Highly selective preparation of conformationally rigid stereoisomeric calix[4]arenes with two carboxymethoxy groups

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Highly selective formation of the 1,3-alternate and partial cone conformational isomers of *p-tert*-butylcalix[4]arene diesters **5** with two butoxy and two methoxycarbonylmethoxy groups was achieved by alkylations of disubstituted calix[4]arenes **3** and **4**, respectively, with KH as the base in THF. The potassium diphenoxide form of **3** was shown by NMR spectroscopy to adopt a 1,3-alternate conformation which provides strong evidence for a template effect of potassium cations on the conformation of the calix[4]arene reactant. Alkylation with subsequent hydrolysis of the diesters provides an effective route for the preparation of the 1,3-alternate and partial cone isomers of *p-tert*-butylcalix[4]arenedicarboxylic acids **6**.

Introduction

Calix[*n*]arenes[1] have been utilized widely as building blocks for various molecular and ionic receptors. By rotation of the phenolic units, calixarene molecules may adopt different conformations. For calix[4]arene compounds, the four limiting conformations are cone, partial cone, 1,3-alternate, and 1,2-alternate (Fig. 1). Attachment of groups larger than ethyl[2] to the lower rim oxygens restricts rotation of the phenolic units in calix[4]arenes, giving rise to the corresponding stereoisomers. Initially, when preparing hosts for ionic recognition, the calix[4]arene moiety was used mostly in the cone conformation as a platform for introducing a variety of ligating groups,[1b] including ethers, esters, amides and/or other functionalities. As other conformational isomers became available, the dependence of complexation properties upon the conformation was probed. For certain metal cations, the 1,3-alternate and partial cone isomers were found[3,4] to possess higher affinities than the analogous cone isomers. Later, π-donor participation of the calixarene benzene rings in coordination of some cations was found,[5,6] and the significance of the calixarene conformation upon cation complexation by such ligands was recognized. The 1,3-alternate conformation is particularly attractive[7] since it provides effective interaction of the guest cation with two side arms, as well as two benzene rings of the calix[4]arene.

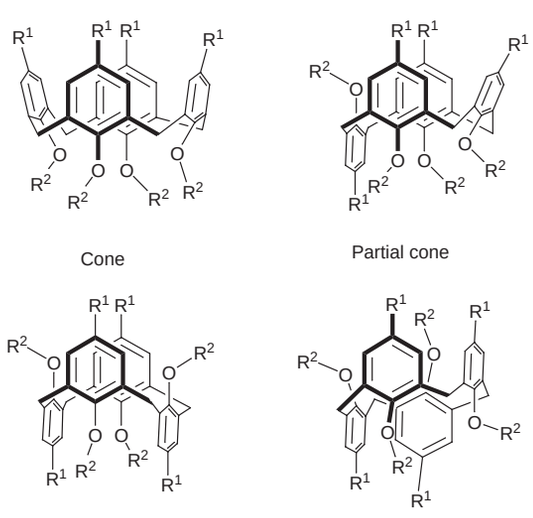
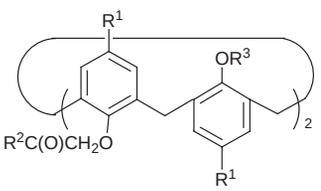


Fig. 1 Four limiting conformations for calix[4]arenes.

Although several 1,3-alternate isomers of calix[4]arenes with carbonylmethoxy ester or amide groups (**1**) have been



1

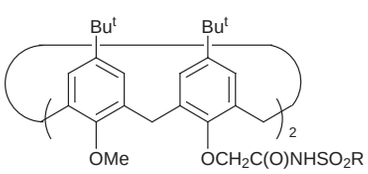
a: $R^1 = Bu^t$, $R^2 = OEt$, $R^3 = CH_2$ 

b: $R^1 = H, Bu^t$, $R^2 = OEt$, $R^3 = CH_2CO_2Et$

c: $R^1 = H$, $R^2 = OMe$, $R^3 = (CH_2)_nCH{=}CH_2$ with $n = 1, 3, 4$

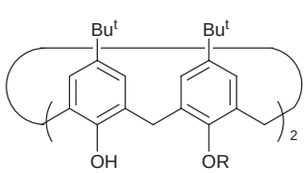
d: $R^1 = H$, $R^2 = NMe_2$, $R^3 = Pr$

e: $R^1 = Bu^t$, $R^2 = NEt_2$, $R^3 = CH_2CONEt_2$



2

R = Me, CF_3, Ph, $C_6H_4NO_2$-4



3 R = Bu
4 R = CH_2CO_2Me

reported,[4,8–11] their preparation involves either protection–deprotection steps,[8] or isolation in low yield from mixtures of stereoisomers.[4,8–11] The availability of more effective, straightforward synthetic routes to the conformational isomers of calix[4]arene carboxylic acids would facilitate the preparation

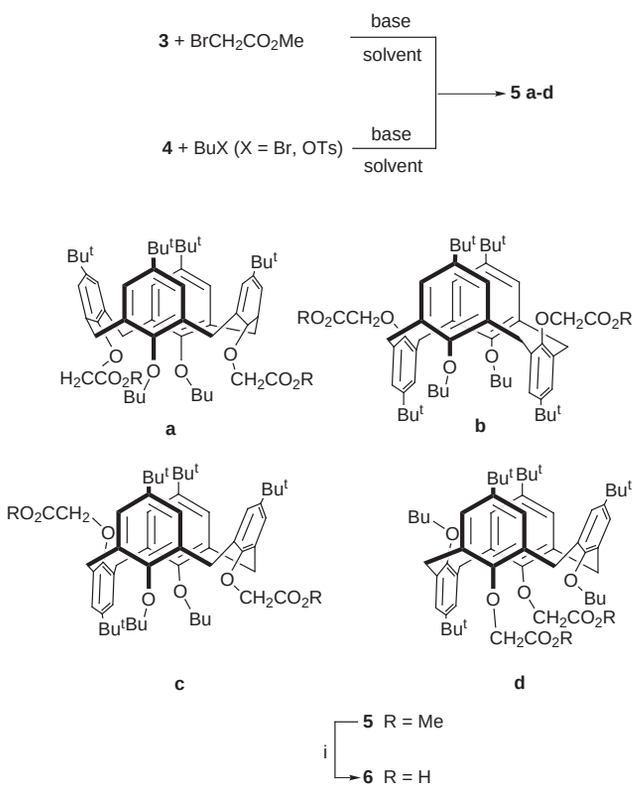
of a variety of functionalized calix[4]arenes which are rigidified in specific conformations.

In the present paper, we report methods for the highly selective preparation of the 1,3-alternate and partial cone isomers of *p-tert*-butylcalix[4]arenedicarboxylic acids.

Results and discussion

In the course of our studies of novel conformationally mobile bis[*N*-(R-sulfonyl)carbamoylmethoxy]calix[4]arenes (**2**),[12] we realized the need to prepare the analogous compounds which are restricted to particular conformations. These isomers would be accessible through the corresponding calix[4]arenedicarboxylic acids. Since the first report by Ungaro *et al.*,[13] alkylation of phenolic oxygens with bromoacetates has become a standard reaction for the preparation of calixarene carboxylic acids.

There have been several studies[1a,c] of the conformational outcome for alkylation of calix[4]arenes depending on the starting material, base, alkylating agent, and reaction conditions (solvent, temperature, *etc.*). Earlier, we observed that alkylation of **3** with ethyl bromoacetate under typical reaction conditions for the preparation of cone isomers[1a] with NaH as a base in DMF, followed by hydrolysis, resulted[12b] in a 75% isolated yield of the cone isomer of calix[4]arenedicarboxylic acid **6a** (Scheme 1).



Scheme 1 *Reagents*: i 1. NMe_4OH–H_2O–THF; 2. HCl.

Often 1,3-alternate calix[4]arene isomers can be formed selectively if the alkylation is conducted with Cs_2CO_3 as the base in DMF[14] or acetonitrile.[7b] Although this method is quite effective in most cases for the introduction of simple alkyl or alkoxyalkyl groups, it does not provide high selectivity for the formation of the 1,3-alternate isomers with carbonyl-containing groups.[4,8,11]

When we performed the reaction of dibutoxy-*p-tert*-butylcalixarene **3** with methyl bromoacetate and Cs_2CO_3 in DMF and in acetonitrile, mixtures containing mostly the 1,3-alternate and partial cone isomers **5b** and **5c** were formed (Table 1). The relative amounts of isomeric products in the crude reaction mixture were determined by ^{1}H NMR spectroscopy by integration of the Bu^t signals.† Interestingly, the proportion of the 1,3-alternate isomer formed in DMF was higher than in acetonitrile. Although the pure isomers could be separated by flash chromatography, the isolated yields were unsatisfactory taking into account the intended use of the calix[4]arene diesters as reactants for further transformations. Therefore, we investigated the conformational distribution of products obtained from performing the alkylation reaction under different conditions. Subsequently, we discovered that conducting the reaction with KH as a base in THF at room temperature produces a much higher proportion (88%) of the desired 1,3-alternate isomer. In previous reports for the use of KH as the base for alkylation of calix[4]arene phenolic oxygens, no selectivity for 1,3-alternate isomer formation was observed.[10,15] For example, the 1,3-alternate isomer **1c** ($n = 3$) was obtained[10] as only a minor product in the reaction of corresponding dialkoxycalix[4]arene with KH and methyl bromoacetate in THF. Interestingly, when we changed the base from KH to NaH for the alkylation of **3** with methyl bromoacetate in THF, exclusive formation of the diester calix[4]arene in the cone conformation was noted (Table 1).

Another potential route to the 1,3-alternate calix[4]arenedicarboxylic acid was alkylation of the bis(methoxycarbonylmethoxy)calix[4]arene **4**. We examined its alkylation under various conditions as well. Although some of the 1,3-alternate isomer **5b** was formed when **4** was reacted with 1-bromobutane or butyl tosylate and Cs_2CO_3 in DMF and acetonitrile, the major product was the partial cone isomer **5d** (Table 1). When the reaction was performed with KH as the base in THF, high conformational selectivity was obtained again. However, in contrast to the reaction of **3** with methyl bromoacetate, the reaction of **4** with 1-bromobutane led to the exclusive formation of the partial cone isomer. Therefore, these reaction conditions are recommended for the preparation of the partial cone isomer **5d**.

Hydrolysis of the calix[4]arene diesters **5** provided quantitative yields of the corresponding diacids **6**. To avoid trapping of metal cations, the hydrolysis was performed with an excess of NMe_4OH in aqueous THF at reflux.[16] Since partial hydrolysis may take place during workup of the calix[4]arene diesters, hydrolysis of the crude diesters with purification at the diacid stage is recommended. In this way, the overall yields of diacids **6b** and **6d** from precursors **3** and **4** were 74 and 90%, respectively. We discovered that the 1,3-alternate diacid **6b** could be purified readily *via* its caesium salt. The caesium salt of **6b** appears to be practically insoluble in $CHCl_3$, while the caesium

† The number, multiplicity and/or intensity of the signals of the Bu^t, methylene and aromatic protons in the ^{1}H NMR spectra were used to establish the symmetry of the calix[4]arene molecules and thereby the conformations. Two singlets of equal intensity are observed in the Bu^t and aromatic regions for the compounds in the cone and 1,3-alternate conformations. Signals from the methylene groups which bridge the phenolic units were employed to distinguish between these two conformations. In the cone conformation, the methylene protons produce two doublets separated by more than 1 ppm. In the 1,3-alternate conformation, the chemical shift difference for the AB protons is much smaller. Also the ^{13}C chemical shifts of the methylene groups were utilized, since they are known[17] to be at 31–32 ppm for calixarene structures with *syn* orientated phenol rings (cone conformation) and at 37–38 ppm for those with the *anti* oriented rings (1,3-alternate). There are three Bu^t signals with a ratio of intensities 1 : 1 : 2 for the two different partial cone isomers **5c** and **5d**. Also similar are the spectral patterns for their aromatic and bridging methylene protons, since the two isomers have the same symmetry at the calix[4]arene moiety. Therefore, the difference in positions of the lower rim substituents was utilized to assign the structures of the partial cone isomers. Ester **5d** has equivalent environments for the two ester groups, but different environments for the two butoxy groups. Also the methylene protons in the ester groups of **5d** are diastereotopic due to the position of these substituents on the partial cone calix[4]arene framework. This provides further support for the assignment of the arrangement of substituents in the partial cone isomer.

Table 1 Calix[4]arene isomer distribution in alkylation reactions of **3** and **4** under various conditions

Entry	Reactant	Alkylating agent	Base	Solvent	Temp./°C	Relative amount of conformational isomer[a] (%)		
						1,3-alt[b]	paco[c]	cone
1	**3**	$BrCH_2CO_2Me$	Cs_2CO_3	DMF	70	64	32	4
2	**3**	$BrCH_2CO_2Me$	Cs_2CO_3	MeCN	70	44	44	12
3	**3**	$BrCH_2CO_2Me$	KH	THF	rt	88	6	6
4	**3**	$BrCH_2CO_2Me$	NaH	THF	66	—	trace	100
5	**4**	BuBr	Cs_2CO_3	MeCN	70	30	58	12
6	**4**	BuOTs	Cs_2CO_3	DMF	rt	33	67	—
7	**4**	BuOTs	Cs_2CO_3	MeCN	70	29	71	trace
8	**4**	BuBr	KH	THF	rt	—	100	—

[a] All dialkylated products (*i.e.*, both esters and acids) are included. [b] The 1,3-alternate isomers. [c] Partial cone isomers **5c** and **6c** in entries 1–4 and **5d** and **6d** in entries 5–8.

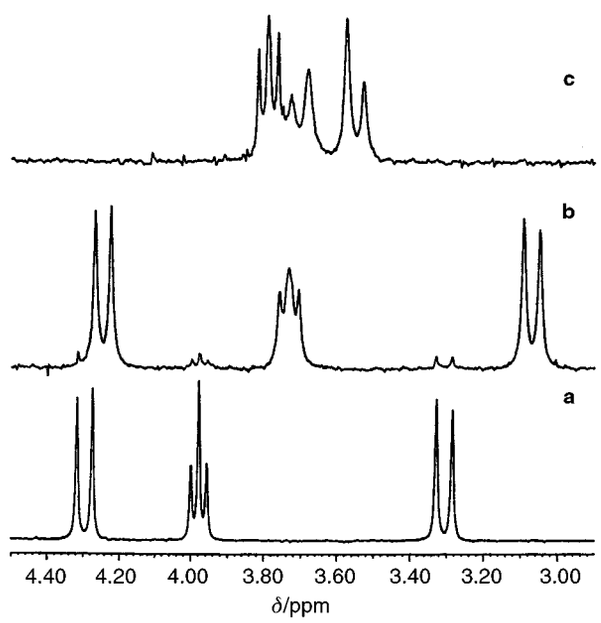


Fig. 2 Partial ^1H NMR spectra (300 MHz, $CDCl_3$) for a) **3**, b) the sodium diphenoxide form of **3**, c) the potassium diphenoxide form of **3**.

salts of the isomeric diacids **6a** and **6c**, as well as other impurities, are quite soluble. ^1H NMR spectra confirmed that diacids **6b** and **6d** retain the same conformations as precursor diesters.

Although changing the base is well known to affect the conformational outcome of calix[4]arene alkylations, the role of a metal ion template effect remains unclear. Thus, when alkylation using Cs_2CO_3 provided the highly selective formation of a 1,3-alternate calix[4]crown-6, a possible template effect of caesium ion was suggested.[7b] In another study,[2] a template effect of sodium ion was deduced, but not for caesium ion. In the current investigation, high conformational selectivity was observed when **3** was alkylated with NaH or KH as the base. In a related alkylation study,[10] a template effect was proposed when NaH was the base, but not with KH.

To obtain insight into the role of metal cations in the immobilization of calix[4]arene conformations, an NMR spectral study of the sodium and potassium diphenoxide forms of **3** was undertaken. The salts were prepared by reaction of **3** with an excess of the corresponding metal hydride in THF. Partial ^1H NMR spectra for the bridging methylene protons of **3** and the salts in $CDCl_3$ are presented in Fig. 2. In spectrum b, a cone conformation is readily evident for the sodium diphenoxide form of **3**. The two close doublets for the methylene protons in the spectrum for the potassium diphenoxide form of **3** indicate that this salt adopts a 1,3-alternate conformation. Additional support for this assessment was derived from the ^{13}C NMR spectra in which the bridging methylene carbons[17] have chemical shifts of 31.87, 33.78 and 38.2 ppm for **3** and its sodium and potassium diphenoxide forms, respectively. This suggests that the predominant formation of different isomers when the alkylation of **3** by methyl bromoacetate was conducted with NaH and with KH in THF (Table 1) arises from a template effect in which metal ion of the base controls the conformation of the diphenoxide calix[4]arene nucleophile.

Experimental

Melting points are uncorrected. IR spectra were recorded with a Perkin-Elmer Model 1600 FT-IR spectrometer, as a deposit from $CHCl_3$ solution on an NaCl plate. ^1H and ^{13}C NMR spectra were recorded with an IBM AF-300 spectrometer at 300 and 75 MHz, respectively. Chemical shifts (δ) are expressed in ppm relative to TMS and J values are given in Hz. Elemental analyses were performed by Desert Analytics Laboratory (Tucson, Arizona). All solvents were dried by customary methods. Unless otherwise specified, commercially available reagents were used without further purification. Methyl bromoacetate was distilled under vacuum from CaH_2.

5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,27-dibutoxy-26,28-dihydroxycalix[4]arene 3[12b]

Compound **3** was prepared similarly to its propyl analog,[2] yield 81%, mp 241–242 °C (from CH_2Cl_2–MeOH) (Found: C, 81.9; H, 9.6. Calc. for $C_{52}H_{72}O_4$: C, 82.1; H, 9.5%); ν_{max}/cm^{-1} 3394, 1196; $\delta_H(CDCl_3)$ 1.01 (18 H, s, 2 × Bu^t), 1.06 (6 H, t, J 7.3, 2 × CH_3), 1.27 (18 H, s, 2 × Bu^t), 1.67–1.81 (4 H, m, 2 × CH_2), 1.94–2.05 (4 H, m, 2 × CH_2), 3.30 (4 H, d, J 12.8, $ArCH_2Ar$), 3.98 (4 H, t, J 6.4, 2 × OCH_2), 4.29 (4 H, d, J 12.8, $ArCH_2Ar$), 6.86 (4 H, s, ArH), 7.03 (4 H, s, ArH), 7.93 (2 H, s, 2 × OH); $\delta_C(CDCl_3)$ 14.09, 19.38, 31.08, 31.69, 31.87 (Ar*C*H_2Ar), 32.20, 33.78, 33.97, 76.25, 125.04, 125.45, 127.71, 132.89, 141.20, 146.65, 150.01, 150.81.

Metal diphenoxide forms of 3. A mixture of **3** (30 mg, 0.09 mmol) and a metal hydride (1 mmol) in THF (3 cm^3) was stirred at room temperature under nitrogen for 8 h. The mixture was filtered and the filtrate was evaporated to dryness. The residue was dissolved in $CDCl_3$ (0.6 cm^3) and the NMR spectrum of the solution was measured.

Sodium diphenoxide form of 3. $\delta_H(CDCl_3)$ 0.68 (6 H, t, J 6.6, 2 × CH_3), 0.75–0.95 (4 H, m, 2 × CH_2), 0.89 (18 H, s, 2 × Bu^t), 1.30–1.45 (4 H, m, 2 × CH_2), 1.31 (18 H, s, 2 × Bu^t), 3.07 (4 H, d, J 13.0, $ArCH_2Ar$), 3.73 (4 H, m, 2 × OCH_2), 4.25 (4 H, d, J 13.0, $ArCH_2Ar$), 6.61 (4 H, s, ArH), 7.06 (4 H, s, ArH); $\delta_C(CDCl_3)$ 33.78 (Ar*C*H_2Ar).

Potassium diphenoxide form of 3. $\delta_H(CDCl_3)$ 1.02 (6 H, t, *J* 7.3, 2 × CH_3), 1.20 (18 H, s, 2 × Bu^t), 1.29 (18 H, s, 2 × Bu^t), 1.38–1.50 (4 H, m, 2 × CH_2), 1.70–1.88 (4 H, m, 2 × CH_2), 3.55 (4 H, d, *J* 13.8, $ArCH_2Ar$), 3.70 (4 H, d, *J* 13.8, $ArCH_2Ar$), 3.79 (4 H, m, 2 × OCH_2), 7.01 (4 H, s, ArH), 7.21 (4 H, s, ArH); $\delta_C(CDCl_3)$ 38.21 ($ArCH_2Ar$).

5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,27-bis(methoxycarbonylmethoxy)-26,28-dihydroxycalix[4]arene 4

A mixture of 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (3.25 g, 5.01 mmol) and K_2CO_3 (1.38 g, 10.02 mmol) was heated under vacuum (0.5 mmHg) at 140 °C for 1 h. After cooling to room temperature, MeCN (70 cm^3) and then a solution of methyl bromoacetate (1.61 g, 10.52 mmol) in MeCN (5 cm^3) were added. The mixture was stirred under nitrogen at 55 °C for 18 h and evaporated. To the residue, CH_2Cl_2 (70 cm^3) was added. Then 10% HCl was added until the pH of the aqueous layer became <1. After shaking the mixture (**CAUTION**: gas evolution!), the organic layer was separated, washed with water, dried over $MgSO_4$, and evaporated to dryness. The residue was dissolved in a minimum amount of boiling $CHCl_3$–MeOH (1:4). After cooling to room temperature, the solution was filtered, the precipitate was washed with MeOH, and the filtrate was evaporated. This residue was dissolved in CH_2Cl_2–MeOH (1:4). The mixture was filtered and the CH_2Cl_2 from the filtrate was allowed to partially evaporate slowly. The precipitated **4** was filtered, washed with MeOH, and dried at 100 °C, yield 3.03 g, 76%, white solid; the mp and spectral data are identical to those reported.[18]

General procedure for the alkylations of 3 and 4

A mixture of the disubstituted calix[4]arene **3** or **4** (0.13 mmol), base (0.8 mmol for metal hydrides, 2.08 mmol for Cs_2CO_3), alkylating agent (0.52 mmol), and solvent (10 cm^3) was stirred under nitrogen for 15 h (details for particular experiments are provided in Table 1). The solvent was evaporated and CH_2Cl_2 and 10% HCl were added to the residue. The organic layer was separated, washed with water, dried over $MgSO_4$, and evaporated to dryness. The residue was used for the studies of isomer distribution by ^{1}H NMR spectroscopy.

5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,27-dibutoxy-26,28-bis(methoxycarbonylmethoxy)calix[4]arenes 5

Cone diester 5a. Compound **5a** was prepared from the known diacid **6a**[12b] and used for its identification in product mixtures from the alkylation reactions. A mixture of diacid **6a** (1.00 g, 1.14 mmol), MeOH (70 cm^3) and 1 drop of concentrated H_2SO_4 was refluxed for 48 h. After evaporation, the residue was dissolved in CH_2Cl_2. The solution was washed with water, dried over $MgSO_4$, and evaporated. The residue was crystallized from $CHCl_3$–MeOH. White solid (0.88 g, 85%), mp 198–199 °C (Found: C, 77.15; H, 8.8. Calc. for $C_{58}H_{80}O_8$: C, 76.95; H, 8.9%); ν_{max}/cm^{-1} 2957, 1766, 1480, 1198, 1126; $\delta_H(CDCl_3)$ 0.99 (24 H, s + t, *J* 7.3, 2 × Bu^t + 2 × CH_3), 1.16 (18 H, s, 2 × Bu^t), 1.38–1.52 (4 H, m, 2 × CH_2), 1.80–2.02 (4 H, m, 2 × CH_2), 3.18 (4 H, d, *J* 12.8, $ArCH_2Ar$), 3.76 (6 H, s, 2 × OCH_3), 3.85 (4 H, m, 2 × OCH_2), 4.60 (4 H, d, *J* 12.8, $ArCH_2Ar$), 4.80 (4 H, s, 2 × OCH_2CO_2), 6.66 (4 H, s, ArH), 6.88 (4 H, s, ArH); $\delta_C(CDCl_3)$ 14.18, 19.36, 31.34, 31.48, 31.62 ($ArCH_2Ar$), 32.20, 33.72, 33.89, 51.34, 70.54, 75.25, 124.81, 125.45, 133.01, 134.07, 144.31, 145.01, 152.91, 153.57, 170.84.

1,3-Alternate diester 5b. To a suspension of KH (0.48 g, 12.0 mmol) in THF (20 cm^3), a solution of **3** (1.90 g, 2.50 mmol) in THF (30 cm^3) was added at room temperature under nitrogen. After 1 h, a solution of methyl bromoacetate (1.53 g, 10.0 mmol) in THF (10 cm^3) was added. The mixture was stirred for 70 h at room temperature. Water (2 cm^3) was added carefully to destroy the excess of KH and the THF was evaporated. To the residue, CH_2Cl_2 (100 cm^3) and water (25 cm^3) were added. The organic layer was separated and washed with water, dried over $MgSO_4$, and evaporated to dryness. The residue was crystallized from $CHCl_3$–MeOH to provide **5b** as a white solid (1.21 g, 54%) (the second crop (0.70 g, 31%) contained an appreciable amount of isomer **5c**), mp 291–292 °C (Found: C, 76.9; H, 9.1. Calc. for $C_{58}H_{80}O_8$: C, 76.95; H, 8.9%); ν_{max}/cm^{-1} 2955, 1762, 1479, 1202, 1128; $\delta_H(CDCl_3)$ 0.85 (6 H, t, *J* 6.9, 2 × CH_3), 1.04–1.22 (8 H, m, 4 × CH_2), 1.23 (18 H, s, 2 × Bu^t), 1.27 (18 H, s, 2 × Bu^t), 3.27 (4 H, s, 2 × OCH_2CO_2), 3.42 (4 H, m, 2 × OCH_2), 3.57 (6 H, s, 2 × OCH_3), 3.82 (4 H, d, *J* 16.0, $ArCH_2Ar$), 4.07 (4 H, d, *J* 16.0, $ArCH_2Ar$), 7.00 (4 H, s, ArH), 7.08 (4 H, s, ArH); $\delta_C(CDCl_3)$ 13.85, 18.93, 30.88, 31.41, 31.50, 33.84, 33.92, 39.06 ($ArCH_2Ar$), 51.22, 68.21, 70.93, 125.42, 126.70, 126.79, 133.13, 134.10, 143.94, 145.07, 153.11, 155.11, 170.67.

Partial cone diester 5c. Compound **5c** was separated from a mixture of isomeric diesters in low yield by column chromatography on silica gel with CH_2Cl_2–MeOH (19:1) as eluent and used only for its identification in the ^{1}H NMR studies of product mixtures from the alkylation reactions; $\delta_H(CDCl_3)$ 0.97 (6 H, t, *J* 7.3, 2 × CH_3), 1.02 (18 H, s, 2 × Bu^t), 1.32 (9 H, s, Bu^t), 1.35–1.52 (4 H, m, 2 × CH_2), 1.40 (9 H, s, Bu^t), 1.65–1.85 (4 H, m, 2 × CH_2), 3.13 (2 H, d, *J* 13.3, $ArCH_2Ar$), 3.56 (5 H, s + m, OCH_3 + OCH_2), 3.70 (2 H, d, *J* 13.6, $ArCH_2Ar$), 3.77 (5 H, s + m, OCH_3 + OCH_2), 3.83 (2 H, d, *J* 13.6, $ArCH_2Ar$), 4.21 (2 H, s, OCH_2CO_2), 4.32 (2 H, d, *J* 13.3, $ArCH_2Ar$), 4.37 (2 H, s, OCH_2CO_2), 6.48 (2 H, d, *J* 2.5, ArH), 7.01 (2 H, d, *J* 2.5, ArH), 7.04 (2 H, s, ArH), 7.27 (2 H, s, ArH).

Partial cone diester 5d. To a suspension of KH (0.47 g, 11.3 mmol) in THF (15 cm^3), a solution of **4** (1.50 g, 1.89 mmol) in THF (20 cm^3) was added at room temperature under nitrogen. After 1 h, a solution of 1-bromobutane (1.55 g, 11.3 mmol) in THF (25 cm^3) was added and the mixture was stirred for 24 h at room temperature. Water (2 cm^3) was added carefully to destroy the excess of KH and the THF was evaporated. To the residue, CH_2Cl_2 (60 cm^3) was added. The organic layer was separated, washed with 5% HCl and water, dried over $MgSO_4$, and evaporated to dryness. The residue was chromatographed on silica gel with ethyl acetate–hexanes (1:1) as eluent and then crystallized from CH_2Cl_2–ethyl acetate. White solid, yield 1.13 g (66%), mp 245–246 °C (Found: C, 76.9; H, 9.0. Calc. for $C_{58}H_{80}O_8$: C, 76.95; H, 8.9%); ν_{max}/cm^{-1} 2955, 1767, 1478, 1191, 1123; $\delta_H(CDCl_3)$ 0.84 (3 H, t, *J* 7.4, CH_3), 0.94 (3 H, t, *J* 7.3, CH_3), 1.03 (18 H, s, 2 × Bu^t), 1.10–1.20 (2 H, m, CH_2), 1.22–1.40 (2 H, m, CH_2), 1.34 (9 H, s, Bu^t), 1.38 (9 H, s, Bu^t), 1.45–1.58 (2 H, m, CH_2), 1.66–1.78 (2 H, m, CH_2), 3.07 (2 H, d, *J* 12.6, $ArCH_2Ar$), 3.53 (2 H, m, OCH_2), 3.64 (2 H, m, OCH_2), 3.65 (2 H, d, *J* 13.8, $ArCH_2Ar$), 3.78 (6 H, s, 2 × OCH_3), 3.85 (2 H, d, *J* 13.8, $ArCH_2Ar$), 4.24 (2 H, d, *J* 12.6, $ArCH_2Ar$), 4.33 (2 H, d, *J* 15.0, OCH_2CO_2), 4.47 (2 H, d, *J* 15.0, OCH_2CO_2), 6.60 (2 H, d, *J* 2.5, ArH), 6.86 (2 H, d, *J* 2.5, ArH), 7.09 (2 H, s, ArH), 7.33 (2 H, s, ArH); $\delta_C(CDCl_3)$ 14.05, 18.88, 19.27, 30.76, 31.34, 31.58, 31.71, 33.06, 33.73, 33.92, 34.06, 37.46, 51.74, 71.11, 72.37, 73.39, 125.42, 125.78, 126.15, 127.75, 131.84, 132.46, 135.58, 143.28, 144.22, 144.81, 153.49, 153.76, 155.11, 170.04.

General procedure for the hydrolysis[16] of esters 5

A mixture of an ester **5** (or a mixture of the isomeric esters) (1.00 mmol), NMe_4OH (15 cm^3 of 25% aqueous solution), THF (40 cm^3) and water (30 cm^3) was refluxed for 30 h and the THF was evaporated. The residue was acidified to pH < 1 with concentrated HCl and CH_2Cl_2 (50 cm^3) was added. The organic layer was separated, washed with water, dried over $MgSO_4$, and evaporated to dryness giving rise to acid **6** (or a mixture of the isomeric acids).

1,3-Alternate diacid 6b. To a solution of the hydrolysis product of crude diester **5b** (2.26 g, 2.50 mmol) in $CHCl_3$ (30 cm^3), Cs_2CO_3 (2.25 g, 6.9 mmol) was added and the mixture was stirred for 4 h. The precipitate was filtered and washed with $CHCl_3$. The filtrate was evaporated and hexanes (15 cm^3) were added. The precipitate was filtered and washed with $CHCl_3$. To the combined precipitates, CH_2Cl_2 (40 cm^3) and 10% HCl solution were added to pH < 1 (**CAUTION**: possible foaming). After stirring the mixture for 0.5 h, the organic layer was separated, washed with 10% HCl and then water, dried over $MgSO_4$, and evaporated. Drying the residue under vacuum (0.5 mmHg) at 120 °C for 12 h gave **6b** as a colorless solid (1.62 g, 74%), mp 291–292 °C (Found: C, 76.75; H, 8.7. Calc. for $C_{56}H_{76}O_8$: C, 76.7; H, 8.7%); ν_{max}/cm^{-1} 3405, 2959, 1755, 1480, 1362, 1334, 1208, 1126, 758; $\delta_H(CDCl_3)$ 0.79 (6 H, t, *J* 7.2, 2 × CH_3), 0.91–1.16 (8 H, m, 4 × CH_2), 1.24 (18 H, s, 2 × Bu^t), 1.30 (18 H, s, 2 × Bu^t), 3.27 (4 H, s, 2 × OCH_2CO_2), 3.43 (4 H, m, 2 × OCH_2), 3.79 (4 H, d, *J* 16.7, $ArCH_2Ar$), 3.93 (4 H, d, *J* 16.7, $ArCH_2Ar$), 7.01 (4 H, s, ArH), 7.05 (4 H, s, ArH), 7.95 (2 H, br s, 2 × CO_2H); $\delta_C(CDCl_3)$ 13.20, 18.91, 31.17, 31.23, 31.44, 33.93, 34.05, 38.61 ($ArCH_2Ar$), 67.27, 69.95, 125.77, 126.09, 132.38, 132.64, 146.13, 146.34, 151.59, 154.13, 168.50.

Partial cone diacid 6d. The product of the hydrolysis of crude diester **5d** (2.26 g, 2.50 mmol) was crystallized from hexanes–CH_2Cl_2 and dried under vacuum (0.5 mmHg) at 180 °C for 4 h to provide **6d** (2.01 g, 90%) as a colorless solid, mp 239–240 °C (Found: C, 74.8; H, 8.6. Calc. for $C_{56}H_{76}O_8 \cdot 1.25H_2O$: C, 74.8; H, 8.8%); ν_{max}/cm^{-1} 3378, 2957, 1758, 1480, 1362, 1199, 1126, 734; $\delta_H(CDCl_3)$ −0.01–0.10 (2 H, m, OCH_2CH_2), 0.36 (3 H, m, CH_3), 0.40–0.50 (2 H, m, CH_2), 0.87 (3 H, t, *J* 7.3, CH_3), 1.12 (9 H, s, Bu^t), 1.20 (2 H, m, CH_2), 1.28 (18 H, s, 2 × Bu^t), 1.34 (9 H, s, Bu^t), 1.68 (2 H, m, CH_2), 2.26 (2 H, m, OCH_2), 3.34 (2 H, d, *J* 12.6, $ArCH_2Ar$), 3.82 (2 H, m, OCH_2), 3.87 (2 H, d, *J* 17.3, $ArCH_2Ar$), 3.98 (2 H, d, *J* 17.3, $ArCH_2Ar$), 4.23 (2 H, d, *J* 15.9, OCH_2CO_2), 4.39 (2 H, d, *J* 15.9, OCH_2CO_2), 4.39 (2 H, d, *J* 12.6, $ArCH_2Ar$), 6.99 (4 H, s + d, ArH), 7.14 (2 H, s, ArH), 7.24 (2 H, d, *J* 2.4, ArH), 9.5 (2 H, br s, 2 × CO_2H) (the ^1H NMR spectrum changed when more water was present); $\delta_C(CDCl_3)$ 13.79, 13.84, 18.79, 18.91, 31.06 ($ArCH_2Ar$), 31.23, 31.45, 33.99, 34.14, 38.79 ($ArCH_2Ar$), 69.50, 69.91, 77.28, 125.32, 125.70, 126.33, 126.60, 132.14, 132.41, 132.90, 135.30, 145.83, 145.94, 147.11, 150.65, 151.79, 154.38, 170.27.

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