4.18, 4.25, and 4.26 ppm. In addition, three vinyl signals at 5.46, 5.92, and 5.96 ppm and several partially overlapping aromatic signals integrating for eighteen protons at the 6.79−7.79 ppm region were observed. **5** displays in the ^{13}C NMR spectrum three C=O signals at 199.18, 200.35, and 200.6 ppm, three C−O signals at δ 81.88, 82.29, and 83.18 ppm, twenty-one signals corresponding to sp^3 carbons and C(sp^2) signals. From these data we conclude that **5** is a Diels−Alder tris adduct of **3** of C_1 symmetry in which, on the basis of the structural characterization of the starting material **3**, the three phenyl cyclohexenone moieties and three phenoxy rings are arranged in an alternate fashion. By analogy with the bis adducts derivatives of **2A/2B**,[3a] we assume that the benzyne addition occurred in the less hindered *exo* face (*anti* to the ether oxygen).



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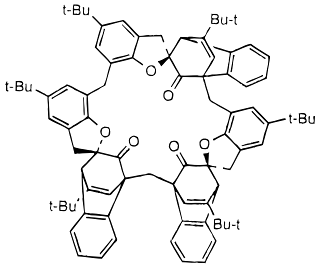

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Rotational Barrier of 5. Lowering of the temperature of a $CDCl_3$ solution of **5** resulted in broadening of all the signals in the ^{1}H NMR, followed by decoalescence and resharpening at low temperature (220 K) into a pattern with a double number of signals (Figure 6). The slow exchange spectrum indicates that the derivative exists in solution in two diastereomeric conformations which on the basis of the relative integration of the ^{1}H NMR signals are almost equally populated. For convenience we concentrated in the vinyl region (5.38−6.32 ppm) in order to follow the dynamic process. The coalescing partners (A/A′, B/B′, C/C′, cf. Figure 6) were

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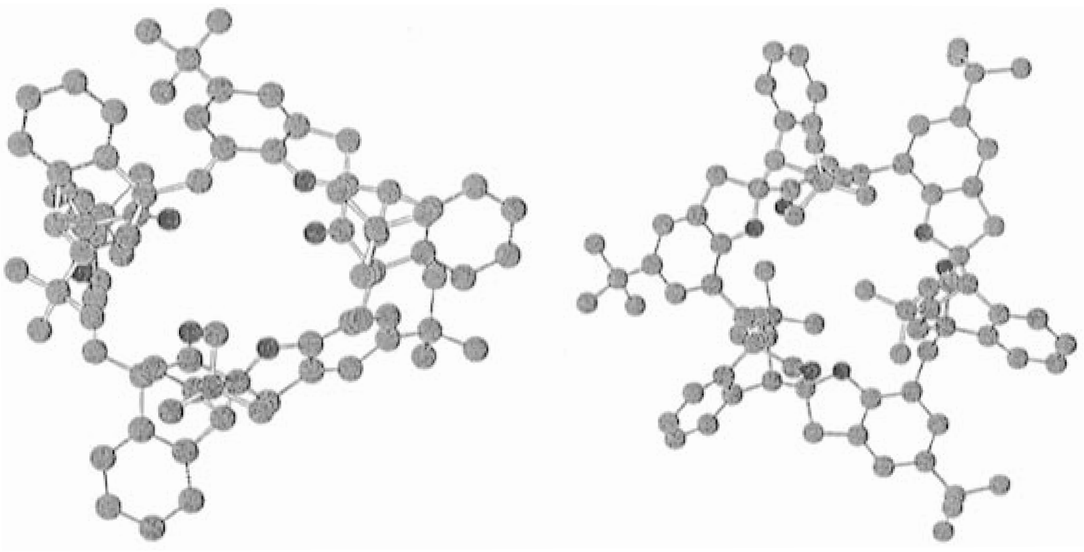
(10) The cavity radius was calculated from the O···O nonbonded distances and the van der Waals oxygen radius (2.0 Å) (Gordon, A. J.; Ford, R. A. *The Chemist's Companion*; Wiley: New York, 1972; p 109).

(11) Adams, R.; Johnson, J. R.; Wilcox, C. F., Jr. *Laboratory Experiments in Organic Chemistry;* Macmillan: New York, 1972; p 109.



5a 5b

Figure 7. Calculated low-energy conformers of **5**. Oxygen atoms are represented by black spheres, hydrogens were omitted for clarity. **5a**: lowest energy conformation of **5**. The carbonyl oxygens are pointing into the molecular cavity. **5b**: conformation analogous to the crystal conformation of **3**, in which the ether groups are pointing to the center of the molecular cavity.

deduced from the magnetization transfer cross peaks observed at 220 K in the 2D NOESY spectrum.

The chemical shifts of some of the vinyl protons are strongly temperature dependent. This is of importance, since the chemical shift differences of the coalescing partners ($\Delta\nu$) at the coalescence temperatures (T_c) are required in order to calculate the diastereomerization barrier.[12,13] These $\Delta\nu$ values for the signals A and A′ (cf., Figure 6) were not temperature dependent, whereas the $\Delta\nu$ values for the pairs B/B′ and C/C′ increased and decreased, respectively, with the increase in temperature. The pairs A/A′, B/B′, and C/C′ (for which the extrapolated $\Delta\nu_c$ values were 264, 33, and 83 Hz at their corresponding T_c) coalesced at 265, 246, and 252 K, respectively, which affords a diastereomerization barrier of 12.1 ± 0.2 kcal mol^{-1}.

The strong temperature dependence of the $\Delta\nu$ values of B/B′ and C/C′ explains an apparent contradiction observed in the fast exchange spectra at 275 K. The average signal resulting from the coalescence of C and C′ is *sharper* than the signal resulting from the coalescence of B and B′. Since the T_c of the pair C/C′ is higher than that of B/B′, it should be expected that at higher temperatures the average signal of C/C′ should be broader than the average B/B′ signal, but the opposite behavior is observed. However, since the $\Delta\nu$ values of the pairs C/C′ and B/B′ show opposite temperature dependence, as shown by the plot of ν vs T, at 275 K the $\Delta\nu$ of C/C′ is smaller than the one of B/B′. This explains the increased broadening of the average signal of B/B′ at 275 K.[13]

Molecular Mechanics Calculations for the Diels–Alder Tris Adduct 5. In order to assign the structures of the diastereomeric forms observed in the low temperature ^{1}H NMR spectrum we resorted to the MM2 force field as implemented by MACROMODEL.[14] Since a complete molecular dynamics study of the system was beyond our computational capabilities, only selected conformations were calculated. Starting from the calculated minimum energy conformation of **3** (obtained from the coordinates of the crystal conformation), we calculated the corresponding Diels–Alder tris adduct by formally fusing in an *exo* fashion three phenyl groups to the dienone subunits. Additional input conformations were chosen by examination of molecular models.

In the conformation of the Diels–Alder tris adduct of lowest steric energy (**5a**, Figure 7), the three carbonyl groups are pointing into the molecular cavity. The phenoxy rings are placed in a non coplanar fashion with regards to the mean macrocyclic plane while the phenylene rings are situated almost coplanar to it. The calculated structure **5b** obtained by fusion of three phenyl rings in an *exo-exo-exo* fashion to the crystal conformation of **3** displays a similar spatial arrangement of the ether and carbonyl groups as **3** and lies 1.3 kcal mol^{-1} above **5a**. In this structure, the ether oxygens point into the molecular cavity, while the carbonyl oxygens are perpendicular to the mean macrocyclic plane (Figure 7). We assign the conformations **5a** and **5b** to the pair of diastereomers of the Diels–Alder tris adduct **5** detected in solution.

Heterodirectional Diels–Alder Tris Adducts. Reaction of the tris(spirodienone) derivative **4** with an excess of benzyne gave the corresponding tris adduct **6** which was purified by preparative TLC (silica gel, eluent: 1:4 CH_2Cl_2/CCl_4; R_f: 0.48). This Diels–Alder tris adduct (CI MS: m/z 1195.8 (MH^+)) allowed us to elucidate the structure of the parent tris(spirodienone) derivative. **6** displays in the ^{1}H NMR spectrum six t-Bu signals,

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[12] The exchange rates at the coalescence temperatures were calculated from the $\Delta\nu$ values according to: Gutowsky, H. S.; Holm, C. H. *J. Phys. Chem.* **1956**, *25*, 1228.

[13] For a given exchange rate, the broadening of the average signal at a temperature T slightly above T_c is dependent of the chemical shift difference between the exchanging signals at T. For a discussion of the lineshape changes in temperature dependent NMR spectra see: Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 219.

[14] Still, W. C.; Mohamadi, F.; Richards, N. J. G.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T. *MACROMODEL V3.0*, Department of Chemistry, Columbia University, New York.

three of them sharp at 1.11, 1.24, and 1.29 ppm and three broader at 0.66, 0.96, and 1.12 ppm, twelve partially overlapping doublets corresponding to the methylene protons in the 2.50−4.20 ppm region, three doublets for the allylic protons (two partially overlapping at 4.21 ppm and the third at 3.97 ppm), three doublets at 5.47, 5.94, and 6.71 ppm for the vinyl signals, and several overlapping aromatic signals integrating for eighteen protons in the 6.58−7.56 ppm region. The ^{13}C NMR spectrum of **6** shows three signals at 197.77, 198.70, and 201.45 ppm for the carbonyls groups, forty two C(sp^3) signals, three signals at 80.47, 81.56, and 83.59 ppm which can be assigned to the C−O carbons and twenty-one C(sp^3) signals. The spectroscopic data indicate that the system is of C_1 symmetry and includes three phenyl substituents, three spiro ethers, and three carbonyl groups.

Lowering the temperature of a solution of **6** in CDCl$_3$ to 220 K resulted in a significant shift of most of the signals but not in a decoalescence process, indicating that the molecule exists essentially in a single conformation, or that the conformational exchange barrier is too low to be detected by our measurements.

A complete assignment of the ^{1}H NMR signals was achieved by a combination of 2D NMR techniques (DQF COSY, NOESY, TOCSY, and ROESY). From the 2D COSY spectrum we assigned the signals belonging to pairs of mutually coupled methylene protons as well as the allyl and vinyl protons at each cyclohexenone ring. On the basis of the NOESY experiment we assigned the three sharp t-Bu signals to the phenoxy rings and the three broad t-Bu signals to the cyclohexenone rings. Notably, a NOE cross peak was observed for two phenoxy aromatic protons at different rings (6.58−7.00 ppm), indicating a heterodirectional arrangement of the spiroenone subunits within the macrocycle, i.e., a nonalternant arrangement of carbonyl and ether functionalities. NOE interactions were also observed between the enone t-Bu signal at 0.96 ppm and the dihydrofuran methylene signals of a vicinal spiroenone group and between the t-Bu signal at 0.66 ppm and the vinyl signal at 5.94 ppm. The complete assignment of the ^{1}H NMR spectrum as well as a summary of the 2D correlations are shown in Figure S1 (supporting information).

The configurations of the spiro carbons of **6** were assigned on the basis of the observed NOEs assuming that all the phenylene groups are fused in an *exo* fashion. In each spiroenone unit the dihydrofuran methylene, the phenylene, and the vinyl groups are oriented nearly perpendicular to the carbonyl plane, with the methylene being in a *cis* and *trans* relationship to the phenylene and vinyl groups, respectively. For the pair of spiroenones arranged in a head to tail fashion, a NOE interaction was observed between the t-Bu group of a hexenone ring and the vinylic signal of the second spiroenone subunit. This indicates that both spiro stereocenters possess identical configurations since both vinylic groups must be oriented in the same direction (both "up" or "down"). The t-Bu group of the remaining spiroenone subunit is in steric proximity to a dihydrofuran methylene group, indicating that both groups are oriented in the same direction. Since the two subunits are oriented in a head to head fashion, the *trans* arrangement between the two vinyl groups indicates that the configurations of the spiro stereocenters are identical.

Assuming that the Diels−Alder reaction retained the stereochemical identity of the spiro sterocenters, we conclude that both **4** and **6** present a nonalternant arrangement of spirodienone units in a C_1 symmetry system with all the spiro stereocenters having identical configurations (e.g., *RRR* or *SSS*).

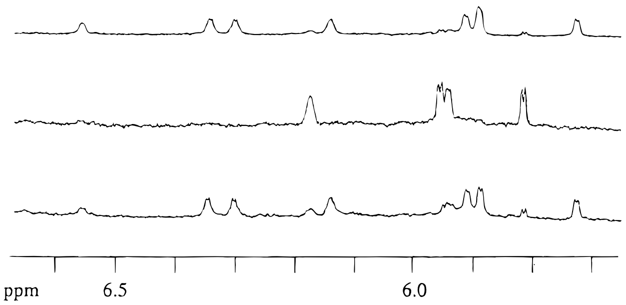
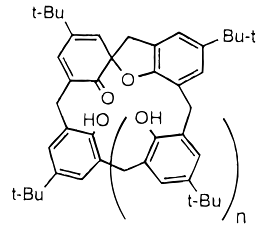


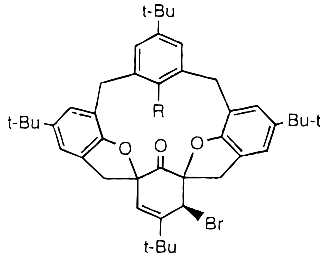
Figure 8. Mutual isomerization of the tris(spirodienones) **3** and **4** in toluene at 85 °C. ^{1}H NMR spectrum (vinyl region) of **3** (top), **4** (center), and of the equilibrium mixture obtained after 20 h (bottom).

Mutual Isomerization in Tris(spirodienone) Calix[6]arene Derivatives. The two tris(spirodienone) derivatives of **1c** (**3** and **4**) mutually interconvert in solution. This behavior is similar to that presented by the bis(spirodienone) derivatives of **1a**. In order to determine their relative thermodynamic stability, an equilibration experiment was conducted by heating samples of the isomers in toluene at 85 °C until isomeric mixtures of identical composition were obtained. The isomeric ratio was estimated by integration of the vinyl signals in the ^{1}H NMR spectra. Starting from either **3** or **4**, the equilibrium composition obtained after 20 h was 71% **3** and 29% **4** (Figure 8). After 120 h of heating, the mixtures showed clear signs of decomposition. Assuming that the thermal isomerization mutually interconverts all possible isomers, it can be concluded from the equilibration data that under the described conditions the isomer obtained in excess in the oxidation reaction (i.e., **3**) is the thermodynamically more stable form. The calculated energy difference between the two isomers is $\Delta G° = 0.66$ kcal mol^{-1}. It should be noted that both **3** and **4** contain two parallel carbonyl groups and a third one in an antiparallel arrangement. The remaining four possible tris(spirodienone) pairs of enantiomers (one homodirectional system of C_3 symmetry and three heterodirectional systems of C_1 symmetry) were not observed, and they are probably both kinetically and thermodynamically less favored. Interestingly, in both the tris(spirodienone) and bis(spirodienone) systems, homodirectional isomers possessing stereocenters of identical configuration are less stable than the corresponding stereoisomers possessing stereocenters of dissimilar configurations. In the former stereoisomers all carbonyl groups should be oriented in a nearly parallel fashion, and the repulsive dipole−dipole interactions between the groups destablize the structure. It seems likely that **3** is favored thermodynamically since in this isomer the three carbonyl dipoles are not oriented in parallel (as in the isomer of C_3 symmetry), nor are two carbonyl groups in spatial proximity (as in the systems with a nonalternant arrangement of groups).

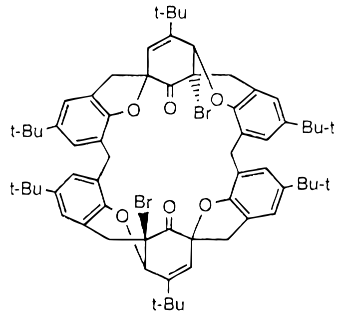
Bis(bromoannulation) of 1c. Monospirodienone calix[4]arene **7a** may undergo a electrophilic addition by bromine with the concomitant formation of a C−O bond involving the carbon α to the carbonyl and the OH of a vicinal phenol ring, yielding **8**.[3b] Since the reagent used in the synthesis of the polyspirodienone systems is an ammonium tribromide salt, and the tribromide may act both as an oxidating agent and as an electrophile, bromospiroannulated derivatives may be formed also during the preparation of the tris(spirodienone) calixarene systems.



7a n=1
7b n=2
7c n=3



8



9

The first eluted material in the chromatographic separation of the product mixture obtained in the oxidation of **1c** with the ammonium tribromide/base was a colorless compound that did not react with benzyne. The compound which was obtained in low yield (3%) displayed in the ^{1}H NMR spectrum three t-Bu signals, six partially overlapping doublets for the methylene protons in the 3.38−4.02 ppm region, four aromatic signals in the 6.66−7.03 region, and two mutually coupled additional signals at 4.86 (d, $J = 1.8$ Hz) and 5.85 (d, $J = 1.8$ Hz) ppm. The ^{13}C NMR of the compound (100.62 MHz, $CDCl_3$, rt) displayed a carbonyl signal at 200.5 ppm, signals at 75.64 and 83.12 ppm characteristic of spiro carbons, and fourteen signals at the 118.12−156.04 ppm region, in agreement with a structure of either C_2 or C_i symmetry in which four aromatic and two cyclohexenone rings are present. This structure was characterized by X-ray crystallography as the bis(bromospiroannulated) derivative **9** of C_i symmetry.[15]

The formation of **9** may involve, at the first stage, the oxidation of **1c** into a system containing two spirodienone moieties at nonvicinal positions, followed by bisbromoannulation, or the bromoannulation of the monospirodienone calix[6]arene derivative **7c**, followed by oxidation and bromoannulation reactions. Interestingly, the **1c** → **9** transformation involved the formation of six stereocenters, two carbonyls and four ether groups.

Oxidation of 1c with $K_3Fe(CN)_6$. Since the tribromide used for the preparation of the spirodienones may act both as an oxidant and as a brominating agent, once a spirodienone is formed, the bromoannulation reaction may compete with the formation of a second spirodienone group. We therefore examined the oxidation of calixarenes with several mild oxidating agents. The best results were obtained with the combination $K_3Fe(CN)_6$/aq KOH.

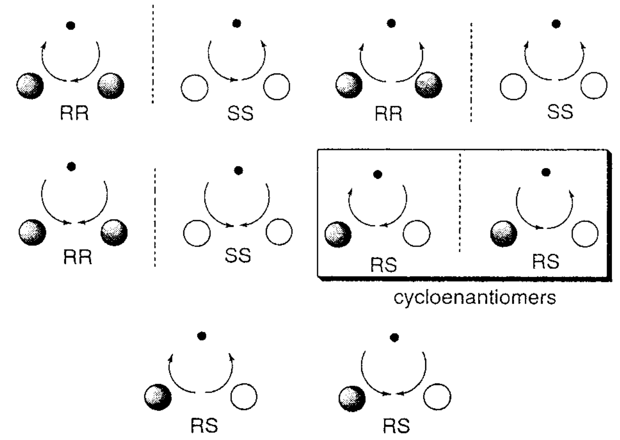


Figure 9. The ten isomeric forms of the bis(spirodienone) derivatives of **1b** in a sphere and curved arrow representation. The black point represents the free phenol group within the macrocyclic structure.

Oxidation of **1a** with excess $K_3Fe(CN)_6$/aqueous KOH yielded a mixture of **2A**, **2A′**, and **2B**.[16] Reaction of **1c** with $K_3Fe(CN)_6$ /aq KOH resulted mostly in **3** (as judged by the ^{1}H NMR pattern) and an additional unidentified product. Separation of **3** from the other compound was achieved by column chromatography affording **3** in 20% yield. The ^{1}H NMR of the unidentified product showed a broad structureless pattern of signals. Under reduction conditions ($NaBH_4$/MeOH) **3** reverted to **1c** while treatment of the additional product did not result in the regeneration of **1c**. This unidentified compound which is most likely a polymeric material, was not further investigated.

Bis(spirodienone) Derivatives of *p*-*t*-Bu-Calix[5]arene. Since each spirodienone subunit is derived from two phenolic groups, a poly(spirodienone) system derived from a calix[*n*]arene possessing an odd number of rings must include an odd number of unreacted phenolic groups. Ten possible isomeric forms (four enantiomeric pairs and two *meso* forms) are possible for the bis(spirodienone) derivative of **1b**. The isomeric forms of the bis(spirodienone) derivatives of **1b** are schematically shown in Figure 9 where the black point represents the unreacted phenyl ring. The enantiomeric pair enclosed in the box is of stereochemical interest since it may qualify as a cycloenantiomeric pair.[17] In a cycloenantiomeric pair both enantiomers possess an identical configuration pattern of stereocenters, but they differ in the sense of direction of the ring.[17,18]

Oxidation of **1b** with either $K_3Fe(CN)_6$/base or phenyltrimethyl ammonium tribromide/base resulted in complex mixture as judged by ^{1}H NMR spectroscopy. However, oxidation of a toluene solution of the mono spirodienone derivative of **1b** (**7b**[5]) by $K_3Fe(CN)_6$/base yielded a mixture of compounds which was separated by column chromatography. The main fraction (22.5%) consisted mostly of a bis(spirodienone) derivative (CI MS: *m*/*z* 807.4 ($\mathrm{MH^+}$) and 811.5 (**1b**$\mathrm{H^+}$)). The last fractions were complex mixtures of compounds which were not investigated.

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[15] The crystallographic structure of **9** is described in reference 6.

[16] This combination was previously used for the oxidation of bis(naphthols) to their corresponding spirodienone derivatives. See: Bennett, D. J.; Dean, F. M.; Herbin, G. A.; Matkin, D. A.; Price, A. W. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1978.

[17] Prelog, V.; Gerlach, H. *Helv. Chim. Acta* **1964**, *47*, 2288. Prelog, V. *Science* **1976**, *17*, 193.

[18] Singh, M. D.; Siegel, J.; Biali, S. E.; Mislow, K. *J. Am. Chem. Soc.* **1987**, *109*, 3397.

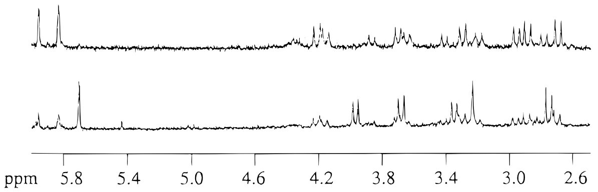


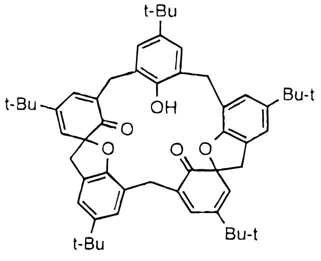
Figure 10. Isomerization of the bis(spirodienone) derivative of **1b**. Top: methylene and selected vinyl region of the ^{1}H NMR spectrum (toluene-d_8) of **10**. Bottom: the same sample after heating at 85 °C during 32 h.

The compound displays in the ^{1}H NMR (400 MHz, $CDCl_3$) five t-Bu signals in the 1.09−1.29 ppm region, ten doublets corresponding to the methylene protons (2.99−4.35 ppm region), two doublets in the vinyl region at 6.08 and 6.11 ppm, eight partially overlapping signals and a OH signal at 8.11 ppm. The ^{13}C NMR (100.62 MHz, $CDCl_3$) displays two carbonyl signals at 196.70 and 200.55 ppm, but only a single signal at 85.19 ppm which is ascribed to two accidentally isochronous spiro carbons. These spectroscopic data are in agreement with a bis(spirodienone) structure of C_1 symmetry.

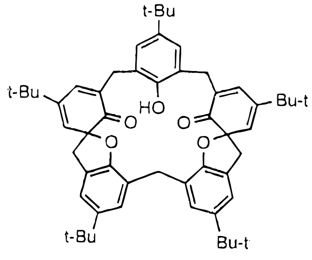
In order to find out the connectivity array in the molecule and to completely assign the NMR signals we carried out 2D NMR DQF COSY and NOESY experiments. Due to the close proximity of some signals in some cases we were unable to conclude which of the two signals is the one correlated. However, the long range coupling interactions found in a TOCSY spectrum together with the NOESY and COSY data enabled us to determine the arrangement of the spirodienone subunits. Since one of two methylene groups flanking the unreacted phenol group is in a spatial proximity to a vinyl proton, while the second group is connected to two aromatic rings, it can be concluded that the two spirodienone subunits exist in a homodirectional arrangement. The system can be either the enantiomeric pair *RR*/*SS* (in which both ketone groups are pointing to the same side of the molecular mean plane), or the cycloenantiomeric pair *RS*/*SR*, where the ketone groups are in an antiparallel arrangement “compensating” their bond moments within the molecule. By analogy with the bis and tris(spirodienone) derivatives of **1a** and **1c**, where the (*RS*) isomer is formed preferrently, we assign to the main product the cycloenantiomeric structure **10**.

Relative Thermodynamic Stability of the Bis(spirodienone) Derivatives of 1b. In order to estimate the thermodynamic stability of the bis(spirodienone) derivatives of **1b**, we isomerized a sample of **10** by heating a toluene-d_8 solution to 85 °C during 32 h, until a constant ratio of isomers was obtained. The resulting mixture consisted of a new bis(spirodienone) derivative, the starting material, and additional compounds in very low concentrations (Figure 10). The new spirodienone derivative displayed in the ^{1}H NMR (toluene-d_8, rt) three singlets in a 2:2:1 ratio at 0.97, 1.21, 1.23 ppm corresponding to the t-Bu groups, four doublets and a *singlet* in a 1:1:1:1:1 ratio for the methylene region resonating at 2.76−3.97 ppm, a doublet at 5.69 ppm corresponding to a vinyl proton, four singlets in the aromatic region at 6.80−7.28 ppm, and a broad singlet for the OH group at 8.07 ppm.

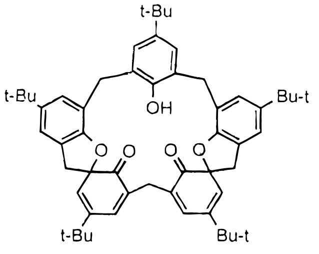
On the basis of the ^{1}H NMR pattern, we assign to the new bis(spirodienone) derivative a C_2 symmetry structure in which the symmetry axis passes through the phenol group and a distal methylene group, rendering the two methylene protons homotopic. Necessarily, due to the presence of a C_2 axis, the two spirodienone subunits must be oriented in a heterodirectional arrangement while the two stereogenic carbons must possess identical configurations (e.g., *RR* or *SS*).



10



11



12

Two isomeric structures in which either the carbonyl or the ether groups are located at neighboring positions are compatible with the spectroscopic data (**11** and **12**). In order to elucidate the structure of the new derivative we performed a 2D DQF COSY spectrum. The 2D data show a coupling correlation between the methylene singlet (3.24 ppm) and one aromatic signal integrating for two protons (6.80 ppm). On the basis of this coupling interaction, it can be concluded that *two* aromatic protons are adjacent to the methylene group located on the C_2 axis. The structure of the new derivative can be therefore unequivocally assigned to a heterodirectional form **11** with two vicinal phenoxy rings. It can be concluded that while the homodirectional isomer **10** represents the kinetic product, the heterodirectional isomer **11** is the one more stable thermodynamically (in a toluene solution). The relative thermodynamic stability of the isomer **11** can be rationalized since in this isomer the carbonyl dipoles are nonvicinal and are oriented in an antiparallel fashion.

Conclusions. Bis- and tris(spirodienone) derivatives of the calixarenes **1b** and **1c** can be prepared by oxidation of the corresponding calixarenes. On the basis of the equilibration studies it can be concluded that the relative stability of the isomers of the calixarene polyspirodienone derivatives is dictated by the position and orientation of the carbonyl groups. Systems possessing carbonyl groups at nonvicinal rings and in which the carbonyl groups can be oriented in antiparallel fashion are thermodynamically more stable.

Experimental Section

General Methods. X-ray diffraction data were measured by with an ENRAF-NONIUS CAD-4 computer-controlled diffractometer. Cu K$_\alpha$ (λ = 1.54178 Å) radiation with a graphite crystal monochromator in the incident beam was used. The crystallographic computing was done on a VAX 9000 computer using the TEXSAN structure analysis software.

Crystal data for **3**: yellow crystals, $C_{66}H_{78}O_6{\cdot}{}^1/_2CH_3CN{\cdot}{}^1/_4CH_2Cl_2{\cdot}{}^1/_4H_2O$, FW: 967.35, space group $P2_{1/n}$, $a = 18.916(3)$ Å, $b = 20.010(6)$ Å, $c = 17.604(3)$ Å, $\beta = 90.37(2)°$, $V = 6663(2)$ Å^3, $z = 4$, $\rho_{calc} = 1.01$ g cm^{-3}, μ(Cu Kα): 6.51 cm^{-1}, no. of unique reflections: 10085, no. of reflections with $I \geq 3\sigma_I$: 5945, R: 0.109, R_w: 0.149.[19]

The mass spectrometry determinations were carried out at the Mass Spectrometry Center at the Technion, Haifa. Melting points were determined on a Mel-Temp II apparatus and are uncorrected.

Materials. All column chromatographies were performed using silica gel 230−400 mesh purchased from Merck. The preparative TLC were performed using precoated glass plates of silica gel 60 F_{254} purchased from Merck. Calixarenes **1b**[20] and **1c**[21] were prepared according to the literature procedures.

Oxidation of 1a with $K_3Fe(CN)_6$. Solid $K_3Fe(CN)_6$ (2.03 g, 6.16 mmol) was added to a toluene solution (50 mL) of **1a** (200 mg, 0.3 mmol) while stirring at room temperature. An aqueous solution of KOH (30 mL, 10%) was then added dropwise into the reaction mixture. After stirring at room temperature for 12 h the organic phase was separated and washed several times with brine and finally with water. The organic phase was dried over $MgSO_4$ and filtered, and the solvent was evaporated, yielding 48 mg (23%) of a mixture of the three bis(spirodienone) derivatives **2A**, **2B**, and **2A′** in a 2:1:1 ratio as judged by integration of the vinyl signals in the ^{1}H NMR spectrum.

Oxidation of 1c with Phenyltrimethylammonium tribromide. A solution of phenyltrimethylammonium tribromide (2.32 g, 6.17 mmol) in 25 mL of CH_2Cl_2 was slowly added dropwise into a stirred solution of **1c** (1 g, 1.02 mmol) in 100 mL CH_2Cl_2. A 50 g amount of aqueous NaOH 30% was then added dropwise to the stirred reaction mixture. After 150 min of reflux, the reaction mixture was cooled to rt and the organic phase was separated and washed several times with brine and finally with water. Evaporation of the solvent yielded 970 mg of a complex mixture of products as judged by the ^{1}H NMR spectrum. Separation of the mixture was carried out by column chromatography (eluted firstly with $CHCl_3$, and finally with $CHCl_3$:MeOH 4:1). The first eluted compound was the colorless *meso* compound **9** (mp 296−299 °C, 35 mg, 3%). Several fractions containing a complex mixture of derivatives were then eluted (400 mg) followed by three fractions containing mostly **4** (145 mg, 21%), several fractions containing a complex mixture of derivatives (100 mg) which were not characterized, and finally 290 mg of a mixture of two compounds which was separated by precipitation from a MeCN solution. A colorless compound (28 mg) which was not characterized separated, while the main product of the reaction, the dark yellow **3** remained in solution. Evaporation of the solvent afforded 250 mg (25%) of **3** mp 200−215 °C dec.

Spectroscopic Data for 3. ^{1}H NMR (400 MHz, $CDCl_3$, rt) δ 0.93 (s, 9H, t-Bu), 0.95 (s, 9H, t-Bu), 1.00 (s, 9H, t-Bu), 1.25 (s, 18H, t-Bu), 1.26 (s, 9H, t-Bu), 3.00 (d, 1H, J = 15.5 Hz, CH_2), 3.05 (d, 1H, J = 15.5 Hz, CH_2), 3.11 (d, 1H, J = 15.4 Hz, CH_2), 3.14 (d, 1H, J = 18.9 Hz, CH_2), 3.21 (d, 1H, J = 17.6 Hz, CH_2), 3.27 (d, 1H, J = 15.6 Hz, CH_2), 3.48 (d, 1H, J = 18.9 Hz, CH_2), 3.56 (d, 1H, J = 17.6 Hz, CH_2), 3.60 (d, 1H, J = 15.5 Hz, CH_2), 3.67 (d, 1H, J = 15.5 Hz, CH_2), 3.83 (d, 2H, J = 15.4 Hz, CH_2), 5.73 (d, 1H, J = 2.2 Hz, CH), 5.89 (d, 1H, J = 2.2 Hz, CH), 5.92 (d, 1H, J = 2.2 Hz, CH), 6.14 (q broad, 1H, J = 1.5 Hz, CH), 6.30 (q, 1H, J = 1.5 Hz, CH), 6.35 (q, 1H, J = 1.5 Hz, CH), 6.90 (d, 1H, J = 1.8 Hz, ArH), 6.91 (d, 1H, J = 1.8 Hz, ArH), 6.94 (d, 1H, J = 1.8 Hz, ArH), 7.11 (m, 2H, ArH) and 7.17 (d, 1H, J = 1.8 Hz, ArH) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, rt) δ 27.45, 28.35, 28.73, 29.08, 29.69, 29.90, 31.82, 34.03, 34.07, 34.25, 34.27, 34.30, 39.56, 40.17, 40.62, 53.40, 82.49 (C−O), 82.94 (C−O), 82.99 (C−O), 118.21, 118.62, 118.73, 119.73, 120.26, 120.32, 125.44, 126.11, 126.49, 126.79, 126.03, 127.25, 127.56, 127.62, 133.63, 133.68, 134.84, 136.35, 137.41, 137.69, 143.23, 143.42, 143.66, 143.77, 143.81, 144.04, 154.28, 154.78, 155.38, 196.93 (C═O), 198.12 (C═O), and 198.76 (C═O) ppm. IR: ν 1689.8, 1613.8 cm^{-1}, CI MS: m/z 967.7 (MH$^+$).

Spectroscopic Data for 4. ^{1}H NMR (400 MHz, $CDCl_3$, rt) δ 0.88 (s, 9H), 0.95 (s, 9H, t-Bu), 1.11 (s, 9H, t-Bu), 1.15 (s, 9H, t-Bu), 1.24 (s, 9H, t-Bu), 1.29 (s, 9H, t-Bu), 2.98 (d, 1H, J = 15.3 Hz, CH_2), 3.12 (three partially overlapping doublets, 3H, CH_2), 3.25 (d, 1H, J = 12.1 Hz, CH_2), 3.41(d, 1H, J = 12.4 Hz, CH_2), 3.48 (d, 1H, J = 17.4 Hz, CH_2), 3.45 (d, 1H, J = 15.4 Hz, CH_2), 3.54 (d, 1H, J = 15.6 Hz, CH_2), 3.64 (d, 1H, J = 15.4 Hz, CH_2), 3.81 (d, 1H, J = 17.4 Hz, CH_2), 3.89 (d, 1H, J = 17.1 Hz, CH_2), 5.81 (d, 1H, J = 2.5 Hz, CH), 5.94 (d, 1H, J = 2.3 Hz, CH), 5.95 (d, 1H, J = 2.4 Hz, CH), 6.17 (broad singlet, 1H, CH), 6.79 (d, 1H, J = 2.1 Hz, CH), 6.96 (d, 1H, J = 2.1 Hz, CH), 7.06−6.98 (six partially overlapping doublets, 1H CH + 5H ArH) and 7.11 (d, 1H, J = 2.5 Hz, ArH) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, rt) δ 26.92, 28.1−28.5 (overlapping signals), 29.08, 31.5−32.3 (overlapping signals), 33.81, 34.08, 34.18, 34.23, 34.28, 34.33, 82.21 (C−O), 82.45 (C−O), 85.30 (C−O), 118.64, 118.95, 120.22, 120.30, 124.07, 124.73, 125.72, 126.50, 127.17, 127.24, 127.31, 128.18, 128.44, 128.99, 129.71, 130.09, 130.49, 130.98, 135.03, 135.92, 139.73, 141.33, 143.18, 143.30, 143.96, 144.88, 145.18, 153.57, 154.21, 154.67, 197.12 (C═O), 197.56 (C═O), 199.01 (C═O) ppm. IR: ν 1689.4 (C═O), 1649.0, 1612.8 cm^{-1}. CI MS: m/z 967.7 (MH$^+$).

Spectroscopic Data for 9. ^{1}H NMR (400 MHz, $CDCl_3$, rt) δ 1.14 (s, 18H, t-Bu), 1.21 (s, 18H, t-Bu), 1.25 (s, 18H, t-Bu), 3.38 (d, 2H, J = 16.1 Hz, CH_2), 3.46 (d, 2H, J = 19.1 Hz, CH_2), 3.47 (d, 2H, J = 16.0 Hz, CH_2), 3.65 (d, 2H, J = 16.0 Hz, CH_2), 3.95 (d, 2H, J = 18.4 Hz, CH_2), 4.02 (d, 2H, J = 16.6 Hz CH_2), 4.86 (d, 2H, J = 1.5 Hz, CH), 5.85 (d, 2H, J = 1.7 Hz, CH), 6.66 (s br, 2H, ArH), 6.90 (d, 2H, J = 1.4 Hz, ArH), 6.98 (s br, 2H, ArH) and 7.03 (s br, 2H, ArH) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, rt) δ 28.22, 28.38, 31.43, 31.79, 34.21, 34.26, 36.21, 45.69, 56.94 (C-Br), 75.64 (C−O) β, 83.12 (C−O) α, 118.12, 119.31, 122.00, 123.43, 124.59, 125.60, 127.99, 129.19, 143.50, 143.92, 146.54, 149.27, 156.04 and 200.5 (C═O) ppm. IR: ν 1737.5, 1667.0, 1608.2 cm^{-1}. CI MS: m/z 1127.6 (MH$^+$).

Oxidation of 1c with $K_3Fe(CN)_6$. A 2.5 g amount of $K_3Fe(CN)_6$ (7.59 mmol) was added to a solution of **1c** (250 mg, 0.26 mmol) in toluene (250 mL). A solution of 40 g of KOH in 300 mL of H_2O was then added dropwise to the reaction mixture which was stirred for 24 h at room temperature. After separation of the organic phase, it was washed several times with brine and finally with water to pH 6. The organic fraction was dried over $MgSO_4$ and filtered. The solvent was evaporated yielding 235 mg of a yellow mixture. The mixture was separated by column chromatography (eluent: $CHCl_3$:CH_2Cl_2 1:1), yielding **3** mp 190−5 °C dec, 225 °C melt (50 mg, 0.052 mmol, 20%).

Preparation of the Diels Alder Tris Adduct 5. Benzenediazonium-2-carboxylate hydrochloride[11] (250 mg) was added to a solution of **3** (100 mg, 0.104 mmol) in 20 mL of freshly distilled 1,2-dichloroethane. Freshly distilled propylene oxide (3 mL) was then added dropwise to the stirred reaction mixture. After 60 min of reflux in a water bath, the mixture was cooled to room temperature and the solvent was evaporated, yielding a brown oily compound. This product was separated by preparative TLC (eluent: 1:1 CH_2Cl_2/CCl_4). The second fraction (R_f: 0.45) contained 30 mg (0.023 mmol) of **5** (90% pure, 22%). Further purification was achieved by recrystallization from $CHCl_3$/MeCN, yielding a product of mp 292−294 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 320 K) δ 0.97 (s, 9H, t-Bu), 0.98 (s, 9H, t-Bu), 1.09 (s, 9H, t-Bu), 1.15 (s, 18H, t-Bu), 1.19 (s, 9H, t-Bu), 2.62 (d, 1 H, J = 16.1 Hz, CH_2), 2.74 (d, 1 H, J = 16.0 Hz, CH_2), four overlapping doublets 2.94−2.82 (4 H, CH_2), 3.26 (d, 1 H, J = 15.6 Hz CH_2), 3.33 (d, 1 H, J = 16.1 Hz, CH_2), 3.38 (d, 1 H, J = 15.7 Hz, CH_2), 3.61 (d, 1 H, J = 15.7 Hz, CH_2), 3.87 (d, 1 H, J = 15.6 Hz, CH_2), 3.90 (d, 1 H, J = 15.7 Hz, CH_2), 4.18 (d, 1 H, J = 2.3 Hz, CH), 4.25 (d, 1 H, J = 2.6 Hz, CH), 4.26 (d, 1 H, J = 2.6 Hz, CH), 5.47 (d, 1 H, J = 2.4 Hz, CH), 5.92 (d, 1 H, J = 2.4 Hz, CH), 5.96 (s, 1H, CH), 6.79 (s, 1H, ArH), 6.89 (s, 2H, ArH), 6.92 (s, 1H, ArH),

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[19] The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the director, Cambridge Crystallographic Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

[20] Stewart, D. R.; Gutsche, C. D. *Org. Prep. Proc. Int.* **1993**, *25*, 137.

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7.03 (s, 1H, ArH), 7.39−7.21 (overlapping signals integrating for 10 H, ArH), 7.66 (d, 1H, J = 7.4 Hz, ArH), 7.70 (d, 1H, J = 7.4 Hz, ArH), and 7.78 (d, 1H, J = 7.4 Hz, ArH) ppm. ^{13}C NMR (100.62 MHz, CDCl$_3$, 320 K) δ 22.21, 24.29, 26.71, 28.66, 28,78, 30.22, 31.51, 31.73, 31.84, 34.13, 34.23, 34.33, 34.64, 34.91, 35.00, 39.79, 39.82, 40.37, 51.49, 51.99, 52.19, 59.48, 59.72, 59.98, 81.88 (C−O), 82.29 (C−O), 83.18 (C−O), 119.26, 119.40, 119.55, 119.74, 120.26, 120.89, 122.09, 123.08, 123.76, 123.82, 125.21, 125,31, 125.44, 125.48, 126.39, 126.43, 126.67, 126.72, 126.78, 127.03, 155.38, 155.65, 156.20, 157.26, 157.50, 199.18 (C═O), 200.35 (C═O), and 200.60 (C═O) ppm. IR: ν 1750.0, 1624.3 cm^{-1}. CI MS: m/z 1195.5 (MH$^+$).

Preparation of the Tris Adduct 6. Benzenediazonium-2-carboxylate hydrochloride (125 mg) was added to a solution of **4** (50 mg, 0.052 mmol) in 15 mL of freshly distilled 1,2-dichloroethane. Freshly distilled propylene oxide (1.5 mL) was then added dropwise to the stirred reaction mixture. After 60 min of reflux in a water bath, the mixture was cooled to room temperature and the solvent was evaporated, yielding a brown oil. The product was separated by preparative TLC (eluent: CH$_2$Cl$_2$:CCl$_4$; 1:4). The second fraction (R_f: 0.48) contained 12 mg (0.01 mmol) of **6** (19%). Further purification was achieved by recrystallization from MeCN yielding pure **6**, mp 328−330 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.66 (s, 9H, t-Bu), 0.96 (s, 9 H, t-Bu), 1.11 (s, 9H, t-Bu), 1.12 (s, 9H, t-Bu), 1.22 (s, 9H, t-Bu), 1.29 (s, 9H, t-Bu), 2.35 (d, 1H, J = 15.5 Hz, CH$_2$), 2.65 (d, 1H, J = 16.0 Hz, CH$_2$), 2.71 (d, 1H, J = 16.3 Hz, CH$_2$), 2.84 (d, 1H, J = 15.9 Hz, CH$_2$), 2.98 (d, 1H, J = 15.7 Hz, CH$_2$), 3.03 (d, 1H, J = 15.3 Hz, CH$_2$), 3.18 (d, 1H, J = 15.2 Hz, CH$_2$), 3.28 (d, 1H, J = 16.9 Hz, CH$_2$), 3.36 (d, 1H, J = 13.6 Hz, CH$_2$), 3.61 (d, 1H, J = 13.8 Hz, CH$_2$), 3.74 (d, 1H, J = 15.5 Hz, CH$_2$), 3.97 (d, 1H, J = 2.1 Hz, CH$_2$), 4.13 (d, J = 17.4 Hz, 1H, CH$_2$), 4.21 (d, J = 2.1 Hz, 1H, CH), 4.22 (d, J = 2.1 Hz, 1H, CH), 5.47 (d, 1H, J = 2.2 Hz, CH), 5.94 (d, 1H, J = 2.2 Hz, CH), 6.58 (d, 1H, J = 2 Hz, CH), 6.71 (d, 1H, J = 2.2 Hz, CH), 6.84 (d, 1H, J = 2.0 Hz, ArH), 6.89 (d, 2H, J = 2.0 Hz, ArH), 7.00 (d, 1H, J = 2.0 Hz, ArH), 7.45−7.05 (overlapping signals integrating for 7 H, ArH), and 7.55 (d, 1H, J = 7.2 Hz, ArH) ppm. ^{13}C-NMR (100.62 MHz, CDCl$_3$) δ 27.87, 28.43, 28.53, 31.66, 31.73, 31.80, 34.11, 34.14, 34.26, 34.47, 34.97, 35.03, 39.30, 40.38, 41.16, 51.35, 51.43, 51.64, 55.05, 58.31, 59.08, 80.47 (C−O), 81.56 (C−O), 83.59 (C−O), 116.17, 117.80, 118.10, 118.41, 119.03, 119.45, 121.51, 121.96, 122.46,122.88, 123.01, 123.09, 124.30, 125.08, 125.16, 125.20, 125.39, 125.42, 126.01, 126.62, 126.67, 126.72, 127.04, 127.17, 128.27, 129.53, 132.90, 140.85, 141.17, 141.33, 141.49, 142.02, 142.12, 142.58, 142.68, 142.75, 151.26, 155.14, 155.24, 156.01, 156.39, 158.47, 197.77 (C═O), 198.70 (C═O), and 201.49 (C═O) ppm. IR: ν 1750.0, 1604.4 cm^{-1}. CI MS: m/z 1195.8 (MH$^+$).

Oxidation of 7b with K$_3$Fe(CN)$_6$. Solid K$_3$Fe(CN)$_6$ (0.16 g, 0.49 mmol) was added to a toluene solution (100 mL) of **7b**[5] (200 mg, 0.25 mmol) while stirring at room temperature. An aqueous solution of KOH (120 mL, 10%) was then added dropwise into the reaction mixture. After stirring at room temperature for 2 h the organic phase was separated and washed several times with brine and finally with water to pH 6. The organic fraction was dried over MgSO$_4$ and filtered. The solvent was evaporated, yielding 160 mg of a mixture of compounds. The mixture was separated by column chromatography (eluent CH$_2$Cl$_2$: petroleum ether 40−60 °C 8:3). The first eluted fraction was unreacted **7b** (9 mg), The second eluted fraction (70 mg) constituted mostly of **10**. The last fractions (13 mg) contained complex mixtures of compounds. Recrystallization of the second fraction from MeOH yielded pure **10** mp 239−240 dec 420−3 °C melt (36 mg, 0.045 mmol, 18%).

^{1}H NMR (400 MHz, CDCl$_3$, rt) δ 1.09 (s, 9H, t-Bu), 1.10 (s, 9H, t-Bu), 1.22 (s, 9H, t-Bu), 1.28 (s, 9H, t-Bu), 1.29 (s, 9H, t-Bu), 2.99 (d, 1H, J = 15.8 Hz, CH$_2$), 3.03 (d, 2H, J = 13.8 Hz, CH$_2$), 3.16 (d, 1H, J = 15.5 Hz, CH$_2$), 3.31 (d, 1H, J = 15.6 Hz, CH$_2$), 3.37 (d, 1H, J = 13.4 Hz, CH$_2$), 3.45 (d, 1H, J = 15.6 Hz, CH$_2$), 3.85 (d, 1H, J = 13.7 Hz, CH$_2$), 3.99 (d, 1H, J = 14.3 Hz, CH$_2$), 4.35 (d, 1H, J = 13.2 Hz, CH$_2$), 6.08 (d, 1H, J = 2.3 Hz, CH), 6.11 (d, 1H, J = 2.3 Hz, CH), 6.90 (2H, overlapping signals, CH), 6.93 (s broad, 1H, ArH), 7.03 (3H, overlapping signals, ArH), 7.14 (d, 1H, J = 2.4 Hz, ArH), 7.24 (1H, hidden by CHCl$_3$, ArH), and 8.11 (s, 1H, OH) ppm. ^{13}C NMR (100.62 MHz, CDCl$_3$, rt) δ 27.98, 28.47, 29.39, 31.23, 31.56, 31.82, 33.89, 34.16, 34.21, 34.25, 40.38, 40.74, 85.19 (C−O), 119.85, 120.21, 120.43, 123.02, 124.04, 124.68, 124.79, 125.78, 125.90, 126.63, 126.71, 128.90, 130.10 (two overlapping signals), 134.53, 135.21, 138.21, 139.42 (two overlapping signals), 142.00, 142.38, 142.52, 143.73, 143.87, 149.41, 154.79, 156.15, 196.70 (C═O) and 200.55 (C═O) ppm. IR: ν 3623.2 (OH), 3267.4 (OH), 1653.2 (C═O) cm^{-1}. CI MS: 811.5 (**1b**H$^+$) and 807.4 (MH$^+$).

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Supporting Information Available: ^{1}H NMR spectra and assignment of the signals of **6** and **10** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS; see any current masthead page for ordering information.

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