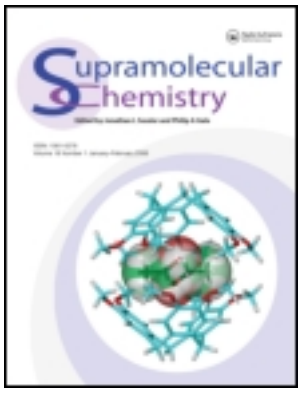

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Synthesis of inherently chiral wide rim ABC substituted calix[6]arene derivatives

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An efficient synthetic route to inherently chiral calix[6]arenes with an ABC substitution pattern at the wide rim and a mesitylenyl unit at the narrow rim in the cone conformation was developed for the first time. Based on the selective formylation and bromination of 1,3,5-bridged calix[6]arene **1**, two new inherently chiral calix[6]arene derivatives **4** and **5** have been prepared with moderate yields. The ^{1}H NMR spectra indicate that these inherently chiral compounds adopt a cone conformation and their three different groups at the wide rim can create a chiral environment inside the cavity that maybe sensed by some chiral guests, which has also been confirmed by X-ray crystal structure of **4** and molecular modelling of **5**. Complexation studies show that **5** displays exceptional properties for the binding of $EtNH_3^+Pic^-$.

Keywords: calix[6]arene; inherently chiral; cone conformation; synthesis

Introduction

Chiral calixarenes, a class of representative chiral macrocyclic compounds, have received increasing interests in recent years, as it is important to develop new chiral receptors and provide potent tools for understanding the stereochemistry of biochemical systems (*1*). Two general strategies have been employed to impart chirality to calixarene structures: appending chiral auxiliaries onto the achiral molecular framework or appending achiral moieties in an asymmetric substitution pattern onto the aromatic residues, thereby creating inherently chiral calixarenes (*2*). Over the past two decades, many inherently chiral calix[4]arenes have been prepared (*3*), and some of them have successfully been applied to chiral recognition and asymmetric catalysis (*1*, *4*). In contrast, only a few examples of the synthesis of inherently chiral calix[6]arenes have been reported (*2*, *5*). These limited results might arise from the difficulties associated with both the immobility of a highly flexible conformation of calix[6]arene and design of a synthetic route to functionalise inherently chiral calix[6]arenes. Herein, we used 1,3,5-bridged calix[6]arene **1** as the starting material, introduced two different monosubstitutions on the wide rim and successfully synthesised two inherently chiral ABC-type calix[6] arenes containing a mesitylenyl unit at the narrow rim. Such an inherently chiral wide rim ABC-substituted calix[6]arene with control of the conformation is very rare. Thus, we wish to report the development of an efficient synthetic route to the inherently chiral wide rim ABC-type calix[6]arenes fixed in a cone conformation.

Results and discussions

The synthesis of inherently chiral calix[6]arenes **4** and **5** was depicted in Scheme 1. 1,3,5-Bridged calix[6]arene **1** reported by Shinkai. et al. (*6*), which is immobilised in a cone conformation by mesitylenyl group on the narrow rim at 30–130°C on the NMR timescale and has three de-*p-tert*-butylated positions on the wide rim, is an ideal platform to introduce inherent chirality by multifunctionalisation. **1** was first monoformylated with hexamethylenetetramine in trifluoroacetic acid at reflux. The monoformylation product, compound **2**, was successfully obtained in a 40% yield by controlling the equivalents of the formylation reagents and reaction time.[1] The ^{1}H NMR spectrum shows only one formyl group (9.98 ppm) that exists in compound **2**. Subsequently, we expected to desymmetrise compound **2** into inherently chiral calix[6]-arene **5** through monobromination on the wide rim. Bromination of compound **2** was carried out with bromine in chloroform at 0°C. Unexpectedly, the desirable compound **5** was not obtained under this reaction condition. However, it is very interesting that a 1,3-bridged calix[6]arene **3** and an inherently chiral 1,3-bridged calix[6]arene **4** were separated from the reaction mixture in 20 and 75% yields, respectively.[2] The result shows that $ArCH_2OAr$ or $ArCH_2OArCHO$ bridge was cleaved when the bromination took place.

It is seen from the ^{1}H NMR spectrum of compound **3** that *tert*-butyl protons appear in 1:2 ratio, methoxy protons in 1:2 ratio and bridging methylene protons in 1:1:1 ratio (three pairs of doublets), which proves that compound **3** is symmetric and adopts a cone conformation (Table 1).

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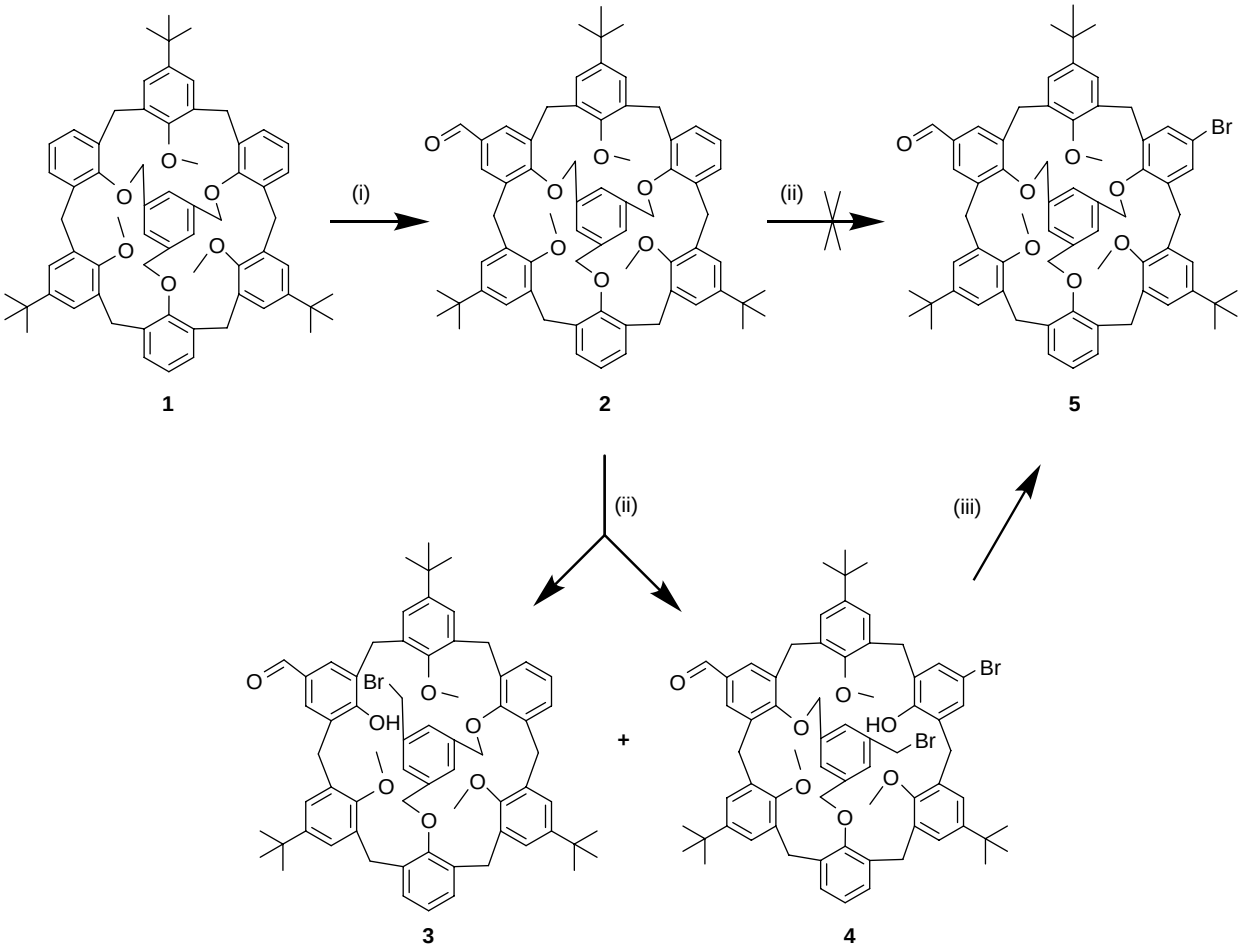

Scheme 1. Reagents and condition: (i) $(CH_2)_6N_4$, CF_3COOH, reflux; (ii) Br_2, $CHCl_3$; (iii) NaH, THF, reflux.

Table 1. ^{1}H NMR chemical shifts of methylene bridge, aromatic *tert*-butyl and aromatic methoxyl protons of compounds **3**, **4** and **5** (ppm).

	$ArOCH_2Ar$[a] (ppm)	$ArCH_2Ar$[b] (ppm)	$ArOCH_3$ (ppm)	Ar^{t}Bu (ppm)
3	4.92 (d, 2H)	4.58 (d, 2H)	3.64 (3H)	1.18 (18H)
	4.70 (d, 2H)	4.36 (d, 2H)	2.96 (6H)	0.82 (9H)
		3.72 (d, 4H)		
		3.50 (d, 4H)		
4	5.02 (d, 1H)	4.70–4.65 (m, 2H)	3.66 (3H)	1.24 (18H)
	4.86 (d, 1H)	4.36 (d, 1H)	2.94 (3H)	0.81 (9H)
	4.63 (d, 1H)	4.31 (d, 1H)	2.79 (3H)	
	4.56 (d, 1H)	3.84 (d, 1H)		
		3.82 (d, 1H)		
		3.59–3.52 (m, 2H)		
		3.51–3.42 (m, 4H)		
5	4.96 (s, 2H)	4.83–4.75 (m, 6H)	3.86 (3H)	0.74 (9H)
	4.87 (s, 2H)	3.71 (d, 2H)	3.85 (3H)	0.73 (9H)
	4.84 (s, 2H)	3.60 (d, 2H)	3.84 (3H)	0.72 (9H)
		3.54 (d, 2H)		

[a] All of the peaks are doublets with coupling constants about 11 Hz.
[b] All of the peaks are doublets with coupling constants about 15 Hz.

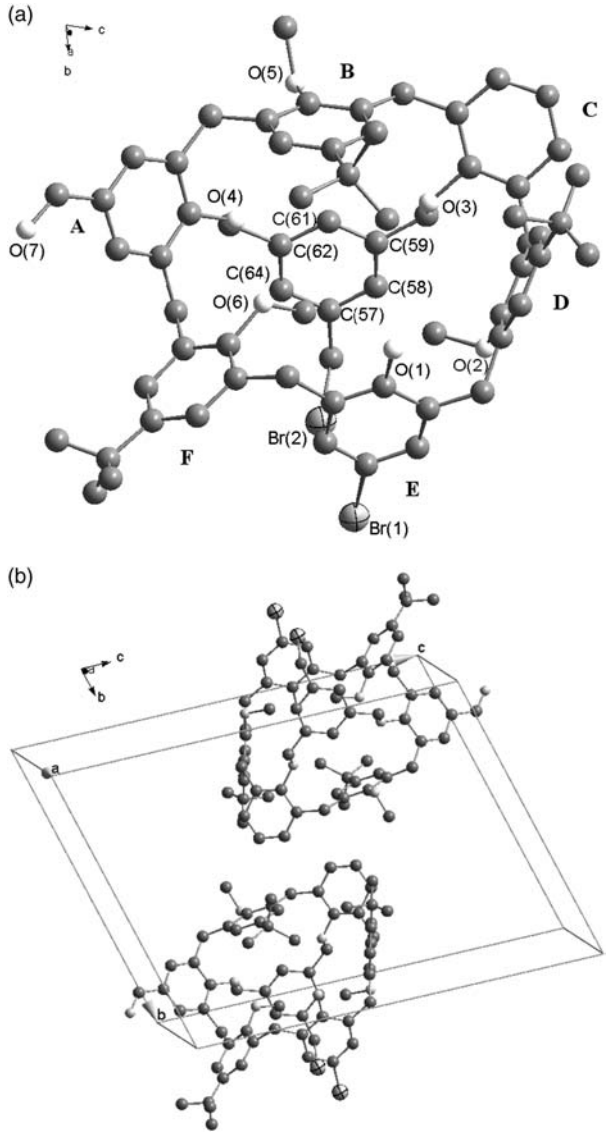

Figure 1. (a) X-ray structure of compound **4**. (b) The packing mode in **4** viewed in the *b* direction. (Hydrogen atoms are omitted for clarity.)

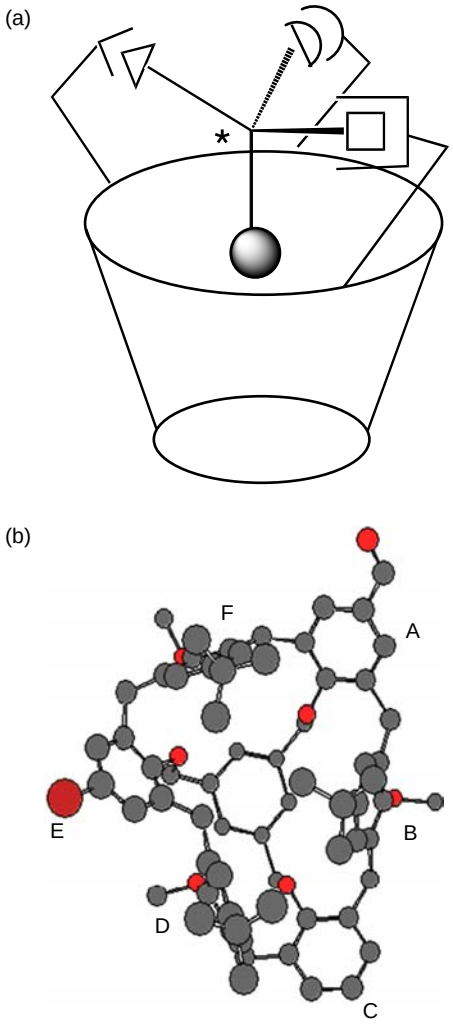

Figure 2. (a) Chiral recognition by compound **4** or **5** and (b) the optimised conformation of compound **5** (top view).

The upfield shift of *tert*-butyl protons (0.82 ppm) and the downfield shift of methoxy protons (3.64 ppm) indicate that one anisole unit should be upright, and, therefore, its *tert*-butyl group is oriented towards the hydrophobic cavity, while its methoxy group is in the out position. Taking the symmetry of this molecule into account, we deduced that the upright anisole unit is between the two bridged phenyl units.

The ^{1}H NMR spectrum of compound **4** presents that three MeO groups show three singlets, and two methylene groups of $ArCH_2OAr$ and $ArCH_2OArCHO$ bridge show four pairs of doublets in AB systems (Table 1). Although its $ArCH_2Ar$ methylene signals are complicated (partly overlapping each other) and therefore difficult to be assigned, four protons of $ArCH_2Ar$ methylene groups (4.36, 4.31, 3.84 and 3.82 ppm) are still clearly found to be splitted into four doublets in AX systems. These signals sufficiently prove that compound **4** is asymmetric and still immobilised in cone.

X-ray quality crystals of **4**[3] were grown from $CHCl_3$/CH_3OH solution. The molecular structure is presented in Figure 1. Coincided with its ^{1}H NMR spectra, the calix[6]arene host stands in a distorted cone conformation with no symmetry. The two bridged phenyl units A and C are flattened, whereas the formyl group of A is outward. The phenyl units B and D are upright, and, interestingly, the methoxyl group is oriented towards the cavity, which may be beneficial to stabilise calix[6]arene's conformation. Other two phenyl units E and F are also flattened and, thus, the bromine group of E and *tert*-butyl group of F are in the out position. It can be seen from its X-ray structure that the asymmetric array of achiral subunits on the calix[6]arene skeleton tries to avoid a steric hindrance. In the unit cell, the enantiomer molecules of **4** are closely packed, building 1D

chains by π–π stacking [$d = 3.455$], C═O···H between formyl groups of unit A and aromatic hydrogen groups of unit E [$d = 3.405$], and CH···π interactions between these outside methylene groups and their nearby aromatic walls [$d = 3.541$]. These 1D chains are interconnected via π–π stacking [$d = 3.543$] of the peripheral anisole units, forming a 2D sheet structure.

In order to synthesise an expected inherently chiral calix[6]arene, compound **4** was intramolecularly etherified with NaH in dried THF under reflux. Fortunately, compound **5** was successfully obtained in a high yield.[4] From its ^{1}H NMR and ^{13}C NMR spectra, we can find that three *tert*-butyl groups show three singlets (^{1}H signal: 0.72, 0.73 and 0.74 ppm), three methoxyl groups show three singlets (^{1}H signal: 3.84, 3.85 and 3.86 ppm; ^{13}C signal: 60.01, 60.05 and 60.08 ppm) and three methylene groups of $ArCH_2OAr$ bridges show three singlets (^{1}H signal: 4.84, 4.87 and 4.96 ppm; ^{13}C signal: 70.92, 71.15 and 71.60 ppm; Table 1). This clearly indicates that the three different groups at the wide rim create a chiral environment inside the cavity that may be sensed by some chiral guests (Figure 2a).

We also chose AM1 level in Gaussian 03 package to optimise the conformation of compound **5** (Figure 2b). The starting model was referenced to the structure deduced from the NMR spectrum and the optimised conformation is shown in Figure 2. It can be seen that the mesitylenyl unit at the narrow rim is bridged with three flattened anisole units A, C and E, respectively, which fix **5** in a cone conformation. The other units B, D and F adopt upright positions, respectively, where their methoxyl groups at the narrow rim in the outward position and *tert*-butyl groups at the wide rim are oriented towards the cavity, which is in agreement with the result from ^{1}H NMR spectra.

^{1}H NMR studies of host–guest complex with ammonium (**5** ⊃ $EtNH_3^+Pic^-$) were carried out at room temperature by introducing a CD_3OD solution of 1 equiv. of ammonium picrate salts into a solution of **5** in $CDCl_3$. Figure 3 exhibits resonances in the high-field region for the guest, implying formation of an *endo*-complex. The presence of a sharp triplet at −1.15 ppm together with a quadruplet at 0.72 ppm is attributed to the strong binding of the ammonium in the heart of the calixarene cavity. The $ArOCH_2Ar$ resonances belonging to a mesitylenyl unit at the narrow rim show about 0.40 ppm of downfield shift, meanwhile the three signals corresponding to the $ArOCH_3$ protons exhibit about 0.31 ppm of downfield shift, which shows a deep change in the conformation of the cap upon complexation. Interestingly, the resonances corresponding to the calixarene core are barely affected by the complexation or by the guest nature, due to its rigidified capped structure. We deduced that the affinity of host **5** towards $EtNH_3^+Pic^-$ may come from hydrogen bonding, cation–π and CH–π interactions. Furthermore, investigations on chiral resolution and recognition properties of **5** that would act as an enantioselective receptor for chiral ammoniums are currently underway.

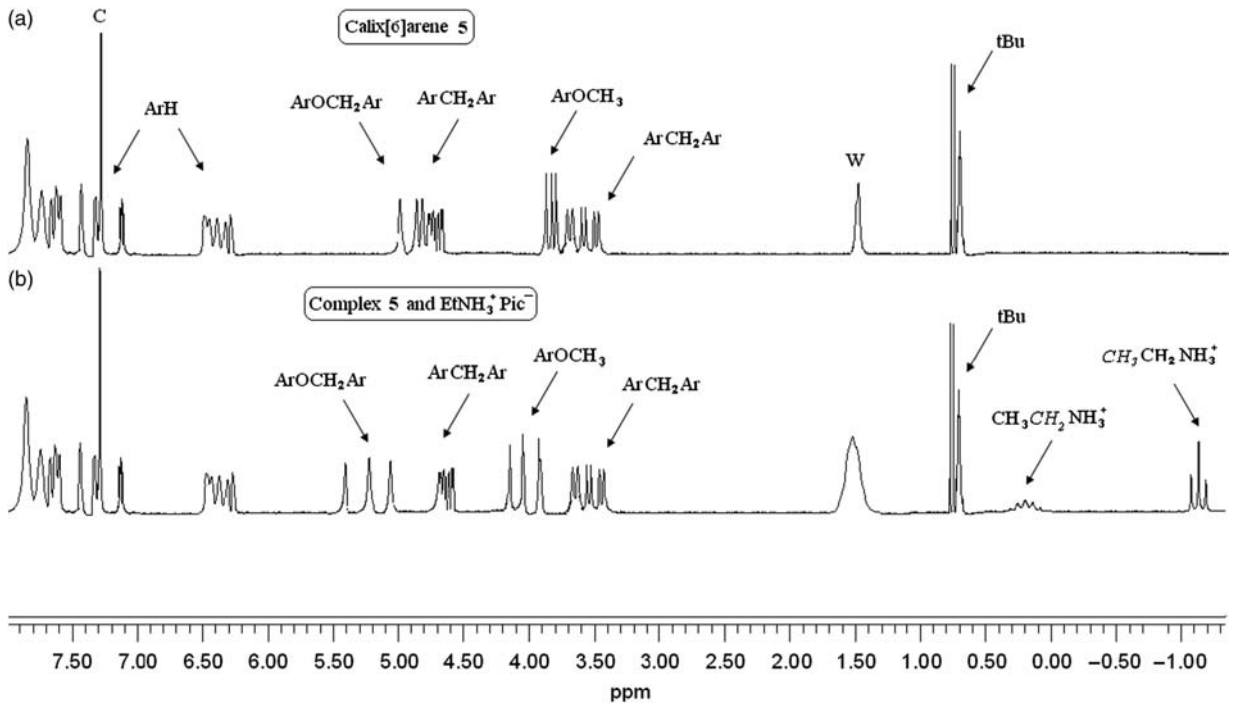

Figure 3. (a) ^{1}H NMR spectrum of compound **5** in $CDCl_3$ at 298 K. (b) ^{1}H NMR spectrum of the complex **5** ⊃ $EtNH_3^+Pic^-$ in $CDCl_3/CD_3OD$ (98.5: 1.5) at 298 K. $CDCl_3$ and water are labelled as C and W, respectively.

Conclusion

In conclusion, we successfully synthesised inherently chiral calix[6]arene **5** through monoformylation and monobromination on the wide rim, and subsequent intramolecular etherification from 1,3,5-bridged calix[6]-arene **1**. An ^{1}H NMR study showed that calix[6]arene **5** can perform *endo*-complexation of cationic ammoniums. Another inherently chiral calix[6]arene intermediate **4** is obtained in the synthesis, which is identified with its NMR spectra and X-ray crystal structure. Our synthesis strategy opens the route to inherently chiral calix[6]arenes presenting an ABC pattern on the wide rim.

Acknowledgements

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Supplementary data

Supplementary data (Crystallographic data for the structure reported in this paper) associated with this article can be found in the online version.

Notes

1. Compound **1** (96 mg, 0.10 mmol) and hexamethylenetetramine (617 mg, 4.40 mmol) were mixed in trifluoroacetic acid (5 mL) and stirred at reflux for 12 h. Then, the reaction mixture was cooled to room temperature, quenched with 1 N HCl (30 mL), continuously stirred for 0.5 h and extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was collected, washed with saturated NaCl solution, dried with anhydrous Na_2SO_4 and evaporated under vacuum pressure. The residue was separated with column chromatography (petroleum ether/acetone, 40:1 v/v) to produce compound **2** (35 mg, yield 40%) as a white solid. mp: >300°C; IR (KBr): ν 2959, 2828, 1697, 1596, 1462, 1436 cm^{-1}; ^{1}H NMR: δ 9.98 (s, 1H, ArCHO), 7.77 (s, 2H, ArH), 7.64–7.63 (m, 3H, ArH), 7.19 (s, 4H, ArH), 7.07–7.05 (t, 2H, J = 7.3 Hz, ArH), 6.36–6.28 (m, 6H, ArH), 4.91–4.83 (m, 8H, $ArCH_2Ar$, $ArOCH_2Ar$), 4.75 (d, 4H, J = 15.2 Hz, $ArCH_2Ar$), 3.79 (s, 9H, $ArOCH_3$), 3.64 (d, 2H, J = 15.4 Hz, $ArCH_2Ar$), 3.53 (d, 4H, J = 15.8 Hz, $ArCH_2Ar$), 0.66 (s, 27H, $C(CH_3)_3$); ^{13}C NMR: δ 191.7, 161.8, 155.8, 151.7, 146.2, 146.0, 137.5, 136.4, 135.3, 134.2, 134.0, 133.5, 132.3, 132.0, 131.9, 131.8, 131.7, 131.6, 130.6, 123.2, 122.8, 122.4, 122.0, 71.7, 71.0, 60.0, 59.9, 34.2, 33.9, 31.9, 31.7, 31.4, 31.3, 29.7; MALDI-TOF MS: m/z 1011 ($[M + Na]^+$), 1027 ($[M + K]^+$); elemental analysis calcd. for $C_{67}H_{72}O_7$: C, 81.34; H, 7.34. Found: C, 80.51; H, 8.10.
2. To a solution of compound **2** (99 mg, 0.10 mmol) in chloroform, 20 mL of a solution of bromine (20 mg, 0.12 mmol) in chloroform (5 mL) was added dropwise at 0°C for 0.5 h. The mixture was stirred for 3 h and then quenched with $NaHSO_3$ solution. The organic layer was collected, washed with distilled water, dried with anhydrous Na_2SO_4 and separated with column chromatography (petroleum ether/acetone, 10:1 v/v) to produce compound **3** (21 mg, yield 20%) and compound **4** (86 mg, yield 75%) as white solids. **3**: mp: 145–147°C; IR (KBr): ν 3270, 2957, 1689, 1596, 1465, 1364 cm^{-1}; ^{1}H NMR: δ 9.69 (s, 1H, ArCHO), 7.47 (s, 2H, ArH), 7.30 (s, 2H, ArH), 7.24–7.20 (m, 2H, ArH), 7.16–7.13 (m, 5H, ArH), 7.03 (s, 2H, ArH), 6.94 (s, 2H, ArH), 6.48 (s, 2H, ArH), 4.92 (d, 2H, J = 11.2 Hz, $ArOCH_2Ar$), 4.70 (d, 2H, J = 11.1 Hz, $ArOCH_2Ar$), 4.58 (d, 2H, J = 15.1 Hz, $ArCH_2Ar$), 4.48 (s, 2H, $ArCH_2Br$), 4.36 (d, 2H, J = 14.7 Hz, $ArCH_2Ar$), 3.72 (d, 4H, J = 15.0 Hz, $ArCH_2Ar$), 3.64 (s, 3H, $ArOCH_3$), 3.50 (d, 4H, J = 15.0 Hz, $ArCH_2Ar$), 2.96 (s, 6H, $ArOCH_3$), 1.18 (s, 18H, $C(CH_3)_3$), 0.82 (s, 9H, $C(CH_3)_3$); ^{13}C NMR: δ 191.6, 153.9, 153.4, 153.0, 150.0, 146.2, 146.1, 145.7, 142.2, 139.1, 136.2, 133.7, 133.5, 133.1, 133.0, 127.7, 127.1, 127.0, 126.6, 125.8, 125.6, 125.4, 125.1, 123.1, 60.8, 60.1, 34.3, 34.1, 33.9, 31.9, 31.6, 31.5, 31.4, 31.1, 31.0, 29.7; MALDI-TOF MS: m/z 1090 ($[M + Na]^+$), 1106 ($[M + K]^+$); elemental analysis calcd. for $C_{67}H_{71}O_7Br$: C, 75.34; H, 6.70. Found: C, 75.83; H, 7.10. **4**: mp: 198–200°C; IR (KBr): ν 3307, 2956, 2867, 1693, 1461, 1435 cm^{-1}; ^{1}H NMR: δ 9.97 (s, 1H, ArCHO), 7.82 (s, 1H, ArH), 7.70 (s, 1H, ArH), 7.29 (s, 1H, ArH), 7.22–7.20 (m, 1H, ArH), 7.16–7.11 (m, 3H, ArH), 7.04–7.00 (m, 4H, ArH), 6.94 (d, 1H, J = 2.1 Hz, ArH), 6.87 (d, 1H, J = 2.1 Hz, ArH), 6.47 (d, 2H, J = 3.7 Hz, ArH), 6.10 (s, 1H, ArH), 5.02 (d, 1H, J = 11.7 Hz, $ArOCH_2Ar$), 4.86 (d, 1H, J = 12.2 Hz, $ArOCH_2Ar$), 4.70–4.65 (m, 2H, $ArCH_2Ar$), 4.63 (d, 1H, J = 10.2 Hz, $ArOCH_2Ar$), 4.56 (d, 1H, J = 10.5 Hz, 1H, $ArOCH_2Ar$), 4.47 (s, 2H, $ArCH_2Br$), 4.36 (d, J = 14.1 Hz, 1H, $ArCH_2Ar$), 4.31 (d, 1H, J = 13.9 Hz, $ArCH_2Ar$), 3.84 (d, 1H, J = 15.1 Hz, $ArCH_2$-Ar), 3.82 (d, 1H, J = 15.1 Hz, $ArCH_2Ar$), 3.66 (s, 3H, $ArOCH_3$), 3.59–3.52 (m, 2H, $ArCH_2Ar$), 3.51–3.42 (m, 4H, $ArCH_2Ar$), 2.94 (s, 3H, $ArOCH_3$), 2.79 (s, 3H, $ArOCH_3$), 1.24 (s, 18H, $C(CH_3)_3$), 0.81 (s, 9H, $C(CH_3)_3$); ^{13}C NMR: δ 191.7, 160.9, 155.5, 154.0, 153.0, 150.8, 146.7, 145.9, 139.1,138.2, 136.4, 136.1, 136.0, 134.7, 134.2, 133.4, 133.2, 132.6, 132.5, 132.2, 131.2, 130.7, 130.6, 130.2, 130.1, 130.0, 126.8, 126.6, 126.0, 125.6, 125.0, 124.8, 123.5, 123.1, 112.1, 73.3, 60.9, 60.6, 60.5, 34.2, 34.0, 33.7, 31.9, 31.5, 31.2, 31.0, 30.5, 29.7; MALDI-TOF MS: m/z 1170 ($[M + Na]^+$), 1186 ($[M + K]^+$); elemental analysis calcd. for $C_{67}H_{72}O_7Br_2{\cdot}C_6H_{14}$: C, 70.98; H, 7.02. Found: C, 71.00; H, 7.08.
3. Crystal data: Mw = 1149.07, triclinic, colourless crystal (0.86 × 0.37 × 0.09 mm^3), a = 10.9057(4) Å, b = 15.6444 (11) Å, c = 20.9416(5) Å, α = 75.205(3)°, β = 81.1520(4)°, γ = 84.411(4)°, V = 3407.0(3) Å^3, space group $P-1$, Z = 2, ρ = 1.120 mg/m^3, μ (Mo Kα) = 12.35 cm^{-1}, 14,144 reflections measured at 293 K (Bruker SMART 1000 diffractometer) in the θ range of 1.48–27.48°, 25064 unique (R_{int} = 0.058), 685 parameters refined on F^2 to final indices $R[F^2 > 4\ \sigma F^2] = 0.1204$, $wR = 0.3299$. [$w = 1/[\sigma^2(F_0^2) + (0.1243P)^2 + 29.0749P]$ where $P = (F_0^2 + 2F_c^2)/3$]. Crystallographic data (excluding structure factors) for the structure reported in this paper were deposited at the Cambridge Data Centre as supplementary publication No. CCDC 799359 for **4**. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.)+ 44(1223)336-033, Email: deposit@ccdc.cam.ac.uk].
4. To a solution of compound **4** (57 mg, 0.05 mmol) in dried THF (20 mL), NaH (3 mg, 0.12 mmol) was added. The mixture was stirred at reflux for 3 h, then evaporated under vacuum pressure and redissolved in CH_2Cl_2. The solution was washed with distilled water, dried with anhydrous

Na_2SO_4 and separated with column chromatography (petroleum ether/acetone, 25:1 v/v) to produce compound **5** (43 mg, yield 80%) as a white solid. mp: >300°C; IR (KBr): ν 2954, 1690, 1462, 1432 cm^{-1}; ^1H NMR: δ 10.1 (s, 1H, ArCHO), 7.83 (s, 2H, ArH), 7.69 (s, 1H, ArH), 7.66–7.65 (m, 3H, ArH), 7.41 (s, 2H, ArH), 7.28 (s, 1H, ArH), 7.11 (t, 1H, $J = 7.0$ Hz, ArH), 6.42–6.44 (m, 3H, ArH), 6.40 (s, 1H, ArH), 6.37–6.36 (m, 2H, ArH), 4.96 (s, 2H, $ArOCH_2Ar$), 4.87 (s, 2H, $ArOCH_2Ar$), 4.84 (s, 2H, $ArOCH_2Ar$), 4.83–4.75 (m, 6H, $ArCH_2Ar$), 3.86 (s, 3H, $ArOCH_3$), 3.85 (s, 3H, $ArOCH_3$), 3.84 (s, 3H, $ArOCH_3$), 3.71 (d, 2H, $J = 16.1$ Hz, $ArCH_2Ar$), 3.60 (d, 2H, $J = 15.5$ Hz, $ArCH_2Ar$), 3.54 (d, 2H, $J = 15.9$ Hz, $ArCH_2Ar$), 0.74 (s, 9H, $C(CH_3)_3$), 0.73 (s, 9H, $C(CH_3)_3$), 0.72 (s, 9H, $C(CH_3)_3$); ^{13}C NMR: δ 191.7, 161.8, 155.8, 155.2, 151.8, 146.5, 146.3, 146.2, 137.6, 137.0, 136.5, 136.3, 135.4, 135.2, 134.2, 134.1, 134.0, 133.6, 133.5, 132.3, 132.0, 131.9, 131.8, 131.7, 131.1, 130.9, 130.8, 130.6, 123.3, 122.8, 122.7, 122.6, 122.4, 122.2, 122.1, 115.6, 71.6, 71.2, 70.9, 60.1, 60.0, 34.1, 33.9, 31.7, 31.5, 31.4, 31.2, 31.0, 29.6, 29.5, 28.0; MALDI-TOF MS: *m/z* 1067 ($[M + H]^+$), 1106 ($[M + K]^+$); elemental analysis calcd. for $C_{67}H_{71}O_7Br$: C, 75.34; H, 6.70. Found: C, 75.40; H, 6.99.

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