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The selective functionalisation and difunctionalisation of *p*-substituted calix[6]arene and calix[8]arenes using hydrophilic moieties

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Received 4th September 2002, Accepted 14th November 2002
First published as an Advance Article on the web 19th December 2002

Methodologies to access water soluble large ringed calixarenes in good yield using efficient synthetic procedures have been investigated. Symmetrical partial functionalisations at the lower rim are described using activated [*n*]ethylene glycol chains and the addition behaviour contrasted with that of bromoalkanenitriles which proceeds with no observed regioselectivity. Full functionalisations of the calixarenes bearing hydrophilic groups are then investigated and a two-step procedure established which appears to be generally applicable for the addition of different [*n*]ethylene glycol chains. Furthermore, difunctionalisation under different reaction conditions are described. Throughout, strategies for the characterisation of these high mass compounds are outlined.

Introduction

In recent years, the chemistry of calixarenes[1] has received much attention where they have been used as building blocks for host molecules with various applications in supramolecular chemistry.[2] Research has focused on regio- and stereoselective functionalisation at the lower and upper rim and a range of procedures for this have been reported.[1] Methods for the etherification of the calix[4]arenes at the lower rim have been well established and general procedures are available for the selective preparation of monoalkoxy-, 1,2- and 1,3-dialkoxy-calix[4]arenes, trialkoxy- and fully *O*-alkylated calix[4]arenes in high yields.[3]

By comparison, the synthesis of derivatives of the larger ring calixarenes, calix[6]arenes and in particular the calix[8]arenes, have been explored to a lesser degree and their chemistry is therefore less established. However, with their larger ring sizes, they have significant potential for use as large molecular receptors for medium and large sized organic compounds or as enzyme mimics. Compared to the calix[4]arenes, the selective *O*-alkylation of calix[6]- and calix[8]arenes at the lower rim is more difficult, and can be unpredictable because of their conformational flexibilities and large number of reactive centres.[4] However, synthetic procedures have been established for the selective monosubstitution, 1,4-disubstitution, 1,2,4,5-tetra-substitution, and hexasubstitution of calix[6]arenes in high yields.[5] Tri-*O*-alkylated 1,2,3- or 1,3,5-calix[6]arenes have been obtained in lower yields.[6] The factors governing the outcome of these reactions include the strength of the base used, the different solubilities of intermediates, the possibility of generating mono- or polyanions which have different stabilities, and conformational and metal template effects.[7,8] However, the selective functionalisations reported have involved, almost exclusively, the use of reactive or unfunctionalised electrophiles such as benzyl and methyl groups where further functionalisation of these groups is not possible.

Similarly, synthetic procedures using calix[8]arenes have been reported to generate 1,3,5,7-tetrabenzyloxy-*O*-substituted derivatives,[7,8] where an alternate alkylation mechanism was proposed to explain the regioselectivity observed.[4,7–9] However, as with the calix[6]arenes most reports involve the addition of reactive or unfunctionalised electrophiles such as the benzyl halides.[4,7–10] Interesting exceptions include the preparation of octopus-type calix[6]arenes in low yield,[11] monosubstituted calix[8]arene using $Cl(CH_2CH_2O)_3Ts$,[12] and the interbridging of calix[6]arenes and calix[8]arenes using mono- to tetraethylene glycol ditosylates.[13] Full ether functionalisations at the lower rim of calix[8]arenes have been reported, generally involving the use of large excesses of strong bases together with a large excess of a reactive electrophile such as the methyl or benzyl halides.[4,8] The full *O*-alkylation of calix[8]arenes using activated [*n*]ethylene glycol monoethers has also been described, but up to 80 equivalents of electrophile were required, and with longer chain ethylene glycols (>diethylene glycols) incomplete reactions were reported.[14,15] There is therefore a significant need to establish simple efficient procedures for the partial or full derivatisation of calix[8]arenes using less reactive functionalised electrophiles, in particular, the attachment at the lower rim of electrophiles of lower reactivity than benzyl and methyl halides, with different properties such as solubilising, catalytic, complexation or fluorescent moieties.

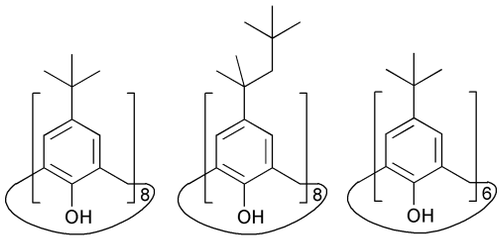
Herein we report our study to establish a general and simple procedure for the full or partial *O*-alkylation of calix[6]arenes and calix[8]arenes using electrophiles including 4-bromobutyronitrile, 7-bromoheptanenitrile and activated tri-, hexa-, and dodecaethylene glycols, due to our interest in the preparation of hydrophilic and functionalised calixarenes.

Results and discussion

In our studies we selected two types of chain for partial or full attachment, the bromoalkanenitriles, which have potential for further elaboration, and poly(ethylene glycol) chains, which have solubilising properties or could be further functionalised. *p-tert*-Butylcalix[8]arene **1**, *p-tert*-octylcalix[8]arene **2** and *p-tert*-butylcalix[6]arene **3** were all used in our study to assess the influence of the group at the upper rim and differences in the effect of ring sizes, and initial experiments were carried out using bromoalkanenitriles.

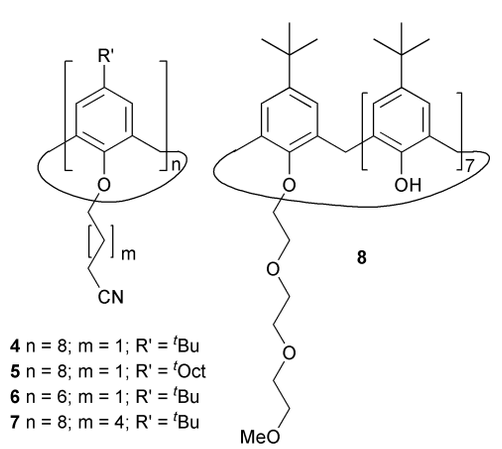
Neri *et al.* have reported the selective alkylation of *tert*-butylcalix[8]arene at the lower rim using benzyl bromides, which under strongly basic conditions led to the formation of octa-substituted products, whilst the use of weak bases (K_2CO_3 and

DOI: 10.1039/b208649m



1 **2** **3**

CsF) generated 1,3,5,7-tetrasubstituted compounds.[4,7] However, when the mild bases were used with methyl iodide the 1,2,4-trimethoxy- and 1,2,3,4-tetramethoxy derivatives predominated.[7] Furthermore, Neri *et al.* rationalised that the size of the electrophile is important and reported that when using butyl iodide both the 1,2,4-tributoxy- and 1,3,5,7-tetrabutoxy- derivatives were generated.[7] In our preliminary study, we investigated the reaction between bromobutyronitrile and *p-tert*-butylcalix[8]arene **1** with NaH in THF or DMF with the aim of generating the fully *O*-alkylated calix[8]arene. However, negligible amounts of alkylated products were generated. Interestingly, when carrying out the same reaction, but using K_2CO_3 as a mild base in acetonitrile, alkylations were readily observed. When using 0.5 to 2 equivalents of bromobutyronitrile (per phenolic OH), the reaction evolved to give a complete mixture of polyalkylated compounds with no preference for the formation of particular partially alkylated derivatives. These were therefore not isolated, but were reacted directly in a second step this time using NaH as the base which promoted the formation of *p-tert*-butyl-octakis(cyanopropoxy)calix[8]arene **4**, using in total 20–32 equivalents of the bromoalkanenitrile (*i.e.* 2.5 to 4 equivalents per phenolic OH) in 30–35% yield over the two steps. Although the use of NaH did not generate the fully *O*-alkylated product in one step, we interestingly observed that **4** could also be formed in 70% yield but in one step using a larger amount of mild base (K_2CO_3) and an extended reaction time. This simple one-step methodology was then used with the calixarenes **2** and **3** forming the butyronitrile derivatives, **5** and **6**, in 72% and 71% yields respectively. The use of K_2CO_3 with **1** and bromoheptanonitrile was similarly effective, and **7** was formed in 80% yield. The solubilities of compounds **1**–**3** are approximately 0.3 mg ml^{-1} in water whilst those of **4**–**7** were measured as 7–8 mg ml^{-1}. Using ^{13}C NMR spectroscopy four aromatic signals were observed indicating conformational interconversion of the calixarenes. Indeed, a reduction in calixarene mobility was only noted for the calix[6]arene derivative **6** where in the ^1H NMR spectra at room temperature signal broadening was observed.



4 n = 8; m = 1; R' = ^{t}Bu
5 n = 8; m = 1; R' = ^{t}Oct
6 n = 6; m = 1; R' = ^{t}Bu
7 n = 8; m = 4; R' = ^{t}Bu

8

These results highlighted two strategies to generate the fully alkylated products: one involving two steps and a combination of a mild base (with no selective *O*-alkylation) and strong base; the second, a one step procedure using larger quantities of a mild base. The requirement for the use of mild bases with bromoalkanenitriles is contrary to previous reports using electrophiles of similar reactivity where for full alkylations, stronger bases have been used.[4] The need for the use of a mild base for initial alkylation is unclear though likely to involve several parameters including greater monoanion stability in the presence of the electrophiles used together with template effects.

Although full alkylations could be achieved using the bromoalkanenitriles, up to 32 equivalents of the electrophile were required. For the synthesis of compounds with greater aqueous solubilities, incorporating groups such as [*n*]ethylene glycols, a more efficient process would be required, particularly if more elaborate compounds were synthesised for attachment. Previous reports have highlighted the challenging nature of such *O*-alkylation reactions.[14,15] Initial studies focussed on the use of *p-tert*-butylcalix[8]arene **1** and mesylate or tosylate activated methoxytriethylene glycol[16] since mesylated or tosylated compounds have been used in previous calixarene additions.[14,15] A range of different bases (NaH, KO*t*-Bu, PhLi, *n*-BuLi), reaction times, temperatures and solvent systems (DMF, THF, DMF–THF, benzene) were used together with a 20-fold excess of the electrophile. However, at best the mono-substituted calix[8]arene **8** was obtained in a 10% yield (Table 1, entry 1), together with traces of disubstituted derivatives detectable by ESMS. The use of further equivalents of electrophile or base had no effect on the reaction outcome. Bearing in mind the ease with which the bromoalkanenitriles had been added, further *O*-alkylations were performed but using 1-(2-bromoethoxy)-2-(2-methoxyethoxy)ethane.[17] When carrying out the reaction with **1** in the presence of NaH using 30 equivalents of base and 60 equivalents of 1-(2-bromoethoxy)-2-(2-methoxyethoxy)ethane, **9** was formed in 55% yield after purification by alumina chromatography (Scheme 1, Table 1, entry 2). The use of a milder base was also explored and when using K_2CO_3 (16 equivalents) and only 8 equivalents of 1-(2-bromoethoxy)-2-(2-methoxyethoxy)ethane, interestingly **9** was also formed, in 40% yield. Remarkably, for the reaction to proceed with NaH a large excess of both base and [*n*]ethylene glycol chain were required and despite this no fully alkylated calixarene was generated. When using *p-tert*-octylcalix[8]arene **2** the use of NaH led to the formation of no *O*-alkylation products (Table 1, entry 4), but with a mild base the 1,3,5,7-substituted product **10** (Scheme 1, Table 1, entry 5) was readily isolated.

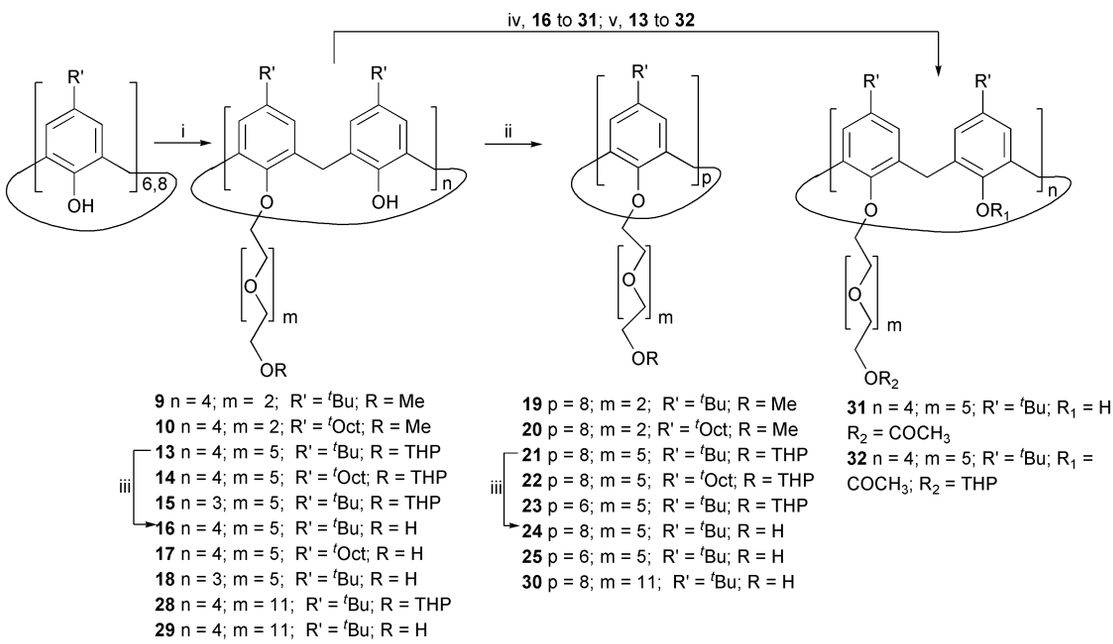
The structural characterisation of compounds **9** and **10** was carried out using mass spectrometry and NMR spectroscopy. Broadening of the signals was observed in the ^1H NMR spectra and the phenolic protons were never observed in this series of compounds. However, ^{13}C NMR proved to be particularly powerful indicating the symmetrical nature of the partially alkylated compounds with two pairs of signals for the *tert*-butyl carbons ($C(CH_3)_3$ and $C(CH_3)_3$) at approximately 31 ppm and 34 ppm for **9** and with a pair of signals corresponding to $C(CH_3)_2$ at 38 ppm for **10**. Two sets of signals for the aromatic carbons were observed in some cases (although for several compounds the signals were superimposed). MS analysis proved to be useful for the *tert*-butyl series, however, with larger groups at the upper rim such as *tert*-octyl molecular ions could not always be observed. The ability of these hydrophilic compounds to complex to several metal ions also led to complications when attempting to observe the molecular ions and in such cases the use of ^{13}C NMR spectroscopy proved to be particularly effective. Compounds **9** and **10** possessed solubilities of 9–10 mg ml^{-1} in water.

Interestingly, **9** and **10** were the products predominantly generated regardless of whether mild or strong bases were used, the amount of base and electrophile present and the reaction conditions. In general, the use of K_2CO_3 was preferable to NaH since fewer equivalents of electrophile (and base) were required and the procedure was more reliable with different groups at the upper rim. The formation of these partially alkylated

Table 1 Selective *O*-alkylations of *p*-alkylcalix[*n*]arenes

Entry	Calixarene	Electrophile/equivalents	Base/equivalents	Product	Yield (%)
1	**1**, R′ = *tert*-Butyl	$MsO(CH_2CH_2O)_3Me$/20 eq.	NaH/20 eq.	**8**	10
2[a]	**1**, R′ = *tert*-Butyl	$Br(CH_2CH_2O)_3Me$/60 eq.	NaH/30 eq.	**9**	55
3[a]	**1**, R′ = *tert*-Butyl	$Br(CH_2CH_2O)_3Me$/8 eq.	K_2CO_3/16 eq.	**9**	40
4[a]	**2**, R′ = *tert*-Octyl	$Br(CH_2CH_2O)_3Me$/60 eq.	NaH/16 eq.	—	—
5[a]	**2**, R′ = *tert*-Octyl	$Br(CH_2CH_2O)_3Me$/8 eq.	K_2CO_3/16 eq.	**10**	41
6[a]	**1**, R′ = *tert*-Butyl	**12**, $Br(CH_2CH_2O)_6THP$/8 eq.	NaH/16 eq.	mono- and di- alkylation	—
7[a]	**1**, R′ = *tert*-Butyl	**12**, $Br(CH_2CH_2O)_6THP$/8 eq.	K_2CO_3/16 eq.	**13**	65
8[a]	**2**, R′ = *tert*-Octyl	**12**, $Br(CH_2CH_2O)_6THP$/8 eq.	NaH/16 eq.	**14**	62
9[a]	**2**, R′ = *tert*-Octyl	**12**, $Br(CH_2CH_2O)_6THP$/8 eq.	K_2CO_3/16 eq.	**14**	63
10[a]	**3**, R′ = *tert*-Butyl	**12**, $Br(CH_2CH_2O)_6THP$/6 eq.	K_2CO_3/12 eq.	**15**	67
11[b]	**9**	$Br(CH_2CH_2O)_3Me$/8 eq.	NaH/16 eq.	**19**	76
12[b]	**10**	$Br(CH_2CH_2O)_3Me$/8 eq.	NaH/16 eq.	**20**	47
13[b]	**13**	**12**, $Br(CH_2CH_2O)_6THP$/8 eq.	NaH/16 eq.	**21**	55
14[b]	**14**	**12**, $Br(CH_2CH_2O)_6THP$/8 eq.	NaH/16 eq.	**22**	45
15[b]	**15**	**12**, $Br(CH_2CH_2O)_6THP$/6 eq.	NaH/12 eq.	**23**	45
16[a]	**1**, R′ = *tert*-Butyl	**27**, $I(CH_2CH_2O)_{12}THP$/8 eq.	K_2CO_3/16 eq.	**29**	[c]25
17[b]	**28**	**27**, $I(CH_2CH_2O)_{12}THP$/8 eq.	NaH/16 eq.	**30**	[c]27
18[d]	**16**	CH_3COCl/20 eq.	NaH/20 eq.	**31**	54
19[d]	**13**	CH_3COCl/10 eq.	Et_3N/10 eq.	**32**	33

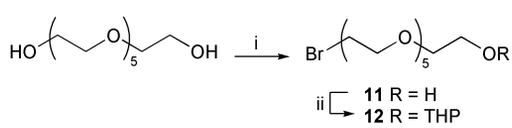
[a] At 80 °C for 4 d. [b] At 70 °C for 4 d. [c] Compound directly deprotected; yield refers to 2-step conversion. [d] At rt for 24 h.



Scheme 1 *Reagents and conditions*: i, K_2CO_3, CH_3CN, electrophile; ii, NaH, THF, electrophile; iii, 10% conc. HCl in $MeOH–CH_2Cl_2$; iv, NaH, CH_3COCl; v, Et_3N, CH_3COCl.

compounds was consistent with the alternate alkylation mechanism.[6,9] The difference in behaviour compared to the bromoalkanenitriles was most likely due to repulsions between the oxygens in the triethylene glycol chains hindering 1,2-addition, or intramolecular H-bonding between the oxygen ethers and neighbouring phenolic hydrogens, increasing the preference for alternate addition. The partial low yielding additions observed when using strong bases suggests poor polyanion stability in the presence of the activated triethylene glycols.

The addition of longer [*n*]ethylene glycol chains including hexaethylene glycol moieties was explored and therefore THP protected and bromo activated hexaethylene glycol **12** was prepared (Scheme 2). Accordingly, hexaethylene glycol was monobrominated to give 17-bromo-3,6,9,12,15-pentaoxaheptadecan-1-ol **11** in 56% yield using Chong's methodology for the preparation of bromoalkanols and **11** was purified using reverse phase chromatography.[18] This was subsequently THP protected to give 17-tetrahydropyranyloxy-3,6,9,12,15-pentaoxaheptadecyl bromide, **12**.



Scheme 2 *Reagents and conditions*: i, HBr (48%); ii, TsOH, THP.

The desymmetrisation of hexaethylene glycol had been initially carried out *via* THP monoprotection and this compound was then brominated using carbon tetrabromide and triphenylphosphine[19] with subsequent purification. However, when **12**, prepared *via* this route, was used in additions to calixarenes, some calix[8]arene products were observed to complex to triphenylphosphine, as observed by MS ($M^+ + PPh_3$). Interestingly, the triphenylphosphine could not be detected in the starting material **12** or products by ^1H and ^{13}C NMR spectroscopy, but could be using ^{31}P NMR spectroscopy. The contamination by triphenylphosphine was clearly undesirable, and therefore the use of this synthetic route was avoided.

Following the results from the additions of short PEG chains, **12** was reacted with *p*-*tert*-butylcalix[8]arene **1** and NaH (Table 1, entry 6), however, an inseparable mixture of mono- and di-alkylated products were formed in low yield, as detected

by ESMS. When using 8 equivalents of **12** and K_2CO_3 as base, the C_4 symmetrical product, 1,3,5,7-tetra-*O*-substituted *tert*-butycalix[8]arene **13** was exclusively formed in 65% yield, after purification by alumina chromatography. Interestingly the alkylation of **2** under strong or mild base conditions led to the formation of **14** in 62% and 63% yield respectively, possibly due to co-solvent or conformational effects in the presence of the substituted hexaethylene glycol. However, for the addition of **12** to **3**, the use of a weak base was required to give the 1,3,5,-tri-*O*-substituted *tert*-butycalix[6]arene **15** (Table 1, entry 10). The THP groups were readily removed from compounds **13**–**15** to give the corresponding alcohols **16**, **17** and **18** using 10% HCl in dichloromethane–methanol which had solubilities of 15–20 mg ml^{-1} in water.

The structural characterisation of compounds **13**–**18** was carried out using MS (ES and MALDI-TOF) and NMR spectroscopy as outlined above. Again, ^{13}C NMR spectroscopy indicated the symmetrical nature of the compounds, as shown in Fig. 1 for compounds **13** and the *tert*-octyl-substituted

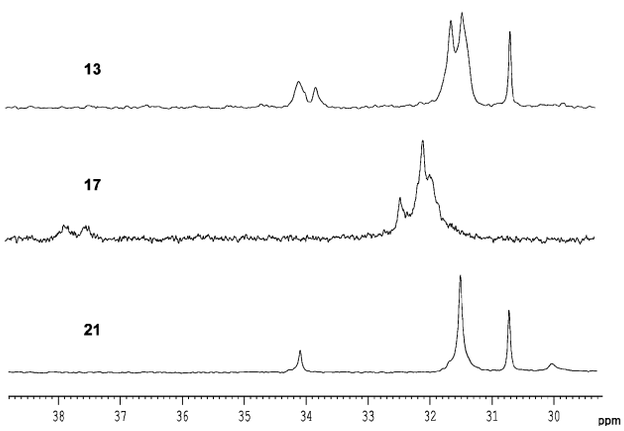


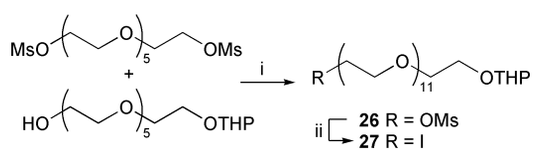
Fig. 1 *tert*-Butyl and *tert*-octyl regions of the ^{13}C NMR spectra for compounds **13**, **17**, and **21**.

calix[8]arene **17**. Compound **13** has two non-identical sets of $C(CH_3)_3$ groups, at approximately 31.5 ppm and 31.7 ppm and non-equivalent quaternary carbons at 33.8 ppm and 34.0 ppm, whilst the non-equivalent quaternary carbons adjacent to the aromatic ring in **17** can be observed at 37.5 ppm and 37.9 ppm. However, with the increasing mass and poor relaxation of these high molecular mass compounds not all of the quaternary aromatic carbons could be observed.

Cornforth *et al.* has previously reported a shift in the UV maxima from 300 nm for unsubstituted calixarenes to 270 nm and 280 nm for the fully alkylated materials.[15] These partially substituted calixarenes exhibited a λ_{max} at approximately 305 nm and 280 nm.

Having established a facile procedure for the synthesis of partially substituted symmetrical calixarenes, the second addition of [*n*]ethylene glycol chains was explored to access fully alkylated materials. The acidities of the four remaining phenolic protons will be different to the unsubstituted calixarenes due to H-bonding with neighbouring hydroxys and ether oxygens. The hydroxys are also more sterically hindered than in unsubstituted calixarenes. We rationalised therefore that for further alkylations the use of stronger bases would be required. This was indeed the case, and we established that when using NaH in THF, **9**, **10**, **13**, **14**, and **15** were converted into their corresponding fully alkylated derivatives, compounds **19**–**23** in 45–76% yield (Table 1, entries 11–15). Again, only 2 equivalents of electrophile were used per phenolic OH, and the products were purified using alumina chromatography. The facile deprotection of the fully *O*-alkylated hexaethylene glycol THP calixarenes was confirmed using the same conditions as for the partially alkylated compounds with, for example, the deprotection of **21** and **23** to give **24** and **25** in 95% and 92%, respectively. Characterisation of the fully PEGylated calixarenes was achieved as described previously, using MS and NMR spectroscopy, although due to the ability of these compounds with increasing numers of [*n*]ethylene glycol chains to complex several metal ions and fragment under MS conditions, it became increasing more difficult to observe molecular ions. The use of ^{13}C NMR spectroscopy again proved to be extremely useful indicating the symmetrical nature of the fully alkylated calixarenes, displaying only one signal for the *tert*-butyl CH_3 and quaternary carbons as shown in Fig. 1 for compound **21**. Furthermore the λ_{max} of the compounds were recorded and observed at approximately 270 nm and 278 nm in agreement with Cornforth *et al.*'s observations.[15]

The general applicability of this methodology was explored further with the attachment of THP protected dodecylethylene glycol PEG chains (PEG12-THP). The synthesis of activated PEG12-THP was initially explored using several strategies, however, the most successful, concise route is shown in Scheme 3. Dimesylate hexaethylene glycol and mono-THP protected



Scheme 3 *Reagents and conditions*: i, NaH; ii, NaI, acetone, then TsOH, THP.

hexaethylene glycol were prepared as previously reported.[20,21] These were then coupled under basic conditions to give PEG12-THP mesylate **26**, in 50% yield after purification by reverse phase chromatography. To improve the efficiency of coupling to the calixarene, activation to give the iodo-derivative was carried out. Accordingly, **26** was reacted with sodium iodide in acetone. However, partial deprotection also occurred under these reaction conditions. The material was therefore directly reprotected to give PEG12-THP iodide, **27** in 90% yield.

Compound **27** was then reacted with calixarene **1** and K_2CO_3 to give the tetrasubstituted symmetrically PEGylated calix-[8]arene **28** (Scheme 1, Table 1, entry 16). Compound **28** was directly deprotected to give **29**. Analysis by MS revealed the formation of multiply charged species and product degradation (for example, a fragment corresponding to $M^+ - C_2H_2O$ was observed). However, further confirmation of the synthesis of the 1,3,5,7-tetrasubstituted compound was provided by ^{13}C NMR analysis. The second coupling between **28** and **27** was as before carried out under strongly basic conditions and the fully alkylated product generated was then directly deprotected to give **30** (with a solubility of 35 mg ml^{-1} in water) in 27% yield over the two steps. Finally ^{13}C NMR confirmed the formation of the fully alkylated product with a single peak for each of the *tert*-butyl carbons and UV analysis revealed peaks at λ_{max} 270 nm and 280 nm.

The selectivity observed in these addition reactions will enable symmetrical difunctionalised calixarenes to be readily prepared possessing combined properties. To investigate the selectivity for the addition of activated carboxylic acid groups, *tert*-butyl-tetra(hexaethylene glycol)tetrahydroxycalix[8]arene **16** was reacted with an excess of acetyl chloride and NaH. Interestingly, addition of the acyl groups to the PEG-OH moieties predominated with the formation of **31** in 54% yield (Scheme 1, Table 1, entry 18). However, when the corresponding THP protected calixarene **13** was reacted with acetyl chloride and triethylamine *tert*-butyl-tetra(hexaethylene glycol THP ether)tetraacetoxycalix[8]arene **32** was generated as the major product (33% yield). ^{13}C NMR spectroscopy again confirmed the highly symmetrical nature of the calixarenes. This differential addition of further functionalities opens up numerous

opportunites for the synthesis of highly functionalised large ringed calixarenes.

In summary we have identified versatile high yielding procedures for the mono-functional full and partial substitution of calix[8]arenes and also for the symmetrical bifunctionalisation of calix[8]arenes. For the addition of ethylene glycol chains the 2-step procedure developed utilised only 16 equivalents of the electrophile to generate the fully alkylated product. This methodology has the potential to significantly extend applications of calix[8]arenes with the introduction of several different properties into one molecule, including solubilising groups, complexation or fluorescent moieties, to numerous applications including the design of sensors and the synthesis of biological probes.

Experimental

All moisture-sensitive reactions were performed under a nitrogen atmosphere using oven-dried glassware. Unless otherwise indicated, reagents were obtained from commercial suppliers and were used without further purification. All solvents were dried over standard drying agents[22] and freshly distilled prior to use. Reactions were monitored by TLC on Kieselgel 60 F_{254} plates or RP-6 F_{254} plates with detection by UV, or permanganate and phosphomolybdic acid stains. Flash column chromatography[23] was carried out using silica gel (particle size 40–63 μm) purchased from BDH. Reverse phase chromatography was carried out using Si60 silanised silica gel (BDH).

^{1}H NMR spectra were recorded at 300 MHz or 500 MHz on a Bruker AMX-300 or Avance-500 spectrometer. ^{13}C NMR spectra were recorded at 75 MHz or 125 MHz. Residual protic solvent was used as internal standard, with $CDCl_3$ as solvent unless otherwise stated, stored over 4 Å molecular sieves and filtered through basic alumina prior to use. Coupling constant (*J*) values are given in Hz. The assignment of signals was aided by decoupling, DEPT and/or homo- and heteronuclear two-dimensional experiments.

Mass spectra were obtained using a Micromass Quattro LC instrument (ES), Bruker Apex III (ES), VG ZAB 2SE (FAB and EI) (FAB mass spectra were acquired using 3-nitrobenzyl alcohol as the matrix), Bruker Reflex III MALDI-TOF (MALDI-TOF), Micromass TofSpec (TOF) and Micromass ZAB-2SE (HRFAB). Infra red spectra were recorded on a Shimadzu FTIR-8700 spectrometer. UV spectra were recorded on a Shimadzu UV-2401 spectrometer using cells of 10 mm pathlength and a solution of potassium hydroxide (1 M) in methanol. CHN analyses were carried out on a Perkin Elmer 2400 CHN Elemental Analyzer. Melting points were taken on a Reichert hot stage instrument and are uncorrected.

The elemental analyses of calixarenes are very often uncorrected[24] with the found carbon values often considerably lower than the calculated ones. The identity and purity of most of the new compounds was therefore established by MS and ^{1}H and particularly ^{13}C NMR analysis. The *p-tert*-butyl- and *p-tert*-octyl-substituted calix[8]arenes and *p-tert*-butylcalix[6]arene were prepared following literature procedures.[14,15,25] 3,6,9-Trioxadecyl methanesulfonate[16] was prepared as previously described and 1-(2-bromoethoxy)-2-(2-methoxyethoxy)-ethane[17] was prepared as previously described or using an identical procedure to that used for the monobromination of hexaethylene glycol. Methanesulfonic acid 2-[2-(2-{2-[2-(2-methanesulfonyloxyethoxy)ethoxy]ethoxy}ethoxy)ethoxy]ethyl ester was prepared as previously reported.[20] Hexaethyleneglycol mono-THP ether was prepared as previously described.[21]

Full alkylation of *p-tert*-butylcalix[8]arene, *p-tert*-octylcalix[8]arene and *p-tert*-butylcalix[6]arene with alkanenitriles

To the calixarenes **1**, **2** or **3** (0.5 mmol) in dry acetonitrile (40 ml) at 40 °C, potassium carbonate (2 mmol per OH) was added and the reaction mixture was stirred for 1 h. Bromobutyronitrile (2 mmol per OH) or bromoheptanenitrile (2 mmol per OH), dissolved in acetonitrile (10 ml) was added dropwise and the contents were heated at 80 °C for 6 d. After removal of the base by filtration the solvent was removed *in vacuo* and the residue purified by column chromatography (ethyl acetate–hexane, 1 : 2) or by recrystallisation from acetonitrile.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54,55,56-octakis(cyanopropoxy)calix[8]arene 4

The procedure outlined above was used to give **4** as a white solid (0.642 g, 70%) (Found: C, 73.3; H, 7.73; N, 5.29; Br 4.4. $C_{120}H_{152}N_8O_8{\cdot}KBr{\cdot}H_2O$ requires: C, 73.1; H, 7.78; N, 5.69; Br, 4.1%); mp 228–230 °C; ν_{max}(Nujol)/cm^{-1} 2960, 2247 (CN), 1583; δ_H(300 MHz; $CDCl_3$) 1.10 (72H, s, C(CH_3)$_3$), 1.85 (16H, tt, *J* 6.7 and 5.8 Hz, CH_2CH$_2$CN), 2.37 (16H, t, *J* 6.7 Hz, CH_2CN), 3.61 (16H, t, *J* 5.8 Hz, OCH_2), 3.98 (16H, s, CH_2 bridge), 6.94 (16H, s, ArH); δ_C(75 MHz; $CDCl_3$) 13.9 (*C*H$_2$CH$_2$CN), 25.9 (*C*H$_2$CN), 29.8 (*C*H$_2$ bridge), 31.3 (C(*C*H$_3$)$_3$), 34.1 (*C*(CH$_3$)$_3$), 70.6 (O*C*H$_2$), 119.5 (*C*N), 126.0 (*C*H), 132.7, 146.3, 152.5; *m/z* (HRFAB) 1856.170 ([M + Na]$^+$, $C_{120}H_{152}N_8O_8Na$ requires 1856.163).

5,11,17,23,29,35,41,47-Octa-*tert*-octyl-49,50,51,52,53,54,55,56-octakis(cyanopropoxy)calix[8]arene 5

The procedure outlined above was used to give **5** as a cream solid (0.830 g, 72%) (Found: C, 80.0; H, 9.32; N, 5.13. $C_{152}H_{216}N_8O_8$ requires: C, 79.9; H, 9.54; N, 4.91%); mp 195–197 °C; ν_{max}(Nujol)/cm^{-1} 2977, 2249 (CN), 1598, 1582; δ_H(300 MHz; $CDCl_3$) 0.71 (72H, s, C(CH_3)$_3$), 1.17 (48H, s, CH$_2$-C(CH_3)$_2$), 1.52 (16H, s, CH_2C(CH$_3$)$_2$), 1.84 (16H, m, CH_2CH$_2$-CN), 2.30 (16H, t, *J* 6.3 Hz, CH_2CN), 3.60 (16H, t, *J* 6.6 Hz, OCH_2), 3.95 (16H, s, CH_2 bridge), 6.96 (16H, s, ArH); δ_C(75 MHz; $CDCl_3$) 13.9 (*C*H$_2$CH$_2$CN), 25.9 (*C*H$_2$CN), 30.2, 31.7, 31.9 (C(*C*H$_3$)$_3$), 32.3, 38.2 (*C*(CH$_3$)$_2$), 56.7 (^{t}octyl *C*H$_2$), 70.9 (O*C*H$_2$), 119.7 (*C*N), 126.9 (*C*H), 132.6, 145.6, 152.5; *m/z* (HRFAB) 2304.660 ([M + Na]$^+$, $C_{152}H_{216}N_8O_8Na$ requires 2304.664).

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexakis-(cyanopropoxy)calix[6]arene 6

The procedure described above was used to give **6** as a white powder (0.488 g, 71%) (Found: C, 78.8; H, 8.23; N, 6.30. $C_{90}H_{114}N_6O_6$ requires: C, 78.6; H, 8.36; N, 6.11%); mp >295 °C; ν_{max}(Nujol)/cm^{-1} 2962, 2246 (CN), 1601, 1580; δ_H(300 MHz; $CDCl_3$) 1.14 (54H, br s, C(CH_3)$_3$), 1.83 (12H, br, CH_2CH$_2$CN), 2.31 (12H, br, CH_2CN), 3.45–4.15 (24H, br m, OCH_2 and CH_2 bridge), 6.99 (12H, s, ArH); δ_C(75 MHz; $CDCl_3$) 13.9 (*C*H$_2$CH$_2$-CN), 25.8 (*C*H$_2$CN), 30.4 (*C*H$_2$ bridge), 31.3 (C(*C*H$_3$)$_3$), 34.0 (*C*(CH$_3$)$_3$), 71.0 (O*C*H$_2$), 119.4 (*C*N), 126.1 (*C*H), 132.6, 146.1, 152.2; *m/z* (HRFAB) 1397.865 ([M + Na]$^+$, $C_{90}H_{114}N_6O_6Na$ requires 1397.870).

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54,55,56-octakis(cyanohexoxy)calix[8]arene 7

The procedure outlined above was used to give **7** as a solid (0.868 g, 80%) (Found: C, 79.8; H, 9.12; N, 5.37. $C_{144}H_{200}N_8O_8$ requires: C, 79.6; H, 9.29; N, 5.16%); mp 272–274 °C; ν_{max}-(Nujol)/cm^{-1} 2922, 2245 (CN), 1590; δ_H(300 MHz; $CDCl_3$) 1.07 (72H, s, C(CH_3)$_3$), 1.40 (32H, m), 1.54 (16H, m), 1.66 (16H, m), 2.23 (16H, t, *J* 6.9 Hz, *C*H$_2$CN), 3.58 (16H, t, *J* 5.6 Hz, CH$_2$O), 4.02 (16H, s, CH_2 bridge), 6.92 (16H, s, ArH); δ_C(75 MHz; $CDCl_3$) 16.9, 25.3, 25.4, 28.5, 29.8, 30.1, 31.4 (C(*C*H$_3$)$_3$), 34.1 (*C*(CH$_3$)$_3$), 72.8 (O*C*H$_2$), 119.7 (*C*N), 125.7 (*C*H), 132.8, 145.8, 153.1; *m/z* (HRFAB) 2192.545 ([M + Na]$^+$, $C_{144}H_{200}N_8O_8Na$ requires 2192.539).

Monoalkylation of *p-tert*-butylcalix[8]arene with 3,6,9-trioxadecyl methanesulfonate

To *p-tert*-butylcalix[8]arene **1** (1.30 g, 1 mmol) was added THF–DMF (120 ml, 5 : 1) and the mixture was stirred at 50 °C until a clear solution was obtained. Sodium hydride (60% dispersion in mineral oil; 0.800 g, 20.0 mmol) was added and stirring was continued for 1 h. 3,6,9-Trioxadecyl methanesulfonate[16] (4.85 g, 20.0 mmol) in THF–DMF (30 ml, 5 : 1) was then added dropwise at rt and the reaction mixture was heated for 2 d at 80 °C. The reaction was quenched with the addition of ice-cold water and extracted with chloroform (3 × 50 ml). The combined organic extracts were washed with saturated LiCl solution (30 ml), brine (30 ml) and water (30 ml), and the solvent evaporated affording a crude product. This was recrystallised using dichlormethane–diethyl ether to yield 5,11,17,23,29,35,41,47-octa-tert-*butyl*-49-mono(3,6,9-trioxadecyloxy)-50,51,52,53,54, 55,56-heptahydroxycalix[8]arene **8** (145 mg, 10%) (Found: C, 78.8; H, 5.51. $C_{95}H_{126}O_{11}$ requires: C, 79.0; H, 5.37%); mp > 315 °C dec; ν_{max}(Nujol)/cm^{-1} 3186, 2923, 2854, 1602; δ_H(300 MHz; $CDCl_3$) 1.23–1.28 (72H, m, C(CH_3)$_3$), 3.08 (3H, s, OCH_3), 3.11 (2H, t, *J* 4.7 Hz, CH_2O), 3.31 (2H, t, *J* 4.7 Hz, CH_2O), 3.57 (2H, t, *J* 4.7 Hz, CH_2O), 3.74–3.98 (22H, m, CH_2 bridge and 3 × CH_2O), 6.87–7.19 (16H, m, ArH), 8.87 (2H, s, O*H*), 9.12 (1H, s, O*H*), 9.33 (4H, s, O*H*); δ_C(75 MHz; $CDCl_3$) 30.6, 30.8, 31.4, 31.5, 32.3, 32.4, 32.7, 34.0, 34.1, 34.3, 59.2 (O*C*H$_3$), 70.2, 70.3, 70.5, 70.9, 71.6, 74.8, 125.3–128.0 (several signals), 133.5, 143.1–150.5 (several signals); *m*/*z* (−ES) 1443.1 (M^+, $C_{95}H_{126}O_{11}$ requires 1442.9).

Partial alkylation of *p-tert*-butylcalix[8]arene 1, *p-tert*-octylcalix[8]arene 2 and *p-tert*-butylcalix[6]arene 3 with bromo[*n*]ethylene glycol ethers

To the calixarenes **1**, **2** or **3** (0.5 mmol) in dry acetonitrile (40 ml) at 40 °C, potassium carbonate (2 mmol per OH) was added and the reaction mixture was stirred for 1 h. 1-(2-Bromoethoxy)-2-(2-methoxyethoxy)ethane[17] (1 mmol per OH) or bromohexaethylene glycol THP ether (**12**) (1 mmol per available OH) dissolved in acetonitrile (10 ml) was then added dropwise and the contents were heated at 80 °C for 4 d. After removal of the base by filtration the solvent was removed in *vacuo* and the residue purified using a neutral alumina column.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,51,53,55-tetrakis-(3,6,9-trioxadecyloxy)-50,52,54,56-tetrahydroxycalix[8]arene 9

The reaction was carried out as described above and the product purified using a neutral alumina column (gradient: ethyl acetate–methanol) to give **9** as a solid (0.376 g, 40%) (Found: C, 72.9; H, 8.93. $C_{116}H_{168}O_{20}\cdot 2H_2O$ requires: C, 72.6; H, 9.04%); mp 53–55 °C; δ_H(300 MHz; $CDCl_3$) 0.86–1.36 (72H, m, C(CH_3)$_3$), 3.16–4.03 (76H, m, OCH_2, OCH_3, CH_2 bridge), 6.79–7.20 (16H, m, ArH); δ_C(75 MHz; $CDCl_3$) 30.0 (*C*H$_2$ bridge), 31.2 and 31.3 (2 × C(*C*H$_3$)$_3$), 33.8 and 34.0 (2 × *C*(CH$_3$)$_3$), 58.7 (O*C*H$_3$), 70.3 (signals superimposed), 71.7, 125.7 and 126.5 (2 × CH), 132.9, 146.1, 152.4; *m*/*z* (−ES) 1881.3 (M^+, $C_{116}H_{168}O_{20}$ requires 1881.2).

5,11,17,23,29,35,41,47-Octa-*tert*-octyl-49,51,53,55-tetrakis-(3,6,9-trioxadecyloxy)-50,52,54,56-tetrahydroxycalix[8]arene 10

The reaction was carried out as described above and the product purified using a neutral alumina column (gradient: ethyl acetate–methanol) to give **10** as an oil (477 mg, 41%): δ_H(300 MHz; $CDCl_3$) 0.49–0.82 (72H, m, C(CH_3)$_3$), 1.01–1.29 (48H, m, CH$_2$C(CH_3)$_2$), 1.50–1.79 (16H, m, CH_2C(CH$_3$)$_2$), 3.17–3.91 (76H, m, OCH_2, OCH_3, CH_2 bridge), 6.78–7.17 (16H, m, ArH); δ_C(75 MHz; $CDCl_3$) 31.5–32.3 (signals superimposed), 37.8 and 38.2 (*C*(CH$_3$)$_2$), 57.0 (*t*octyl *C*H$_2$), 58.9 (O*C*H$_3$), 70.5 (signals superimposed), 71.9, 126.4 (CH), 132.7, 146.6.

17-Bromo-3,6,9,12,15-pentaoxaheptadecan-1-ol 11

To hexaethylene glycol (8.00 g, 28.3 mmol) in toluene (50 ml) was added hydrobromic acid (48%; 5.1 ml, 45.3 mmol) and the reaction was heated at reflux for 3 d.[18] Sodium hydrogencarbonate was added and the solvent was removed *in vacuo*. Then ethyl acetate (30 ml) was added and the residual sodium hydrogencarbonate was removed by filtration. The removal of solvents *in vacuo* gave the title compound[26] (5.50 g, 56%) as an oil, which could be further purified using reverse phase chromatography (gradient: water–acetonitrile, 100% water to 100% acetonitrile): δ_H(300 MHz; $CDCl_3$) 3.15 (1H, s, OH), 3.39 (2H, t, *J* 6.2 Hz, CH_2Br), 3.53–3.66 (20H, m, CH_2O), 3.73 (2H, t, *J* 6.2 Hz, CH_2CH$_2$Br); δ_C(75 MHz; $CDCl_3$) 30.3, 61.5, 70.1–70.5 (signal overlap), 72.5 (*C*H$_2$-CH$_2$Br); *m*/*z* (+ES) 345 (MH^+, 28%), 195 (23), 151 (41), 133 (94), 89 (100).

17-(2*H*-Tetrahydropyran-2-yloxy)-3,6,9,12,15-pentaoxaheptadecyl bromide 12

To 17-bromo-3,6,9,12,15-pentaoxaheptadecan-1-ol (**11**) (7.60 g, 22.1 mmol) in CH_2Cl_2 (60 ml) was added toluene-*p*-sulfonic acid monohydrate (0.42 g, 2.21 mmol) and 3,4-dihydro-2*H*-pyran (2.05 g, 24.4 mmol). The reaction was stirred at rt for 2 d, then washed with water (20 ml) and dried (sodium sulfate). The solvent was removed *in vacuo* to give the title compound as a clear oil (7.27 g, 77%): ν_{max}(film)/cm^{-1} 2924, 2869, 1456; δ_H(300 MHz; $CDCl_3$) 1.38–1.78 (6H, m, 3 × CH_2), 3.39 (2H, t, *J* 6.3 Hz, CH$_2$Br), 3.54–3.58 (22H, m), 3.74 (2H, t, *J* 6.3 Hz, CH_2CH$_2$Br), 4.56 (1H, dd, *J* 3.8 and 3.2 Hz, C*H*O); δ_C(75 MHz; $CDCl_3$) 19.5, 25.4, 30.2, 30.5, 62.2, 66.6, 70.5–70.6 (signals superimposed), 71.2, 99.0 (*C*HO); *m*/*z* (−ES) 429.36 (MH^+, 7), 389 (60), 305 (27), 287 (100).

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,51,53,55-tetrakis-[17-(2*H*-tetrahydropyran-2-yloxy)-3,6,9,12,15-pentaoxaheptadecyloxy]-50,52,54,56-tetrahydroxycalix[8]arene 13

The reaction was carried out as described above and purified using a neutral alumina column (gradient: ethyl acetate–methanol) to give **13** as a viscous oil (0.874 g, 65%) (Found: C, 66.2; H, 9.26. $C_{136}H_{240}O_{86}\cdot 8H_2O$ requires C, 66.1; H, 9.03%); λ_{max}/nm (1 M KOH in MeOH) 305, 280, 235; ν_{max}(film)/cm^{-1} 3388, 2950, 1474; δ_H(500 MHz; $CDCl_3$) 0.95–1.35 (72H, m, C(CH_3)$_3$), 1.49–1.92 (24H, m, CH_2-THP), 3.43–3.78 (80H, m, CH_2O), 3.84 (16H, m, CH_2O), 3.92 (8H, br s, CH_2 bridge), 4.03 (8H, br s, CH_2 bridge), 4.61 (4H, dd, *J* 4.1 and 3.3 Hz, C*H*O), 7.05 (16H, m, ArH); δ_C(75 MHz; $CDCl_3$) 19.5, 25.5, 29.9 (*C*H$_2$ bridge) 30.6, 31.5 and 31.7 (2 × C(*C*H$_3$)$_3$), 33.8 and 34.0 (2 × *C*(CH$_3$)$_3$), 62.2, 66.7, 70.6 (signals superimposed), 72.5, 99.0 (*C*HO), 125.3 and 125.4 (2 × *C*H), 132.9, 142.8 and 145.9, 152.7; *m*/*z* (−ES) 2689.6 ([M − H]$^+$, $C_{156}H_{239}O_{36}$ requires 2689.7).

5,11,17,23,29,35,41,47-Octa-*tert*-octyl-49,51,53,55-tetrakis-[17-(2*H*-tetrahydropyran-2-yloxy)-3,6,9,12,15-pentaoxaheptadecyloxy]-50,52,54,56-tetrahydroxycalix[8]arene 14

The reaction was carried out as described above and the product purified using a neutral alumina column (gradient: ethyl acetate–methanol) to give **14** as a viscous oil (0.973 g, 62%); δ_H(300 MHz; $CDCl_3$) 0.47–0.66 (72H, m, C(CH_3)$_3$), 1.06–1.19 (40H, m, CH$_2$C(CH_3)$_2$), 1.45–1.60 (48H, m, CH_2C(CH$_3$)$_2$), 3.22–4.11 (120H, m, CH_2O and CH_2 bridge), 4.55 (4H, m, C*H*O), 6.81–7.07 (16H, m, ArH); δ_C(75 MHz; $CDCl_3$) 19.1, 25.1, 30.2, 31.2–32.0 (signals superimposed), 37.4 and 37.6 (*C*(CH$_3$)$_2$), 56.5 (*t*octyl CH$_2$), 61.7, 66.2, 70.2 (signals superimposed), 72.2, 98.5 (*C*HO), 126.0 and 126.7 (2 × *C*H), 132.3, 141.5 and 144.4, 152.9; *m*/*z* (−ES) 3138.3 (M^+, $C_{188}H_{304}O_{36}$ requires 3138.2).

5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-tris[17-(2*H*-tetrahydropyran-2-yloxy)-3,6,9,12,15-pentaoxaheptadecyloxy]-38,40,42-trihydroxycalix[6]arene 15

The reaction was carried out as described above and the product purified using a neutral alumina column (gradient: ethyl acetate–methanol) to give **15** as a viscous oil (0.676 g, 67%): δ_H(300 MHz; $CDCl_3$) 1.13–1.35 (54H, m, C(CH_3)$_3$), 1.43–1.88 (18H, m), 3.56–4.03 (90H, m, CH_2O and CH_2 bridge), 4.61 (3H, m, C*H*O), 6.70–7.24 (12H, m, ArH); δ_C(75 MHz; $CDCl_3$) 19.2, 25.2, 30.3–31.5 (signals superimposed), 33.6 and 34.0 (2 × *C*(CH$_3$)$_2$), 62.0, 66.4, 69.8–70.4 (signals superimposed), 72.3, 98.7 (*C*HO), 125.3 and 126.3 (2 × *C*H), 132.9, 142.3 and 146.0, 149.2 and 151.2; *m*/*z* (−ES) 2017.1 (M^+, $C_{117}H_{180}O_{27}$ requires 2017.3).

THP deprotection of partially alkylated *p*-*tert*-butylcalix[8]arene, *p*-*tert*-octylcalix[8]arene and *p*-*tert*-butylcalix[6]arene

The calixarenes **13**, **14** or **15** were stirred in dichloromethane–methanol (50 : 50, 10 ml) containing 10% conc. HCl for 3 h at rt. Sodium hydrogencarbonate was added to neutralise the solution and the solvent removed *in vacuo*. The product was suspended in ethyl acetate and the inorganic salts removed by filtration. The ethyl acetate was then removed *in vacuo* to reveal the deprotected calixarenes.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,51,53,55-tetrakis-(17-hydroxy-3,6,9,12,15-pentaoxaheptadecyloxy)-50,52,54,56-tetrahydroxycalix[8]arene 16

Compound **13** (150 mg, 0.06 mmol) was deprotected as described above to give **16** as an oil (123 mg, 94%): δ_H(300 MHz; $CDCl_3$) 0.86–1.30 (72H, m, C(CH_3)$_3$), 2.82 (4H, br s, CH$_2$O*H*), 3.36–3.86 (96H, m, CH_2O), 3.86–4.02 (16H, br m, CH_2 bridge), 6.76–7.08 (16H, m, ArH); δ_C(75 MHz; $CDCl_3$) 29.7 (*C*H$_2$ bridge), 31.4 and 31.6 (2 × C(*C*H$_3$)$_3$), 33.9 and 34.0 (2 × *C*(CH$_3$)$_3$), 61.7, 70.3 (signals superimposed), 72.6, 125.5 and 126.5 (*C*H), 132.8, 145.8; *m*/*z* (−ES) 2353.2 (M^+, $C_{136}H_{208}O_{32}$ requires 2353.5).

5,11,17,23,29,35,41,47-Octa-*tert*-octyl-49,51,53,55-tetrakis-(17-hydroxy-3,6,9,12,15-pentaoxaheptadecyloxy)-50,52,54,56-tetrahydroxycalix[8]arene 17

Compound **14** (168 mg, 0.054 mmol) was deprotected as described above to give **17** as an oil (138 mg, 92%): δ_H(300 MHz; $CDCl_3$) 0.49–0.76 (72H, m, C(CH_3)$_3$), 1.00–1.30 (48H, m, CH$_2$C(CH_3)$_2$), 1.46–1.70 (16H, m, CH_2C(CH$_3$)$_2$), 2.76 (4H, s, OH), 3.30–3.98 (112H, m, CH$_2$O and CH_2 bridge), 6.76–7.11 (16H, m, ArH); δ_C(75 MHz; $CDCl_3$) 31.9–32.3 (signals superimposed), 37.5 and 37.9 (*C*(CH$_3$)$_2$), 56.8 (^{t}octyl *C*H$_2$), 61.6, 70.3–70.5 (signals superimposed), 72.5, 125.5 (CH), 132.1, 144.4; *m*/*z* (−ES) 2802.7 (M^+, $C_{168}H_{272}O_{32}$ requires 2802.0).

5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-tris(17-hydroxy-3,6,9,12,15-pentaoxaheptadecyloxy)-38,40,42-trihydroxycalix[6]arene 18

Compound **15** (77 mg, 0.038 mmol) was deprotected as described above to give **18** as an oil (61 mg, 90%): δ_H(300 MHz; $CDCl_3$) 1.00–1.35 (54H, m, C(CH_3)$_3$), 3.52–3.95 (84H, m, CH_2O and CH_2 bridge), 6.70–7.18 (12H, m, ArH); δ_C(75 MHz; $CDCl_3$) 29.7 (*C*H$_2$ bridge), 31.3 and 31.6 (2 × C(*C*H$_3$)$_3$), 33.9 and 34.2 (2 × *C*(CH$_3$)$_3$), 61.6, 70.2–70.6 (signals superimposed), 72.6, 125.6 and 126.6 (2 × *C*H), 133.0, 146.2; *m*/*z* (−ES) 1765.0 (M^+, $C_{102}H_{156}O_{24}$ requires 1765.1).

Second alkylation of *p*-*tert*-butylcalix[6]arene and *p*-*tert*-butylcalix[8]arenes or *p*-*tert*-octylcalix[8]arenes with bromo[*n*]ethylene glycol ethers

To the calixarenes **9**, **10**, **13**, **14** or **15** (0.5 mmol) in dry THF (40 ml), was added sodium hydride (60% dispersion in mineral oil; 2 equivalents per OH). After 20 min the activated PEG chain (2 equivalents per OH) was added in dry THF (10 ml) and the reaction mixture was heated at reflux for 4 d. Water (2 ml) was added and the solvent removed *in vacuo* to give an oil which was purified using neutral alumina chromatography (gradient: ethyl acetate–methanol).

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54,55,56-octakis(3,6,9-trioxadecyloxy)calix[8]arene 19

The reaction was carried out as described above using **9** (160 mg, 0.085 mmol) to give **19** as an oil (159 mg, 76%): ν_{max}(film)/cm^{-1} 2928, 1598, 1572; δ_H(300 MHz; $CDCl_3$) 0.90–1.24 (72H, m, C(CH_3)$_3$), 3.31–3.84 (120H, m, CH_2O and OCH_3), 4.01 (16H, s, CH_2 bridge), 6.70–6.94 (16H, m, ArH); δ_C(75 MHz; $CDCl_3$) 31.3 (signals superimposed) 33.9 (*C*(CH$_3$)$_3$), 58.8 (O*C*H$_3$), 70.3–70.5 (signals superimposed), 71.8, 125.7 (CH), 133.0, 145.7, 153.0; *m*/*z* (−ES) 1255.800 ([MNa$_2$/2]$^+$, $C_{77}H_{112}O_{16}Na$ requires 1255.785).

5,11,17,23,29,35,41,47-Octa-*tert*-octyl-49,50,51,52,53,54,55,56-octakis(3,6,9-trioxadecyloxy)calix[8]arene 20

The reaction was carried out as described above using **10** (51 mg, 0.022 mmol) to give **20** as an oil (30 mg, 47%): λ_{max}/nm (1 M KOH in MeOH) 277, 270, 235; δ_H(300 MHz; $CDCl_3$) 0.53–0.82 (72H, m, C(CH_3)$_3$), 0.99–1.35 (48H, m, CH$_2$-C(CH_3)$_2$), 1.45–1.75 (16H, m, CH_2C(CH$_3$)$_2$), 3.35 (24H, s, OCH_3), 3.42–3.90 (136H, m, OCH_2 and CH_2 bridge), 6.69–7.20 (16H, m, ArH); δ_C(75 MHz; $CDCl_3$) 30.3 (*C*H$_2$ bridge), 31.9 (signals superimposed), 38.0 (*C*(CH$_3$)$_2$), 57.3 (^{t}octyl CH$_2$), 59.0 (O*C*H$_3$), 70.4–70.6 (signals superimposed), 72.0, 126.9 (*C*H), 132.9, 145.2 and 153.2; *m*/*z* (+ES) 2957.5 ([MNa$_2$ − 3H]$^+$. $C_{176}H_{285}O_{32}Na_2$ requires 2957.1).

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54,55,56-octakis[17-(2*H*-tetrahydropyran-2-yloxy)-3,6,9,12,15-pentaoxaheptadecyloxy]calix[8]arene 21

The reaction was carried out as described above using **13** (187 mg, 0.070 mmol) to give **21** as an oil (150 mg, 55%): λ_{max}/nm (1 M KOH in MeOH) 280, 270, 235; ν_{max}(film)/cm^{-1} 2869, 1458, 1353; δ_H(300 MHz; $CDCl_3$) 0.74–1.40 (72H, m, C(CH_3)$_3$), 1.40–1.90 (48H, m, CH_2-THP), 3.39–4.04 (208H, m, CH_2O and CH_2 bridge), 4.59 (8H, m, C*H*O), 6.66–7.09 (16H, m, ArH); δ_C(75 MHz; $CDCl_3$) 19.4, 25.4, 30.1, 30.7 (*C*H$_2$ bridge), 31.5 (C(*C*H$_3$)$_3$), 34.1 (*C*(CH$_3$)$_3$), 62.1, 66.6, 70.4–70.6 (signals superimposed), 72.5, 98.8 (*C*HO), 125.6 (*C*H), 133.1, 145.9, 152.7; *m*/*z* (MALDI-TOF) 3935.1 ([MNa − 2THP]$^+$, $C_{214}H_{350}O_{62}Na$ requires 3935.4).

5,11,17,23,29,35,41,47-Octa-*tert*-octyl-49,50,51,52,53,54,55,56-octakis[17-(2*H*-tetrahydropyran-2-yloxy)-3,6,9,12,15-pentaoxaheptadecyloxy]calix[8]arene 22

The reaction was carried out as described above using **14** (195 mg, 0.062 mmol) to give **22** as an oil (180 mg, 64%): λ_{max}/nm (1 M KOH in MeOH) 278, 270, 230; δ_H(300 MHz; $CDCl_3$) 0.49–0.88 (72H, m, C(CH_3)$_3$), 0.98–1.39 (48H, m, CH$_2$C(CH_3)$_2$), 1.45–1.88 (64H, m, CH_2C(CH$_3$)$_2$ + CH_2-THP), 3.38–3.99 (224H, m, CH_2O and CH_2 bridge), 4.61 (8H, dd, *J* 3.2 and 3.2 Hz, C*H*O), 6.55–7.11 (16H, m, ArH); δ_C(75 MHz; $CDCl_3$) 19.3, 25.3, 30.4, 31.7–32.2 (signals superimposed), 37.9 (*C*(CH$_3$)$_2$), 56.8 (^{t}octyl CH$_2$), 62.0, 66.5, 70.0–70.4 (signals superimposed), 72.2, 126.4 (*C*H), 132.5, 144.9 and 153.0; *m*/*z* (MALDI-TOF) 4362 ([MH − 2THP]$^+$, $C_{246}H_{414}O_{62}$ requires 4361.9).

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexakis-[17-(2*H*-tetrahydropyran-2-yloxy)-3,6,9,12,15-pentaoxaheptadecyloxy]calix[6]arene 23

The reaction was carried out as described above using **15** (598 mg, 0.30 mmol) to give **23** as an oil (635 mg, 70%): δ_H(300 MHz;

$CDCl_3$) 0.92–1.85 (102H, m, $C(CH_3)_3$), 3.42–3.95 (168H, m, CH_2O and CH_2 bridge), 4.61 (6H, m, CHO), 6.65–7.15 (12H, m, ArH); δ_C(75 MHz; $CDCl_3$) 19.2, 25.2, 29.4, 31.4 (signals superimposed), 33.9 ($C(CH_3)_3$), 61.9, 66.4, 69.8–70.3 (signals superimposed), 98.7 (CHO), 125.3 (CH), 133.2, 145.2 and 152.9; *m*/*z* (MALDI-TOF) 3062 (M^+, $C_{168}H_{276}O_{48}$ requires 3061.9).

THP deprotection of fully alkylated *p-tert*-butylcalix[8]arene and *p-tert*-butylcalix[6]arene

The calixarenes **21** or **23** were stirred in dichloromethane–methanol (50 : 50, 10 ml) containing 10% conc. HCl for 3 h at rt. Sodium hydrogencarbonate was added to neutralise the solution and the solvent removed *in vacuo*. The product was suspended in ethyl acetate and the inorganic salts removed by filtration. The ethyl acetate was then removed *in vacuo* to reveal the deprotected calixarenes.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54,55,56-octakis(17-hydroxy-3,6,9,12,15-pentaoxaheptadecyloxy)-calix[8]arene 24

Compound **21** (150 mg, 0.038 mmol) was deprotected as described above to give **24** as an oil (124 mg, 95%): δ_H(300 MHz; $CDCl_3$) 0.92–1.25 (72H, m, $C(CH_3)_3$), 2.75–3.15 (8H, br s CH_2OH), 3.40–3.77 (192H, m, CH_2O), 3.82–4.05 (16H, br m, CH_2 bridge), 6.81–7.12 (16H, m, ArH); δ_C(75 MHz; $CDCl_3$) 31.5 (signals superimposed), 33.8 ($C(CH_3)_3$), 62.6, 70.2–70.5 (signals superimposed), 72.5, 125.3 (CH) 132.6, 145.3, 152.6; *m*/*z* (MALDI-TOF) 3432.6 ([MNa-H]$^+$. $C_{184}H_{303}O_{56}Na$ requires 3432.1).

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexakis-(17-hydroxy-3,6,9,12,15-pentaoxaheptadecyloxy)calix[6]arene 25

Compound **23** (77 mg, 0.025 mmol) was deprotected as described above to give **25** as an oil (59 mg, 92%): δ_H(300 MHz; $CDCl_3$) 0.92–1.34 (54H, m, $C(CH_3)_3$), 2.87 (6H, s, OH) 3.48–3.88 (156H, m, CH_2O and CH_2 bridge), 6.61–7.15 (12H, m, ArH); δ_C(75 MHz; $CDCl_3$) 29.2 (CH_2 bridge), 31.4 ($C(CH_3)_3$), 33.9 ($C(CH_3)_3$), 61.5, 70.2–70.5 (signals superimposed), 72.5, 125.6 (CH) 132.9, 145.2; *m*/*z* (−ES) 2579.5 (M^+, $C_{138}H_{227}O_{42}Na$ requires 2579.6).

35-(2*H*-Tetrahydropyran-2-yloxy)-3,6,9,12,15,18,21,24,27,30,33-undecaoxapentatriacontyl methanesulfonate 26

To sodium hydride (60% dispersion in mineral oil; 477 mg, 11.9 mmol) was added hexaethylene glycol THP ether[21] (2.91 g, 7.95 mmol) in THF (60 ml) and the solution was stirred at 0 °C for 10 min. Hexaethylene glycol bis(methanesulfonate)[20] (6.96 g, 15.9 mmol) in THF (5 ml) was then added and the reaction was stirred at 70 °C for 4 d. The reaction was quenched with water (2 ml) and extracted into dichloromethane (3 × 50 ml), dried (sodium sulfate) then evaporated to give a yellow oil. The product was purified using reverse phase chromatography (gradient: water–acetonitrile, 100% water to 100% acetonitrile) to give the title compound (2.82 g, 50%): ν_{max}(film)/cm^{-1} 2928s, 1480s, 1380s; δ_H(300 MHz; $CDCl_3$) 1.26–1.80 (6H, m, CH_2-THP), 3.01 (3H, s, CH_3), 3.36–3.69 (44H, m), 3.78 (2H, m, CH_2CH_2OMs), 4.32 (2H, m, CH_2OMs), 4.54 (1H, dd, *J* 3.9 and 3.1 Hz, CHO); δ_C(75 MHz; $CDCl_3$) 19.3, 25.2, 30.4, 37.5 (CH_3), 62.0, 66.5, 68.9, 69.2, 70.4 (signal overlap), 98.8; *m*/*z* (+ES) 731.52 (MNa^+, 65%), 490 (73), 473 (100).

35-(2*H*-Tetrahydropyran-2-yloxy)-3,6,9,12,15,18,21,24,27,30,33-undecaoxapentatriacontyl iodide 27

To **26** (4.00 g, 5.65 mmol), in acetone (40 ml) was added sodium iodide (8.47 g, 56.5 mmol) and the reaction was heated at reflux for 4 d. After filtration the filtrate was concentrated *in vacuo,* redissolved in dichloromethane and any remaining salt was removed by filtration. The removal of solvent *in vacuo* and NMR analysis revealed some loss of the THP protecting group. This material was therefore directly reprotected.

To the intermediate (3.80 g, approx. 5.1 mmol) in dichloromethane (50 ml) was added 3,4-dihydro-2*H*-pyran (0.428 g, 5.1 mmol) and toluenesulfonic acid (104 mg, 0.51 mmol) and the reaction was stirred for 18 h. The mixture was washed with water (2 ml), the organic phase dried (sodium sulfate) and evaporated *in vacuo* to give **27** as a viscous oil (3.70 g, 90%) which was used immediately: ν_{max}(film)/cm^{-1} 2942s, 1471s, 1351s; δ_H(300 MHz; $CDCl_3$) 1.41–1.83 (6H, m, CH_2-THP), 3.20 (2H, t, *J* 6.9 Hz, CH_2I), 3.53–3.83 (48H, m, CH_2O), 4.57 (1H, dd, *J* 3.4 and 3.3 Hz, CHO); δ_C(75 MHz; $CDCl_3$) 3.4 (CH_2I), 19.3, 24.8, 29.6, 53.3, 64.3, 66.9, 67.1, 68.3–69.4 (signal overlap), 71.7, 100.6 (CHO); *m*/*z* (+ES) 763.27 (MNa^+, 30%), 473 (100).

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,51,53,55-tetrakis-(35-hydroxy-3,6,9,12,15,18,21,24,27,30,33-undecaoxapenta-triacontyloxy)-50,52,54, 56-tetrahydroxycalix[8]arene 29

The tetraalkylation using iodododecaethylene glycol THP ether **27** was carried out as described above to give **28** as a viscous oil (650 mg, 45%). However, not all residual **27** (approx. 10%) could be removed by alumina chromatography (gradient: ethyl acetate–methanol). Therefore, after initial NMR analysis (see below) to confirm the selectivity, the material was directly deprotected: δ_H(300 MHz; $CDCl_3$) 0.95–1.28 (72H, m, $C(CH_3)_3$), 1.47–1.79 (24H, m, CH_2-THP), 3.33–4.06 (216H, m, CH_2O and CH_2 bridge), 4.61 (4H, dd, *J* 3.9 and 2.9 Hz, CHO), 6.74–7.12 (16H, m, ArH); δ_C(75 MHz; $CDCl_3$) 19.1, 25.1, 30.2 (signals superimposed), 31.0 and 31.2 (2 × $C(CH_3)_3$), 33.5 and 33.7 (2 × $C(CH_3)_3$), 61.8, 66.3, 69.7–70.2 (signals superimposed), 72.2, 98.5 (CHO), 125.1 (CH), 132.5.

Compound **28** (325 mg, 0.09 mmol) was deprotected as described above and purified using alumina chromatography (gradient: ethyl acetate–methanol) to give **29** as an oil (169 mg, 55%): δ_H(300 MHz; $CDCl_3$) 0.95–1.26 (72H, m, $C(CH_3)_3$), 2.65 (4H, s, CH_2OH), 3.36–3.09 (208H, m, CH_2O and CH_2 bridge), 6.74–7.10 (16H, m, ArH); δ_C(75 MHz; $CDCl_3$) 29.7 (CH_2 bridge), 31.3 and 31.6 (2 × $C(CH_3)_3$), 33.9 and 34.1 (2 × $C(CH_3)_3$), 61.8, 70.3–70.6 (signals superimposed), 72.6, 125.5 (CH), 132.9, 145.7; *m*/*z* (+ES) 3368.158 ([M − C_2H_2O]$^+$, $C_{278}H_{494}O_{103}$ requires 3368.083).

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54,55,56-octakis(35-hydroxy-3,6,9,12,15,18,21,24,27,30,33-undecaoxa-pentatriacontyloxy)calix[8]arene 30

The full alkylation reaction was carried out as described above using **28**, and the material was directly deprotected by alumina chromatography (gradient: ethyl acetate–methanol) to give **30** as an oil (134 mg, 27% over the two steps): λ_{max}/nm (1 M KOH in MeOH) 280, 270, 235; δ_H(300 MHz; $CDCl_3$) 0.80–1.41 (72H, m, $C(CH_3)_3$), 3.51–3.76 (400H, m, CH_2O and CH_2 bridge), 6.72–7.12 (16H, m, ArH); δ_C(75 MHz; $CDCl_3$) 29.4 (CH_2 bridge), 31.1 ($C(CH_3)_3$), 33.8 ($C(CH_3)_3$), 61.4, 70.0–70.2 (signals superimposed), 72.3, 125.5, 133.0, 145.8.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,51,53,55-tetrakis-(20-acetoxy-3,6,9,12,15-pentaoxaheptadecyloxy)-50,52,54,56-tetrahydroxycalix[8]arene 31

To sodium hydride (60% dispersion in mineral oil; 83 mg, 2.2 mmol) in THF (20 ml) was added **16** (118 mg, 0.05 mmol) and acetyl chloride (85 mg, 1.1 mmol) and the reaction was stirred for 24 h. The reaction was quenched with water (5 ml) and the product extracted into ethyl acetate (3 × 20 ml), dried (sodium sulfate) and evaporated. The product was purified

using a neutral alumina column (gradient: ethyl acetate–methanol) to give **31** as an oil (68 mg, 54%): λ_{max}/nm (1 M KOH in MeOH) 300, 280, 270, 235; δ_H(300 MHz; $CDCl_3$) 0.65–1.30 (72H, m, $C(CH_3)_3$), 2.04 (12H, s, CH_3CO), 3.35–4.15 (104H, m, CH_2O and CH_2 bridge), 4.18 (8H, t, *J* 4.8 Hz, CH_2OCOMe), 6.73–7.15 (16H, m, ArH); δ_C(75 MHz; $CDCl_3$) 20.9 ($COCH_3$), 29.5 (CH_2 bridge), 31.4 ($C(CH_3)_3$, br), 34.1 and 34.3 (2 × $C(CH_3)_3$), 63.6, 69.1, 70.5 (several signals superimposed), 72.8, 125.4 (CH, br), 133.1, 145.7, 153.1, 171.0; *m*/*z* (−ES) 2521.0 (M^+, $C_{144}H_{216}O_{36}$ requires 2521.4).

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,51,53,55-tetra-[17-(2*H*-tetrahydropyran-2-yloxy)-3,6,9,12,15-pentaoxaheptadecyloxy]-50,52,54,56-tetraacetoxycalix[8]arene 32

To **13** (200 mg, 0.074 mmol) in THF (20 ml) were added triethylamine (75 mg, 0.74 mmol) and acetyl chloride (58 mg, 0.74 mmol) and the reaction was stirred for 24 h. The reaction was quenched with water (5 ml) and the product extracted into ethyl acetate (3 × 20 ml), dried (sodium sulfate) and evaporated. The product was purified using a neutral alumina column (gradient: ethyl acetate–methanol) to give **32** (70 mg, 33%): δ_H(300 MHz; $CDCl_3$) 0.90–1.33 (72H, m, $C(CH_3)_3$), 1.43–1.97 (24H, m, CH_2-THP), 2.06 (12H, s, CH_3CO), 3.43–4.05 (112H, m, CH_2O and CH_2 bridge), 4.61 (4H, m, CHO), 6.65–7.18 (16H, m, ArH); δ_C(75 MHz; $CDCl_3$) 19.5, 20.2 ($COCH_3$), 25.4, 30.6, 30.9–31.8 (signals superimposed), 34.1 and 34.3 (2 × $C(CH_3)_3$), 62.2, 66.6, 70.6 (several signals superimposed), 72.5, 98.9, 125.8 (CH, br), 131.3 and 132.7, 145.2 and 145.9, 148.2 and 153.1, 168.9; *m*/*z* (−ES) 2820.6 ([MNa − $C_2H_4O_2$]$^+$, $C_{162}H_{244}O_{38}Na$ requires 2820.7).

Acknowledgements

We are grateful to the BBSRC for financial support (grant 31/B10963 for D. U. H., G. H and A.-C. H.) and to Glaxo Smith-Kline (Action TB programme) for a studentship (to K. J. G). We thank James Stygall and Matthias Witt for help with obtaining MS data and the ULIRS Mass Spectrometry Facility at the University of London School of Pharmacy for MS services.

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