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Meso-piperidine calix[4]pyrrole: synthesis, structure and ion binding studies

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ABSTRACT

We report the synthesis, structure and preliminary solution phase ion binding properties of the calix[4]pyrrole **3a**–**c**. Calix[4]pyrrole **3a** and **3b**, the first to be prepared via one-pot reaction, were obtained by reacting the ketone **7** with pyrrole in the presence of an acid catalyst. On the basis of ^{1}H NMR spectroscopic analyses and the titrations of UV spectrophotometry, it was concluded that compound **3a** possesses significantly enhanced selectivity for fluoride anion in chloroform, and formes 1:1 (ligand: anion) complexes with fluoride and chloride anions.

1. Introduction

Meso-octamethylcalix[4]pyrrole **1**, a tetrapyrrolic macrocycle, was found in 1996 by Sessler and co-workers to act as an efficient receptor for anionic and electron-rich neutral guests in organic solvents,[1] though it has been synthesized in 1886 by Baeyer.[2] Since that time, calix[4]pyrrole **1** caused great interest as an anion receptor with considerable effort having been devoted to produce a number of calix[4]pyrroles and study their binding affinity and selectivity for specific anionic guests.[3–7] In addition, calix[4]pyrroles adapt their core conformation (Fig. 2) in order to bind strongly with a variety of hydrogen bond acceptor substrates, ranging from neutral aprotic molecules to halide ions and oxyanions.[8] To enhance affinity and selectivity towards anions, all the meso positions of calix[4]pyrroles were substituted by aryl groups (**2a**–**b**) to achieve a deep cavity and resulted in the formation of four configurational isomers (see Fig. 1).[9]

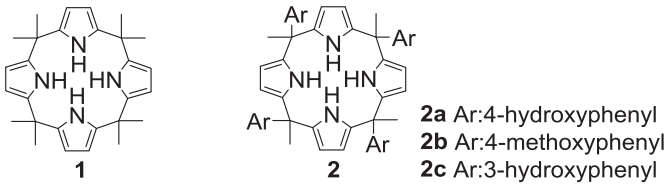

Fig. 1. Structures of *meso*-octamethylcalix[4]pyrrole **1** and deep cavity calixpyrroles **2**.

However, all of these isomeric receptors displayed a negative selectivity towards anions, compared to **1** owing to steric congestion.[10] Separately, *meso*-tetramethyltetrakis(3-hydroxyphenyl)calix[4]pyrrole **2c** was synthesized by Namor and co-workers, and its αααββ and αβαβ isomers also were isolated. The αααββ isomer shows higher affinity for $H_2PO_4^-$ in acetonitrile while the αβαβ derivative prefers the F^- ion.[11] To achieve selectively binding anion, we decided to synthesize αααββ derivatives possessing functionality periphery. Herein we report one-pot synthesis of calix[4]pyrrole **3a** and **3b**, in addition to their solid state structure and anion binding studies. To date and to the best of our knowledge, there are no examples reported in the literature for the synthesis of **3a**–**c**.

2. Results and discussion

The synthesis of **3a**–**c** is outlined in Scheme 1. They started with 1-Boc-piperidine-4-carboxylic acid **4**, which was subjected to condensation by treating with Meldrum's acid. Then **5** was heated in ethanol under reflux, the ethanolysis took place smoothly with the evolution of carbon dioxide to afford β-Keto Esters **6**. Hydrolysis of this latter β-Keto Esters with the solution of 6.0 M NaOH gave the ketone **7**. Condensation of this latter ketone with pyrrole in the presence of 1.5 equiv of Methanesulfonic acid (MSA), then gave the desired calix[4]pyrrole derivatives **3a** in 19.7% yield and **3b** in 26.6%

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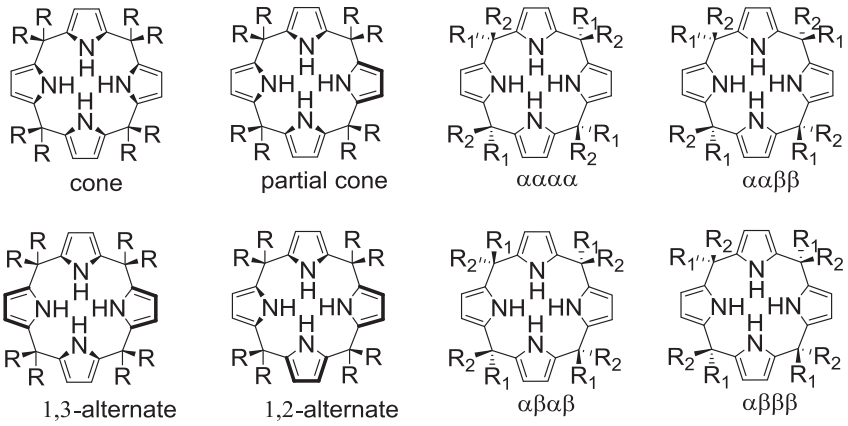
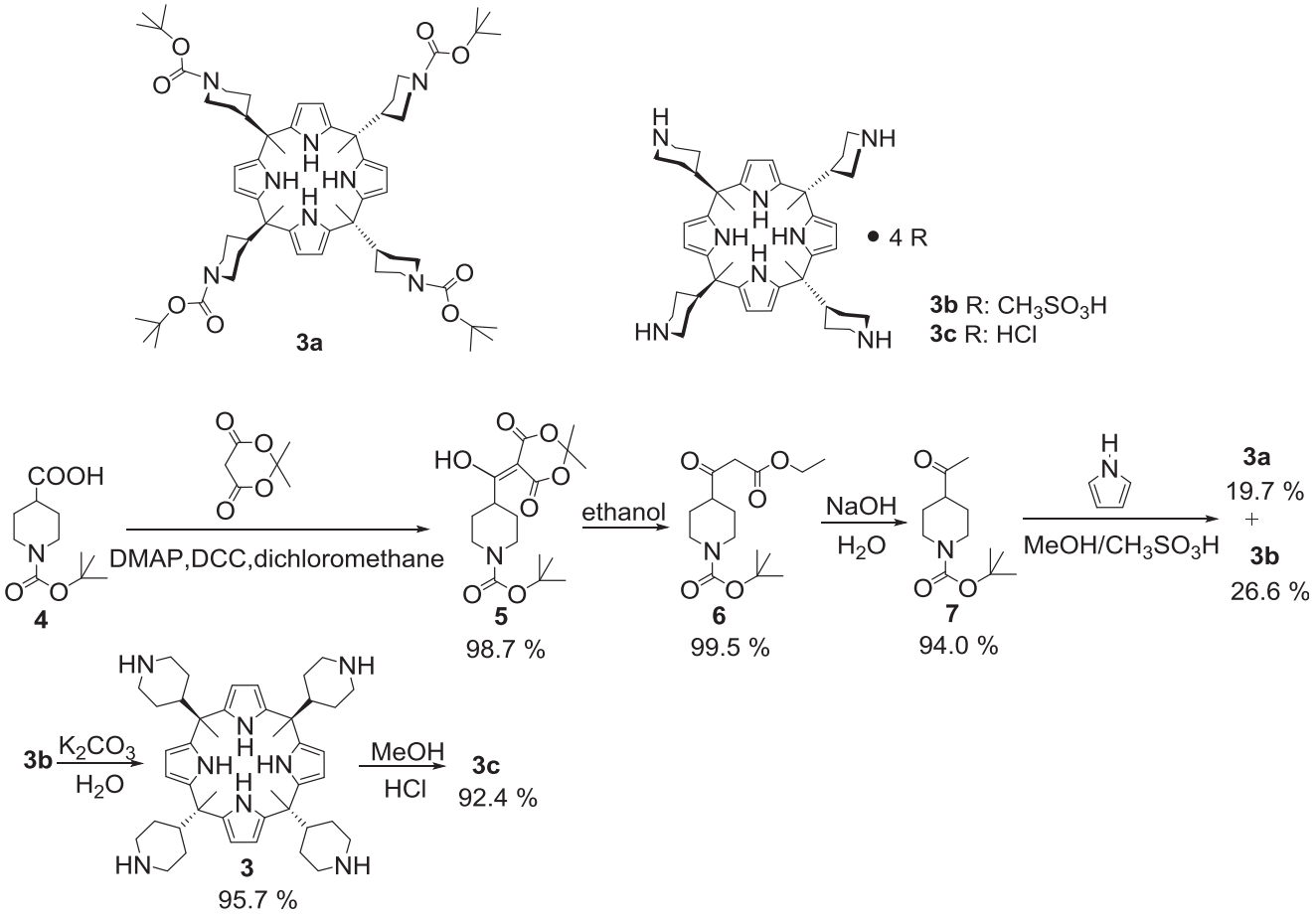


Fig. 2. Conformational isomers of calix[4]pyrroles (left) and Structural isomers of calix[4]pyrroles (right).

yield. Treatment of **3b** with excess potassium carbonate in water served to remove the Methanesulfonic acid, this gave calix[4]pyrrole **3** in 95.7% yield. The acidification of **3** with 4.0 M hydrogen chloride solution in dioxane gave **3c** in 92.4% yield.



Scheme 1. Synthesis of compound **3a**–**c**.

Calix[4]pyrrole **3a**–**c** were characterized by single-crystal X-ray diffraction analysis. Single crystals of **3a**–**c** suitable for X-ray diffraction were grown from DMF/CH_2Cl_2 (4/1) and CH_3CN/H_2O (10/1). Then, the resulting structures revealed that in the solid state calix[4]pyrrole **3a**–**c** adopts the so-called 1, 2-alternate conformation and parcial cone. In **3a**·$(DMF)_2$, Fig. 3, the two DMF guest molecules are hydrogen bonded, one above and one below, with the adjacent pyrrole-NH groups of the calix[4]pyrrole donor in the 1, 2-alternate conformation. In contrast, In Fig. 4, the resulting structure revealed that calix[4]pyrrole **3b** adopts the so-called partial cone conformation in the solid state with one $CH_3SO_3^-$ bound to the pyrrolic NH protons. The included $CH_3SO_3^-$ is held within this cleft by a series of N–H···O hydrogen bonding interactions involving the three N–H groups of the four pyrrole rings. To study the complex with Cl^-, however, single crystal of **3c**·$(H_2O)_2$ is obtained through slow evaporation of the mixture of **3c** and TBACl made up in CH_3CN/H_2O

(10/1). Unfortunately, in the case of **3c**·$(H_2O)_2$, four Cl^- are dispersed around the macrocycle periphery, two H_2O guest molecules are hydrogen bonded, one above and one below, with the adjacent pyrrole-NH groups of the calix[4]pyrrole donor in the 1, 2-alternate conformation, and excess Cl^- failed in bounding to the pyrrolic NH protons. Simultaneously, it means that Cl^- failed in the competition with H_2O. Compared to $CH_3SO_3^-$, parent **3** possesses lower affinity to Cl^- (at least in the solid state) (see Fig. 5).

for NH, and an upfield shift for β-CH proton signals with gradual addition of fluoride anion. It also displayed evidence of very fast complexation–decomplexation equilibrium in the case of **3a**-F^- complex, since the addition of approximately 0.15 equiv of TBAF resulted in the broadening of the pyrrole NH signals until addition of ~1 equiv of the salt and subsequent becoming singlet (Fig. S1 in the Supplementary data).

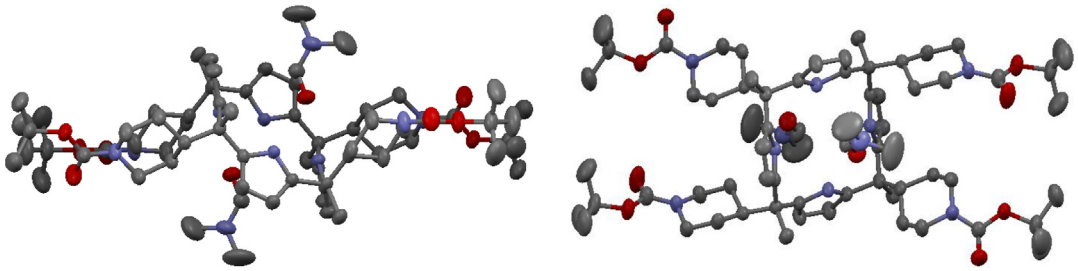


Fig. 3. Side and top views of the X-ray structures of DMF⊂**3a**. Displacement ellipsoids are scaled to the 50% probability level. Hydrogen atoms have been removed for clarity. Colour code: red: O, blue: N, grey: C.

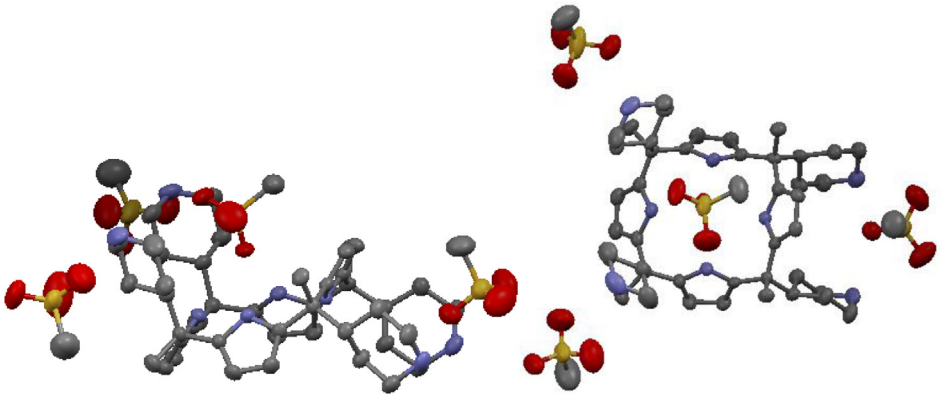


Fig. 4. Side and top views of the X-ray structures of **3b**. Displacement ellipsoids are scaled to the 50% probability level. Hydrogen atoms have been removed for clarity. Colour code: red: O, blue: N, grey: C.

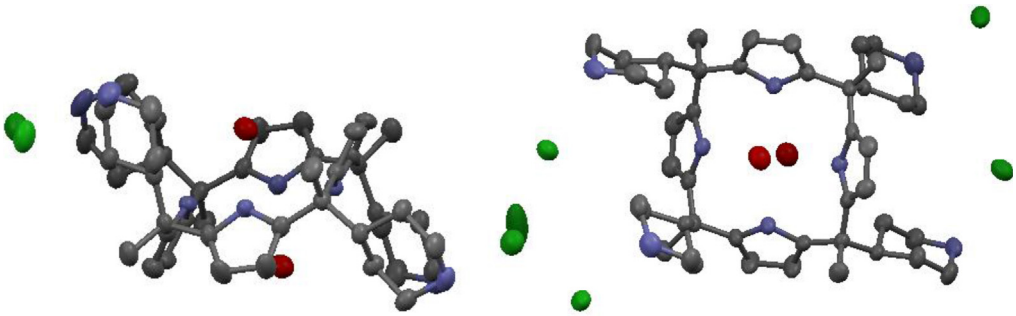


Fig. 5. Side and top views of the X-ray structures of H_2O⊂**3c**. Displacement ellipsoids are scaled to the 50% probability level. Hydrogen atoms have been removed for clarity. Colour code: red: O, blue: N, grey: C, green: Cl.

Proton NMR spectroscopy was used to probe the effect of anion binding in solution. Preliminary anion binding studies were carried out on **3a** using ^1H NMR titration studies in $CDCl_3$ (due to the poor solubility of **3a** in acetonitrile) with various anions (F^-, Cl^-, Br^-) as their tetrabutyl ammonium (TBA) salts. Here, it was found that under conditions of strong binding, such as proved true for fluoride interacting with **3a**, addition of the substrate served to lock the system into the expected[3] cone conformation. As expected, quantitative ^1H NMR titration studies showed a distinct downfield shift

On the other hand, in the case of Cl^- and Br^-, the NH signal and β-CH proton signals remain intact under low concentrations of chloride and bromide anions. This lack of change is ascribed to the fact that the chloride and bromide are bound only weakly and that calix[4]pyrrole undergoes fast conformational 'flipping' in the presence of the anions. Support for this conclusion comes from the fact that only relatively small downfield shifts in the NH proton resonance are seen upon the addition of TBACl and TBABr (Fig. 6A, Fig. S2 and S3 in the Supplementary data). Simultaneously, The

changing for the pyrrole NH signals under high concentrations of chloride and bromide anions is consistent with the ααββ isomer of **2b** with high concentrations of fluoride anion and displaying weak binding. And high concentrations of chloride and bromide anions served to lock the system into the separate, well-defined conformation that, on the basis of symmetry considerations, was assigned as being the conformationally accessible cone like form.[3]

donor solvents, such as water and methanol, because strong hydrogen bonding to the solvent should lower the available fluoride ion.[12] Unfortunately, in the case of the calix[4]pyrroles **3a** and **3c**, the NH signal and β-CH proton signal remain intact for accurate NMR titrations with halide ion for high concentrations in water. This suggests the presence of water could serve to reduce the strength of the presumed receptor-anion interactions.

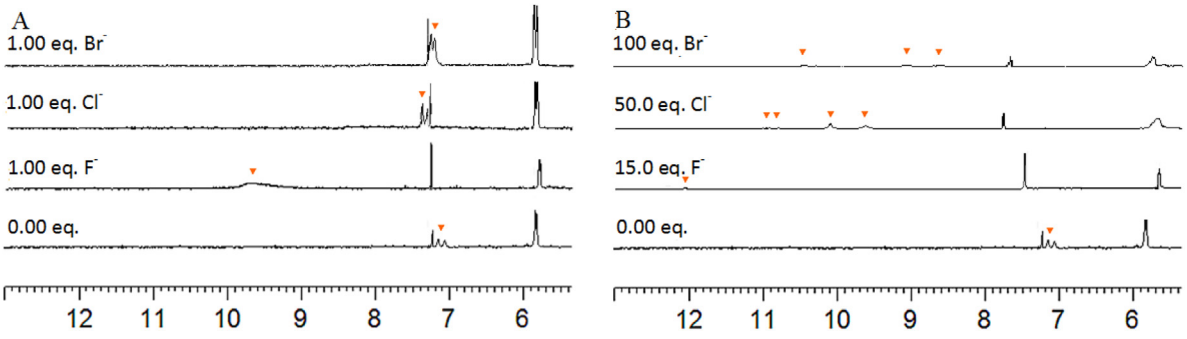


Fig. 6. Proton NMR spectra of **3a** recorded at room temperature in $CDCl_3$ before and after the addition tetrabutylammonium salts of different anions: (A) low concentrations of fluoride, chloride and bromide anions. (B) high concentrations of fluoride, chloride and bromide anions. (Tetrabutylammonium fluoride was added as the trihydrate.).

In an effort to test the above assumption, UV spectroscopy was used. The $CDCl_3$ solution of **3a** (1.5×10^{-4} M) was mixed with anions (1.5×10^{-4} M) such as fluoride and chloride. The UV spectroscopy revealed that **3a** bind fluoride and chloride with 1:1 stoichiometry. Because the absorption of the parent OMCP macrocycle generally occurs in the deep UV region, the investigation of binding affinity for anions is generally carried out by NMR and ITC. Here, however, the calix[4]pyrrole **3a** possesses piperidine side-arms that absorb light in the near-UV. This allows performing anion titrations using a UV spectroscopy. Fig. 7 shows UV spectra of **3a** upon the addition of fluoride and chloride in $CHCl_3$ (The changing for UV spectroscopy upon the addition of bromide wasn't obvious). Calix[4]pyrrole **3a** exhibited a distinctly increasing of absorbance upon fluoride addition, but a negligible change upon chloride addition, which suggests that the affinity and selectivity of **3a** for fluoride anion are

3. Conclusions

In summary, three new ααββ derivatives **3a**, **3b** and **3c** have been synthesized, and their structure unambiguously characterized by X-ray crystallography. The binding stoichiometry of **3a** and anions was investigated by UV spectroscopy. It was concluded that **3a** possesses significantly enhanced selectivity for fluoride anion in chloroform. And it was also concluded that **3a** formes 1:1 (ligand:anion) complexes with fluoride and chloride anions. Also we have illustrated the first example of a one-pot synthesis of functionalized derivatives. Presently, we are exploring whether flexible anchors endowed with suitable functionality at the calix[4]pyrrole periphery may enhance the affinity towards suitable anions. This may spur the development of new functionalized building blocks leading to interesting porphyrinoids.

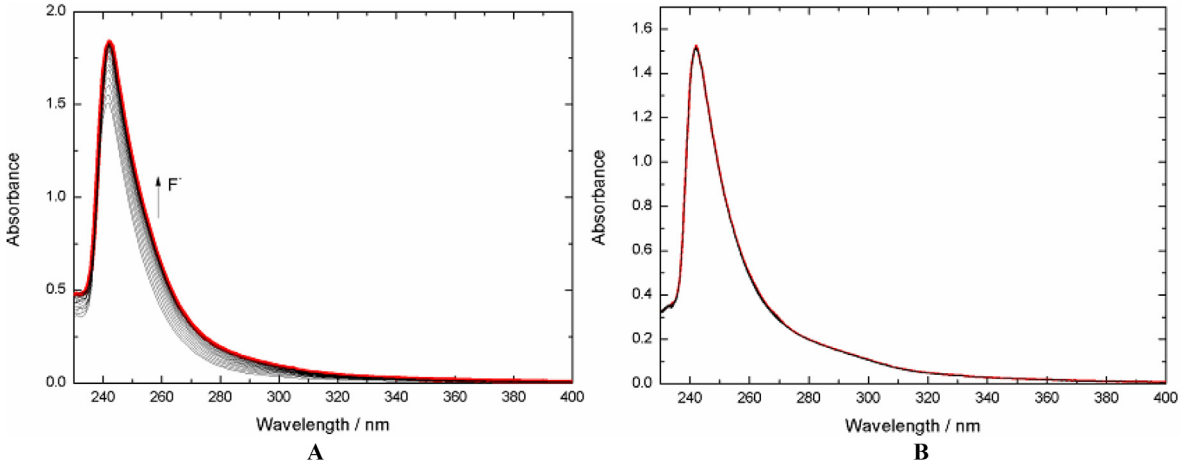


Fig. 7. Absorption spectra of **3a** upon the addition of tetrabutylammonium fluoride (A), tetrabutylammonium chloride (B) in $CHCl_3$ at rt, [Fluoride]/[chloride]=0–300 μM. Bottom (at 260 nm): Fitting of UV/Vis titration data. Tetra-butylammonium fluoride was added as the trihydrate.

stronger than for chloride anion in chloroform. The binding affinities of **3a** for fluoride is $>10^3$ M^{-1} and chloride is <5 M^{-1} (UV). Compared to **1**, calix[4]pyrrole **3a** exhibited higher selectivity for fluoride.[1]

As mentioned in the recent report, the theoretical predictions suggest that the relative fluoride ion to chloride ion affinities of calix[4]pyrrole **1** should reverse [i.e., K(Cl)>K(F)] in hydrogen bond

4. Experimental section

4.1. General

Methods and Materials. ^1H NMR and ^{13}C NMR spectra were recorded on a 300 MHz and 75 MHz spectrometer. All solvents were dried prior to use. 1-Boc-piperidine-4-carboxylic acid

was commercially available and used without further purification.

4.2. Synthesis of 5

To an oven-dried 250 mL round-bottomed flask containing 1-Boc-piperidine-4-carboxylic acid (9.20 g 40.0 mmol), DMAP (7.70 g 63.0 mmol), Meldrum's acid (6.40 g 44.4 mmol) was added dry dichloromethane (100 mL). The mixture of DCC (9.50 g 46.0 mmol) and dichloromethane (50 mL) was added dropwise through a dropping funnel. From the last addition, the reaction was kept at room for a further 24 h. The reaction mixture was filtered and the filtrate was quenched by addition of a solution of 1 M HCl. The collected organic layers were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure, affording 14.0 g (98.7% yield) of a light yellow solid that was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.22 (br m, 2H), 3.95 (m, 1H), 2.82 (br m, 2H), 1.75–1.80 (m, 10H), 1.48 (s, 9H).

4.3. Synthesis of 6

In a 250 mL round-bottomed flask filled with dry ethanol (70 mL) was added **5** (13.0 g 36.7 mmol). The reaction mixture was heated under reflux for 8 h, then the solvent was evaporated, affording 10.9 g (99.5% yield) light yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.09 (s, 0.14H, enol OH), 4.89 (s, 0.14H, enol C–H), 4.13–4.20 (m, 4H), 3.47 (s, 2H), 2.63–2.74 (m, 2H), 2.55–2.60 (m, 1H), 1.80 (m, 2H), 1.48–1.57 (m, 2H),1.45 (s, 9H), 1.26–1.28 (t, 3H).

4.4. Synthesis of 7

In a 100 mL round-bottomed flask filled with a solution of 6.0 M NaOH (50 mL) was added **6** (9.00 g 30.2 mmol). The reaction mixture was heated under reflux for 20 h, then diluted with 300 mL water and was quenched by addition 240 mL dichloromethane. The collected organic layers were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure, affording 6.42 g (94.0% yield) light yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.07–4.11 (m, 2H), 2.74–2.81 (m, 2H), 2.41–2.48 (m, 1H), 2.15 (s, 3H), 1.81–1.84 (m, 2H), 1.48–1.57 (m, 2H), 1.44 (s, 9H).

4.5. Synthesis of calixpyrrole 3a and 3b

To a 100 mL round-bottomed flask containing a solution of pyrrole (1.53 mL 22.1 mmol) in MeOH (50 mL) was added ketone **7** (5.00 g 22.1 mmol). The mixture was stirred for 5 min, then methanesulfonic acid (3.18 g 33.2 mmol) was added slowly, and the reaction was left at rt overnight. A pink precipitate formed, which was collected by filtration, washed with methanol until being colourless, and dried to afford a white microcrystalline solid, then subjected to column chromatography (SiO_2, MeOH: CH_2Cl_2, 1:30) to afford 1.19 g (19.7% yield) white solid, **3a**, and the filtrate was collected. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.86–6.99 (d, 1H), 5.83–5.86 (d, 2H), 4.08–4.13 (m, 2H), 2.60 (m, 2H), 1.85–1.89 (m, 1H), 1.52–1.58 (m, 2H), 1.42 (s, 9H), 1.37 (s, 3H), 1.06 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.2, 135.6, 135.3, 104.2, 103.8, 78.8, 43.7, 41.6, 27.9, 27.7, 27.4. Elem. Anal. Calcd for **3a**·H_2O: C 68.42; H 8.79; N 9.97. Found: C 68.21; H 9.28; N 9.90. MS (m/z): HRMS (ESI) calcd for $C_{64}H_{97}N_8O_8$ ($[M+H]^+$): 1105.7429, found: 1105.7435. And the collected filtrate was evaporated in vacuo to give brown oil liquid which was recrystallized by methanol, affording 1.60 g (26.6% yield) of a white solid, **3b**. ^{1}H NMR (300 MHz, D_2O): δ 6.09–6.12 (d, 2H), 3.42 (m, 2H), 3.00 (m, 2H), 2.82 (s, 3H), 2.36 (m, 1H),1.76–1.88 (m, 2H), 1.52 (s, 3H), 1.30–1.45 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.1, 142.6, 112.2, 110.8, 51.4, 51.2, 48.8, 47.7, 45.5, 32.1, 31.1, 29.4. MS (m/z): HRMS (ESI) calcd for $C_{48}H_{79}N_8O_{12}S_4$ ($[M-H]^-$): 1087.4700, found: 1087.4693.

4.6. Synthesis of 3c

To a 10 mL round-bottomed flask containing a solution of K_2CO_3 (0.13 g, 0.94 mmol) in water (5 mL) was added **3b** (0.50 g 0.46 mmol). A white precipitate formed, which was collected by filtration, washed with water until being colourless, and dried to afford 0.31 g (95.7% yield) **3**.

To a 10 mL round-bottomed flask filled with MeOH (2 mL) was added **3** (0.10 g 0.14 mmol), then add 4.0 M hydrogen chloride solution in 1,4-dioxane to pH 2. A white precipitate was formed, which was collected by filtration, washed with ethanol until colourless, and dried to afford 0.11 g (92.4% yield) of a white solid, **3c**. ^{1}H NMR (300 MHz, D_2O): δ 5.97–6.01 (d, 2H), 3.31–3.35 (m, 2H), 2.85–2.93 (m, 2H), 2.21–2.29 (m, 1H), 1.69–1.78 (m, 2H), 1.41 (s, 3H), 1.19–1.34 (m, 2H). MS (m/z): HRMS (ESI) calcd for $C_{44}H_{65}N_8$ ($[M+ H]^+$): 705.5332, found: 705.5330 (**3c** was decomposed to **3** under the condition of MS).

Acknowledgements

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Supplementary data

Supplementary data (NMR spectroscopic data, UV absorption and X-ray structural data are available. Single crystal data for compounds **3a** (CCDC 1047323), **3b** (CCDC 1047324), and **3c** (CCDC 1047325) have been deposited in the Cambridge Crystallographic Data Center.) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.08.032. These data include MOL files and InChiKeys of the most important compounds described in this article.

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