Chiral lactic acid and ethyl lactate *p-tert*-butylcalix[4]arene derivatives

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Ethyl (*S*)-(−)-*O*-tosyllactate reacted with *p-tert*-butylcalix[4]arene in K_2CO_3–acetone with inversion of configuration on the asymmetric centre, and only the bis-substitution product on the distal oxygens was obtained. Further attempts to react the bis(lactate) *p-tert*-butylcalix[4]arene derivative with $BrCH_2CO_2CH_3$ under the same conditions failed. X-Ray analysis of the lactate derivative shows two independent molecules in the unit cell; one CH_3 of the ethyl radical is immersed in the cavity of the other molecule. Both adopt a slightly distorted cone conformation. NMR analysis shows that carbons and hydrogens of the methylene bridges and *meta* positions are diastereotopic. Ester hydrolysis was carried out without racemization, and the diastereotopic behaviour of the lactic acid derivative was maintained.

Introduction

Calixarenes are versatile macrocycles, which, when properly functionalized, have their conformational mobility restricted, allowing the obtention of host molecules with functional groups in well-defined positions. Thus, especially in the cone conformation, they can be used as a basic skeleton [1] in the preparation of synthetic receptors that possess sites with convergent functional groups for binding of ions or neutral molecules.

The exhaustive alkylation of calix[4]arenes with alkyl bromoacetates furnishes products used as selective ionophores for sodium ions.[2] Furthermore, ketone,[3] amide and sulfonamide [4] correlates have been synthesized, displaying interesting properties as hosts to alkaline and alkaline earth as well as transition metals, which have been attributed to the convergent location of electron-rich atoms. On the other hand, there are no examples of asymmetric calixarenes obtained by an analogous procedure.

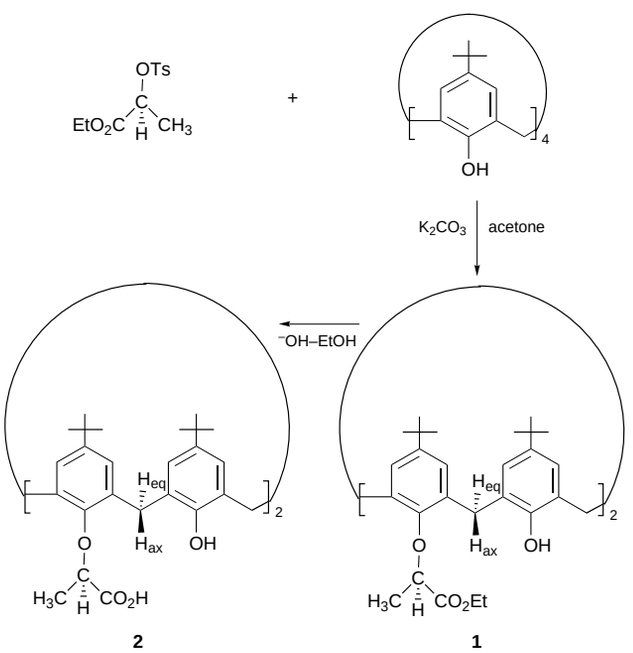
Two synthetic pathways for the preparation of chiral calixarenes are possible. The first is a stepwise synthesis yielding inherently chiral calixarenes, which was used by Shinkai *et al.*[5] to prepare the first resolved chiral calixarene. Other asymmetric calixarenes with different groups have been synthesized,[6,7] without resolution. The second method is the introduction of a chiral residue into the calixarene structure through functionalization at the lower [8,9] or upper rim.[10] The only example of a chiral calixarene that is capable of acting as a chiral receptor, prepared by this method, was a calix[4]crown ether developed by Pappalardo and Parisi.[11]

In this work, we report the reaction of ethyl (*S*)-(−)-*O*-tosyllactate with *p-tert*-butylcalix[4]arene, which yields a chiral bis(ethyl lactate) *p-tert*-butylcalix[4]arene derivative. The chiral lactate moieties impose asymmetry upon the calixarene structure, as is established *via* ^1H and ^{13}C NMR experiments.

Results and discussion

The reaction of *p-tert*-butylcalix[4]arene with ethyl (*S*)-(−)-*O*-tosyllactate in potassium carbonate–acetone resulted in bis-substitution on the distal phenolic oxygens (compound **1**, in Scheme 1). The degree of alkylation did not increase, even in the presence of 10 equiv. of the tosyllactate. The reaction proceeds *via* an S_N2 mechanism, with inversion of the asymmetric centre, and the formation of a diastereoisomeric pair was not observed *via* NMR spectroscopy.[12]

Under identical conditions, the reaction of *p-tert*-butylcalix[4]arene with ethyl bromoacetate furnishes exclusively the tetrasubstituted product,[13] the bis-substituted product being obtained only by the use of 2 equiv. of $BrCH_2CO_2Et$.[14] The complete substitution of **1** at the remaining phenolic oxygens was attempted with the less bulky $BrCH_2CO_2Me$, but failed to occur under the same conditions (K_2CO_3–acetone).



Scheme 1

The infrared analysis of **1** shows a broad absorption at 3390 cm^{-1}, revealing intramolecular hydrogen bonding. This correlates with a 'cone' conformation, where the remaining phenolic hydrogens are at a suitable distance from the vicinal oxygens.

The hydrolysis of the lactate ester **1** in EtOH–OH^- yields the lactic acid **2** without racemization.

NMR Data

The ^1H NMR spectra (Fig. 1) exhibited two singlets, at δ 1.30 and 0.93 for **1** and δ 1.31 and 1.02 for **2**, corresponding to the *tert*-butyl groups linked to the unsubstituted and substituted rings with the lactate (**1**) and lactic acid moieties (**2**), respectively. The hydrogens and carbons of the *calix* structure, outside the axis defined by the phenolic oxygen and the carbon linked to the *tert*-butyl groups, are diastereotopic and distinct by NMR analysis due to the presence of the chiral moiety. For

Table 1 Chemical shifts of bis-substituted calixarenes

R	δ_{ax}	δ_{eq}	$\Delta\delta = \delta_{ax} - \delta_{eq}$
1 $CH(CH_3)CO_2Et$	4.35; 4.45	3.32; 3.33	1.03; 1.12
2 $CH(CH_3)CO_2H$	4.05; 4.23	3.42; 3.47	0.63; 0.76
3a CH_2CO_2Et [a]	4.48	3.25	1.23
3c CH_2CO_2H [a]	4.23	3.38	0.85
3b CH_2COMe [a]	4.21	3.31	0.90
3d CH_2CONEt_2 [a]	4.43	3.23	1.20
3e CH_2CONH_2 [a]	4.17	3.41	0.76
3f CH_2CN	4.24	3.42	0.82

[a] Values extracted from ref. 14.

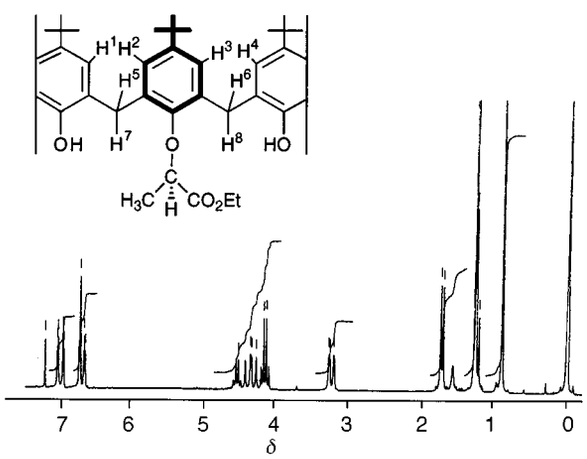


Fig. 1 ^{1}H NMR spectrum of **1** in $CDCl_3$

example, the methylene hydrogens of **1** give four doublets; the signals corresponding to the equatorial hydrogens are centred at δ 3.30 and 3.29, and the axial hydrogens are centred at δ 4.46 and 4.38. The *meta* hydrogens of the aromatic rings give four doublets ($J = 2$ Hz). Surprisingly, the difference between the signals of the aromatic hydrogens without the ethyl lactate moiety (δ 7.01 and 7.09) is higher than that of the substituted rings (δ 6.72 and 6.78). It is noteworthy that the methylenic hydrogens of the CH_2CH_3 group, which may rotate freely, are not split by the asymmetric centre, so the rigidity of the calix cavity is important to the splitting of signals.

This diastereotopic behaviour remains after the hydrolysis of the ester. The difference in chemical shift between the axial hydrogens of compound **1** is *ca.* 0.1 ppm and increases to *ca.* 0.18 ppm in compound **2**. The splitting of the equatorial hydrogens is smaller and increases from 0.01 ppm (lactate calix **1**) to 0.05 ppm (lactic calix **2**) upon hydrolysis of the lactate moiety.

Our data indicate that the compounds are in the cone conformation in solution, since $\Delta\delta$ ($\Delta\delta = \delta_{eq} - \delta_{ax}$) is *ca.* 0.9 ± 0.2 ppm for a system in the cone conformation and zero for a system in the 1,3 alternate conformation. The value $\Delta\delta$ decreases drastically from 1.03–1.12 for compound **1** to 0.63–0.76 for **2** (see Table 1). The signal of the axial methylenic hydrogen of compound **2**, which is lower than those reported for similar compounds (Table 1), may be due to the proximity of the lactic acid moiety.

This reported behaviour is typical of diastereotopic systems and demonstrates that the introduction of the chiral lactate group induces the asymmetric phenomena observed.

The aromatic carbons of **1** and **2** consistently generate 12 peaks (Fig. 2). This fact indicates that the *ortho* and *meta* carbons from the same rings are different from one another. The DEPT analysis of **1** and **2** reveals that the four most intense aromatic peaks belong to carbons linked to hydrogens, as expected. The methylenic carbons of **2** split into two signals very near δ 32.4 and 32.6, while with **1** this splitting was not observed.

The ^{1}H and ^{13}C NMR signals of the *tert*-butyl groups and

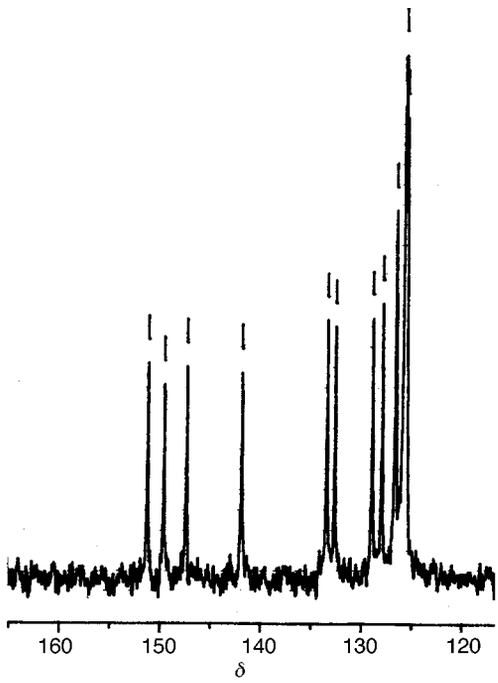
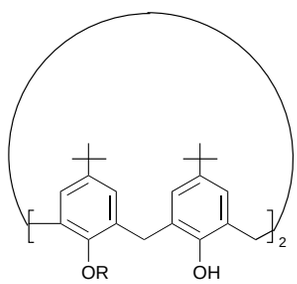


Fig. 2 ^{13}C NMR spectrum (aromatic carbons) of **1** in $CDCl_3$

aromatic hydrogens of **1** are more shielded than **2**, while the aromatic carbons linked to the phenolic oxygens and the signals due to the lactic moiety are less shielded. We believe that the *lactic acid* moieties of **2** are more closed than the *lactate* moieties of **1**. This makes the substituted rings of **1** more parallel, communicating a major distinction for the equatorial and axial hydrogens. In fact, for a series of bis-substituted calixarene derivatives **3**, the groups where $\Delta\delta = \delta_{eq} - \delta_{ax}$ is smaller are those whose substituents are also smaller, as seen in Table 1.



3

X-Ray structural analysis of compound 1

The cone conformation predicted from IR and NMR data agrees with the X-ray analysis of **1** (Fig. 3). The crystallographic cell contains two independent molecules, which caused difficulties in the treatment of the data, but there are no important differences between the geometrical parameters of molecule A and molecule B.

An ethoxy group of molecule B is immersed in the cavity of molecule A, and the methyl group lies midway from the centre of the aromatic rings. Least-square planes show that the aromatic rings are planar, and their planes intercept the plane formed by the four methylenes with angles of 111.0, 125.6, 116.0 and 126.5° for molecule A and 114.5, 123.8, 116.1 and 125.7° for molecule B, revealing that molecules A and B adopt a cone shape with little distortion. The substituted rings present the smaller angles for both molecules.

The lactate moieties spread away from one another, and the carbonyls are oriented outwards from the cavity, pointing towards opposite sides. The two α-methyls also point towards opposite sides, and apparently block the remaining phenolic oxygens, confirming their low reactivity to further reactions.

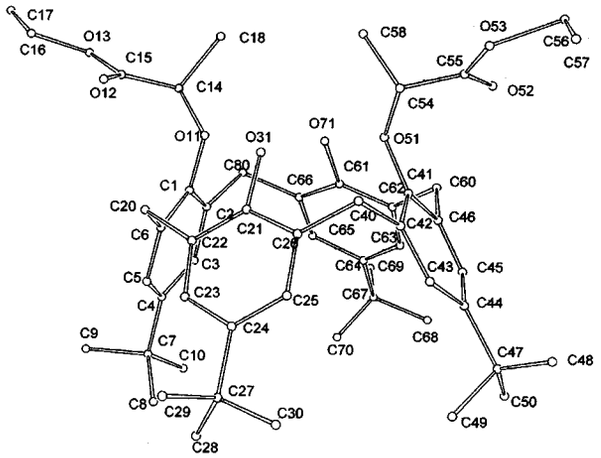


Fig. 3 An ORTEP view of molecule A of compound **1** showing the atomic numbering. For clarity, all the atoms are shown as small spheres of arbitrary size.

The X-ray analysis shows the absence of a rigid pre-organised cavity formed by the O–C–C=O moieties in the solid state, to which the complexation ability of the tetrasubstituted ethoxycarbonylmethylcalix[4]arenes may be attributed.

Each molecule exhibits two intramolecular O–H · · · O hydrogen bonds between the phenolic oxygen and ethereal oxygen atoms, as may be deduced by the distances of the vicinal oxygens [O31 · · · O11 = 2.76(2), O51 · · · O71 = 2.62(2), O31′ · · · O11′ = 2.81(2), O51′ · · · O71′ = 2.70(2) Å].

The X-ray data are in accordance with the cone conformations deduced from the NMR data, allowing us to understand the low reactivity of the remaining phenolic hydroxy groups of **1**. The effect of the asymmetric centre on the methylene and aromatic sites occurs through space, due to the low mobility of the structure.

Conclusion

The preparation of chiral bis[(*R*)-ethyl lactate] and bis[(*R*)-lactic acid] *p*-*tert*-butylcalix[4]arene derivatives in good yields has been achieved. The chiral moieties communicate asymmetry to all elements of the calixarene structure, which adopts a slightly distorted cone conformation. The reported method allows the introduction of chiral moieties on the lower rim of calixarenes.

To the best of our knowledge, the asymmetric phenomena observed in the NMR spectra, where the hydrogens and carbons of the calix structure are diastereotopic and distinct, has not been reported for *p*-*tert*-butylcalix[4]arene derivatives. Thus, compounds **1** and **2** represent the first examples of this type of behaviour.

Experimental

Mps were obtained on a double plate melting-point apparatus and are uncorrected, infrared spectra on an FT-IR Bomem device as KBr discs. ^{1}H NMR spectra were obtained on a Bruker 200 spectrometer, using $CDCl_3$ solutions with tetramethylsilane as internal reference. Coupling constants (J) are given in Hz. Acetone was dried over K_2CO_3. Ethyl (*S*)-(−)-*O*-tosyllactate was synthesized according to a process described in the literature.[15]

5,11,17,23-Tetra-*tert*-butyl-25,27-bis[(*R*)-(+)-1-ethoxycarbonylethoxy]-26,28-dihydroxycalix[4]arene 1

p-*tert*-Butylcalix[4]arene (1.0 g, 1.54 mmol), ethyl (*S*)-(−)-*O*-tosyllactate (3.0 g, 11.1 mmol) and K_2CO_3 (1.0 g, 7.14 mmol) were suspended in 20 ml of acetone under N_2. The mixture was heated under reflux for 24 h. The solvent was evaporated and water was added to the residue. This mixture was extracted three times with 20 ml of CH_2Cl_2, the organic phase was washed with 1 M HCl and brine, and dried over $MgSO_4$. The solvent was evaporated and the residue was recrystallized from ethanol–water giving 1.05 g of colourless crystals. Yield: 78%; mp 151 °C; ^{1}H NMR δ 7.09 (d, Ar-H, 2 H, J 2), 7.01 (d, Ar-H, 2 H, J 2), 6.78 (d, Ar-H, 2 H, J 2), 6.72 (d, Ar-H, 2 H, J 2), 4.60 (q, CH, 2 H, J 6.8), 4.46 (d, $ArCH_2Ar$, 2 H, J 13.8), 4.38 (d, $ArCH_2Ar$, 2 H, J 12.8), 4.41 (q, CH_2, J 7.14 H), 3.30 (d, $ArCH_2Ar$, 2 H, J 13.8), 3.29 (d, $ArCH_2Ar$, 2 H, J 12.8), 1.76 (d, 6 H, CH_3, J 6.6), 1.30 [s, 18 H, $C(CH_3)_3$], 1.28 (t, 6 H, J 7.1, CH_3), 0.93 [s, 18 H, $C(CH_3)_3$]; ^{13}C NMR δ 172.3, 151.3, 149.7, 147.4, 141.9, 133.5, 132.7, 129.0, 128.0, 126.7, 125.9, 125.8, 125.6, 80.6, 61.9, 34.5, 32.9, 32.4, 31.6, 18.6, 14.7; ν_{max}(KBr)/cm^{-1} 3300 (O–H), 2960 (C–H), 1750 (C=O) (Calc. for $C_{54}H_{72}O_8$: C, 76.38; H, 8.55. Found: C, 76.43; H, 8.05%); $[\alpha]_D$ +40 (c 5, $CHCl_3$).

5,11,17,23-Tetra-*tert*-butyl-25,27-bis[(*R*)-(+)-1-carboxyethoxy]-26,28-dihydroxycalix[4]arene 2

To a suspension of **1** (138 mg, 0.16 mmol) in 5 ml of ethanol was added two drops 1 M NaOH. The mixture was stirred at room temperature for 12 h and then acidified to pH 1. The precipitate formed was filtered and recrystallized from ethanol–water, giving 100 mg of colourless crystals. Yield: 77%; mp 250 °C (decomp.); ^{1}H NMR δ 7.10 (d, Ar-H, 2 H, J 2), 7.05 (d, Ar-H, 2 H, J 2), 6.96 (d, Ar-H, 2 H, J 2), 6.89 (d, Ar-H, 2 H, J 2), 4.70 (q, CH, J 6.8, 2 H), 4.23 (d, $ArCH_2Ar$, 2 H, J 13.7), 4.05 (d, $ArCH_2Ar$, 2 H, J 13.2), 3.47 (d, $ArCH_2Ar$, 2 H, J 13.7), 3.42 (d, $ArCH_2Ar$, 2 H, J 13.2), 1.70 (d, CH_3, 6 H, J 6.7), 1.31 [s, $C(CH_3)_3$, 18 H], 1.02 [s, $C(CH_3)_3$, 18 H]; ^{13}C NMR δ 172.5, 149.3, 148.2, 147.3, 143.1, 132.6, 132.3, 127.3, 127.1, 126.9, 125.7, 125.6, 125.4, 80.8, 34.1, 33.9, 32.6, 32.4, 31.6, 30.9, 17.1; ν_{max}(KBr)/cm^{-1} 1730 (C=O) (Calc. for $C_{50}H_{64}O_8 + H_2O$: C, 74.03; H, 8.21. Found: C, 74.20; H, 8.08%); $[\alpha]_D$ −27 (c 5, $CHCl_3$).

Crystallographic data for 1

$C_{54}H_{72}O_8$, M = 849.17, triclinic, a = 11.484(3), b = 12.865(2), c = 18.656(6) Å, α = 76.21(2), β = 84.40(3), γ = 74.02(2)°, V = 2572.1(9) Å^3 (by least-squares refinement on diffractometer angles for 23 automatically centred reflections, λ = 0.710 73 Å), space group $P1$, Z = 2, D_c = 1.096 kg m^{-3}, μ(Mo-Kα) = 0.673 cm^{-1}, F(000) = 920. A transparent crystal of approximate dimensions 0.30 × 0.45 × 0.65 mm was used for data collection. Data were measured at room temperature on a CAD4 automatic four-circle diffractometer in the range 2.2–24°. 8423 reflections were collected of which 6872 were unique and 4326 were observed with $I \geqslant 3\sigma(I)$. Data were corrected for Lorentz and polarization effects but not for absorption. The structure was solved by direct methods[16] and refined using the MOLEN[17] program package. In the final least-squares cycles, only the non-hydrogen atoms of the phenyl rings were refined anisotropically due to the small number of observed reflections, in comparison to the large number of parameters to be refined (two independent molecules in the asymmetric unit). H atoms were included at calculated positions with fixed distance of 0.95 Å, and B_{iso} = 4.0 Å^2, except for OH groups. A weighting scheme $w^{-1} = [\sigma^2(F) + (0.02F)^2 + 1]$ was used. The thermal parameters are generally large, which are characteristic of calixarene crystals.[18–20] For these reasons the final R converged at 0.11, R_w = 0.12 and S = 1.297 for 854 refined parameters, the final difference Fourier map showing features from 0.48 to −0.35 e Å^{-3}.

Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 2*, available *via* the RSC Web pages (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 188/120.

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