

Chemically Modified Calix[4]arenes. Regioselective Synthesis of 1,3-(Distal) Derivatives and Related Compounds. X-Ray Crystal Structure of a Diphenol-Dinitrile

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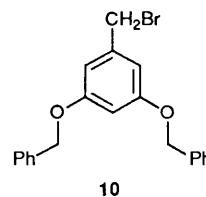
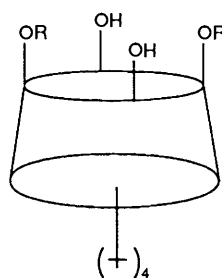
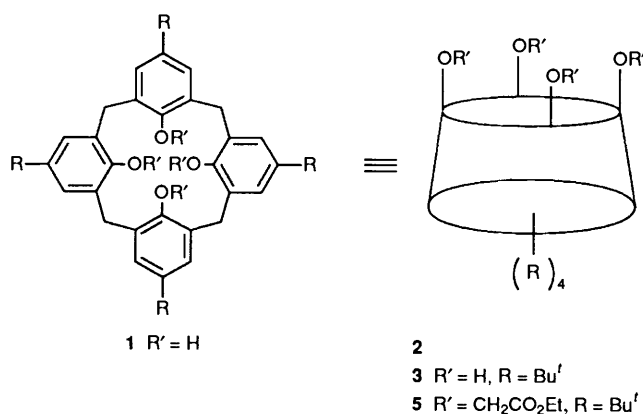
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p-*tert*-Butylcalix[4]arene has been chemically modified in a regioselective manner at the 1,3-(distal) phenolic groups of the lower rim using electrophiles such as ethyl bromoacetate, chloroacetone, bromopinacolone, chloroacetonitrile, and prop-2-ynyl bromide. X-Ray diffraction analysis of one of these 1,3-derivatives reveals that it exists in a highly distorted cone conformation. Crystals of the dinitrile **7** are triclinic, space group $P\bar{1}$, with two molecules in a cell of dimensions $a = 13.191(3)$, $b = 16.755(3)$, $c = 10.424(1)$ Å; $\alpha = 100.32(1)$, $\beta = 93.23(1)$, $\gamma = 84.89(2)^\circ$. The structure was solved by direct methods and refined by full-matrix least squares calculations; $R = 0.066$ for 4155 observed reflections. The two phenolic rings (A and C) are tilted (interplanar angle 102.3°) so as to place the hydroxy groups inside the cavity, whereas rings B and D bearing OCH_2CN moieties are almost parallel to each other (interplanar angle 13.3°). This arrangement allows for relatively facile intramolecular hydrogen bond formation between proximal hydroxy and ether functional groups [$\text{O}(\text{H}) \cdots \text{O}$ 2.941(3) and 2.903(3) Å]. These products are useful precursors of other 1,3-disubstituted derivatives including double calixarenes and of a variety of tetrasubstituted calix[4]arenes with dual functionality on the lower rim.

Calix[4]arenes **1** are readily converted into a wide variety of derivatives at the lower rim by alkylation of the phenolic groups. This type of chemical modification was first introduced by Gutsche¹ as part of his study of conformational change in calix[4]arenes² and since then it has been used widely by several groups to produce derivatives with pendant ether,³ carboxylate,⁴ ester,⁵ amide⁶ and keto⁷ groups. The vast majority of these modified calixarenes exist in the cone conformation **2** in which the mutually *syn* pendant groups possess a considerable degree of preorganisation and define the boundaries of a hydrophilic cavity suitable for ion reception. Indeed, the most significant feature of the chemistry of these molecules is their ability to bind selectively alkali and alkaline earth cations inside the cavity. Although less extensively studied, chemically modified calix[6]- and [8]-arenes also possess receptor properties for selected inorganic and organic cations.⁸

We have extended our study of chemically modified calix[4]arenes to include derivatives with more than one type of functionality around the calix and recently we demonstrated one approach to the synthesis of a tetramer bearing one carboxylic acid and three ester groups.⁹ This derivative has proved useful in the construction of double calixarenes.¹⁰ We now discuss the design and synthesis of conformationally stable modifications having the 2 + 2' functional group disposition with distal (1,3)-regiochemistry.¹¹ The alternative proximal (1,2)-arrangement is also possible as Pappalardo and his co-workers¹² have recently demonstrated.

It was already known from Gutsche's work² that *p*-*tert*-butylcalix[4]arene **3** reacts with diazomethane to produce the distal diether **4** and the same regiochemical preference was also observed by Ungaro's group⁴ for reaction of **3** with 2 equiv. of

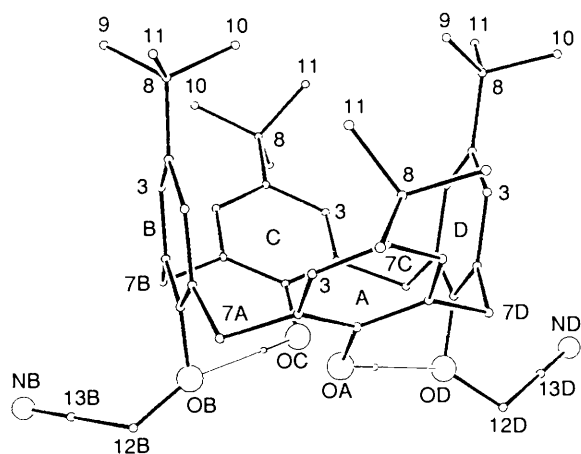


- 4 R = Me
6 R = CH₂CO₂Et
7 R = CH₂CN
8 R = CH₂COMe
9 R = CH₂CONH₂
11 R = CH₂C≡CH
12 R = CH₂C₆H₃(OPh)_{2-3,5}
13 R = CH₂COCl
14 R = CH₂CO₂H
15 R = CH₂CONC₅H₁₀
16 R = CH₂CONEt₂

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Table 1 Some mean molecular dimensions and important intramolecular distances (Å)

Aromatic C–C	1.389(6)
(aromatic) C–C(sp ³)	1.516(6)
(aromatic) C–OH	1.368(4)
(aromatic) C–O(CH ₂)	1.396(4)
C–N	1.137(6)
C(sp ³)–CN	1.463(6)
C(sp ³)–C(sp ³)(<i>tert</i> -butyl)	1.487(11)
OA...OB	3.076(4)
OA...OC	3.182(4)
OA...OD	2.941(3)
OB...OC	2.903(3)
OB...OD	4.994(3)
OC...OD	3.055(3)
HOA...OD	1.99
HOC...OB	1.95

**Fig. 1** A view of molecule 7; carbon and oxygen atoms are shown as spheres of arbitrary radius. The four aromatic rings A–D are shown.

tert-butyl bromoacetate, and more recently, with allyl, benzyl and methyl bromide.¹³ In our original preparation of the tetraester 5,⁵ calix[4]arene 3 was exposed to a large excess of ethyl bromoacetate for several days. Reduction of the calixarene:bromoacetate ratio and shorter reaction times yielded mixtures of products representing various stages of alkylation. Eventually, we found that a 1:2 molar ratio of reactants in the presence of potassium carbonate for 15 h in acetone under reflux furnished the diester 6, m.p. 182–184 °C in 70–80% yield. The ¹H NMR spectrum of 6 exhibited two *tert*-butyl singlets at δ 0.96 and 1.24, a single AB system for the bridging methylene groups at δ 3.25 and 4.48 (J 12.6 Hz), a singlet for the two remaining methylene groups, two singlets for the aromatic protons, a singlet for the two phenolic protons, and the usual pattern for the ethyl groups of the ester moieties. These data alone are sufficient to establish that the substitution pattern in 6 is indeed of the distal type rather than the proximal type, but they do not distinguish between a cone conformation and a 1,3-alternate conformation. However, evidence was forthcoming from a related compound which suggested that the diester 6 almost certainly does exist in the cone conformation at ordinary temperatures.

Since we were interested also in the synthesis of nitrogen-containing calixarenes suitable for transition metal complexation we treated calix[4]arene 3 with bromoacetonitrile (12 equiv.) in acetone containing potassium carbonate. After 12 h this reaction furnished a crystalline product which proved to be dicyano-diphenol 7. Interestingly, in this case, despite the large excess of the electrophile, products of further alkylation were not found, nor were we able to find satisfactory conditions for

synthesis of the tetranitrile by this route. A more efficient procedure for the dinitrile 7 involved exposure of calix[4]arene 3 to chloroacetonitrile (4 equiv.) and potassium carbonate in hot acetone with sodium iodide present to bring about halogen exchange in the electrophile. Analytical and spectroscopic data confirmed that the product was a dinitrile and the similarity between its ¹H NMR spectrum and that of the diester 6 confirmed that this derivative also was of the distal type in either the cone conformation or the 1,3-alternate conformation. X-Ray diffraction analysis provided a definitive answer for the crystalline state: the dinitrile 7 (and by inference the diester 6) does adopt the cone conformation, albeit in a very distorted form (Fig. 1). This is revealed clearly by the angles between the plane through the four CH₂ carbon atoms linking the aromatic rings and the planes of the individual benzene rings: 140.9° (A), 95.5° (B), 141.4° (C) and 97.8° (D). Thus, the two benzene rings (B and D) bearing OCH₂CN moieties are almost parallel to each other (interplanar angle 13.3°), tilted so as to increase the *tert*-butyl...*tert*-butyl separation; this leads to an O(B)...O(D) separation of 4.994(3) Å. The two phenolic rings (A and C) are tilted so as to place the hydroxy groups inside the cavity, with an O(A)...O(C) separation of 3.182(3) Å. This arrangement allows for easy hydrogen bond formation between proximal hydroxy and ether functional groups [O(A)(H)...O(D) 2.941(3) Å and O(C)(H)...O(B) 2.903(3) Å] and is probably responsible for the relatively large (102.3°) interplanar angle between the two phenolic rings. While conformations similar to that reported here have been found in other calix[4]arene systems devoid of intramolecular hydrogen bonds,⁵ the interplanar angle between the more tilted pair of rings has ranged from 88 to 98°. The two CH₂CN groups are oriented in an *exo*-fashion, with torsion angles COCH₂CN 73.4(4) and –44.1(4)° (for rings B and D respectively). Bond length data are unexceptional and are summarised in Table 1. The *tert*-butyl carbon atoms are probably slightly disordered about their mean positions and have large thermal parameters. There are no unusual intermolecular contacts.

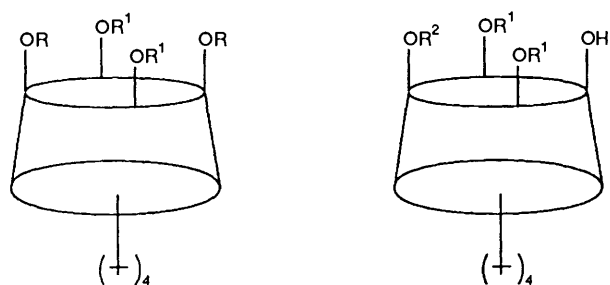
Chloroacetone was also used to effect partial alkylation of calix[4]arene 3. As in the dinitrile preparation, reaction was facilitated by halogen exchange with sodium iodide and the distal diketone 8, m.p. 135–136 °C, was isolated in 83% yield. For the direct synthesis of a distal diamide, 3 was exposed to 2-chloroacetamide in dry dimethyl sulphoxide containing potassium bromide and potassium carbonate at room temperature for 5 days, whereupon the diamide 9, m.p. 209–211 °C, was obtained in 78% yield. The diketone 8 and the diamide 9 exhibited ¹H NMR features closely similar to those of the diester 6 and the dinitrile 7 from which we presumed that these derivatives too possess distorted cone conformations. Two further examples of distal substitution were obtained when prop-2-ynyl bromide and the benzyl bromide 10 were used as electrophiles. With the former (2 equiv.) the diprop-2-ynyl adduct 11, was produced in 50% yield, whereas with the latter the dendryl-like adduct 12 was obtained in 65% yield. Again, the ¹H NMR data were consistent with cone conformations for both these products.

The ready availability of the distal diester 6 opened up the way to a variety of other derivatives, the most useful of which was the diacid chloride 13. Hydrolysis of 6 with 15% sodium hydroxide in ethanol under reflux gave, after acidification, the crystalline diacid 14 (97% yield), a compound previously obtained from the di-*tert*-butyl ester.⁴ Treatment of the diacid 14 with thionyl chloride in benzene under reflux yielded the diacid chloride in quantitative yield. Despite the normal incompatibility of acid chloride and phenol, compound 13 was moderately stable if stored under nitrogen. No attempts were made to purify the crude product, the NMR spectrum having indicated it was already of sufficient quality for further use as

was easily demonstrated by adding ethanol, whereupon the original diester was reproduced in excellent yield.

The distal diacid chloride **13** is useful synthetically in a number of ways. Simple replacement of chlorine can lead directly to other distal modifications. Alternatively, with difunctional reagents it can be bridged across the lower rim, or if *trans*-cavity bridging is precluded on steric grounds, it can be dimerised using appropriate spacers, e.g. 1,2-diaminoethane, to yield double calixarenes. Both of these latter uses have recently been demonstrated.^{14,10} Treatment of **13** with piperidine in ether furnished the dipiperidyl amide **15**, m.p. 303–305 °C, in 38% yield. A similar reaction employing diethylamine produced the analogous amide **16**, m.p. 246–248 °C in 45% yield. The close similarities in the ¹H NMR signals for the calixarene moiety of compounds **13**–**16** confirmed that they were conformationally alike.

The availability of a series of 1,3-difunctionalised calix[4]arenes in the conformation most appropriate to preorganisation of potential binding sites made possible the synthesis of several mixed ligand receptors. Thus, treatment of the diester **6** with chloroacetone in the presence of sodium iodide furnished the diketone diester combination **17** which was isolated from the reaction mixture as its sodium iodide complex. Exposure of the complex to hot water released **17** as the free ligand, m.p. 179–180 °C, in 93% yield. That this derivative also possessed the cone conformation was clearly indicated by its ¹H NMR spectrum. Stability constant measurements in methanol revealed that **17** is sodium ion selective with a Na⁺/K⁺ selectivity



- 17** R = CH₂CO₂Et, R' = CH₂COMe
18 R = R' = CH₂COMe
19 R = CH₂CO₂Et, R' = CH₂CN
21 R = CH₂COMe, R' = CH₂CN
22 R = CH₂CONH₂, R' = CH₂CO₂Et
23 R = CH₂CONEt₂, R' = CH₂CO₂Et

comparable to that of the tetraester **6** and greater than that of tetramethyl ketone **18**.¹⁵ An alternative approach to **17** involved exposure of diketone **8** to ethyl bromoacetate. In a similar manner it was possible to prepare a dicyano-diester either from the diester **6** and chloroacetonitrile in the presence of sodium iodide or from the dinitrile **7** and ethyl bromoacetate, both routes furnishing **19**, m.p. 221–223 °C, in good yield. Interestingly, in the former route when bromoacetonitrile was used as the alkylating electrophile without halide exchange with sodium iodide, an isolable intermediate was found which proved to be the monocyno-diester **20**, m.p. 195–197 °C. The NMR data were fully in accord with this structure, the ¹H spectrum displaying *inter alia* signals for three *tert*-butyl groups, two different AB systems for the bridging methylene groups, and one phenolic hydroxy group. The ¹³C spectrum with 28 signals confirmed the assignment.

Other combinations of functionality are also accessible. For example, the dinitrile **7** and chloroacetone in the presence of sodium iodide furnished cyano-diketone **21**, whereas ethyl bromoacetate and the amides **9** and **16** furnished the diamido-diester **22** and **23**, respectively. The ¹H NMR spectra of these fully alkylated calixarenes are completely consistent with the

presence of the cone conformation in each. The diamido-diester **23**, like the tetraester **5** and the tetraketone **19**, showed a high affinity for Na⁺, but unlike **5** and **19** it has an even larger affinity for Ag⁺.

These synthetic studies should facilitate the design and construction of new calixarene-based receptors in which a variety of oxygen and nitrogen-containing functional groups are assembled on the calixarene substructure.

Experimental

M.p.s were determined on a Thomas Hoover apparatus and are uncorrected. ¹H NMR spectra were recorded on a Hitachi Perkin-Elmer R-20 A spectrometer (60 MHz) or on a JEOL JNM-GSX spectrometer (270 MHz), with tetramethylsilane as internal standard. Elemental analysis were performed by the Microanalysis Laboratory, University College, Cork. Merck PF₂₅₄ silica gel was used for all forms of chromatography. The drying agent employed was magnesium sulphate.

5,11,17,23-Tetra-tert-butyl-25,27-diethoxycarbonylmethoxy-26,28-dihydroxycalix[4]arene 6.—A mixture of *p-tert*-butylcalix[4]arene (1.0 g), potassium carbonate (0.42 g), and ethyl bromoacetate (0.34 cm³) in dry acetone (50 cm³) was stirred and heated under reflux for 15 h. The cooled solution was filtered through a bed of Celite and the filtrate and dichloromethane washings of the Celite were combined and concentrated to dryness. Recrystallisation of the residue from ethanol furnished the diester **6** (0.99 g, 78%) as white crystals, m.p. 182–184 °C (Found: C, 74.1; H, 8.5. C₅₂H₆₈O₈·EtOH requires C, 74.2; H, 8.5%; ν_{max}(KBr)/cm⁻¹ 3430 and 1755; δ_H(CDCl₃) 0.96 (18 H, s, Bu^t), 1.24 (18 H, s, Bu^t), 1.30 (6 H, t, CH₃ of Et), 3.25 (4 H, d, *J* 12.6, ArCH₂Ar), 4.23 (4 H, q, CH₂ of Et), 4.48 (4 H, d, *J* 12.6, ArCH₂Ar), 4.75 (4 H, s, OCH₂CO), 6.91 (4 H, s, ArH), 7.11 (4 H, s, ArH) and 7.12 (2 H, s, OH).

5,11,17,23-Tetra-tert-butyl-25,27-dicyanomethoxy-26,28-dihydroxycalix[4]arene 7.—A mixture of *p-tert*-butylcalix[4]arene (10.0 g), potassium carbonate (8.53 g), chloroacetonitrile (4 cm³), and sodium iodide (9.25 g) in dry acetone (250 cm³) was stirred and heated under reflux for 7 h. The cooled mixture was filtered through a bed of Celite and the filtrate and dichloromethane washings of the Celite were combined and concentrated to dryness. Recrystallisation of the residue from ethanol furnished the dinitrile **7** (6.4 g, 57%), m.p. > 290 °C (decomp.) (Found: C, 79.2; H, 7.8; N, 3.9. C₄₈H₅₈N₂O₄ requires C, 79.3; H, 8.0; N, 3.9%; ν_{max}(KBr)/cm⁻¹ 3500; δ_H(CDCl₃) 0.88 (18 H, s, Bu^t), 1.34 (18 H, s, Bu^t), 3.42 (4 H, d, *J* 13.2, ArCH₂Ar), 4.24 (4 H, d, *J* 13.2, ArCH₂Ar), 4.84 (4 H, s, OCH₂CN), 5.60 (2 H, s, ArOH), 6.83 (4 H, s, ArH) and 7.22 (4 H, s, ArH).

25,27-Diacetyloxy-5,11,17,23-tetra-tert-butyl-26,28-dihydroxycalix[4]arene 8.—A mixture of *p-tert*-butylcalix[4]arene (20.0 g), potassium carbonate (12.9 g), chloroacetone (4.9 cm³) and sodium iodide (9.3 g) in dry acetone (200 cm³) was heated under reflux for 4 h. The reaction mixture was then processed exactly as described above to furnish the diketone **8** (15.4 g, 65%), m.p. 135–136 °C (from ethanol), as colourless crystals (Found: C, 79.2; H, 8.8. C₅₀H₆₄O₆ requires C, 78.9; H, 8.5%; ν_{max}(KBr)/cm⁻¹ 3420 and 1722; δ_H(CDCl₃) 0.92 (18 H, s, Bu^t), 1.30 (18 H, s, Bu^t), 2.53 (6 H, s, COMe), 3.31 (4 H, d, *J* 13.2, ArCH₂Ar), 4.21 (4 H, d, *J* 13.2, ArCH₂Ar), 4.53 (4 H, s, OCH₂CO), 6.90 (4 H, s, ArH), 6.95 (2 H, s, ArOH) and 7.18 (4 H, s, ArH).

5,11,17,23-Tetra-tert-butyl-25,27-dicarbamoyloxymethoxy-26,28-dihydroxycalix[4]arene 9.—A mixture of *p-tert*-butylcalix[4]arene (4.9 g), potassium bromide (3.6 g), potassium

carbonate (8.4 g), and 2-chloroacetamide (4.2 g) in dry dimethyl sulphoxide (100 cm³) was stirred under nitrogen at room temperature for 5 days and then was heated at 75 °C for 24 h. The cooled reaction mixture was poured into 3% sulphuric acid and the precipitate formed was filtered off, washed with water, and dried *in vacuo* to afford the diamide **9** (4.5 g, 78%), m.p. 209–211 °C (from ethanol) (Found: C, 74.8; H, 8.1; N, 3.4. C₄₈H₆₂N₂O₆·C₂H₅OH requires C, 74.2; H, 8.5; N, 3.5%); ν_{\max} (cm⁻¹) 3420 and 1680; δ_{H} (CDCl₃) 1.07 (18 H, s, Bu'), 1.30 (18 H, s, Bu'), 3.41 (4 H, d, *J* 13.8, ArCH₂Ar), 4.17 (4 H, d, *J* 13.8, ArCH₂Ar), 4.57 (4 H, s, OCH₂CO), 6.57 (4 H, br s, NH₂), 6.92 (4 H, s, ArH), 7.07 (4 H, s, ArH) and 7.73 (2 H, s, OH).

5,11,17,23-Tetra-*tert*-butyl-26,28-dihydroxy-25,27-diprop-2-ynyloxy-calix[4]arene **11**.—A mixture of *p*-*tert*-butylcalix[4]arene **3** (4.0 g) prop-2-ynyl bromide (1.5 cm³) and potassium carbonate (1.8 g) in dry acetone (120 cm³) was heated under reflux for 17 h. The cooled reaction mixture was processed exactly as described above for diester **6** to afford the diacetylene **11** (4.5 g, 98%). NMR and the analysis established that the crude product was of >95% purity. An analytical sample, recrystallised from methanol had m.p. >280 °C (Found: C, 82.8; H, 8.5. C₅₀H₆₀O₄ requires C, 82.9; H, 8.3%); δ_{H} (CDCl₃) 0.90 (18 H, s, Bu'), 1.31 (18 H, s, Bu'), 2.54 (2 H, s, C=CH), 3.33 (4 H, d, *J* 12.0, ArCH₂Ar), 4.38 (4 H, d, *J* 12.0, ArCH₂Ar), 4.75 (4 H, d, CH₂C=C), 6.72 (4 H, s, ArH) and 7.07 (4 H, s, ArH).

5,11,17,23-Tetra-*tert*-butyl-25,27-dicarboxymethoxy-26,28-dihydroxycalix[4]arene **14**.—A mixture of the diester **6** (6.3 g) and 15% aq. sodium hydroxide (20 cm³) in ethanol (300 cm³) was stirred and heated under reflux for 24 h after which most of the ethanol was distilled off. The residue was diluted with cold water (300 cm³) and hydrochloric acid (3 mol dm⁻³) was added with vigorous mixing until pH 1 was reached. The solid was then filtered off, dried in air and taken up in chloroform. The solution was washed with hydrochloric acid (3 mol dm⁻³) and brine, dried and concentrated to afford the diacid **14** (5.6 g, 97%). NMR and TLC analysis indicated that the crude product was >95% pure. An analytically pure sample, obtained by recrystallisation from aq. acetone, had m.p. >220 °C (decomp.) (Found: C, 72.1; H, 8.0. C₄₈H₆₀O₈·2H₂O requires C, 72.0; H, 8.1%); ν_{\max} (KBr)/cm⁻¹ 3430br and 1740; δ_{H} (CDCl₃) 1.03 (18 H, s, Bu'), 1.30 (18 H, s, Bu'), 3.38 (4 H, d, *J* 13.8, ArCH₂Ar), 4.23 (4 H, d, *J* 13.8, ArCH₂Ar), 4.70 (4 H, s, OCH₂CO), 6.88 (4 H, s, ArH), 7.08 (4 H, s, ArH) and 7.93 (4 H, br s, OH and CO₂H).

5,11,17,23-Tetra-*tert*-butyl-25,27-bis(chloroformylmethoxy)-26,28-dihydroxycalix[4]arene **13**.—A solution of the diacid **14** (2.0 g) in dry benzene (100 cm³) containing thionyl chloride (2.5 cm³) was heated under reflux under nitrogen for *ca.* 3.5 h. Removal of the solvent and residual thionyl chloride under reduced pressure furnished the diacyl chloride **13** as an off-white solid in quantitative yield; ν_{\max} (KBr)/cm⁻¹ 3500 and 1810; δ_{H} (CDCl₃) 0.90 (18 H, c, Bu'), 1.30 (18 H, s, Bu'), 3.31 (4 H, d, *J* 13.8, ArCH₂Ar), 4.28 (4 H, d, *J* 13.8, ArCH₂Ar), 4.97 (4 H, s, OCH₂CO), 6.70 (4 H, s, ArH), 7.0 (4 H, s, ArH) and 7.17 (2 H, s, OH). The product was used in subsequent preparations without purification. On prolonged storage at room temperature decomposition was evident from the disappearance of the IR band at 1810 cm⁻¹.

5,11,17,23-Tetra-*tert*-butyl-25,27-bis(3,5-diphenoxymethoxy)-26,28-dihydroxycalix[4]arene **12**.—A mixture of *p*-*tert*-butylcalix[4]arene **3** (1.5 g), the bromide **10** (1.22 g), and potassium carbonate (0.89 g) in dry acetone (25 cm³) was heated under reflux for 17 h. The cooled reaction mixture was

processed exactly as described above for the diester **6** to afford **12** (1.92 g, 96%) which was of >95% purity by NMR analysis. An analytical sample, recrystallised from dichloromethane-methanol had m.p. 83.5–84.4 °C (Found: C, 79.9; H, 7.7. C₈₆H₉₂O₈·CH₃OH requires C, 79.8; H, 7.4%); ν_{\max} (KBr)/cm⁻¹ 3414; δ_{H} (CDCl₃) 0.95 (18 H, s, Bu'), 1.302 (18 H, s, Bu'), 3.26 (4 H, d, *J* 13.0, ArCH₂Ar), 4.28 (4 H, d, *J* 13.0, ArCH₂Ar), 6.94 (4 H, s, ArCH₂O), 7.06 (4 H, s, PhCH₂Ar), and 7.25–7.37 (20 H, m, ArH) and 7.37 (2 H, s, OH).

5,11,17,23-Tetra-*tert*-butyl-26,28-dihydroxy-25,27-bis(piperidylcarbonylmethoxy)calix[4]arene **15**.—To a stirred solution of piperidine (0.3 cm³) in diethyl ether (10 cm³) under nitrogen was added dropwise a solution of diacyl chloride (0.61 g) in diethyl ether (40 cm³). Immediate precipitation occurred. After 4 days at room temperature the mixture was filtered and the filtrate was concentrated to dryness. The solid residue was taken up in dichloromethane, and the solution washed with water and brine, dried and evaporated to furnish the crude product (0.57 g). Recrystallisation of this from dichloromethane-methanol yielded pure **15** (0.38 g, 38%), m.p. 302–305 °C (Found: C, 77.0; H, 8.7; N, 3.2. C₅₈H₇₈N₂O₆ requires C, 77.5; H, 8.7; N, 3.1%); ν_{\max} (KBr)/cm⁻¹ 3400 and 1650; δ_{H} (CDCl₃) 1.06 (18 H, m, Bu'), 1.19 (18 H, s, Bu'), 1.67 (12 H, m, CH₂CH₂CH₂), 3.28 (4 H, d, *J* 13.5, ArCH₂Ar), 3.56 (4 H, m, NCH₂), 3.62 (4 H, m, NCH₂), 4.44 (4 H, d, *J* 13.5, ArCH₂Ar), 4.83 (4 H, s, OCH₂CO), 6.87 (4 H, s, ArH), 6.92 (4 H, s, ArH) and 7.78 (2 H, s, OH).

5,11,17,23-Tetra-*tert*-butyl-25,27-bis(diethylcarbamoylmethoxy)-26,28-dihydroxycalix[4]arene **16**.—The diacyl chloride **13** was treated with diethylamine in diethyl ether exactly as described above for piperidine. Recrystallisation of the crude product from methanol-ether furnished the amide **16** as a colourless solid (45% yield), m.p. 246–248 °C (Found: C, 76.7; H, 8.9; N, 3.12. C₅₆H₇₈N₂O₆ requires C, 76.9; H, 9.0; N, 3.2%); ν_{\max} (KBr)/cm⁻¹ 3390 and 1650; δ_{H} (CDCl₃) 1.03 (18 H, s, Bu'), 1.20 (18 H, s, Bu'), 1.23 (12 H, t, CH₃ of Et), 3.23 (4 H, d, *J* 12.6, ArCH₂Ar), 3.44 (8 H, q, CH₂ of Et), 4.43 (4 H, d, *J* 12.6, ArCH₂Ar), 4.77 (4 H, s, OCH₂CO) 6.80 (4 H, s, ArH), 6.85 (4 H, s, ArH) and 7.60 (2 H, s, OH).

25,27-Diacetonyloxy-5,11,17,23-tetra-*tert*-butyl-26,28-diethoxycarbonylcalix[4]arene **17**.—A mixture of the diester **6** (5.0 g), sodium iodide (3.6 g), chloroacetone (1.9 cm³) and potassium carbonate (3.3 g) in dry acetone (250 cm³) was stirred and heated under reflux for 5 days. The cooled reaction mixture was filtered and the filtrate and acetone washings of the solids were combined and concentrated to afford a yellow solid. This was suspended in water at 60–70 °C for 4 h with stirring and then was extracted into dichloromethane. The extract was washed with 10% aq. sodium thiosulphate and water, dried, and evaporated to furnish the title compound **17** (5.4 g, 96%). Recrystallisation of this from ethanol furnished an analytically pure sample, m.p. 179–180 °C (Found: C, 75.1; H, 8.4. C₅₈H₇₆O₁₀ requires C, 74.7; H, 8.2%); ν_{\max} (KBr)/cm⁻¹ 1755 and 1735; δ_{H} (CDCl₃) 1.04 (18 H, s, Bu'), 1.10 (18 H, s, Bu'), 1.24 (6 H, t, CH₃ of Et), 2.27 (6 H, s, COCH₃), 3.15 (4 H, d, *J* 12.6, ArCH₂Ar), 4.14 (4 H, q, CH₂ of Et), 4.73 (8 H, s, OCH₂CO), 4.77 (4 H, d, *J* 12.6, ArCH₂Ar), 6.73 (4 H, s, ArH) and 6.79 (4 H, s, ArH).

5,11,17,23-Tetra-*tert*-butyl-25,27-bis(cyanomethoxy)-26,28-diethoxycarbonylmethoxycalix[4]arene **19**.—A mixture of sodium iodide (0.75 g), chloroacetonitrile (0.32 cm³), potassium carbonate (0.69 g) and diester **6** (1.0 g) in dry acetone (20 cm³) was heated under reflux for 4 days. The cooled mixture was filtered and the filtrate was concentrated to afford a solid which

was taken up in dichloromethane. The extract was washed with water and brine, dried and concentrated to afford a solid. Recrystallisation of this from ethanol furnished **19** (0.65 g, 58%), m.p. 221–222 °C (Found: C, 74.6; H, 7.7; N, 2.9. $C_{56}H_{70}N_2O_8$ requires C, 74.8; H, 7.8; N, 3.1%); $\nu_{\max}/\text{cm}^{-1}$ 1750; $\delta_{\text{H}}(\text{CDCl}_3)$ 0.82 (18 H, s, Bu'), 1.37 (18 H, s, Bu'), 1.37 (6 H, t, CH_3 of Et), 3.18 (4 H, d, J 13.2, ArCH_2Ar), 4.26 (4 H, q, CH_2 of Et), 4.43 (4 H, s, OCH_2CO), 4.43 (4 H, d, J 13.2, ArCH_2Ar), 5.27 (4 H, s, OCH_2CN), 6.47 (4 H, s, ArH) and 7.15 (4 H, s, ArH).

5,11,17,23-Tetra-tert-butyl-25-cyanomethoxy-26,28-diethoxy-carbonylmethoxy-27-hydroxycalix[4]arene **20**.—A mixture of the diester **6** (0.86 g), potassium carbonate (0.58 g) and bromoacetonitrile (0.3 cm^3) in dry acetone (50 cm^3) was heated under reflux for 18 h. The cooled reaction mixture was processed exactly as described above for the preceding compound to furnish the title compound **20** (0.55 g, 60%), m.p. 195–197 °C, after recrystallisation from ethanol (Found: C, 75.5; H, 7.8; N, 1.5. $C_{54}H_{69}NO_8$ requires C, 75.4; H, 8.1; N, 1.6%); $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 3460 and 1760; $\delta_{\text{H}}(\text{CDCl}_3)$ 0.83 (18 H, s, Bu'), 1.34 (9 H, s, Bu'), 1.36 (9 H, s, Bu'), 1.36 (6 H, t, CH_3 of Et), 3.25 (2 H, d, J 8.1, ArCH_2Ar), 3.30 (2 H, d, J 8.1, ArCH_2Ar), 4.20 (2 H, d, ArCH_2Ar), 4.41 (4 H, q, CH_2 of Et), 4.56 (4 H, s, OCH_2CO), 4.59 (2 H, d, ArCH_2Ar), 5.28 (2 H, s, OCH_2CN), 6.48 (2 H, d, ArH), 6.56 (1 H, d, ArOH), 6.60 (2 H, d, ArH), 7.09 (2 H, s, ArH) and 7.12 (2 H, s, ArH); $\delta_{\text{C}}(\text{CDCl}_3)$ 14.20 (q), 30.93 (q), 31.39 (t), 31.55 (q), 31.76 (q), 32.21 (t), 33.71 (s), 33.84 (s), 34.28 (s), 57.98 (t), 61.22 (t), 72.04 (t), 118.58 (s), 124.86 (d), 125.12 (d), 125.44 (d), 126.30 (d), 127.97 (s), 131.64 (s), 131.80 (s), 135.75 (s), 141.18 (s), 146.42 (s), 147.67 (s), 150.75 (s), 151.05 (s), 151.71 (s) and 169.15 (s).

25,27-Diacetonyloxy-5,11,17,23-tetra-tert-butyl-26,28-bis(cyanomethoxy)calix[4]arene **21**.—A mixture of the dinitrile **7** (3.0 g), sodium iodide (2.4 g), chloroacetone (1.28 cm^3) and potassium carbonate (2.2 g) in dry acetone (50 cm^3) was heated under reflux for 5 days. The cooled mixture was processed exactly as described above for the preceding compound to furnish **21** as colourless crystals (2.1 g, 60%), m.p. 235–236 °C (Found: C, 77.2; H, 7.9; N, 3.6. $C_{54}H_{66}N_2O_6$ requires C, 77.3; H, 7.9; N, 3.3%); $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 1735; $\delta_{\text{H}}(\text{CDCl}_3)$ 0.79 (18 H, s, Bu'), 1.34 (18 H, s, Bu'), 2.16 (6 H, s, COCH_3), 3.19 (4 H, d, J 13.2, ArCH_2Ar), 4.46 (4 H, d, J 13.2, ArCH_2Ar), 4.61 (4 H, s, OCH_2CO), 5.40 (4 H, s, OCH_2CN), 6.56 (4 H, s, ArH) and 7.27 (4 H, s, ArH).

5,11,17,23-Tetra-tert-butyl-25,27-bis(carbamoylmethoxy)-26,28-diethoxycarbonylmethoxycalix[4]arene **22**.—A mixture of the diamide **9** (0.3 g), potassium carbonate (0.23 g) and ethyl bromoacetate (0.18 cm^3) in dry acetone (50 cm^3) was heated under reflux for 7 days. The cooled mixture was filtered and the filtrate was processed exactly as described above for compound **17** (including the hot water treatment) to furnish the title compound **22** (0.23 g, 65%) after recrystallisation from ethanol, m.p. 253–255 °C (Found: C, 71.6; H, 7.8; N, 2.9. $C_{54}H_{74}N_2O_{10}$ requires C, 71.2; H, 8.2; N, 3.1%); $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 1760 and 1680; $\delta_{\text{H}}(\text{CDCl}_3)$ 0.83 (18 H, s, Bu'), 1.33 (24 H, s and t, Bu' and CH_3 of Et), 3.24 (4 H, d, J 13.2, ArCH_2Ar), 4.26 (4 H, q, CH_2 of CH_3), 4.40 (4 H, s, OCH_2), 4.47 (4 H, d, J 13.2 Hz, ArCH_2Ar), 4.63 (4 H, s, OCH_2), 6.55 (4 H, s, ArH), 7.12 (4 H, s, ArH), and 8.32 (4 H, br s, NH_2).

5,11,17,23-Tetra-tert-butyl-25,27-bis(diethylcarbamoylmethoxy)-26,28-diethoxycarbonylmethoxycalix[4]arene **23**.—A mixture of the diamide **16** (0.40 g) potassium carbonate (0.25 g), and ethyl bromoacetate (0.20 cm^3) in dry acetone (50 cm^3) was heated under reflux for 7 days. The cooled reaction mixture was processed exactly as described above for compound **17** to

Table 2 Atomic coordinates and their esds for compound **7**

Atom	x	y	z
O(A)	0.1425(2)	0.0706(2)	0.0757(2)
C(1A)	0.0694(3)	0.1267(2)	0.1334(3)
C(2A)	-0.0167(3)	0.1434(2)	0.0562(3)
C(3A)	-0.0940(3)	0.1975(2)	0.1122(4)
C(4A)	-0.0883(3)	0.2376(2)	0.2416(4)
C(5A)	0.0002(3)	0.2199(2)	0.3132(4)
C(6A)	0.0795(3)	0.1651(2)	0.2627(3)
C(7A)	-0.0218(3)	0.1057(3)	-0.0873(4)
C(8A)	-0.1745(3)	0.2977(3)	0.2966(4)
C(9A)	-0.2731(4)	0.2548(5)	0.2878(8)
C(10A)	-0.1584(5)	0.3320(5)	0.4353(7)
C(11A)	-0.1962(7)	0.3611(5)	0.2195(8)
O(B)	0.1565(2)	0.0265(1)	-0.2225(2)
C(1B)	0.1311(3)	0.1089(2)	-0.2248(3)
C(2B)	0.1993(3)	0.1510(2)	-0.2785(3)
C(3B)	0.1774(3)	0.2336(2)	-0.2736(4)
C(4B)	0.0909(3)	0.2756(2)	-0.2176(4)
C(5B)	0.0270(3)	0.2307(3)	-0.1630(4)
C(6B)	0.0454(3)	0.1475(2)	-0.1628(3)
C(7B)	0.2993(3)	0.1104(2)	-0.3309(4)
C(8B)	0.0726(4)	0.3675(3)	-0.2072(4)
C(9B)	0.0959(6)	0.3933(3)	-0.3363(6)
C(10B)	0.1386(7)	0.4077(4)	-0.1018(8)
C(11B)	-0.0372(6)	0.3982(4)	-0.1824(9)
C(12B)	0.0974(3)	-0.0279(2)	-0.3112(4)
C(13B)	0.1244(3)	-0.0333(2)	-0.4474(4)
NB	0.1444(3)	-0.0371(3)	-0.5530(4)
OC	0.3459(2)	0.0637(2)	-0.0776(2)
C(1C)	0.4064(3)	0.1144(2)	-0.1211(3)
C(2C)	0.4866(3)	0.1415(2)	-0.0384(3)
C(3C)	0.5518(3)	0.1915(2)	-0.0804(4)
C(4C)	0.5387(3)	0.2162(2)	-0.2029(4)
C(5C)	0.4561(3)	0.1872(2)	-0.2803(3)
C(6C)	0.3900(3)	0.1374(2)	-0.2430(3)
C(7C)	0.4979(3)	0.1214(2)	0.0981(4)
C(8C)	0.6134(3)	0.2694(3)	-0.2439(4)
C(9C)	0.7167(4)	0.2244(4)	-0.2615(7)
C(10C)	0.5785(4)	0.3000(4)	-0.3694(5)
C(11C)	0.6262(7)	0.3428(4)	-0.1394(8)
O(D)	0.3425(2)	0.0535(1)	0.2119(2)
C(1D)	0.3439(3)	0.1381(2)	0.2381(3)
C(2D)	0.2656(3)	0.1859(2)	0.3061(3)
C(3D)	0.2692(3)	0.2689(2)	0.3287(4)
C(4D)	0.3476(3)	0.3065(2)	0.2841(4)
C(5D)	0.4207(3)	0.2570(2)	0.2123(4)
C(6D)	0.4207(3)	0.1725(2)	0.1854(3)
C(7D)	0.1735(3)	0.1484(2)	0.3459(3)
C(8D)	0.3496(4)	0.3991(3)	0.3106(5)
C(9D)	0.2584(7)	0.4381(4)	0.2642(11)
C(10D)	0.3545(10)	0.4293(4)	0.4546(10)
C(11D)	0.4400(7)	0.4268(4)	0.2682(13)
C(12D)	0.3869(3)	0.0122(2)	0.3118(4)
C(13D)	0.4829(3)	0.0434(2)	0.3650(4)
ND	0.5572(3)	0.0688(2)	0.4078(4)

furnish the title compound **23** (0.23 g, 41%), m.p. 205–207 °C after recrystallisation from acetonitrile (Found: C, 73.8; H, 8.5; N, 3.6. $C_{64}H_{90}N_2O_{10} \cdot \text{CH}_3\text{CN}$ requires C, 73.4; H, 8.4; N, 3.8%); $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 1755 and 1670; $\delta_{\text{H}}(\text{CDCl}_3)$ 1.02 (18 H, Bu'), 1.15 (30 H, m, Bu' and CH_3 of Et), 1.25 (6 H, t, CH_3 of Et), 1.57 (12 H, m, CH_2), 1.83 (3 H, s, CH_3CN), 3.17 (4 H, d, J 12.0, ArCH_2Ar), 3.48 (8 H, m, NCH_2), 4.14 (4 H, q, CH_2 of Et), 4.80 (4 H, s, OCH_2CO), 4.90 (4 H, d, J 10, 12.0, ArCH_2Ar), 4.92 (4 H, s, OCH_2CO), 6.63 (4 H, s, ArH) and 6.91 (4 H, s, ArH).

X-Ray Diffraction Analysis.—Crystal data for compound **7**. $C_{48}H_{58}N_2O_4$, M_r 727.0, triclinic, $a = 13.191(3)$, $b = 16.755(3)$, $c = 10.424(1)$ Å, $\alpha = 100.32(1)$, $\beta = 93.23(1)$, $\gamma = 84.89(2)^\circ$, $U = 2256(1)$ Å³, $Z = 2$, $D_c = 1.07$ g cm⁻³, $F(000) = 784$, $\lambda(\text{Mo-K}_\alpha) = 0.71073$ Å, $\mu(\text{Mo-K}_\alpha) = 0.6$ cm⁻¹, space

group $P\bar{1}$ or $P1$, $P\bar{1}$ assumed and confirmed by the successful analysis. Colourless crystals of **7** were grown from ethanol.

Structure determination. Accurate cell dimensions and crystal orientation matrix were determined by a least squares treatment of the setting angles of 25 reflections (with $14 < \theta < 22^\circ$). Data were collected on a CAD4 diffractometer using graphite monochromated Mo- K_α radiation (data collection was terminated after 2θ of 48° as there were no significant reflections being measured). Intensities of three reflections measured every 5 h showed no decay. A total of 7372 unique reflections were collected of which the 4155 with $I > 3\sigma(I)$ were retained as 'observed'.

The structure was solved by direct methods using MULTAN-82¹⁶ which revealed all the non-hydrogen atoms. Refinement was by full-matrix least-squares calculations, initially with isotropic and finally with anisotropic thermal parameters. Hydrogen atoms were clearly visible in difference maps computed at various stages of the refinement. In the final rounds of refinement they were positioned on geometric grounds (C-H, O-H 0.95 Å) and included as riding atoms in the structure factor calculations. The final cycle of refinement included 488 variable parameters, $R = 0.066$, $wR = 0.094$, goodness-of-fit 2.548, $w = 1/[\sigma F_o^2 + 0.055 F_o^2]$. Max. shift/error 0.07; density in final difference map $\pm 0.50 \text{ e}\text{\AA}^{-3}$ (adjacent to *tert*-butyl C atoms); there were no chemically significant features. Scattering factors were taken from reference.¹⁷ All calculations were performed on a PDP-11/73 computer using SDP-Plus.¹⁸ Atomic coordinates and details of molecular geometry are given in Tables 1 and 2. Fig. 1 is a view of the molecule prepared using ORTEP II.¹⁹

Additional material available from Cambridge Crystallographic Data Centre comprises thermal parameters, H-atom coordinates and full details of molecular geometry. Copies of the structure factor listing are available from M. A. McK. or G. F.

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