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Preparation of macrocyclon analogues: calix[8]arenes with extended polyethylene glycol chains

François A. Loiseau,[a,†] Alison M. Hill[b] and King Kuok (Mimi) Hii[a,*]

[a]*Department of Chemistry, Imperial College London, Exhibition Road, South Kensington SW7 2AZ, UK*
[b]*School of Biosciences, University of Exeter, Stocker Road, Exeter EX4 4QD, UK*

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Abstract—A one-pot methodology has been developed for the preparation of macrocyclon mimics, i.e., calix[8]arenes containing hydrophobic alkyl substituents on the upper rim and hydrophilic polyethylene glycol chains on the lower rim. Compounds containing PEG chains of up to 24 repeating ethylene oxide (EO) units can be prepared. With increasing molecular weight, these amphiphilic compounds can be classified as macromolecules, and can be difficult to characterise as single molecules. The limitations of conventional analytical techniques are discussed.

1. Introduction

Tuberculosis (TB) is one of the oldest diseases, yet it remains among the top ten causes of death in the World. Declared in 2006 as a growing global pandemic by the World Health Organization, the TB bacilli is estimated to be carried by one-third of the global population, with a rate of one infection per second and causes 5000 deaths every day.[1] Tragically, it is particularly prevalent amongst the impoverished communities in developing and developed countries; largely due to rapid global demographic changes and the HIV epidemic, which allow the disease to spread quickly. The problem is compounded by the inadequate implementation of TB therapy, which led to the recurrence of the disease, as well as the development of drug resistant (DR) and multi-drug resistant (MDR) TB,[2] fueling demands for more effective drug therapies to combat the disease.[3]

In 1951, Cornforth and co-workers discovered a non-ionic surface-active agent that suppresses experimental tuberculosis in mice. This led to the examination of compounds with analogous structures as anti-tuberculosis agents.[4] The precursors were synthesised by the condensation of *tert*-alkyl substituted phenols with formaldehyde, to afford crystalline substances, from which high-melting compounds HOC and HBC (High Octyl and Butyl Compounds, respectively) were isolated.

The condensation of HOC with 45–50 molecules of ethylene oxide under alkaline conditions produced a water-soluble derivative, which was non-toxic and exhibits greater anti-tuberculosis activity than Streptomycin. Given the name of *macrocyclon*, the compound was originally thought to be conformational isomers of cyclic calix[4]arenes containing glycol chains of between 10 and 12.5 ethylene oxide units. Subsequently, work by Gutsche and co-workers[5] established that HOC and HBC are, in fact, calix[8]arene derivatives. Thus, the structure of macrocyclon has been revised to contain a *p*-octyl-calix[8]arene, flanked by highly substituted alkyl groups on the upper rim and variable polyethylene glycol chains on the lower rim (Fig. 1).

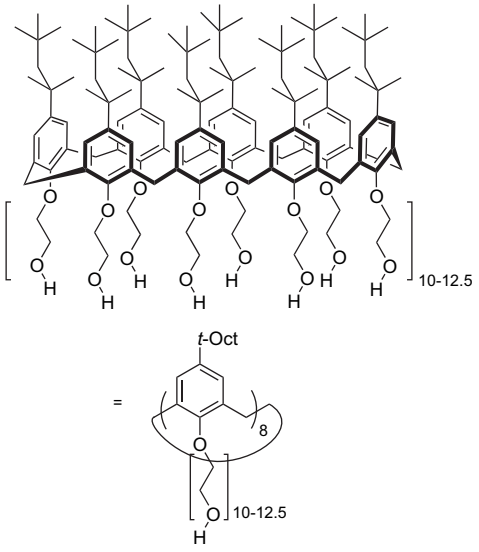

Figure 1. Proposed structure of macrocyclon.

* Corresponding author. E-mail: mimi.hii@imperial.ac.uk
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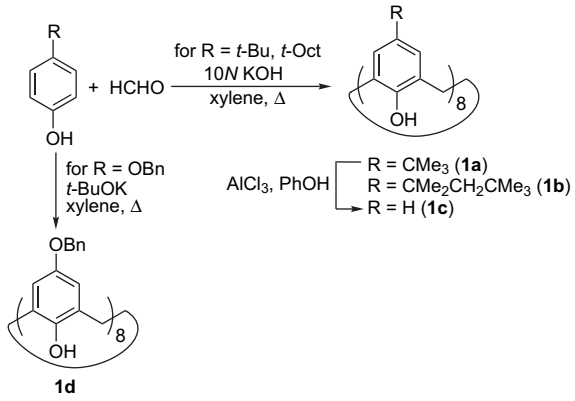
More recently, biological studies showed that macrocyclon exhibits a novel mechanism of action that is different from drugs currently used against tuberculosis.[6] This has re-ignited substantial interest in the molecule as an exciting therapeutic candidate for the treatment of MDR-TB.

In the original work by Cornforth, the length of the polyethylene glycol chain was reported to have a profound effect on the tuberculostatic properties.[7] The objective of our project is to synthesise a series of macrocyclon analogues, with systematic variations in the *p*-substituent (R), the terminal group (R') and the chain length (*n*), such that the biological effect of each of these components can be delineated by SAR studies.

2. Results and discussion

2.1. Synthesis of calix[8]arenes

Following published procedures, *p*-*tert*-butylcalix[8]arene **1a** and *p*-*tert*-octylcalix[8]arene **1b** were prepared on a large scale by condensing the corresponding *p*-alkylphenol and formaldehyde in a basic solution (Scheme 1).[8] From **1a**, the unsubstituted *p*-*H*-calix[8]arene **1c** can be prepared in 88% yield by a reverse Friedel–Craft reaction.[9] On the other hand, *O*-substituted calix[8]arenes allow the attachment of PEG chains on both upper and lower rims. The corresponding reaction between *p*-benzyloxyphenol and formaldehyde required an elevated temperature (170 °C), which led to an unpredictable exothermic reaction. This can be avoided by using an alternative procedure with a stronger base (*t*-BuOK) and a different reaction stoichiometry, allowing the reaction to proceed smoothly at 150 °C to furnish **1d** in 61% yield.[10]

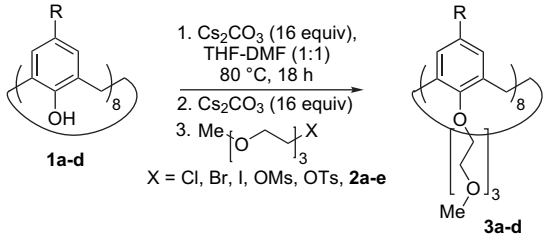


Scheme 1. Synthesis of various calix[8]arenes.

2.2. PEGylation of calix[8]arenes: reaction optimisation

The full functionalisation of calix[8]arenes at the lower rim can be dependant on the nature of the *p*-substituent, as well as the choice of base and electrophiles. The reaction outcome is not always very predictable and, very often, only partial functionalisation can be achieved. To date, the attachment of eight [*n*]ethylene glycols has been reported only once before,[11] which was achieved in two steps, employing different bases in each: K_2CO_3 was used in the first step to furnish a partially functionalised macrocycle, followed by NaH to deprotonate the remaining phenolic units in the second step. Each PEGylation required 4 days, and column chromatography was required for the purification of the partially functionalised intermediate.

In earlier work, we observed that longer polyethylene glycol chains are unstable and are prone to elimination reactions in the presence of strong bases such as *t*-BuOK and NaH.[12] With this in mind, we investigated the use of Cs_2CO_3 as a milder base, which has been shown to deprotonate calix[8]arenes slowly at multiple sites.[13] Consequently, calix[8]arenes **1a–d** was treated twice with Cs_2CO_3 (2×16 equiv) over 24 h to allow full deprotonation to take place. MeO–PEG_3–X of 16 equiv (**2a–e**, where X=Cl, Br, I, OMs and OTs, respectively) was subsequently added and the reaction mixture was refluxed for 3 days (Scheme 2, Table 1).



Scheme 2. PEGylation of calix[8]arenes.

The results show, unequivocally, that iodide derivatives afford the best yield of the fully PEGylated calix[8]arene. A slightly lower yield was achieved using the bromide precursor under Finkelstein conditions (Table 1, entry 9). The results also suggest that the *p*-substituent of the calix[8]arene ring exerts little influence on these reactions (entries 3, 6, 10 and 15). Subsequent examination of reaction stoichiometry revealed that the amount of electrophile can be reduced to 10 equiv (equating to 1.25 equiv of PEG for each phenolic unit) without significant erosion in yield. Further increase in reaction time and amount of base did not lead to any

Table 1. Effect of nucleofuges[a]

Entry	R	X	Product	Yield[b] (%)	*m/z*[c]
1	*t*-Bu (**1a**)	OTs	**3a**	44	2488.7 (F)
2	*t*-Bu (**1a**)	Br	**3a**	46	
3	*t*-Bu (**1a**)	I	**3a**	61	
4	*t*-Oct (**1b**)	OTs	**3b**	37	2937.2 (E)
5	*t*-Oct (**1b**)	Br	**3b**	44	
6	*t*-Oct (**1b**)	I	**3b**	56	
7	H (**1c**)	Cl	**3c**	19	2040.2 (E)
8	H (**1c**)	Br	**3c**	54	
9	H (**1c**)	Br[d]	**3c**	68	
10	H (**1c**)	I	**3c**	74	
11	H (**1c**)	OMs	**3c**	38	
12	H (**1c**)	OTs	**3c**	53	
13	OBn (**1d**)	OTs	**3d**	35	2887.1 (F)
14	OBn (**1d**)	Br	**3d**	48	
15	OBn (**1d**)	I	**3d**	69	

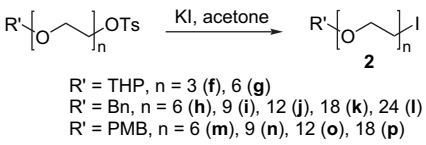
[a] Calixarene (1 equiv), THF/DMF (1:1), Cs_2CO_3 (2×16 equiv), electrophile (16 equiv).
[b] Isolated yields following purification by column chromatography.
[c] Observed molecular ion: F=FAB; E=Electrospray.
[d] KI of 16 equiv was added with the electrophile.

improvement. On the other hand, replacement of Cs_2CO_3 by other bases ($MgCO_3$, $CaCO_3$, Na_2CO_3, K_2CO_3, KOH, CsOH, *t*-BuOK, NaH and KH) led to much lower yields (Supplementary data), suggesting that the presence of caesium is crucial, probably by exerting a template effect through complexation with phenolic and/or ether oxygen.[14]

Compared to the previous procedure, the new synthetic method has several advantages: it is conducted in one-pot using a single base, effectively halving the reaction time. Furthermore, it offers a better yield, demonstrated by comparing the isolated yields obtained for compounds **3a** and **3b** (Table 1, entries 3 and 6), which are 2–3 times greater than that previously achieved using the two-step procedure (yields of 30% and 19%, respectively). The products **3a–d** can be purified by flash chromatography on silica gel. These compounds were fully characterised by ^1H and ^{13}C NMR spectroscopy, and MS analysis showed the molecular ions as sodium adducts.

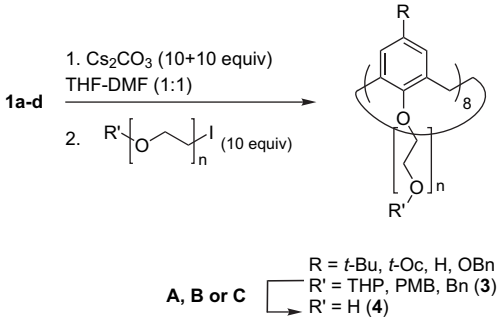
2.3. Macrocyclon analogues containing PEG_{3-6}

To access the target molecules, iodo precursors $R'(OCH_2CH_2)_nI$ (**2f–p**, where n=3–24) were prepared by the treatment of the corresponding monotosylates[12] with potassium iodide (Scheme 3). All of these reactions proceeded smoothly in yields of >90%.



Scheme 3. Preparation of iodide precursors **2f–p**. PMB=*p*-methoxybenzyl ($4\text{-}MeOC_6H_4CH_2$).

With the precursors in hand, a library of 30 PEGylated calix[8]arenes was initially assembled under optimised reaction conditions. Some of these can be deprotected to release terminal OH groups, giving a further 16 functionalised calix[8]arenes (Scheme 4, Table 2).



Scheme 4. PEGylation of calix[8]arenes and deprotection of the PEG chain. Condition **A** (R=THP): HCl, CH_2Cl_2/CH_3OH (1:1), 4 h, rt; condition **B** (R=PMB): cerium ammonium nitrate (20 equiv), CH_3CN/CH_3OH (4:1), 6 h, rt; condition **C**: 20% $Pd(OH)_2/C$, EtOH, 1,4-cyclohexadiene, 18 h, reflux.

During the course of this work, the choice of the protecting group was found to dictate the length of the ethylene glycol chain that can be used in the reaction. Hence, for the purpose of this discussion, the products are classified according to length of the PEG chain (n) and its protecting group (R').

Unsymmetrical $THP(OCH_2CH_2)_nI$ were initially used to furnish calix[8]arenes up to 4500 Da, where n=3 and 6 (Table 2, entries 1–8). Moderate to good yields of compounds **3e–l** can be obtained and their NMR spectra can be recorded with good resolution, to enable accurate integration of the proton signals that reflects the extent of functionalisation. The integrity of the terminal THP protecting group can be further verified by ^{13}C NMR spectroscopy, as the methylene signal adjacent to the protecting group (CH_2OTHP, 67 ppm) shifts upfield to 62 ppm upon cleavage to CH_2OH.

The THP ether can then be removed by treatment with acid, to give compounds **4a–h** (Table 2, entries 9–16). Much better yields were obtained by employing non-aqueous conditions, to minimise loss of the water-soluble product during work-up. The structures of these unprotected compounds were characterised by UV–vis, NMR and mass spectrometry.

As was observed by other researchers, the purity of the products cannot be established by elemental analysis reliably, as they are prone to absorb atmospheric H_2O and CO_2.[15] In the present case, the problem is exacerbated by the presence of polyethylene glycol chains, which enhanced the hydrophilicity of the calix[8]arenes. Thus, to ensure homogeneity, the compounds were subjected to repeated column chromatography. Depending on the length of the PEG chain attached to the calix[8]arene, up to four chromatographic runs may be necessary to ensure the purity of the sample. The first column was to remove starting materials, followed by further chromatographic runs until a homogeneous sample can be obtained, as indicated by TLC analysis. The presence of any unreacted phenolic units was cross-checked by performing UV–vis spectrometry: PEGylated calix[*n*]arenes exhibit a pair of UV absorption bands around 270 and 280 nm. The addition of a base such as KOH deprotonates any unreacted phenolic moieties, causing a distinctive bathochromic shift to 300 nm.[7]

Interesting observations were made during the analysis of these molecules by mass spectrometry: FAB ionisation was mostly incompatible with these compounds, as it caused many of the molecular mass ions to undergo extensive fragmentation. Thus, in most cases, ESI is a more suitable technique for establishing molecular identities. Even so, the loss of the THP (entries 1, 2, 5, 6 and 8) or ethylene oxide (entries 13–15) units was inevitable in some cases. The interpretation of the ESI-MS spectra can be further complicated by the occurrence of multiply charged ions and the formation of Na adducts. Employment of the MALDI technique failed to deliver a better alternative: In addition to interference of adduct ions, the THP groups are generally unstable, giving rise to fragmented ions in the spectra. For example, the spectrum of compound **3i** (M^+=4097.5) showed the molecular ion as a weak sodium adduct ion complexed with α-CHCA (α-cyano-4-hydroxycinnamic acid, used to generate the matrix), accompanied by fragmented ions in a recurring pattern of 84 amu apart—corresponding to the successive loss of C_5H_8O (dihydropyran) units (Fig. 2). In comparison, analysis of this compound by ESI-MS revealed a doubly charged

Table 2. Calix[8]arenes with PEG_{3-6} chains[a]

Entry	R	R′	*n*	Yield (%)	*m/z* (observed)[b]	*m/z* (calculated)[c]	Assignment
1	*t*-Bu	THP	3	55 (**3e**)	2963.7 (ET)	2962.8	$[MNa-C_5H_9O_2]^+$
2	*t*-Oct	THP	3	58 (**3f**)	1675.15 (E)	1674.65	$[MNa_2-C_5H_9O-C_5H_9O_2]^{2+}$
3	H	THP	3	63 (**3g**)	2578.6 (F)	2578.4	$[MH]^+$
4	OBn	THP	3	49 (**3h**)	3363.4 (F)	3363.7	$[MNa-C_5H_9]^+$
5	*t*-Bu	THP	6	43 (**3i**)	1979.0 (E)	1979.2	$[MNa_2-C_5H_8O-C_5H_9O_2]^{2+}$
6	*t*-Oct	THP	6	50 (**3j**)	2203.4 (E)	2203.4	$[MNa_2-C_5H_8O-C_5H_9O_2]^{2+}$
7	H	THP	6	48 (**3k**)	1825.5 (E)	1825.5	$[M+H_2O-H]^{2+}$
8	OBn	THP	6	51 (**3l**)	2179.1 (E)	2179.1	$[MNa_2-2C_5H_9O]^{2+}$
9	*t*-Bu	H	3	82 (**4a**)	2376.8 (F)	2376.4	$[MK-CH_2OH]^+$
10	*t*-Oct	H	3	87 (**4b**)	1422.0 (E)	1422.0	$[M+Na+4H]^{2+}$
11	H	H	3	80 (**4c**)	1927.6 (F)	1927.9	$[MNa]^+$
12	OBn	H	3	84 (**4d**)	2776.0 (F)	2776.2	$[MNa]^+$
13	*t*-Bu	H	6	86 (**4e**)	3389.2 (E)	3389.1	$[MNa-C_2H_3O_2]^+$
14	*t*-Oct	H	6	86 (**4f**)	1930.3 (E)	1930.3	$[MNa_2-C_2H_3O_2]^{2+}$
15	H	H	6	81 (**4g**)	2940.6 (E)	2940.6	$[MNa-C_2H_4O]^+$
16	OBn	H	6	85 (**4h**)	1925.9 (E)	1924.4	$[MNa_2-H]^{2+}$

[a] Isolated yield of the purified compound. See Section 4 for general reaction conditions.
[b] Observed molecular ion. Ionisation technique given in parenthesis: F=FAB; E=ESI; ET=ES-TOF.
[c] Calculated from average atomic mass.

mass ion at 1979.0356 (Table 2, entry 5), corresponding to the di-sodium adduct with lost of C_5H_8O and OTHP groups.

Due to the high molecular weight, the assignment of multiply charged molecular ions obtained using ESI-MS can also be difficult based on calculated value of M^+. For example, the compound **4h** was detected as a doubly charged sodium adduct. A good match between relative isotopic distribution patterns of the observed and simulated ions indicates good monodispersity and purity of the compound (Fig. 3). However, given the large number of oxygen atoms present, the average mass calculated for the anticipated molecular species $[C_{208}H_{281}Na_2O_{64}]^{2+}$ (1924.4265) is lower than the simulated mass ion (1926.43), while the observed ion is found between these two values (1925.9253). This margin of uncertainty increases with molecular weight. As a result, an error of 1–2 Da can be easily accommodated within the resolution of the mass spectrum.

2.4. Macrocyclon analogues containing PEG_{6-12}

The fragility of the THP-protected compounds prompted us to utilise PMB and Bn protecting groups for the preparation of calix[8]arenes with longer [*n*]ethylene glycol chains (where $n \geq 6$). Moderate yields of the fully functionalised calix[8]arenes can be obtained (Table 3), and the resultant compounds are more stable than their THP analogues for MS analysis (Table 2, entry 12 vs Table 3, entries 1 and 8). Nevertheless, with molecular masses in excess of 4500 Da, structural characterisation of these compounds by NMR spectroscopy became problematic—by increasing the PEG chain length to ≥ 12, the spectra were dominated by intense

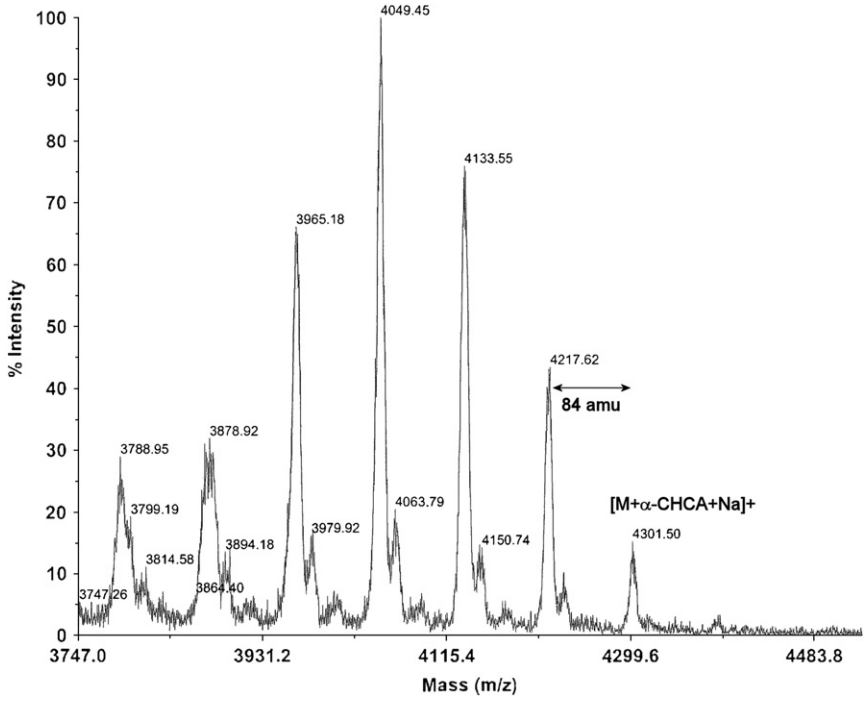


Figure 2. MALDI-TOF spectrum for **3i**, showing successive loss of THP protecting groups (84 amu).

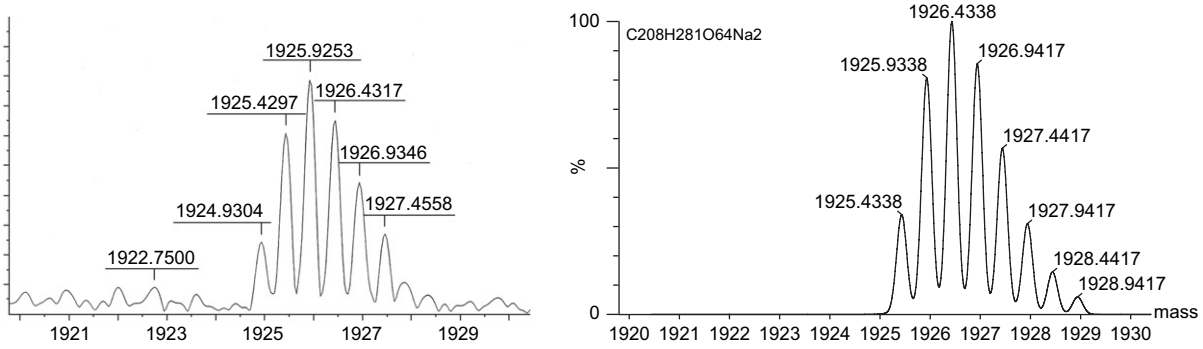


Figure 3. Observed (left) and simulated (right) isotopic distribution patterns for **4h** (a doubly charged Na adduct).

resonance signals of the ethereal protons. As a result, the aromatic protons of the benzyl protecting group or the core of the calix[8]arene were obscured, such that accurate integration was no longer possible. More problematically, slow molecular tumbling caused the appearance of resonance signals to become broad and featureless (see ^{1}H NMR spectrum of compound **3y** in Supplementary data). Attempts to improve the appearance of the spectra either by VT NMR (up to 60 °C) or by suppressing the ethereal protons' resonance signal, proved futile. The problem was even more pronounced in ^{13}C NMR spectra, where resonance signals of tertiary and quaternary carbons are practically invisible or unresolved. For example, the bridging methylene carbon of compound **3v** appeared as an extremely broad resonance signal at ca. 29 ppm (Supplementary data).

Hence, mass spectrometry remained as the chief characterisation technique for these compounds, in particular ESI and MALDI-TOF mass spectrometry, to provide the molecular composition of these large, involatile and amphilic molecules. Using the ESI technique, the molecular ions were mainly observed as multiply charged species, often as Na adducts. Where the analysis was complicated or ambiguous, MALDI-TOF was employed in a complementary manner, to provide singly charged ions. As before, the formation of adducts between molecular ions and Na are common. However, in some cases, fragment ions resulting from the interaction with α-CHCA were also observed[16] (Table 3, entries 1 and 5). The loss of a methyl group from the highly substituted upper rim was observed for some compounds (Table 3, entries 2, 6 and 11). Not all compounds are amenable to analysis by both ESI and MALDI-TOF techniques. For example, most dodecathyelene glycol derivatives could only be analysed by ESI, except **4m**, which was only observable using MALDI-TOF.

The PMB protecting groups can be removed using cerium ammonium nitrate (CAN), substituting the water used in the normal protocol by methanol, providing the hydroxy compounds **4i**–**n**. For compounds **3t**–**w**, a transfer hydrogenation protocol using Pearlman's catalyst, $Pd(OH)_2$, was applied for the removal of the benzyl group, whereas the benzyloxy groups present on the upper rim of calixarenes derived from **1d** were also transformed into phenolic units, to give compound **4o**.

Whilst the debenzylation works well for compounds containing up to PEG_9, the reaction of **3v**–**y** failed to deliver any products. For the *p*-benzyloxy substituted compound **3y**, neither OBn groups can be removed despite our best

Table 3. Functionalised calix[8]arenes with PEG_{6-12} chains (Scheme 4)

Entry	R	R′	*n*	Yield[a] (%)	*m*/*z*[b]	*m*/*z* (calculated)[c]	Assignment
1	OBn	PMB	6	52 (**3m**)	4799.8 (MT)	4799.4	$[M+COH^*]^+$
2	*t*-Bu	PMB	9	38 (**3n**)	2736.6 (E)	2736.6	$[MNa_2-CH_3]^{2+}$
3	*t*-Oct	PMB	9	42 (**3o**)	2958.7 (E)	2958.9	$[MNa+4H]^{2+}$
4	H	PMB	9	46 (**3p**)	2489.5 (E)	2490.3	$[MH_2]^{2+}$
5	OBn	PMB	9	37 (**3q**)	5916.8 (MT)	5916.0	$[M+C_7H_5^*]^+$
6	*t*-Bu	PMB	12	36 (**3r**)	3265.0 (E)	3264.9	$[MNa_2-CH_3]^{2+}$
7	OBn	PMB	12	34 (**3s**)	3483.0 (E)	3483.3	$[MNa_2K-2H]^{2+}$
8	OBn	Bn	6	45 (**3t**)	2288.1 (E)	2288.1	$[MNa_2]^{2+}$
9	OBn	Bn	9	43 (**3u**)	5587.7 (MT)	5587.9	$[MH]^+$
10	*t*-Bu	Bn	12	38 (**3v**)	3142.9 (E)	3142.9	$[MNa+4H]^{2+}$
11	*t*-Oct	Bn	12	33 (**3w**)	3369.2367 (E)	3369.1042	$[MNa_2-CH_3]^{2+}$
12	H	Bn	12	31 (**3x**)	2920.6 (E)	2920.6	$[MNa_2]^{2+}$
13	OBn	Bn	12	29 (**3y**)	3341.5 (E)	3341.8	$[MHNa]^{2+}$
14	*t*-Bu	H	9	73 (**4i**)	1554.1 (ET)	1554.2	$[McsNa_2+2H]^{3+}$
15	*t*-Oct	H	9	78 (**4j**)	2478.7 (E)	2478.6	$[MNa_2-H_2O-H]^{2+}$
16	H	H	9	81 (**4k**)	4069.9 (MT)	4069.2	$[MNa+2H+CN^*]^+$
17	OBn	H	9	75 (**4l**)	4889.3 (MT)	4889.5	$[MNa]^+$
18	*t*-Bu	H	12	68 (**4m**)	5614.2 (MT)	5613.4	$[MH+C_6H_3^*]^+$
19	OBn	H	12	65 (**4n**)	2940.8 (E)	2940.6	$[MNa_2-C_4H_8O_2]^{2+}$
20	OH	H	9	71 (**4o**)	2096.9 (E)	2096.6	$[MNa_2+H]^{2+}$

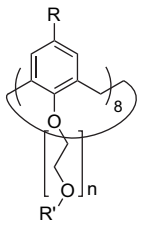
[a] Isolated yield of the purified compound. See Section 4 for general reaction conditions.
[b] Observed molecular ion. Ionisation technique given in parenthesis: F=FAB; E=ESI; ET=ES-TOF.
[c] Calculated from average atomic mass. *Fragment generated from α-CHCA.

efforts, including increasing the catalyst loading and prolonged reaction time (up to 3 days). We speculate that the physical properties of the compounds are, somehow, prohibiting the interaction of the *O*-benzyl moieties and the heterogeneous catalyst under these reaction conditions.

Yet again, the unprotected PEG derivatives **4i–o** were much less stable towards MS analysis, as the spectra were complicated by adduct formation and/or fragmentation of the molecular ions (Table 3, entries 17 and 18).

2.5. Macrocyclon analogues containing $PEG_{18–24}$

Finally, attempts were made to introduce even longer PEG_n chains (n=18 and 24). At this point of the synthesis, the reactions were extremely sluggish and decomposition of the elongated PEG chains became a competitive process. However, by employing the more stable benzyl-protected PEG iodides, the corresponding macromolecules can be obtained in low yields (Fig. 4, 9–24%).



n = 18, R = *t*-Bu, R' = Bn (**5a**), 24%
R = *t*-Oc, R' = Bn (**5b**), 17%
R = H, R' = Bn (**5c**), 21%
R = OBn, R' = PMB (**5d**),16%
R = OBn, R' = Bn (**5e**), 23%
R = OBn, R' = H (**5f**), 51%

n = 24, R = *t*-Bu, R' = Bn (**6a**), 18%
R = *t*-Oc, R' = Bn (**6b**), 12%
R = H, R' = Bn (**6c**), 19%
R = OBn, R' = Bn (**6d**), 9%

Figure 4. Calix[8]arenes containing PEG_{18} and PEG_{24} units.

The compounds can be purified by multiple column chromatography. Addition of KOH did not cause any shift in the UV absorption band, thus supporting the absence of free phenolic groups. With fully functionalised lower rims, molecular weights of these compounds range between 7.2 and 11 kDa, whereupon ESI and MALDI-TOF MS remain the only reliable characterisation techniques.[17] However, neither of these could provide the required molecular mass data. The propensity of these compounds to form multiple adducts prevented determination of mass ions by ESI-MS. On the other hand, very little or no molecular ion can be detected with MALDI-TOF. For example, close scrutiny of the spectrum recorded with compound **5b** revealed a poorly resolved peak at 9093.33 amu. However, the signal was too weak to allow resolution of the isotopic distribution pattern. We conclude that these compounds possess certain combinations of physical properties (amphiphilicity, ability to capture small molecules within its cavity, high molecular weight), which allow it to interact strongly with the matrix, and affected its detection by TOF.

The same physical properties may explain the failure of our subsequent attempts to remove the benzyl groups by hydrogenation. The only success was the synthesis of **5f** by the removal of the PMB group of **5d** was achieved in a comparatively low 51% yield.

3. Conclusion

This work demonstrates that calix[8]arenes can be fully derivatised at the lower rim with [*n*]ethylene glycol units, to a certain level, by using a one-pot procedure. This allows the systematic modification of the macrocyclon structure, containing different substitution at the upper rim and well-defined PEG_n chains (n=3, 6, 9, 12, 18 and 24) on the lower rim. Benzyloxy ether protecting groups are much more suitable than pyran ethers, as they are more stable during the reaction and subsequent analysis. Beyond a certain molecular weight and chain length (ca. n>12), the amphiphilic macromolecules are difficult to analyse due to their unique physical properties. Nevertheless, chemically distinct compounds that mimic the component mixture of macrocyclon can be produced.

Preliminary results of the anti-tuberculosis properties of some of these compounds have been previously communicated.[6] New compounds prepared in this project will be assessed, along with related compounds prepared by our collaborators in a separate program of work, to be reported in due course.

4. Experimental section

4.1. General

Reactions were performed using standard laboratory glassware (dried overnight in a hot oven, T>100 °C), or using a Radley's 12-place reaction carousel under an inert atmosphere. Commercially available reagents were purchased and used as received, unless otherwise indicated.

Calix[8]arenes **1a**,**b**,[8] **1c**,[9] **1d**,[10] **2a**,[18] **2b**,[19] **2d**,[20] **2e**[21] and unsymmetrical tosylated PEG's[12] were prepared according to the literature procedures. NMR spectra were acquired using a Bruker AM-360 spectrometer (operating frequencies of 360 and 90.5 MHz for ^{1}H and ^{13}C, respectively) and $CDCl_3$ as solvent. The peak positions are reported in parts per million (δ), ^{1}H NMR spectra were referenced to residual $CHCl_3$ in the solvent (δ_H 7.27), and ^{13}C to $CDCl_3$ (δ_C 77.00). Mass spectra were recorded using a Bruker APEC-III spectrometer for electrospray (ES) technique or a VG ZAB 2SE spectrometer for FAB (3-nitrobenzyl alcohol as the matrix). MALDI-TOF spectra were recorded by Mr. E. Samuel at the London School of Pharmacy, using an ABI-Voyager DE-STR mass spectrometer (using α-CHCA as the matrix). UV–vis spectra were recorded on a DU7400 Beckman Spectrometer using a thermostated (25 °C) quartz cell of 1 cm path length. Samples were prepared as solutions in methanol. Infrared spectra were recorded on a Perkin–Elmer FTIR Spectrum One spectrometer. Liquid samples were recorded as thin films between NaCl plates.

Characterisation data for novel compounds **2f–p**, **5a–f** and **6a–d**, tables summarising the result of reaction optimisation, including the choice and stoichiometry of base and selected ^{1}H (compounds **3a** and **3g**) and ^{13}C (compounds **3c**, **3g** and **3v**) NMR spectra are provided in the Supplementary data.

For brevity, the terminology of elongated polyethylene glycol chains suggested in our previous paper[12] is adopted here, i.e., the positions of oxygen atoms in the PEG chains are

denoted by the mathematical shorthand for arithmetic progressions, e.g., 1-benzyloxy-35-iodo-3n^3_{33}-undecaoxapentatriacontane (**2j**) refers to 35-benzyloxy-35-iodo-3,6,9,12,15,18,21,24,27,30,33-undecaoxapentatriacontane.

4.2. General procedure for the preparation of iodo-derivatives of polyethylene glycols (Scheme 2)

Sodium iodide (5 equiv) was added to a solution of the mono-protected tosylated glycol $R(OCH_2CH_2)_nOTs$[12] (R=THP, Bn or PMB, n=3–24, 1 equiv) in acetone and the solution was heated at reflux for 20–24 h. After this time, the inorganic salts were removed by filtration and the filtrate was concentrated under reduced pressure. The residue was dissolved in a mixture of EtOAc/H_2O (1:1, v/v) and separated. The combined organic extracts were washed with water and saturated aq sodium thiosulfate, dried over $MgSO_4$, filtered and evaporated under vacuum. The residue was purified by column chromatography. Full characterisation data for these compounds are provided in Supplementary data.

4.3. General procedure for the PEGylation of calix[8]arenes at the lower rim (Scheme 3)

Cs_2CO_3 (10 equiv) was added to a solution of the requisite calix[8]arene (1 equiv) in a mixture of DMF/THF (1:1, v/v) at 80 °C. After stirring for 18 h, another portion of Cs_2CO_3 (10 equiv) was added. After 6 h, a solution of the polyethylene glycol iodide (10 equiv) in THF was added dropwise via cannula. After 3 days, the reaction mixture was quenched by the addition of 1 N HCl until a clear solution was obtained and this was extracted with EtOAc. The organic extracts were combined and washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The remaining oil was purified by column chromatography.

4.3.1. 5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54,55,56-octakis-[8-methoxy-3n^3_6-dioxaoctyloxy]-calix[8]arene (3a).[11] Isolated as an orange oil, from *tert*-butylcalix[8]arene **1a** (0.50 g, 0.39 mmol) and I–PEG_3–OMe **2c** (1.06 g, 3.85 mmol). Yield: 57% (0.54 g). R_f 0.61 (EtOAc/hexane, 5:1). λ_{max}/nm 277 and 269; ν_{max} (film)/cm^{-1} 1114 (CO); δ_H: 0.89–0.98 (72H, m, 24×CH_3), 3.27 (24H, s, 8×OCH_3), 3.39–3.87 (96H, m, 40×CH_2O and 8×$ArCH_2Ar$), 3.93–3.96 (16H, m, 8×CH_2OCH_3), 6.81–6.83 (16H, m, 16×H_{meta}); δ_C: 30.1 (8×$ArCH_2Ar$), 31.4 (24×CH_3), 34.1 (8×$C(CH_3)_3$), 58.7 (8×OCH_3), 69.8–71.3 (40×CH_2O), 72.7 (8×CH_2O), 125.4 (16×C_{meta}), 133.8 (16×C_{ortho}), 145.9 (8×C_{para}), 154.9 (8×C_{ipso}); *m*/*z* (FAB) 2488.7 ($[MNa]^+$), $C_{144}H_{224}NaO_{32}$ requires 2488.6.

4.3.2. 5,11,17,23,29,35,41,47-Octa-*tert*-octyl-49,50,51,52,53,54,55,56-octakis-[8-methoxy-3n^3_6-dioxaoctyloxy]-calix[8]arene (3b).[11] Isolated as an orange oil, from *tert*-octylcalix[8]arene **1b** (0.50 g, 0.29 mmol) and I–PEG_3–OMe **2c** (0.78 g, 2.86 mmol). Yield: 54% (0.45 g). R_f 0.53 (EtOAc/hexane, 5:1). λ_{max}/nm 278 and 268; ν_{max} (film)/cm^{-1} 1104 (CO); δ_H: 0.64–0.77 (72H, m, 8×$(CH_3)_3$), 1.04–1.26 (48H, m, 8×$(CH_3)_2$), 1.41–1.59 (16H, m, 8×$CH_2C(CH_3)_3$), 3.28 (24H, s, 8×OCH_3), 3.41–3.98 (112H, m, 48×CH_2O and 8×$ArCH_2Ar$), 6.53–6.70 (16H, m, 16×H_{meta}); δ_C: 30.1 (8×$ArCH_2Ar$), 32.3–32.9 (40×CH_3 and 8×$C(CH_3)_3$), 38.0 (8×$C(CH_3)_2$), 57.4 (8×$CH_2C(CH_3)_3$), 59.1 (8×OCH_3), 70.0–71.3 (40×CH_2O), 72.8 (8×CH_2O), 126.4 (16×C_{meta}), 132.7 (16×C_{ortho}), 145.0 (8×C_{para}), 153.3 (8×C_{ipso}); *m*/*z* (ES) 2937.2084 ($[MNa^+]$), $C_{176}H_{288}NaO_{32}$ requires 2937.0931.

4.3.3. 5,11,17,23,29,35,41,47-Octakis-[8-methoxy-3n^3_6-dioxaoctyloxy]-calix[8]arene (3c). Isolated as an orange oil, from calix[8]arene **1c** (0.50 g, 0.59 mmol) and I–PEG_3–OMe **2c** (1.61 g, 5.89 mmol). Yield: 64% (0.76 g). R_f 0.63 (EtOAc/hexane, 4:1). Found: C, 66.65; H, 8.00. $C_{112}H_{160}O_{32}$ requires C, 66.65; H, 7.99%; λ_{max}/nm 276 and 268; ν_{max} (film)/cm^{-1} 1109 (CO) and 768 (CH); δ_H: 3.24 (24H, s, 8×OCH_3), 3.37–3.75 (80H, m, 32×CH_2O and 8×$ArCH_2Ar$), 3.80–3.82 (16H, m, 8×CH_2OCH_3), 3.99 (16H, s, 8×$ArOCH_2$), 6.62–6.83 (24H, m, 16×H_{meta} and 8×H_{para}); δ_C: 28.3 (8×$ArCH_2Ar$), 57.7 (8×OCH_3), 68.9–69.4 (32×CH_2O), 71.0 (8×CH_2O), 71.5 (8×CH_2O), 124.0 (8×C_{para}), 128.8 (16×C_{meta}), 134.2 (16×C_{ortho}), 154.9 (8×C_{ipso}); *m*/*z* (FAB) 2040.8 (MNa^+, 46%), 2018.7 ($[MH]^+$, 13), 265.1 (6) and 103.0 (100); *m*/*z* (ES) 2040.23 ($[MNa]^+$, $C_{112}H_{160}NaO_{32}$ requires 2040.08).

4.3.4. 5,11,17,23,29,35,41,47-Octa-benzyloxy-49,50,51,52,53,54,55,56-octakis-[8-methoxy-3n^3_6-dioxaoctyloxy]-calix[8]arene (3d). Isolated as an orange oil, from *p*-benzyloxycalix[8]arene **1d** (0.50 g, 0.29 mmol) and I–PEG_3–OMe **2c** (0.81 g, 2.94 mmol). Yield: 62% (0.52 g). R_f 0.49 (EtOAc/hexane, 4:1). λ_{max}/nm 278 and 269; ν_{max} (film)/cm^{-1} 1121 (CO); δ_H: 3.22 (24H, s, 8×OCH_3), 3.31–3.72 (96H, m, 40×CH_2O and 8×$ArCH_2Ar$), 3.89–3.90 (16H, m, 8×CH_2OCH_3), 4.52 (16H, s, 8×CH_2Ph), 6.42–6.53 (16H, m, 16×H_{meta}), 7.00–7.31 (40H, m, 8×H_{ortho}, H_{meta}, H_{para}); δ_C: 30.3 (8×$ArCH_2Ar$), 58.4 (8×OCH_3), 69.9–71.1 (40×CH_2O), 72.3 (8×CH_2O), 73.3 (8×CH_2Ph), 115.3 (16×C_{meta}), 127.9–128.8 (40×C_{ortho}, C_{meta}, C_{para}), 132.5 (16×C_{ortho}), 137.7 (8×C_{ipso}), 149.2 (8×C_{para}), 154.9 (8×C_{ipso}); *m*/*z* (FAB) 2887.1 ($[MNa]^+$), $C_{168}H_{208}NaO_{40}$ requires 2888.4.

4.3.5. 5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54,55,56-octakis-[8-(2*H*-tetrahydropyran-2-yloxy)-3n^3_6-dioxaoctyloxy]-calix[8]arene (3e). Isolated as an orange oil, from *tert*-butylcalix[8]arene **1a** (0.50 g, 0.39 mmol) and I–PEG_3–OTHP **2f** (1.32 g, 3.85 mmol). Yield: 55% (0.64 g). R_f 0.43 (EtOAc/hexane, 6:1). λ_{max}/nm 276 and 268; ν_{max} (film)/cm^{-1} 1098 (CO); δ_H: 0.86–1.01 (72H, m, 24×CH_3), 1.43–1.75 (48H, m, 8×H3, H4, H5), 3.52–3.82 (128H, m, 48×CH_2O, 8×$ArCH_2Ar$ and 8×H6), 4.54–4.58 (8H, m, 8×H2), 6.80–6.89 (16H, m, 16×H_{meta}); *m*/*z* (ES-TOF) 2963.7 ($[MNa-C_5H_9O_2]^+$), $C_{172}H_{266}NaO_{38}$ requires 2962.8.

4.3.6. 5,11,17,23,29,35,41,47-Octa-*tert*-octyl-49,50,51,52,53,54,55,56-octakis-[8-(2*H*-tetrahydropyran-2-yloxy)-3n^3_6-dioxaoctyloxy]-calix[8]arene (3f). Isolated as an orange oil, from *tert*-octylcalix[8]arene **1b** (0.50 g, 0.29 mmol) and I–PEG_3–OTHP **2f** (0.98 g, 2.86 mmol). Yield: 58% (0.58 g). R_f 0.48 (EtOAc/hexane, 5:1). λ_{max}/nm 282 and 271; ν_{max} (film)/cm^{-1} 1118 (CO); δ_H: 0.61–0.83 (72H, m, 8×$(CH_3)_3$), 1.00–1.24 (48H, m, 8×$(CH_3)_2$), 1.31–1.85 (64H, m, 8×H3, H4, H5 and 8×$CH_2C(CH_3)_3$), 3.28 (24H, s, 8×OCH_3), 3.31–3.87 (128H, m, 48×CH_2O,

8×$ArCH_2Ar$ and 8×H6), 4.39–4.44 (8H, m, 8×H2), 6.58–6.82 (16H, m, 16×H_{meta}); *m/z* (ES) 1675.1561 ([$MNa_2-C_5H_9O-C_5H_9O_2]^{2+}$). $C_{199}H_{321}Na_2O_{37}$ requires 3349.3032.

4.3.7. 5,11,17,23,29,35,41,47-Octakis-[8-(2*H*-tetrahydropyran-2-yloxy)-49,50,51,52,53,54,55,56-dioxaoctyloxy]-calix[8]arene (3g). Isolated as an orange oil, from calix[8]arene **1c** (0.50 g, 0.59 mmol) and I–PEG_3–OTHP **2f** (2.03 g, 5.89 mmol). Yield: 63% (0.96 g). R_f 0.34 (EtOAc/hexane, 8:1). λ_{max}/nm 275 and 266; ν_{max} (film)/cm^{-1} 1111 (CO) and 773 (CH); δ_H: 1.29–1.63 (48H, m, 8×H3, H4, H5), 3.31–3.79 (128H, m, 48×CH_2O, 8×$ArCH_2Ar$ and 8×H6), 4.43–4.48 (8H, m, 8×H2), 6.71–7.01 (24H, m, 16×H_{meta} and 8×H_{para}); *m/z* (FAB) 2578.6 ([MH]$^+$), $C_{144}H_{208}O_{40}$ requires 2578.4.

4.3.8. 5,11,17,23,29,35,41,47-Octa-benzyloxy-49,50,51,52,53,54,55,56-octakis-[8-(2*H*-tetrahydropyran-2-yloxy)-3n^3_6-dioxaoctyloxy]-calix[8]arene (3h). Isolated as an orange oil, from *p*-benzyloxycalix[8]arene **1d** (0.50 g, 0.29 mmol) and I–PEG_3–OTHP **2f** (1.01 g, 2.94 mmol). Yield: 49% (0.49 g). R_f 0.65 (EtOAc/hexane, 12:1). λ_{max}/nm 279 and 268; ν_{max} (film)/cm^{-1} 1106 (CO); δ_H: 1.37–1.69 (48H, m, 8×H3, H4, H5), 3.34–3.93 (128H, m, 48×CH_2O, 8×$ArCH_2Ar$ and 8×H6), 4.51–4.60 (24H, s, 8×CH_2Ph and 8×H2), 6.71–6.93 (16H, m, 16×H_{meta}), 7.04–7.33 (40H, m, 8×H_{ortho}, H_{meta}, H_{para}); *m/z* (FAB) 3363.4 ([$MNa-C_5H_9]^+$), $C_{195}H_{247}NaO_{47}$ requires 3363.7.

4.3.9. 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)-3n^3_{15}-pentaoxaheptadecyloxy]-calix[8]arene (3i).[11] Isolated as an orange oil, from *tert*-butylcalix[8]arene **1a** (0.50 g, 0.39 mmol) and I–PEG_6–OTHP **2g** (1.83 g, 3.85 mmol). Yield: 43% (0.68 g). R_f 0.76 (EtOAc/acetone, 3:1). λ_{max}/nm 276 and 268; ν_{max} (film)/cm^{-1} 1100 (CO); δ_H: 0.93–1.07 (72H, m, 24×CH_3), 1.40–1.84 (48H, m, 8×H3, H4, H5), 3.41–3.79 (224H, m, 96×CH_2O, 8×$ArCH_2Ar$ and 8×H6), 4.50–4.57 (8H, m, 8×H2), 6.76–6.91 (16H, m, 16×H_{meta}); *m/z* (ES) 1979.0356 ([$MNa_2-C_5H_8O-C_5H_9O_2]^{2+}$), $C_{215}H_{353}Na_2O_{61}$ requires 3957.4316.

4.3.10. 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)-3n^3_{15}-pentaoxaheptadecyloxy]-calix[8]arene (3j).[11] Isolated as an orange oil, from *tert*-octylcalix[8]arene **1b** (0.50 g, 0.29 mmol) and I–PEG_6–OTHP **2g** (1.36 g, 2.86 mmol). Yield: 50% (0.65 g). R_f 0.80 (EtOAc/acetone, 3:1). λ_{max}/nm 275 and 267; ν_{max} (film)/cm^{-1} 1109 (CO); δ_H: 0.64–0.86 (72H, m, 8×$(CH_3)_3$), 0.97–1.21 (48H, m, 8×$(CH_3)_2$), 1.30–1.97 (64H, m, 8×H3, H4, H5 and 8×$CH_2C(CH_3)_3$), 3.38–3.91 (224H, m, 96×CH_2O, 8×$ArCH_2Ar$ and 8×H6), 4.40–4.47 (8H, m, 8×H2), 6.47–6.76 (16H, m, 16×H_{meta}); *m/z* (ES) 2203.4539 ([$MNa_2-C_5H_8O-C_5H_8O_2]^{2+}$), $C_{247}H_{418}Na_2O_{61}$ requires 4406.9402.

4.3.11. 49,50,51,52,53,54,55,56-Octakis-[17-(2*H*-tetrahydropyran-2-yloxy)-3n^3_{15}-pentaoxaheptadecyloxy]-calix[8]arene (3k). Isolated as an orange oil, from calix[8]arene **1c** (0.50 g, 0.59 mmol) and I–PEG_6–OTHP **2g** (2.80 g, 5.89 mmol). Yield: 48% (1.03 g). R_f 0.51 (EtOAc/acetone, 5:2). λ_{max}/nm 279 and 268; ν_{max} (film)/cm^{-1} 1109 (CO); δ_H: 1.15–1.57 (48H, m, 8×H3, H4, H5), 3.24–3.85 (224H, m, 96×CH_2O, 8×$ArCH_2Ar$ and 8×H6), 4.42–4.47 (8H, m, 8×H2), 6.61–6.98 (24H, m, 16×H_{meta} and 8×H_{para}); *m/z* (ES) 1825.4683 ([$M+H_2O-H]^{2+}$), $C_{192}H_{305}O_{65}$ requires 3651.0561.

4.3.12. 5,11,17,23,29,35,41,47-Octa-benzyloxy-49,50,51,52,53,54,55,56-octakis-[17-(2*H*-tetrahydropyran-2-yloxy)-3n^3_{15}-pentaoxaheptadecyloxy]-calix[8]arene (3l). Isolated as an orange oil, from *p*-benzyloxycalix[8]arene **1d** (0.50 g, 0.29 mmol) and I–PEG_6–OTHP **2g** (1.40 g, 2.94 mmol). Yield: 51% (0.67 g). R_f 0.67 (EtOAc/acetone, 3:1). λ_{max}/nm 279 and 269; ν_{max} (film)/cm^{-1} 1109 (CO); δ_H: 1.23–1.75 (48H, m, 8×H3, H4, H5), 3.23–3.91 (224H, m, 96×CH_2O, 8×$ArCH_2Ar$ and 8×H6), 4.45–4.67 (24H, m, 8×CH_2Ph and 8×H2), 6.71–6.93 (16H, m, 16×H_{meta}), 7.04–7.33 (40H, m, 8×H_{ortho}, H_{meta}, H_{para}); *m/z* (ES) 2179.0839 ([$MNa_2-2C_5H_9O]^{2+}$), $C_{238}H_{334}Na_2O_{70}$ requires 4358.2371.

4.3.13. 5,11,17,23,29,35,41,47-Octa-benzyloxy-49,50,51,52,53,54,55,56-octakis-[17-(*p*-methoxybenzyloxy)-3n^3_{15}-pentaoxaheptadecyloxy]-calix[8]arene (3m). Isolated as an orange oil, from *p*-benzyloxycalix[8]arene **1d** (0.50 g, 0.29 mmol) and I–PEG_6–OPMB **2m** (1.51 g, 2.94 mmol). Yield: 52% (0.73 g). R_f 0.67 (EtOAc/acetone, 4:3). λ_{max}/nm 278 and 270; ν_{max} (film)/cm^{-1} 1115 (CO); δ_H: 3.17–3.71 (208H, m, 96×CH_2O and 8×$ArCH_2Ar$), 3.95 (24H, s, OCH_3), 4.48–4.57 (32H, m, 8×CH_2Ph and 8×CH_2), 6.51–6.91 (32H, m, 16×H_{meta} and 16×H_{meta}), 7.03–7.32 (56H, m, 8×H_{ortho}, H_{meta}, H_{para} and 16×H_{ortho}); δ_C: 30.1 (8×$ArCH_2Ar$), 55.4 (8×OCH_3), 69.6–71.0 (88×CH_2O), 72.9 (8×CH_2O), 73.3 (8×CH_2Ph), 73.4 (8×CH_2), 114.3 (16×C_{meta}), 116.1 (16×C_{meta}), 127.9–128.9 (40×C_{ortho}, C_{meta}, C_{para}), 129.6 (16×C_{ortho}), 130.6 (8×C_{ipso}), 135.9 (16×C_{ortho}), 138.0 (8×C_{ipso}), 149.2 (8×C_{para}), 155.1 (8×C_{ipso}), 159.8 (8×C_{para}); *m/z* (MALDI-TOF) 4799.75 ([M+COH]$^+$), $C_{273}H_{353}O_{73}$ requires 4799.39.

4.3.14. 5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54,55,56-octakis-[26-(*p*-methoxybenzyloxy)-3n^3_{24}-octaoxahexacosyloxy]-calix[8]arene (3n). Isolated as an orange oil, from *tert*-butylcalix[8]arene **1a** (0.40 g, 0.31 mmol) and I–PEG_9–OPMB **2n** (1.98 g, 3.08 mmol). Yield: 38% (0.75 g). R_f 0.43 (EtOAc/acetone, 1:2). λ_{max}/nm 277 and 270; ν_{max} (film)/cm^{-1} 1097 (CO); δ_H: 0.91–1.20 (72H, m, 24×CH_3), 3.23–3.78 (304H, m, 144×CH_2O and 8×$ArCH_2Ar$), 3.87 (24H, s, 8×OCH_3), 4.51 (16H, s, 8×CH_2), 6.48–6.83 (32H, m, 16×H_{meta} and 16×H_{meta}), 7.08–7.25 (16H, m, 16×H_{ortho}); δ_C: 29.9 (8×$ArCH_2Ar$), 31.4 (24×CH_3), 34.0 (8×$C(CH_3)_3$), 55.8 (8×OCH_3), 69.9–72.0 (136×CH_2O), 72.4 (8×CH_2O), 73.3 (8×CH_2), 114.6 (16×C_{meta}), 125.6 (16×C_{meta}), 129.7 (16×C_{ortho}), 130.9 (8×C_{ipso}), 132.8 (16×C_{ortho}), 145.0 (8×C_{para}), 153.6 (8×C_{ipso}), 159.9 (8×C_{para}); *m/z* (ES) 2736.5727 ([$MNa_2-CH_3]^{2+}$), $C_{296}H_{464}Na_2O_{88}$ requires 2736.5814.

4.3.15. 5,11,17,23,29,35,41,47-Octa-*tert*-octyl-49,50,51,52,53,54,55,56-octakis-[26-(*p*-methoxybenzyloxy)-3n^3_{24}-octaoxahexacosyloxy]-calix[8]arene (3o). Isolated as an orange oil, from *tert*-octylcalix[8]arene **1b** (0.30 g, 0.17 mmol) and I–PEG_9–OPMB **2n** (1.11 g, 1.72 mmol). Yield: 42% (0.42 g). R_f 0.46 (EtOAc/acetone, 1:2). λ_{max}/nm

278 and 271; ν_{max} (film)/cm^{-1} 1110 (CO); δ_H: 0.60–0.84 (72H, m, 8×$(CH_3)_3$), 0.92–1.15 (48H, m, 8×$(CH_3)_2$), 1.41–1.63 (16H, m, 8×$CH_2C(CH_3)_3$), 3.27–3.84 (304H, m, 144×CH_2O and 8×$ArCH_2Ar$), 3.95 (24H, s, 8×OCH_3), 4.46 (16H, s, 8×CH_2), 6.49–6.87 (32H, m, 16×H_{meta} and 16×H_{meta}), 7.17–7.30 (16H, m, 16×H_{ortho}); δ_C: 29.8 (8×$ArCH_2Ar$), 31.5–32.3 (40×CH_3 and 8×$C(CH_3)_3$), 37.9 (8×$C(CH_3)_2$), 55.6 (8×OCH_3), 57.3 (8×$CH_2C(CH_3)_3$), 69.9–71.9 (136×CH_2O), 72.7 (8×CH_2O), 73.4 (8×CH_2), 114.4 (16×C_{meta}), 125.6 (16×C_{meta}), 129.7 (16×C_{ortho}), 130.8 (8×C_{ipso}), 132.8 (16×C_{ortho}), 145.0 (8×C_{para}), 153.6 (8×C_{ipso}), 160.0 (8×C_{para}); *m/z* (ES) 2958.7341 ($[MNa+4H]^{2+}$), $C_{329}H_{535}NaO_{88}$ requires 5917.7286.

4.3.16. 49,50,51,52,53,54,55,56-Octakis-[26-(*p*-methoxybenzyloxy)-3n^3_{24}-octaoxahexacosyloxy]-calix[8]arene (3p). Isolated as an orange oil, from calix[8]arene **1c** (0.30 g, 0.35 mmol) and I–PEG_9–OPMB **2n** (2.28 g, 3.53 mmol). Yield: 46% (0.81 g). R_f 0.39 (EtOAc/acetone, 2:3). λ_{max}/nm 275 and 268; ν_{max} (film)/cm^{-1} 1107 (CO); δ_H: 3.27–3.80 (304H, m, 144×CH_2O and 8×$ArCH_2Ar$), 3.65 (24H, s, 8×OCH_3), 4.47 (16H, s, 8×CH_2), 6.51–6.78 (40H, m, 16×H_{meta}, 8×H_{para} and 16×H_{meta}), 7.02–7.21 (16H, m, 16×H_{ortho}); δ_C: 30.1 (8×$ArCH_2Ar$), 55.7 (8×OCH_3), 69.9–71.8 (136×CH_2O), 72.7 (8×CH_2O), 73.4 (8×CH_2), 114.6 (16×C_{meta}), 124.0 (8×C_{para}), 129.1 (16×C_{meta}), 129.8 (16×C_{ortho}), 131.0 (8×C_{ipso}), 134.0 (16×C_{ortho}), 154.8 (8×C_{ipso}), 159.8 (8×C_{para}); *m/z* (ES) 2489.4638 ($[MH_2]^{2+}$), $C_{264}H_{401}O_{88}$ requires 4980.6981.

4.3.17. 5,11,17,23,29,35,41,47-Octa-benzyloxy-49,50,51,52,53,54,55,56-octakis-[26-(*p*-methoxybenzyloxy)-3n^3_{24}-octaoxahexacosyloxy]-calix[8]arene (3q). Isolated as an orange oil, from *p*-benzyloxycalix[8]arene **1d** (0.40 g, 0.24 mmol) and I–PEG_9–OPMB **2n** (1.52 g, 2.36 mmol). Yield: 37% (0.51 g). R_f 0.51 (EtOAc/acetone, 1:2). λ_{max}/nm 279 and 269; ν_{max} (film)/cm^{-1} 1110 (CO); δ_H: 3.12–3.68 (304H, m, 144×CH_2O and 8×$ArCH_2Ar$), 3.87 (24H, s, OCH_3), 4.44–4.53 (32H, m, 8×CH_2Ph and 8×CH_2), 6.62–6.99 (32H, m, 16×H_{meta} and 16×H_{meta}), 7.07–7.31 (56H, m, 8×H_{ortho}, H_{meta}, H_{para} and 16×H_{ortho}); δ_C: 30.0 (8×$ArCH_2Ar$), 55.7 (8×OCH_3), 69.9–71.5 (136×CH_2O), 73.1 (8×CH_2O), 73.3 (8×CH_2Ph), 73.5 (8×CH_2), 114.4 (16×C_{meta}), 116.0 (16×C_{meta}), 128.0–129.0 (40×C_{ortho}, C_{meta}, C_{para}), 129.7 (16×C_{ortho}), 130.8 (8×C_{ipso}), 136.0 (16×C_{ortho}), 138.1 (8×C_{ipso}), 149.2 (8×C_{para}), 155.1 (8×C_{ipso}), 159.7 (8×C_{para}); *m/z* (MALDI-TOF) 5916.81 ($[M+C_7H_5]^+$), $C_{327}H_{453}O_{96}$ requires 5916.05.

4.3.18. 5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54,55,56-octakis-[35-(*p*-methoxybenzyloxy)-3n^3_{33}-undecaoxapentatriacontyloxy]-calix[8]arene (3r). Isolated as an orange oil, from *tert*-butylcalix[8]arene **1a** (0.30 g, 0.23 mmol) and I–PEG_{12}–OPMB **2o** (1.79 g, 2.31 mmol). Yield: 36% (0.54 g). R_f 0.56 (EtOAc/acetone, 1:5). λ_{max}/nm 276 and 267; ν_{max} (film)/cm^{-1} 1102 (CO); δ_H: 0.82–1.17 (72H, m, 24×CH_3), 3.17–3.82 (400H, m, 192×CH_2O and 8×$ArCH_2Ar$), 3.78 (24H, s, 8×OCH_3), 4.46–4.51 (16H, m, 8×CH_2Ar), 6.50–6.84 (32H, m, 16×H_{meta} and 16×H_{meta}), 7.03–7.31 (16H, m, 16×H_{ortho}); δ_C: 29.8 (8×$ArCH_2Ar$), 31.5 (24×CH_3), 33.9 (8×$C(CH_3)_3$), 55.7 (8×OCH_3), 69.8–71.9 (184×CH_2O), 72.7 (8×CH_2O), 73.2 (8×CH_2Ar), 114.7 (16×C_{meta}), 125.6 (16×C_{meta}), 129.9 (16×C_{ortho}), 131.0 (8×C_{ipso}), 132.8 (16×C_{ortho}), 145.0 (8×C_{para}), 153.7 (8×C_{ipso}), 159.9 (8×C_{para}); *m/z* (ES) 3265.0435 ($[MNa_2-CH_3]^{2+}$), $C_{344}H_{560}Na_2O_{112}$ requires 6529.7920.

4.3.19. 5,11,17,23,29,35,41,47-Octa-benzyloxy-49,50,51,52,53,54,55,56-octakis-[35-(*p*-methoxybenzyloxy)-3n^3_{33}-undecaoxapentatriacontyloxy]-calix[8]arene (3s). Isolated as an orange oil, from *p*-benzyloxycalix[8]arene **1d** (0.40 g, 0.24 mmol) and I–PEG_{12}–OPMB **2o** (1.83 g, 2.36 mmol). Yield: 34% (0.55 g). R_f 0.81 (EtOAc/acetone, 1:6). λ_{max}/nm 280 and 268; ν_{max} (film)/cm^{-1} 1108 (CO); δ_H: 3.17–3.74 (400H, m, 192×CH_2O and 8×$ArCH_2Ar$), 3.91 (24H, s, OCH_3), 4.46–4.67 (32H, m, 8×CH_2Ph and 8×CH_2), 6.59–6.97 (32H, m, 16×H_{meta} and 16×H_{meta}), 7.03–7.35 (56H, m, 8×H_{ortho}, H_{meta}, H_{para} and 16×H_{ortho}); δ_C: 30.0 (8×$ArCH_2Ar$), 55.6 (8×OCH_3), 69.5–71.7 (184×CH_2O), 73.0 (8×CH_2O), 73.4 (8×CH_2Ph), 73.7 (8×CH_2Ar), 114.6 (16×C_{meta}), 116.1 (16×C_{meta}), 127.9–129.0 (40×C_{ortho}, C_{meta}, C_{para}), 129.8 (16×C_{ortho}), 130.8 (8×C_{ipso}), 136.0 (16×C_{ortho}), 138.1 (8×C_{ipso}), 149.3 (8×C_{para}), 155.1 (8×C_{ipso}), 159.8 (8×C_{para}); *m/z* (ES) 3483.0287 ($[(MNa_2+K-2H]^{2+}$), $C_{368}H_{542}KNa_2O_{120}$ requires 6966.5742.

4.3.20. 5,11,17,23,29,35,41,47-Octa-benzyloxy-49,50,51,52,53,54,55,56-octakis-[17-benzyloxy-3n^3_{15}-pentaoxaheptadecyloxy]-calix[8]arene (3t). Isolated as an orange oil, from *p*-benzyloxycalix[8]arene **1d** (0.50 g, 0.29 mmol) and I–PEG_6–OBn **2h** (1.42 g, 2.94 mmol). Yield: 45% (0.60 g). R_f 0.67 (EtOAc/acetone, 4:3). λ_{max}/nm 280 and 272; ν_{max} (film)/cm^{-1} 1109 (CO); δ_H: 3.29–3.73 (208H, m, 96×CH_2O and 8×$ArCH_2Ar$), 4.36–4.61 (32H, m, 16×CH_2Ph), 6.66–6.79 (16H, m, 16×H_{meta}), 7.00–7.32 (80H, m, 16×H_{ortho}, H_{meta}, H_{para}); δ_C: 30.0 (8×$ArCH_2Ar$), 69.4–71.2 (88×CH_2O), 72.9 (8×CH_2O), 73.4 (8×CH_2Ph), 73.7 (8×CH_2Ph), 115.9 (16×C_{meta}), 127.9–129.0 (80×C_{ortho}, C_{meta}, C_{para}), 135.7 (16×C_{ortho}), 137.9–138.1 (16×C_{ipso}), 149.1 (8×C_{para}), 155.1 (8×C_{ipso}); *m/z* (ES) 2288.1698 ($[MNa_2]^{2+}$), $C_{264}H_{336}Na_2O_{64}$ requires 4576.2833.

4.3.21. 5,11,17,23,29,35,41,47-Octa-benzyloxy-49,50,51,52,53,54,55,56-octakis-[26-benzyloxy-3n^3_{24}-octaoxahexacosyloxy]-calix[8]arene (3u). Isolated as an orange oil, from *p*-benzyloxycalix[8]arene **1d** (0.30 g, 0.18 mmol) and I–PEG_9–OBn **2i** (1.09 g, 1.77 mmol). Yield: 43% (0.43 g). R_f 0.42 (EtOAc/acetone, 1:2). λ_{max}/nm 281 and 273; ν_{max} (film)/cm^{-1} 1117 (CO); δ_H: 3.30–3.78 (304H, m, 144×CH_2O and 8×$ArCH_2Ar$), 4.33–4.59 (32H, m, 16×CH_2Ph), 6.57–6.83 (16H, m, 16×H_{meta}), 6.97–7.37 (80H, m, 16×H_{ortho}, H_{meta}, H_{para}); δ_C: 30.1 (8×$ArCH_2Ar$), 69.6–71.4 (136×CH_2O), 73.0 (8×CH_2O), 73.3 (8×CH_2Ph), 73.6 (8×CH_2Ph), 116.1 (16×C_{meta}), 127.9–129.1 (80×C_{ortho}, C_{meta}, C_{para}), 135.8 (16×C_{ortho}), 137.9–138.1 (16×C_{ipso}), 149.1 (8×C_{para}), 155.0 (8×C_{ipso}); *m/z* (MALDI-TOF) 5587.73 (MH^+), $C_{312}H_{433}O_{88}$ requires 5587.94).

4.3.22. 5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54,55,56-octakis-[35-benzyloxy-3n^3_{33}-undecaoxapentatriacontyloxy]-calix[8]arene (3v). Isolated as an

orange oil, from *tert*-butylcalix[8]arene **1a** (0.40 g, 0.31 mmol) and I–PEG_{12}–OBn **2j** (2.30 g, 3.08 mmol). Yield: 38% (0.73 g). R_f 0.44 (EtOAc/acetone, 1:5). λ_{max}/nm 276 and 268; ν_{max} (film)/cm^{-1} 1105 (CO); δ_H: 0.83–1.22 (72H, m, 24×CH_3), 3.203–3.81 (400H, m, 192×CH_2O and 8×$ArCH_2Ar$), 4.44–4.49 (16H, m, 8×CH_2Ph), 6.52–6.77 (16H, m, 16×H_{meta}), 6.98–7.26 (40H, m, 8×H_{ortho}, H_{meta}, H_{para}); δ_C: 28.7 (8×$ArCH_2Ar$), 30.3 (24×CH_3), 33.0 (8×$C(CH_3)_3$), 68.7–69.9 (184×CH_2O), 72.7 (8×CH_2O), 73.7 (8×CH_2Ph), 124.8 (16×C_{meta}), 127.8–129.0 (40×C_{ortho}, C_{meta}, C_{para}), 132.1 (16×C_{ortho}), 138.3 (8×C_{ipso}), 144.7 (8×C_{para}), 152.1 (8×C_{ipso}); *m*/*z* (ES) 3142.8937 ($[MNa+4H]^{2+}$), $C_{337}H_{551}NaO_{104}$ requires 6285.7725.

4.3.23. 5,11,17,23,29,35,41,47-Octa-*tert*-octyl-49,50,51,52,53,54,55,56-octakis-[35-benzyloxy-3n^3_{33}-undecaoxapentatriacontyloxy]-calix[8]arene (3w). Isolated as an orange oil, from *tert*-octylcalix[8]arene **1b** (0.40 g, 0.23 mmol) and I–PEG_{12}–OBn **2j** (1.71 g, 2.29 mmol). Yield: 33% (0.51 g). R_f 0.64 (EtOAc/acetone, 1:5). λ_{max}/nm 277 and 270; ν_{max} (film)/cm^{-1} 1109 (CO); δ_H: 0.57–0.88 (72H, m, 8×$(CH_3)_3$), 0.97–1.23 (48H, m, 8×$(CH_3)_2$), 1.37–1.62 (16H, m, 8×$CH_2C(CH_3)_3$), 3.27–3.97 (400H, m, 192×CH_2O and 8×$ArCH_2Ar$), 4.40–4.51 (16H, m, 8×CH_2Ph), 6.49–6.87 (16H, m, 16×H_{meta}), 6.97–7.37 (40H, m, 8×H_{ortho}, H_{meta}, H_{para}); δ_C: 29.9 (8×$ArCH_2Ar$), 31.3–32.4 (40×CH_3 and 8×$C(CH_3)_3$), 38.0 (8×$C(CH_3)_2$), 57.5 (8×$CH_2C(CH_3)_3$), 69.7–72.0 (184×CH_2O), 72.7 (8×CH_2O), 73.6 (8×CH_2Ph), 125.6 (16×C_{meta}), 127.9–129.0 (40×C_{ortho}, C_{meta}, C_{para}), 132.8 (16×C_{ortho}), 138.7 (8×C_{ipso}), 145.0 (8×C_{para}), 153.6 (8×C_{ipso}); *m*/*z* (ES) 3369.2367 ($[MNa_2-CH_3]^{2+}$), $C_{368}H_{608}Na_2O_{104}$ requires 6738.2083.

4.3.24. 49,50,51,52,53,54,55,56-Octakis-[35-benzyloxy-3n^3_{33}-undecaoxapentatriacontyloxy]-calix[8]arene (3x). Isolated as an orange oil, from calix[8]arene **1c** (0.30 g, 0.35 mmol) and I–PEG_{12}–OBn **2j** (2.64 g, 3.53 mmol). Yield: 31% (0.63 g). R_f 0.78 (EtOAc/acetone, 1:5). λ_{max}/nm 278 and 267; ν_{max} (film)/cm^{-1} 1121 (CO); δ_H: 3.27–3.80 (400H, m, 192×CH_2O and 8×$ArCH_2Ar$), 4.47–4.56 (16H, m, 8×CH_2Ph), 6.51–6.78 (24H, m, 16×H_{meta} and 8×H_{para}), 7.01–7.28 (40H, m, 8×H_{ortho}, H_{meta}, H_{para}); δ_C: 30.2 (8×$ArCH_2Ar$), 69.8–71.8 (184×CH_2O), 72.6 (8×CH_2O), 73.4 (8×CH_2), 124.0 (8×C_{para}), 129.2 (16×C_{meta}), 127.9–129.2 (40×C_{ortho}, C_{meta}, C_{para}), 134.0 (16×C_{ortho}), 138.0 (8×C_{ipso}), 154.8 (8×C_{ipso}); *m*/*z* (ES) 2920.6518 ($[MNa_2]^{2+}$), $C_{304}H_{480}Na_2O_{104}$ requires 5841.2067.

4.3.25. 5,11,17,23,29,35,41,47-Octa-benzyloxy-49,50,51,52,53,54,55,56-octakis-[35-benzyloxy-3n^3_{33}-undecaoxapentatriacontyloxy]-calix[8]arene (3y). Isolated as an orange oil, from benzyloxycalix[8]arene **1d** (0.40 g, 0.24 mmol) and I–PEG_{12}–OBn **2j** (1.76 g, 2.36 mmol). Yield: 29% (0.45 g). R_f 0.71 (EtOAc/acetone, 1:7). λ_{max}/nm 280 and 273; ν_{max} (film)/cm^{-1} 1115 (CO); δ_H: 3.53–4.03 (400H, m, 192×CH_2O and 8×$ArCH_2Ar$), 4.51–4.69 (32H, m, 16×CH_2Ph), 6.47–6.67 (16H, m, 16×H_{meta}), 7.03–7.44 (80H, m, 16×H_{ortho}, H_{meta}, H_{para}); δ_C: 30.0 (8×$ArCH_2Ar$), 69.8–70.8 (184×CH_2O), 72.8 (8×CH_2O), 73.4 (8×CH_2Ph), 73.6 (8×CH_2Ph), 115.8 (16×C_{meta}), 127.9–129.2 (80×C_{ortho}, C_{meta}, C_{para}), 135.8 (16×C_{ortho}), 137.9 (8×C_{ipso}), 138.5 (8×C_{ipso}), 149.1 (8×C_{para}), 155.1 (8×C_{ipso}); *m*/*z* (ES) 3341.4598 ($[(MHNa]^{2+}$), $C_{361}H_{533}NaO_{112}$ requires 6683.5909.

4.4. Removal of protecting groups

4.4.1. Removal of THP ethers. The THP-protected calix[8]arene was dissolved in a mixture of CH_3OH and CH_2Cl_2 (1:1). A few drops of concd HCl were added and the solution was stirred at room temperature for 3 h. $NaHCO_3$ was added to neutralise the solution and the solvents were removed under reduced pressure. EtOAc was added to the residue and the resulting suspension was filtered to remove the inorganic salt. Finally, the solvent was removed and the product was subjected to column chromatography.

4.4.2. Removal of benzyl ethers. Pearlman's catalyst (20% $Pd(OH)_2$, 0.27 g) was added to benzyl-protected calix[8]arene (1.90 mmol) in a mixture of ethanol and cyclohexa-1,4-diene (25 mL, 3:2 v/v). After refluxing for 18 h, the cooled reaction mixture was filtered through a small pad of Celite, which was washed with EtOAc (100 mL). The combined filtrate was concentrated and the remaining oil was purified by column chromatography.

4.4.3. Removal of PMB ethers. The PMB-protected calix[8]arene was dissolved in a mixture of CH_3CN/CH_3OH (9:1, v/v) and cooled to 0 °C. Cerium ammonium nitrate (3 equiv) was added slowly portionwise over 1.5 h. The reaction mixture was then allowed to warm to room temperature, where it was stirred for further 2.5 h. The mixture was diluted with CH_2Cl_2 and filtered through a short pad of Celite. The filtrate was evaporated, before purification by column chromatography.

4.4.3.1. 5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54,55,56-octakis-[8-hydroxy-3n^3_6-dioxaoctyloxy]-calix[8]arene (4a). Isolated as an orange oil, from **3e** (0.51 g, 0.17 mmol). Yield: 82% (0.33 g). R_f 0.47 (EtOAc). λ_{max}/nm 276 and 267; ν_{max} (film)/cm^{-1} 3432 (OH) and 1105 (CO); δ_H: 0.91–1.09 (72H, m, 24×CH_3), 2.79 (8H, s, 8×OH), 3.52–3.82 (112H, m, 48×CH_2O and 8×$ArCH_2Ar$), 6.62–6.76 (16H, m, 16×H_{meta}); δ_C: 29.9 (8×$ArCH_2Ar$), 31.2 (24×CH_3), 33.9 (8×$C(CH_3)_3$), 61.8 (8×CH_2OH), 70.0–71.6 (32×CH_2O), 72.8 (8×CH_2O), 125.3 (16×C_{meta}), 133.8 (16×C_{ortho}), 145.9 (8×C_{para}), 155.0 (8×C_{ipso}); *m*/*z* (FAB) 2376.8 ($[MK-CH_2OH]^+$), $C_{136}H_{208}KO_{31}$ requires 2377.4.

4.4.3.2. 5,11,17,23,29,35,41,47-Octa-*tert*-octyl-49,50,51,52,53,54,55,56-octakis-[8-hydroxy-3n^3_6-dioxaoctyloxy]-calix[8]arene (4b). Isolated as an orange oil from **3f** (0.43 g, 0.12 mmol). Yield: 87% (0.30 g). R_f 0.56 (EtOAc). λ_{max}/nm 275 and 264; ν_{max} (film)/cm^{-1} 3456 (OH) and 1106 (CO); δ_H: 0.64–0.87 (72H, m, 8×$(CH_3)_3$), 0.97–1.19 (48H, m, 8×$(CH_3)_2$), 1.41–1.63 (16H, m, 8×$CH_2C(CH_3)_3$), 2.89 (8H, s, 8×OH), 3.31–3.87 (112H, m, 48×CH_2O and 8×$ArCH_2Ar$), 6.53–6.79 (16H, m, 16×H_{meta}); δ_C: 30.0 (8×$ArCH_2Ar$), 31.9–32.6 (40×CH_3 and 8×$C(CH_3)_3$), 38.1 (8×$C(CH_3)_2$), 57.6 (8×$CH_2C(CH_3)_3$), 62.0 (8×CH_2OH), 70.0–71.3 (32×CH_2O), 72.8 (8×CH_2O), 125.8 (16×C_{meta}), 132.6 (16×C_{ortho}), 144.9 (8×C_{para}), 153.5 (8×C_{ipso}); *m*/*z*

(ES) 1422.0047 ([MNa+4H]$^{2+}$), $C_{169}H_{278}NaO_{32}$ requires 2844.0102.

4.4.3.3. 49,50,51,52,53,54,55,56-Octa-[8-hydroxy-3n^3_6-dioxaoctyloxy]-calix[8]arene (4c). Isolated as a brown oil, from **3g** (0.78 g, 0.30 mmol). Yield: 80% (0.46 g). R_f 0.63 (EtOAc/hexane, 4:1). λ_{max}/nm 275 and 263; ν_{max} (film)/cm^{-1} 3389 (OH) and 1120 (CO); δ_H: 2.61 (8H, s, 8×OH), 3.45–3.73 (112H, m, 48×CH_2O and 8×$ArCH_2Ar$), 6.62–6.83 (24H, m, 16×H_{meta} and 8×H_{para}); δ_C: 29.8 (8×$ArCH_2Ar$), 62.3 (8×CH_2OH), 70.2–71.4 (40×CH_2O), 72.8 (8×CH_2O), 123.9 (8×C_{para}), 128.9 (16×C_{meta}), 134.0 (16×C_{ortho}), 154.6 (8×C_{ipso}); *m/z* (FAB) 1927.6 ([MNa]$^+$), $C_{104}H_{144}NaO_{32}$ requires 1927.9.

4.4.3.4. 5,11,17,23,29,35,41,47-Octa-benzyloxy-49,50,51,52,53,54,55,56-octakis-[8-hydroxy-3n^3_6-dioxaoctyloxy]-calix[8]arene (4d). Isolated as a brown oil, from **3h** (0.38 g, 0.11 mmol). Yield: 84% (0.26 g). R_f 0.54 (EtOAc). λ_{max}/nm 281 and 271; ν_{max} (film)/cm^{-1} 3412 (OH) and 1118 (CO); δ_H: 2.67 (8H, s, 8×OH), 3.26–3.69 (112H, m, 48×CH_2O and 8×$ArCH_2Ar$), 4.58 (16H, s, 8×CH_2Ph), 6.50–6.61 (16H, m, 16×H_{meta}), 7.04–7.29 (40H, m, 8×H_{ortho}, H_{meta}, H_{para}); δ_C: 30.2 (8×$ArCH_2Ar$), 61.9 (8×CH_2OH), 70.0–71.4 (32×CH_2O), 72.6 (8×CH_2O), 73.2 (8×CH_2Ph), 115.6 (16×C_{meta}), 128.0–128.9 (40×C_{ortho}, C_{meta}, C_{para}), 135.7 (16×C_{ortho}), 137.8 (8×C_{ipso}), 149.1 (8×C_{para}), 155.0 (8×C_{ipso}); *m/z* (FAB) 2776.0 ([MNa]$^+$), $C_{160}H_{192}NaO_{40}$ requires 2776.3.

4.4.3.5. 5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54,55,56-octakis-[17-hydroxy-3n^3_{15}-pentaoxaheptadecyloxy]-calix[8]arene (4e).[11] Isolated as a brown oil, from **3i** (0.51 g, 0.12 mmol). Yield: 86% (0.37 g). R_f 0.41 (EtOAc/acetone, 3:1). λ_{max}/nm 280 and 270; ν_{max} (film)/cm^{-1} 3428 (OH) and 1110 (CO); δ_H: 0.93–1.12 (72H, m, 24×CH_3), 2.98 (8H, s, 8×OH), 3.43–3.85 (208H, m, 96×CH_2O and 8×$ArCH_2Ar$), 6.57–6.81 (16H, m, 16×H_{meta}); δ_C: 29.8 (8×$ArCH_2Ar$), 31.3 (24×CH_3), 34.0 (8×$C(CH_3)_3$), 61.9 (8×CH_2OH), 70.1–71.8 (80×CH_2O), 73.0 (8×CH_2O), 125.4 (16×C_{meta}), 133.8 (16×C_{ortho}), 146.0 (8×C_{para}), 155.1 (8×C_{ipso}); *m/z* (ES) 3389.1941 ([MNa−$C_2H_3O_2$]$^+$), $C_{183}H_{303}NaO_{54}$ requires 3389.0940.

4.4.3.6. 5,11,17,23,29,35,41,47-Octa-*tert*-octyl-49,50,51,52,53,54,55,56-octakis-[17-hydroxy-3n^3_{15}-pentaoxaheptadecyloxy]-calix[8]arene (4f).[11] Isolated as a brown oil, from **3j** (0.47 g, 0.10 mmol). Yield: 86% (0.34 g). R_f 0.37 (EtOAc/acetone, 3:1). λ_{max}/nm 276 and 268; ν_{max} (film)/cm^{-1} 3441 (OH) and 1112 (CO); δ_H: 0.58–0.83 (72H, m, 8×$(CH_3)_3$), 0.95–1.12 (48H, m, 8×$(CH_3)_2$), 1.38–1.59 (16H, m, 8×$CH_2C(CH_3)_3$), 3.02 (8H, s, 8×OH), 3.31–3.87 (208H, m, 96×CH_2O and 8×$ArCH_2Ar$), 6.49–6.68 (16H, m, 16×H_{meta}); δ_C: 29.9 (8×$ArCH_2Ar$), 31.7–32.5 (40×CH_3 and 8×$C(CH_3)_3$), 38.0 (8×$C(CH_3)_2$), 57.4 (8×$CH_2C(CH_3)_3$), 61.8 (8×CH_2OH), 69.8–71.5 (80×CH_2O), 72.6 (8×CH_2O), 125.6 (16×C_{meta}), 132.5 (16×C_{ortho}), 144.8 (8×C_{para}), 153.5 (8×C_{ipso}); *m/z* (ES) 1930.3768 ([MNa_2−$C_2H_3O_2$]$^{2+}$), $C_{215}H_{368}Na_2O_{54}$ requires 1930.2923.

4.4.3.7. 49,50,51,52,53,54,55,56-Octakis-[17-hydroxy-3n^3_{15}-pentaoxaheptadecyloxy]-calix[8]arene (4g). Isolated as a brown oil, from **3k** (0.85 g, 0.23 mmol). Yield: 81% (0.56 g). R_f 0.45 (EtOAc/acetone, 5:2). λ_{max}/nm 275 and 263; ν_{max} (film)/cm^{-1} 3389 (OH) and 1120 (CO); δ_H: 2.93 (8H, s, 8×OH), 3.35–3.81 (208H, m, 96×CH_2O and 8×$ArCH_2Ar$), 6.57–6.91 (24H, m, 16×H_{meta} and 8×H_{para}); δ_C: 29.9 (8×$ArCH_2Ar$), 62.1 (8×CH_2OH), 70.0–71.5 (80×CH_2O), 73.0 (8×CH_2O), 124.0 (8×C_{para}), 129.0 (16×C_{meta}), 134.0 (16×C_{ortho}), 154.7 (8×C_{ipso}); *m/z* (ES) 2940.6127 ([MNa−C_2H_4O]$^+$), $C_{150}H_{236}NaO_{55}$ requires 2940.5668.

4.4.3.8. 5,11,17,23,29,35,41,47-Octa-benzyloxy-49,50,51,52,53,54,55,56-octakis-[17-hydroxy-3n^3_{15}-pentaoxaheptadecyloxy]-calix[8]arene (4h). Isolated as a brown oil, from **3l** (0.50 g, 0.11 mmol). Yield: 85% (0.36 g). R_f 0.48 (EtOAc/acetone, 3:1). λ_{max}/nm 279 and 270; ν_{max} (film)/cm^{-1} 3409 (OH) and 1104 (CO); δ_H: 3.01 (8H, s, 8×OH), 3.29–3.73 (208H, m, 96×CH_2O and 8×$ArCH_2Ar$), 4.50–4.61 (16H, m, 8×CH_2Ph), 6.57–6.68 (16H, m, 16×H_{meta}), 7.07–7.32 (40H, m, 8×H_{ortho}, H_{meta}, H_{para}); δ_C: 30.2 (8×$ArCH_2Ar$), 62.0 (8×CH_2OH), 69.8–71.3 (80×CH_2O), 72.9 (8×CH_2O), 73.4 (8×CH_2Ph), 115.9 (16×C_{meta}), 127.9–128.8 (40×C_{ortho}, C_{meta}, C_{para}), 135.7 (16×C_{ortho}), 137.9 (8×C_{ipso}), 149.1 (8×C_{para}), 155.1 (8×C_{ipso}); *m/z* (ES) 1925.9253 ([MNa_2−H]$^{2+}$), [$C_{208}H_{281}Na_2O_{64}$]$^{2+}$ is 3848.853.

4.4.3.9. 5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54,55,56-octakis-[26-hydroxy-3n^3_{24}-octaoxahexacosyloxy]-calix[8]arene (4i). Isolated as a brown oil, from **3n** (0.53 g, 0.10 mmol). Yield: 73% (0.44 g). R_f 0.73 (EtOAc/acetone, 1:3). λ_{max}/nm 277 and 266; ν_{max} (film)/cm^{-1} 3431 (OH) and 1106 (CO); δ_H: 0.87–1.10 (72H, m, 24×CH_3), 3.00 (8H, s, 8×OH), 3.35–3.91 (304H, m, 144×CH_2O and 8×$ArCH_2Ar$), 6.62–6.94 (16H, m, 16×H_{meta}); δ_C: 29.9 (8×$ArCH_2Ar$), 31.4 (24×CH_3), 33.9 (8×$C(CH_3)_3$), 62.0 (8×CH_2OH), 69.9–71.9 (128×CH_2O), 73.1 (8×CH_2O), 125.5 (16×C_{meta}), 133.8 (16×C_{ortho}), 146.0 (8×C_{para}), 155.0 (8×C_{ipso}); *m/z* (ES) 1554.1 ([$MCsNa_2$+2H]$^{3+}$), $C_{233}H_{405}CsNa_2O_{80}$ requires 4662.64.

4.4.3.10. 5,11,17,23,29,35,41,47-Octa-*tert*-octyl-49,50,51,52,53,54,55,56-octakis-[26-hydroxy-3n^3_{24}-octaoxahexacosyloxy]-calix[8]arene (4j). Isolated as a brown oil, from **3o** (0.31 g, 0.05 mmol). Yield: 78% (0.20 g). R_f 0.81 (EtOAc/acetone, 1:3). λ_{max}/nm 277 and 269; ν_{max} (film)/cm^{-1} 3424 (OH) and 1107 (CO); δ_H: 0.61–0.87 (72H, m, 8×$(CH_3)_3$), 0.96–1.16 (48H, m, 8×$(CH_3)_2$), 1.33–1.61 (16H, m, 8×$CH_2C(CH_3)_3$), 2.87 (8H, s, 8×OH), 3.23–3.79 (304H, m, 144×CH_2O and 8×$ArCH_2Ar$), 6.51–6.72 (16H, m, 16×H_{meta}); δ_C: 30.0 (8×$ArCH_2Ar$), 31.6–32.4 (40×CH_3 and 8×$C(CH_3)_3$), 37.9 (8×$C(CH_3)_2$), 57.6 (8×$CH_2C(CH_3)_3$), 62.1 (8×CH_2OH), 69.7–71.6 (128×CH_2O), 72.9 (8×CH_2O), 125.7 (16×C_{meta}), 132.5 (16×C_{ortho}), 144.9 (8×C_{para}), 153.5 (8×C_{ipso}); *m/z* (ES) 2478.7321 ([MNa_2−H_2O−H]$^{2+}$), $C_{265}H_{464}Na_2O_{79}$ requires 2478.6043.

4.4.3.11. 49,50,51,52,53,54,55,56-Octakis-[26-hydroxy-3n^3_{24}-octaoxahexacosyloxy]-calix[8]arene (4k). Isolated as a brown oil, from **3p** (0.58 g, 0.12 mmol). Yield: 81% (0.38 g). R_f 0.66 (EtOAc/acetone, 1:4). λ_{max}/nm 277 and 265; ν_{max} (film)/cm^{-1} 3394 (OH) and 1114 (CO); δ_H: 3.01 (8H, s, 8×OH), 3.31–3.78 (304H, m, 144×CH_2O and

8×ArCH$_2$Ar), 6.61–6.97 (24H, m, 16×H$_{meta}$ and 8×H$_{para}$); δ_C: 29.9 (8×ArCH$_2$Ar), 62.0 (8×CH$_2$OH), 70.0–71.8 (128×CH$_2$O), 72.9 (8×CH$_2$O), 123.9 (8×C$_{para}$), 129.1 (16×C$_{meta}$), 133.9 (16×C$_{ortho}$), 154.8 (8×C$_{ipso}$); *m/z* (MALDI-TOF) 4069.98 ([MNa+2H+CN]$^+$), $C_{201}H_{338}NNaO_{80}$ requires 4069.23.

4.4.3.12. 5,11,17,23,29,35,41,47-Octa-benzyloxy-49,50,51,52,53,54,55,56-octakis-[26-hydroxy-3*n*$^3_{24}$-octaoxahexacosyloxy]-calix[8]arene (4l). Isolated as a brown oil, from **3q** (0.35 g, 0.06 mmol). Yield: 75% (0.22 g). R_f 0.69 (EtOAc/acetone, 1:3). λ_{max}/nm 277 and 268; ν_{max} (film)/cm^{-1} 3454 (OH) and 1099 (CO); δ_H: 3.04 (8H, s, 8×OH), 3.31–3.78 (304H, m, 144×CH$_2$O and 8×ArCH$_2$Ar), 4.53–4.62 (16H, m, 8×CH$_2$Ph), 6.53–6.71 (16H, m, 16×H$_{meta}$), 7.05–7.29 (40H, m, 8×H$_{ortho}$, H$_{meta}$, H$_{para}$); δ_C: 30.3 (8×ArCH$_2$Ar), 62.2 (8×CH$_2$OH), 70.0–72.1 (128×CH$_2$O), 73.1 (8×CH$_2$O), 73.5 (8×CH$_2$Ph), 116.0 (16×C$_{meta}$), 128.0–128.9 (40×C$_{ortho}$, C$_{meta}$, C$_{para}$), 135.9 (16×C$_{ortho}$), 138.0 (8×C$_{ipso}$), 149.1 (8×C$_{para}$), 155.2 (8×C$_{ipso}$); *m/z* (MALDI-TOF) 4889.31 ([MNa]$^+$), $C_{256}H_{384}NaO_{88}$ requires 4889.54.

4.4.3.13. 5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54,55,56-octakis-[35-hydroxy-3*n*$^3_{33}$-undecaoxapentatriacontyloxy]-calix[8]arene (4m). Isolated as a brown oil, from **3r** (0.38 g, 0.06 mmol). Yield: 68% (0.22 g). R_f 0.39 (EtOAc/acetone, 1:6). λ_{max}/nm 275 and 266; ν_{max} (thin film)/cm^{-1} 3452 (OH) and 1121 (CO); δ_H: 0.83–1.07 (72H, m, 24×CH$_3$), 3.04 (8H, s, 8×OH), 3.36–3.97 (400H, m, 192×CH$_2$O and 8×ArCH$_2$Ar), 6.57–6.90 (16H, m, 16×H$_{meta}$); δ_C: 29.7 (8×ArCH$_2$Ar), 31.6 (24×CH$_3$), 34.1 (8×C(CH$_3$)$_3$), 62.4 (8×CH$_2$OH), 69.5–71.7 (176×CH$_2$O), 73.0 (8×CH$_2$O), 125.6 (16×C$_{meta}$), 133.8 (16×C$_{ortho}$), 146.1 (8×C$_{para}$), 155.0 (8×C$_{ipso}$); *m/z* (MALDI-TOF) 5614.18 ([MH+C$_6$H$_3$]$^+$), $C_{287}H_{503}O_{104}$ requires 5614.40.

4.4.3.14. 5,11,17,23,29,35,41,47-Octa-benzyloxy-49,50,51,52,53,54,55,56-octakis-[35-hydroxy-3*n*$^3_{33}$-undecaoxapentatriacontyloxy]-calix[8]arene (4n). Isolated as a brown oil, from **3s** (0.34 g, 0.05 mmol). Yield: 65% (0.19 g). R_f 0.72 (EtOAc/acetone, 1:6). λ_{max}/nm 276 and 269; ν_{max} (film)/cm^{-1} 3444 (OH) and 1103 (CO); δ_H: 3.08 (8H, s, 8×OH), 3.30–3.82 (400H, m, 192×CH$_2$O and 8×ArCH$_2$Ar), 4.55–4.63 (16H, m, 8×CH$_2$Ph), 6.49–6.77 (16H, m, 16×H$_{meta}$), 7.03–7.31 (40H, m, 8×H$_{ortho}$, H$_{meta}$, H$_{para}$); δ_C: 30.1 (8×ArCH$_2$Ar), 62.0 (8×CH$_2$OH), 70.0–72.7 (176×CH$_2$O), 73.0 (8×CH$_2$O), 73.6 (8×CH$_2$Ph), 116.1 (16×C$_{meta}$), 127.9–129.1 (40×C$_{ortho}$, C$_{meta}$, C$_{para}$), 135.9 (16×C$_{ortho}$), 138.0 (8×C$_{ipso}$), 149.0 (8×C$_{para}$), 155.0 (8×C$_{ipso}$); *m/z* (ES) 2940.8313 ([MNa$_2$−2C$_2$H$_4$O]$^{2+}$), $C_{300}H_{472}Na_2O_{110}$ requires 2940.5568.

4.4.3.15. 5,11,17,23,29,35,41,47-Octa-hydroxy-49,50,51,52,53,54,55,56-octakis-[26-hydroxy-3*n*$^3_{24}$-octaoxahexacosyloxy]-calix[8]arene (4o). Isolated as a brown oil, from **3u** (0.35 g, 0.06 mmol). Yield: 71% (0.18 g). R_f 0.63 (EtOAc/acetone, 1:3). ν_{max} (film)/cm^{-1} 3257 (OH) and 1103 (CO); δ_H: 2.75 (8H, s, 8×OH), 3.28–3.87 (304H, m, 144×CH$_2$O and 8×ArCH$_2$Ar), 6.50–6.91 (16H, m, 16×H$_{meta}$), 9.46 (8H, s, 8×OH); δ_C: 30.0 (8×ArCH$_2$Ar), 61.9 (8×CH$_2$OH), 69.9–71.8 (128×CH$_2$O), 73.1 (8×CH$_2$O), 116.9 (16×C$_{meta}$), 132.1 (16×C$_{ortho}$), 136.8 (8×C$_{ipso}$), 154.9 (8×C$_{para}$); *m/z* (ES) 2096.8627 ([MNa$_2$+H]$^{2+}$), $C_{200}H_{337}Na_2O_{88}$ requires 4193.17.

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Supplementary data

(1) Characterisation data for compounds **2f**–**p**, **5a**–**f** and **6a**–**d**; (2) tables summarising the result of reaction optimisation, including the choice and stoichiometry of base and (3) selected ^{1}H (compounds **3a** and **3g**) and ^{13}C (compounds **3c**, **3g** and **3v**) NMR spectra were provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.07.057.

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