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Synthesis and NMR Elucidation of Novel Octa-Amino Acid Resorcin[4]arenes Derivatives

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ABSTRACT

The synthesis of nine novel protected amino acid cavitands is reported. All have four pendant *n*-undecyl chains and 'headgroups' connected by a two-carbon spacer at eight positions on the aromatic rings. The amino acids employed are glycine, alanine, phenylalanine, leucine, proline, tryptophan, serine, glutamine and lysine. The structures of the compounds were elucidated using one and two-dimensional NMR techniques which verified that all octa-substituted cavitands have symmetrical C_{2v} conformation at room temperature. These compounds have potential synthetic ion channel applications.

KEYWORDS

Octa-amino acid resorcin[4]arenes, ^{1}H-NMR, COSY, HSQC, C_{4v} symmetry, C_{2v} symmetry.

1. Introduction

Resorcin[4]arenes are well-known macrocyclic oligomers formed when resorcinol condenses with aliphatic or aromatic aldehydes under acidic conditions.[1] The reaction with formaldehyde is excluded from this 'family' as it often forms linear polymers. Even though it is possible to form resorcinarenes with formaldehyde,[2] the use of aliphatic aldehydes resulting in side chains or 'feet' is preferred for potential synthetic ion channels.[3] These macrocyclic compounds are known to possess hydrophilic (upper rim) and hydrophobic (lower rim) regions and a cavity, that can accommodate small organic molecules.[4]

Resorcin[4]arenes are not planar and can adopt five possible conformational arrangements: the C_{4v} symmetrical '*crown*' conformation, C_{2v} symmetrical '*boat*' conformation, C_{2h} symmetrical '*chair*' conformation, C_s symmetrical '*diamond*' conformation, and S_4 symmetrical '*saddle*' conformation as illustrated in Fig. 1.[4b]

The presence of two electron-releasing hydroxyl groups on the aromatic rings especially at the '*ortho*' position makes compounds of this family a convenient platform for the design and synthesis of various supramolecular structures. To obtain these architectures, various methods have been developed for selective chemical modifications of the resorcin[4]arenes.[4b,5] Functionalization of the resorcin[4]arene platform with amino acid moieties could create structural features that provide valuable insight into factors governing biologically relevant host-guest chemistry.[6] These types of compounds also have found applications as synthetic ion channels.[3,7].

This study demonstrates an effort to functionalize resorcin[4] arene with amino acid residues at the upper rim. Very few examples have been reported where 'flexible' resorcin[4]arenes have been modified with amino acids. An example employing L-proline *via* Mannich reactions has been reported by several researchers.[8] Botta *et al.* using a different approach have modified resorcin[4]arenes at the lower rim with several amino acids for chiral recognition.[9]

The synthesis of our target compounds began by utilizing dodecanal, as the alkyl aldehyde component for the condensation reaction with resorcinol, to produce the resorcin[4]arene, **1** in good yield as reported in literature.[1b,10] Acylations and alkylations of hydroxyl groups have produced cavitands, carcerands, hemicarcerands, velcrands,[4a] molecular capsules,[11] receptors and sensors for biologically-active compounds,[12] and metal ion extraction agents.[13]

The synthetic route towards novel compounds **4a–i** (Scheme 1), involves alkylation of compound **1** with methyl-2-bromoacetate in dry acetonitrile in the presence of potassium carbonate and a catalytic amount of sodium iodide. The reaction occurs at elevated temperature for 48 h and after workup and recrystallization pure **2** was obtained in 77 % yield.[13a,14]

2. Results and Discussion

These compounds may find application as synthetic ion channels, but testing of the compounds reported herein for that, falls outside the scope of the current NMR investigation.

The structures of these compounds were established on the basis of one- and two-dimensional NMR experiments. A discussion of the complete elucidation of compound **4a** is presented, followed with a short discussion of 2D results for **4b**. Elucidation of the remainder of the compounds is presented in the online supplement. A summary of the NMR data are presented in Tables 1–3.

Octa-acid resorcin[4]arene **3** was transformed into the octa-acyl chloride upon treatment with oxalyl chloride in dry CH_2Cl_2 (Scheme 1). Since the acyl chloride is very unstable and undergoes rapid hydrolysis if moisture is present, it was used in the next step without further purification and characterization. This acyl chloride was reacted with nine equivalents of each amino acid, to the get the novel derivatives.[15] A number of the amino acids required side chain protection (e.g. L-glutamic acid, L-serine, and L-lysine). The crude materials obtained were purified on silica gel chromatography, using 3 % methanol in chloroform. The octa-amino acid resorcin[4]arene derivatives **4a–i** were obtained in good yields (59–76 %).

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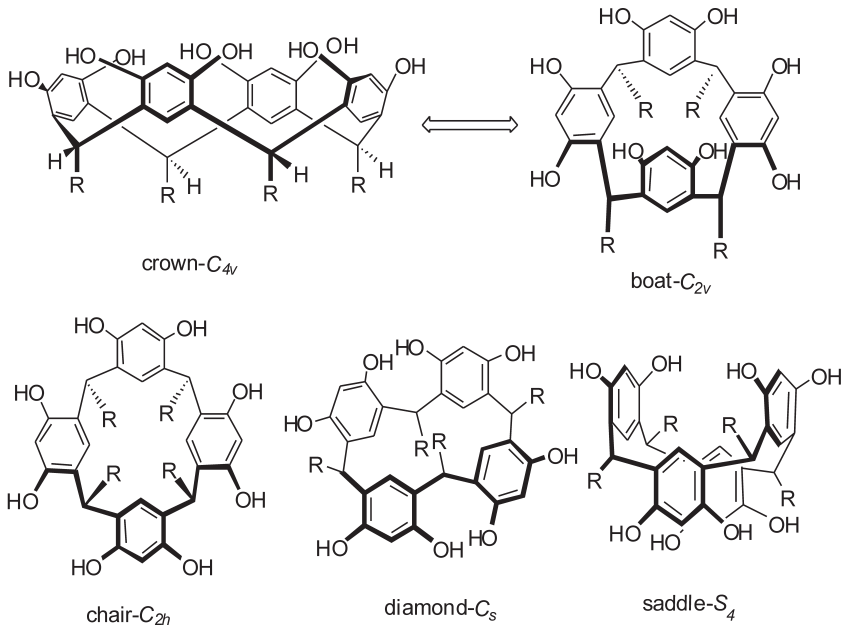
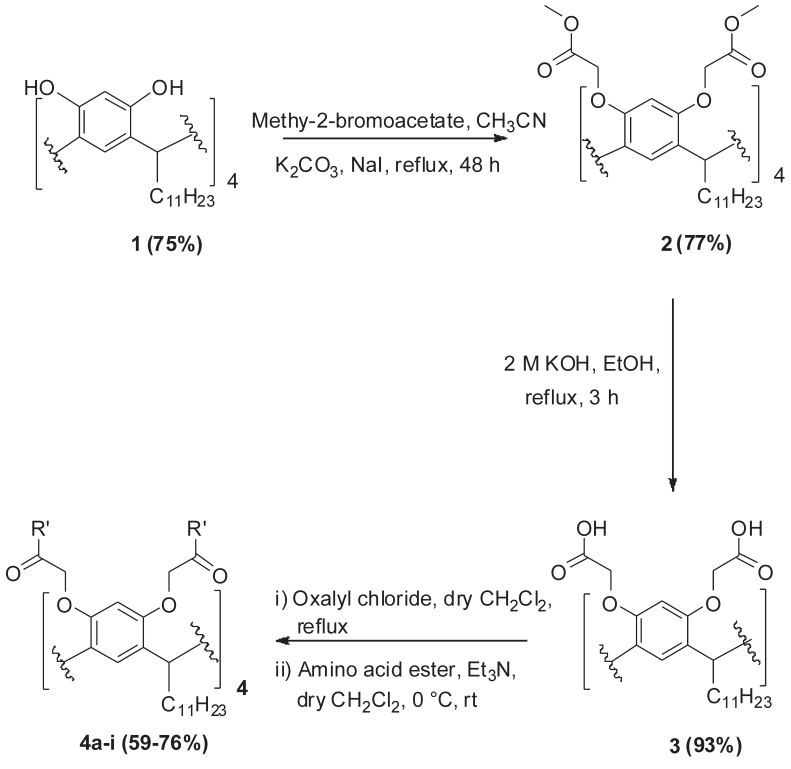


Figure 1 The different conformations of macrocyclic resorcin[4]arene.[4b]

The ^{1}H NMR spectra of these derivatives (**4a–i**) in $CDCl_3$ at room temperature showed a considerable broadening of the various signals. The relatively broad signals from these compounds are a result of the multiple conformations possible for the cavitand bowl. On the NMR timescale, they have a slow rate of interconversion. *Boat* conformations convert to a symmetrical *crown* conformation and *vice versa*[1a,10a,16]. A similar observation was made when the spectra of these molecules were taken in polar organic solvents at room temperature (d_6-acetone and d_6-DMSO). Figures 2, 3 and 4 illustrate these observations



4a R' = Gly ethyl ester
4b R' = L-Ala methyl ester
4c R' = L-Phe methyl ester
4d R' = L-Leu methyl ester
4e R' = L-Pro methyl ester
4f R' = L-Trp methyl ester
4g R' = L-Ser (Ot-but) t-butyl ester
4h R' = L-Glu (OMe) methyl ester
4i R' = L-Lys (Z) benzyl ester

Scheme 1 Synthetic pathway towards the octa-amino acid-resorcin[4]arene derivatives **4a–i** *via* modification of all eight hydroxyl groups.

Table 1 ^{1}H NMR data for compounds **4a–c** in DMSO-d_6 at 70 °C (600 MHz).

Proton	Chemical shift/ppm (multiplicity, coupling constant, integration)		
	4a	**4b**	**4c**
H_2	4.69 (*t*, *J* = 8.0 Hz, 4)	4.67 (*t*, *J*= 5.0 Hz, 4)	4.64 (*t*, *J*= 8.0 Hz, 4)
H_3	6.73 (*s*, 4)	6.73 (*s*, 4)	6.89 (*s*, 4)
H_4	6.57 (*s*, 4)	6.56 (*s*, 4)	6.33 (*s*, 4)
H_5	4.36 (*d*, *J* = 14.7 Hz, 8); 4.27 (*d*, *J* = 14.7 Hz, 8)	4.35 (*q*, *J* = 5.0 Hz, 8); 4.24 (*q*, *J* = 5.0 Hz, 8)	4.20 (*q*, *J* = 7.1 Hz, 8); 4.28 (*q*, *J* = 7.1 Hz, 8)
NH	7.72 (*t*, *J* = 5.1 Hz, 8 H) 7.82 (*d*, *J* = 7.3 Hz, 4)	7.80 (*d*, *J* = 7.3 Hz, 4); 7. 77 (*d*, *J* = 8.2 Hz, 4)	7.60 (*d*, *J* = 8.2 Hz, 4);
AAH*	4.12 (*q*, *J* = 7.0 Hz, 16); 3.96 (*d d*, *J* = 5.1 Hz, 8); 3.85 (*d d*, *J* = 5.8 Hz, 8); 1.20 (*t*, *J* = 8.5 Hz 24)	4. 42 (*q*, *J* = 8.5 Hz, 8); 3.64 (*d*, *J* = 7.0 Hz, 24); 1.34 (*t*, *J* = 7.2 Hz, 24)	7.04–7.15 (*m*, 40); 4.64 (*q*, *J* = 6.3 Hz, 8); 3.59 (*d*, *J* = 7.1 Hz, 24); 3.11 (*d d*, *J* = 6.0 Hz, 4); 3.04 (*d d*, *J* = 6.0 Hz, 4); 3.03 (*d d*, *J* = 6.3 Hz, 4); 2.87 (*d d*, *J* = 6.3 Hz, 4)
Feet	1.81 (*q*, *J* = 6.5 Hz, 8); 1.22–1.27 (*m*, 72); 0.84 (*t*, *J* = 7.5 Hz, 12)	1.83 (*q*, *J* = 6.5 Hz, 8); 1.20–1.28 (*m*, 72); 0.84 (*t*, *J* = 6.0 Hz, 12)	2.17 (*q*, *J* = 7.0 Hz, 8); 1.20–1.28 (*m*, 72); 0.83 (*t*, *J* = 6.3 Hz, 12)

AAH* denotes amino acid ester peaks.

for compound **4a** in different solvents. The ^{1}H NMR spectra of this derivative show relatively broad signals corresponding to the aromatic protons (assigned *a* and *b*).

In an attempt to confirm that the broadening in the ^{1}H NMR spectra is the result of these conformational changes, **4a** in d_6-DMSO was heated in the NMR spectrometer (600 MHz). By increasing the temperature stepwise, the various signals began to sharpen. At 70 °C, only the signals of the *crown* conformation are visible in the spectrum. ^{1}H NMR spectrum of this compound shows sharp single peaks corresponding to the aromatic protons (assigned at 6.73 ppm and 6.57 ppm) (Fig. 5).

To further establish the conformational behaviour for these compounds (**4a–i**), a low temperature ^{1}H NMR experiment was recorded for compound **4a** in d_6-acetone at 600 MHz from 0 °C to –60 °C. The most notable change in the ^{1}H NMR spectrum occurred for the signals of the aromatic protons (H_3 and H_4, Fig. 3). As the solution cooled down to –40 °C, the signals for H_3 and H_4 broadened and separated into four signals (6.30 ppm and 6.57 ppm for H_4, and 6.89 ppm and 7.47 ppm for H_3) (Fig. 6).

Figure 6 illustrates the splitting of the aromatic protons signals into four broad singlets at low temperature, indicating the flattened conformations corresponded to a C_{2v} symmetry for **4a**, in which the aromatic rings lie spatially in pairs. As anticipated, the ^{1}H NMR spectrum in Fig. 3 also displayed some changes in the non-aromatics regions for this compound.

To discuss the proton (^{1}H) NMR spectrum of compound **4a** in DMSO-d_6 at 70 °C reference will be made to Fig. 7, which shows the numbering of the protons present in this molecule. According to this expanded structure, the various resonances present in the ^{1}H NMR spectra of the macrocycles **4b–i** were assigned.

The ^{1}H NMR spectrum for compound **4a** in d_6-DMSO at 70 °C demonstrates signals characteristic for the glycine ethyl ester

Table 2 ^{1}H NMR data for compounds **4d–f** in DMSO-d_6 at 70 °C (600 MHz).

Proton	Chemical shift/ppm (multiplicity, coupling constant, integration)		
	4d	**4e**	**4f**
H_2	4.77 (*t*, *J* = 7.5 Hz, 4)	4.68 (*t*, *J* = 7.9 Hz, 4)	4.63 (*t*, *J* = 8.0 Hz, 4)
H_3	6.89 (*s*, 4)	6.82 (*br s*, 4)	6.80 (*s*, 4)
H_4	6.53 (*s*, 4)	6.38 (*br s*, 4)	6.47 (*s*, 4)
H_5	4.46 (*q*, *J* = 7.1 Hz, 8); 4.36 (*t*, *J* = 7.6 Hz, 8)	4.48 (*br d*, 16)	4.32 (*q*, *J* = 7.0 Hz, 8); 4.26 (*q*, *J* = 7.2 Hz, 8)
NH	8.02 (*d*, *J* = 8.1 Hz, 4); 7.79 (*d*, *J* = 8.1 Hz, 4)	–	7.63 (*d*, *J* = 7.56 Hz, 4); 7.55 (*d*, *J* = 7.68 Hz, 4)
AAH*	4.47 (*q*, *J* = 3.56 Hz, 8); 3.62 (*d*, *J* = 17.5 Hz, 24); 1.45–1.67 (*m*, 24); 0.87 (*t*, *J* = 7.5 Hz, 24); 0.77 (*t*, *J* = 7.2 Hz, 24)	4.38 (*q*, *J* = 5.66 Hz, 8); 3.69 (*d*, *J* = 7.3Hz, 24); 3.56 (*m*, 16); 1.90 (*q*, *J* = 4.3 Hz, 8); 2.00 –2.15 (*m*, 24)	10.42 (*s*, 4); 10.32 (*s*, 4); 7.48 (*t*, *J* = 6.5 Hz, 8); 7.29 (*d d*, *J* = 8.10 Hz, 8); 7.02 (*t*, *J* = 7.4 Hz, 8); 7.00 (*t*, *J* = 7.5 Hz, 8); 6.90 (*s*, 4); 4.71 (*q*, *J* = 7.1 Hz, 8); 3.68 (*d*, *J* = 6.5 Hz, 24);
Feet	1.81 (*q*, *J* = 6.7 Hz, 8); 1.20–1.28 (*m*, 72); 0.84 (*t*, *J* = 7.1 Hz, 12)	2.41 (*m*, 8); 1.20–1.30 (*m*, 72); 0.86 (*t*, *J* = 6.5 Hz, 12)	1.83 (*q*, *J*= 7.7 Hz, 8); 1.20–1.28 (*m*, 72); 0.85 (*t*, *J* = 6.5 Hz, 12)

AAH* denotes amino acid ester peaks.

Table 3 ^{1}H NMR data for compounds **4g–i** in d_6-DMSO at 70 °C (600 MHz).

Proton	Chemical shift/ppm (multiplicity, coupling constant, integration)		
	4g	**4h**	**4i**
H_2	4.63 (*t*, *J* = 8.0 Hz, 4)	4.69 (*t*, *J* = 7.2 Hz, 4)	4.68 (*t*, *J* = 7.2 Hz, 4)
H_3	6.73 (*s*, 4)	6.81 (*s*, 4)	6.84 (*s*, 4)
H_4	6.53 (*s*, 4)	6.55 (*s*, 4)	6.59 (*s*, 4)
H_5	4.36 (*d*, *J* = 14.70 Hz, 4); 4.28 (*d*, *J* = 14.94 Hz, 4); 4.25 (*d*, *J* = 14.88 Hz, 4); 4.18 (*d*, *J* = 14.82 Hz, 4)	4.32 (*q*, *J* = 8.56 Hz, 8); 4.30 (*q*, *J* = 7.9 Hz, 8)	4.35 (*q*, *J* = 8.42 Hz, 8); 4.27 (*q*, *J* = 8.0 Hz, 8)
NH	7.27 (*d*, *J* = 8.2 Hz, 4); 7.24 (*d*, *J* = 8.1 Hz, 4)	7.66 (*d d*, *J* = 7.4 Hz, 8)	7.61 (*d d*, *J* = 7.8 Hz, 8)
AAH*	4.46 (*q*, *J* = 5.72 Hz, 8); 3.70 (*d d*, *J* = 3.1 Hz, 8); 3.54 (*d d*, *J* = 2.6 Hz, 8); 1.40 (*d*, *J* = 3.5 Hz, 72); 1.09 (*d*, 72)	4.44 (*q*, *J* = 8.56 Hz, 8); 3.70 (*s*, 24); 3.58 (*d*, *J* = 3.81 Hz, 24); 2.36 (*q*, *J* = 4.2 Hz, 16); 2.13 (*m*, 8); 1.96 (*m*, 8)	7.26–7.36 (*m*, 80); 6.61 (*br t*, 8); 5.13 (*m*, 16); 4.77 (*s*, 16); 4.44 (*q*, *J* = 6.1 Hz, 8); 3.10 (*q*, *J* = 5.2 Hz, 16); 1.82 (*m*, 8); 1.78 (*m*, 8); 1.39 (*m*, 32)
Feet	1.86 (*q*, *J* = 6.4 Hz, 8); 1.20–1.28 (*m*, 72); 0.86 (*t*, *J* = 6.5 Hz, 12)	1.86 (*q*, *J* = 5.1 Hz, 8); 1.20–1.29 (*m*, 72); 0.87 (*t*, *J* = 6.5 Hz, 12)	1.86 (*q*, *J* = 6.8 Hz, 8); 1.20–1.28 (*m*, 72); 0.80 (*t*, *J* = 6.7 Hz, 12)

AAH* denotes amino acid ester peaks.

and the resorcin[4]arene scaffold. The signal related to the methylene group of the ethyl ester at 4.12 ppm appears as a quartet, integrating to 16. The signal associated with the methyl group of this ester at 1.20 ppm is a triplet, integrating to 24. The signal related to the α-protons (Fig. 7) appears as two pairs of doublets at 3.96 ppm and 3.85 ppm, each of these integrates to eight. The signal for the amide NH protons for this derivative appears as a triplet at 7.72 ppm, integrating to eight.

The signal for the methylene protons (H_5) of the OCH_2CO groups appears as two doublets at 4.36 ppm and at 4.27 ppm, each of these signals integrates to eight. This splitting could be attributed to the presence of two glycine residues on each aromatic ring. The signals related to the protons of aromatic rings (H_3 and H_4) appear as two singlets at 6.73 ppm for H_3 protons and at 6.57 ppm for H_4 protons, each of these integrates to four. The signal associated with the methine protons (H_2) at 4.69 ppm is a triplet, integrating to four. The signals related to the undecyl 'feet' (R) have resolved into three signals: a quartet at 1.81 ppm, integrating to eight, multiplets at 1.22–1.27 ppm, integrating to 72, and a triplet at 0.84 ppm, integrating to 12.

The IR spectrum for **4a** shows the characteristic appearance of the amide NH stretching peak at 3414 cm^{-1} whereas the carbonyl peaks at 1757 and 1731 cm^{-1} corresponding to the ester and *amide* carbonyl stretching frequencies, respectively. Mass spectrometry

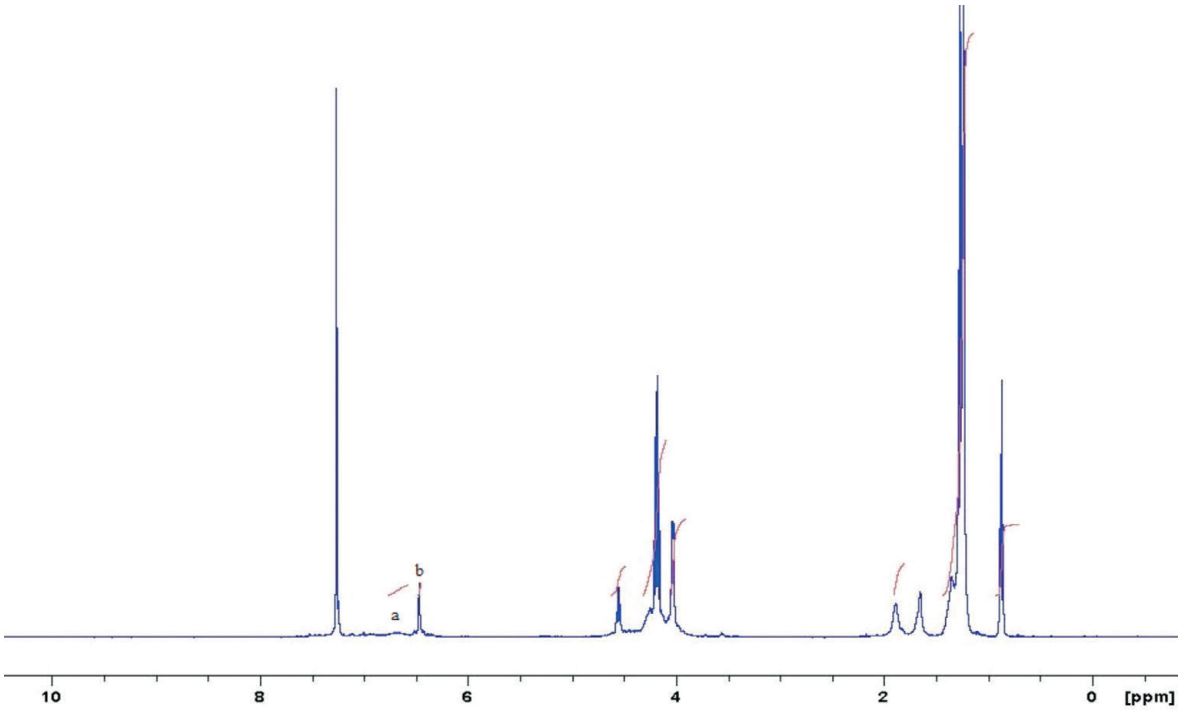


Figure 2 ^{1}H NMR spectrum of compound **4a** in $CDCl_3$ at room temperature (400 MHz).

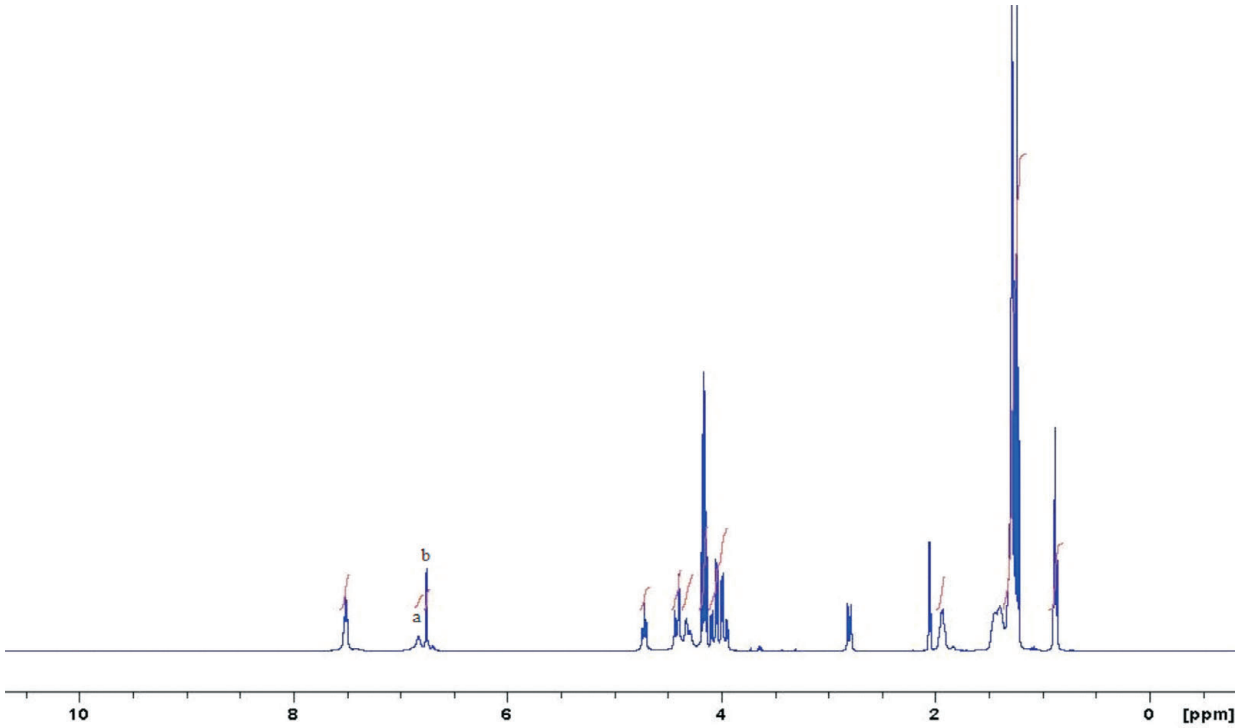


Figure 3 ^{1}H NMR spectrum of compound **4a** in d_6-acetone at room temperature (400 MHz).

(MS) (using ESI-TOF methods) additionally gave a molecular ion *m*/*z* signal of 2273.2926, which matches the expected mass for **4a** of 2273.2942.

Compound **4b** was synthesized in 73 % yield by reacting L-alanine methyl ester with the octa-acid resorcin[4]arene **3**. The ^{1}H NMR data for compounds **4a–c** are summarized in Table 1.

Subsequent COSY and HSQC NMR analysis confirmed the presence of the target compounds, showing the expected couplings between the various protons. Figure 7 displays ^{1}H-^{1}H COSY couplings for compound **4b**, as an example of a two-dimensional NMR experiment at 70 °C (600 MHz.)

Analysis of the COSY spectrum shows (Fig. 8) that the α-protons (Ala-CH-) at 4.35 ppm are coupled to the amide NH protons at 7.82 ppm and 7.80 ppm as well as the β-protons (Ala-CH_3) at 1.34 ppm. The methine protons (H_2) at 4.67 ppm which bridge the aromatic moieties, are coupled to the methylene protons of the 'feet' (-CH_2-) at 1.83 ppm. The methylene protons at 1.83 ppm are coupled to the protons of the 'feet' at 1.20–1.28 ppm. The

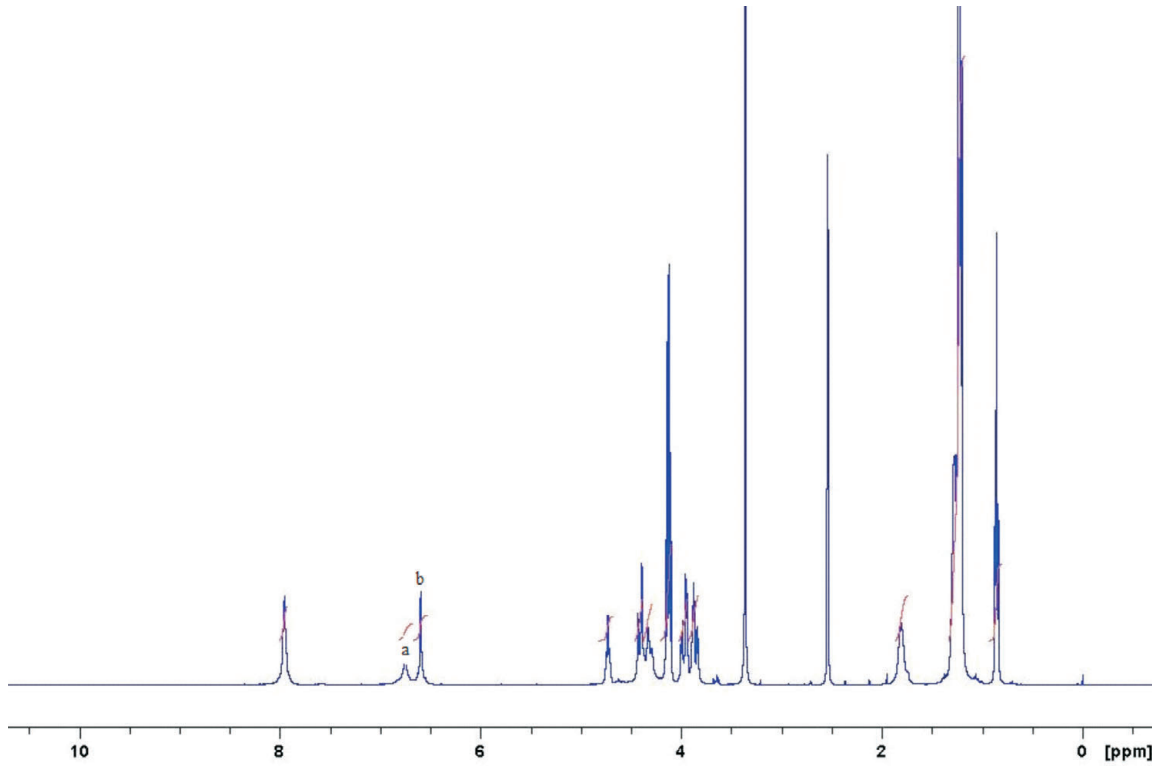


Figure 4 ^{1}H NMR spectrum of compound **4a** in d_6-DMSO at room temperature (400 MHz).

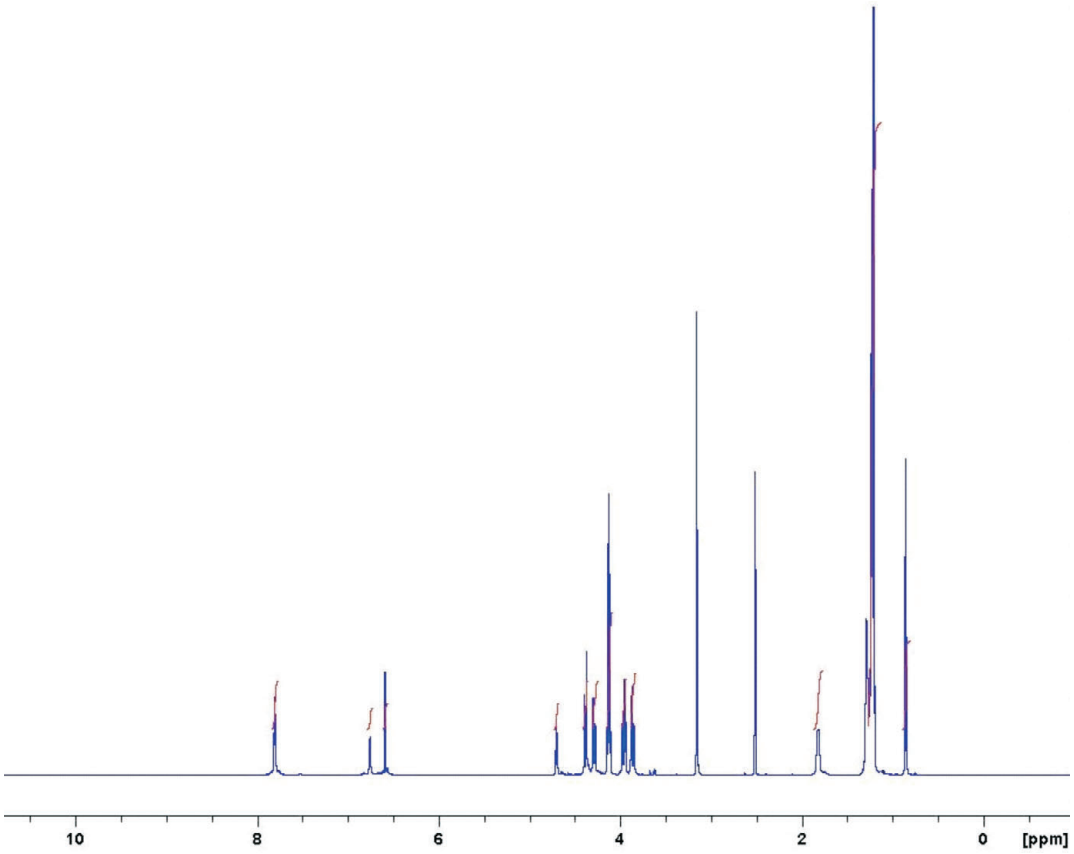


Figure 5 ^{1}H NMR spectrum of compound **4a** in d_6-DMSO at 70 °C (600 MHz).

terminal methyl groups of the 'feet' at 0.84 ppm are coupled to the methylene groups at 1.20–1.28 ppm.

Compound **4d** was synthesized in 72 % yield by reacting L-leucine methyl ester with the octa-acid resorcin[4]arene **3**. Reaction of the octa-acyl chloride resorcin[4]arene **3** with L-proline methyl ester afforded compound **4e** in 69 % yield. The octa-acyl chloride resorcin[4]arene **3** reacted with L-proline methyl ester afforded compound **4e** in 69 % yield. Compound **4f**

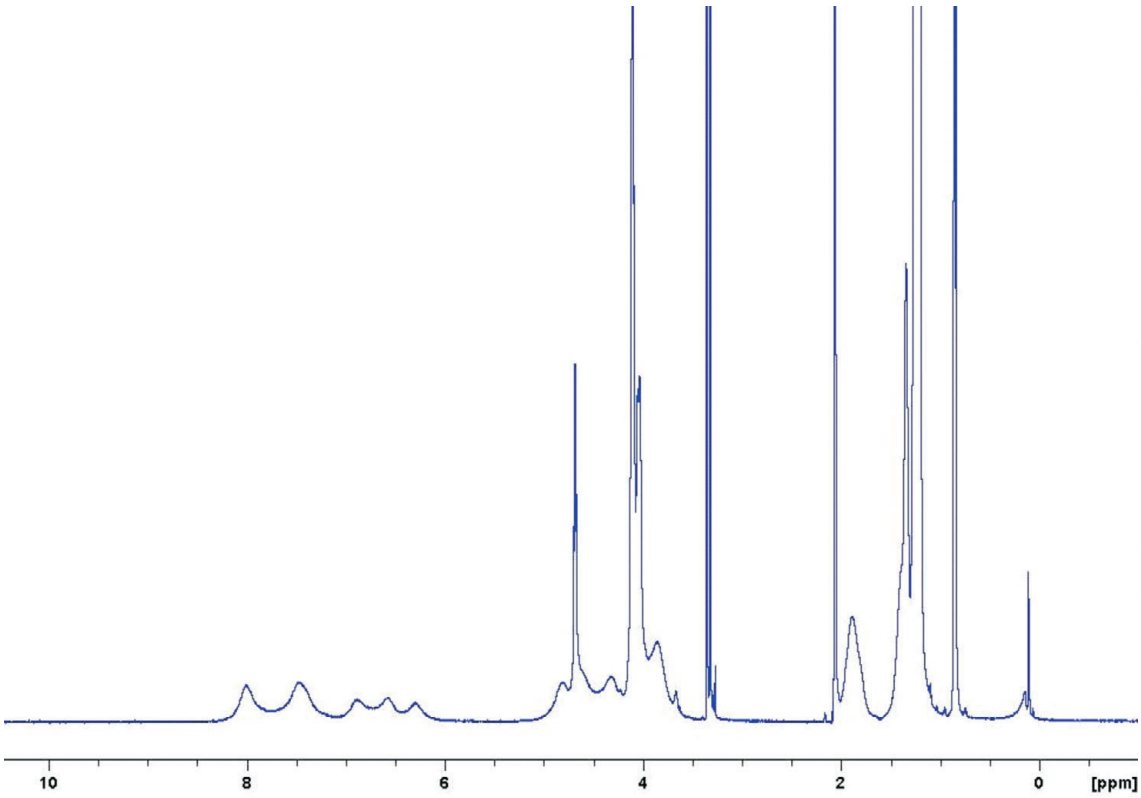


Figure 6 ^{1}H NMR spectrum of compound **4a** in d_6-acetone at –40 °C (600 MHz).

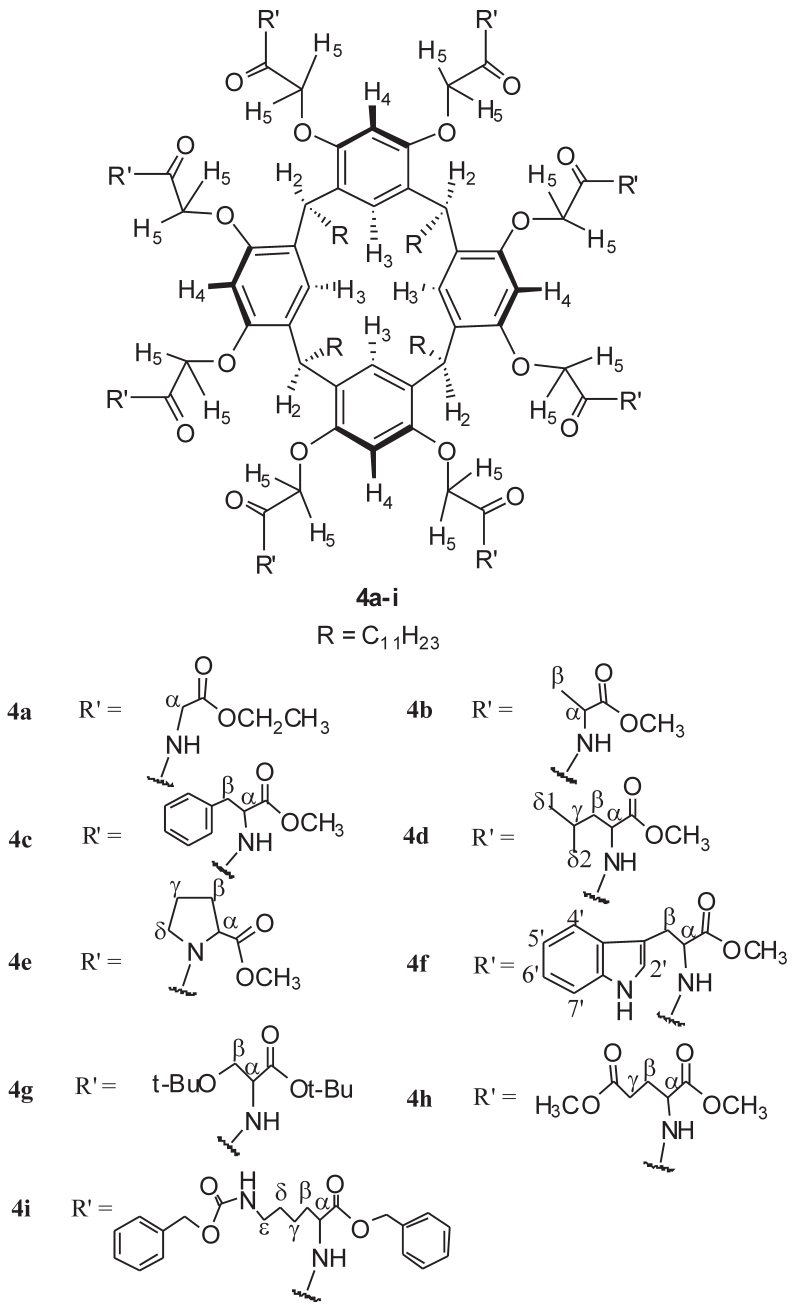


Figure 7 Expanded structure of **4a–i**, showing distinctive protons.

was synthesized in 64 % yield by reacting L-tryptophan methyl ester with the octa-acid resorcin[4]arene **3**. The ^{1}H NMR data for compounds **4d–f** are summarized in Table 2.

Subsequent COSY and HSQC NMR analysis confirmed the presence of the target compounds, showing the expected couplings between the various protons.

Reaction of O-*t*-butyl-L-serine *t*-butyl ester with the acyl chloride resorcin[4]arene gave compound **4g** in 59 % yield. Compound **4h** was synthesized in 60 % yield by reacting L-glutamic acid dimethyl ester with the octa-acid resorcin[4]arene **3**. Compound **4i** was isolated in 67 % yield by reacting *N*ε-Cbz-L-lysine benzyl ester with the octa-acid resorcin[4]arene **3**. The ^{1}H NMR data for compounds **4g–i** are summarized in Table 3.

Subsequent COSY and HSQC NMR analysis confirmed the presence of the target compounds, showing the expected couplings between the various protons.

With reference to Fig. 7, the ^{1}H NMR data (Tables 1, 2 and 3) for these compounds clearly demonstrated that: all compounds had characteristic appearance of the amide NH protons, which appear at a lower frequency indicating the involvement of these protons in intermolecular hydrogen bonding with the water molecules present in the NMR solvent (DMSO), except compound **4e.**[17] The signal for the diastereotopic methylene protons (H_5, Fig. 6) appears as a pair of quartets in the ^{1}H NMR spectra for compounds **4b**, **4c**, **4d**, **4f**, **4g**, **4h**, and **4i**. This splitting can be attributed to the presence of two chiral amino acid units on each aromatic ring[15a,15b]. In compound **4a** where there is no chiral centre, this signal appears as a pair of doublets since the protons are enantiotopic.

The signals for the aromatic protons (H_3 and H_4) appear as two singlets for all compounds. This indicates the symmetric positions of these protons in a *crown* (C_{4v}) conformation at elevated temperature. Therefore, at high temperature, the rate of conformational interchange is high on the NMR timescale and only the signals associated with the *crown* conformation are observed[10a].

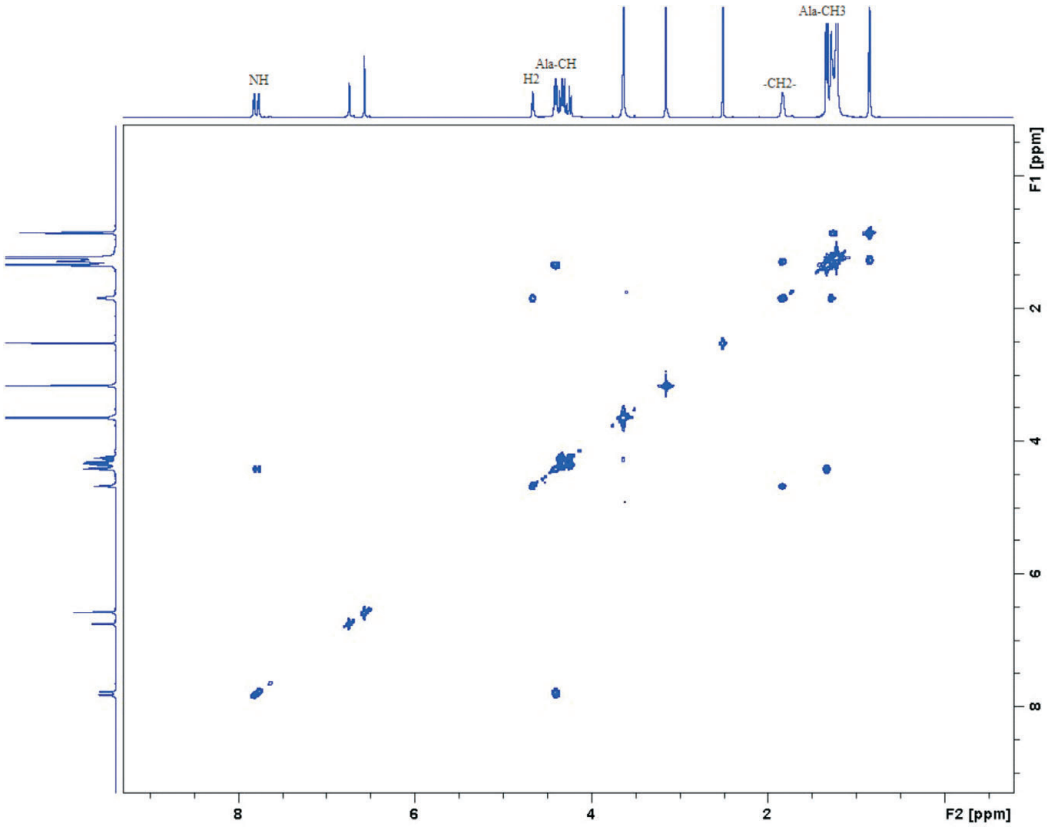


Figure 8 The ^{1}H-^{1}H COSY spectrum for compound **4b** in d_6-DMSO at 70 °C (600 MHz).

The signal related to the methine protons (H_2) which bridge the aromatic moieties, appears as a triplet in ^{1}H NMR spectra for these compounds. The signals associated with the undecyl 'feet' remain essentially unchanged in terms of multiplicity and integration. However, these protons have experienced very small changes in terms of chemical shift.

3. Conclusion

A series of new resorcin[4]arenes appended with amino acid moieties at the upper rim (**4a–i**) were synthesized in good yields (59–76 %). The key step for this synthesis is the amide bond formation between the amine functional group of amino acid units and carboxylic acid group of the octa-acid resorcinarene, **3**. The structure of these octa-substituted resorcinarene derivatives was established on the basis of one and two-dimensional NMR experiments, and confirmed by IR and MS spectra. The ^{1}H NMR data obtained for the protons related to the aromatic rings of resorcin[4]arene scaffold (H_3 and H_4, Fig. 6) verified that these derivatives adopted stable crown conformations (C_{4v} symmetry) at high temperature. Low temperature NMR experiments confirmed that a *boat* conformation predominates for these compounds, which is expected for resorcinarenes with eight bulky substituents. These structures are very similar to previously reported ion channel molecules; we presume that they will be capable of ion translocation activity.

Experimental

Starting materials obtained from commercial suppliers were used without further purification unless otherwise stated. Air- or moisture-sensitive reactions were performed using oven-dried glassware under an inert atmosphere of dry nitrogen. Tetrahydrofuran (THF) was distilled from sodium benzophenoneketyl and dichloromethane was distilled from calcium hydride. Dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) were stored over 4 Å molecular sieves prior to use. Thin layer chromatography (TLC) was performed on aluminium-backed, pre-coated silica gel plates (Merck, silica gel 60 F_{254}, 20 cm × 20 cm). Mobile phases are reported as volume ratios or volume per cent. Compounds were visualized using UV light, *p*-anisaldehyde, or iodine stains. Column chromatography was performed on silica gel 60 (Merck, particle size 0.040–0.063 mm). Eluting solvents are reported as volume ratios or volume per cent. Melting points were recorded and are uncorrected. ^{1}H NMR spectra were recorded on a 400 MHz Bruker AVANCE III or 600 MHz BrukerUltrashield spectrometer, the chemical shifts were referenced to the solvent peak, namely δ = 7.24 ppm for $CDCl_3$, δ = 2.50 ppm for $(CD_3)_2SO$ and δ = 2.05 ppm for $(CD_3)_2CO$ at ambient temperature. The ^{1}H NMR spectra were recorded at a transmitter frequency of 600.1 MHz (spectral width, 12335.5 Hz; acquisition time, 1.328 s; 90 ° pulse width, 15 μs; scans, 16; relaxation delay, 1.0 s) for the Bruker AVANCE III 600 instrument while the ^{1}H NMR spectra were recorded at a transmitter frequency of 400.2 MHz (spectral width, 8223.7 Hz; acquisition time, 3.98 s; 90 ° pulse width, 10 μs; scans, 16; relaxation delay, 1.0 s) for the Brucker AVANCE III 400 instrument. The ^{13}C NMR spectra were recorded at 150.9 MHz (spectral width, 36057.7 Hz; acquisition time, 0.908 s; 0.908 s, 90 ° pulse width, 9.00 μs; scans, 4800; relaxation delay, 2.00 s) for the Bruker AVANCE III 600 instrument while the ^{13}C NMR spectra were recorded at 100.6 MHz (spectral width, 24038.5 Hz; acquisition time, 1.363 s; 90 ° pulse width, 8.40 μs, scans, 3200; relaxation delay, 2.00 s) for the Bruker AVANCE III 400 instrument.

The 2D experimental data parameters obtained on the Bruker AVANCE III 400 were as follows: 90 ° pulse width, 10 μs for all spectra, spectral width for ^{1}H, 3731.3, 3521.1, 3401.3, 3676.4, 3125.0 and 4065.0, 4065.0, 3731.3, 3546.1 Hz for **4a**, **4b**, **4c**, **4d**, **4e**, **4f**, **4g**, **4h** and **4i**, respectively, (COSY and HSQC) spectral width

for ^{13}C, 166670.4 Hz (HSQC) for **4a–i**, number of data points per spectrum, 2048 (COSY), 1024 (HSQC) for compounds **4a–i**; number of time incremental spectra 128 (COSY), 256 (HSQC) for compounds **4a–i**; relaxation delays for compounds for compounds **4a**, **4f**, **4g**, **4h** and **4i** was 1.4s and **4b**, **4c**, **4d** and **4e** was 1.3 s for COSY experiments while the relaxation delay for HSQC experiments had 1.4 s for **4a–i**, respectively. Data are reported as positions in parts per million (δ in ppm), multiplicity (s = singlet, d = doublet, dd = double of doublets, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (J in Hz) and integration (number of protons). ^{13}C NMR spectra were recorded on a 400 MHz Bruker AVANCE (100 MHz) or 600 MHz Bruker Ultrashield spectrometer (150 MHz). Data are reported as positions in parts per million (δ in ppm). Optical rotation data were acquired on a Perkin Elmer Model 341 Polarimeter using a 1 mL cell with a path length of 100 mm. Infrared (IR) spectra were recorded on a Perkin Elmer spectrum 100 instrument with a universal attenuated total reflection (ATR) attachment at room temperature. Wave numbers are reported in units of cm^{-1}. Mass spectra were recorded using a Burker microTOF-Q II Electron Spray Ionization (ESI) Mass Spectrometer (MS).

Synthesis

C-undecyl Resorcin[4]arene Octa-ester, (2)[13a,14]

To a stirring suspension of octol **1** (5.52 g, 5.0 mmol), oven-dried (110 °C) K_2CO_3 (7.6 g, 55 mmol) and a catalytic amount of sodium iodide (NaI) in dry acetonitrile (CH_3CN) (50 mL) was added methyl-2-bromo acetate (3.9 mL, 40.5 mmol). The suspension was refluxed at 82 °C with stirring under a nitrogen atmosphere for 48 hours. After 24 hours another portion of methyl-2-bromoacetate (3.9 mL) was added. After cooling to room temperature, the mixture was filtered and the filtrate was extracted twice with diethyl ether (50 mL). The filtrate was concentrated under reduced pressure to give the crude product, which was re-crystallized from dichloromethane-methanol in 1:1 ratio. The precipitate was filtered and washed with methanol to yield the title compound as a white crystal. (6.5 g, 77 %); mp 90–93 °C [Literature mp 92–94 °C] ; ^{1}H NMR [$CDCl_3$, 400 MHz]: δ = 6.58 (s, 4 H, Ar*H*), 6.20 (s, 4 H, Ar*H*), 4.57 (t, 4 H, C*H* (methine)), 4.30 (s, 16 H, ArOC*H*$_2$), 3.77 (s, 24 H, OC*H*$_3$), 1.90 (q, 8 H, C*H*$_2$(CH$_2$)$_9$CH$_3$), 1.20–1.30 (m, 72 H, CH$_2$(CH$_2$)$_9$CH$_3$), 0.87 (t, 12 H, C*H*$_3$) ppm; ^{13}C NMR [$CDCl_3$, 100 MHz]: δ= 169.81, 154.46, 128.51, 126.56, 100.76, 67.14, 51.91, 35.70, 34.52, 31.93, 30.01, 29.88, 29.79, 29.72, 29.39, 28.08, 22.69, 14.10 ppm; FT-IR/ATR: 2920, 2851, 1756, 1729, 1610, 1586, 1501, 1436, 1405, 1303, 1210, 1179, 1105, 1082, 979, 903, 850, 719, 584, 527 cm^{-1}.

C-undecyl Resorcin[4]arene Octa-acid (3)[14]

To a stirring suspension of **2** (6.0 g, 3.57 mmol) in a mixture of 100 mL of ethanol and 50 mL of water was added potassium hydroxide (5.6 g, 99.96 mmol). The mixture was refluxed under a nitrogen atmosphere for 3 hours. The resulting mixture was concentrated under reduced pressure. The alkaline solution was acidified with 6 M HCl, and the suspension was extracted with ethyl acetate (100 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the crude product was re-crystallized from methanol/water in 1:1 ratio. After drying *in vacuo* the product was obtained as a white solid. (5.20 g, 93 %); mp 183–185 °C [Literature mp 180 °C]; ^{1}H NMR [DMSO-d$_6$, 400 MHz]: δ = 6.49 (s, 4 H, Ar*H*), 6.35 (s, 4 H, Ar*H*), 4.48 (t, 4 H, C*H* (methine)), 4.41 (d, 8 H, J = 16.3 Hz, OC*H*$_2$-COOH), 4.23 (d, 8 H, J = 16.4 Hz, OC*H*$_2$-COOH), 1.75 (q, 8 H, C*H*$_2$(C*H*$_2$)$_9$CH$_3$), 1.20–1.29 (m, 72 H, CH$_2$(C*H*$_2$)$_9$CH$_3$), 0.82(t, 12 H, C*H*$_3$) ppm; ^{13}C NMR [DMSO-d$_6$, 100 MHz]: δ = 170.39, 154.00, 126.12, 125.29, 100.02, 65.89, 38.84, 34.93, 34.09, 31.29, 29.50, 29.25, 29.14, 29.06, 28.73, 27.68, 22.06, 13.85 ppm; FT-IR/ATR: 3195, 2920, 2850, 1719, 1612, 1587, 1499, 1435, 1407, 1298, 1184, 1127, 1105, 1072, 905, 812, 720, 665, 570 cm^{-1}.

General Procedure for the Synthesis of Amino Acid Resorcin[4]arene Derivatives (4a–i)15

To a suspension of **3** (1.0 g, 0.64 mmol) in dry CH_2Cl_2 (30 mL) was added freshly distilled oxalyl chloride (1.1 mL, 12.80 mmol), and the mixture was refluxed for 18 hours under a nitrogen atmosphere. The unreacted oxalyl chloride and solvent were removed *in vacuo*, and the product obtained was dried under vacuum for 1 hour. Subsequently, it was dissolved in dry CH_2Cl_2 (20 mL), and slowly added to a cooled solution (0 °C) of amino acid ester hydrochloride (5.74 mmol) and triethyl amine (Et_3 N) (1.35 mL, 9.80 mmol) in dry CH_2Cl_2 (20 mL). The reaction mixture was allowed to warm up to room temperature and stirred under a nitrogen atmosphere for 18 hours. The solution mixture was treated with 1M HCl (30 mL), and the organic layer was separated, washed with water (30 mL), and brine (30 mL). The organic layer was dried over anhydrous Na_2SO_4. The solution was filtered, and the solvent was removed under pressure, yielding a sticky residue. The residue obtained was purified on silica gel chromatography using 3 % methanol in chloroform as a mobile phase. The fractions collected were concentrated with a rotary evaporator to give a white gum. These products were triturated with methanol to yield the title compounds as white solids.

Octa-glycine ethyl ester resorcinarene (4a)

Glycine ethyl ester hydrochloride (0.80 g, 5.74 mmol) was used as in the general procedure. The product was obtained as a white solid. (1.09 g, 76 %), R_f = 0.42 (3 % MeOH/CH_3Cl), mp 97–100 °C; ^{1}H NMR [DMSO-d$_6$, 600 MHz, 70 °C]: δ = 7.72 (t, J = 5.1 Hz 8 H, N*H*), 6.73 (s, 4 H, Ar*H*), 6.57 (s, 4 H, Ar*H*), 4.69 (t, J = 8.0 Hz 4 H, C*H* (methine)), 4.36 (d, J = 14.7 Hz, 8 H, ArOC*H*$_2$), 4.27 (d, J = 14.7 Hz, 8 H, ArOC*H*$_2$), 4.12 (q, J = 7.0 Hz 16 H, COOC*H*$_2$CH$_3$), 3.96 (dd, J = 5.1 Hz 8 H, Gly-C*H*$_2$), 3.85 (dd, J = 5.8 Hz, 8 H, Gly-C*H*$_2$), 1.81 (q, J = 6.5 Hz 8 H, C*H*$_2$(CH$_2$)$_9$CH$_3$), 1.20 (t, J = 8.5 Hz 24 H, COOCH$_2$C*H*$_3$), 1.22–1.27 (m, 72 H, CH$_2$(C*H*$_2$)$_9$CH$_3$), 0.84 (t, J = 7.5 Hz 12 H, C*H*$_3$) ppm; ^{13}C NMR [DMSO-d$_6$, 150 MHz, 70 °C]: δ = 169.83, 168.82, 154.16, 127.08, 126.24, 100.84, 68.60, 60.89, 35.27, 35.14, 31.70, 29.90, 29.55, 29.51, 29.44, 29.10, 27.84, 22.44, 14.41, 14.19 ppm; FT-IR/ATR: 3414, 2920, 2851, 1757, 1731, 1664, 1586, 1501, 1437, 1406, 1376, 1293, 1191, 1126, 1085, 1025, 904, 850, 720, 582 cm^{-1}; MS (ESI-TOF) Calculated for $C_{120}H_{184}O_{32}N_8Na$ [M+Na]$^+$: m/z = 2273.2942, Found: *m*/*z* = 2273.2926.

Octa-alanine Methyl Ester Resorcinarene (4b)

L-Alanine methyl ester hydrochloride (0.80 g, 5.74 mmol) was used as in the general procedure. The product was obtained as a white solid. (1.05 g, 73 %); R_f = 0.45 (3 % MeOH/CH_3Cl); mp 96–99 °C; $[\alpha]^{20}_D$ = –9.09 (c = 1.10, $CHCl_3$); ^{1}H NMR [DMSO-d$_6$, 600 MHz, 70 °C]: δ = 7.82 (d, J = 7.3 Hz, 4 H, N*H*), 7.80 (d, J = 7.3 Hz, 4 H, N*H*), 6.73 (s, 4 H, Ar*H*), 6.56 (s, 4 H, Ar*H*), 4.67 (t, J = 5.0 Hz 4 H, C*H* (methine)), 4.42 (q, J = 8.5 Hz 8 H, Ala-α H), 4.35 (q, J = 5.0 Hz 8 H, ArOC*H*$_2$), 4.24 (q, J = 5.0 Hz 8 H, ArOC*H*$_2$), 3.64 (d, J = 7.0 Hz 24 H, OC*H*$_3$), 1.83 (q, J = 6.5 Hz 8 H, C*H*$_2$(CH$_2$)$_9$CH$_3$), 1.34 (t, J = 7.2 Hz 24 H, Ala-C*H*$_3$), 1.20–1.28 (m, 72 H, CH$_2$(C*H*$_2$)$_9$CH$_3$), 0.84 (t, J = 6.0 Hz 12 H, C*H*$_3$) ppm; ^{13}C NMR [DMSO-d$_6$, 150 MHz, 70 °C]: δ = 172.92, 172.84, 168.18, 168.09, 154.40, 127.19, 127.13, 126.27, 101.43, 68.80, 68.76, 52.27, 47.83, 47.77, 35.39, 35.13, 31.69, 29.88, 29.50, 29.41, 29.08, 28.09, 22.44, 17.46, 17.43, 14.18 ppm; FT-IR/ATR: 3408, 2923, 2853, 1741, 1676,

1613, 1568, 1521, 1499, 1436, 1345, 1293, 1211, 1157, 1107, 1055, 987, 905, 851, 756, 720, 634, 541 cm^{-1}; MS (ESI-TOF) Calculated for $C_{120}H_{184}O_{32}N_8Na$ $[M+Na]^+$: *m/z* = 2273.2942, Found: *m/z* = 2273.2969.

Octa-phenylalanine Methyl Ester Resorcinarene (4c)

L-Phenylalanine methyl ester hydrochloride (1.24 g, 5.74 mmol) was used as in the general procedure. The product was obtained as a white solid. (1.30 g, 71 %); R_f = 0.56 (3 % MeOH/CH_3Cl); mp 58–61 °C; $[\alpha]^{20}_D$ = +24.24 (*c* = 1.10, $CHCl_3$); ^{1}H NMR [DMSO-d_6, 600 MHz, 70 °C]: ddd = 7.77 (d, *J* = 8.2 Hz, 4 H, N*H*), 7.60 (d, *J* = 8.2 Hz, 4 H, N*H*), 7.04–7.15 (m, 40 H, Phe-Ar*H*), 6.96 (s, 4 H, Ar*H*), 6.33 (s, 4 H, Ar*H*), 4.64 (q, *J* = 8.0 Hz 8 H, Phe-α *H*), 4.64 (t, *J* = 6.3 Hz 4 H, C*H* (methine)), 4.28 (q, *J* = 7.1 Hz, 8 H, ArOCH_2), 4.20 (q, *J* = 7.1 Hz, 8 H, ArOCH_2), 3.59 (d, , *J* = 7.1 Hz, 24 H, OCH_3), 3.11 (dd, , *J* = 6.0 Hz, 4 H, Phe-ArCH_2), 3.04 (dd, , *J* = 6.0 Hz, 4 H, Phe-ArCH_2), 3.03 (dd, *J* = 6.3 Hz, 4 H, Phe-ArCH_2), 2.87 (dd, *J* = 6.3 Hz, 4 H, Phe-ArCH_2), 2.17 (q, *J* = 7.0 Hz, 8 H, CH_2(CH_2)$_9$$CH_3$), 1.20–1.28 (m, 72 H, C$H_2$($CH_2$)$_9$$CH_3$), 0.83 (t, *J* = 6.3 Hz, 12 H, CH_3) ppm; ^{13}C NMR [DMSO-d_6, 150 MHz, 70 °C]: δ = 171.77, 171.73, 168.32, 168.27, 154.16, 137.27, 137.07, 129.36, 129.33, 128.67, 128.57, 128.52, 127.07, 126.87, 126.77, 126.35, 125.31, 100.43, 68.33, 53.59, 53.42, 52.23, 52.20, 37.39, 37.26, 36.07, 34.78, 34.59, 31.71, 30.95, 29.96, 29.59, 29.52, 29.43, 29.11, 27.86, 22.44, 21.42, 14.17 ppm; FT-IR/ATR: 3411, 3030, 2923, 2853, 1741, 1682, 1607, 1586, 1497, 1436, 1358, 1288, 1192, 1123, 1060, 905, 849, 815, 743, 699, 540, 490 cm^{-1}; MS (ESI-TOF) Calculated for $C_{168}H_{216}O_{32}N_8Na$ $[M+Na]^+$: m/z = 2881.5446, Found: *m/z* = 2881.7059.

Octa-leucine Methyl Ester Resorcinarene (4d)

L-Leucine methyl ester hydrochloride (1.04 g, 5.74 mmol) was used as in the general procedure. The product was obtained as a white solid. (1.22 g, 72 %); R_f = 0.56 (3 % MeOH/CH_3Cl); mp 61–64 °C; $[\alpha]^{20}_D$ = –20.00 (*c* = 1.05, $CHCl_3$); ^{1}H NMR [DMSO-d_6, 600 MHz, 70 °C]: δ = 8.02 (d, *J* = 8.1 Hz, 4 H, N*H*), 7.79 (d, *J* = 8.1 Hz, 4 H, N*H*), 6.89 (s, 4 H, Ar*H*), 6.53 (s, 4 H, Ar*H*), 4.77 (t, *J* = 7.5 Hz, 4 H, C*H* (methine)), 4.47 (q, *J* = 3.56 Hz, 8 H, Leu-α *H*), 4.46 (q, *J* = 7.1 Hz, 8 H, ArOCH_2), 4.36 (q, *J* = 7.6 Hz, 8 H, ArOCH_2), 3.62 (d, *J* = 17.5 Hz, 24 H, OCH_3), 1.81 (q, *J* = 6.7 Hz, 8 H, CH_2(CH_2)$_9$$CH_3$), 1.45–1.67 (m, 24 H, Leu-C*H* and Leu-CH_2), 1.20–1.28 (m, 72 H, CH_2(CH_2)$_9$$CH_3$), 0.87 (t, *J* = 7.5 Hz, 24 H, Leu-CH_3), 0.84 (t, *J* = 7.1 Hz, 12 H, CH_3), 0.77 (t, *J* = 7.2 Hz, 24 H, Leu-CH_3) ppm; ^{13}C NMR [DMSO-d_6, 150 MHz, 70 °C]: δ = 172.83, 172.70, 168.36, 168.27, 154.32, 154.11, 127.38, 127.11, 126.41, 100.99, 68.81, 68.55, 52.18, 50.42, 35.82, 34.81, 31.68, 29.96, 29.55, 29.52, 29.50, 29.39, 29.08, 28.05, 24.83, 24.69, 22.98, 22.92, 22.42, 21.80, 21.72, 14.15 ppm; FT-IR/ATR: 3415, 2924, 2853, 1742, 1679, 1613, 1585, 1523, 1498, 1437, 1368, 1275, 1196, 1154, 1104, 1056, 985, 902, 827, 721, 546, 466 cm^{-1}; MS (ESI-TOF) Calculated for $C_{144}H_{232}O_{32}N_8Na$ $[M+Na]^+$: *m/z* = 2609.3198, Found: *m/z* = 2609.3148.

Octa-proline Methyl Ester Resorcinarene (4e)

L-Proline methyl ester hydrochloride (0.95 g, 1.75 mmol), was used as in the general procedure. The product was obtained as a white solid. (1.08 g, 69 %); R_f = 0.43 (3 % MeOH/CH_3Cl); mp 65–68 °C; $[\alpha]^{20}_D$ = –80.00 (*c* = 1.00, $CHCl_3$); ^{1}H NMR [DMSO-d_6, 600 MHz, 70 °C]: δ = 6.82 (br s, 4 H, Ar*H*), 6.38 (br s, 4 H, Ar*H*), 4.68 (t, *J* = 7.9 Hz, 4 H, C*H* (methine)), 4.48 (br d, 16 H, ArOCH_2), 4.38 (q, *J* = 5.66 Hz, 8 H, Pro-α *H*), 3.69 (d, *J* = 7.3 Hz, 24 H, OCH_3), 3.56 (m, 16 H, Pro-δ *H*), 2.41(m, 8 H, Pro-β *H*), 2.00–2.15 (m, 24 H, Pro-β *H* and γ *H*), 1.90 (q, *J* = 4.3 Hz, 8 H, CH_2(CH_2)$_9$$CH_3$), 1.20–1.30 (m, 72 H, CH_2(CH_2)$_9$$CH_3$), 0.86 (t, *J* = 6.5 Hz,12 H, CH_3) ppm; ^{13}C NMR [DMSO-d_6, 150 MHz, 70 °C]: δ = 172.61, 167.00, 154.85, 126.46, 99.99, 68.91, 68.82, 59.18, 51.95, 46.39, 41.08, 35.87, 34.89, 31.65, 29.80, 29.50, 29.49, 29.44, 29.37, 29.01, 28.85, 28.00, 24.94, 22.34, 14.01 ppm; FT-IR/ATR: 3473, 2923, 2852, 1740, 1645, 1499, 1433, 1343, 1294, 1171, 1126, 1043, 910, 842, 720, 540, 416 cm^{-1}; MS (ESI-TOF) Calculated for $C_{136}H_{200}O_{32}N_8Na$ $[M+Na]^+$: *m/z* = 2481.4193, Found: *m/z* = 2481.4062.

Octa-tryptophan Methyl Ester Resorcinarene (4f)

L-Tryptophan methyl ester hydrochloride (1.46 g, 5.74 mmol), was used as in the general procedure. The product was obtained as a white solid. (1.29 g, 64 %), R_f = 0.42 (3 % MeOH/CH_3Cl), mp 64–67 °C; $[\alpha]^{20}_D$ = +50.00 (*c* = 1.00, $CHCl_3$); ^{1}H NMR [DMSO-d_6, 600 MHz, 70 °C]: δ = 10.42 (s, 4 H, N*H*-Indole), 10.32 (s, 4 H, N*H*-Indole), 7.63 (d, *J* = 7.56 Hz, 4 H, N*H*), 7.55 (d, *J* = 7.68 Hz, 4 H, N*H*), 7.48 (t, *J* = 6.5 Hz, 8 H, *H*7-Indole), 7.29 (dd, *J* = 8.10 Hz, 8 H, *H*4-Indole), 7.02 (t, *J* = 7.4 Hz, 8 H, *H*5-Indole), 7.00 (t, *J* = 7.5 Hz, 8 H, *H*6-Indole), 6.90 (s, 8 H, *H*2-Indole), 6.80 (s, 4 H, Ar*H*), 6.47 (s, 4 H, Ar*H*), 4.71 (q, *J* = 7.1 Hz, 8 H, Trp-α *H*), 4.63 (t, *J* = 8.0 Hz, 4 H, C*H* (methine)), 4.32 (q, *J* = 7.0 Hz, 8 H, ArOCH_2), 4.26 (q, *J* = 7.2 Hz, 8 H, ArOCH_2), 3.68 (d, *J* = 6.5 Hz, 24 H, OCH_3), 3.11–3.25 (m, 16 H, Trp-β *H*), 1.83 (q, *J* = 7.7 Hz, 8 H, CH_2(CH_2)$_9$$CH_3$), 1.20–1.28 (m, 72 H, CH_2(CH_2)$_9$$CH_3$), 0.85 (t, *J* = 6.5 Hz, 12 H, CH_3) ppm; ^{13}C NMR [DMSO-d_6, 150 MHz, 70 °C]: δ = 172.19, 172.14, 168.44, 168.35, 154.46, 139.53, 136.68, 136.65, 127.67, 127.60, 125.33, 123.97, 123.92, 121.36, 118.86, 118.39, 111.82, 111.79, 109.68, 109.56, 101.37, 68.85, 68.72, 53.41, 53.28, 52.12, 52.09, 35.39, 35.26, 34.80, 31.85, 30.96, 29.99, 29.65, 29.53, 29.44, 29.11, 28.02, 27.87, 27.84, 22.44, 21.42,14.19 ppm; FT-IR/ATR: 3403, 3056, 2923, 2852, 1738, 1671, 1585, 1496, 1435, 1341, 1287, 1213, 1179, 1098, 1059, 928, 860, 739, 548, 424 cm^{-1}; MS (ESI-TOF) Calculated for $C_{184}H_{224}O_{32}N_{16}Na$ $[M+Na]^+$: *m/z* = 3194.6348, Found: *m/z* = 3194.6451.

Octa-serine (O-t-butyl) *t*-Butyl Ester Resorcinarene (4g)

O-*t*-Butyl-L-serine *t*-butyl hydrochloride (1.46 g, 5.74 mmol), was used in the general method. The product was obtained as a white solid. (1.19 g, 59 %), R_f = 0.62 (3 % MeOH/CH_3Cl), mp 56–59 °C; $[\alpha]^{20}_D$ = +20.00 (*c* = 1.00, $CHCl_3$); ^{1}H NMR [DMSO-d_6, 600 MHz, 70 °C]: δ = 7.27 (d, *J* = 8.2 Hz, 4 H, N*H*), 7.24 (d, *J* = 8.1 Hz, 4 H, N*H*), 6.73 (s, 4 H, Ar*H*), 6.53 (s, 4 H, Ar*H*), 4.63 (t, *J* = 8.0 Hz, 4 H, C*H* (methine)), 4.46 (q, *J* = 5.72 Hz, 8 H, Ser-α *H*), 4.36 (d, *J* = 14.70 Hz, 4 H, ArOCH_2), 4.28 (d, *J* = 14.94 Hz, 4 H, ArOCH_2), 4.25 (d, *J* = 14.88 Hz, 4 H, ArOCH_2), 4.18 (d, *J* = 14.82 Hz, 4 H, ArOCH_2), 3.70 (dd, *J* = 3.1Hz, 8 H, Ser-β CH_2), 3.54 (dd, *J* = 4.6 Hz, 8 H, Ser-β CH_2), 1.86 (q, *J* = 6.4 Hz, 8 H, CH_2(CH_2)$_9$$CH_3$), 1.40 (d, J = 3.5 Hz, 72 H, Ser-*t-But*), 1.20–1.28 (m, 72 H, CH_2(CH_2)$_9$$CH_3$), 1.09 (d, *J* = 3.8 Hz, 72 H, Ser-*t-But*), 0.86 (t, *J* = 6.5 Hz, 12 H, CH_3) ppm; ^{13}C NMR [DMSO-d_6, 150 MHz, 70 °C]: δ 169.19, 168.22, 168.00, 154.69, 154.46, 154.39, 127.69, 127.58, 126.40, 101.57, 81.44, 81.35, 81.33, 73.12, 73.06, 73.03, 69.43, 69.04, 62.37, 62.28, 53.46, 53.40, 53.32,. 35.72, 35.25, 31.61, 30.70, 29.58, 29.49, 29.44, 29.32, 29.00, 27.89, 22.33, 22.31, 14.01 ppm; FT-IR/ATR: 3430, 2973, 2926, 2855, 1738, 1684, 1587, 1500, 1468, 1365, 1293, 1247, 1192, 1147, 1098, 1058, 989, 906, 877, 848, 736, 646, 566 cm^{-1}; MS (ESI-TOF) Calculated for $C_{176}H_{296}O_{40}N_8Na$ $[M+Na]^+$: *m/z* = 3187.1331, Found: *m/z* = 3187.1433.

Octa-gulatmicacid (O -methoxy) Methyl Ester Resorcinarene (4h)

L-Glutamic acid dimethyl ester hydrochloride (1.22 g, 5.74 mmol), was used as in the general method. The product was obtained as a white solid. (1.10 g, 60 %), R_f = 0.46 (3 % MeOH/CH_3Cl), mp 54–57 °C; $[\alpha]^{20}_D$ = –10.00 (*c* = 1.00, $CHCl_3$); ^{1}H NMR [DMSO-d_6, 600 MHz, 70 °C]: δ = 7.66 (d d, *J* = 7.4 Hz, 8 H, N*H*), 6.81 (s, 4 H, Ar*H*), 6.55 (s, 4 H, Ar*H*), 4.69 (t, *J* = 7.2 Hz,

4 H, C*H* (methine)), 4.44 (q, *J* = 8.56 Hz, 8 H, Glu-α *H*), 4.32 (q, *J* = 8.56 Hz, 8 H, ArOCH_2), 4.30 (q, *J* = 7.9 Hz, 8 H, ArOCH_2), 3.70 (s, 24 H, OCH_3), 3.58 (d, *J* = 3.81 Hz, 24 H, OCH_3), 2.36 (q, *J* = 4.2 Hz,16 H, Glu-γ *H*), 2.13 (m, 8 H, Glu-β *H*), 1.96 (m, 8 H, Glu-β *H*), 1.86 (q, *J* = 5.1 Hz, 8 H, CH_2(CH$_2$)$_9$CH$_3$), 1.20–1.29 (m, 72 H, CH$_2$(CH_2)$_9$CH$_3$), 0.87 (t, *J* = 6.5 Hz, 12 H, CH_3) ppm; ^{13}C NMR [DMSO-d$_6$, 150 MHz, 70 °C]: δ = 172.89, 172.87, 171.97, 171.93, 168.59, 154.47, 154.37, 127.26, 126.38, 101,26, 68.86, 68.65, 52.33, 52.32, 51.65, 51.62,51.45, 51.40, 35.11, 31.69, 30.12, 30.01, 29.95, 29.58, 29.51, 29.42, 29.09, 28.02, 26.74, 26.70, 22.44, 14.18 ppm; FT-IR/ATR: 3408, 2924, 2853, 1736, 1680, 1585, 1522, 1499, 1436, 1369, 1293, 1194, 1170, 1126, 1056, 985, 901, 824, 721, 638, 556 cm^{-1}; MS (ESI-TOF) Calculated for $C_{144}H_{216}O_{48}N_8Na$ [M+Na]$^+$: *m*/*z* = 2849.4632, Found: *m*/*z* = 2849.4642.

Octa-lysine (Nε-benzyloxyl) Benzyl Ester Resorcinarene (4i)

*N*ε-Cbz-L-lysine benzyl ester hydrochloride (2.34 g, 5.74 mmol), was used as in the general procedure. The product was obtained as a white solid. (1.88 g, 67 %), R$_f$ = 0.52 (3 % MeOH/CH$_3$Cl), mp 57–60 °C; $[\alpha]^{20}_D$ = +7.69 (*c* = 1.26, CHCl$_3$); ^{1}H NMR [DMSO-d$_6$, 600 MHz, 70 °C]: δ = 7.61 (dd, *J* = 7.8 Hz, 8 H, N*H*), 7.26–7.36 (m, 80 H, Lys-Ar*H*), 6.84 (s, 4 H, Ar*H*), 6.61 (br t, 8 H, Lys-ε N*H*), 6.59 (s, 4 H, Ar*H*), 5.13 (m, 16 H, Lys-cbz-CH_2O), 4.77 (s, 16 H, Lys-Bn-CH_2O,), 4.68 (t, *J* = 7.2 Hz, 4 H, C*H* (methine)), 4.44 (q, *J* = 6.1 Hz, 8 H, Lys-α *H*), 4.35 (q, *J* = 8.42 Hz, 8 H, ArOCH_2), 4.27 (q, *J* = 8.0 Hz, 8 H, ArOCH_2), 3.10 (q, J = 5.2 Hz, 16 H, Lys-ε CH_2), 1.86 (q, *J* = 6.8 Hz, 8 H, CH$_2$(CH$_2$)$_9$CH$_3$), 1.82 (m, 8 H, Lys-β CH_2), 1.78 (m, 8 H, Lys-β CH_2), 1.39 (m, 16 H, Lys-δ CH_2), 1.39 (m, 16 H, Lys-γ CH_2), 1.20–1.28 (m, 72 H, CH$_2$(CH_2)$_9$CH$_3$), 0.80 (t, *J* = 6.7 Hz, 12 H, CH_3) ppm, ^{13}C NMR [DMSO-d$_6$, 150 MHz, 70 °C]: δ = 171.84, 171.82, 168.52, 168.44, 156.50, 154.76, 154.66, 137.87, 136.32, 136.29, 128.80, 128.42, 128.33, 128.13, 128.12, 127.96, 127.71, 126.49, 125.29, 101.92, 69.35, 69.14, 66.63, 66.60, 65.73, 52.43, 52.40, 49.05, 35.51, 34.75, 31.63, 31.55, 31.02, 29.99, 29.58, 29.50, 29.46, 29.39, 29.02, 28.05, 22.99, 22.33, 14.00 ppm; FT-IR/ATR: 3324, 3064, 3033, 2924, 2854, 1682, 1585, 1521, 1498, 1455, 1345, 1244, 1177, 1128, 1055, 1027, 910, 824, 735, 695, 576, 458 cm^{-1}; MS (ESI-TOF) Calculated for $C_{256}H_{320}O_{48}N_{16}Na$ [M+Na]$^{+½}$: *m*/*z* = 2217.1575, Found: *m*/*z* = 2217.1494.

Supplementary material

The proton and carbon NMR data can be found in the online supplement.

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