

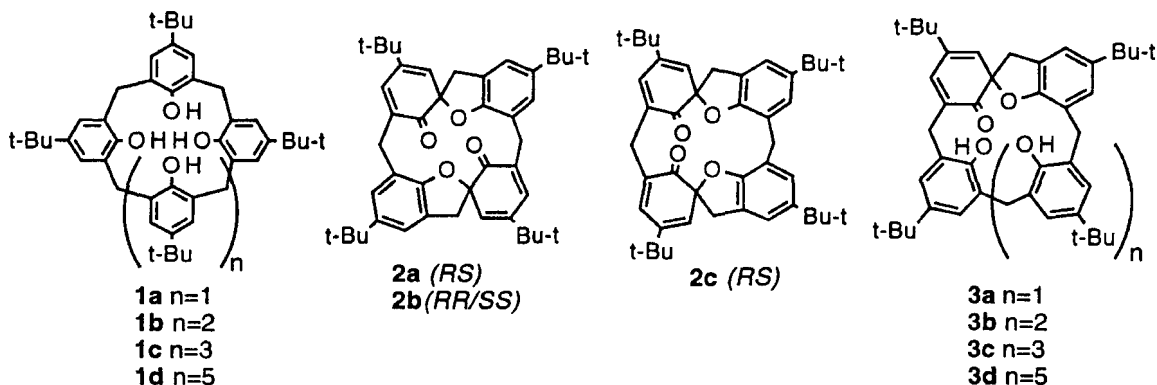
Synthesis and reactions of large-ring spirodienone calixarene derivatives

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Abstract: The isomerism of the polyspirodienone derivatives of the large-ring *p*-*tert*-butylcalix[*n*]arenes (*n*=5,6,8) is analyzed. Mono- and polyspirodienone calix[*n*]arene derivatives were prepared by mild oxidation of the respective calix[*n*]arenes and the obtained products were characterized. Reactions of the monospirodienone derivatives with hydrazines and their rearrangements to xanthenocalixarenes are described.

Introduction. Extensive synthetic efforts have been invested in the last years in developing synthetic methodologies for the selective functionalization of the calix[*n*]arenes (1,2). Oxidation of *p*-*tert*-butylcalix[4]arene (**1a**) with a mild oxidizing agent (such as tetrabutylammonium tribromide or $K_3Fe(CN)_6$) in the presence of base results in the formation of bis(spirodienone) calixarene derivatives (3-5). Three bis(spirodienone) derivatives (**2a-2c**) were obtained which were separated by chromatography and characterized by X-ray crystallography (4). This reaction is notable because in one step the four OH groups of the calixarene are converted into ether and carbonyl groups, and two stereocenters are introduced into the macrocycle. The isomer which is more stable thermodynamically is a *meso* compound with an alternant arrangement of carbonyl and ether groups and opposite configurations of the two stereocenters (the spiro carbons). However, the cavity defined by the four oxygens in the bis(spirodienone) calixarene derivatives is too small for the inclusion of a metal atom. Spirodienone systems derived from larger calixarenes should be of interest since they should be capable of completely enveloping a cation or a small organic molecule. In addition, these compounds may serve as potential synthetic intermediates for the preparation of selectively functionalized large-ring calixarenes.



Monospirodienone calixarene derivatives. The preparation of the monospirodienone derivatives of the large calixarenes is rather straightforward. Oxidation of an excess of the *p*-*tert*-butylcalix[*n*]arenes **1a-d** with phenyltrimethylammonium tribromide in the presence of a weak base (aq. $NaHCO_3$) at low temperatures results in the formation of the corresponding monospirodienone derivatives (**3a-d**) in good yields (6,7). Due to the presence of a single stereocenter, these systems are chiral. The structures of the monospirodienone derivatives **3a** and **3b** were determined by X-ray crystallography, which indicates that the compounds adopt different conformations (6,7).

Polyspirodienone derivatives of large calixarenes.

(a) *Bis(spirodienone) calix[5]arene derivatives.* The most convenient way for analyzing the isomerism of the polyspirodienone derivatives of the calixarenes is to envision the systems as possessing two independent stereogenic elements: the spiro stereocenters and the directionality of each spirodienone moiety (8). Six isomeric forms (two enantiomeric pairs and two *meso* forms) exist for bis(spirodienone) derivatives of **1a** (4) but the number of isomeric forms becomes larger with the increase in number of rings in the macrocycle.

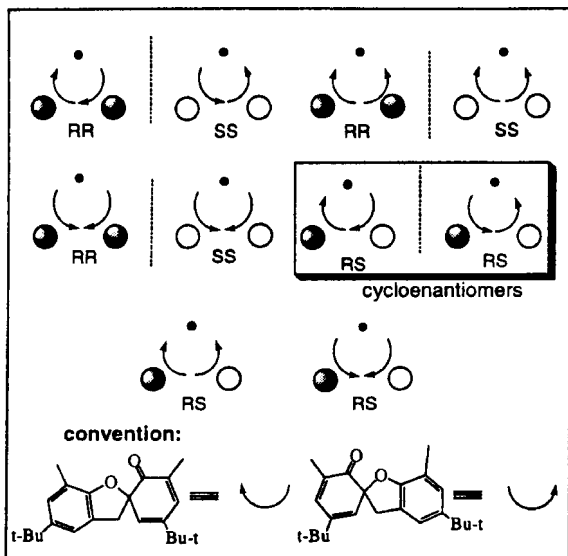


Fig. 1. Bis(spirodienone) calix[5]arene derivatives

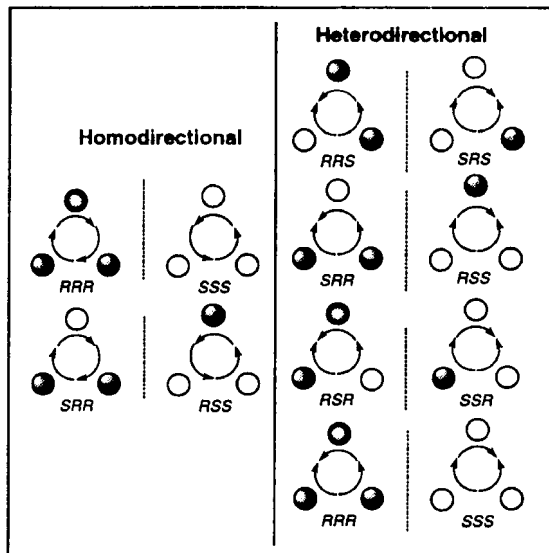
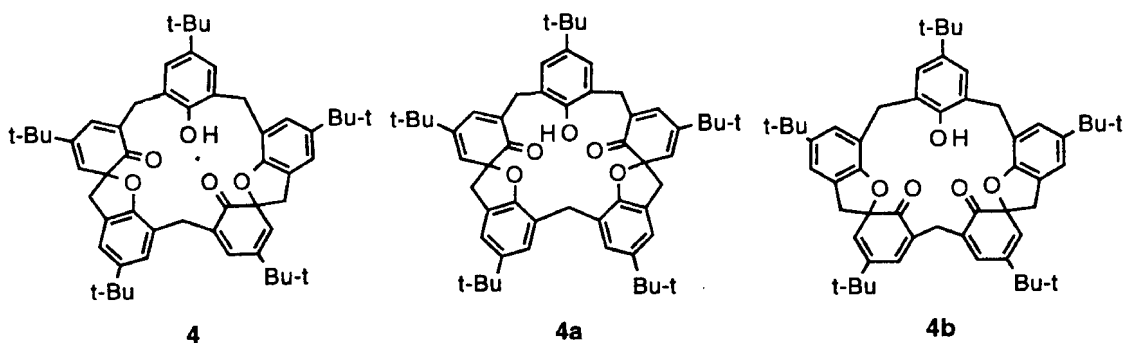


Fig. 2. Isomerism in tris(spirodienone) calix[6]arene derivatives

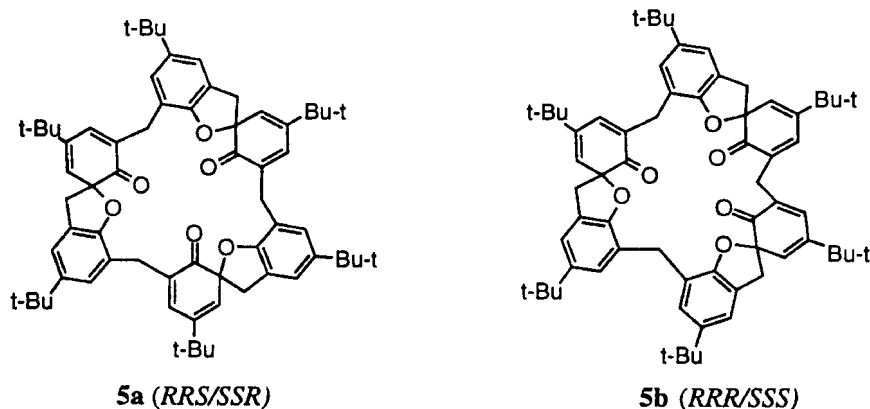
The possible isomeric bis(spirodienone) derivatives of **1b** are depicted in Figure 1, where clockwise and counterclockwise curved arrows represent the possible directionality senses of the spirodienone subunits, and filled and empty spheres represent the configurations (*R* or *S*) of the spiro carbons. Since *p*-*tert*-butylcalix[5]arene has an odd number of phenol rings, its bis(spirodienone) derivatives should have two spirodienone subunits and a free phenol ring (represented by a dot in Figure 1). The spirodienone groups can be arranged in homodirectional (the two curved arrows both pointing clockwise or counterclockwise) or heterodirectional arrangements, which correspond to alternant or non alternant dispositions of the carbonyl and ether groups, respectively. Disregarding conformational isomerism, the system should exist in 10 isomeric forms: four enantiomeric pairs and two *meso* forms. The pair in the square box is of particular interest since it represents a pair of cycloenantiomers (9,10). The two enantiomers can be viewed as having an identical pattern of stereocenters, but having opposite directionality. The pair fulfills the *meso* condition (10) since the formal removal of the directionality of the spirodienone units will result in an achiral (*meso*) system.

The preparation of a bis(spirodienone) calix[5]arene derivative was accomplished by oxidation of the monospirodienone **3b** with $K_3Fe(CN)_6$ /base yielding the bis(spirodienone) derivative **4** in 22% yield. The 1H NMR spectrum of **4** displays five *tert*-butyl singlets and five pairs of doublets for the methylene protons indicating that the molecule is asymmetric. The structural characterization of the compound was accomplished by a combination of 2D NMR techniques (TOCSY, COSY, NOESY). The spectroscopic data indicate that the compound displays a homodirectional arrangement of spirodienone units (11). Isomerization of a sample of **4** was accomplished by heating a solution of the compound in toluene-*d*₈ at 85 °C for 32 hours. The molecule isomerizes to a thermodynamically more stable bis(spirodienone) derivative of C_2 symmetry, as indicated by the pattern of the methylene groups in the 1H NMR, (two pairs of doublets and a singlet) and of the *tert*-butyl groups (three signals in a 1:2:2 ratio). These patterns are compatible only with a structure in which a twofold symmetry axis passes through the phenol and the methylene group distal to it (e.g., either **4a** or **4b**). 2D COSY NMR experiments enable us to assign structure **4a** to the compound.



The mechanism of the mutual isomerization between the bis(spirodienone) derivatives most likely involves the homolytic cleavage of the spiro C-O bond giving two phenoxy radicals. The formation of the C-O bond can take place with either retention or inversion of the configuration of the stereocenter, or with retention or inversion of the sense of direction of the spirodienone unit, resulting in the mutual interconversion of alternant and nonalternant isomers.

(b) *Tris(spirodienone) derivatives of p-tert-butylcalix[6]arene*. Twelve isomeric forms (six enantiomeric pairs) exist for the tris(spirodienone) derivatives of *p-tert*-butylcalix[6]arene (Figure 2). Since an odd number of stereocenters is present, all isomers are chiral and no *meso* form is possible. Reaction of a CH_2Cl_2 solution of **1c** with excess phenyltrimethylammonium tribromide/aq. NaOH resulted in the formation of a mixture of tris(spirodienone) derivatives and bromination/oxidation products from which two tris(spirodienone) products (**5a** (29%), and **5b** (15%)) were separated by column chromatography (5).



The ^1H and ^{13}C NMR spectra of both compounds are in agreement with tris(spirodienone) structures possessing C_1 symmetry. The structural characterization of the compounds was carried out by 2D NMR techniques and examination of molecular models. Based on these studies we concluded that the main isomer has a homodirectional arrangement of spirodienone units with different configurations at the stereocenters (i.e., *RRS/SSR*), while a structure with a non-alternant array of carbonyl and ether groups was assigned to **5b**, with most likely an identical arrangements of the stereocenters. The assignment of the major isomer was corroborated by X-ray crystallography (Figure 3). The crystal structure could be refined only to a relatively high *R* factor due to disorder of the solvent molecules included in the crystal (methylene chloride). The tris(spirodienone) derivative **5a** exists in the crystal in a conformation of a somewhat triangular shape in which the three dihydrofuran oxygens are pointing into the center of the cavity, while the carbonyl groups are oriented perpendicularly to the mean macrocyclic plane. This conformation is similar to the ones observed in the crystal structures of the bis(spirodienone) derivatives of the calix[4]arenes (4).

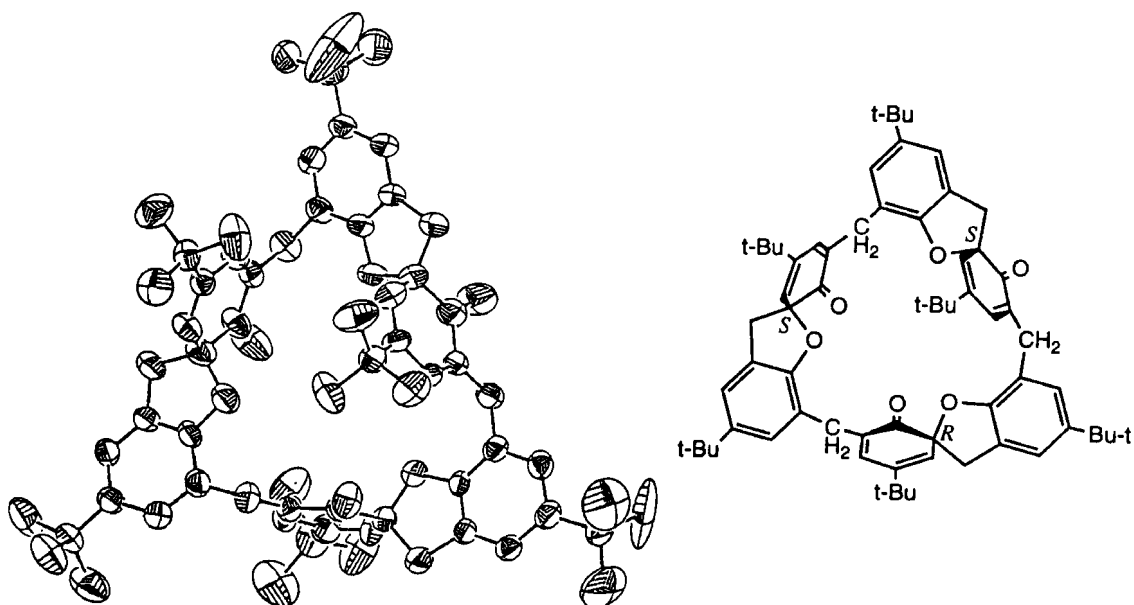


Fig. 3. X-ray structure of the tris(spirodienone) derivative of **1c**

The two isomeric tris(spirodienone) derivatives mutually isomerize in solution. Heating either isomer in toluene at 85 °C for 20 hours resulted in a 3:1 equilibrium mixture of both isomers (11). On the basis of the equilibration studies we conclude that the isomer obtained in excess in the oxidation reaction (5a) is the one most stable thermodynamically. Interestingly, for both the bis(spirodienone) and tris(spirodienone) systems 2 and 5, homodirectional isomers having all stereocenters with identical configurations are less stable than the corresponding stereoisomers with dissimilar configurations. In the isomer with identical configurations of the stereocenters, the carbonyl groups must be oriented in a nearly parallel fashion, and the resulting repulsive dipole-dipole interactions may destabilize the structure.

The tris(spirodienones) 5a and 5b react with excess benzyne (generated *in situ* from benzenediazonium 2-carboxylate hydrochloride) yielding the corresponding tris Diels Alder adducts (5). In both cases a main product was obtained, indicating that the reaction proceeds with high diastereofacial selectivity. By analogy with the bis(spirodienones) derived from 3, we assume that the benzyne adds in an *all-exo* fashion. Interestingly, the tris-adduct derived from 5a displays temperature-dependent ¹H NMR and upon lowering the temperature the signals undergo broadening and decoalescence (Fig. 4). From the low-temperature NMR it can be concluded that the adduct exists in two diastereomeric conformations with nearly identical populations. Coalescence studies indicate that the barrier for the diastereomerization process is 12.0 kcal/mol (11). The geometry of the two conformers is at present unknown, and tentatively, we assign to these conformers geometries in which either the carbonyl or ether oxygens are pointing to the center of the cavity.

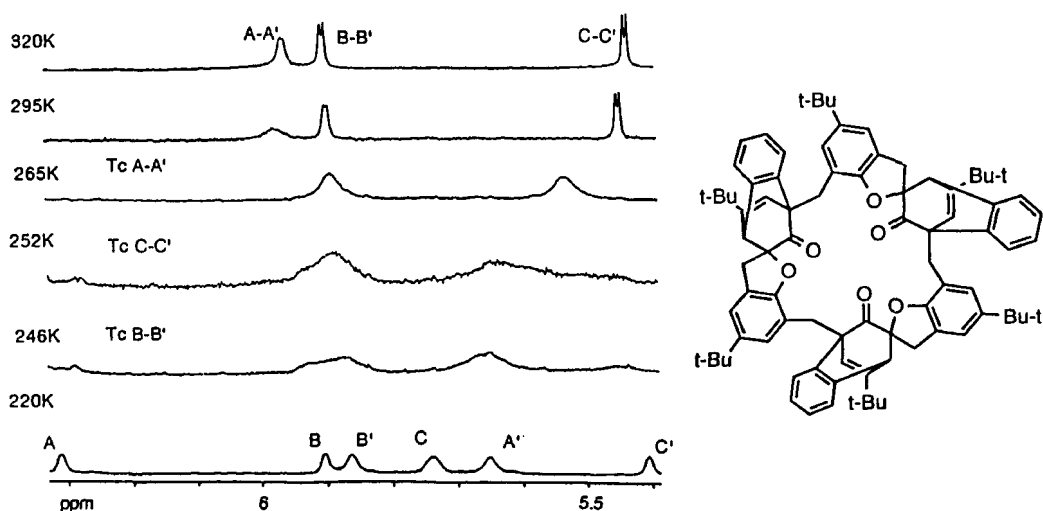
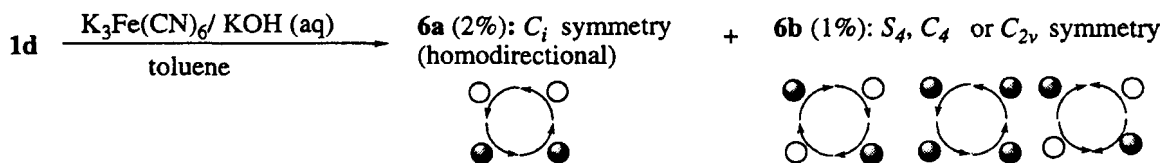


Fig. 4. Variable temperature ¹H NMR spectrum of the vinylic region of the tris Diels Alder adduct of 5a

(c) *Tetrakis(spirodienone) derivatives p-tert-butylcalix[8]arene*. The tetrakis(spirodienone) derivatives of 1d may exist in 39 isomeric forms: 7 *meso* forms and 16 enantiomeric pairs (Figure 5). Six stereoisomeric forms exist in which all the carbonyl and ether groups are arranged in an alternate fashion.

Oxidation of 1d ($K_3Fe(CN)_6$, aq NaOH/toluene) gave a very complex mixture, consisting mostly of decomposition products. Soxhlet extraction of the crude reaction mixture with dichloroethane afforded the tetrakis(spirodienone) derivatives 6a and 6b in ca. 2% and 1%, respectively (11). 6a displays in the ¹H NMR a signal pattern which is compatible only with a structure of C_i symmetry. Examination of the symmetries of the isomers depicted in Figure 5, suggests that the compound has a homodirectional arrangement of spirodienone groups. The second tetrakis(spirodienone) derivative displays only two t-Bu signals, and two pairs of doublets for the methylene protons, in agreement with a homodirectional arrangement of either C_4 or S_4 symmetry, or a heterodirectional arrangement of C_{2v} symmetry.



Since in both the bis- and tris(spirodienone) derivatives the isomers possessing a homodirectional arrangement of the spirodienone groups are kinetically favored over isomers having a heterodirectional arrangement, we tentatively assign to 6b a structure of either C_4 or S_4 symmetry with an alternant arrangement of carbonyl and ether groups.

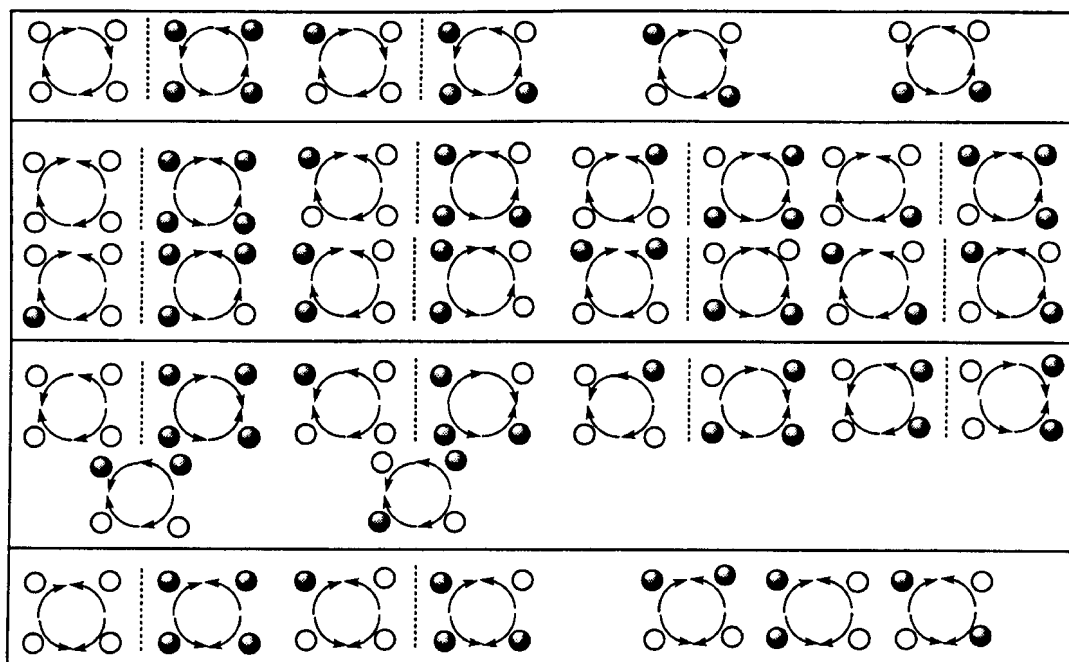
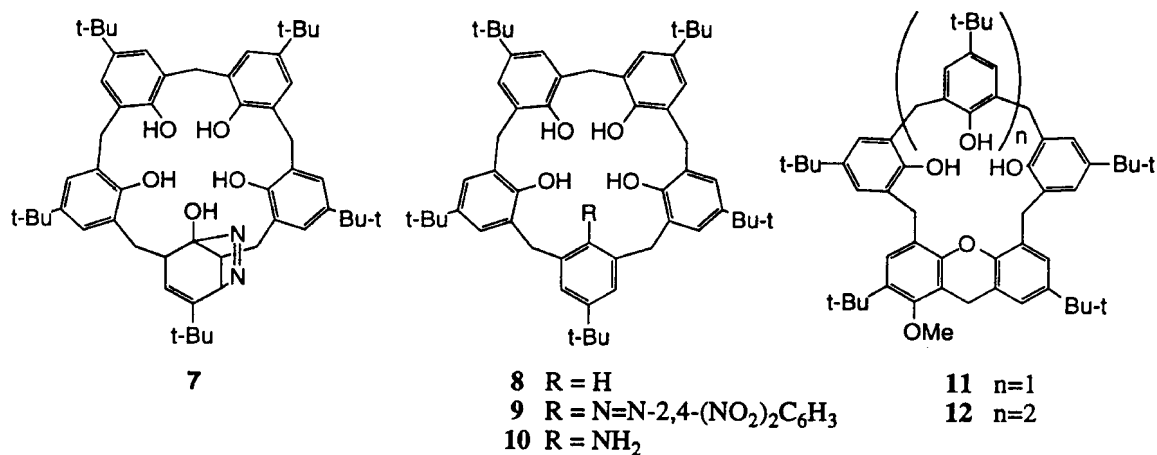


Figure 5. Isomeric tetrakis(spirodienone) calix[8]arene derivatives

Reactions of the monospirodienone derivatives. Reaction of the monospirodienone **3b** with hydrazine under mildly acidic conditions at room temperature results in a derivative (**7**), characterized by X-ray crystallography, displaying a spirohexenol ring with an azo group bridging the 1 and 3 positions (**7**). The formation of **7** probably involves an acid catalyzed addition of hydrazine to the dienone. After tautomerization of the dienol, acid catalyzed intramolecular nucleophilic addition of the free end of the hydrazine takes place. Due to the bicyclic structure of the product, no elimination of water (with the concomitant formation of a hydrazo group) can take place. The bridging hydrazo group is finally oxidized (most likely by a spirodienone group) yielding **7**. The reaction with hydrazine under basic conditions yields the monodehydroxylated calix[5]arene **8** in a Wolff Kishner-type reaction.

Monospirodienone **3b** reacts with 2,4-dinitrophenylhydrazine yielding in good yield (53%) the azocalixarene **9**. The ^1H NMR spectrum of **9** displays three pair of doublets (two doublets accidentally overlapping) in a 2:2:1 ratio for the methylene protons, in agreement with a structure of C_3 symmetry, in which the cone-to-cone process has been frozen on the NMR timescale. Reductive cleavage of the azo group was achieved by treating **9** with aq HI/hexane yielding the monoaminotetrahydroxycalix[5]arene **10**. The aminocalixarene **10** readily undergoes protonation by tosylic acid yielding the corresponding tosylate salt, as previously observed for an aminocalix[4]arene system (**12**). The two step transformation **4b** \rightarrow **9** \rightarrow **10** represents an excellent method for the *intra*annular introduction of an amino group in a calix[5]arene (**7**).



Rearrangements. Treating a methanolic solution of **3b** with a few drops of H₂SO₄ resulted in the formation of the xanthenocalix[5]arene **11** together with a linear pentamer. Rearrangement of **3c** by treatment with MeOH/H⁺ gave, as judged by ¹H NMR, almost quantitatively the xanthenocalix[6]arene **12** which was structurally characterized by X-ray crystallography. The mechanism of the formation of the xanthen unit probably involves activation of the diene to nucleophilic addition of a methanol molecule, ketonization of the resulting dienol, and acid catalyzed ring expansion followed by elimination of water. Molecules **11** and **12** represent first examples of calixarene systems incorporating a xanthen moiety. Xanthenocalix[6]arene **12** crystallizes from MeCN as a 1:1 complex with two molecules in the unit cell related by an inversion center, and two OH groups at different rings *intermolecularly* hydrogen bonded as indicated by their short mutual distance (2.839 Å). The two molecules display self-fitting in the crystal. In addition to serve as a host to the MeCN, each molecule can be viewed as serving both as a host and as a guest of the neighboring calixarene molecule in the hydrogen bonded dimer. The xanthenocalix[6]arene **12** could be further functionalized by protection of the phenol rings and oxidation of the xanthen group to xanthone (13).

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