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Synthesis of Functionalized, Sterically Congested Calix[4]phyrin Macrocycles Using Donor–Acceptor-Substituted Cyclopropanes – First Example of a Mono-*meso*-spirolactone Incorporated into a Calix[4]phyrin

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Dedicated to the memory of Professor Dr. Emanuel Vogel

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Calix[4]phyrins are an important class of hybrid macrocyclic systems at the interface between porphyrins and calixpyrroles (porphyrinogens). A new stepwise synthesis of oxidation-resistant *meso*-hydrogenated calix[4]phyrins is reported, which allows variable substitution in the residues of their sp^2-*meso*-centers without the need for a porphyrin intermediate. It relies on the acid-catalyzed condensation of a sterically hindered donor–acceptor-substituted cyclopropane precursor with pyrrole to form a sterically congested dipyrromethane. This was subsequently condensed with a wide range of alkyl and aryl aldehydes bearing electron-donating or electron-withdrawing substituents followed by an oxidation step to form stable calix[4]phyrin(**1**.*1*.**1**.*1*)s with bridging *meso*-C*H* hydrogen atoms through an acid-promoted dehydrative condensation. The methodology avoids any need for premetallation of the macrocycle and/or the use of organometallic catalysts or reagents and allows the incorporation of the bulky cyclopropane-derived substituents specifically into the 5,15-*meso*-like positions. The resulting regioisomerically pure products display conformational features that reflect their mixed nature between porphyrins and calixpyrroles and they were assessed by X-ray diffraction analysis, NMR techniques and UV/Vis spectroscopy. The possibility to introduce key functional groups enables subsequent modification of these calix[4]phyrins and allows their connection to other groups such as biologically active moieties. Of special interest is an unprecedented example of an acid-driven lactonization that results in the incorporation of a mono-*meso*-spirolactone into a calix[4]phyrin(**1**.*1*.**1**.*1*). Moreover, it is demonstrated that this approach to calix[4]phyrins is also applicable to other sterically congested dipyrromethanes.

Introduction

Calix[4]phyrin(**1**.*1*.**1**.*1*)s[1] (also known as *trans*-porphodimethenes) are a class of hybrid compounds with functional properties derived from both porphyrins and calixpyrroles. They can be regarded as an assembly of two dipyrrin fragments linked through sp^3-hybridized *meso*-carbon atoms, which interrupts the ring current in the macrocycle and leads to drastic conformational changes and significant modifications in their overall physicochemical properties.[2] Whereas porphyrins and calixpyrroles contain only sp^2- or sp^3-hybridized *meso*-carbon bridges, respectively, calix[4]phyrins are their macrocyclic analogues that contain sp^2- and sp^3-hybridized *meso*-carbon bridges. Because of their partially flexible framework as well as the rather rigid π-conjugated network, they exhibit new features derived from their mixed nature between porphyrins and calixpyrroles. For example, calixphyrins are promising in coordination chemistry,[3] as catalysts,[4] and as sensors for anions, cations, or neutral substrate recognition in supramolecular chemistry.[2c,3,5] Their intramolecular proton transfer has also been studied recently.[6] They can be regarded as a four-electron oxidation product of calixpyrroles or a two-electron (photo)reduction product of porphyrin systems (Scheme 1). Furthermore, in living systems, reduced porphyrins are important intermediates in the heme biosynthetic pathway and because of the increased flexibility of such molecules, their metabolism is enhanced and they enable transfer across cellular membranes.[7,8]

Because of the absence of suitable general synthetic procedures for calix[4]phyrin(**1**.*1*.**1**.*1*)s, their chemistry has been quite limited because of their general instability towards air and light. They have been obtained from several described

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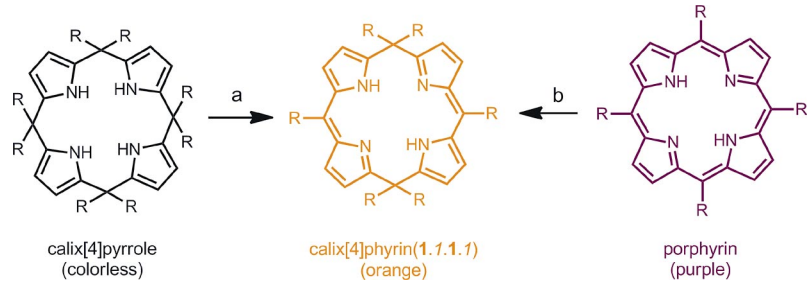


Scheme 1. Two principal synthetic pathways to calix[4]phyrins: a) four-electron oxidation/deprotonation (dealkylation) of calix[4]pyrroles or b) two-electron (photo)reduction/protonation (alkylation) of porphyrins.

pathways: i. the conversion of phlorin salts (three sp^2-hybridized *meso*-carbon atoms, three NH hydrogen atoms) under strong acidic conditions;[9] ii. the aerobic oxidation of β-octamethyl-*meso*-tetraphenylcalix[4]pyrroles followed by metallation with zinc acetate resulting in *meso*-hydrogenated β-octamethyl-*meso*-tetraphenylcalix[4]phyrins, which are unstable towards oxygen;[10] iii. the dealkylation of *meso*-octaalkylcalix[4]pyrroles, which requires previous metallation and is limited to the formation of hexahomoalkyl-*meso*-substituted metallo-calix[4]phyrin(**1**.*1*.**1**.*1*)s;[11] iv. (photo)reduction of metalloporphyrins, which necessarily requires β-pyrrole alkyl substituents to ensure stability towards oxidation,[12] or reaction of Fe^{II}TPP (TPP = *meso*-tetraphenylporphyrinato dianion) with allyl bromide under anaerobic conditions, which requires a reducing agent and unselectively gives a mixture of stereoisomers of the 5,15-diallyl–Fe^{II}TPP complex, being unstable towards oxygen;[13] v. the nucleophilic addition of organolithium reagents to substituted metalloporphyrins;[14] vi. condensation reactions of 5-aryldipyrromethanes with vicinal diketones to produce spiro-di- or tricyclic calix[4]phyrin(**1**.*1*.**1**.*1*)s;[15] vii. condensation of formylated dialkyldipyrromethanes with 5,5-dialkyldipyrromethanes (MacDonald approach), which requires Ni^{II} templating to achieve acceptable yields;[16] viii. condensations with sterically demanding aldehydes such as pivalaldehyde with pyrrole, which unselectively produced five different compounds with yields of less than 1% for each product,[17] or the condensation of sterically demanding aldehydes like ferrocenecarboxaldehyde with alkyl-substituted dipyrromethane to enhance the stability towards oxidation;[18] ix. condensation of 5-adamantyldipyrromethane with benzaldehyde, which gave the unfunctionalized 5,15-*meso*-hydrogenated calix[4]phyrin;[19] x. condensation of 5-substituted dipyrromethanes with ketones (mostly acetone),[5a,20,21] or condensation of 5,5-disubstituted dipyrromethanes with aromatic aldehydes;[5d,21,22] both methods result in substituents other than hydrogen at the sp^3-hybridized *meso*-centers. Moreover, with these methods it is difficult to synthesize calix[4]phyrin(**1**.*1*.**1**.*1*)s functionalized at both the sp^2- and sp^3-hybridized *meso*-carbon bridges.[21] In fact, as the instability of the calix[4]phyrin(**1**.*1*.**1**.*1*)s is attributed primarily to the presence of hydrogen atoms in their *meso*-like positions, these methods are mostly limited to calix[4]phyrin(**1**.*1*.**1**.*1*)s that contain a quaternary carbon atom at their sp^3-hybridized carbon centers (*meso*-dialkylated centers), which prevents oxidation to the corresponding porphyrin.

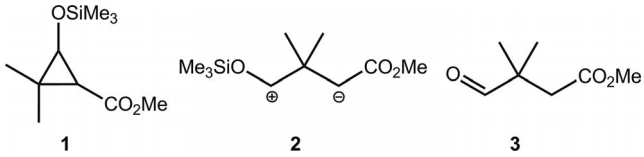
As the harsh conditions required for macrocycle transformations are generally incompatible with the presence of sensitive groups and based on the abovementioned limitations in known pathways, the ability to vary the substituents at the *meso*-positions of the calix[4]phyrin(**1**.*1*.**1**.*1*)s still remains rather limited and challenging. To expand the diversity of calixphyrin macrocycles, we herein report a tunable and efficient synthesis of β-unsubstituted, stable calix[4]phyrin(**1**.*1*.**1**.*1*)s with bridging *meso*-C*H* hydrogen atoms by an acid-catalyzed condensation of functionalized dipyrromethanes with a wide variety of aldehydes. The dipyrromethane building block incorporating the future sp^3-hybridized *meso*-carbon center of the calix[4]phyrin(**1**.*1*.**1**.*1*) was synthesized by reaction of a donor–acceptor-substituted cyclopropane (d–a cyclopropane) precursor with pyrrole. The introduction of a substituent with high steric bulk to the dihydroporphyrin skeleton resulted in a pronounced stability towards oxidation and permitted the isolation of the calix[4]phyrin(**1**.*1*.**1**.*1*)s directly from the oxidation of the corresponding calixpyrrole.

Results and Discussion

As part of an ongoing project directed towards new synthetic applications of d–a cyclopropanes[23] as well as new tetrapyrrole macrocycles,[24] we planned to design a series of tunable calixphyrin-type systems by employing sterically hindered d–a cyclopropanes and pyrrole, thus allowing the synthesis of novel calix[4]phyrin(**1**.*1*.**1**.*1*)s that are not readily accessible by the known alternative strategies.

In the synthesis of *meso*-substituted porphyrins, corroles, expanded and reduced porphyrins, and related compounds, *meso*- or 5-substituted dipyrromethanes are important precursors. In particular, they play a key role in the regioisomerically pure synthesis of porphyrins and related macrocyclic systems by predesignating the orientation of *meso*-substituents. For instance, using dipyrromethane building blocks, *trans*-A_2B_2-porphyrins can be synthesized efficiently by direct [2+2] condensation of dipyrromethanes with aldehydes.[25] Hence, we considered that this approach would also be feasible for the synthesis of calix[4]phyrin(**1**.*1*.**1**.*1*) derivatives based on d–a cyclopropane-derived dipyrromethanes.

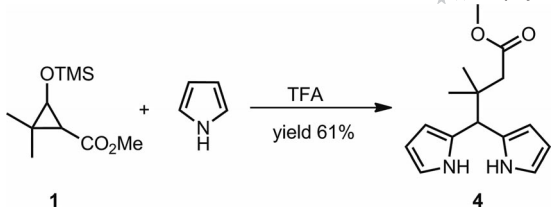
Cyclopropane derivatives substituted by donor and acceptor groups are particularly suitable for synthetic applications because the electronic effects of the substituents activate the strained compound and provide high versatility of the respective products after ring cleavage.[23] Cyclopropane derivative **1** serves as a 1,3-zwitterionic synthon **2** and generates product **3** (Scheme 2) in situ in the presence of protic solvents, mild acids, or fluoride ions.[26] Compound **3** is a useful building block owing to the 1,4-distance between the two carbonyl groups. We selected the easily available cyclopropane **1**[27] as starting material as the in situ formed aldehyde **3** can be used in the condensation step with pyrrole and its methoxycarbonyl group should enable subsequent transformations.



Scheme 2. Structure of d–a cyclopropane **1**, which serves as a 1,3-zwitterionic synthon **2** and generates **3**.

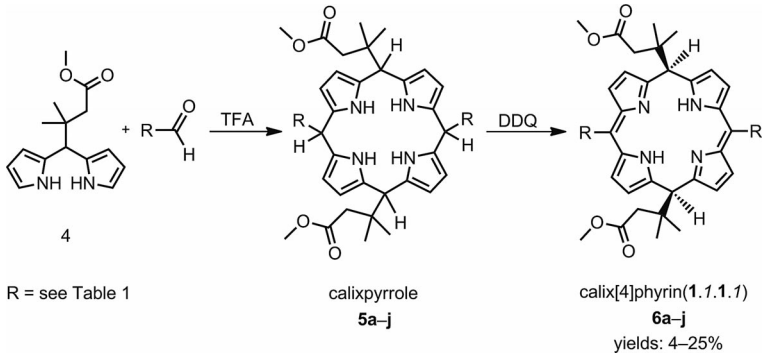
Cyclopropane **1** seemed particularly attractive as an aldehyde equivalent for the planned dipyrromethane synthesis as it contains two methyl groups adjacent to the masked aldehyde functionality and hence should exert steric strain on the desired dipyrromethane as well as the future tetrapyrrole condensation product. This strain in the *meso*-positions as described above is known to stabilize calix[4]phyrin(**1**.*1*.**1**.*1*) structures.[19]

For the synthesis of the dipyrromethane, **1** was treated with an excess of pyrrole in a solvent-free condensation in the presence of a catalytic amount of trifluoroacetic acid (TFA, 10 mol-%).[28] After work up, the stable dipyrromethane **4** containing the bulky residue was obtained in 61% yield (Scheme 3). Performing the two reaction steps in one pot (ring opening of the cyclopropane and condensation with excess pyrrole) and purifying only at the final step reduces the effort and allows a good overall yield.[29]



Scheme 3. Condensation of **1** with an excess of pyrrole in a solvent-free condensation reaction leading to functionalized dipyrromethane **4**.

With a multigram amount of dipyrromethane **4** in hand, we reacted it with different aldehydes in an acid-catalyzed condensation to form calixpyrrole systems, which were then oxidized to investigate the formation of functionalized calix[4]phyrin systems (Scheme 4). As the stability of calixpyrroles towards oxidants is dependent on the substitution pattern of the sp^3-hybridized *meso*-carbon atoms, and because **4** has a special structure with a quaternary carbon atom adjacent to the *meso*-bridge, we assumed that this steric hindrance could influence the final oxidation step and thus yield calix[4]phyrins instead of porphyrins, similarly to a recent report in which 5-adamantyldipyrromethane is condensed with benzaldehyde[19]. Therefore, as a test reaction, dipyrromethane **4** was condensed with benzaldehyde at room temperature in the presence of a catalytic amount of TFA (20 mol-%) in dichloromethane (DCM) as described for other dipyrromethane condensations[30] to furnish the corresponding calixpyrrole **5**. After subsequent oxidation with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ),[31] the orange-red crystalline product **6a** was isolated by column chromatography in 19% yield. According to literature reports, calix[4]phyrin(**1**.*1*.**1**.*1*)s are most stable as *syn*-stereoisomers, in which the bulky substituents adopt an axial conformation (cf. also Scheme 7).[2,32] As anticipated, oxidation occurred only at those *meso*-positions that carried the sterically less demanding aryl substituent. The steric hindrance exerted by the bulky cyclopropane-derived residues presumably interrupts the full six-electron oxidation of the calixpyrrole[10,33] and results in the preferential formation of the stable calix[4]phyrin(**1**.*1*.**1**.*1*) **6a** (cf. X-



Scheme 4. Acid-catalyzed condensation of **4** with aldehydes to form calix[4]phyrin(**1**.*1*.**1**.*1*)s **6** via calixpyrrole intermediate **5**.

ray data in Figure 1). To the best of our knowledge, this is the first report in which cyclopropane-derived dipyrromethanes are utilized in the synthesis of tetrapyrroles, which give rise to calix[4]phyrins with 5,15-*trans*-hydrogenated *meso*-positions owing to the steric hindrance caused by bulky substituents. Following these promising results, we tested the generality and functional group tolerance of this procedure for the synthesis of calix[4]phyrin(**1**.*1*.**1**.*1*)s. Therefore, we examined the one-pot reaction of a range of substituted aromatic and aliphatic aldehydes with dipyrromethane **4** in a 1:1 ratio under the conditions used for the synthesis of **6a** to obtain the corresponding calix[4]phyrin(**1**.*1*.**1**.*1*)s, which are functionalized at both residues of their sp^3- and sp^2-hybridized *meso*-centers.

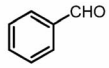
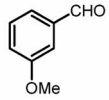
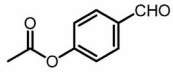
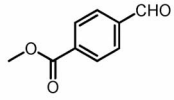
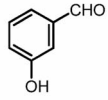
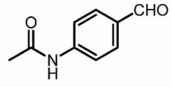
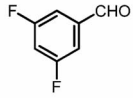
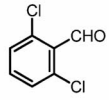
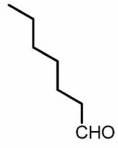
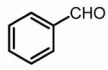
As shown in Table 1, steric and electronic variations in the aldehydes bearing electron-donating or electron-withdrawing substituents were tolerated and did not change the efficiency of the reaction and resulted in the formation of the desired calix[4]phyrin(**1**.*1*.**1**.*1*)s **6a**–**j** in acceptable yields (4–25%). For example, several key functional groups such as acetyl, methoxycarbonyl, and acetamido groups are tolerated under the mild reaction conditions (Table 1, Entries 3, 4, and 6). In addition, a sterically hindered 2,6-dichlorophenyl substituent could readily be introduced into the calix[4]phyrin(**1**.*1*.**1**.*1*) skeleton (Table 1, Entry 8). The use of paraformaldehyde resulted in calix[4]phyrin(**1**.*1*.**1**.*1*) **6j** in 4% yield, which possesses free 10- and 20-*meso*-positions (Table 1, Entry 10). To examine the feasibility of this method on a larger preparative scale, the model reaction that leads to **6a** was performed on a 20 mmol scale. The reaction proceeded similarly to the small-scale reaction and provided the desired calix[4]phyrin(**1**.*1*.**1**.*1*) in 16% yield after 23 h (Table 1, Entry 11).

As an example, compound **6a** was subjected to alkaline hydrolysis of the ester groups. This conversion proceeded in quantitative yield to produce the calix[4]phyrin(**1**.*1*.**1**.*1*) dicarboxylic acid **7**, which exemplifies the possibility of further functionalization of the calix[4]phyrin(**1**.*1*.**1**.*1*)s at their saturated *meso*-residues (Scheme 5).

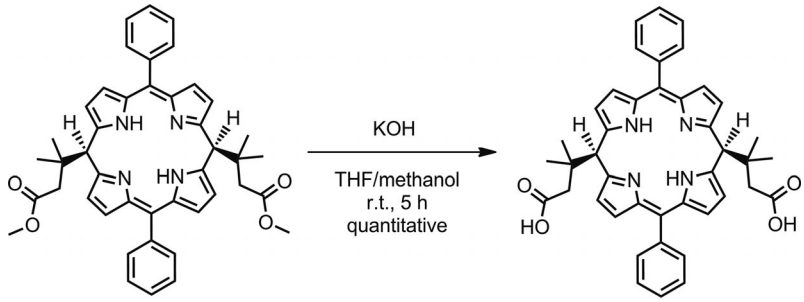
Thus, by using functionalized aldehydes in the condensation reaction, the overall products are calix[4]phyrin(**1**.*1*.**1**.*1*)s that are functionalized at the residues of both their sp^3- and their sp^2-hybridized *meso*-centers. A specific advantage of this approach is that bulky residues are introduced during the dipyrromethane synthesis. The dipyrromethane is more flexible and less sensitive to steric hindrance, therefore the inclusion of these bulky residues prior to the ring-forming step promotes the efficacy of the reaction.[21]

The functionalized bulky residue of **4** can be regarded as similar to a *tert*-butyl group. Therefore, we set out to test the applicability of the dipyrromethane building block approach for calix[4]phyrin(**1**.*1*.**1**.*1*)s directly with pivalaldehyde as a simple sterically demanding aldehyde. The hitherto unknown dipyrromethane **8** was prepared and subsequently treated with benzaldehyde under the reaction conditions described for calix[4]phyrin(**1**.*1*.**1**.*1*) **6a**. Gratifyingly, the expected calix[4]phyrin(**1**.*1*.**1**.*1*) **9** was isolated in 27% yield; to date, this had only been isolated as a byproduct with a yield < 1% (Scheme 6).[17] These results, which are consistent with another example from the literature,[19]

Table 1. TFA-catalyzed condensation of dipyrromethane **4** with different aldehydes (1:1 ratio) at room temperature in DCM followed by oxidation with DDQ furnishing functionalized *meso*-hydrogenated calix[4]phyrin(**1**.*1*.**1**.*1*)s **6**.

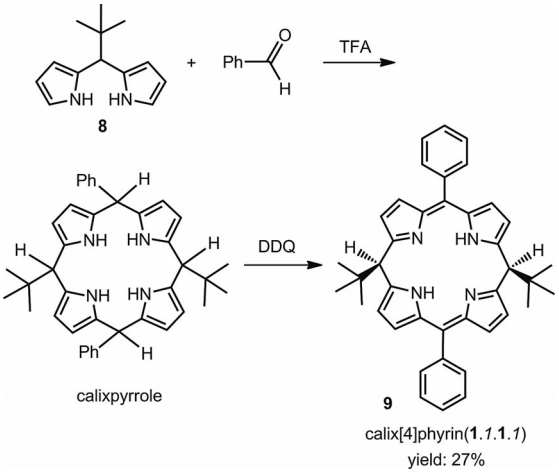
Entry	Aldehyde	Product	Time [h]	Yield [%][a]
1		**6a**	16	19
2		**6b**	18	15
3		**6c**	18	19
4		**6d**	18	12
5		**6e**	18	13
6		**6f**	18	25
7		**6g**	23	16
8		**6h**	23	12
9		**6i**	18	12
10[b]		**6j**	30	4
11[c]		**6a**	23	16

[a] Yield of purified product. [b] Paraformaldehyde was used. [c] The reaction was performed on a 20 mmol scale.



Scheme 5. Synthesis of calix[4]phyrin(**1**.*1*.**1**.*1*) dicarboxylic acid **7** by saponification of calix[4]phyrin(**1**.*1*.**1**.*1*) **6a**.

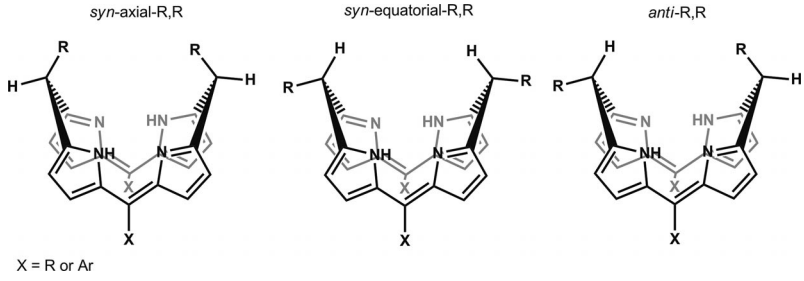
strongly suggest that the [2+2] dipyrromethane building block approach to calix[4]phyrin(**1**.*1*.**1**.*1*)s can also be applied to other sterically demanding aldehydes.



Scheme 6. TFA-catalyzed condensation of **8** with benzaldehyde to yield calix[4]phyrin(**1**.*1*.**1**.*1*) **9** via the corresponding calixpyrrole intermediate.

In calix[4]phyrin(**1**.*1*.**1**.*1*)s with unsymmetrically substituted sp^3-*meso*-carbon centers there are two possible diastereomeric forms, *syn* and *anti*, which refer to the position of the residues at the saturated *meso*-carbon centers. For the *syn* isomer, two conformers can be distinguished denoted as *syn*-axial and *syn*-equatorial. Among these three possible stereoisomers, the *syn*-axial stereoisomer is more stable than the two alternative stereoisomers because steric repulsion between substituents at the tetravalent centers is minimized (Scheme 7).[2a] Although the conjugation within the macrocycle is interrupted at the saturated *meso*-positions, it is known from the literature that far-ranging electronic induction effects in the two dipyrrin units still exist, and that the substituents significantly modify conformational transition barriers, equilibrium geometries, and relative conformer energies throughout the complete calix[4]phyrin structure.[21,32]

Information on the detailed structure of the calix[4]phyrin(**1**.*1*.**1**.*1*)s was obtained by single-crystal X-ray diffraction analyses of **6a** and **6c**. Compound **6a** exhibits crystallographic C_2 symmetry with half of the molecule forming the asymmetric unit (cf. Table 2). However, the alkyl side chains are disordered as shown in Figure 1 (top). Figure 1 (bottom) shows calix[4]phyrin(**1**.*1*.**1**.*1*) **6a** as a *syn*-axial *meso*-hydrogenated calix[4]phyrin with marked kinks enforced by its two sterically congested alkyl residues at the sp^3 hybridized *trans*-*meso*-positions along the 5,15-C axis, which results in the typical "roof-like" (i.e. V-shaped) structure with an angle of approximately 112° between the dipyrrin halves. The two hydrogen atoms at C5 and C15 point outward and the bulky alkyl residues occupy a *syn*-axial conformation. The system also displays regions of local planarity corresponding to the two dipyrrin halves, which is in accordance to their description as "hybrid molecules" that resemble both the aromatic porphyrins and their nonplanar, six-electron-reduced calixpyrrole analogues. The two phenyl rings are positioned with an angle of approximately 55° relative to the dipyrrin plane. There is an intramolecular hydrogen bond [*d*(H···N) 2.16 Å] within the dipyrrin unit.



Scheme 7. Schematic representation of the three possible stereoisomers of calix[4]phyrin(**1**.*1*.**1**.*1*)s.

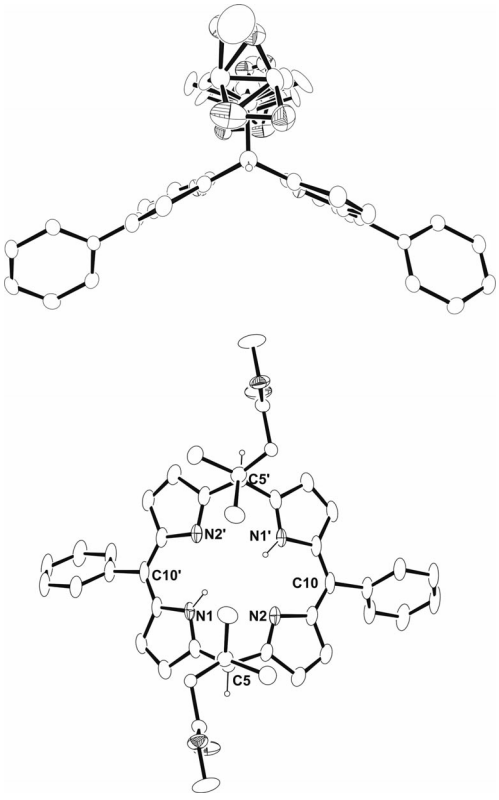


Figure 1. ORTEP[35] plots of macrocycle **6a**. Thermal ellipsoids are scaled to 50% probability level. Top: Roof-like structure showing the disorder. Hydrogen atoms, except those bonded to the nitrogen atoms and to the carbon atoms 5 and 5′, have been omitted for clarity (in the plot, C15 is denoted as C5′).

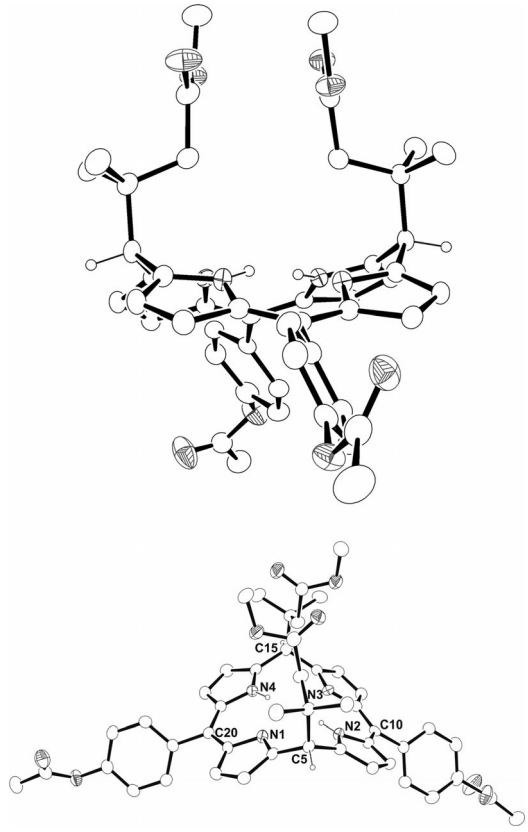


Figure 2. ORTEP[35] plots of macrocycle **6c**. Thermal ellipsoids are scaled to 50% probability level. Hydrogen atoms, except those bonded to the nitrogen atoms and to the carbon atoms 5 and 15, have been omitted for clarity.

The second calix[4]phyrin(**1**.*1*.**1**.*1*) **6c**, which bears 4-acetoxyphenyl substituents at the sp^2-hybridized *meso*-carbon centers, exhibits noncrystallographic C_2 symmetry (Figure 2). The geometries of **6c** are in general in accordance with the features already observed for the parent compound **6a**. There is a V-shaped conformation between the two dipyrrin halves (angle ca. 112°), and the two alkyl residues occupy a *syn*-axial configuration (cf. Table 2). The two substituted phenyl rings are positioned with angles of approximately 53 and 57° relative to the dipyrrin plane. There are intramolecular hydrogen bonds [*d*(H···N) 2.15 and 2.25 Å] within each of the dipyrrin units.

For metallation, owing to their partially unconjugated nature, calix[4]phyrin(**1**.*1*.**1**.*1*)s exhibit more distortion than their aromatic porphyrin parent molecules. Hence, only a limited number of examples of the direct metallation of calix[4]phyrin(**1**.*1*.**1**.*1*) ligands is reported in the literature.[5a,5d,15a,15b,15d,16,34a,34d] In our experiments, the metallation of calix[4]phyrin(**1**.*1*.**1**.*1*) **6a** with $Ni(OAc)_2{\cdot}4H_2O$, $Cu(OAc)_2{\cdot}H_2O$, $Zn(OAc)_2{\cdot}2H_2O$, and $Pd(OAc)_2$, which are some of the most common metal salts used for metallation of tetrapyrrole systems, failed even when harsh conditions were employed [heated to reflux in *N*,*N*-dimethylformamide (DMF) over several hours]. Based on the crystal structure of **6a**, it may be assumed that because of the "roof-like" structure, the approach of the metal ion from the bottom of the macrocycle to the inner core is sterically hindered. Additionally, the bulky alkyl substituents at the saturated *meso*-carbon atoms with *syn*-axial configuration protect the inner core from an insertion of the metal ion from the upper face. However, the remarkable resistance of calix[4]phyrin(**1**.*1*.**1**.*1*) **6a** towards metallation could also simply be due to the discrepancy between the stereochemical requirements of the metal coordination sphere and the geometry of the molecule.

To evaluate the oxidation resistance of the calix[4]phyrin(**1**.*1*.**1**.*1*)s presented here, model compound **6a** was treated with two equivalents of cerium(IV) ammonium nitrate (CAN) or silver(I) oxide for 2 h in DCM at room temperature and also with an excess of DDQ under reflux conditions in DCM for 1 h. In addition, **6a** was also reacted with three equivalents of tritylium tetrafluoroborate (Ph_3CBF_4)[36] at room temperature to abstract hydride ions from the sp^3-hybridized *meso*-hydrogenated bridges. However, in all four experiments neither the formation of the corresponding isoporphyrin (vide infra) nor the porphyrin was observed and the starting material was essentially recovered.

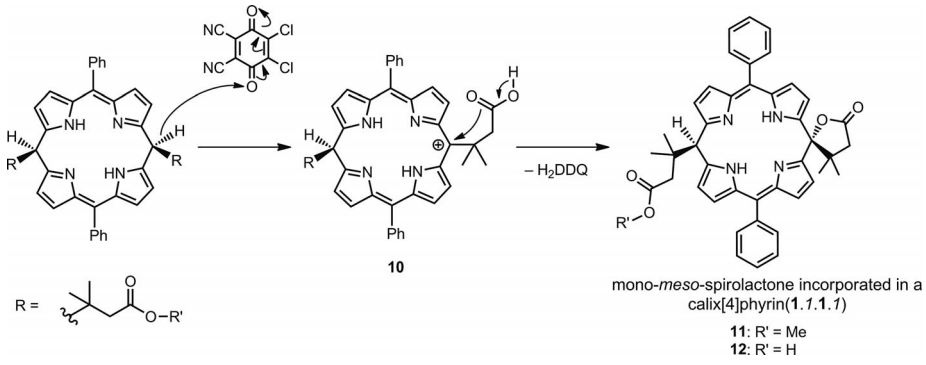
In an additional set of experiments, the effect of the acidic catalyst on the calix[4]phyrin(**1**.*1*.**1**.*1*) formation was investigated in DCM by using catalysts that are common

for tetrapyrrole syntheses such as TFA, boron trifluoride diethyl etherate, *p*-toluenesulfonic acid (*p*-TSA), and polyphosphoric acid (PPA).[5a] These model experiments were again performed using dipyrromethane **4** and benzaldehyde as precursors. The acid catalyst plays a significant role in terms of reaction rate and isolated yield. With TFA as a catalyst (20 mol-%), calix[4]phyrin(**1**.*1*.**1**.*1*) **6a** was isolated in 19% after 16 h (cf. Table 1). However, with $BF_3{\cdot}OEt_2$ (20 mol-%), **6a** was isolated in only 8% after 16 h. In both cases, traces of TPP (*meso*-tetraphenylporphyrin) were detected. It has also been reported that calix[4]phyrins are the only macrocycles isolated when the condensation reaction is performed in DCM in the presence of TFA as catalyst.[20,21] Reactions of **4** with benzaldehyde catalyzed by *p*-TSA and PPA (20 mol-% of acid for both cases) resulted in the formation of only traces of **6a** and in the former case, a trace amount of TPP was also detected. The formation of TPP as a side product can be explained by the partial occurrence of "scrambling" of the dipyrromethane **4**. This scrambling of dipyrromethanes is frequently observed in porphyrin synthesis.[37] The effect of a higher TFA loading was also investigated for the model reaction, and when using TFA in equimolar amounts, the yield could be increased to 25% (compare with Table 1, Entry 1). If heptanal as an aliphatic aldehyde was chosen instead of benzaldehyde, the product yield increased to 16% under the same conditions (compare to Table 1, Entry 9). These results suggest that in cases where interference of the acid catalyst with functional groups is not an issue, a higher acid catalyst loading can also be applied and leads to slightly better results.

We discovered that this interference of the acid catalyst with the functional groups can indeed be relevant when we evaluated the influence of reaction time. For this, the reaction time for the synthesis of **6a** was extended from 16 to 46 h. Interestingly, after DDQ oxidation and column chromatography, an orange-red crystalline side product was isolated in 7% yield in addition to the main product **6a**. The ^{1}H NMR spectrum of this side product showed the same pattern as the calix[4]phyrin(**1**.*1*.**1**.*1*) **6a**, but one of the methyl groups of the ester residues was missing. The mass spectrum of this side product was not in accordance with a product arising from a simple ester hydrolysis. We thus concluded that an intramolecular reaction at one of the *meso*-positions to yield lactone **11** had occurred (Scheme 8, Figure 3). The formation of this side product may be rationalized by the following proposed mechanistic pathway: The methoxycarbonyl group is partially hydrolyzed owing to the presence of TFA and water, which is generated in the course of the condensation reaction. During the oxidation step, a Linstead dehydrogenation at one of the *meso*-hydrogenated centers occurs through a hydride shift to DDQ[31] to yield the carbenium ion **10**. Subsequently, this intermediate is intramolecularly attacked by the neighboring carboxylic acid group (Scheme 8) to yield **11**. Alternatively, the carbenium ion in the *meso*-position could also be attacked by water, generated through the dipyrromethane–aldehyde condensation, to form the corresponding *meso*-hydroxy calix[4]phyrin(**1**.*1*.**1**.*1*), which undergoes lactonization with the neighboring carboxylic acid group. It should be noted that the formation of such a *meso*-hydroxy substituent at an sp^3-hybridized center has already been reported by Sessler et al.[20a] for calix[4]phyrins and by Osuka et al.[38] for calix[5]phyrins. The unusual calix[4]phyrin(**1**.*1*.**1**.*1*) **11**, which contains a mono-*meso*-spirolactone moiety, is formed. To the best of our knowledge compounds of this type are without precedents in the literature.

This mechanistic proposal is further supported by the following observations: Subjecting **6a** to a mixture of acid catalyst (TFA 20 mol-%) and DDQ (1.5 equiv.) for 28 h did not result in any reaction and **6a** was recovered. However, when **7**, the hydrolysis product of **6a**, was treated with TFA (20 mol-%) and DDQ (1.5 equiv.), product **12** containing the mono-*meso*-spirolactone moiety was formed, which strongly suggests the hydrolysis of one of the ester groups of **6a** prior to the lactonization step. The formation of the conceivable bis-spiro compound was not observed.

Finally, the structure of **11** was confirmed by an X-ray diffraction analysis (cf. Table 2). In the resulting ORTEP plot (Figure 3), it can be seen that the quaternary carbon atoms have the *syn*-axial orientation and that the lactonization has occurred in a way that the oxygen atom in the lactone occupies an equatorial position with distortions found in the five-membered lactone ring.



Scheme 8. Mechanistic proposal for the TFA/DDQ mediated formation of mono-*meso*-spirolactone containing calix[4]phyrin(**1**.*1*.**1**.*1*)s **11** and **12**.

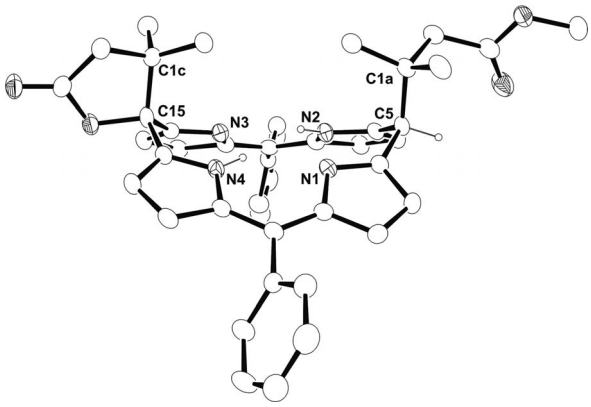
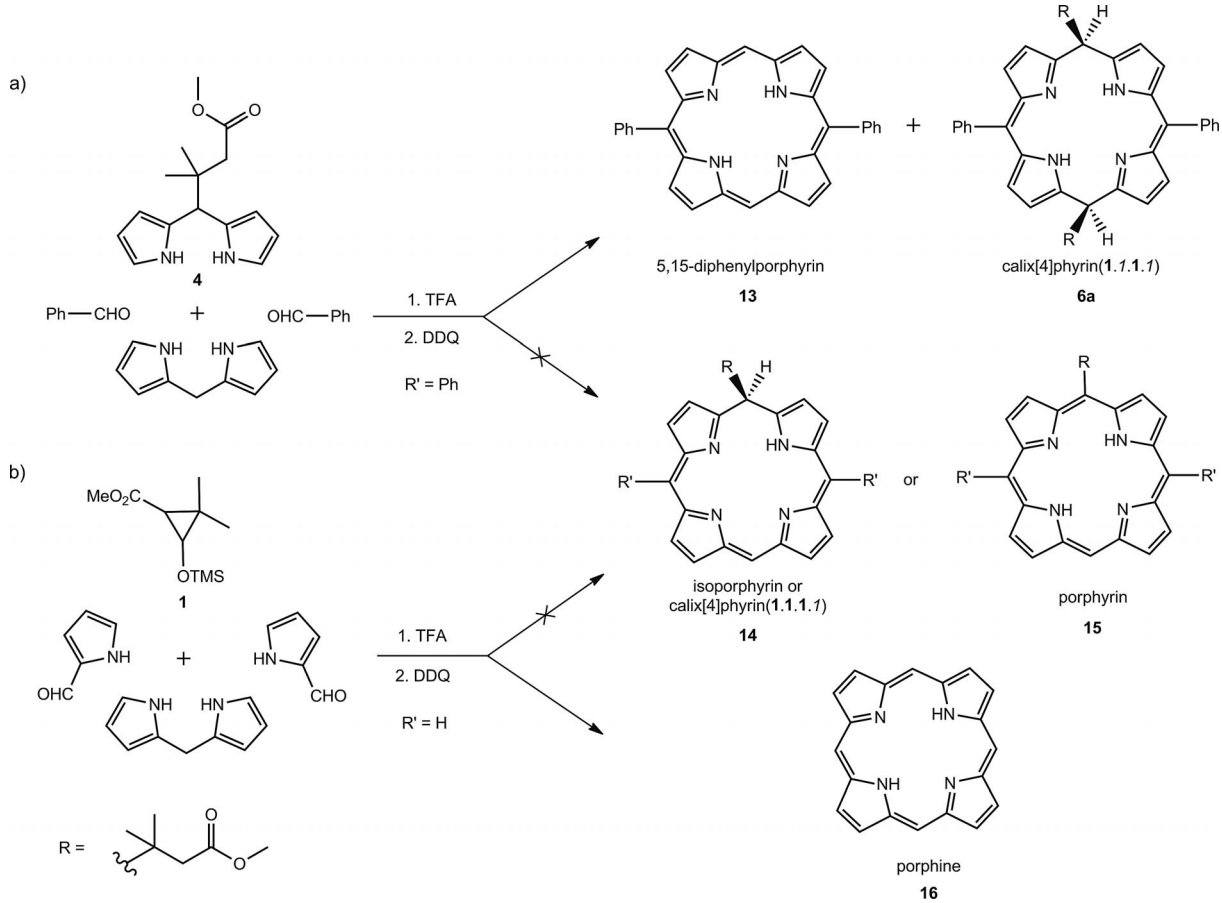


Figure 3. ORTEP[35] plot of **11**. Thermal ellipsoids are scaled to 50% probability level. Hydrogen atoms, except those bonded to the nitrogen atoms and to the carbon atom 5, have been omitted for clarity.

However, the effect of the lactonization on the overall structure of the calix[4]phyrin is small. The same roof-like appearance (angle ca. 112°) present in structures **6a** and **6c** is also adopted in the structure of **11**, and the core skeleton is folded along the line between the two saturated *meso*-carbon atoms. Again, the two dipyrrin halves are essentially planar. In this case the differences in the torsion angles (57 and 75°) of the phenyl rings are larger probably because of the asymmetry of the molecule. Again, hydrogen bonding [d(H···N) 2.19 and 2.20 Å] is observed within the two dipyrrin halves.

The UV/Vis spectra are consistent with the absence of full conjugation in the calix[4]phyrin(**1**.*1*.**1**.*1*)s. As an example, the UV/Vis spectra of **6a** and **11** are shown in Figure 4. Both compounds feature a strong Soret-like band at λ_{max} = 420 and 418 nm, respectively, which is considerably broadened compared to those of porphyrins.[15c] In addition, weak accompanying shoulders were observed for both compounds with absorption intensities of $\varepsilon < 6500$ L mol^{-1} cm^{-1} and maxima at λ_{max} = 486 and 484 nm, respectively.

We finally examined the use of the key precursor dipyrromethane **4** and cyclopropane **1** in the synthesis of isoporphyrins, another calix-type porphyrin analogue that contains a mixture of sp^2- and sp^3-hybridized bridging *meso*-carbon centers. Isoporphyrins, or calix[4]phyrin(**1**.**1**.**1**.*1*)s, are calix-type tetrapyrrole systems with 22 π electrons that contain three sp^2-hybridized *meso*-carbon atoms and one NH hydrogen atom. Two experiments were designed: a) condensation of one equivalent of dipyrromethane **4** and unsubstituted dipyrromethane with two equivalents of benzaldehyde; and b) condensation of one equivalent of cyclopropane **1** and unsubstituted dipyrromethane with two equivalents of pyrrole-2-carbaldehyde (Scheme 9). However,



Scheme 9. Two model experiments [conditions a) and b)] to incorporate one unit of the cyclopropane-derived sterically hindered residue into the tetrapyrrole skeleton.

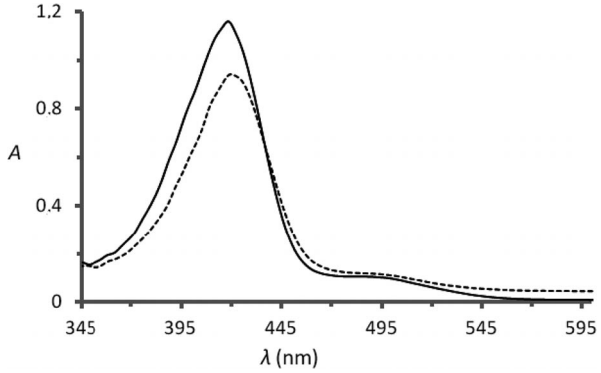


Figure 4. UV/Vis spectra of **6a** (dashed line) and **11** (solid line) recorded in CH_2Cl_2 (room temp., 1.55×10^{-5} M).

in both experiments, neither the corresponding isoporphyrin **14** nor porphyrin **15**, which incorporates just one cyclopropane-derived substituent, was detected. In the former case, 5,15-diphenylporphyrin **13** was isolated in 8% yield together with traces of calix[4]phyrin(**1***.1*.**1***.1*) **6a**. In the latter case, small amounts of porphine **16** were isolated, probably due to scrambling of the unsubstituted dipyrromethane.

Conclusions

We have presented the first example of an application of a d–a cyclopropane as a precursor for the synthesis of dipyrromethanes, which were subsequently utilized in acid-catalyzed [2+2] condensation reactions with a series of aromatic and aliphatic aldehydes. This new approach provides a flexible entry to novel *meso*-hydrogenated calix[4]phyrins with free *beta* positions that are exceptionally stable towards air and light owing to the incorporation of the bulky cyclopropane-derived substituent into the macrocyclic skeleton. The method is highly selective as it only leads to the formation of *trans*-porphodimethenes instead of a mixture of other potential isomers of the calixphyrin family such as porphomethenes, *cis*-porphodimethenes, isoporphyrins, or phlorins. The general applicability of this dipyrromethane approach to *meso*-hydrogenated calix[4]phyrins could additionally be exemplified with an example of a pivalaldehyde-derived dipyrromethane precursor. Of special interest was the detection and isolation of an acid-driven lactonization that leads to the formation of the first calix[4]phyrin(**1***.1*.**1***.1*) that incorporates a mono-*meso*-spirolactone moiety.

The field of hydroporphyrin chemistry is rapidly expanding; however, practical applications in medicine or materials science require simple and straightforward syntheses. The method described herein contributes to the field by providing a synthetic route to a series of functionalized calix[4]phyrins. It enables a systematic and variable substitution that is suitable for further modifications at the moieties in the sp^3- and sp^2-hybridized *meso*-centers. Following these promising results, research efforts are in progress devoted to exploring the application of d–a cyclopropane precursors to other tetrapyrrole systems.

Experimental Section

General Remarks: Reactions were generally performed under argon in oven-dried flasks. Reagents were added with syringes. Solvents were dried by using standard procedures. Dichloromethane (DCM) was distilled and stored over molecular sieves (4 Å) under an atmosphere of argon. Other reagents were purchased and were used as received without further purification unless otherwise stated. Products were purified by chromatography on silica gel (40–63 μm) and detection was carried out with a CAMAG variable UV detector (λ = 254/366 nm). Yields refer to chromatographically purified products, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) analysis. NMR spectra were recorded with Bruker (AC 250, AC 500, AVIII 700) and JOEL (Eclipse 500) instruments. Chemical shifts are reported relative to tetramethylsilane (TMS, ^{1}H: δ = 0.00 ppm), $CHCl_3$ (^{1}H: δ = 7.26 ppm), and $CDCl_3$ (^{13}C: δ = 77.0 ppm) in $CDCl_3$ solution. Integrals are in accordance with assignments; coupling constants are given in Hz. All ^{13}C spectra are proton decoupled. Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), m (multiplet), m_c (centered multiplet), dd (doublet of doublets), br. s (broad singlet). For detailed peak assignments, 2D spectra were measured (^{1}H–^{1}H COSY, ^{1}H–^{13}C HMQC, and ^{1}H–^{13}C HMBC). IR spectra were measured with a Jasco FT/IR-4100 spectrometer equipped with an attenuated total reflectance (ATR) attachment (PIKE MIRacle). The UV/Vis spectra were measured with a SPECORD S300 VIS UV/Vis spectrometer (Analytik Jena, Jena, Germany) with DCM as the solvent and quartz cuvettes of 1 cm path length. HRMS analyses were performed with an Agilent 6210 ESI-TOF instrument (Agilent Technologies, Santa Clara, CA, USA). The solvent flow rate was adjusted to 4 μL min^{-1} and the spray voltage was 4 kV. The drying gas flow rate was 15 psi (1 bar). All other parameters were adjusted for maximum abundance of the respective $[M + H]^+$ ions. (ESI-TOF = electrospray ionization/time of flight). Elemental analyses were carried out in CHN mode with a Vario EL instrument (Elementar Analysensysteme GmbH). Melting points were measured with a Reichert Thermovar apparatus. Methyl 2,2-dimethyl-3-(trimethylsiloxy)-1-cyclopropanecarboxylate (**1**) was prepared from 2-methyl-1-(trimethylsiloxy)propene and methyl diazoacetate.[27]

X-ray Crystallography: X-ray quality single crystals were obtained by slow diffusion of hexane into a DCM solution of the calix[4]phyrin(**1***.1*.**1***.1*) and the data are summarized in Table 2.

Suitable single crystals for the X-ray diffraction experiment were selected by using a microscope and were mounted on the top of a glass fiber. Data were collected with a Bruker-AXS SMART CCD diffractometer using Mo-K_α radiation (λ = 0.71073 Å, graphite monochromator). The structures were solved by direct methods and refined anisotropically (C, N, O) by least-squares methods using the SHELX-97 program suite.[39] The hydrogen atoms were included and were calculated positions (riding model).

CCDC-897952 (for **6a**), -897953 (for **11**), and -897954 (for **6c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

5-(3-Methoxy-1,1-dimethyl-3-oxopropyl)dipyrromethane (4): The reaction was performed in a 250 mL three-necked round-bottom

Table 2. Details of the crystallographic data collection of **6a**, **6c**, and **11**.

	6a	**6c**	**11**
Formula	$C_{44}H_{44}N_4O_4$	$C_{48}H_{48}N_4O_8$	$C_{43}H_{40}N_4O_4$
Formula mass	692.83	808.90	676.79
Crystal system	orthorhombic	orthorhombic	triclinic
Space group	*Pbcn*	$P2_12_12_1$	$P\bar{1}$
Z	4	4	2
T [K]	100	133	133
a [Å]	23.315(5)	12.120(2)	10.620(2)
b [Å]	12.420(3)	14.547(2)	13.943(2)
c [Å]	12.545(4)	23.206(3)	13.951(2)
α [°]	90	90	78.189(4)
β [°]	90	90	71.276(4)
γ [°]	90	90	85.042(4)
V [Å^3]	3632.6(15)	4091.5(11)	1914.5(6)
Calcd. density [g/cm^3]	1.267	1.313	1.174
F(000)	1472	1712	716
Crystal form	prism	needle	prism
Crystal color	red	red	orange
Crystal size [mm^3]	$0.23\times0.21\times0.16$	$0.45\times0.21\times0.11$	$0.40\times0.20\times0.15$
λ [Å]	Mo-K_α, 0.7107	Mo-K_α, 0.7107	Mo-K_α, 0.7107
2*θ* [°]	50.18	52.86	50.12
Collected reflections	36308	33929	13354
Unique reflections	3228	8284	6755
Observed [$I>2\sigma(I)$]	2583	6825	4984
Completeness [%]	99	98	99
R_{int}	0.0783	0.0390	0.0230
wR_2	0.2095	0.0982	0.1198
R_1 ($I > 2\ \sigma\ I$)	0.0896	0.0389	0.0411
GoF	1.224	1.041	1.060

flask fitted with a septum port, a bubble counter, and a gas inlet port. A solution of methyl 2,2-dimethyl-3-(trimethylsiloxy)-1-cyclopropanecarboxylate (**1**) (1.56 g, 7.21 mmol) and pyrrole (25 mL, 362 mmol) was degassed by bubbling with argon for 10 min, and then TFA (0.05 mL, 0.72 mmol) was added. The solution was stirred for 2 h at room temperature, at which point no starting cyclopropane **1** was identified by TLC analysis. The TLC plate was developed in a mixture of DCM/EtOAc/NEt_3 (98:1:1), and the bands were visualized by exposure of the air-dried TLC plate to bromine vapor. The reaction mixture was diluted with DCM (200 mL) and was then then washed with aqueous NaOH (0.1 N, 20 mL), washed with water, and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the unreacted pyrrole was removed by vacuum distillation. The resulting dark viscous oil was dissolved in a minimal quantity of the eluent and was purified by silica column chromatography with DCM/EtOAc/NEt_3 (98:1:1) as eluent. Any remaining pyrrole elutes first, followed slowly by the dipyrromethane **4** (R_F 0.45) and followed later by tailing materials. Colorless oil, yield 1.14 g (61%). IR (ATR): $\tilde{\nu}_{max}$ = 3385 (N–H), 3100 (C–H pyrrole), [40] 2950 (C–H), 2875 (CH_3), 1710 (C=O), 1555 (N–H), 1465 (CH_2), 1430 (N–H pyrrole), 1390 (C–H pyrrole), 1365 (CH_3), 1330 (C–N), 1215 (C–O), 1150 (C–O), 1115 (C–N), 1090 (C–H pyrrole), 1025 (C–H pyrrole), 885 (C–H pyrrole) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.06 (s, 6 H, 2×C*H*$_3$), 2.23 (s, 2 H, C*H*$_2$), 3.70 (s, 3 H, OC*H*$_3$), 4.29 (s, 1 H, *meso*-*H*), 6.14–6.17 (m, 4 H, β-pyrrole-*H*), 6.63 (m_c, 2 H, α-pyrrole-*H*), 8.43 (s, 2 H, 2×N*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 25.3 (2×*C*H$_3$), 38.0 [*C*(CH$_3$)$_2$], 44.7 (*C*H$_2$), 46.6 (5-*meso*-*C*), 51.3 (O*C*H$_3$), 106.8 (pyrrole-*C*), 108.1 (pyrrole-*C*), 115.9 (pyrrole-*C*), 130.2 (pyrrole-*C*), 173.7 (*C*=O) ppm. HRMS (ESI-TOF): calcd. for $C_{15}H_{21}N_2O_2$ $[M + H]^+$ 261.1603; found 261.1600; calcd. for $C_{15}H_{20}N_2O_2Na$ $[M + Na]^+$ 283.1422; found 283.1419; calcd. for $C_{15}H_{20}N_2O_2K$ $[M + K]^+$ 299.1162; found 299.1147. $C_{15}H_{20}N_2O_2$ (260.2): calcd. C 69.20, H 7.74, N 10.76; found C 69.12, H 7.52, N 10.78.

General Procedure for the Synthesis of *meso*-Hydrogenated Calix[4]phyrin(1.*1*.1.*1*) Derivatives 6: A standard reaction was performed in a 1 L three-necked round-bottom flask fitted with a septum port, bubble counter, and a gas inlet port with argon flow. 5-(3-Methoxy-1,1-dimethyl-3-oxopropyl)dipyrromethane (**4**) (520 mg, 2.00 mmol) and the appropriate aldehyde (2.00 mmol) were dissolved in dry DCM (500 mL). The resulting solution was degassed by bubbling with an argon flow for 10 min, and TFA (30 μL, 0.40 mmol) was added by syringe with vigorous stirring. The reaction mixture was stirred under argon in the dark at room temperature for a specific time as indicated for each individual experiment in Table 1. After the indicated time, the calixpyrrole intermediate was subjected to oxidation for 2 h by the addition of DDQ (690 mg, 3.00 mmol), followed by neutralization of TFA with NEt_3 (500 μL, 3.60 mmol). The reaction mixture was filtered through a glass frit loaded with silica gel and eluted with a mixture of DCM/EtOAc (ratio depending on product, see individual procedures) to afford the crude products. After concentration of the filtrate under reduced pressure, the residue was dissolved in a minimum volume of solvent and applied to gradient elution silica gel column chromatography with hexane/DCM (ratio depending on product, see individual procedures) for further purification. Three successive fractions could be collected depending on the aldehyde applied and the reaction times in Table 1. The first purple band contains the porphyrin-type side product in a trace amount (less than 1%), the second yellow-orange band contains the *meso*-hydrogenated calix[4]phyrin-(**1**.*1*.**1**.*1*) **6** in yields between 4 and 25% as the main product; with an extended reaction time for the synthesis of **6a**, the third yellow-orange band contains the mono-*meso* spirolactone side product **11** in 7% yield. Finally, recrystallization of the main fraction from a

chloroform/hexane mixture gave the desired crystalline form of the products.

5,15-Bis(3-methoxy-1,1-dimethyl-3-oxopropyl)-10,20-diphenylcalix[4]phyrin(1.*1*.1.*1*) (6a): According to the general procedure, a mixture of dipyrromethane **4** (520 mg, 2.00 mmol) and benzaldehyde (20 μL, 2.00 mmol) was reacted in the presence of TFA (30 μL, 0.40 mmol) in dry DCM (500 mL). After 16 h, the oxidation step was performed with DDQ (690 mg, 3.00 mmol), followed by neutralization with NEt_3 (500 μL, 3.60 mmol). The reaction mixture was then filtered through a glass frit loaded with silica gel and eluted with a mixture of DCM/EtOAc (90:10) to afford the crude products. After concentration of the filtrate under reduced pressure, the residue was dissolved in a minimum volume of solvent and applied to gradient elution silica gel column chromatography with hexane/DCM (50:50 to 0:100) for further purification. Finally, recrystallization of the main fraction from a DCM/hexane mixture gave the desired crystalline form of the product. Orange crystals, yield 131 mg (19%), m.p. 192 °C. IR (ATR): $\tilde{\nu}_{max}$ = 3305 (N–H), 2960 (CH_3), 2935 (CH_2), 2875 (CH_3), 2855 (CH_2), 1730 (C=O), 1580 (N–H), 1420 (CH_2), 1440 (CH_3), 1410 (C–H pyrrole),[40] 1375 (CH_3), 1200 (C–O), 1115 (C–N), 1045 (C–H pyrrole), 1015 (C–H pyrrole), 955 (C–H pyrrole), 755 (=C–H), 720 (=C–H) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.26 (s, 12 H, 4 × C*H*$_3$), 2.48 (s, 4 H, 2 × C*H*$_2$), 3.67 (s, 6 H, 2 × OC*H*$_3$), 4.35 (s, 2 H, 2 × 5,15-*meso*-*H*), 6.23 (d, *J* = 4.0 Hz, 4 H, β-pyrrole-*H*), 6.37 (d, *J* = 4.0 Hz, 4 H, β-pyrrole-*H*), 7.35–7.44 (m, 8 H, Ar), 7.50–7.53 (m, 2 H, Ar), 13.18 (s, 2 H, 2 × N*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 26.0 (4 × *C*H_3), 38.8 [2 × *C*$(CH_3)_2$], 44.8 (2 × *C*H_2), 50.5 (5,15-*meso*-*C*), 51.3 (2 × O*C*H_3), 120.2 (Ar), 127.4 (Ar), 127.4 (Ar), 128.5 (Ar), 130.7 (Ar), 130.9 (Ar), 137.7 (Ar), 140.2 (Ar), 140.5 (Ar), 156.6 (Ar), 172.8 (2 × *C*=O) ppm. HRMS (ESI-TOF): calcd. for $C_{44}H_{45}N_4O_4$ $[M + H]^+$ 693.3441; found 693.3393; calcd. for $C_{44}H_{44}N_4O_4Na$ $[M + Na]^+$ 715.3260; found 715.3212. UV/Vis (CH_2Cl_2): λ_{max} [log(ε/L mol^{-1} cm^{-1})] = 420 [4.75], 486 [3.72] nm.

Procedures for Oxidation Resistance Test Reactions of Calix[4]phyrin(1.*1*.1.*1*) (6a): Oxidation was attempted with (A) cerium(IV) ammonium nitrate, (B) silver(I) oxide, (C) triphenylcarbenium tetrafluoroborate (tritylium tetrafluoroborate), and (D) excess 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ). (A): Compound **6a** (21 mg, 0.03 mmol) was dissolved in dry DCM (10 mL) in a 50 mL round-bottom flask containing cerium(IV) ammonium nitrate (33 mg, 0.06 mmol). The solution was then stirred for 1 h at room temperature, during which time no indication of the formation of either the corresponding isoporphyrin or porphyrin was detected by TLC analysis. The TLC plates were developed by using a mixture of hexane/DCM (1:1), and the bands were visualized by exposure of the air-dried TLC plate to UV radiation (λ = 254/366 nm). The reaction mixture was diluted with DCM (100 mL), filtered through a glass frit loaded with silica gel, and eluted with a mixture of DCM/EtOAc (90:10). After that, the filtrate was evaporated to dryness under reduced pressure, and the residual solid was dissolved in DCM (100 mL), washed with water (3 × 100 mL), and dried with anhydrous Na_2SO_4. The crude product was then applied to gradient elution silica gel column chromatography with hexane/DCM (15:85 to 0:100) for further purification, which resulted in isolation and recovery of starting material. (B): Under the same reaction conditions as those described for (A), **6a** (21 mg, 0.03 mmol) was dissolved in dry DCM (10 mL) in a 50 mL round-bottom flask containing silver(I) oxide (14 mg, 0.06 mmol). The solution was then stirred for 1 h at room temperature, during which time no indication of the formation of either the corresponding isoporphyrin or porphyrin was detected by TLC analysis. After quenching the reaction followed by performing the same work-up procedure as described for (A), the starting material was recovered. (C): Under the same reaction conditions as described for (A), triphenylcarbenium tetrafluoroborate (30 mg, 0.09 mmol) was added to a stirred suspension of **6a** (21 mg, 0.03 mmol) in dry DCM (10 mL), and the resulting solution was stirred for 1 h at room temperature, during which time the solution initially turned dark green. However, no indication for the formation of either the corresponding isoporphyrin or porphyrin was detected by TLC analysis. After quenching the reaction followed by performing the same work up procedure as described for (A), the starting material was recovered. (D): Under the same reaction conditions as described for (A), DDQ (27 mg, 0.12 mmol) was added to a stirred suspension of **6a** (21 mg, 0.03 mmol) in dry DCM (10 mL), and the resulting solution was stirred for 1 h under reflux conditions, during which time no indication of the formation of either the corresponding isoporphyrin or porphyrin was detected using TLC analysis. After quenching the reaction followed by performing the same work up procedure as described for (A), the starting material was recovered.

5,15-Bis(2-carboxy-1,1-dimethylethyl)-10,20-diphenylcalix[4]phyrin-(1.*1*.1.*1*) (7): Calix[4]phyrin(**1**.*1*.1.*1*) **6a** (70 mg, 0.10 mmol) was dissolved in THF (20 mL). To this solution was added a solution of potassium hydroxide (561 mg, 10.0 mmol) dissolved in methanol (10 mL), and the solution was stirred for 5 h at room temperature. TLC analysis showed the consumption of all starting material. After this time the reaction mixture was transferred to a separatory funnel and water (100 mL) and ethyl acetate (100 mL) were added. During phase separation, the solution was neutralized by adding 25% hydrochloric acid. After neutralization, the organic phase was washed with water (3 × 150 mL). The organic phase was then dried with anhydrous Na_2SO_4. The drying agent was removed and the organic phase was evaporated to dryness. The resulting solid was redissolved in DCM/methanol (1:2, v/v; 5 mL) and again evaporated to dryness. Upon evaporation an orange solid powder was formed, which was then dried in vacuo. Yield: quantitative (66 mg), m.p. 262 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.22 (s, 12 H, 4 × C*H*$_3$), 2.93 (s, 4 H, 2 × C*H*$_2$), 3.95 (s, 2 H, 2 × 5,15-*meso*-*H*), 6.20 (d, *J* = 4.1 Hz, 4 H, β-pyrrole-*H*), 6.38 (d, *J* = 4.1 Hz, 4 H, β-pyrrole-*H*), 7.34–7.40 (m, 4 H, Ar), 7.41–7.45 (m, 4 H, Ar), 7.52–7.56 (m, 2 H, Ar), 12.39 (br. s, 2 H, CO_2H), 13.07 (br. s, 2 H, 2 × N*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 26.7 (4 × *C*H_3), 39.1 [2 × *C*$(CH_3)_2$], 42.8 (2 × *C*H_2), 53.7 (5,15-*meso*-*C*), 120.3 (β-pyrrole-*C*), 127.4 (Ar), 127.5 (Ar), 128.5 (Ar), 128.7 (β-pyrrole-*C*), 130.6 (Ar), 131.0 (Ar), 137.6 (Ar), 140.5 (α-pyrrole-*C*), 156.1 (α-pyrrole-*C*), 180.2 (2 × *C*=O) ppm. HRMS (ESI-TOF): calcd. for $C_{42}H_{41}N_4O_4$ $[M + H]^+$ 665.3128; found 665.3149. UV/Vis (CH_2Cl_2): λ_{max} [log(ε/L mol^{-1} cm^{-1})] = 421 [4.61], 485 [3.57] nm.

5-(1,1-Dimethylethyl)dipyrromethane (8): The reaction was performed in a 250 mL three-necked round-bottom flask fitted with a septum port, a bubble counter, and a gas inlet port. A solution of pivaldehyde (1.7 mL, 15.0 mmol) and freshly distilled pyrrole (52.0 mL, 750 mmol) was degassed by bubbling with argon for 10 min, and then TFA (103 μL, 1.40 mmol) was added. The solution was stirred for 2 h at room temperature, at which point no starting pivaldehyde was identified by TLC analysis. The TLC plate was developed in a mixture of hexane/DCM/NEt_3 (50:49:1), and the bands were visualized by exposure of the air-dried TLC plate to bromine vapor. The reaction mixture was diluted with DCM (400 mL) and then washed with aqueous NaOH (0.1 N, 40 mL), washed with water, and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the unreacted pyrrole was removed by vacuum distillation. Recrystallization of the ob-

tained resulting viscous oil from DCM/pentane mixture gave the desired crystalline form of the product. Colorless crystals, yield 1.75 g (58%). IR (ATR): $\tilde{\nu}_{max}$ = 3382 (N–H), 3360 (N–H), 3095 (C–H pyrrole),[40] 2970 (CH_3), 2950 (C–H), 2910 (C–H), 2865 (CH_3), 1550 (N–H), 1470 (CH_2), 1450 (CH_3), 1390 (C–H pyrrole), 1360 (CH_3), 1350 (C–N), 1115 (C–N), 1095 (C–H pyrrole), 1025 (C–H pyrrole), 890 (C–H pyrrole) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.01 (s, 9 H, 3 × C*H*$_3$), 3.77 (s, 1 H, *meso*-*H*), 6.10–6.13 (m, 2 H, pyrrole-*H*), 6.16 (m_c, 2 H, pyrrole-*H*), 6.62 (m_c, 2 H, pyrrole-*H*), 7.94 (s, 2 H, 2 × N*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 28.6 (3 × *C*H$_3$), 35.5 [*C*(CH$_3$)$_3$], 50.4 (5-*meso*-*C*), 106.5 (pyrrole-*C*), 108.4 (pyrrole-*C*), 116.0 (pyrrole-*C*), 131.4 (pyrrole-*C*) ppm. HRMS (ESI-TOF): calcd. for $C_{13}H_{19}N_2$ [M + H]$^+$ 203.1548; found 203.1544; calcd. for $C_{13}H_{18}N_2Na$ [M + Na]$^+$ 225.1368; found 225.1354. $C_{13}H_{18}N_2$ (202.2): calcd. C 77.18, H 8.97, N 13.85; found C 76.57, H 8.90, N 13.60.

5,15-Bis(1,1-dimethylethyl)-10,20-diphenylcalix[4]phyrin(1.*1*.1.*1*) (9): According to the general procedure, a mixture of **8** (405 mg, 2.00 mmol) and benzaldehyde (20 μL, 2.00 mmol) was reacted in the presence of TFA (30 μL, 0.40 mmol) in dry DCM (500 mL). After 16 h, the oxidation step was performed with DDQ (690 mg, 3.00 mmol), followed by neutralization with NEt_3 (500 μL, 3.60 mmol). The reaction mixture was then filtered through a glass frit loaded with silica gel and eluted with a mixture of DCM/EtOAc (95:5) to afford the crude products. After concentration of the filtrate under reduced pressure, the residue was dissolved in a minimum volume of solvent and applied to gradient elution silica gel column chromatography with hexane/DCM (70:30 to 20:80) for further purification. Finally, recrystallization of the main fraction from a DCM/pentane mixture gave the desired crystalline form of the product. Orange crystals, yield 156 mg (27%), m.p. 214 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.15 (s, 18 H, 6 × C*H*$_3$), 3.90 (s, 2 H, 2 × 5,15-*meso*-*H*), 6.18 (d, *J* = 4.0 Hz, 4 H, β-pyrrole-*H*), 6.37 (d, *J* = 4.0 Hz, 4 H, β-pyrrole-*H*), 7.35–7.39 (m, 2 H, Ar), 7.39–7.44 (m, 6 H, Ar), 7.51–7.55 (m, 2 H, Ar), 13.21 (s, 2 H, 2 × N*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 28.9 (6 × *C*H$_3$), 36.6 [2 × *C*(CH$_3$)$_3$], 53.1 (5,15-*meso*-*C*), 120.0 (Ar), 127.3 (Ar), 127.4 (Ar), 128.1 (Ar), 128.3 (Ar), 130.8 (Ar), 130.9 (Ar), 137.9 (Ar), 139.7 (Ar), 140.3 (Ar), 157.5 (Ar) ppm. HRMS (ESI-TOF): calcd. for $C_{40}H_{41}N_4$ [M + H]$^+$ 577.3331; found 577.3312; calcd. for $C_{40}H_{40}N_4Na$ [M + Na]$^+$ 599.3151; found 599.3144. UV/Vis (CH_2Cl_2): λ_{max} [log(ε/L mol^{-1} cm^{-1})] 420 [4.88], 486 [3.81] nm.

Calix[4]phyrin(1.*1*.1.*1*) Containing a Mono-*meso*-spirolactone Moiety (11): According to the general procedure for the synthesis of *meso*-hydrogenated calix[4]phyrin(**1**.*1*.**1**.*1*)s, a mixture of **4** (520 mg, 2.00 mmol) and benzaldehyde (200 μL, 2.00 mmol) was reacted in the presence of TFA (30 μL, 0.40 mmol) in dry DCM (500 mL). After 46 h, the oxidation step was performed for 4 h using DDQ (690 mg, 3.00 mmol), and the reaction was then neutralized by the addition of NEt_3 (500 μL, 3.60 mmol). The reaction mixture was then filtered through a glass frit loaded with silica gel, eluted with a mixture of DCM/EtOAc (80:20) to afford the crude products. After concentration of the filtrate under reduced pressure, the residue was dissolved in a minimum volume of solvent and applied to gradient elution silica gel column chromatography with hexane/DCM (50:50 to 0:100) for further purification. The first orange band contained **6a** in 10% yield (69 mg) as the main product, and the second orange band contained the side product **11** in 7% yield (47 mg). Finally, recrystallization of the second fraction from a DCM/hexane mixture gave the desired crystalline form of the side product **11**. Orange crystals, m.p. 192 °C. IR (ATR): $\tilde{\nu}_{max}$ = 3310 (N–H), 2970 (CH_3), 2925 (CH_2), 2870 (CH_3), 2855 (CH_2), 1790 (C=O$_{lactone}$), 1735 (C=O), 1585 (N–H), 1415 (CH_2), 1440 (CH_3), 1410 (C–H pyrrole),[40] 1370 (CH_3), 1195 (C–O), 1115 (C–N), 1050 (C–H pyrrole), 1010 (C–H pyrrole), 955 (C–H pyrrole), 755 (=C–H), 720 (=C–H) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.27 (s, 6 H, 2 × C*H*$_{3,lactone}$), 1.30 (s, 6 H, 2 × C*H*$_3$), 2.49 (s, 2 H, C*H*$_2$), 2.53 (s, 2 H, C*H*$_{2,lactone}$), 3.68 (s, 3 H, OC*H*$_3$), 4.40 (s, 1 H, 15-*meso*-*H*), 6.28 (d, *J* = 4.1 Hz, 2 H, β-pyrrole-*H*), 6.43 (m_c, 4 H, β-pyrrole-*H*), 6.46 (d, *J* = 4.0 Hz, 2 H, β-pyrrole-*H*), 7.42 (m_c, 8 H, Ar), 7.47–7.50 (m, 2 H, Ar), 13.06 (s, 2 H, 2 × N*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 24.3 (2 × *C*H$_{3,lactone}$), 26.0 (2 × *C*H$_3$), 39.4 [*C*(CH$_3$)$_2$], 43.2 (*C*H$_{2,lactone}$), 44.8 (*C*H$_2$), 45.9 [*C*(CH$_3$)$_{2,lactone}$], 50.4 (15-*meso*-*C*), 51.4 (O*C*H$_3$), 89.7 (5-*meso*-*C*), 115.8 (Ar), 121.0 (Ar), 127.5 (Ar), 127.6 (Ar), 128.9 (Ar), 129.4 (Ar), 130.7 (Ar), 130.9 (Ar), 137.3 (Ar), 141.1 (Ar), 172.6 (*C*=O), 175.9 (*C*=O$_{lactone}$) ppm. HRMS (ESI-TOF): calcd. for $C_{43}H_{41}N_4O_4$ [M + H]$^+$ 677.3128; found 677.3144; calcd. for $C_{43}H_{40}N_4O_4Na$ [M + Na]$^+$ 699.2947; found 699.2971. UV/Vis (CH_2Cl_2): λ_{max} [log(ε/L mol^{-1} cm^{-1})] = 418 [4.79], 484 [3.80] nm.

Mechanistic Test Reactions for the Preparation of 11 and 12: A standard reaction was performed in a 1 L three-necked round-bottom flask fitted with a septum port, a bubble counter, and a gas inlet port with argon flow. Compound **6a** (42 mg, 0.06 mmol) was dissolved in dry DCM (500 mL). The resulting solution was degassed by bubbling with an argon flow for 10 min. TFA (0.9 μL, 0.012 mmol) was then added with a syringe under vigorous stirring. After 15 min, DDQ (21 mg, 0.09 mmol) was added, and the reaction mixture was stirred under argon in the dark at room temperature for 28 h; and the reaction mixture was then neutralized with the addition of NEt_3 (14 μL, 0.10 mmol). The reaction mixture was filtered through a glass frit loaded with silica gel and eluted with a mixture of DCM/EtOAc (80:20) to afford the crude products. After concentration of the filtrate under reduced pressure, it was transferred to a separatory funnel and water (100 mL) and ethyl acetate (100 mL) were added, and the organic phase was washed with water (3 × 150 mL). The organic phase was dried with anhydrous Na_2SO_4. The drying agent was removed, and the organic phase was evaporated to dryness. The resulting solid was redissolved in hexane/DCM (50:50, v/v; 2 mL) and was applied to gradient elution silica gel column chromatography with hexane/DCM (50:50 to 0:100) for further purification, which resulted in the recovery of starting material without any indication of the formation of **11**.

In another experiment, under the same reaction conditions and with the same molar ratios of starting material and reagents, **7** was treated with TFA and DDQ. After work up and silica gel column chromatography [eluent for filtration through silica gel: DCM/MeOH (60:40) and for gradient elution chromatography: DCM/MeOH (90:10 to 60:40)], product **12** (3 mg, 7%) was obtained. ^1H NMR (700 MHz, $CDCl_3$): δ = 1.31 (s, 6 H, 2 × C*H*$_{3,lactone}$), 1.37 (s, 6 H, 2 × C*H*$_3$), 2.56 (s, 2 H, C*H*$_{2,lactone}$), 2.57 (s, 2 H, C*H*$_2$), 4.40 (s, 1 H, 15-*meso*-*H*), 6.32 (d, *J* = 4.1 Hz, 2 H, β-pyrrole-*H*), 6.46 (d, *J* = 4.0 Hz, 4 H, β-pyrrole-*H*), 6.50 (d, *J* = 4.2 Hz, 2 H, β-pyrrole-*H*), 7.40–7.53 (m, 10 H, Ar), 13.05 (br. s, 2 H, 2 × N*H*) ppm. ^{13}C NMR (176 MHz, $CDCl_3$): δ = 24.3 (2 × *C*H$_{3,lactone}$), 26.0 (2 × *C*H$_3$), 39.2 [*C*(CH$_3$)$_2$], 43.1 (*C*H$_{2,lactone}$), 44.1 (*C*H$_2$), 45.8 [*C*(CH$_3$)$_{2,lactone}$], 50.2 (15-*meso*-*C*), 89.6 (5-*meso*-*C*), 115.9 (Ar), 120.9 (Ar), 127.4 (Ar), 127.5 (Ar), 128.8 (Ar), 129.4 (Ar), 130.6 (Ar), 130.8 (Ar), 137.2 (Ar), 141.2 (Ar), 174.4 (*C*=O), 175.8 (*C*=O$_{lactone}$) ppm. HRMS (ESI-TOF): calcd. for $C_{42}H_{39}N_4O_4$ [M + H]$^+$ 663.2971; found 663.2977; calcd. for $C_{42}H_{38}N_4O_4Na$ [M + Na]$^+$ 685.2791; found 685.4343; calcd. for $C_{42}H_{38}N_4O_4K$ [M + K]$^+$ 701.2530; found 701.4122.

Supporting Information (see footnote on the first page of this article): Preparation and characterization data for calix[4]phyrins **6b**–

6j. Procedures for attempted synthesis of calix[4]phyrin(**1**.*1*.**1**.*1*) **14** and porphyrin **15**. ^{1}H and ^{13}C NMR and HRMS (ESI-TOF) spectra of **4**, **6b**–**6j** and **7**–**11**. ^{1}H–^{1}H COSY, ^{1}H–^{13}C HMQC, and ^{1}H–^{13}C HMBC NMR spectra of **6a**.

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[1] Based on the proposed systematic nomenclature of calix[*n*]-phyrins by Sessler et al. mentioned in ref.[2a] the calix[*n*]phyrins are named starting with the highest order sp^2-center in the direction in which the nearest sp^2-center lies and the bracketed number refers to the number of pyrroles in the macrocycle. Each individual bold and italicized number denotes the number of bridging *meso*-centers between each pyrrole subunit. Bold numbers refer to sp^2-centers, and italicized numbers refer to sp^3-centers.

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