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Inherently chiral cone-calix[4]arenes via a subsequent upper rim ring-closing/opening methodology†

José Augusto Berrocal, ^a Matthew B. Baker, ^b Laura Baldini, ^c
Alessandro Casnati ^c and Stefano Di Stefano ^d

Access to chiral calix[4]arenes can unlock novel supramolecular architectures for enantioselective catalysis and molecular recognition. However, accessibility to these structures has been significantly hindered so far. We report herein the synthesis and characterization of di- and trifunctionalized cone-calix[4]arenes featuring a lactone moiety spanning the distal positions at the upper rim. The lactones force the whole skeleton to assume pinched-cone conformations. The ring-closure is favored by the high conformational flexibility of the calixarene scaffold. The new lactones are remarkably stable in the solid state, while a quick hydrolysis to restore the parent carboxylic acids occurs in solution under acidic/basic conditions. Slow aminolyses of lactones **2–3** yield inherently chiral products featuring three different functionalities at the upper rim, at room temperature. The subsequent ring-closing/opening methodology presented here highlights the versatility of these lactones as powerful synthons for the preparation of a variety of threefold upper rim functionalized, inherently chiral calix[4]arenes fixed in the cone structure.

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Introduction

Since the identification of tetra-*t*-butylcalix[4]arene by Zincke and Ziegler in 1944, and the recognition of the calix 3D structure by Gutsche in the early 1970s, calix[4]arenes have attracted considerable interest in the chemical community. Today, after almost 50 years of development in the field, that interest is still alive, as witnessed by the relevant number of books^{1–4} and reviews^{5–8} on the topic. The shape and ease of functionalization of calix[4]arenes have made them appealing scaffolds for the preparation of a number of supramolecular complexes, devices and materials. The upper rim functionalization has

particularly shown promising applications in the recognition of biologically relevant species, mostly proteins^{9,10} and DNA,¹¹ and as catalytically active systems.^{12–16}

In order to push the field towards biological systems even further, envisioning new strategies for the preparation of inherently chiral calixarenes^{17–20} is pivotal. Effective procedures for the synthesis of symmetrically tetra-, distally- and proximally-upper rim-substituted calix[4]arenes have been extensively developed;²¹ however, to the best of our knowledge, only two examples of inherently chiral ABCH²² and ABCD-upper rim²³ functionalized derivatives have been reported so far by other authors. Such reports consist of either long and tedious fragment condensation sequences²³ or a number of steps that rely on induced selectivity based on the lower rim substitution.²² These examples nevertheless showed the enantioselective catalytic potential of inherently chiral calix[4]arenes, but are limited in terms of ease or modularity of synthesis.

The distal positions of the upper rim of cone calix[4]arenes have a special relationship in terms of chemical reactivity,²⁴ which is the direct consequence of the conformational motions of these scaffolds. Indeed, a cone calix[4]arene tetra-alkylated at the lower rim retains some conformational flexibility and in solution a dynamic equilibrium is established between two structures of *C*_{2v} symmetry, called flattened or pinched cone conformations, in which two opposite aromatic rings point outward and the other two are almost parallel (see

^aInstitute for Complex Molecular Systems and Laboratory of Macromolecular and Organic Chemistry, Eindhoven University of Technology, 5600 MB Eindhoven, the Netherlands. E-mail: j.berrocal@tue.nl

^bMERLN Institute for Technology-Inspired Regenerative Medicine, Maastricht University, 6200 MD, Maastricht, the Netherlands

^cDipartimento di Scienze Chimiche, della Vita e della Sostenibilità Ambientale, Università degli Studi di Parma, Parco Area delle Scienze 17/A, 43124 Parma, Italy

^dDipartimento di Chimica and IMC – CNR Sezione Meccanismi di Reazione, Università La Sapienza, 00185 Roma, Italy

† Electronic supplementary information (ESI) available: Characterization including ¹H NMR, ¹³C NMR, FT-IR and MALDI-TOF-MS spectra of all new synthesized compounds. ¹H NMR comparisons between lactones, and lactones and their corresponding precursors. GPC, chiral HPLC and NMR separation of the lactones racemic mixtures. Ring opening experiments. Computational details. See DOI: 10.1039/c8ob01813h

Electronic supplementary information (ESI) Fig. S1†). The barrier for such interconversion is estimated to be $10.2 \text{ kcal mol}^{-1}$,²⁵ hence very rapid conformational motions occur at room temperature. For example, interconversion for upper-rim unsubstituted compounds can be observed only below 250 K.²⁵ Such high proximity between distal positions can be covalently “trapped”, as witnessed by a number of reports in which these two positions were connected by 3-,^{26–30} 2-,^{31–34} and even a 1-atom bridge.³⁵

In the recent past, we have exploited this high proximity with a simple method for the desymmetrization of a symmetrical *cone* distal-diformylcalix[4]arene.³⁶ The strategy was based on a highly efficient intramolecular hydride transfer during a Cannizzaro reaction (aldehyde disproportionation) with an Effective Molarity³⁷ (EM) as high as 600 M.³⁶ The procedure was then extended to AAAH trifunctionalized *cone*-derivatives, for which regiospecificity of the two reactive functions on the distal aromatic rings was observed.³⁸ We could easily prepare racemic mixtures of inherently chiral ABCH *cone*-calix[4]arenes by exploiting this irreversible process. The derivatives could be resolved with chiral HPLC and showed promising results for the chiral discrimination of amino acids *via* Schiff base formation.³⁸ Hence, the covalent recognition of the amino acid was performed by the aldehyde functionality. As an alternative and complementary approach towards the application of these inherently chiral calix[4]arenes, we envisioned a new strategy based on the covalent functionalization of the alcohol and carboxylic acid generated in the Cannizzaro reaction.^{36,38}

Here we present a new family of di- and tri-functionalized *cone*-derivatives in which the distal rings are spanned by 3 carbon atom bridges of a lactone moiety. The chemical structures of lactones 1–3 are presented in Fig. 1. For ease of representation, we report only the *M*-enantiomer³⁹ throughout the text. We show that the introduction of the cyclic skeleton at the upper rim of the calix[4]arene forces the entire structure to assume a pinched-*cone* conformation, as confirmed spectroscopically and computationally. The obtained lactones are remarkably stable in bulk, while they undergo instantaneous hydrolysis under acidic or basic conditions in CDCl_3 at 298 K. By contrast, they undergo slow aminolysis at room temperature, affording the desired amides in 7 days. Overall, our synthetic strategy based on subsequent ring-closing (lactonization) and

-opening (aminolysis) allows for the easy preparation of amides 7 and 8, the latter resulting to be inherently chiral (Fig. 1), through a simple mix-and-match procedure. Exemplifying the necessity of this approach, attempts to form amides from the parent carboxylic acids 4–6 (Fig. 1) and coupling agents, either failed to give the desired products, or simply afforded lactonized compounds 1–3. In other words lactones 1 and 2 are the only starting materials to achieve amides 7 and 8, respectively. Finally, the introduction of the lactone moiety in racemic mixtures of inherently chiral 2 and 3 allows for a user-friendly chiral HPLC resolution of the individual enantiomers. This underlines the significance of our lactones as key synthetic intermediates for the preparation of inherently chiral, upper rim multifunctionalized *cone*-calix[4]arenes.

Results and discussion

Synthesis and stability of the lactones

Lactones 1–2 were first serendipitously obtained from attempts at synthesizing esters and amides *via* 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC·HCl)-promoted couplings between 4–5 and alcohols/amines in the presence of 4-dimethylaminopyridine (DMAP) or 1-hydroxybenzotriazole (HOBT). Further synthetic attempts afforded lactones 1–2 even in the absence of the nucleophilic catalyst (Scheme 1). The intramolecular reaction was observed also in the presence of a large excess of the coupling partner (100 mol equivalents of alcohol or amine), in line with the high proximity reported in the previous Cannizzaro reactions.^{36,38}

Oxidation of 2 with H_2O_2 and NaClO_2 in a buffered $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ 1 : 1 mixture⁴⁰ afforded lactone 3, with low amounts of ring-opened 6 (7% by ^1H NMR), showing reliable stability to water under mild reaction conditions (Scheme 2). Compound 3 could also be synthesized from the oxidation of 5 to 6 under identical experimental conditions, followed by lactonization. Applying the lactonization procedure to compound 6 afforded, in fact, 3 as sole lactone, despite the simultaneous presence of two carboxylic groups at comparable distances from the alcohol function (Scheme 1). Such regiospecificity is again in

Fig. 1 Chemical structures of the lactones 1–3 (±), open precursors 4–6 (±) and pyrrolidinamides 7–8 (±).

Scheme 1 Intramolecular reactions of precursors 4–6 (±) to yield lactones 1–3 (±). The yield of 3 is denoted with an asterisk because it is related to the crude product obtained (7% of impurity present in the sample).

Scheme 2 Oxidation of the aldehyde function of **2** ($\pm$) affords compound **3** ($\pm$) with low amounts of ring-opened **6** ($\pm$).

Scheme 3 Aminolysis of lactones **1** and **2** ($\pm$) in the presence of pyrrolidine affords derivatives **7** and **8** ($\pm$) (reaction conditions: 5 mM **1** or **2**, 5 mM pyrrolidine, CDCl_3 , 298 K).

line with the previously reported Cannizzaro reaction: the process exclusively involves the two reactive groups in the distal positions due to their favored geometry. Detailed calculations (*vide infra*) show a significant difference in energy between the two potential products, with an overwhelming stability bias towards the distal isomer. Similar differences are also expected for the corresponding transition states and intermediates along the related lactonizations. Although the **6** $\rightarrow$ **3** transformation occurs with high regioselectivity, every attempt to isolate **3** by chromatography on silica gel failed due to identical RF with **6**.

Compounds **1–3** were obtained as off-white waxes and their stability was tested in both bulk and solution phase. For their full characterization please see ESI.† Storing **1–3** under argon and in the absence of water allowed preserving the lactones intact for 5 months. Neither signs of ring opening, nor decomposition were detected by proton Nuclear Magnetic Resonance ($^1\text{H-NMR}$) analysis. The solution phase stability of **1–3** was investigated in CDCl_3 by $^1\text{H-NMR}$ spectroscopy in sealed NMR tubes (see ESI†). The traces of acidic impurities present in this halogenated solvent and the presence of H_2O in ppm concentrations suffice to promote the ring-opening and regenerate precursors **4–6**. The process, however, is very slow and after 28 days at 298 K over 90% of the material is still in the lactone form (ESI, Fig. S21†). Flushing the halogenated solvent through basic alumina (basic Al_2O_3) removes the acidic impurities and helps to retain the lactone functionality in solution for over a month. We will hereafter refer to CDCl_3 flushed through basic Al_2O_3 as “treated CDCl_3 ”.

We then attempted basic- or acid-catalyzed ring-opening studies in treated CDCl_3 (in the presence of solid K_2CO_3 , or with 5 mol% trifluoroacetic acid (TFA), respectively). Under both reaction conditions, we witnessed the immediate and quantitative conversion to precursors **4–6** without being able to monitor the reaction progress in 3 minutes (time necessary to measure the ^1H NMR spectrum since the addition of the hydrolyzing reagent).

Next, we investigated the amine-promoted ring-opening under neutral conditions (neutral aminolysis). Lactones **1** and **2** were dissolved in treated CDCl_3 at 5 mM in the presence of an equimolar amount of amine. We chose butylamine and pyrrolidine as nucleophiles (Scheme 3). The neutral aminolyses highlighted a very low reactivity in the presence of neutral,

nitrogen-based nucleophiles under our experimental conditions. Neither aminolysis (of **1** or **2**), nor parallel imine formation of the free aldehyde (in **2**), was detected in the presence of butylamine even after weeks. The lack of imine formation was remarkably surprising, since benzaldehyde derivatives⁴¹ and calixaldehyde systems⁴² have been previously shown to afford fast imine formation/transimination with butylamine in a number of organic solvents. We speculate that the highly pinched conformation imposed by the lactone ring-closure (*vide infra*) severely limits the reactivity of the aldehyde groups in **2**. The more nucleophilic pyrrolidine afforded quantitative conversion (sealed NMR tube) to amide derivatives **7** and **8** only after 7 days at room temperature, instead. Moderately lower yields (90%) were obtained when the procedure was scaled up (50 mg) and carried out in round bottom flasks. Starting from racemic **2**, compound **8** was obtained as a racemic mixture.

The high reactivity difference displayed by lactones **1** and **2** in the hydrolysis/aminolysis experiments is remarkable, yet it is not unusual for lactone moieties. Some systems require high temperature or catalysts for appreciable aminolysis rates,⁴³ while others can show the same lack of reactivity towards hydrolysis. It is well established that relative rates of hydrolysis and aminolysis of activated esters can be manipulated *via* changes in strain^{44,45} (as seen in smaller lactones) and electronics^{46,47} (as seen in activated esters). The analysis of the π^* -antibonding orbitals (LUMO) furnished plausible explanations concerning the reactivity of other calix[4]arene systems.⁴⁸ Our DFT calculations show that the accessibility of the reactive π^* -antibonding orbital of the lactone is relatively hindered for larger nucleophiles (Fig. S55†). In other words, larger nucleophiles can only approach the lactone from outside the calixarene scaffold, while smaller nucleophiles (*e.g.* water) could approach from either outside or within the cavity. We hypothesize this to be the cause for the high reactivity difference. Despite the slow aminolysis observed at room temperature, the conversion of **2** into **8** afforded a chiral tri-functionalized *cone*-calix[4]arene very neatly. The high bulk stability, the high degree of functionalization achieved at the upper rim through the subsequent ring-closing/opening methodology, with substitution on three out of the four aromatic rings, and the ease

of preparation *via* a simple mix-and-match approach make these lactones powerful synthons in the preparation of upper rim multifunctionalized chiral calix[4]arenes.

Computational study

We conducted a Density Functional Theory (DFT) computational study to investigate the molecular structure, including

Fig. 2 Molecular representations for the lowest energy structure of covalently bridged compound **1** (**I**, left) and H-bond bridged compound **4** (**IV**, right) as calculated in the gas phase utilizing RB3LYP/6-31G** methodology. Space filling top (top), stick top (middle), stick side (bottom). See ESI† for comparisons to other low energy conformations of **4** (namely non-H bonded, **IV-noHbond**, or open conformers, **IV-open**).

NMR predictions (in CHCl₃) based on observed minima of key compounds. The calculations were performed on model compounds where the –OCH₂CH₂OCH₂CH₃ groups were replaced with simple –OCH₃ groups to minimize computational costs. In lieu of crystal structure information, this investigation allowed us to characterize the 3D structure and conformational energetics of these compounds, clarify the observed experimental spectra, and provided insight into the observed reactivity in ring-opening reactions.

The bridging of the distal aromatic rings in lactones **1–3** results in an extremely pinched conformation and closing of the molecular cavity of the calix[4]arene, as illustrated by the molecular representation of **1** (structure **I**, Fig. 2 and Fig. S50†), and shown by the proximity of distal carbons (3.69 Å). In compound **1**, there is not much expected conformational freedom. Two main stable structures were found, notably the *syn* (**I**) and *anti* (**I-anti**) lactone conformations (see Fig. S52†), with the *syn* conformer (**I**) shown to be ~9 kcal mol^{–1} more stable in the gas phase (see ESI† for structures and energetics).

A pinched conformation and closing of the molecular cavity is also observed in the lowest energy conformers in parent compounds **4–6**, (structures **IV–VI**, see Fig. 2 and Fig. S50–S52†). This stability of the pinched conformation can be attributed to a regular 6-membered ring hydrogen bonding network between the acid and the alcohol (exemplified *via* the molecular representation of **IV** in Fig. 2, right). Nearly identical H-bond geometries are found within the series **4–6** (Fig. S50–S52†), with the COOH–O bond appearing to be slightly stronger than the C=O–HO bond (Table 1). The observed H-bond lengths and angles place these H-bonds in a moderately strong binding category, the stabilization offered is modest when compared to non-hydrogen bonded conformers (see Fig. S52 and S53 and Table S1 and S3† for details). This lack of significant energy preference for **IV** (as compared to the non-H bonded conformers) is likely due to the geometric strain intro-

Table 1 Geometric descriptors of model compounds in their lowest energy conformation^a

Structure		Distance between rings ^b (Å)		Methylene bond angles ^c (°)		Bond distances (Å)		Bond angles (°)	
		1–3	2–4	Avg	Var	Lactone geometries			
						C=O	C–O	C _{Ar} –C(=O)–O	C _{Ar} –C(=O)–O–CH ₂
Parent calix[4]arene I		5.54	9.91	111.72	0.00	—	—	—	—
		3.69	10.29	110.87	1.80	1.214	1.367	112.54	-44.32
						H-Bonding geometries			
						C=O–HO	HO–HOOC	(C=O)O–H–O	(C=O)O–H–O
IV	4.50	10.18	111.42	2.97	1.90	1.81	141.10	149.90	
VII	4.85	10.07	111.33	0.47	1.87	—	167.56	—	

^a RB3LYP/6-31G** level of theory. Structures **I**, **IV**, and **VII** are shown as representatives for the series **I–III**, **IV–VI**, and **VII–VIII**, respectively. Compounds within these series showed highly similar ground state geometries, and full tables can be found in the ESI. ^b Distance between rings was defined as the inter-atomic distance between carbon atoms. ^c Methylene bridge bond angle defined as the angle between C_{Ar,ortho}–CH₂–C_{Ar,ortho}.

duced into the calixarene framework upon the formation of the H-bond network.

Several characteristic molecular distances, bond lengths, and angles for structures **I**, **IV** and **VII** are shown in Table 1 (for the full data set including non-hydrogen bonded and *anti* conformers, please see Tables S1 and S2†) and evidence for a small degree of strain introduced into these structures in their hydrogen-bonded or lactonized form. Tracked *via* the interatomic distance between apical carbons (Ring 1–3 and Ring 2–4), the Ring 1–3 distance is only 4.50 Å in the H-bonded conformer of **IV** compared to 5.54 Å for **parent calix[4]arene** (upper-rim unfunctionalized calix[4]arene, Fig. S49†), and is further decreased to 3.69 Å in the closed lactone **I**. The strain imposed by this bridging can also be observed from the decrease of the bond angles of the methylene bridges (Ar–CH₂Ar). The **parent calix[4]arene** was found to have a fairly symmetric structure in the gas phase with C_{Ar}–C–C_{Ar} bond angles of 111.7° with a low variance (0°), indicating a slightly strained, but highly symmetric macrocyclic structure. Lactone **I** is characterized by a slightly smaller average bond angle (110.9°), yet with a larger variance (1.80°), while its precursor **IV** has similar average bond angle (111.4°), but presents the highest variance among all structures measured (2.97°), due to the non-symmetric pinching of the 1 and 3 rings (Fig. 2). The lactones, themselves, of **I–III** also geometrically show some small evidence of strain distortion. Again illustrated by compound **I**, the bond lengths (C=O and C(=O)–O), and bond angle (C_{Ar}–C(=O)–O) are not significantly distorted from values observed for relatively unstrained benzoate esters; however, the dihedral (C_{Ar}–C(=O)–O–CH₂) angles are twisted with respect to an ideal geometry (–44 vs. 0°, respectively).

The lactonization of compound **6** further poses an interesting question as to the regioselectivity of the distal vs. proximal lactone formation. Due to the spectroscopic similarities between the series of lactones **1–3**, the working assumption has been that the distal-lactone is exclusively formed in this structural pair. Modeling a proximal and comparing to a distal lactone (**1,2-lactone** vs. **I**, Fig. S52 and Table S1†), quickly shows a geometrically distorted structure at a large energetic penalty (>40 kcal mol^{–1} gas phase) for the former, supporting the hypothesis that the distal lactone **3** is formed exclusively in this reaction system.

NMR calculations in CHCl₃ were performed to aid in elucidating the complex experimental NMR spectra obtained, and provide corroboration between the experimentally observed spectra of compounds and their computationally derived structures. Basic methodology for the computational evaluation of NMR has been previously outlined,⁴⁹ and a similar approach has been employed in this study. Furthermore, recent results have confirmed the suitability for NMR prediction with the B3LYP functional within a calix[4]arene structure.⁵⁰ Based on the numbering of hydrogens shown in Fig. 3, the H_a, H_i, and H_j protons are the most affected by the ring closure of **IV** into **I**, nicely mirroring the large shifts of these protons in the experimental ¹H NMR spectra (Table 2). Furthermore, the calculated NMR spectra suggest the following assignment for the

Fig. 3 Numbering of calixarene protons for ¹H NMR calculations.

Table 2 Experimental and calculated shifts in NMR resonances upon lactonization^a

Proton	Δ 4 to 1 ($\Delta\delta_{\text{exp}}$) ^b	Δ IV to I ($\Delta\delta_{\text{calc}}$) ^c
H _a	–0.88	–0.61
H _b	— ^d	–0.18
H _c	0.00	0.02
H _d	0.25	0.08
H _e	0.30	0.11
H _f	0.35	0.08
H _g	— ^d	–0.11
H _h	0.00	0.04
H _i	–0.25	–0.45
H _j	0.85	0.38

^a Calculations were performed at the RB3LYP/6-31G** level of theory with PCM solvation in CHCl₃, with Boltzmann weighting of conformers. Differences are shown going from **4** to **1** (observed) or **IV** to **I**.

^b ppm as observed in CDCl₃ NMR (δ_{exp}). ^c Shift in ppm relative to TMS calculated in CHCl₃ at 6-31G** (δ_{calc}). ^d Experimental assignment not possible with confidence, due to superimposition with other signals.

peaks of **4**: H_a, 7.1 ppm; H_c, 4.5 ppm; H_i, 6.4 ppm. In gratifying agreement with our experimental NMR measurements, the calculated NMR spectrum of **1** shows the diagnostic signal of H_j at 4.75 ppm. The other peaks can be partially assigned according to Table S4.† When going from **1** to **4** the significant downfield shifts of protons H_a and H_i, along with the upfield shifts of H_d, H_e, and H_f are nicely predicted (going from **I** to **IV**) in direction and with moderate accuracy in magnitude. Notably, when comparing the experimentally observed difference in shifts between **1** and **4** with either **I** and **IV**, or **I-anti** and **IV**, there is a lower mean absolute error (0.20 and 0.62, respectively) with the calculated changes between **I** and **IV**. This comparison, along with the higher energy in chloroform (+8.33 kcal mol^{–1}) of **I-anti**, strengthens the support for the *syn* lactone being the most populated conformer of **1** in solution at room temperature.

Chromatographic GPC separation and chiral resolution

We first evaluated the consequences of the cyclization on the chromatographic separation between lactones **1–3** and their precursors **4–6** by means of Gel Permeation Chromatography (GPC) using THF as eluent. Although the technique is typically

applied in polymer chemistry and provides its best performances with high molecular weight materials, we obtained surprisingly remarkable separations between molecules differing only by the formal absence/presence of a water molecule, *i.e.* the lactones and their hydroxyl-acid precursors. We show here the overlaid GPC chromatograms of **1** and **4** as example (Fig. 4, top), while the rest of the comparisons can be found in ESI (Fig. S41–S45†). It appears evident that lactones **1–3** possess larger retention times than their respective precursors **4–6** (Fig. 4, top; Fig. S41–S45†). This result cannot certainly be explained by the rather small 18 Da (H_2O) decrease in molecular weight, since this corresponds roughly only to 2% of the mass of the investigated molecules. The ring closure (lactonization) causes drastic changes in the molecular shape and, consequently, solvent–solute interactions.

Next, we focused on the resolution of the racemic mixtures of lactone **2** by means of chiral High-Performance Liquid Chromatography (chiral HPLC). We used an amylose-based standard phase and a hexane/iso-propanol (IPA) 85:15 mixture as eluent. An example of the chromatograms obtained with **2** is shown in Fig. 4, bottom. The sharp separation between the narrow peaks of the two enantiomers is an excellent indication of the successful experimental conditions.

Fig. 4 Top: Overlaid GPC chromatograms (298 K, eluent THF, followed by UV at $\lambda = 254$ nm) of **1** (full line) and **4** (dashed line). Bottom: Chiral HPLC resolution of racemic **2** (298 K, amylose tris(3,5-dimethyl-phenylcarbamate) stationary phase, 85:15 v/v Hex/IPA, followed by UV at $\lambda = 274$ nm).

An unsatisfactory chromatogram, characterized by very broad and overlapping peaks, was obtained when the same chromatographic settings were attempted on **5**. This result can be partially attributed to the scarce solubility of the compound in this specific eluent. Admittedly, previous literature already showed the possibility to separate the two enantiomers of **5** with chiral HPLC by increasing the IPA percentage in the eluent mixture up to 80%.³⁸ The intramolecular “protection” of the carboxylic moiety in **2** tremendously improves the solubility in hexane, allowing for a significant reduction of much more viscous iso-propanol in the eluent mixture, whose polarity is instead necessary with precursor **5**. The experimental conditions applied on lactone **2** improve the scope of the chiral resolution of *cone*-calix[4]arenes. First, they offer more narrow peaks. Secondly and more importantly, they significantly reduce the pressure to apply due to a lower percentage of dense IPA in the eluent mixture. Once again, the introduction of the lactone functionality brought about remarkable differences in terms of chromatographic separation. No experiments could be carried out on lactone **3** due to its limited solubility in the eluent mixture. However, the easy oxidation of (separable) **2** into **3** overcomes this only apparent limitation.

Finally, the differentiation of the two enantiomers of lactone **2** was also possible by means of 1H -NMR spectroscopy using (*R*)-(-)-1-(9-Anthryl)-2,2,2-trifluoroethanol as chiral NMR additive. The aldehyde singlet of **2** at 10 ppm was high-field shifted and split into two distinguishable singlets after addition of the chiral NMR additive (Fig. S48†). Minor differences were also observed in the aliphatic region between **5** and **3** ppm (Fig. S48†).

Conclusions

In conclusion, we reported the synthesis and characterization of di- and tri-functionalized lactones of *cone*-calix[4]arenes. The compounds were obtained through an intramolecular process that exploits the special relationship between the distal positions at the upper rim of the *meta* cyclophanes. The *ab initio* calculations convincingly show the close proximity of the distal positions in this series of calix[4]arenes, with good agreement between the observed trends and theoretical predictions in NMR chemical shifts upon ring closure. Furthermore, the modeling showed evidence of a slightly strained ring system in all lactonized structures, yet allowed the exclusion of a highly strained proximal lactone as potential regioisomer of **3**. The lactones are stable in solid state if stored under argon, whereas they undergo immediate solution-phase hydrolysis under acidic/basic conditions. Room temperature aminolysis with pyrrolidine affords trifunctionalized compounds featuring an amide moiety, which can only be obtained from the lactones. Hence, we presented a sequential ring-closing/opening strategy that leads to multifunctionalized inherently chiral *cone* calix[4]arenes. The ease of preparation and chiral HPLC separation of these compounds make them powerful synthons

for such synthetic task. It is envisioned that with further optimization following lactone aminolysis, our strategy can lead to libraries of multifunctionalized derivatives where the alcoholic and aldehyde functionalities can be further transformed, paving the way to possible applications in asymmetric catalysis and chiral recognition events.

Experimental

General experimental details

Unless stated otherwise, all reagents and chemicals were obtained from commercial sources (TCI Chemicals and Sigma Aldrich) at the highest purity available and used without further purification. All solvents were of AR quality and purchased from Biosolve. Flash chromatography was performed on a Grace Reveleris flash chromatography system equipped with an evaporative light scattering detector using Reveleris Silica Flash Cartridges.

Reactions were followed by thin-layer chromatography (pre-coated 0.25 mm, 60-F254 silica gel plates from Merck).

^1H NMR and ^{13}C NMR spectra were recorded either on a Varian Mercury Vx 400 MHz (100 MHz for ^{13}C) or Varian Oxford AS 500 MHz (125 MHz for ^{13}C) NMR spectrometers. Chemical shifts are given in ppm (δ) values relative to residual solvent or tetramethylsilane (TMS). Splitting patterns are labelled as s, singlet; d, doublet; t, triplet; q, quartet; p, quintuplet; m, multiplet.

Matrix assisted laser desorption/ionisation mass spectra were obtained on a PerSeptive Biosystems Voyager DE-PRO spectrometer or a Bruker autoflex speed spectrometer using α -cyano-4-hydroxycinnamic acid (CHCA) and 2-[(*E*)-3-(4-*tert*-butylphenyl)-2-methylprop-2-enylidene]malononitrile (DCTB) as matrices.

Electrospray Ionization-Time Of Flight mass spectrometry was performed with an ESI/QTOF mass spectrometer.

Infrared spectra were recorded on a PerkinElmer Spectrum One 1600 FT-IR spectrometer or a PerkinElmer Spectrum Two FT-IR spectrometer, equipped with a PerkinElmer Universal ATR Sampler Accessory.

UV-Vis measurements were performed on a Perkin-Elmer UV/Vis spectrometer Lambda 40, using quartz cuvettes with 1 cm optical path.

Gel Permeation Chromatography (GPC) was performed using Shimadzu Prominence LC-2030C, and solutions were dissolved at 1 mg mL $^{-1}$ and filtered through 0.2 μm Whatman Anaport 10 filters before injection.

Chiral HPLC separations were performed on a Shimadzu LC-10AD instrument, using Chiralpak IA-3 (amylose tris(3,5-dimethylphenyl)carbamate stationary phase) columns from Daicel Corporation and a 85:15 v/v hexane/iso-propanol as eluent mixture. The chiral separation was performed at 0.2 mL min $^{-1}$ flow rate and followed by UV-Vis absorption at 254 nm wavelength. Solutions were prepared at 1 mg mL $^{-1}$ and filtered through 0.2 μm Whatman Anaport 10 filters before injection.

Materials and methods

Compounds **4** and **5** were available from previous investigations.^{36,38}

Synthesis of lactone **1**

Compound **4** (50 mg, 0.062 mmol) and DMAP (7.6 mg, 0.062 mmol) were dissolved in CH_2Cl_2 (3.0 mL) at 0 $^\circ\text{C}$. EDC-HCl (89 mg, 0.46 mmol) was added to the reaction mixture. The resulting mixture was stirred at room temperature for three days. The reaction mixture was then washed with a 1 M KHSO_4 solution and once with brine. The organic phases were dried over Na_2SO_4 , filtered and evaporated. Chromatographic purification (SiO_2 , hexane/ethyl acetate 8 : 2) afforded compound **1** (20 mg, 0.026 mmol, 43% yield, off-white waxy solid) and unreacted **1** (30 mg). ^1H NMR (300 MHz, CDCl_3) δ : 1.14 (t, 6H, J = 8 Hz), 1.21 (t, 3H, J = 8 Hz), 1.23 (t, 3H, J = 8 Hz), 3.15 (d, 2H, J = 14 Hz), 3.19 (d, 2H, J = 14 Hz), 3.34–3.50 (m, 4H), 3.52–3.60 (m, 4H), 3.71–3.76 (m, 8H), 3.87–3.90 (m, 2H), 4.00–4.23 (m, 6H), 4.45 (d, 2H, J = 14 Hz), 4.47 (d, 2H, J = 14 Hz), 4.74 (s, 2H), 6.11 (s, 2H), 6.28 (s, 2H), 7.01 (t, 2H), 7.16 (d, 4H, J = 3 Hz). ^{13}C NMR (300 MHz, CDCl_3) δ : 15.20, 15.25, 30.86, 31.24, 66.17, 66.54, 66.61, 66.40, 69.48, 69.65, 72.35, 72.40, 73.63, 73.77, 122.32, 128.01, 128.81, 129.50, 129.78, 130.80, 131.29, 134.08, 134.43, 136.74, 137.14, 155.40, 158.37, 159.55, 172.94. HR-MS (ESI-TOF) calcd for $\text{C}_{46}\text{H}_{56}\text{O}_{10} + \text{Na}^+$: 791.3771, found: 791.3726. UV-Vis (CH_2Cl_2), [λ_{max} /nm ($\epsilon/\text{mol}^{-1} \text{ L cm}^{-1}$)]: 300 (2135), 264 (10 916), 230 (33 540) FT-IR (ATR) ν (cm^{-1}): 2973, 2920, 2866, 1713, 1599, 1465, 1451, 1383, 1370, 1349, 1279, 1235, 1214, 1174, 1149, 1121, 1053, 954, 764.

Synthesis of lactone **2**

Compound **5** (250 mg, 0.31 mmol) and DMAP (38 mg, 0.31 mmol) were dissolved in CH_2Cl_2 (10 mL) at 0 $^\circ\text{C}$. EDC-HCl (455 mg, 2.38 mmol) was added to the reaction mixture. The resulting mixture was stirred at room temperature for three days. The reaction mixture was then washed with a 1 M KHSO_4 solution and once with brine. The organic phases were dried over Na_2SO_4 , filtered and evaporated. Chromatographic purification (SiO_2 , hexane/ethyl acetate 10 : 1 $\rightarrow$ 5 : 1 $\rightarrow$ 1 : 1) afforded compound **4** (125 mg, 0.16 mmol, 52% yield, off-white waxy solid). ^1H NMR (400 MHz, CDCl_3) δ : 1.09 (t, J = 8 Hz, 3H), 1.15 (t, J = 8 Hz, 3H), 1.22 (t, J = 8 Hz, 3H), 1.23 (t, J = 8 Hz, 3H), 3.14–3.34 (m, 4H), 3.42–3.49 (m, 4H), 3.53–3.59 (m, 4H), 3.68–3.77 (m, 8H), 3.89–3.91 (m, 2H), 4.00–4.10 (m, 2H), 4.15–4.33 (m, 2H), 4.43–4.58 (m, 4H), 4.69–4.79 (m, 2H), 6.09 (s, 1H), 6.14 (s, 1H), 6.27 (s, 1H), 6.30 (s, 1H), 7.03 (t, J = 8 Hz, 1H), 7.17–7.20 (m, 2H), 7.71–7.73 (m, 2H), 10.01 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ : 15.37, 15.41, 31.01, 31.08, 31.43, 66.31, 66.41, 66.71, 66.79, 69.54, 69.62, 70.38, 72.41, 72.78, 73.30, 73.95, 74.07, 122.74, 128.36, 129.00, 129.28, 129.83, 130.04, 130.52, 130.82, 131.52, 131.71, 131.89, 133.38, 133.62, 134.33, 134.85, 136.79, 137.29, 137.83, 138.04, 155.57, 158.36, 159.68, 164.76, 172.75, 191.97. UV-Vis (CH_2Cl_2), [λ_{max} /nm ($\epsilon/\text{mol}^{-1} \text{ L cm}^{-1}$)]: 273 (14 182), 237 (19 908). HR-MS

(MALDI-TOF) calcd for $C_{47}H_{56}O_{11} + Na^+$: 819.37; found: 819.39. FT-IR (ATR) ν (cm^{-1}): 2973, 2926, 2866, 2728, 1713, 1689, 1595, 1452, 1384, 1370, 1349, 1280, 1237, 1150, 1124, 1052, 951.

Synthesis of lactone 3 with lactonization procedure

Compound 6 (250 mg, 0.31 mmol) and DMAP (38 mg, 0.31 mmol) were dissolved in CH_2Cl_2 (10 mL) at 0 °C. EDC-HCl (455 mg, 2.38 mmol) was added to the reaction mixture. The resulting mixture was stirred at room temperature for three days. The reaction mixture was then washed with a 1 M $KHSO_4$ solution and once with brine. The organic phases were dried over Na_2SO_4 , filtered and evaporated. The chromatographic purifications (SiO_2 , hexane/ethyl acetate 10:1 $\rightarrow$ 5:1 $\rightarrow$ 1:1) attempted to isolate 3 failed because of identical RF values with precursor 6. However, the spectroscopic characterization (1H NMR, ^{13}C -NMR, UV-Vis and FT-IR) was still possible because of the low amount of impurity (7%) present (obtained 130 mg of total impure material, 50% crude yield). 1H NMR (400 MHz, $CDCl_3$) δ : 1.12 (t, J = 8 Hz, 3 H), 1.15 (t, J = 8 Hz, 3 H), 1.23 (t, J = 8 Hz, 3 H), 1.24 (t, J = 8 Hz, 3 H), 3.13–3.32 (m, 4H), 3.44–3.51 (m, 4H), 3.54–3.60 (m, 4H), 3.70–3.77 (m, 8H), 3.89–3.92 (m, 2H), 4.00–4.11 (m, 4H), 4.16–4.32 (m, 4H), 4.44–4.56 (m, 4H), 4.70–4.81 (m, 2H), 6.10–6.14 (m, 2H), 6.30 (s, 2H), 7.03 (t, J = 8 Hz, 1H), 7.18 (t, J = 8 Hz, 2H), 7.95–7.98 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ : 15.35, 29.80, 30.96, 31.31, 31.40, 66.30, 66.36, 66.49, 66.55, 66.68, 66.76, 69.50, 69.59, 69.62, 70.26, 72.38, 72.68, 73.04, 73.84, 73.97, 122.64, 122.93, 128.27, 128.96, 129.10, 129.24, 129.77, 129.97, 130.49, 131.51, 131.63, 131.96, 133.69, 133.85, 134.12, 134.71, 136.70, 137.10, 137.24, 137.33, 155.50, 158.37, 159.63, 163.89, 171.82, 172.84. UV-Vis (CH_2Cl_2), [λ_{max}/nm ($\epsilon/mol^{-1} L cm^{-1}$)]: 262 (13 567), 241 (13 781). HR-MS (MALDI-TOF) calcd for $C_{47}H_{56}O_{12} + Na^+$ 835.37; found: 835.38. FT-IR (ATR) ν (cm^{-1}): 2973, 2926, 2867, 1713, 1682, 1598, 1452, 1423, 1384, 1371, 1349, 1280, 1237, 1211, 1175, 1150, 1120, 1051, 950, 934.

Synthesis of lactone 3 via oxidation of 2

Compound 2 (100 mg, 0.12 mmol) and 35% H_2O_2 solution (1 mL) were dissolved in CH_3CN (5 mL). A 5 mL solution of $NaClO_2$ (17.5 mg, 0.19 mmol) in 1 M NaH_2PO_4 was added. The resulting mixture was stirred overnight at room temperature. CH_3CN was evaporated and the water phase extracted twice with CH_2Cl_2 . The organic phases were dried over Na_2SO_4 , filtered and evaporated to yield compound 3 with 7% of ring-opened 6 present (94.5 mg, 95% crude yield).

Synthesis of compound 6

Compound 5 (102 mg, 0.125 mmol) and 35% H_2O_2 solution (1 mL) were dissolved in CH_3CN (5 mL). A 5 mL solution of $NaClO_2$ (17.1 mg, 0.19 mmol) in 1 M NaH_2PO_4 was added. The resulting mixture was stirred overnight at room temperature. CH_3CN was evaporated and the water phase extracted twice with CH_2Cl_2 . The organic phases were dried over Na_2SO_4 , filtered and evaporated to yield compound 6 (100 mg, 0.122 mmol, 98% yield, off-white waxy solid). 1H NMR (400 MHz, $CDCl_3$) δ : 1.16–1.22 (m, 12 H), 3.12–3.32 (m, 4H),

3.49–3.57 (m, 48H), 3.54–3.60 (m, 8H), 3.78–3.82 (m, 8H), 4.07–4.25 (m, 8H), 4.46–4.58 (m, 4H), 4.70–4.81 (m, 2H), 6.58–6.69 (m, 5H), 7.36–7.45 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ : 172.07, 171.92, 161.53, 157.23, 156.32, 135.75, 135.29, 134.95, 134.84, 134.65, 130.90, 130.54, 129.60, 129.25, 128.75, 127.30, 123.55, 123.27, 122.94, 73.65, 73.52, 73.45, 73.21, 69.82, 69.79, 69.72, 66.56, 66.54, 66.51, 30.94, 15.38, 15.33. UV-Vis (CH_2Cl_2), [λ_{max}/nm ($\epsilon/mol^{-1} L cm^{-1}$)]. HR-MS (MALDI-TOF) calcd for $C_{47}H_{58}O_{13} + Na^+$ 853.38 g mol^{-1} ; found m/z 853.38. FT-IR (ATR) ν (cm^{-1}): 2975, 2927, 2869, 1783, 1715, 1683, 1600, 1454, 1423, 1386, 1371, 1343, 1300, 1288, 1214, 1202, 1170, 1138, 1122, 1052, 1015, 925, 776.

General procedure for the synthesis of amides 7–8

Lactone 1 or 2 was weighed in a screw-cap vial and dissolved in treated $CDCl_3$ to reach a 5 mM concentration. The solutions were immediately transferred into an NMR tube. 1 equivalent of pyrrolidine was added *via* syringe and the NMR tubes were subsequently capped. The mixtures were kept at RT and in darkness, and monitored *via* 1H -NMR spectroscopy. When final conversion was achieved, the mixtures were worked up by removing the solvent and redissolving the crude product in a 5:95 v/v TFA/ $CHCl_3$ mixture. The obtained solutions were washed twice with water, dried over Na_2SO_4 , filtered and evaporated to obtain pure amides 7–8 in quantitative yields (99%).

The entire procedure can be scaled up (50 mg) in round bottom flasks, provided the reaction mixtures are protected by an Ar or N_2 atmosphere (90% yield under these experimental conditions).

Amide 7 (off-white waxy solid). 1H NMR (400 MHz, $CDCl_3$) δ : 1.17 (t, 6H, J = 8 Hz), 1.22 (t, 6H, J = 8 Hz), 1.74 (p, 2H, J = 8 Hz), 1.84 (p, 2H, J = 8 Hz), 3.10–3.16 (m, 6H), 3.45 (t, 2H, J = 8 Hz), 3.51 (q, 4H, J = 8 Hz), 3.56 (q, 4H, J = 8 Hz), 3.80 (q, 4H, J = 8 Hz), 3.84–3.93 (m, 4H), 3.98 (t, 2H, J = 8 Hz), 4.02 (t, 2H, J = 8 Hz), 4.14 (s, 2H), 4.19–4.30 (m, 4H), 4.48 (d, 2H, J = 8 Hz), 4.52 (d, 2H, J = 8 Hz), 6.37 (s, 2H), 6.57 (s, 2H), 6.79 (t, 2H, J = 8 Hz), 6.89–6.85 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ : 169.94, 157.26, 157.02, 154.61, 136.19, 136.12, 135.55, 133.95, 133.64, 130.45, 129.11, 128.65, 127.39, 125.90, 122.64, 73.89, 72.80, 69.82, 69.80, 69.77, 66.64, 66.59, 66.37, 64.26, 49.64, 46.41, 31.05, 30.98, 26.52, 24.41, 15.49, 15.42, 15.41. UV-Vis (CH_2Cl_2), [λ_{max}/nm ($\epsilon/mol^{-1} L cm^{-1}$)]: 231 (35 827), 281 (2741). HR-MS (MALDI-TOF) calcd for $C_{50}H_{65}NO_{10}Na^+$ 862.45; found 862.46. FT-IR (ATR) ν (cm^{-1}): 3403, 2973, 2922, 2867, 1610, 1575, 1454, 1428, 1351, 1281, 1247, 1216, 1120, 1056, 919, 836, 761.

Amide 8 (off-white waxy solid). 1H NMR (400 MHz, $CDCl_3$) δ : 1.13 (t, J = 8 Hz, 3H), 1.18 (t, J = 8 Hz, 3H), 1.22 (t, J = 8 Hz, 6H), 1.77 (p, J = 8 Hz, 2H), 1.85 (p, J = 8 Hz, 2H), 3.13–3.27 (m, 8H), 3.43–3.58 (m, 10H), 3.77–3.88 (m, 8H), 3.97–4.05 (m, 2H), 4.15 (d, J = 4 Hz, 2H), 4.19–4.63 (m, 8H), 6.33–6.41 (m, 2H), 6.51–6.58 (m, 2H), 6.78 (t, J = 8 Hz, 1H), 6.88–6.94 (m, 2H), 7.45–7.47 (m, 2H), 9.83 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ : 192.00, 169.91, 163.41, 157.16, 157.01, 154.60, 137.29, 136.78, 136.32, 136.16, 135.41, 134.28, 133.82, 133.15, 132.69, 131.44, 131.15, 130.69, 129.95, 129.19, 128.66, 127.68, 127.01, 126.38, 125.81, 122.76, 74.03, 73.97, 73.41, 72.87, 70.10, 69.78,

69.72, 66.65, 66.60, 66.41, 66.33, 64.04, 49.71, 46.44, 31.10, 31.05, 31.01, 30.96, 26.46, 24.38, 15.47, 15.41. UV-Vis (CH₂Cl₂), [λ_{max} /nm (ϵ /mol⁻¹ L cm⁻¹): 231 (37 478), 281 (11 533). HR-MS (MALDI-TOF) calcd for C₅₁H₆₅NO₁₁Na⁺ 890.44; found 890.48. FT-IR (ATR) ν (cm⁻¹): 3385, 2973, 2925, 2867, 1688, 1599, 1431, 1384, 1371, 1352, 1283, 1246, 1216, 1191, 1176, 1119, 1052, 1016, 939, 921, 881, 799, 763.

¹H-NMR observation of racemic 2

Lactone 2 was dissolved in treated CDCl₃. An equimolar amount of (*R*)-(-)-1-(9-Anthryl)-2,2,2-trifluoroethanol was then added. The mixture was equilibrated for 30 minutes at room temperature prior to the ¹H NMR spectrum measurement. The mixture was kept at room temperature and in darkness for a week, and frequently followed by ¹H NMR. No further changes were observed in the ¹H NMR spectrum throughout this time.

Conflicts of interest

There are no conflicts to declare.

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