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Functionalization of the Methylene Groups of *p-tert*-Butylcalix[4]arene: S−C, N−C, and C−C Bond Formation

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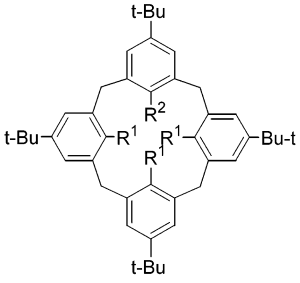
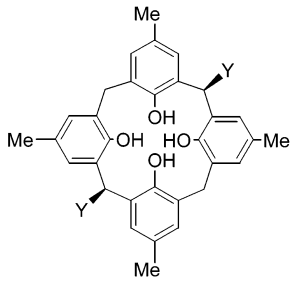
Reaction of the calixarene derivative **7** with two exocyclic double bonds with carbon-, nitrogen-, oxygen-, or sulfur-containing nucleophiles afforded bis(spirodienone) derivatives substituted at two opposite methylene groups in a trans fashion. $LiAlH_4$ reduction of the bis(spirodienone) derivatives with two methylenes functionalized by thiomethoxy, diethyl malonate, or anilino substituents yielded trans methylene-substituted calix[4]arenes. Upon standing in solution, the calixarene derivative incorporating SMe groups on the bridges underwent trans ⇌ cis isomerization. An equilibration study performed on this calixarene derivative (tetrachloroethane-d_2, 430 K) indicated that the cis isomer is the form of lower free energy.

Introduction

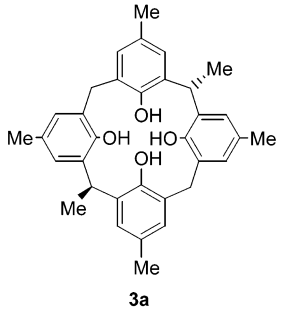
The calix[*n*]arenes are macrocyclic compounds consisting of several phenol rings interconnected by methylene groups, which are currently extensively studied as ligands and as building blocks for the construction of molecular hosts.[1,2] The smallest synthetically available calixarene is *p-tert*-butylcalix[4]arene (**1a**).[3] To modify its properties, the calixarene scaffold has been chemically modified, usually by reaction at the aryl rings.[1,2] The functionalization of the bridging methylene groups has remained a difficult synthetic task. One possible approach for the preparation of methylene-functionalized calix[4]arenes involves the cyclocondensation of two suitable precursors that incorporate the desired substituent(s). This approach (the "fragment condensation method")[4] has been used successfully for the preparation of calixarene derivatives with alkyl or aryl groups attached to one or two methylene bridges (e.g., **2**).[5] In the case of the bis-alkanediyl calix[4]arenes both cis and trans forms are possible. The product distribution of the cyclocondensation reaction usually reflects the relative stability of the two forms. For example, synthesis of bis(1,1-alkanediyl) calixarene derivatives via the fragment condensation route afforded mainly or exclusively the most stable cis isomers (**2a**−**d**). Only when the substituents at the bridges were methyls (the smallest substituent examined) was a small amount (0.2%) of the trans form **3a** also isolated.[5e]



1a $R^1 = R^2 = OH$
1b $R^1 = R^2 = OMe$
1c $R^1 = OH$, $R^2 = H$



2a Y = Me
2b Y = Et
2c Y = i-Pr
2d Y = t-Bu



3a

A second approach for the preparation of calixarenes chemically modified at the methylene groups uses a calixarene as the starting material. Görmar and co-

(1) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713. Gutsche, C. D. *Aldrichimica Acta* **1995**, *28*, 1. Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, 1998.

(2) For very recent reviews on calixarenes, see: *Calixarenes 2001*; Asfari, Z.; Böhmer, V.; Harrowfield, J.; Vicens, J.; Eds., Kluwer Academic Publishers: Dordrecht, 2001.

(3) Gutsche, C. D.; Iqbal, M. *Org. Synth.* **1989**, *68*, 234.

(4) For a review on the synthesis of calixarenes via the stepwise and fragment condensation methods, see: Böhmer, V.; *Liebigs Ann./Recueil* **1997**, 2019.

(5) See for example: (a) Tabatai, M.; Vogt, W.; Böhmer, V. *Tetrahedron Lett.* **1990**, *31*, 3295. (b) Sartori, G.; Maggi, R.; Bigi, F.; Arduini, A.; Pastorio, A.; Porta, C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1657. (c) Sartori, G., Bigi, F.; Porta, C.; Maggi, R.; Mora, R. *Tetrahedron Lett.* **1995**, *36*, 2311, (d) Grüttner, C.; Böhmer, V., Vogt, W.; Thondorf, I., Biali, S. E.; Grynszpan, F. *Tetrahedron Lett.* **1994**, *35*, 6267. (e) Biali, S. E.; Böhmer, V., Cohen, S.; Ferguson, G.; Grüttner, C.; Grynszpan, F.; Paulus, E. F.; Thondorf, I., Vogt, W. *J. Am. Chem. Soc.* **1996**, *118*, 12938. (f) Biali, S. E.; Böhmer, V., Columbus, I.; Ferguson, G.; Grüttner, C.; Grynszpan, F.; Paulus, E. F.; Thondorf, I. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2261.

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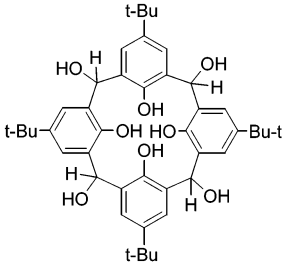
workers synthesized the tetraalcohol derivative **4**[6] by protection of the phenolic moieties of **1a** via acetylation, followed by CrO_3 oxidation of the methylenes to carbonyls, hydrolysis of the acetate groups, and reduction of the carbonyls to alcohol functionalities. The four methylene groups of the tetramethyl ether of *p-tert*-butylcalixarene **1b** have been monobrominated under radical conditions yielding **5**.[7] More recently, one or two methylene groups of a calix[4]arene have been modified via homologous anionic ortho Fries rearrangement,[8] or monofunctionalized via lithiation of the tetraether derivative **1b** followed by reaction with a carbon electrophile (e.g., CO_2, RX).[9]



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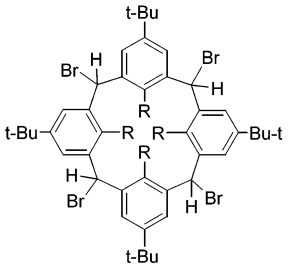
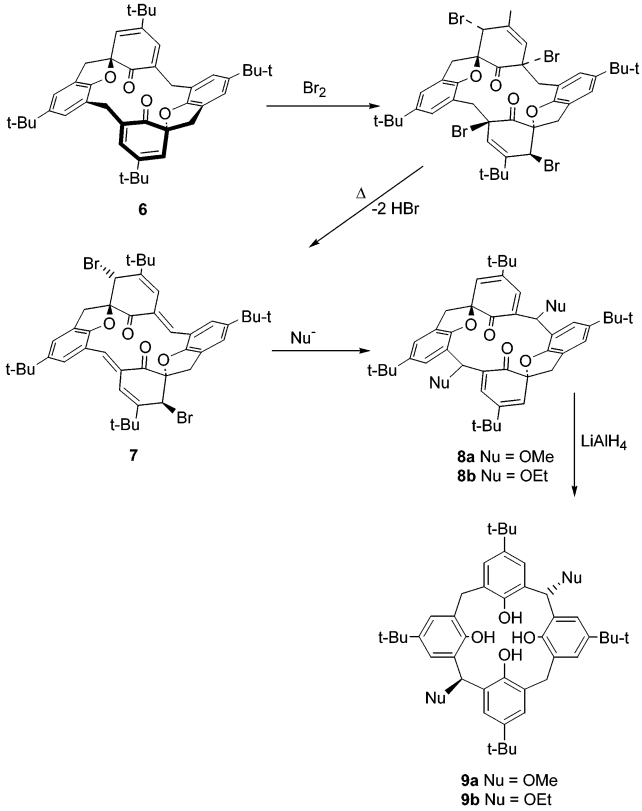


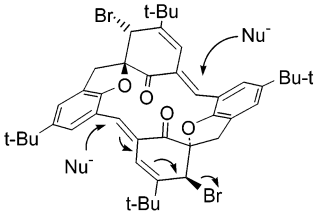
5 R = OMe

We have recently described a new method for the stereoselective functionalization of two distal (i.e., nonvicinal) methylene groups of the calixarene scaffold.[10] The method is based on the reactions depicted in Scheme 1 and involves initially a bromination/dehydrobromination reaction sequence on the bis(spirodienone) calixarene derivative **6**.[11−13] Reaction of the resulting spiro derivative **7** (possessing two exocyclic double bonds) with nucleophiles afforded the trans disubstituted bis(spirodienone) derivative **8**. Finally, reduction of **8** with $LiAlH_4$ yielded the substituted calixarene **9** in which two distal methylenes are functionalized in a trans fashion.[14] By this method were prepared calix[4]arene derivatives incorporating two deuterium atoms or two alkoxy groups in the methylene bridges. In the case of the ethoxy-substituted bis(spirodienone) derivative **8b**, the trans disposition of the methylene substituents was corroborated by X-ray crystallography.[10] In this article we report a study of the reactivity of the spiro derivative **7**, the rotational barriers of the substituted calixarenes, and the

SCHEME 1



SCHEME 2



trans ⇌ cis interconversion of the thiomethoxy methylene-substituted calixarene derivative.

Results and Discussion

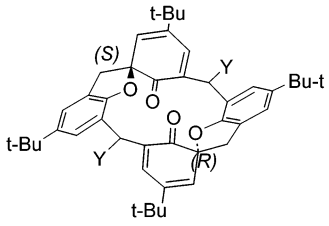
General Considerations. X-ray crystallography indicated that **7** is a *meso* compound in which necessarily the two spiro stereocenters possess opposite configurations.[10] The key step in the reaction sequence depicted in Scheme 1 is the attack of the nucleophile on the exocyclic double bonds of **7**. This attack is accompanied by double bonds shifts and the expulsion of the bromine leaving groups (Scheme 2).

Since the reaction does not affect the stereochemistry of the spiro stereocenters, the cis or trans disposition of the methylene substituents in the product can be readily determined by analysis of the NMR signal pattern. Only if the two substituents are incorporated in a trans fashion, can the C_i symmetry of **7** be retained in the product; for example, in the ^{1}H NMR spectrum a single signal should be observed for the two methine protons. If on the other hand the two substituents are incorporated cis, the molecular symmetry is lowered to C_1 and pairs of methine groups, cyclohexadienone and aryl

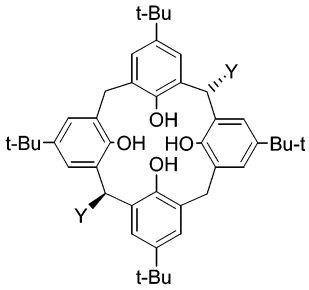
(6) Görmar, G.; Seiffarth, K.; Schultz, M.; Zimmerman, J.; Flämig, G. *Macromol. Chem.* **1990**, *191*, 81.
(7) Klenke, B.; Näther, C.; Friedrichsen, W. *Tetrahedron Lett.* **1998**, *39*, 8967.
(8) Middel, O.; Greff, Z.; Taylor, N. J.; Verboom, W.; Reinhoudt, D. N.; Snieckus, V. *J. Org. Chem.* **2000**, *65*, 667.
(9) Scully, P. A.; Hamilton, T. M.; Bennett, J. L. *Org. Lett.* **2001**, *3*, 2741.
(10) Agbaria, K.; Biali, S. E. *J. Am. Chem. Soc.* **2001**, *123*, 12495.
(11) (a) Litwak, A. M.; Grynszpan, F.; Aleksiuk, O.; Cohen, S.; Biali, S. E. *J. Org. Chem.* **1993**, *58*, 393. (b) Wang, W.-G.; Zhang, W.-C.; Huang, Z.-T. *J. Chem. Res. (S)* **1998**, 462.
(12) For reviews on spirodienone calixarene derivatives, see: (a) Aleksiuk, O.; Grynszpan, F.; Litwak, M. A.; Biali, S. E. *New J. Chem.* **1996**, *20*, 473. (b) Biali, S. E. in ref 2, p 266−279.
(13) For spirodienone derivatives of calixnaphthols and dihydroxymetacyclophanes, see: Georghiou, P. E.; Ashram, M.; Clase, H. J.; Bridson, J. N. *J. Org. Chem.* **1998**, *63*, 1819. Yamato, T.; Matsumoto, T.; Sato, J. M.; Fujita, K.; Nagano, Y. *J. Chem. Res. (S)* **1997**, 74; *J. Chem. Res. (M)* **1997**, 518.
(14) Reduction of **7** with the milder reducing agent $NaBH_4$ affords a bis(spirodienol) derivative (ref 10). See also: Agbaria, K.; Wöhnert, J.; Biali, S. E. *J. Org. Chem.* **2001**, 66, 7059.

rings within the macrocycle are rendered symmetry nonequivalent. On this basis and precluding accidental isochrony, the cis form should display twice the number of signals than the trans form.

Reaction of 7 with Nucleophiles. The reaction sequence described in Scheme 1 worked well for the alkoxide nucleophiles.[10] The present study was conducted to determine the generality of the reaction, and in particular, to find out if nitrogen-, carbon-, and sulfur-containing nucleophiles react with **7** in a similar fashion and are incorporated into the methylene groups of the bis(spirodienones) calixarene derivatives.

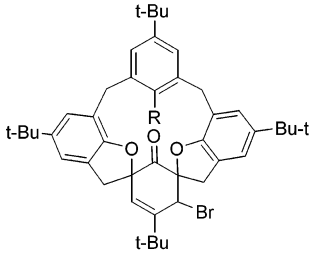


10 Y = SMe
11 Y= NHC_6H_5
12 Y= N_3
13 Y = *p*-OC_6H_4Bu-t,
14 Y = $CH(COCH_3)_2$
15 Y = $CH(COOEt)_2$

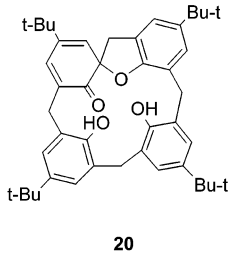


16 Y = SMe
17 Y= NHC_6H_5
18 Y = $CH(CH_2OH)_2$

Sulfur Nucleophile. Sulfur nucleophiles excel in S_N2 reactions on primary aliphatic substrates due to the high polarizability of the sulfur atom.[15] The reaction of **7** with excess NaSMe was conducted using THF as solvent and proved dependent on the dryness of the THF. When the reaction was conducted using "wet" THF as solvent (prepared by mixing dry THF with a small amount of water), the sodium thiomethoxide salt was completely soluble in the medium and the reaction yielded the expected disubstituted bis(spirodienone) calixarene **10**. The product displayed ^1H and ^{13}C NMR patterns consistent with a trans disposition of the two thiomethoxy groups (e.g., a single SMe signal). When the reaction was performed in THF freshly dried over sodium benzophenone ketyl, the NaSMe dissolved poorly in the medium and the reaction afforded a major product characterized as the trans methylene-substituted calix[4]arene **16** (see below) and in low yield a compound possessing *three* SMe residues incorporated into the macrocycle. The NMR spectra of the minor product resembled the spectra of the bis(spiroannulated) derivatives **19a** and **19b**, previously obtained by reaction of the monospirodienone derivative of **1a** (i.e., **20**) and the trihydroxycalixarene **1c** with 1 and 2.5 equiv of benzyltriethylammonium tribromide, respectively.[16] Two distinct isomeric forms are compatible with the NMR data (**21a** and **21b**). The NOESY spectra displayed NOE cross-peaks (indicating steric proximity) between a single SMe group (at δ 2.25 ppm, assigned to the SMe the group attached to the six-membered ring) and the pair of methylene protons at 3.98 and 4.02 ppm. On the basis of the steric proximity between the SMe and CH_2 groups, we assign structure **21b** to the product isolated. The same NOE data indicate that the SMe is oriented toward the external (exo) face of the six-membered ring, since as inspection of molecular models shows, only in this configuration are the SMe and CH_2 groups in steric proximity.



19a R = H
19b R = OH



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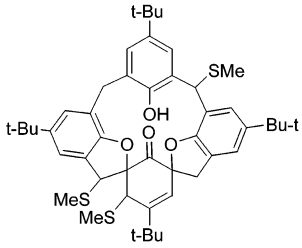
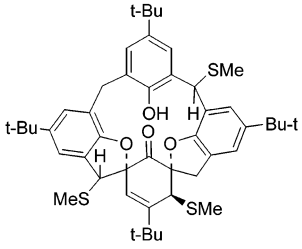


21a



21b

$LiAlH_4$ reduction of spirodienone **10** afforded the trans disubstituted calixarene **16,** obtained also in the reaction of **7** with NaSMe in dry THF. In a cone or conelike conformation (the preferred one for calix[4]arenes with four OH groups at the *intra*annular positions) the two trans thiomethoxy groups substituents must be located one in an axial and one in an equatorial position of the bridges (Figure 1). A cone-to-cone inversion process relocates the axial substituent into an equatorial position and vice versa, mutually exchanging the two substituents. The ^1H NMR spectrum displayed broad methylene and methine signals at room temperature consistent with such a process rapidly occurring on the NMR time scale. At 220 K in $CDCl_3$ the ^1H NMR displayed one singlet each for the axial and equatorial methine protons (δ 5.72 and 5.00, respectively)[17] in full agreement with a trans disposition of substituents (Figure 3). From the chemical shift difference of the methine signals under slow exchange conditions (292.8 Hz) and the coalescence temperature (290.7 K), a barrier of 13.2 kcal mol^{-1} was calculated for the cone-to-cone inversion process.[18,19] This barrier is somewhat lower than the barrier measured for the dialkoxy calixarenes **9a** and **9b** (14.1 and 14.3 kcal mol^{-1}, respectively) and for the parent **1a** (15.7 kcal mol^{-1}, in $CDCl_3$).[20]

(15) Swain, C. G.; Scott, C. B. *J. Am. Chem. Soc.* **1953**, *75*, 141. Edwards, J. O.; Pearson, R. G. *J. Am. Chem. Soc.* **1962**, *84*, 16. Wells, P. R. *Chem. Rev.* **1963**, *63*, 171.

(16) Grynszpan, F.; Aleksiuk, O.; Biali, S. E. *J. Org. Chem.* **1994**, *59*, 2070.

(17) In the cone conformation of **1a** the axial methylene protons resonate at a lower field that the equatorial ones. Böhmer, V.; Dörrenbächer, R.; Vogt, W.; Zetta, L. *Tetrahedron Lett.* **1992**, *33*, 769; Zetta, L.; Wolff, A.; Vogt, W.; Platt, K.-L.; Böhmer, V. *Tetrahedron* **1991**, *47*, 1911. Alfieri, C.; Dradi, E.; Pochini, A.; Ungaro, R. *Gazz. Chim. Ital.* **1989**, *119*, 335.

(18) A rotational process (such as the cone-to-cone ring inversion) cannot modify the trans arrangement of two substituents on the methylene bridges. For a detailed discussion, see ref 5e.

(19) Gutowsky, H. S.; Holm, C. H. *J. Chem. Phys.* **1956**, *25*, 1228.

(20) Gutsche, C. D.; Bauer, L. J. *J. Am. Chem. Soc.* **1985**, *107*, 6052.

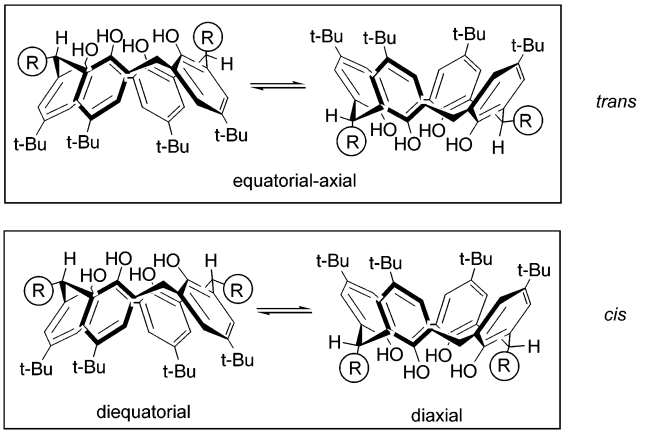


FIGURE 1. Cis and trans forms of a calix[4]arene (adopting a cone conformation) substituted at two distal methylene bridges. Only one disposition of substituents is possible in the trans form (top) with one substituent located in an axial and one in an equatorial position. Cone-to-cone inversion of the macrocycle mutually exchanges the magnetic environments of the two substituents and results in topomerization. In contrast to the trans form, two distinct conformers are possible for the cis form since the substituents can be located at diequatorial or diaxial positions (bottom). A cone-to-cone process mutually exchanges the two conformations. Under a fast cone-to-cone inversion, the trans form should display a singlet for the bridging methylene protons, while those protons on the cis form should appear as a pair of doublets.

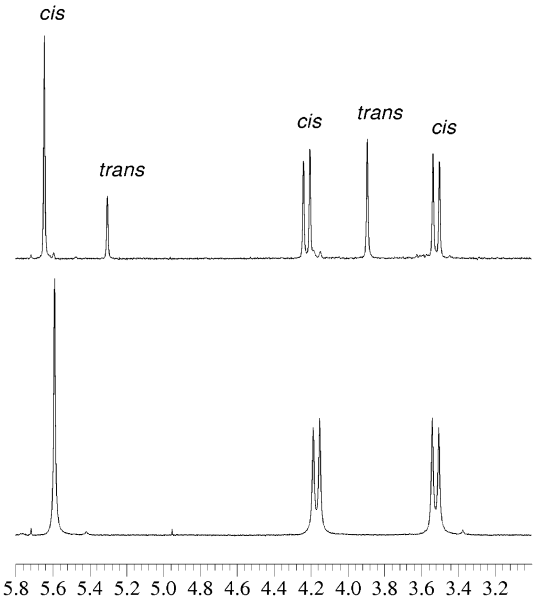


FIGURE 2. Isomerization of the *cis*-thiomethoxy methylene-functionalized calixarene **22**. Bottom: room temperature ^{1}H NMR spectrum (400 MHz, methylene and methine region) obtained immediately after dissolving in CCl_2DCCl_2D. Top: Spectrum obtained at 400 K after heating at that temperature for 2 h.

Cis/Trans Isomerization of the Methylene-Functionalized Calixarene. During the NMR studies of **16** we observed that upon standing, new signals appeared in the ^{1}H NMR spectrum at room temperature. The new compound displayed in the ^{1}H NMR spectrum a singlet and a pair of doublets for the methine and methylene protons, respectively. This pattern of signals is consistent

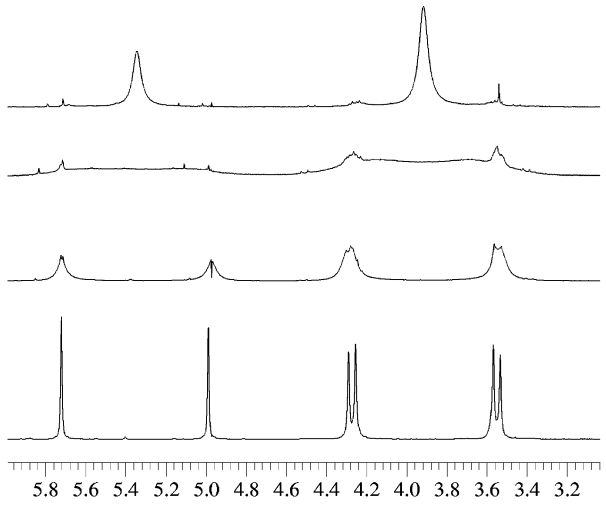
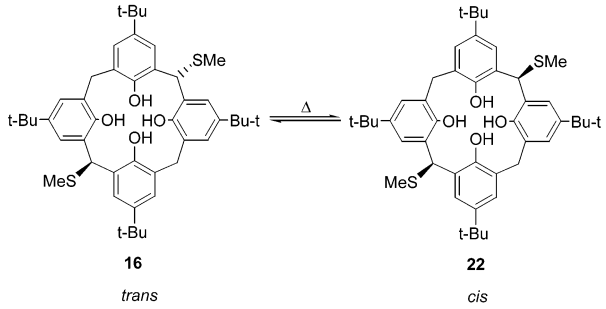


FIGURE 3. Temperature dependence of the ^{1}H NMR spectrum (400 MHz, $CDCl_3$, methylene and methine region) of the *trans*-thiomethoxy methylene-functionalized calixarene **16**. From top to bottom: spectra at 320, 300, 270, and 200 K.

with a disubstituted calixarene with a cis disposition of substituents (i.e., **22**), indicating that compound **16** isomerizes in solution to its cis form. The single methine signals of **22** resonated at a chemical shift (δ 5.59 ppm) characteristic of an axial methine proton.[17] It can be concluded that in the cis form the major conformer present in solution is the one with the two SMe substituents located in equatorial positions. Similar conformational preferences were observed for the cis bis(1,1′-alkyldiyl) calixarenes **2a**−**d**.[5e]



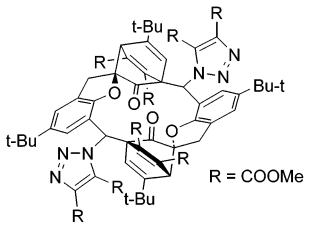
Equilibration studies were conducted in 1,1,2,2-tetrachloroethane-d_2 at 400 K starting from pure samples of **16** and **22** (Figure 2). Under these conditions, a constant ratio between the two isomers was reached after 3 h, as judged from the ^{1}H NMR spectrum. The $K_{cis/trans}$ ratio was 3.3 at that temperature ($-\Delta G° = 0.96$ kcal mol^{-1}). From this study it can be concluded that the cis and trans forms mutually interconvert, and that the cis stereoisomer **22** is the form most stable thermodynamically. The trans form **16** is probably destabilized by the repulsive steric interactions resulting from the present of an axial thiomethoxy group. This is in agreement with the calculations (TRIPOS force field) of bis-alkanediyl calix[4]-arenes **2**, which indicated that the cis isomers are of lower steric energy than the trans forms.[5e]

Nearly pure **22** could be conveniently isolated by slow (two weeks) evaporation of a chloroform solution of **16**. It seems likely that under these conditions initially a

microcrystal of the cis form separates from the solution, providing a seed for the crystallization of **22**. To reestablish the equilibrium concentration of the cis form in the solution, the trans form isomerizes. By a combination of the selective crystallization of the **22** and the mutual isomerization in solution, essentially all the sample precipitates as the cis form.

Nitrogen Nucleophiles. (i) Reaction with Azide Ion. Reaction of **7** with sodium azide proceeded rapidly and yielded the bis(azido) spirodienone derivative **12**. The incorporation of azide groups within the calix macrocycle could be ascertained using a characteristic reaction of the groups, the Huisgen 1,3-dipolar cycloaddition of azides with acetylenes to yield 1,2,3-triazoles.[21] Reaction of **12** with dimethyl acetylenedicarboxylate proceeded readily and afforded the tetra adduct **23** resulting from 1,3-dipolar cycloaddition of the azide groups and Diels−Alder reaction of the diene subunits with the alkyne.[22] Compound **23** displayed four methoxy signals in the ^{1}H NMR since, in contrast to the alkyne starting material, the two vicinal methoxy groups within a triazole group are nonequivalent.

The 1,3-dipolar cycloaddition reaction of the azide group at the bridges could be conducted without the concomitant Diels−Alder reaction of the diene functionalities via a chemical modification of the substrate. $NaBH_4$ reduction of the substituted bis(spirodienone) **12** yielded the bis(spirodienol) derivative **24**.[14] Treatment of **24** with dimethyl acetylenedicarboxylate afforded the spirodienol **25** possessing two 1,2,3-triazole groups at the bridges.



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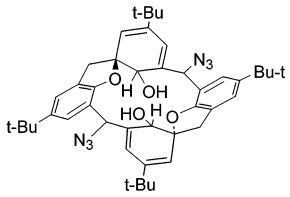

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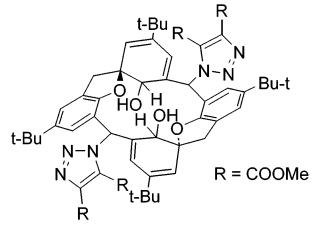

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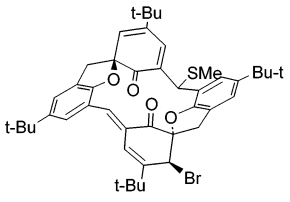

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(ii) Reaction with Aniline. In contrast to the other nucleophiles examined, the aniline molecule is not negatively charged. However, aniline is a very good nucleophile toward primary sp^3 carbons and in protic solvents its *n* nucleophilicity value (4.5) is larger than that of OH^- (4.2) and azide (4.0).[15] The reaction of the spiroalkene **7** with aniline proceeded readily. The ^{1}H NMR spectrum of the product displayed for the aniline residues a doublet and two triplets in a 2:2:1 ratio, indicating that the nucleophile attacked exclusively via the nitrogen atom. On this basis, structure **11** derived from N attack of the aniline on the exocyclic double bonds was assigned to the product. Spirodienone **11** could be obtained in only 94% purity (according to the ^{1}H NMR).

$LiAlH_4$ reduction of the substituted bis(spirodienone) **11** yielded the calixarene **17**. Under slow exchange conditions at the NMR time scale ($CDCl_3$, 220 K) the molecule displayed a signal pattern characteristic of a trans disubstituted system. From the chemical shift difference between the axial and equatorial methine protons ($\Delta\nu$ = 484.79 Hz) and their coalescence temperature (T_c = 318.8 K) a barrier of 14.8 kcal mol^{-1} was determined for the cone-to-cone inversion process.[23]

Carbon Nucleophiles. Preliminary experiments conducted by addition of excess of MeLi or PhLi to **7**, indicated, as judged by ^{1}H NMR spectroscopy, that no incorporation of the carbon nucleophile had occurred. We therefore examined "softer" negatively charged carbon nucleophiles (i.e., with the negative charge spread over several atoms).

The alkylation reaction of phenolates can proceed via C- or O-alkylation.[24] However, reaction of **7** with sodium *p-tert*-butylphenolate yielded a product (**13**) that according to its spectroscopic data was derived from an O-alkylation of the phenolate.

Reaction of **7** with the sodium enolates of acetylacetone or diethylmalonate yielded the corresponding disubstituted bis(spirodienone) derivatives (**14** and **15**, respectively) resulting from C-alkylation of the nucleophiles. The two C(=O)R groups (R = OEt, Me) within a given $CH(C(=O)R)_2$ residue are diastereotopic, even under fast CH−CH rotations since the two groups are not symmetry equivalent. Separate signals were observed for the two acetyl group of the substituted bis(spirodienone) **14** in both the ^{1}H NMR (δ 2.16 and 2.10 ppm) and in the ^{13}C NMR spectra (δ 202.99 and 202.82 ppm). The ^3J coupling observed between the methine protons of the bridge and the side chain (12.7 Hz) indicates a preferred anti conformation of the substituent on the bridges.

Reaction of **15** with $LiAlH_4$ reductively cleaved the spiro bonds and reduced the ester groups into alcohol functionalities, yielding a calixarene (**18**) with two methylene bridges substituted by 2-propyl-1,3-diol groups. The ^{1}H NMR spectrum of **18** displayed at room-temperature broad signals, but at 430 K (in DMSO-d_6) the signals were sharp. At this temperature the spectrum displayed a singlet for the bridging methylene protons. This is the expected pattern (under fast exchange conditions) for a calix[4]arene substituted by identical substituents at two distal methylenes in a trans fashion (cf. Figure 1). Although the four hydroxymethyl groups are equivalent, the two methylene protons within a CH_2OH unit were anisochronous as expected, since neither fast

(21) For a recent example of the use of this reaction, see: Lewis, W. G.; Green, L. G.; Grynszpan, F.; Radic, Z.; Carlier, P. R.; Taylor, P.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 1053.

(22) Bis(spirodienones) calixarenes derivatives undergo a Diels−Alder cycloaddition reaction with benzyne. The adducts obtained are derived from attack to the external (exo) faces of the diene subunits (ref 11a). See also: Grynszpan, F.; Biali, S. E. *J. Org. Chem.* **1996**, *61*, 9512.

(23) Preliminary ^{1}H NMR experiments indicate that at 400 K calixarene **17** undergoes trans ⇌ cis isomerization, but accompanied by decomposition. No isomerization was observed upon heating **18**.

(24) For studies of the C- vs O-alkylation of phenolates, see: Kornblum, N.; Berrigan, P. J.; Le Noble, W. J. *J. Am. Chem. Soc.* **1963**, *85*, 1141.

C−CH_2OH rotations (nor any other rotational process) can mutually exchange the environments of these two symmetry nonequivalent protons.

Attempts to Synthesize Monofunctionalized Bis(spirodienone) Calixarene Derivatives. In principle it could be imagined that the reaction sequence described in Scheme 1 should be applicable also for the preparation of bis(spirodienones) calixarenes derivatives functionalized at a single methylene bridge if excess **7** is reacted with the nucleophile. In an attempt to achieve this transformation, **7** was treated with an equimolar amount of a nucleophilic salt (NaSMe) in "wet" THF. NMR analysis of the reaction product indicated that it consisted of a ca. 1:1 mixture of the bis(functionalized) derivative **10** and starting material **7**. This "all or nothing" reactivity pattern can be explained if the product of the displacement of a single bromine (i.e., **26**) is substantially more reactive than the starting material **7**. Apparently, the steric strain resulting from the presence of a single exocyclic double bond within the calix scaffold of **26** renders it more reactive than **7**.

Conclusions

The synthetic scheme depicted in Scheme 1 appears to be a general one for the preparation of calixarenes with substituents attached to two methylene bridges. A wide range of S-, N, O-, and C-containing nucleophiles are effective for the displacement reaction of the bromines of **7** (Scheme 2), provided the nucleophiles are "soft". The calixarene trans-functionalized at two methylenes with thiomethoxy substituents thermally isomerizes to the more stable cis form.

Experimental Section

Reaction of 7 with NaSMe in Moist THF. 7 (0.7 g, 0.87 mmol) was dissolved in 100 mL of THF, and to this solution was added sodium thiomethoxide (0.4 g, 5.7 mmol). After the solution was stirred for 1 h at room temperature, the solvent was evaporated and the residue dissolved in 50 mL of CH_2Cl_2. After being washed twice with water, the organic phase was evaporated. The residue was purified by recrystallization from $CHCl_3$/EtOH, yielding 0.44 g of **10** (68%): mp 212 °C. ^{1}H NMR (400.133 MHz, $CDCl_3$, rt) 7.67 (d, J = 1.5 Hz, 2H), 7.15 (d, J = 1.5 Hz, 2H), 6.68 (d, J = 2.4 Hz), 5.85 (d, J = 2.4 Hz), 5.23 (s, 2H), 3.78 (d, J = 15.4 Hz, 2H), 3.08 (d, J = 15.5 Hz, 2H), 2.04 (s, 6H), 1.35 (s, 18H), 1.03 (s, 18H) ppm. ^{13}C NMR (100.133 MHz, $CDCl_3$, rt) δ 194.0, 152.8, 146.2, 144.0, 139.5, 136.3, 127.4, 126.8, 122.5, 121.6, 120.1, 82.5, 39.9, 37.7, 34.6, 34.4, 31.9, 28.3, 16.1 ppm. CI MS (+DCI) m/z 737.4 (MH^+).

Preparation of 16. To 0.25 g of compound **10** (0.34 mmol) dissolved in 50 mL of dry THF was added $LiAlH_4$ (0.3 g, 8 mmol), and the solution was stirred under an inert atmosphere for 2 h. After being quenched with water, the reaction mixture was extracted with CH_2Cl_2. The organic phase was washed once with a 1 M HCl solution and twice with water. After evaporation of the solvent, the residue was chromatographed (silica, eluent: $CHCl_3$) yielding 0.1 g (40%) **16**: mp 223 °C. ^{1}H NMR (400.133 MHz, $CDCl_3$, 220 K) 7.53 (s, 2H), 7.20 (s, 2H), 7.07 (s, 2H), 7.02 (br s, 2H), 5.72 (s, 1H), 5.00 (s, 1H), 4.27 (d, J = 13.8 Hz, 2H), 3.56 (d, J = 13.9 Hz, 2H), 2.19 (s, 3H), 2.04 (s, 3H), 1.22 (s, 36H). ^{13}C NMR (100.133 MHz, $CDCl_3$, 230K) δ 147.7, 145.8, 144.6, 144.1, 143.3, 128.3, 128.0, 127.7, 127.2, 127.0, 126.5, 125.9, 122.9, 34.1, 33.9, 31.9, 31.2, 31.2 ppm. CI MS (-DCI) m/z 740.4 ($M^{-\bullet}$)

Reaction of 7 with NaSMe in Dry THF. To a solution of **7** (1 g, 1.25 mmol) in 150 mL of dry THF was added 0.7 g (10 mmol) of sodium thiomethoxide, and the suspension was stirred under an inert atmosphere for 3 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 and washed with water. NMR analysis of the residue indicated it consisted of a mixture of **21b** and the substituted calixarene **16**. The products were separated by chromatography (silica, eluent: 1:3 dichloromethane/hexane) to yield 0.05 g (5%) of **21b**, mp 142 °C (dec), and 0.46 g (50%) of **16**.

Spectroscopic data for 21b: ^{1}H NMR (400.133 MHz, $CDCl_3$, rt) δ 7.75 (s, 1H, Ar−H), 7.24 (s, 1H, Ar−H), 7.13 (s, 1H, Ar−H), 7.01 (d, J = 2.5 Hz, 1H, Ar−H), 7.00 (s, 1H, Ar−H), 6.87 (d, J = 2.4 Hz, 1H, Ar−H), 6.25 (s, 1H, C═C−H), 6.11 (s, 1H, C*H*SMe), 6.05 (s, 1H, OH), 4.89 (s, 1H, C*H*SMe), 4.30 (d, J = 14.4 Hz, 1H, CH_2), 4.00 (d, J = 16.1 Hz, 1H, CH_2), 3.68 (s, 1H, C*H*SMe), 3.44 (d, J = 14.5 Hz, 1H, CH_2), 3.10 (d, J = 16.1 Hz, 1H, CH_2), 2.24 (s, 3H, SMe), 2.07 (s, 3H, SMe), 2.06 (s, 3H, SMe), 1.35 (s, 9H, *t*-Bu), 1.33 (s, 9H, *t*-Bu), 1.32 (s, 9H, *t*-Bu), 1.10 (s, 9H, *t*-Bu). ^{13}C NMR (100.133 MHz, $CDCl_3$, rt) δ 197.4, 152.6, 151.7, 151.3, 147.8, 145.6, 145.2, 144.9, 132.5, 128.2, 127.8, 126.7, 125.8, 124.9, 124.7, 124.0, 122.8, 122.4, 120.5, 119.4, 91.3, 86.7, 54.7, 50.9, 41.7, 36.4, 34.6, 34.5, 34.1, 33.7, 33.4, 31.7 (2 peaks), 31.6, 31.3, 29.4, 22.6, 18.3, 15.9, 15.6, 14.1 ppm. CI MS (-DCI) m/z 784.3 ($M^{\bullet-}$).

Isomerization of 16. In a 5 mL flask was dissolved 100 mg of **16** in 2 mL of $CHCl_3$, and the solvent was slowly evaporated over a period of 2 weeks. During this period, crystals were formed that NMR analysis indicated they consisted exclusively of the cis derivative **22**: mp 248 °C. ^{1}H NMR (400.133 MHz, $CDCl_2CDCl_2$, rt) δ 10.29 (s, 4H), 7.50 (s, 4H), 7.04 (s, 4H), 5.59 (s, 2H), 4.17 (d, J = 14.0 Hz, 2H), 3.52 (d, J = 14.1 Hz, 2H), 1.97 (s, 6H), 1.20 (s, 36H). ^{13}C NMR (100.133 MHz, $CDCl_3$, rt) δ 146.2, 144.9, 128.2, 127.3, 126.1, 123.3, 42.8, 34.3, 32.5, 31.3, 15.8 ppm.

Preparation of 11. In a solution of 100 mL of THF and 1 mL of aniline was dissolved 0.5 g of **7** (0.6 mmol), and the mixture was stirred in the dark at room temperature for 4 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 and was washed with water. After evaporation of the solvent, the yellow residue was recrystallized from $CHCl_3$/MeOH yielding 0.34 g (66%) of **11** that was 94% pure according to the ^{1}H NMR, mp 268 °C. ^{1}H NMR (400.133 MHz, $CDCl_3$, rt) δ 7.30 (s, 2H), 7.16 (s, 2H), 7.13 (t, J = 7.2 Hz, 4H), 6.76 (d, J = 2.2 Hz, 2H), 6.68 (t, J = 6.9 Hz, 2H), 6.60 (d, J = 7.9 Hz, 4H), 5.98 (d, J = 2.3 Hz, 2H), 5.71 (s, 2H), 3.79 (d, J = 15.3 Hz, 2H), 3.79 (br s, 2H), 3.08 (d, J = 15.5 Hz, 2H), 1.25 (s, 18 H), 1.07 (s, 18H) ppm. ^{13}C NMR (100.133 MHz, $CDCl_3$, rt) δ 194.2, 152.4, 147.3, 145.0, 143.6, 138.6, 138.0, 128.9, 128.5, 126.2, 123.5, 121.0, 120.0, 118.0, 114.2, 48.4, 37.8, 34.4 (2 peaks), 31.8, 28.4. CI MS (+DCI) m/z 827.4 (MH^+).

Preparation of 17. Spirodienone **11** (0.5 g, 0.6 mmol) was dissolved in 80 mL of dry THF, and to this solution was added 0.5 g (13 mmol) $LiAlH_4$. The solution was stirred under an inert atmosphere for 4 h. After being quenched with water, the solution was extracted with CH_2Cl_2 and the organic phase was washed with 1 M HCl and twice with water. The residue obtained after evaporation of the solvent was chromatographed (silica, eluent: 4:1 CH_2Cl_2:hexane) yielding 0.25 g (50%) of **17**: mp 169−173 °C. ^{1}H NMR (400.133 MHz, $CDCl_3$, 230 K) δ 10.23 (br, OH), 7.45 (s, 2H), 7.24 (t, J = 7.4 Hz, 2H), 7.17 (t, J = 7.4 Hz, 2H), 7.10 (s, 2H), 6.90 (t, J = 7.3 Hz, 1H), 6.80 (d, J = 8.1 Hz, 2H), 6.76 (partially hidden t, J = 7.2 Hz, 1H), 6.62 (d, J = 8.0 Hz, 2H), 5.93 (s, 2H), 5.39 (s, 2H), 4.28 (d, J = 13.8 Hz, 2H), 3.53 (d, J = 13.9 Hz, 2H), 1.23 (s, 18H), 1.21 (s, 18H). ^{13}C NMR (100.133 MHz, $CDCl_3$, 230 K) δ 148.5, 147.9, 147.5, 145.7, 144.7, 143.1, 130.0, 129.2, 128.9, 127.5, 126.5, 126.4, 126.1, 124.5, 120.8, 119.9, 118.0, 115.0, 114.0, 68.1, 51.2, 34.2, 33.9, 31.8, 31.6, 31.2, 22.7, 14.3 ppm. CI MS (-DCI) m/z 828.2 ($M^{\bullet-}$ - H_2).

Reaction of 7 with Azide. 7 (3 g, 3.7 mmol) was dissolved in a mixture of 500 mL of THF, 100 mL of MeOH, and 100

mL of CH_2Cl_2, and to the solution was added NaN_3 (5 g, 77 mmol). After stirring the mixture at room temperature for 8 h, the solvent was evaporated and the yellow solid residue dissolved in 150 mL of CH_2Cl_2. The organic layer was washed several times with water. The solvent was evaporated and the residue dissolved with 10 mL of $CHCl_3$. After 100 mL of MeOH was added, a yellow precipitate formed which was filtered and dried under suction yielding 2.3 g (93%) of **12**: mp 245 °C (dec). ^{1}H NMR (400.133 MHz, $CDCl_3$, rt) δ 7.39 (s, 2H), 7.22 (s, 2H), 6.73 (d, J = 2.1 Hz, 2H), 5.95 (d, J = 2.0 Hz, 2H), 5.90 (s, 2H), 3.88 (d, J = 15.5 Hz, 2H), 3.10 (d, J = 15.8 Hz, 2H), 1.38 (s, 18H), 1.06 (s, 18H). ^{13}C NMR (100.133 MHz, $CDCl_3$, rt) δ 194.2, 151.4, 145.7, 144.3, 140.2, 134.3, 128.6, 126.5, 121.4, 121.0, 120.5, 82.7, 54.5, 37.2, 34.7, 34.4, 31.9, 28.3 ppm. CI MS: *m*/*z* 726.5.

Reaction of 12 with Dimethyl Acetylenedicarboxylate. To 1 g (1.38 mmol) of **12** dissolved in 150 mL of CH_2Cl_2 was added 1 mL of dimethyl acetylenedicarboxylate (8.1 mmol). The solution was refluxed under stirring for 6 h. After evaporation of the solvent, the residue was treated with $CHCl_3$/MeOH to afford 1.5 g (84%, 1.16 mmol) of the adduct **23**: mp 356 °C (dec). ^{1}H NMR (400.133 MHz, $CDCl_3$, rt) δ 7.71 (s, 2H), 7.11 (s, 2H), 5.44 (s, 4H) 4.30 (s, 2H), 4.01 (s, 6H), 3.98 (s, 6H), 3.74 (s, 6H), 3.45 (d, J = 15.8 Hz, 2H), 3.36 (s, 6H), 2.77 (d, J = 15.8 Hz, 2H), 1.12 (s, 18H), 1.03 (s, 18H). ^{13}C NMR (100.133 MHz, $CDCl_3$, rt) δ 190.3, 164.8, 164.5, 160.8, 157.6, 152.1, 151.0, 145.2, 141.9, 140.8, 140.1, 132.4, 125.9, 122.4, 121.9, 118.9, 118.5, 78.3, 64.7, 58.4, 53.6, 53.0, 52.9, 52.6, 48.8, 40.6, 34.8, 34.4, 31.4, 27.8 ppm. CI MS (+DCI) *m*/*z* 1295.4 (MH^+).

Preparation of Spirodienol 24. A 1 g portion (1.38 mmol) of **12** was dissolved in a mixture of 100 mL of THF and 40 mL of EtOH, and 1 g (26.4 mmol) of $NaBH_4$ was added. The mixture was stirred at room temperature for 3 h, the solvent was evaporated, and the residue was dissolved in CH_2Cl_2 and washed twice with water. After evaporation of the solvent, the residue was treated with $CHCl_3$/EtOH yielding 0.6 g (0.82 mmol, 59%) **24**: mp 183 °C. ^{1}H NMR (400.133 MHz, $CDCl_3$, rt) δ 7.33 (s, 2H), 7.17 (s, 2H), 5.77 (t, J = 2 Hz, 2H), 5.74 (s, 2H), 5.65 (s, 2H), 4.45 (dd, J = 12.4, 1.6 Hz, 2H, C*H*OH), 3.52 (d, J = 15.7, 2H), 3.34 (d, J = 15.7 Hz, 2H), 2.35 (d, J = 12.7 Hz, 2H, OH), 1.36 (s, 18H), 0.98 (s, 18H). ^{13}C NMR (100.133 MHz, $CDCl_3$, rt) δ 152.6, 147.3, 144.0, 141.0, 125.7, 123.4, 120.9, 120.8, 120.5, 88.0, 75.0, 56.6, 41.6, 34.6, 34.2, 31.9, 28.4 ppm. CI MS (+DCI) *m*/*z* 688.3 ($M - N_3$).

Reaction of Spirodienol 24 with Dimethyl Acetylenedicarboxylate. To 1 g (1.37 mmol) of **24** dissolved in 100 mL of 1,2-dichloroethane was added 1 mL of dimethyl acetylenedicarboxylate (8.1 mmol), and the mixture was refluxed with stirring for 6 h. The solvent was evaporated and the residue treated with $CHCl_3$/MeOH to yield 0.7 g (50%) of **25**: mp 245 °C. ^{1}H NMR (400.133 MHz, $CDCl_3$, rt) δ 7.29 (s, 2H), 7.16 (s, 2H), 6.51 (s, 2H), 6.38 (br s, 2H), 5.71 (s, 2H), 4.28 (d, J = 11.5 Hz, 2H, C*H*OH), 3.97 (s, 6H), 3.84 (s, 6H), 3.52 (d, J = 16.0 Hz, 2H), 3.33 (d, J = 15.8 Hz, 2H), 2.31 (d, J = 12.8 Hz, OH), 1.19 (s, 18H), 1.02 (s, 18 H). ^{13}C NMR (100.133 MHz, $CDCl_3$, rt) δ 160.6, 158.6, 152.6, 148.4, 144.4, 139.2, 137.9, 132.1, 128.8, 126.0, 121.4, 120.7, 120.6, 119.4, 88.5, 74.4, 56.5, 53.4, 52.7, 41.4, 34.5, 31.7, 28.4 ppm. CI MS (+DCI) *m*/*z* 830 ($MH^+ - C_6N_3O_4H_6$).

Reaction of 7 with Sodium *p*-*tert*-Butylphenolate. To a solution of 4-*tert*-butylphenol (0.5 g, 3.3 mmol) dissolved in 100 mL of dry THF was added 0.1 g of NaH (4 mmol), and the mixture was stirred for 1 h under an inert atmosphere. To the mixture was added **7** (0.5 g, 0.6 mmol), and the stirring was continued for 3 h at room temperature. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2 and washed with water several times. The organic phase was evaporated and the residue recrystallized from $CHCl_3$/EtOH to yield 0.5 g of **13** (85%): mp 262 °C. ^{1}H NMR (400.133 MHz, $CDCl_3$, rt) 7.55 (s, 2H), 7.22 (d, J = 9.2 Hz, 4H), 7.14 (s, 2H), 6.99 (s, 2H), 6.97 (d, J = 8.4 Hz, 4H), 6.45 (s, 2H), 5.92 (s, 2H), 3.69 (d, J = 15.4 Hz, 2H), 3.06 (d, J = 15.3 Hz, 2H), 1.32 (s, 18H), 1.26 (s, 18H), 1.04 (s, 18H) ppm. ^{13}C NMR (100.133 MHz, $CDCl_3$, rt) δ 194.2, 155.6, 151.5, 144.6, 143.7, 143.6, 140.7, 135.6, 128.8, 126.3, 126.0, 123.4, 120.2, 120.2, 115.7, 82.2, 68.3, 38.4, 34.5, 34.3, 34.0, 31.8, 31.5, 28.4 ppm. CI MS (+DCI) *m*/*z* 941.3 (MH^+), 791.3 ($MH^+ - t$-BuC_6H_5OH).

Reaction of 7 with Sodium Acetylacetonate. To 1 mL of acetylacetone (0.01 mol) dissolved in 100 mL of dry THF was added NaH (0.25 g, 0.01 mol), and the mixture was stirred under an inert atmosphere for 15 min. **7** (1 g, 1.25 mmol) was added, and the mixture was stirred for 90 min. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2, and the solution was washed with water. After evaporation of the organic solvent, the residue was recrystallized from $CHCl_3$/MeOH yielding 0.9 g (86%) **14**: mp 254 °C. ^{1}H NMR (400.133 MHz, $CDCl_3$, rt) 7.05 (s, 2H), 6.88 (s, 2H), 6.67 (d, J = 2.2 Hz, 2H), 5.87 (d, J = 2.2 Hz, 2H), 5.19 (d, J = 12.7 Hz, 2H), 4.44 (d, J = 12.7 Hz, 2H), 3.50 (d, J = 15.5 Hz, 2H), 3.07 (d, J = 15.6 Hz, 2H), 2.16 (s, 6H), 2.10 (s, 6H), 1.29 (s, 18H), 1.06 (s, 18H). ^{13}C NMR (100.133 MHz, $CDCl_3$, rt) δ 203.0, 202.8, 194.4, 153.2, 144.8, 143.8, 140.3, 134.4, 128.0, 127.6, 122.8, 120.0, 119.9, 81.6, 73.7, 39.4, 34.5, 34.3, 33.7, 31.8, 29.3, 28.7, 28.2 ppm. CI MS (+DCI) *m*/*z* 841.3 (MH^+).

Reaction of 7 with the Sodium Enolate of Diethyl Malonate. Diethyl malonate (0.5 mL, 3 mmol) was dissolved in 100 mL of dry THF, and to the solution was added under an inert atmosphere 0.1 g (4 mmol) of NaH. After the mixture was stirred at room temperature for 15 min, 0.5 g (0.62 mmol) of **7** was added, and the mixture was stirred for an additional 90 min. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 and washed twice with water. The residue obtained after evaporation of the organic phase was recrystallized from $CHCl_3$/MeOH yielding 0.45 g (75%) **18**: mp 268 °C. ^{1}H NMR (400.133 MHz, $CDCl_3$, rt) 7.04 (s, 2H), 6.99 (s, 2H), 6.61 (s, 2H), 5.85 (s, 2H), 5.01 (d, J = 12.4 Hz, 2H), 4.07 (m, 10H), 3.61 (d, J = 15.2 Hz, 2H), 3.02 (d, J = 15.3 Hz, 2H), 1.29 (s, 18H, *t*-Bu), 1.16 (t, J = 7.1 Hz, 6H), 1.10 (t, J = 7.1 Hz, 6H), 1.04 (s, 18H). ^{13}C NMR (100.133 MHz, $CDCl_3$, rt) δ 194.2, 167.6, 167.5, 153.1, 145.3, 143.3, 139.2, 134.7, 127.4, 126.9, 123.2, 119.7, 119.7, 81.8, 61.5, 61.4, 55.9, 38.5, 34.4, 34.3, 34.1, 31.8, 28.2, 14.0 (2 signals) ppm. CI MS (+DCI) *m*/*z* 961.2 (MH^+).

Reduction of 15 with $LiAlH_4$. To 0.4 g (0.47 mmol) of **15** dissolved in 100 mL of dry THF was added $LiAlH_4$ (0.4 g, 10 mmol), and the mixture was stirred at room temperature for 3 h under an inert atmosphere. The excess $LiAlH_4$ was quenched with water, and the reaction mixture was extracted with CH_2Cl_2. After being washed with 1 M aq HCl, the organic phase was evaporated and the residue purified by chromatography (silica, eluent: $CHCl_3$) yielding 0.25 g (66%) **18**: mp 192 °C. ^{1}H NMR (400.133 MHz, DMSO-d_6, 430 K) 7.1 (AB system, 4H), 4.35 (d, J = 12.0 Hz, 2H), 3.86 (s, 4H,), 3.65 (dd, ^2J = 10.5, ^3J = 3.2 Hz, 4H), 3.47 (dd, ^2J = 10.5, ^3J = 6.3 Hz, 4H), 2.97 (m, 2H), 1.21 (s, 36H). ^{13}C NMR (100.133 MHz, DMSO-d_6, 430 K) δ 148.2, 144.7, 130.6, 129.1, 126.1, 62.1, 43.5, 34.6, 32.8, 32.0, 26.0 ppm. CI MS (+DCI) *m*/*z* 797.5 (MH^+)

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Supporting Information Available: ^{1}H NMR spectra of compounds **10**−**18**, **21b**, and **22**−**25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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