Proximal Intraannular Modifications of Calix[4]arene *via* its Spirodienone Derivative

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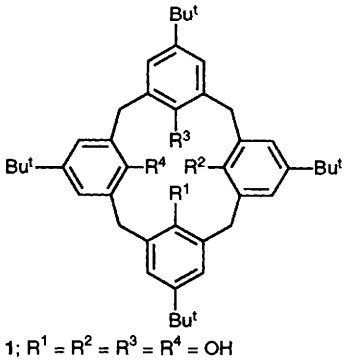
Mild oxidation of *p-tert*-butylcalix[4]arene **1** yields the chiral spirodienone **3** which is used as an intermediate for the preparation of proximally disubstituted and didehydroxylated calixarenes; the crystal structure of **3** has been determined.

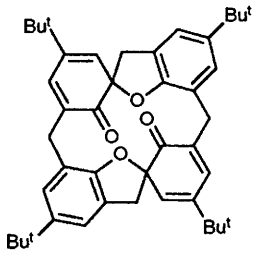
Calixarenes[1] are cyclic oligomers of phenol and formaldehyde which usually undergo disubstitution at distal (1,3) positions.[1,2] Pappalardo and coworkers have reported the first example of a proximally (1,2) disubstituted calixarene obtained by treatment of *p-tert*-butylcalix[4]arene **1** with NaH in dimethylformamide (DMF) and 2-(chloromethyl)pyridine.[3] Proximal disubstitution by selective demethylation of the tetramethyl ether derivative of **1**[4] or in moderate yields (15–55%) by treating **1** in DMF or MeCN with NaH and 2.2 equiv. of the alkylating agent was later reported by other groups.[5]

While CrO_3 oxidation of **1** yields tetraoxocalix[4]arene,[6] mild oxidation of **1** results in the formation of spirodienone derivatives such as **2**.[7] These compounds readily revert to **1** on reduction. We reasoned that oxidation of **1** under controlled conditions could lead to the chiral mono(spirodienone) system **3**. Inspection of Dreiding models suggests that the spirocyclization should involve exclusively two proximal rings since the oxygen atom of a given OH group is too far away from the carbons of the distal ring to create the ether bond. We expected that system **3** with two proximal OH groups could be used as an intermediate for the preparation of hitherto unknown proximally modified calixarenes *via* derivatization of the two unmasked OH groups and reduction of the spirodienone moiety.

Treatment of a solution of **1** in CH_2Cl_2 at 0 °C with 1 equivalent of trimethylphenylammonium tribromide and a saturated solution of $NaHCO_3$ resulted in the formation of **3**.†‡ This one-step reaction converts calixarene **1** into a chiral system with three different functional groups (OH, carbonyl and ether). The use of a weak base in this step is of importance since the use of a stronger base (aq. NaOH) resulted in formation of larger amounts of bis(spirodienone) products. Dienone **3** displays in the ^1H NMR spectrum ($CDCl_3$, 400 MHz, room temp.) two signals for the OH groups (δ 7.45 and 7.44), and eight doublets (δ 3.00, 3.39, 3.44, 3.59, 3.62, 3.74, 4.00 and 4.16) for the methylene protons, in agreement with a chiral compound of C_1 symmetry in which these protons are diastereotopic; its ^{13}C NMR spectrum showed 36 signals (δ



1; $R^1 = R^2 = R^3 = R^4 = OH$
5; $R^1 = R^2 = OPO(OPr^i)_2$, $R^3 = R^4 = OH$
6; $R^1 = R^2 = H$, $R^3 = R^4 = OH$
7; $R^1 = R^3 = H$, $R^2 = R^4 = OH$



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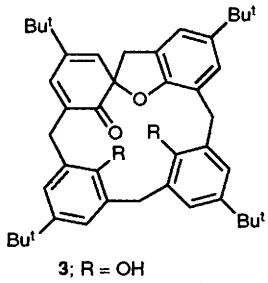

3; R = OH
4; $R = OPO(OPr^i)_2$

† ^1H NMR analysis of the crude product indicates the presence of **3** (73%), unchanged **1** and traces of the bis(spirodienone) derivatives of **1** (*cf.* ref. 7). After chromatography and recrystallization from MeCN pure **3** was isolated in 20% yield.

‡ All new compounds were fully characterized by IR, ^1H NMR, ^{13}C NMR, MS and high resolution MS.

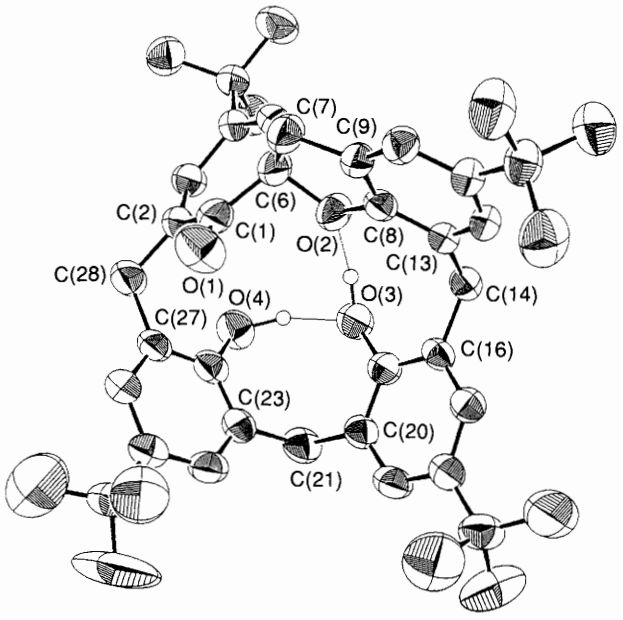

Fig. 1 Molecular structure of **3**. The acetonitrile molecule has been omitted for clarity. Selected geometrical parameters (Å, °): O(2)–C(6) 1.496(4), O(2)–C(8) 1.396(4), C(1)–C(2) 1.467(5), C(1)–C(6) 1.537(5), C(4)–C(5) 1.325(5), C(5)–C(6) 1.492(5), C(6)–C(7) 1.541(5), O(1)···O(2) 2.989(4), O(2)···O(3) 2.829(3), O(3)···O(4) 2.692(4), O(1)···O(4) 4.185(4), O(1)–C(1)–C(2) 122.3(4), O(2)–C(8)–C(9) 113.0(3), C(6)–O(2)–C(8) 108.1(3), C(1)–C(6)–C(7) 111.8(3), C(5)–C(6)–C(7) 113.9(3), C(6)–C(7)–C(9) 104.0(3), C(2)–C(28)–C(27) 115.1(3), C(13)–C(14)–C(16) 115.2(3), C(20)–C(21)–C(23) 110.8(3).

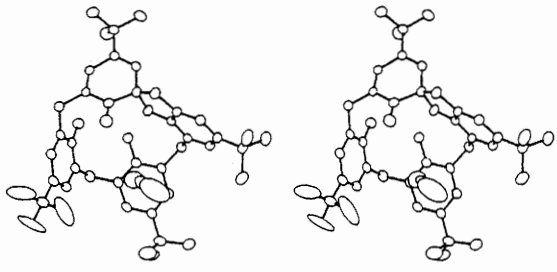

Fig. 2 Stereoview of the crystal strucutre of **3**·MeCN

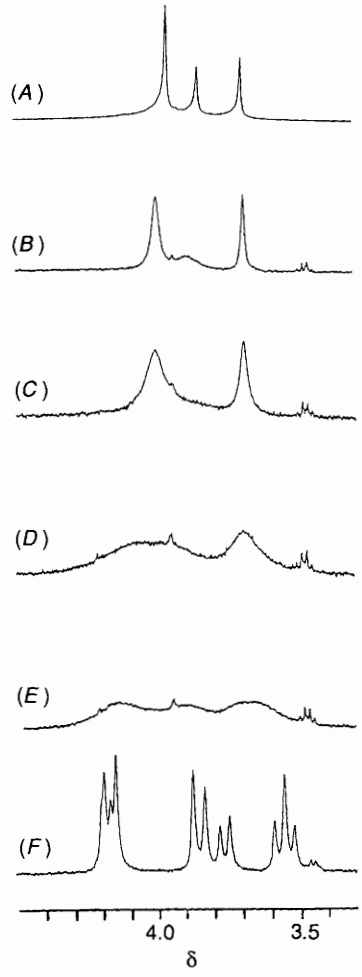

Fig. 3 400 MHz ^{1}H NMR spectrum of **6** in $CDCl_3$ (*A*, at 295 K) and in $CDCl_2F$ (*B*: at 250 K; *C*: 239 K, *D*: 226 K; *E*: 221 K; *F*: 190 K)

82.2 and 194.9 for the spiro and carbonyl carbons respectively).

The structure of **3**·MeCN was corroborated by X-ray crystallography (Figs. 1 and 2.)§ The molecule crystallizes in the achiral space group $P\bar{1}$ with two enantiomers present in the unit cell. It exists in the crystal in a 'partial cone'[1] conformation in which the two hydroxy groups and the dihydrobenzofuran oxygen are in a *syn* arrangement. The acetonitrile molecule is located inside the molecular cavity (Fig. 2).[8]

§ *Crystal data*: $C_{44}H_{54}O_4 \cdot CH_3CN$, space group $P\bar{1}$, $a = 14.130(2)$, $b = 15.467(2)$, $c = 9.906(2)$ Å, $\alpha = 92.04(1)$, $\beta = 105.96(2)$, $\gamma = 82.92(2)°$; $V = 2065.6(6)$ Å^3, $Z = 2$, $D_c = 1.11$ g cm^{-3}, no. of unique reflections: 7281, no. of reflections with $I > 3\,\sigma I$: 3799, $R = 0.059$, $R_W = 0.075$. All non-hydrogen atoms were found by using the results of the SHELXS-86 direct method analysis. After several cycles of refinement the positions of the hydrogen atoms were calculated and added to the refinement process. A final difference Fourier synthesis map showed several peaks less than 0.3 e Å^3 scattered about the unit cell without a significant feature. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

Hydrogen bonds exist between O(3) and O(4) and between O(3) and O(2). A 11.2×10^{-3} mol dm^{-3} solution of **3** in dry CCl_4 displays in the IR spectrum a C=O stretching at 1681 cm^{-1}, and a OH stretching at 3356 cm^{-1} which is compatible with hydrogen-bonded OH groups. No change in the OH region was observed when the solution was diluted to 2.7×10^{-3} mol dm^{-3}, which indicates that both OH groups of **3** are engaged in solution in intramolecular hydrogen bonds.

In principle the partial cone conformation present in **3** could undergo a ring inversion process (analogous to the one present in **1**)[1] leading to a diastereoisomeric partial cone conformation in which the two hydroxy groups are *syn* to the carbonyl oxygen. Cooling a sample of **3** in $CDCl_2F$[9] to 145 K did not result in any decoalescence process in the ^{1}H NMR spectrum which indicates that either the barrier to ring inversion is lower than 7.5 kcal mol^{-1} (1 cal = 4.184 J), or that **3** exists in a single conformation (most likely the crystallographic one) which is almost exclusively populated. Heating a sample of **3** in $C_6D_5NO_2$ to 405 K resulted (^{1}H NMR) in the gradual regeneration of **1**.

We decided to attempt the disubstitution of **3** with dialkylphosphate esters since these groups are useful intermediates in the preparation of dehydroxylated[10] and aminocalixarenes.[11] The disubstitution of **3** could be carried out by deprotonation of the OH groups by treatment with the non-nucleophilic base, lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C, followed by treatment of the dilithium salt of **3** with an excess of diisopropyl chloro-

phosphate[12] yielding the 1,2-bis(diisopropylphosphate) ester **4** (55%). Reduction of the spirodienone moiety to phenol rings was achieved by treatment of **4** with EtOH–HBr yielding the proximally disubstituted bis(diisopropylphosphate ester) calixarene **5**. Treatment of **4** with potassium in liquid ammonia resulted in reduction of the spirodienone moiety to phenol rings and reductive cleavage of the phosphate groups[10] yielding the proximally didehydroxylated calixarene **6** in 45% yield. Calixarene **6** displays in the ^{1}H NMR ($CDCl_3$, room temp.) two Bu^t signals (δ 1.29 and 1.32), one OH signal (δ 6.29), one signal for the intraannular aromatic protons (δ 6.45) and three singlets in a 1:1:2 ratio for the methylene protons (δ 3.70, 3.85 and 3.96, respectively) in agreement with a conformationally flexible (on the NMR time scale) 1,2-didehydroxycalix[4]arene structure. Lowering the temperature of a $CDCl_2F$ solution of **6** resulted in decoalescence of the methylene protons (Fig. 3). The ^{1}H NMR spectrum at 190 K displays two doublets integrating for four protons at δ 3.86 and 4.48 and four additional doublets at δ 3.54, 3.58, 3.77 and 4.19 each integrating for one proton. Precluding accidental isochrony, the slow-exchange NMR spectrum is compatible with a cone conformation or with a 1,2-alternate conformation in which the two phenol rings are in a mutual *syn* orientation. From the dynamic NMR data a barrier of 10.6 kcal mol^{-1} was calculated for the ring inversion process.[13] This barrier is higher than the inversion barrier (9.6 kcal mol^{-1})[14] of the isomeric distal didehydroxylated calixarene **7**.

In summary, we have shown that spirodienone **3** can be used for the preparation of proximally modified calixarenes.

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