Cyclization and Reductive Cleavage of Monospirodienone Calix[4]arene Derivatives. Trihydroxy-*p*-*tert*-butylcalix[4]arene Revisited

Flavio Grynszpan, Oleg Aleksiuk, and Silvio E. Biali*

Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem 91904, Israel

Received August 13, 1993 (Revised Manuscript Received February 2, 1994•)

The monospirodienone derivative of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrahydroxycalix[4]arene (**2**) undergoes in the presence of an ammonium tribromide salt a spiroannulation reaction at the α-position to the carbonyl. Reaction of **2** with an equimolar amount of LDA followed by treatment with a phosphorylating agent yielded a monosubstituted spirodienone. Reductive cleavage of the latter (K/NH_3) afforded 5,11,17,23-tetra-*tert*-butyl-25,26,27-trihydroxycalixarene (**10**). The structure of **10** was corroborated indirectly by X-ray crystallography of its bromo dispiro derivative **11**. It is concluded that the compound obtained by cleavage of the bis(diethyl phosphate) ester derivative **13**, and previously described by us as **10**, is 5,11,17,23-tetra-*tert*-butyl-25,27-dihydroxy-26-monoaminocalix[4]arene (**12**). The latter readily forms a tosylate salt in $CDCl_3$ solution. Considering this reassignment, the inversion barriers of several OH-depleted aminocalixarenes and their salts are reexamined.

Introduction

One of the main synthetic goals in calixarene chemistry is the modification of the binding OH groups.[1,2] We have recently described the preparation of the monospirodienone derivative of **1** (i.e., **2**).[3] This system is of interest since it may be capable of undergoing reactions at the carbonyl group, at the diene moiety, and at the hydroxyl groups. Spirodienone **2** was converted into monoaminotrihydroxy-*p*-*tert*-butylcalix[4]arene (**3**) in two steps by reaction of the carbonyl group with hydrazine followed by aromatization and N–N cleavage of the product.[4,5] As shown for the bis(spirodienone) derivatives of **1**, the diene part of a spirodienone may undergo a Diels–Alder reaction.[6] In the present paper we describe the chemically reversible transformation of **2** by α-cyclization into a system with two spiro groups and an unconjugated carbonyl and the preparation of the mono(diisopropyl phosphate) ester derivative of **2**. This compound is of interest since, by reductive cleavage, it should yield trihydroxy-*p*-*tert*-butylcalix[4]arene which we claimed to have obtained in the past in a mixture with dihydroxy-*p*-*tert*-butylcalix[4]arene (**4**).[7] This synthesis led us to reinvestigate the compound (**X**) we have previously assumed to be trihydroxy-*p*-*tert*-butylcalix[4]arene.[7,8] .

Results and Discussion

Spiroannulation of 2. Calixarenes possessing proximal spirodienone and phenolic moieties may react with electrophiles and undergo spiroannulation leading to a nonconjugated ketone group. Inspection of molecular models indicates that two annulations (α (**5**) and β (**6**)) to the carbonyl group are possible. The α-annulation results in the formation of a dispiran[9] while the β-cyclization results in an ether ring catacondensed[10] to the cyclohexenone. In any case the reaction results in the creation of two new stereocenters in the ring, in addition to the one present (the spiro carbon) in the starting material. Based on steric considerations, it should be expected that the electrophile should attack the *exo* face of the dienone (i.e. *anti* to the ether oxygen),[6] while the new ether bond should be formed at the *endo* face. We decided to attempt this reaction using bromine as the electrophile in the form of a ammonium tribromide salt.

Reaction of **2** with 1 equiv of phenyltrimethylammonium tribromide in $CHCl_3$ in the absence of base resulted in the formation of a main product (**7**). In contrast to the spirodienone derivatives of the calixarenes which are yellow,[3,6] **7** is colorless due to the absence of a conjugated dienone moiety. The ^1H NMR spectrum of **7** is in agreement with a structure of C_1 symmetry. Thirty-nine signals were observed in the ^{13}C NMR spectrum, which include one C=O signal at δ 195.64 ppm, two C–O signals at 88.27 and 82.78 ppm, and one C–Br sp^3 signal at 49.91 ppm, indicating that a carbonyl and two spiro C–O groups are present.

The molecule crystallizes from MeCN as a 1:1 adduct. A single crystal of **7** was submitted to X-ray crystallography.[11] The numbering scheme and a stereoscopic view of the crystal structure are shown in Figures 1 and 2. As

• Abstract published in *Advance ACS Abstracts*, March 1, 1994.

(1) For reviews on calixarenes see: (a) Gutsche, C. D. *Calixarenes*; Royal Society of Chemistry: Cambridge, 1989. (b) *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer: Dordrecht, 1991. (c) Böhmer, V.; McKervey, M. A. *Chemie in unserer Zeit* **1991**, 195.

(2) For a recent review on the selective functionalization of calixarenes see: van Loon, J.-D.; Verboom, W.; Reinhoudt, D. N. *Org. Prep. Proc. Int.* **1992**, *24*, 437.

(3) Aleksiuk, O.; Grynszpan, F.; Biali, S. E. *J. Chem. Soc., Chem. Commun.* **1993**, 11.

(4) Aleksiuk, O.; Grynszpan, F.; Biali, S. E. *J. Org. Chem.* **1993**, *58*, 1994.

(5) For a recent investigation on the reaction of spirodienones with hydroxylamine see: Kasturi, T. R.; Jayaram, S. K.; Pragnacharyulu, P. V. P.; Sattigeri, J. A.; Reddy, G. M.; Kumar, K. A. *Tetrahedron* **1993**, *49*, 113.

(6) Litwak, A. M.; Grynszpan, F.; Aleksiuk, O.; Cohen, S.; Biali, S. E. *J. Org. Chem.* **1993**, *58*, 393.

(7) Grynszpan, F.; Goren, Z.; Biali, S. E. *J. Org. Chem.* **1991**, *56*, 532.

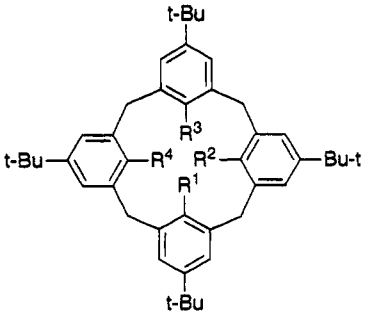
(8) In the present paper we will designate the compound described in ref 7 as trihydroxy-*p*-*tert*-butylcalix[4]arene as **X**. The designations **X** and **Y** (see text) will refer to the compounds and not to the structures assigned to them.

(9) For a review on polyspiranes see: Ginsburg, D. *Top. Curr. Chem.* **1987**, *137*, 1.

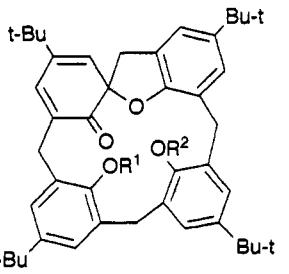
(10) Dale, J. *Stereochemistry and Conformational Analysis*; Verlag Chemie: Oslo, 1978; p 217.

0022-3263/94/1959-2070$04.50/0

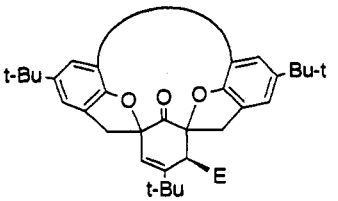
Chart 1



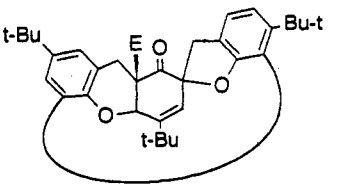
1 $R^1 = R^2 = R^3 = R^4 = OH$
3 $R^1 = NH_2$, $R^2 = R^3 = R^4 = OH$
4 $R^1 = R^3 = H$, $R^2 = R^4 = OH$
10 $R^1 = H$, $R^2 = R^3 = R^4 = OH$
12 $R^1 = NH_2$, $R^3 = H$, $R^2 = R^4 = OH$
13 $R^1 = R^3 = OPO(OEt)_2$, $R^2 = R^4 = OH$
14 $R^1 = R^2 = H$, $R^3 = R^4 = OH$



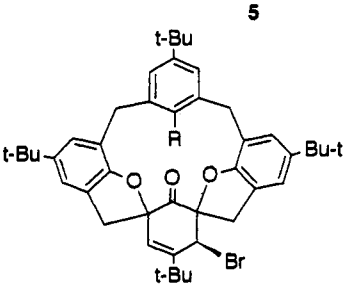
2 $R^1 = R^2 = H$
8a R^1 = substituent, $R^2 = H$
8b $R^1 = H$, R^2 = substituent



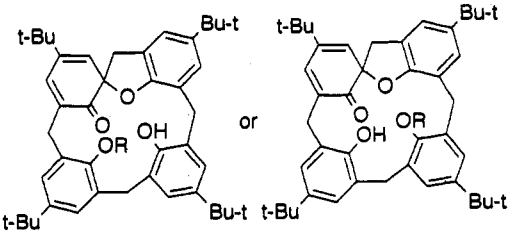
5



6



7 R = OH
11 R = H



9 $R = P(O)(Oi\text{-}Pr)_2$

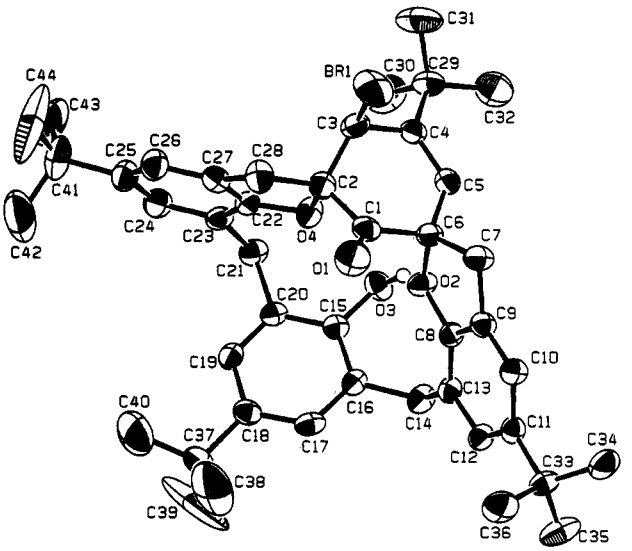


Figure 1. Top view and numbering scheme of the molecular structure of **7**. The acetonitrile molecule has been omitted for clarity.

shown in the figures, the molecule adopts a conformation in the crystal which resembles a partial cone and in which the carbonyl-bearing ring is oriented in an opposite direction to the other three rings. Both spiro bonds are located α to the carbonyl group. The bromine atom and the two spiro oxygens are located at pseudoaxial positions of the cyclohexenone ring. The spiro oxygens are located *endo* and pointing to the center of the molecular cavity, while the bromine is located *exo*. The phenolic OH group is hydrogen bonded to one of the ether oxygens, as judged by the O(3)···O(2) nonbonded distance (2.792(3) Å). The MeCN molecule is only partially included in the molecular cavity.

Monospirodienones as Intermediates in the Preparation of Monosubstituted Calixarenes. Two features make spirodienone **2** a potential intermediate for the preparation of intraannular monosubstituted calixarenes. Firstly, since two OH groups are "masked" in the spirodienone moiety only two OH groups are "free" to react. This structural feature was used in the past for the preparation of proximally (1,2) disubstituted calixarenes.[3] Secondly, monospirodienone calixarene derivatives readily revert to calixarenes.[3] We reasoned that if the molecule could be monodeprotonated, monosubstitution of the spirodienone could be achieved, and these compounds could be used as intermediates in the preparation of intraannular monosubstituted calixarenes. In principle, monoderivatization of **2** should yield two monosubstituted

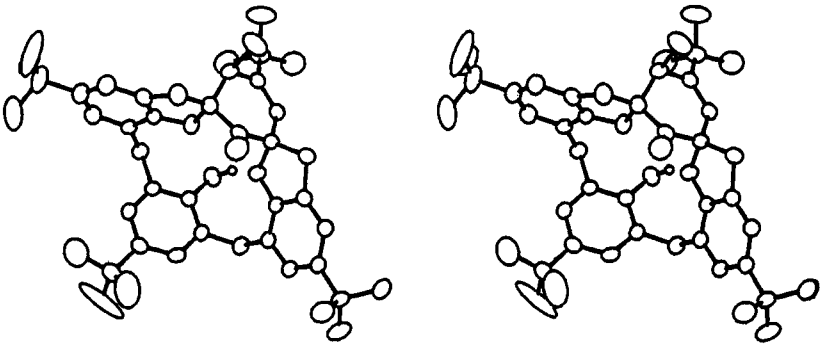


Figure 2. Stereoscopic representation of the view of 7·MeCN.

spirodienone derivatives (**8a** and **8b**). However, both compounds should lead by reduction of the spirodienone moiety to the same monosubstituted calixarene.

For the preparation of the mono(diisopropyl phosphate) ester derivative of the spirodienone **9**, we reacted **2** with 1 equiv of LDA in dry THF at −78 °C followed by addition of diisopropyl chlorophosphate. Interestingly, according to the ^{1}H NMR spectrum of the product, only one of the two possible regioisomers was formed. The ^{1}H NMR spectrum is in agreement with a structure of C_1 symmetry, but unfortunately, on the basis of the spectroscopic data, we were unable to decide which regioisomer was formed. We attempted the one-step reduction of the spirodienone and reductive cleavage of the phosphate ester group of **9** by treatment with K/NH_3.[12] The expected product of the reaction was trihydroxy-*p*-*tert*-butylcalix[4]arene (**10**) which we claimed we prepared and characterized by NMR and X-ray crystallography.[7] Surprisingly, the reaction of **9** with K/NH_3 at −78 °C gave a compound (**Y**)[8] with the expected mass but with a ^{1}H NMR spectrum *different* to the one previously observed for **X**. The ^{1}H NMR spectrum of **Y** (400 MHz, $CDCl_3$, rt) displays three *tert*-butyl signals (in a 1:1:2 ratio), two singlets for the methylene protons (δ 3.83 and 3.88 ppm), and an AB system, one singlet and one doublet for the aromatic protons. A 2D NMR TOCSY spectrum clearly showed that the aromatic doublet is coupled to a hidden triplet located at about δ 6.94. Compound **Y** displays at room temperature (1:1 $CDCl_3$:CD_2Cl_2) a ^{1}H-NMR spectrum compatible with a structure which is flexible on the NMR time scale, as indicated by the presence in the methylene region of two singlets at δ 3.80 and 3.78 ppm. Lowering the temperature caused a broadening of these signals, followed by decoalescence and resharpening as two pairs of doublets. From the coalescence temperature (T_c = 213 K), the chemical shift differences ($\Delta\nu$ = 257 and 286.4 Hz), and the coupling constants, a barrier of $\Delta G_c^{\ddagger}$ = 9.6 kcal mol^{-1} was calculated for the ring-inversion process.[13] We attempted to grow crystals of **Y** suitable for X-ray crystallography. However, the crystals obtained belonged to a tetragonal symmetry group, indicating a 4-fold disorder of the molecules in the crystal.

In order to determine the structure of **Y** indirectly we decided to transform it into a derivative suitable for X-ray diffraction. We reasoned that if **Y** has a trihydroxy subunit, its reaction with a mild brominating agent in the presence of base would yield in the first step a monospirodienone system. This spirodienone should subsequently undergo under the reaction conditions an annulation reaction leading to a bromo dispiro system in a similar fashion as **7** is obtained from **2**.

Treatment of a CH_2Cl_2 solution of **Y** with 2.5 equiv of phenyltrimethylammonium tribromide in the presence of aqueous $NaHCO_3$ yielded the bispiro system **11** as the main product. The ^{1}H-NMR spectrum (400 MHz, $CDCl_3$, rt) of **11** is very similar to that obtained for **7**. A single crystal of **11** was grown in *n*-hexane and submitted to X-ray crystallography. The molecule crystallizes in the $P2_1/c$ space group. In general the crystal structure conformation of **11** (which resembles a partial cone) is very similar to that of **7**. The presence of a *p*-*tert*-butylphenyl ring in **11** suggests that **Y** is indeed trihydroxy-*p*-*tert*-butylcalix[4]-arene (**10**), provided that the transformation **Y** → **11** did not affect the basic structure of the molecule. In this case it should be possible to obtain the starting material by reduction of **11**. Pyrolysis of **11** yielded **Y** proving that the latter compound is indeed the trihydroxycalixarene **10**. Fukazawa et al.[14] synthesized, by a route similar to that developed by Böhmer,[15] a 5,11,17-trimethyl-23-*tert*-butyl-25,26,27-trihydroxycalix[4]arene. The chemical shift of H_a and the inversion barrier found by us for **10** are similar to those reported by Fukazawa (δ H_a 6.94; $\Delta G_c^{\ddagger}$ (CD_2Cl_2) = 9.3 kcal mol^{-1}),[14] which further strengthens our structural assignment of **Y**.

Reinvestigation of the Structure of X. In light of the results mentioned above, we resubmitted **X** to mass spectroscopy. The compound displayed in the CI MS a molecular peak at *m/z* 632 corresponding to the protonated MH^+ form. Redetermination of the EI MS again showed that the molecular peak appears at *m/z* 632, but at low sample concentration it appears at *m/z* 631. This seems to indicate that the compound undergoes self protonation. On the basis of this evidence and on the C_s symmetry indicated by the NMR spectra, we realized that **X** is 5,11,17,23-tetra-*tert*-butyl-25,27-dihydroxy-26-monoaminocalix[4]arene (**12**). The C and H percents previously determined by microanalysis (C: 83.80%, H: 9.29%)[7] could fit both structures **10** and **12** due to the similarity in their molecular mass and composition. Resubmission

(11) The authors have deposited atomic coordinates for the structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(12) For examples of reductive cleavage of the dialkyl phosphate esters of calixarenes see: (a) Goren, Z.; Biali, S. E. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1484. (b) Ting, Y.; Verboom, W.; Groenen, L. C.; van Loon, J.-D.; Reinhoudt, D. N. *J. Chem. Soc., Chem. Commun.* **1990**, 1432. (c) McMurry, J. E.; Phelan, J. C. *Tetrahedron Lett.* **1991**, *41*, 5655.

(13) The barrier was calculated from the exchange rates at the coalescence temperatures according to Kurland, R. J.; Rubin, M. B.; Wise, W. B. *J. Chem. Phys.* **1964**, *40*, 2426.

(14) Fukazawa, Y.; Demaya, K.; Usui, Sh. *Tetrahedron Lett.* **1992**, *33*, 5803.

(15) Böhmer, V.; Chhim, P.; Kämmerer, H. *Makromol. Chem.* **1979**, *180*, 2503.

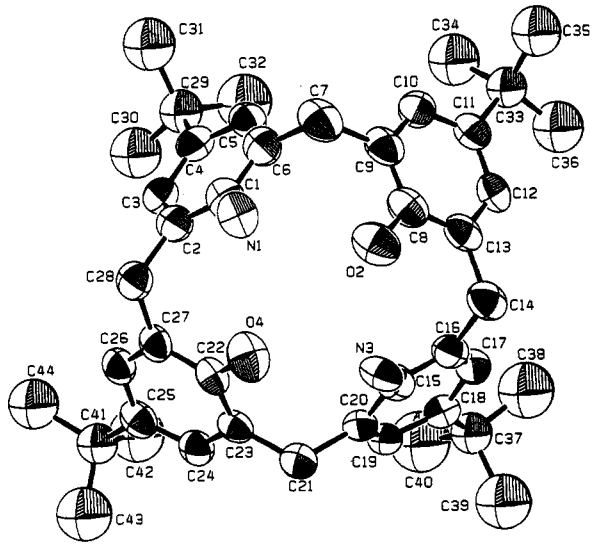


Figure 3. Numbering scheme of the crystal structure of **12**. A single nitrogen atom is disordered at two positions (N(1) and N(3)).

of **X** to microanalysis revealed that the compound contains nitrogen (N% calcd 2.22, found 1.81).

Provided that the structure of **X** is indeed **12**, the molecule, by analogy with **3**,[4] should have basic properties. Adding tosylic acid to a solution of **12** in $CDCl_3$ resulted in the solubilization of an equimolar amount of the acid, as indicated by the ^{1}H-NMR integration ratio of the tosylate protons and the calixarene protons. The methylene signals that in **12** appeared as two singlets ($CDCl_3$, rt) became, after the addition of the tosylic acid, two pairs of doublets. Notably, H_a was shifted downfield to δ 7.83 ppm. We ascribe those changes to the formation of the salt **12**·H^+TosO^-.

12 displays in the ^{1}H-NMR spectrum (toluene-d_8, rt) two methylene singlets. Lowering the temperature caused a broadening of the signals, and from the decoalescence data, a barrier of $\Delta G_c^{\ddagger}$ = 10.8 kcal mol^{-1} was calculated for the ring inversion process.[7] From the coalescence of the methylenic signals of the salt **12**·H^+TosO^- in toluene-d_8, the barrier for the ring inversion process was calculated as $\Delta G_c^{\ddagger}$ = 13.4 kcal mol^{-1}.[13]

The X-ray structure of **12** was previously described by us in terms of a trihydroxycalixarene structure.[7] The misassignment of the nitrogen atom as an oxygen was probably due to the presence of disorder of one heavy atom.[7] We grew a new single crystal of **12** from pyridine and redetermined its crystal structure by X-ray crystallography. Although the data collected were better, the hydrogen atoms near the disordered positions could not be located. The structure was refined assuming half occupancy of a nitrogen atom at two positions (N(1) and N(3)). In addition, two *tert*-butyl groups were disordered in two positions and were refined assuming half occupancy. The numbering scheme of the crystal structure is shown in Figure 3. Our previous conclusions[7] regarding the conformation of the molecule (cone) and the inclusion pattern of the pyridine molecules remain unchanged.

Compound **12** has been described by Shinkai and coworkers[16] as one of the products of the reaction of **13** with KNH_2 in NH_3/K at −78 °C. The formation of **12** in the reaction of **13** with K/NH_3 in the absence of KNH_2 is unexpected.[17] The higher temperature (−33 °C) of the reaction plays a crucial role in the aminodephosphorylation since at lower temperatures (−78 °C) the only product obtained was the OH-depleted calixarene **4**. Most likely, at the higher temperature some KNH_2 is formed *in situ* which replaces one of the phosphate groups of **13** while the second phosphate is reductively cleaved.[18] Interestingly, the preparation of **X** represents an example of the substitution of OH by NH_2 in a calixarene.

In light of the reassignment of the structure of **X**, we decided to repeat our reaction in order to see whether **10** is formed at all under the reaction conditions. Examination of the crude product of the reaction of 1.1 g of **13** with K/NH_3 at −33 °C according to the conditions previously described[7] showed that the two main products are **12** and **4**. Chromatography of the product yielded 212 mg of **4**, 100 mg of **12**, 28 mg of **1**, and in the last fraction 25 mg of **10**, indicating that some ArO–P cleavage took place.

Inversion Barriers of OH-Depleted and Aminocalixarenes. Two main factors should determine the inversion barriers in the systems. Firstly, the stronger the hydrogen bonds and the larger the number of intramolecular hydrogen bonds present, the higher the barrier. Secondly, if the molecule forms an endo-calix complex with a solvent molecule, this should increase the barrier.[1] The difference between the energy barriers of **1** and **10** is about 6.1 kcal mol^{-1}, which is larger than the barrier difference previously reported by us.[7] Indeed, Fukazawa and co-workers noted correctly that the barrier difference reported by us between **1** and **X** seemed to be too small.[13] Interestingly, the inversion barrier of **10** is lower than the barrier found for the dihydroxycalixarene **14**[3] and similar to **4**. This is rather unexpected since, if the inversion barrier is mainly determined by the hydrogen bonds, the barrier should drop with the decrease in the number of hydrogen bonds.

The inversion barrier measured in $CDCl_3/CD_2Cl_2$ for the amino system **12** is higher than the barrier for the trihydroxycalixarene **10**. This is in contrast with the behavior observed for the parent **1**, where replacement of one or two hydroxyl groups by amino groups reduces the inversion barrier. As in the case of **3**, the tosylate salt of **12** is more rigid than the free base, but the increase in rigidity is somewhat larger for **12** (2.6 kcal mol^{-1}) than for **3** (1.6 kcal mol^{-1}).

Conclusions

Monospirodienone calixarene derivatives can be used as intermediates for the synthesis of monosubstituted calix[4]arenes. The preparation of trihydroxycalixarene **10** by this route lead us to reassign to **X** the monoamino dihydroxycalixarene structure **12**.

Experimental Section

The X-ray diffraction data were measured with a PW1100/20 Philips Four Circle Computer-Controlled Diffractometer or an ENRAF-NONIUS CAD-4 automatic diffractometer. Mo K_α (λ = 0.71069 Å) or Cu K_α (λ = 1.54178 Å) radiation with a graphite

(16) Ohseto, F.; Murakami, H.; Araki, K.; Shinkai, S. *Tetrahedron Lett.* **1992**, *33*, 1217.

(17) Rossi, R. A.; Bunnett, J. F. *J. Org. Chem.* **1973**, *38*, 2314.

(18) Higher temperatures facilitate the decomposition of solutions of alkali metal in ammonia. See: Thompson, J. C. *Electrons in Liquid Ammonia;* Clarendon Press: Oxford, 1976; pp 8–10.

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

(20) Grynszpan, F.; Biali, S. E. *Tetrahedron Lett.* **1991**, *32*, 5155.

(21) Araki, K.; Murakami, H.; Ohseto, F.; Shinkai, S. *Chem. Lett.* **1992**, 539.

crystal monochromator in the incident beam was used. All crystallographic computing was done on a VAX 9000 computer using the TEXSAN structure analysis software.

Crystal data for 7: $C_{44}H_{53}BrO_4 \cdot CH_3CN$, space group $P\bar{1}$, a = 9.882(2) Å, b = 23.105(4) Å, c = 9.537(2) Å, α = 101.26(1), β = 97.03(3), γ = 97.15(3)°; V = 2095(1) Å^3, z = 2, ρ_{calc} =1.22 g cm^{-3}, μ(Mo Kα) = 10.10 cm^{-1}, no. of unique reflections = 7397, no. of reflections with $I \geq 3\sigma_I$ = 5355, R = 0.051, R_w = 0.071. Crystal data for 11: $C_{44}H_{53}O_3Br \cdot {}^1/_2C_6H_{14}$, space group $P2_1/c$, a = 18.049-(2) Å, b = 18.366(4) Å, c = 12.935(2), V = 4267(1) Å^3, z = 4, ρ_{calc} = 1.17 g cm^{-3}, μ(Cu Kα) = 15.80 cm^{-1}, no. of unique reflections = 6338, no. of reflections with $I \geq 3\sigma_I$ = 5368, R = 0.056, R_w = 0.088. Crystal data for 12: $C_{44}H_{57}NO_2 \cdot 2C_5H_5N$, space group $P2_12_12_1$, a = 20.539(3) Å, b = 24.435(2) Å, c = 9.452(1), V = 4744(1) Å^3, z = 4, ρ_{calc} = 1.11 g cm^{-3}, μ(Cu Kα) = 4.78 cm^{-1}, no. of unique reflections: 3972, no. of reflections with $I \geq 2.5\sigma_I$ = 3494, R = 0.095, R_w = 0.134.

General Methods. LDA and phenyltrimethylammonium tribromide were purchased from Aldrich. All column chromatographies were performed using silica gel 230–400 mesh purchased from Merck.

Preparation of the Monospirodienone Calix[4]arene 2. A sample of 10 g of *p-tert*-butylcalix[4]arene (1)[22] was dissolved in 8 L of CH_2Cl_2 and a solution of 5 g of phenyltrimethylammonium tribromide in 1 L of CH_2Cl_2 was slowly added to the stirred solution during a 1.5-h period. After the addition was complete, the mixture was stirred for an additional 1.5 h. To the solution was added during a 2.5 h period 2.5 L of saturated aqueous $NaHCO_3$. After stirring for 24 h, the solvent was evaporated and the residue treated with 200 mL of hot MeCN and the undissolved solid 1 filtered. Evaporation of the solvent gave 4.7 g of 2, 95% pure according to NMR. Further purification was achieved by column chromatography (eluent: $CHCl_3$) yielding 3.2 g (38%) of 2: mp 266–270 °C dec; ^{1}H NMR δ 1.21 (s, t-Bu, 18H), 1.24 (s, t-Bu, 9H), 1.27 (s, t-Bu, 9H), 3.00 (d, 1H, J = 15.7 Hz), 3.39 (d, 1H, J = 13.6 Hz), 3.44 (d, 1H, J = 16.4 Hz), 3.60 (dd, 2H), 3.74 (d, 1H, J = 14.5 Hz), 4.00 (d, 1H, J = 14.4 Hz), 4.16 (d, 1H, J = 13.6 Hz), 5.99 (d, 1H, J = 2.4 Hz), 6.90 (d, 1H, J = 2.4 Hz), 7.02 (d, 1H, J = 2.4 Hz), 7.02 (d, 1H, J = 2.4 Hz), 7.03 (m, 1H), 7.12 (m, 3H), 7.45 (s, 1H, OH), 7.73 (s, 1H, OH); ^{13}C-NMR (100.62 MHz, $CDCl_3$) δ 28.52, 31.43, 31.51, 31.71, 32.24, 32.61, 33.88, 34.02, 34.31, 34.46, 36.75, 38.39, 83.23 (spiro C), 120.71, 121.98, 124.87, 125.05, 125.35, 126.04, 126.14, 126.26, 126.45, 126.73, 127.24, 128.05, 130.98, 135.41, 138.48, 143.14, 144.83, 145.43, 145.55, 147.16, 149.02, 151.67, 194.87 (C=O); high resolution MS (EI) calcd for $C_{44}H_{54}O_4$ 646.4022, found 646.4028. Anal. calcd for $C_{44}H_{54}O_4 \cdot CH_3CN$: C, 80.31; H, 8.35. Found: C, 79.99; H, 8.35.

The X-ray structure of 2·MeCN is reported in ref 3.

Preparation of the Bromo Dispiro System 7. A solution of 2 (20 mg, 0.031 mmol) and phenyltrimethylammonium tribromide (30 mg, 0.08 mmol) in $CHCl_3$ was refluxed with stirring for 8 h. Evaporation of the solvent and separation of the products by liquid chromatography (eluent: $CHCl_3$) yielded 10 mg (0.013 mmol) of pure 7 (43%): mp 165–170 °C dec; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.11 (s, 9H), 1.28 (s, 9H),1.32 (s, 9H),1.33 (s, 9H), 3.06 (d, 1H, J = 15.8 Hz), 3.21 (d, 1H, J = 16.7 Hz), 3.27 (d, 1H, J = 13.1 Hz), 3.47 (d, 1H, J = 14.7 Hz), 3.90 (d, 1H, J = 15.8 Hz), 4.07 (d, 1H, J = 16.6 Hz), 4.36 (d, 1H, J = 14.5 Hz), 4.66 (d, 1H, J = 13.0 Hz), 4.79 (d, 1H, J = 1.5 Hz), 5.89 (s, 1H, OH), 6.02 (d, 1H, J = 1.6 Hz), 6.87 (d, 1H, J = 2 Hz), 6.90 (s, 1H), 7.01 (s, 1H), 7.05 (s, 1H), 7.10 (s, 1H), 7.12 (s, 1H), 7.20 (s, 1H); ^{13}C-NMR (100.62 MHz, $CDCl_3$) δ 29.23, 30.01, 31.32, 31.7, 31.75, 33.92, 34.07, 34.28, 34.36, 34.94, 35.87, 37.16, 49.91, 82.78, 88.27, 119.2, 119.91, 123.11, 124.0, 124.85, 125.33, 125.44, 125.5, 125.54, 126.06, 126.54, 129.03, 131.19, 144.58, 145.23, 148.33, 149.81, 152.1, 153.36, 195.64; IR 3447 (OH), 1742 (C=O) cm^{-1}; MS (CI) m/z 725.5 (MH$^+$). Anal. Calcd for $C_{44}H_{53}O_4Br \cdot CH_3CN$: C, 72.05; H, 7.36. Found: C, 71.84; H, 7.49.

Monophosphorylation of 2. A solution of 2 (0.85 g, 1.3 mmol) in 50 mL of dry THF under a static argon atmosphere was cooled to −78 °C and treated with a 1.5 M solution of LDA (0.87 mL, 1.3 mmol). Diisopropyl chlorophosphate[23] (0.32 g, 1.6 mmol) was added after 20 min and the mixture was stirred for 60 min. The solution was allowed to warm up to room temperature and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 and washed several times with water. After evaporation of the CH_2Cl_2, the product was purified by chromatography (eluent: $CHCl_3$) yielding 9 in 47% (0.498 g): mp 96–100 °C dec; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.99 (d, J = 6.4 Hz, 6H), 1.10 (s, 9H), 1.14 (s, 9H), 1.30 (s, 9H), 1.33 (s, 9H), 3.05 (d, J = 15.7 Hz, 1H), 3.07 (d, J = 13.6 Hz, 1H), 3.31 (d, J = 15.7 Hz, 1H), 3.32 (d, J = 14.1 Hz, 1H), 3.78 (d, J = 14.9 Hz, 1H), 3.88 (d, J = 13.6 Hz, 1H), 4.12 (d, J = 14.1 Hz, 1H), 4.36 (d, J = 14.9 Hz, 1H), 4.55 (d, J = 6.4 Hz, 2H), 5.91 (d, J = 2.2 Hz, 1H), 6.17 (s, 1H), 6.85 (d, J = 2.4 Hz, 1H), 6.92 (d, J = 2.4 Hz, 1H), 6.97 (d, J = 2.2 Hz, 1H), 7.00 (d, J = 1.8 Hz, 1H), 7.08 (d, J = 2.2 Hz, 1H), 7.21 (d, J = 1.8 Hz, 1H), 7.24 (d, J = 2.2 Hz, 1H); ^{13}C-NMR (100.62 MHz, $CDCl_3$) δ 23.80, 26.89, 28.52, 30.16, 31.25, 31.73, 31.86, 33.96, 34.01, 34.14, 34.24, 37.58, 39.88, 72.78, 81.85, 119.59, 123.91, 124.20, 125.32, 125.42, 126.23, 126.89, 127.06, 127.26, 128.81, 129.42, 131.52, 132.81, 135.54, 138.14, 142.80, 142.88, 143.00, 143.60, 146.82, 149.59, 153.91, 200.98; ^{31}P-NMR (161.99 MHz, $CDCl_3$) δ −7.67; CI MS (isobutane) m/z 813.5 (MH$^+$ + 2H).

5,11,17,23-Tetra-*tert*-Butyl-25,26,27-trihydroxycalix[4]-arene (10). Potassium metal (0.75 g) was added to 50 mL of liquid ammonia while cooling the reaction flask to −78 °C. After 45 min of stirring an additional 0.25 g of potassium was added. The mixture was stirred for 15 min and then a solution of 9 (70 mg, 0.086 mmol) in 2 mL of dry ether was dropped to the solution. After 15 min, the reaction mixture was quenched with NH_4Cl. After evaporation of the NH_3 the residue was treated with 50 mL of hot ether. Filtration, evaporation of the ether, and recrystallization of the product from $CHCl_3$–CH_3CN yielded 31 mg (57%) of pure 10: mp 285 °C dec; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 18H), 1.24 (s, 9H), 1.27 (s, 9H), 3.83 (s, 4H), 3.88 (s, 4H), 7.00 (d and hidden t, 3H), 7.03 (d, 2H), 7.06 (s, 2H), 7.13 (d, J = 1.2 Hz, 2H); ^{1}H-NMR (400 MHz, C_6D_6) δ 1.09 (s, 18H), 1.16 (s, 18H), 3.84 (s, 4H), 3.85 (s, 4H), 6.99 (s, 2H), 7.03 (AB q, 4H), 7.06 (d, 2H), 7.38 (t, 1H); ^{13}C-NMR (100.62 MHz, $CDCl_3$) δ 31.34, 31.44, 32.72, 33.94, 34.01, 34.54, 38.08, 124.02, 124.62, 125.58 (2 overlapping signals), 126.13, 127.27, 127.49, 127.50, 141.05, 143.78, 144.38, 147.42, 148.67, 151.58. CI MS: 633.4 (MH$^+$); HRMS calcd for $C_{44}H_{56}O_3$ 632.4229, found 632.4251.

Bromospiroannulation of 10. A solution of phenyltrimethylammonium tribromide (0.25 g, 0.664 mmol) in 10 mL of CH_2Cl_2 was slowly dropped into a stirred solution of 10 (0.17 g, 0.27 mmol) in 6 mL CH_2Cl_2. The mixture was stirred at room temperature during 90 min and then a saturated aqueous solution of $NaHCO_3$ (15 mL) was dropped into the reaction mixture. The solution was stirred overnight, and the organic phase was then separated and washed several times with water. The solvent was evaporated and the main product 11 isolated by liquid chromatography (eluent: $CHCl_3$) yielding 33 mg 11 (19%): mp 234–236 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.19 (s, 9H),1.26 (s, 9H), 1.28 (s, 9H), 1.30 (s, 9H), 3.05 (d, J = 15.7 Hz, 1H), 3.13 (d, J = 16.3 Hz, 1H), 3.56 (d, J = 14.2 Hz, 1H), 3.64 (d, J =13.8 Hz, 1H), 3.68 (d, J = 16.1 Hz, 1H), 3.85 (d, J = 13.4 Hz, 1H), 3.99 (d, J = 14.2 Hz, 1H), 4.07 (d, J = 16.4 Hz, 1H), 4.78 (d, J = 1.9 Hz, 1H), 5.93 (d, J = 1.9 Hz, 1H), 6.97 (m, 2H), 7.01 (m, 2H), 7.04 (d, 1H), 7.13 (d, J = 2.0 Hz, 1H), 7.43 (t, 1H); ^{13}C-NMR (100.62 MHz, $CDCl_3$) δ 29.51, 31.42, 31.70, 31.80, 34.28, 34.39, 35.34, 35.66, 37.71, 38.23, 40.20, 50.12, 82.10, 88.23, 119.39, 119.42, 122.10, 122.77, 123.73, 124.02, 124.91, 125.79, 125.82, 126.54, 126.68, 129.82, 138.15, 139.00, 143.95, 145.06, 147.69, 150.18, 153.86, 154.7, 197.25; EI MS (15 eV) m/z 630.6 (B, M − Br + H$^+$).

Acknowledgment. We thank Dr. Shmuel Cohen for the X-ray determinations, the Mass Spectrometry Center at the Technion, Haifa, for the mass spectra determinations, and the Israel Academy of Science for support of this work.

Supplementary Material Available: Numbering scheme of the crystal structure of 11 (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(22) Gutsche, C. D.; Iqbal, M. *Org. Synth.* **1989**, *68*, 234.
(23) McCombie, H.; Saunders, B. C.; Stacey, G. J. *J. Chem. Soc.* **1945**, 380.