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Direct access to upper rim substituted mono- and diaryloxy calix[4]arenes via bis(spirodienone) route

Sreeja Thulasi, Jisha Babu, Adarsh Babukuttannair, Viji Sreemathi, Ramavarma Luxmi Varma *

Organic Chemistry Section, Chemical Sciences and Technology Division, National Institute for Interdisciplinary Science and Technology, Trivandrum-695019, Kerala, India

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ABSTRACT

A seemingly ipso-like nucleophilic substitution of the upper rim of *p*-*tert*-butylcalix[4]arene is accomplished by an indirect method involving calix[4]arene derived bis(spirodienone). This method not only provides both mono and 1,3-diaryloxy calixarenes but also enables the synthesis of upper rim monothio substituted calix[4]arenes. A modification of the methodology can be successfully extended for the selective synthesis of mono- and 1,3-diquinone calix[4]arenes having free hydroxyl groups at the lower rim, in fewer steps.

1. Introduction

Calixarenes[1] are molecular receptors that occupy an envious position among supramolecular hosts.[2] They have been most befittingly described as 'hosts with (almost) unlimited possibility' by Bohmer et al.[3] due to their easy availability and amenability for chemical transformations to 3-dimensional functional molecules that can perform a myriad of functions as host components in sensors,[4] pseudo-stationary phases in capillary electrophoresis,[5] phase transfer catalysts,[6] enzyme mimics,[6c] non-linear optics[6c] etc. to mention a few. Hence development of newer techniques for easy functionalization of calixarenes remains an attractive field. Among the various types of modifications reported on the calixarene skeleton, functionalization of the upper rim either selectively or exhaustively is cumbersome due to the involvement of multiple steps viz. protection of the lower rim hydroxyls and de-*tert*-butylation followed by electrophilic substitution at the reactive *para*-position. Reactions reported under this category are halogenation,[7] nitration,[8] sulfonation,[9] chloromethylation,[10] acylation,[11] formylation[12] etc. Selective ipso-substitutions such as sulfonation,[13] chlorosulfonation,[14] nitration,[15] and formylation[16] of calixarenes requiring prior protection of the narrow rim hydroxyls have also been reported.

Direct methodologies to introduce nucleophilic groups (eg., −OH, −OR, −SR etc.) to the upper rim of calixarenes are limited due to the inherent nucleophilicity of the aromatic rings. However, a few indirect methods are available but often marred by lengthy procedures. Ungaro et al. have carried out exhaustive hydroxylation of the lower rim protected formyl calixarene via Bayer/Villiger oxidation followed by hydrolysis of the formate derivative.[17] Selective hydroxylation at one of the upper rim of calix[4]arene has also been achieved by a six-step synthetic strategy by Lin et al.[27a] Neri et al. have reported a novel '*p*-bromodienone route' to functionalize the calixarene *exo* rim with *O*-nucleophiles.[18a] Recently the same group has also reported the reaction of *p*-bromodienone with aromatic nucleophiles for appending aromatic moieties to the *para*- and *meta*- positions of the calix[4]arene phenol ring.[18b] Appending aromatic groups at the upper rim give rise to calixarenes with pi-electron rich extended cavity, which have numerous applications.[19]

Our group has recently reported a new methodology by which the calix[4]arene derived bis(spirodienone)[20] can be transformed into functionalized calix[4]arenes having alkoxy substitution at the upper rim.[21] The synthetic methodology adapted involved an acid-mediated reaction of the bis(spirodienone) with primary alcohols to afford upper rim substituted mono- and 1,3-dialkoxy calix[4]arenes unprotected at the lower rim in a single step. These results prompted us to look into the reactivities of other nucleophiles like phenols, thiols, amines etc. and our findings in this direction form the subject matter of this article.

The paper also demonstrates the usefulness of our methodology to synthesize mono- and 1,3-diquinone calix[4]arenes selectively. To the best of our knowledge this would be the first report of the synthesis of mono- and diquinones with unprotected hydroxyls at the lower rim.

2. Results and discussion

Our experiments started by reacting *p*-cresol, an activated phenol, with bis(spirodienone) **1** in the presence of 5.0 equiv of *p*-Toluene Sulfonic Acid (*p*-TSA) under toluene reflux conditions for 6 h. Despite noticeable charring of the reaction mixture, four products were isolated from it by column chromatography over silica gel in

* Corresponding author. Tel.: +91 471 2515275; fax: +91 471 2491712; e-mail address: lux_varma@rediffmail.com (R.L. Varma).

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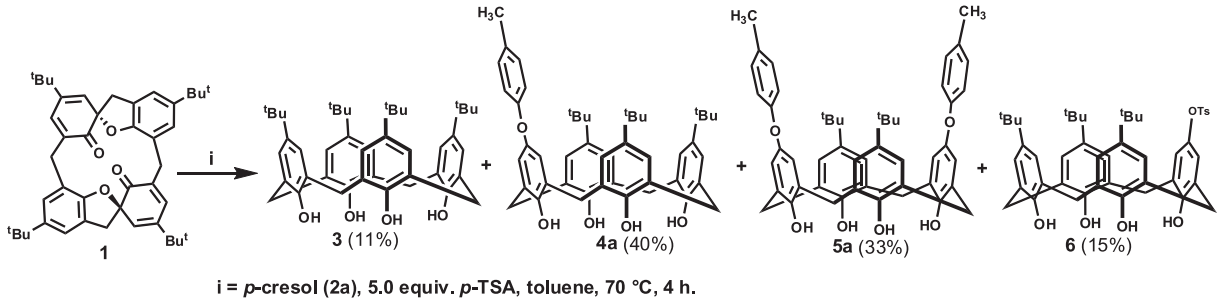
low yields. Subsequently the reaction was repeated at less drastic conditions: at an optimum temperature of 70 °C after 4 h, the reaction yielded four products in acceptable yields (Scheme 1).



Scheme 1. *p*-TSA mediated reaction of calix[4]bis(spirodienone) **1** with *p*-cresol.

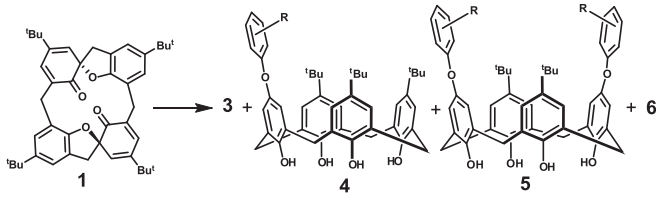
While products **3** and **6** were identified as *p*-*tert*-butylcalix[4]arene and upper rim monotosylated calixarene on comparison with literature data,[21] the structures of **4a** and **5a** were established by various spectroscopic techniques. In the ^{1}H NMR spectrum of compound **4a**, the exclusively hydrogen bonded phenolic hydroxyls appeared as a singlet at δ 10.20 ppm and the methyl group of the cresol part appeared at δ 2.33 ppm as a sharp singlet. The *tert*-butyl protons occurred as two singlets at δ 1.22 and 1.19 ppm in a 2:1 ratio. In the ^{13}C NMR spectrum, the signal due to the methyl group of the *p*-cresol part appeared at δ 20.0 ppm. The chemical shift values in ^{13}C NMR and the ^{1}H and ^{13}C NMR pattern further confirm that **4a** is present in the cone conformation.[22] The structure was further confirmed by CHN analysis (Anal. Calcd for $C_{47}H_{54}O_5$: C, 80.77; H, 7.79. Found: C, 80. 74; H, 7.75).

The ^{1}H NMR spectrum of **5a** showed one singlet for OH (δ 10.07 ppm), two singlets for the aromatic protons of the calixarene moiety (δ 6.81 and 6.64 ppm), one pair of doublets for the methylene bridges (δ 4.20 and 3.39 ppm, J=13.5 Hz) and one singlet for the *tert*-butyl protons (δ 1.23 ppm), in agreement with the C_{2v} symmetrical structure. The ^{13}C NMR and the elemental analysis supported the formation of **5a**.

The scope of the reaction was explored with other substituted phenols and the results are summarized in Table 1.

In general, phenols with electron donating substituents were found to react with bis(spirodienone) **1** satisfactorily to give both mono- and di-phenoxy substituted calixarenes in acceptable yields (Table 1, entries 1–7). In the case of sterically hindered phenols (entries 5 and 6), the yields of the mono- and di-substituted products obtained were comparatively low, with calix[4]arene **3** being the major product. Phenols with electron withdrawing substituent (entries 8–10) failed to react and the substrate **1** was recovered unchanged.

Table 1
Generalization of the reaction with various phenols



Entry	Phenol **2**(a–j)	Yield (%)			
		3	**4**	**5**	**6**
1	(4-Me)C_6H_4OH (**2a**)	11	**4a**/40	**5a**/33	15
2	(4-OMe)C_6H_4OH (**2b**)	17	**4b**/42	**5b**/35	20
3	(4-Br)C_6H_4OH (**2c**)	20	**4c**/35	**5c**/25	26
4	(4-I)C_6H4OH (**2d**)	22	**4d**/32	**5d**/23	28
5	(2-I)C_6H_4OH (**2e**)	25	**4e**/22	**5e**/18	23
6	(2,4-di-I)C_6H_3OH (**2f**)	30	**4f**/17	**5f**/6	20
7	(4-Ph)C_6H_4OH (**2g**)	20	**4g**/30	—	17
8	(4-Nitro)C_6H_4OH (**2h**)		No reaction		
9	(4-Nitro)C_6H_4OH (**2i**)		No reaction		
10	(4-Formyl)C_6H_4OH (**2j**)		No reaction		

Reaction conditions: 2 (4.0 equiv), *p*-TSA(5.0 equiv), toluene, 70 °C, 4 h.

A mechanism similar to the one proposed for the attack of alcohols on spiro(dienones) has been invoked to explain the formation of new products (Scheme 2).[21] Attack of the nucleophile at carbon bearing *tert*-butyl group is facilitated by the protonation of spiro-oxygens.

This would in turn result in the cleavage of the spiro bond and in the formation of a cross-dienone. Aromaticity of the cross-dienone can be achieved by the removal of the *tert*-butyl group resulting in the formation of the disubstituted product **5**. The formation of monosubstituted product **4** can be rationalized on the basis of acid-assisted reductive cleavage of the remaining spiro bond.[23]

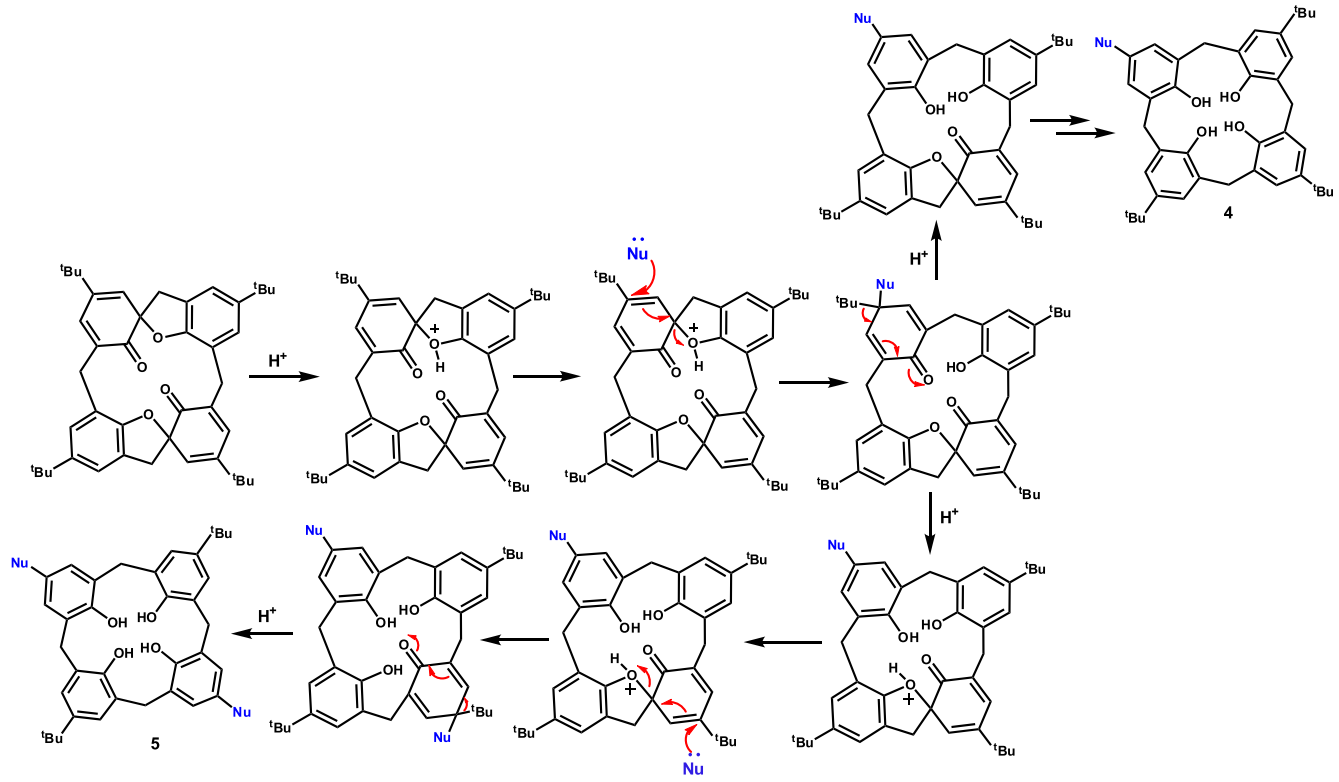
Thus our methodology offers a single step procedure for the synthesis of mono- and di-phenoxy calix[4]arenes, within very short reaction times in 'one-pot', in contrast to the coupling reactions that has been earlier reported for the synthesis of deep-cavity calixarenes.[7,24]

To examine the versatility of this process, we also looked into the reactivity of bis(spirodienone) with thiols, which turned out to be excellent nucleophiles for the title reaction. When bis(spirodienone) **1** was reacted with *n*-pentanethiol under the optimized conditions, monothio ether derivative **7** was obtained in good yield (Scheme 3). The structure of **7** was established on the basis of various spectroscopic techniques. In the ^{1}H NMR spectrum of **7**, the OH protons resonated as a singlet at δ 10.21 ppm and the $-SCH_2$ protons occurred at 3.77 ppm as a triplet. The *tert*-butyl groups appeared as two singlets at δ 1.22 and δ 1.19 integrating in 2:1 ratio. The peak corresponding to $-SCH_2$ carbon was observed at δ 43.5 ppm in the ^{13}C NMR spectrum. The cone conformation was confirmed by the ^{13}C NMR spectrum, which showed the methylene bridge carbons at δ 34.0and δ 32.6.[22]

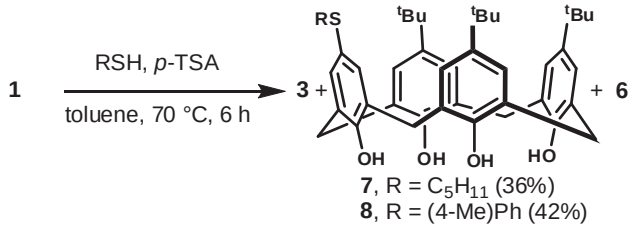
The reaction under the stipulated conditions failed to fetch the dithiosubstituted product.

As representative examples for aromatic thiols, we chose *p*-thiocresol and *p*-trifluoromethylthiophenol for the title reaction. Under the above reaction conditions, *p*-thiocresol reacted smoothly with bis(spirodienone) to fetch the corresponding monothio ether derivative in moderate yields, but the *p*-trifluoromethylthiophenol failed to react with the substrate. This reaction is noteworthy as it is the first synthesis of calix[4]arene with a thioether moiety attached directly at the upper rim.[25]

Amines were selected as the next nucleophilic candidates to undergo the reaction. When substrate **1** reacted with diethyl amine in the presence of *p*-TSA (5.0 eqiuv) in toluene at reflux temperature, reaction failed to occur. Substituting *p*-TSA with other Lewis acids like AgOTf, $Sc(OTf)_2$ etc. did not produce any results. The non-



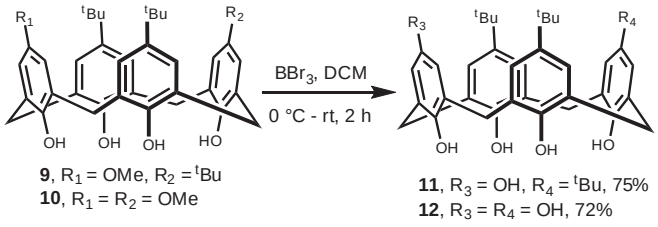
Scheme 2. Proposed mechanistic pathways for the reaction between bis(spirodienone) **1** and nucleophiles in the presence of *p*-TSA.



Scheme 3. *p*-TSA mediated reaction of calix[4]bis(spirodienone) **1** with thiols.

reactive nature of amines could be due to its protonation under the reaction conditions employed. The non-availability of lone-pair of electrons on the amino group obliterates its nucleophilic character.

We also demonstrate here the usefulness of the bis(spirodienone) methodology of the upper rim modification of calix[4]arene for the selective synthesis of mono- and diquinone calixarenes, which are otherwise difficult to synthesise. The mono- and dimethoxy calixarenes[21] reported in our previous communication were demethylated using BBr_3 to give excellent yields of the corresponding upper rim hydroxylated calixarenes (Scheme 4).[26]



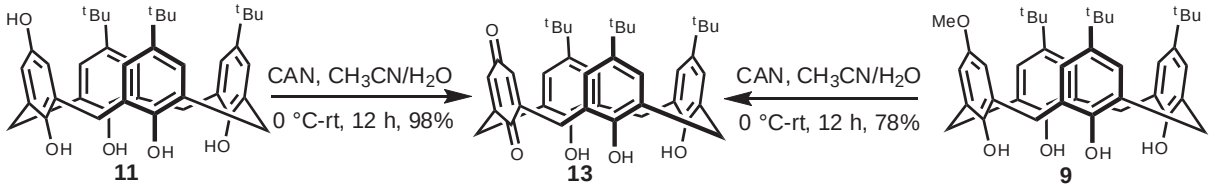
Scheme 4. Synthesis of 5-hydroxy and 5,17-dihydroxycalix[4]arenes.

The structure of **12** was established by NMR spectroscopy and MALDI-TOF MS. The ^{1}H NMR spectra of **12** showed a deshielded singlet at δ 10.14 ppm due to the resonance of the hydrogen bonded OH protons. Other important features of the ^{1}H NMR spectra are the absence of the methoxy peaks, which were so conspicuous in the parent compound and the presence of a pair of doublets for the methylene bridge protons. The upper rim hydroxyl groups however could not be detected in the ^{1}H NMR spectra probably due to fast flipping of hydroquinone moiety. The ^{13}C NMR spectra and MALDI-TOF analyses were in agreement with the assigned structure. Although there has been a report on the synthesis of detertiarybutylated 5-hydroxy calix[4]arene,[26a] to best of our knowledge, this is the first synthesis of 5-hydroxy and 5,17-dihydroxycalix[4]arenes.

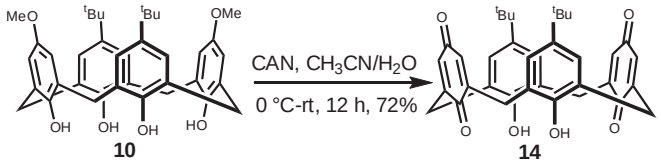
Since compounds **11** and **12** contained one and two hydroquinone units, they can be readily oxidised to the respective mono- and diquinones. Oxidation of **11** with cerium(IV)ammonium nitrate (CAN) in CH_3CN/H_2O mixture at 0 °C, calix[4]monoquinone **13** was obtained in quantitative yield. The oxidation of **9** using CAN also afforded **13** in 78% yield (Scheme 5).

The product **13** was characterized on the basis of spectroscopic data. In the IR spectrum of **13**, a peak at 3259 cm^{-1} corresponding to the –OH absorption and another one at 1647 cm^{-1} corresponding to the carbonyl was observed. In the ^{1}H NMR spectrum, the OH protons were discernible as two singlets at δ 9.13 and δ 8.88 ppm in 1:2 ratio integrating for three protons. The signal due to the protons of the quinone was observed at δ 6.68 ppm. Two singlets at δ 3.86 and 3.76 ppm were assigned to the bridging methylene protons. The *tert*-butyl appeared as two singlets at δ 1.21 and 1.20 ppm. The structure was further supported by ^{13}C NMR spectrum showing two carbonyl peaks positioned at δ 190.5 and 187.4 ppm. The OH attached carbon resonated at δ 148.2 ppm.

Similarly, **10** on oxidation with CAN offered the 1,3-calix[4]diquinone **14** in 72% yield (Scheme 6). To date there are only a few



Scheme 5. Synthesis of calix[4]monoquinone **13**.



Scheme 6. Synthesis of calix[4]diquinone **14**.

reports regarding the synthesis of calixquinones.[26c,27] The most widely used method is the oxidation using thallium triflate starting from *p-tert*-butylcalix[4]arene.[28] However, for the selective oxidation to mono, di, and triquinones, the procedures encounter protection of the phenolic OH groups. In this context, using our methodology, both mono and diquinones having free OH groups at the lower rim can be selectively synthesized.

The ^{1}H NMR spectrum of **14** showed singlets for all the protons in the compound. The OH proton appeared at δ 7.31 ppm, the aromatic region showed two peaks at δ 6.89 and 6.68 ppm, corresponding to aryl and quinone protons, respectively and the *tert*-butyl groups resonated at δ 1.14 ppm. Interestingly, the ^{1}H NMR spectrum displayed a broad singlet at δ 3.72 ppm for the methylene protons, which suggested fast flipping of quinone as well as the aromatic rings. To understand the conformational preference of **14**, a variable temperature ^{1}H NMR study was conducted and two significant changes were observed as the temperature was lowered from 298 to 223 K. The singlet due to the methylene bridge gradually broadens on cooling before collapsing near 223 K. This observation is a clear indication that **14** is dynamic in solution even at 223 K. Thus, it is concluded that calix[4]diquinone possesses a highly mobile structure in solution.

Anticipating complexation behavior of calixquinones toward alkali metal ions, ^{1}H NMR titrations with various alkali metal ions were conducted. However, addition of Li^+, Na^+, and K^+ to solution of **13** and **14** (in 4:1 $CDCl_3/CD_3CN$) did not cause any change in their ^{1}H NMR spectra, indicating absence of any complexation between the ligands and the metal ions. This could be due to the presence of high degree of intramolecular hydrogen bonding present in these compounds.

Among the functionalized calixarenes, calixquinones are of particular interest because of their potential use as redox systems, as participants in charge-transfer complexes[29] and as synthetic intermediates. Hence the electrochemical properties of **13** and **14** were investigated in dichloromethane/acetonitrile (1:9) using cyclic voltametry with $(Bu^n)_4NPF_6$ as the supporting electrolyte. The compound **13** did not give any characteristic peaks of quinone moieties present, as it was highly insoluble in the medium employed. The insolubility can be attributed to the high degree of intramolecular hydrogen bonding present in **13**. The calixdiquinone **14** (Fig. 1) showed three redox waves in its voltamogram, two of which are close together and reversible, 2/2′ and 3/3′, and the other wave, 1, occurring at a less negative potential, being irreversible. In simple calixdiquinones, the redox waves 1 and 2 are considered to be two one-electron process and wave 3 is considered to be a two-

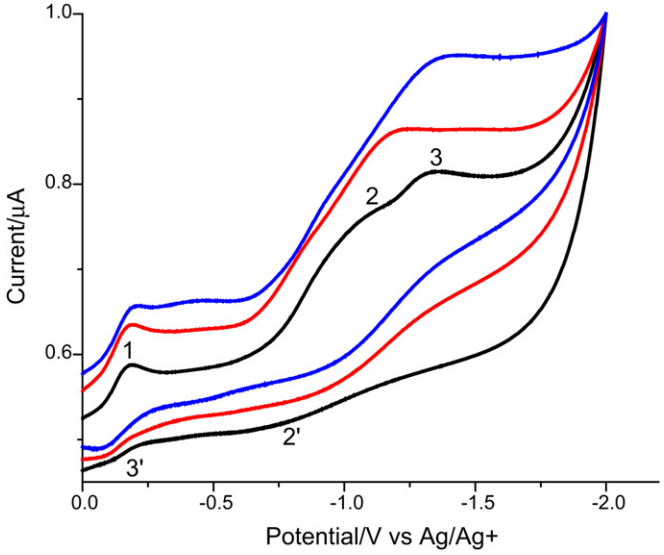


Figure 1. CVs at various scan rates(in the order of increasing amplitude of current: 50, 100, 200 mV s^{-1}) of **14** (1.4×10^{-3} M) in 1:9 CH_2Cl_2/CH_3CN.

electron process.[30] The irreversibility of wave 1 may be due to the formation of insoluble hydroquinone species.[31]

3. Conclusion

In summary, a direct and efficient acid-mediated protocol for the selective upper rim aryloxy substitution of calix[4]arene via bis(spirodienone) chemistry has been opened up. The transformation is distinguished by mild reaction conditions, experimental simplicity and considerable generality. Moreover, this ipso-like nucleophilic substitution reaction of bis(spirodienone) furnishes upper rim modification of calix[4]arene without resorting to any protection/deprotection strategy involving the lower rim of calixarenes. A straightforward methodology for the selective introduction of thioether moiety at the upper rim of calix[4]arene has also been accomplished. Our investigations have also uncovered a relatively simple and efficient strategy for the synthesis of 5-hydroxy and 5,23-dihydroxycalix[4]arene, which are otherwise difficult to synthesize. The paper also deals with a highly selective method for the synthesis of calix[4]mono- and diquinones in good yield. Our current efforts are focused on exploring the use of this methodology in the synthesis of complex molecular receptors for ionic and molecular recognition.

4. Experimental

4.1. General procedures and materials

All reactions were conducted in oven-dried glassware. Solvents used for the experiments were distilled and dried as specified. All reactions were monitored by TLC (Silica gel 60 F_{254}, 0.25 mm, Merck), visualization was effected with UV and/or in I_2 chamber.

Chromatography refers to open column chromatography on silica gel (100–200 mesh). NMR spectra were recorded at 300 (^{1}H) and 75 (^{13}C) MHz, respectively on a Bruker Advance DPX-300 MHz. Chemical shifts are reported in δ (ppm) relative to TMS (^{1}H) or $CDCl_3$ (^{13}C) as internal standards. IR spectra were recorded on Bomem MB series FT-IR spectrometer; absorptions are reported in cm^{-1}. Mass spectra were recorded under under MALDI-TOF mechanism in Axima-CFR Plus spectrometer. Elemental analysis was done using Perkin–Elmer-2400 CHNS analyser. Cyclic voltammetry (CV) measurements were carried out with the model 1100A electrochemical analyzer (CH Instruments). This instrument is a conventional three electrode cell that uses a Pt button working electrode of 2 mm in diameter, Pt wire as the counter electrode, and Ag/AgCl as the reference electrode. The experiment was carried out using 0.1 M Bu_4NPF_6 as the supporting electrolyte under nitrogen gas protection. All the reported analyses were carried out in our laboratory (NIIST, Trivandrum).

4.2. General procedure for the reaction of calix[4]bis (spirodienone) with phenols

A mixture of bis(spirodienone) **1** (50 mg, 0.08 mmol), phenol (4.0 equiv), and *p*-TSA (5.0 equiv) in toluene was taken in a 50 ml R. B. flask and was stirred at 70 °C. The reaction was continued till the reaction was complete as shown by TLC (~4 h). The solvent was removed under reduced pressure. The reaction mixture was worked up using dichloromethane/water mixture and the solid mass obtained was purified by column chromatography.

*4.2.1. 11,17,23-Tri-tert-butyl-5-O-(4-methyl)phenylcalix[4]arene (**4a**).* Yield: 40% as white solid. R_f: 0.90 (9:1 hexane/EtOAc). Mp: decomposed >240 °C. IR (KBr) ν_{max}: 3173, 2960, 2858, 1800, 1259, 1053 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.19 (s, OH, 4H), 7.07 (s, ArH, 4H), 6.98 (s, ArH, 2H), 6.83 (m, ArH, 4H), 6.67 (s, ArH, 2H), 4.22 (d, J=13.5 Hz, $ArCH_2Ar$, 4H), 3.41 (d, J=13.5 Hz, $ArCH_2Ar$, 4H), 2.33 (s, $-CH_3$, 3H), 1.22 (s, *t*-Bu, 18H), 1.19 (s, *t*-Bu, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.3 (C–OH), 150.9, 146.2, 144.0, 143.4, 131.6, 129.4, 128.8, 126.6, 125.3, 125.2, 118.1, 117.8, 113.3 (Ar–C), 33.4, 31.9, 31.7, 30.9, 30.8, 20.0 ($ArCH_2Ar$, $-CH_3$, *t*-Bu). Anal. Calcd for $C_{47}H_{54}O_5$: C, 80.77; H, 7.79. Found: C, 80. 74; H, 7.75.

*4.2.2. 11,23-Di-tert-butyl-5,17-di-O-(4-methyl)phenylcalix[4]arene (**5a**).* Yield: 33% as white solid. R_f: 0.84 (9:1 hexane/EtOAc). Mp: decomposed >240 °C. IR (KBr) ν_{max}: 3173, 2960, 2858, 1800, 1259, 1053 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.07 (s, OH, 4H), 7.02 (m, ArH, 4H), 6.96 (s, ArH, 4H), 6.81 (m, ArH, 4H), 6.64 (s, ArH, 4H), 4.20 (d, J=13.5 Hz, $ArCH_2Ar$, 4H), 3.39 (d, J=13.5 Hz, $ArCH_2Ar$, 4H), 2.30 (s, $-CH_3$, 6H), 1.23 (s, *t*-Bu, 18H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.2 (C–OH), 146.4, 144.7, 143.5, 131.3, 129.3, 128.9, 126.8, 125.6, 125.3, 118.2, 117.7, 113.4 (Ar–C), 34.0, 31.7, 30.8, 30.5, 20.1, 16.5, 16.3 ($ArCH_2Ar$, $-CH_3$, *t*-Bu). Anal. Calcd for $C_{50}H_{52}O_6$: C, 80.18; H, 7.00. Found: C, 80.15; H, 6.96.

*4.2.3. 11,17,23-Tri-tert-butyl-5-O-(4-methoxy)phenylcalix[4]arene (**4b**).* Yield: 42% as white solid. R_f: 0.91 (9:1 hexane/EtOAc). Mp: decomposed >240 °C. IR (KBr) ν_{max}: 3173, 2960, 2858, 1800, 1259, 1053 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.14 (s, OH, 4H), 6.96 (m, ArH, 8H), 6.74 (s, ArH, 2H), 6.49 (s, ArH, 2H), 4.17 (d, J=11.2 Hz, $ArCH_2Ar$, 4H), 3.58 (s, OCH_3, 3H), 3.39 (br s, $ArCH_2Ar$, 4H), 1.24 (s, *t*-Bu, 18H), 1.19 (s, *t*-Bu, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.4 (C–OH), 146.9, 146.3, 144.4, 144.2, 142.5, 137.5, 129.2, 129.1, 127.9, 127.7, 125.8, 125.7, 125.6, 119.2, 118.5 (Ar–C), 57.2 ($-OCH_3$), 34.1, 34.0, 32.6, 31.9, 31.5, 31.4, 30.1, 29.7, 28.5, 23.6, 15.1 ($ArCH_2Ar$, *t*-Bu). Anal. Calcd for $C_{47}H_{54}O_6$: C, 78.96; H, 7.61. Found: C, 79.23; H, 7.57.

*4.2.4. 11,23-Di-tert-butyl-5,17-di-O-(4-methyl)phenylcalix[4]arene (**5b**).* Yield: 35% as white solid. R_f: 0.84 (9:1 hexane/EtOAc). Mp: decomposed >240 °C. IR (KBr) ν_{max}: 3172, 2957, 2859, 1802, 1260, 1055 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.05 (s, OH, 4H), 7.30 (m, ArH, 4H), 7.04 (s, ArH, 4H), 6.55 (s, ArH, 4H), 6.52 (s, ArH, 4H), 4.23 (d, J=13.2 Hz, $ArCH_2Ar$, 4H), 3.64 (s, OCH_3, 6H), 3.43 (d, J=14.7 Hz, $ArCH_2Ar$, 4H), 1.24 (s, *t*-Bu, 18H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.2 (C–OH), 152.2, 147.4, 145.7, 144.5, 132.3, 130.3, 129.9, 127.8, 126.6, 126.3, 119.2, 118.7, 114.3 (Ar–C), 55.6 ($-OCH_3$), 34.0, 31.7, 30.8, 20.2, 16.3 ($ArCH_2Ar$, *t*-Bu). Anal. Calcd for $C_{50}H_{52}O_8$: C, 76.90; H, 6.71. Found: C, 76.86; H, 6.69.

*4.2.5. 11,17,23-Tri-tert-butyl-5-O-(4-bromo)phenylcalix[4]arene (**4c**).* Yield: 35% as white solid. R_f: 0.89 (9:1 hexane/EtOAc). Mp: decomposed >240 °C. IR (KBr) ν_{max}: 3173, 2960, 2858, 1800, 1259, 1053 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.30 (s, OH, 4H), 7.34 (d, J=9.0 Hz, ArH, 2H), 7.05 (m, ArH, 6H), 6.95 (s, ArH, 2H), 6.69 (s, ArH, 2H), 4.24 (d, J=10.5 Hz, $ArCH_2Ar$, 4H), 3.50 (m, $ArCH_2Ar$, 4H), 1.22 (s, *t*-Bu, 18H), 1.21 (s, *t*-Bu, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.9 (C–OH), 150.3, 146.7, 146.5, 145.1, 144.6, 144.4, 144.2, 132.5, 129.8, 127.8, 127.7, 127.6, 126.9, 126.2, 125.9, 125.8, 119.9, 119.2, 115.1, 114.7 (Ar–C), 34.0, 32.7, 31.5, 30.8, 29.7, 22.7, 14.1 ($ArCH_2Ar$, *t*-Bu). Anal. Calcd for $C_{46}H_{51}BrO_5$: C, 72.33; H, 6.73. Found: C, 72.29; H, 6.75.

*4.2.6. 11,23-Di-tert-butyl-5,17-di-O-(4-bromo)phenylcalix[4]arene (**5c**).* Yield: 25% as white solid. R_f: 0.81 (9:1 hexane/EtOAc). Mp: decomposed >240 °C. IR (KBr) ν_{max}: 3172, 2957, 2859, 1802, 1260, 1055 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.15 (s, OH, 4H), 7.18 (m, ArH, 4H), 6.92 (s, ArH, 4H), 6.44 (s, ArH, 4H), 6.40 (s, ArH, 4H), 4.24 (d, J=12.9 Hz, $ArCH_2Ar$, 4H), 3.43 (d, J=11.74 Hz, $ArCH_2Ar$, 4H), 1.24 (s, *t*-Bu, 18H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.1 (C–OH), 147.8, 145.1, 144.7, 142.6, 132.5, 132.2, 130.7, 129.2, 128.8, 128.3, 127.3, 125.7, 113.9 (Ar–C), 34.0, 32.4, 31.5, 30.6, 29.7, 27.7, 21.6, 19.2 ($ArCH_2Ar$, *t*-Bu). Anal. Calcd for $C_{48}H_{46}Br_2O_6$: C, 65.61; H, 5.28. Found: C, 65.66; H, 5.25.

*4.2.7. 11,17,23-Tri-tert-butyl-5-O-(4-iodo)phenylcalix[4]arene (**4d**).* Yield: 32% as white solid. R_f: 0.91 (9:1 hexane/EtOAc). Mp: decomposed >240 °C. IR (KBr) ν_{max}: 3173, 2960, 2858, 1800, 1259, 1053 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.21 (s, OH, 4H), 7.05 (s, ArH, 4H), 6.96 (m, ArH, 2H), 6.81 (m, ArH, 4H), 6.65 (s, ArH, 2H), 4.23 (d, J=12.5 Hz, $ArCH_2Ar$, 4H), 3.42 (d, J=13.5 Hz, $ArCH_2Ar$, 4H), 1.22 (s, *t*-Bu, 18H), 1.19 (s, *t*-Bu, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.3 (C–OH), 150.9, 146.2, 144.0, 143.4, 131.6, 129.4, 128.8, 126.6, 125.3, 125.2, 118.1, 117.8, 113.3 (Ar–C), 34.0, 32.4, 31.9, 31.2, 30.9, 20.0 ($ArCH_2Ar$, *t*-Bu). Anal. Calcd for $C_{46}H_{51}IO_5$: C, 68.14; H, 6.34. Found: C, 68.10; H, 6.29.

*4.2.8. 11,23-Di-tert-butyl-5,17-di-O-(4-iodo)phenylcalix[4]arene (**5d**).* Yield: 23% as white solid. R_f: 0.80 (9:1 hexane/EtOAc). Mp: decomposed >240 °C. IR (KBr) ν_{max}: 3172, 2957, 2859, 1802, 1260, 1055 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.11 (s, OH, 4H), 7.13 (m, ArH, 8H), 7.07 (s, ArH, 6H), 6.66 (s, ArH, 2H), 4.24 (d, J=13.2 Hz, $ArCH_2Ar$, 4H), 3.46 (d, J=12.3 Hz, $ArCH_2Ar$, 4H), 1.24 (s, *t*-Bu, 18H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.4 (C–OH), 146.9, 146.3, 144.4, 144.3, 137.7, 129.2, 129.1, 127.9, 127.7, 127.3, 126.0, 125.8, 125.6, 115.2, 114.5 (Ar–C), 34.1, 32.6, 32.0, 31.4, 30.1, 29.7, 28.5 ($ArCH_2Ar$, *t*-Bu). Anal. Calcd for $C_{48}H_{46}I_2O_6$: C, 59.27; H, 4.77. Found: C, 59.24; H, 4.75.

*4.2.9. 11,17,23-Tri-tert-butyl-5-O-(2-iodo)phenylcalix[4]arene (**4e**).* Yield: 22% as white solid. R_f: 0.88 (9:1 hexane/EtOAc). Mp: decomposed >240 °C. IR (KBr) ν_{max}: 3176, 2957, 2868, 1770, 1269, 1066 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.21 (s, OH, 4H), 7.08 (m, ArH, 4H), 7.02 (m, ArH, 2H), 6.86 (m, ArH, 4H), 6.67 (s, ArH, 2H), 4.23 (d, J=12.5 Hz, $ArCH_2Ar$, 4H), 3.42 (d, J=13.5 Hz, $ArCH_2Ar$, 4H), 1.22 (s, *t*-Bu, 18H), 1.19 (s, *t*-Bu, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.5 (C–OH), 147.9, 147.2, 146.0, 144.4, 132.6, 130.4, 129.8, 126.4, 125.2, 117.1, 116.8, 114.6 (Ar–C), 34.0, 32.4, 31.9, 31.2, 30.9, 20.0 ($ArCH_2Ar$,

t-Bu). Anal. Calcd for $C_{46}H_{51}IO_5$: C, 68.14; H, 6.34. Found: C, 68.21; H, 6.25.

*4.2.10. 11,23-Di-tert-butyl-5,17-di-O-(2-iodo)phenylcalix[4]arene (**5e**).* Yield: 18% as white solid. R_f: 0.78 (9:1 hexane/EtOAc). Mp: decomposed >240 °C. IR (KBr) ν_{max}: 3172, 2957, 2859, 1802, 1260, 1055 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.19 (s, OH, 4H), 7.12 (m, ArH, 4H), 6.96 (m, ArH, 8H), 6.62 (m, ArH, 4H), 4.24 (d, J=13.5 Hz, $ArCH_2Ar$, 4H), 3.44 (d, J=12.6 Hz, $ArCH_2Ar$, 4H), 1.23 (s, *t*-Bu, 18H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.9 (C–OH), 146.2, 145.4, 144.8, 133.6, 130.7, 129.7, 128.8, 128.5, 127.3, 125.4, 113.9 (Ar–C), 33.9, 32.4, 31.5, 30.6, 29.7, 27.6, 21.4 ($ArCH_2Ar$, *t*-Bu). Anal. Calcd for $C_{48}H_{46}I_2O_6$: C, 59.27; H, 4.77. Found: C, 59.16; H, 4.81.

*4.2.11. 11,17,23-Tri-tert-butyl-5-O-(2,4-diiodo)phenylcalix[4]arene (**4f**).* Yield: 17% as white solid. R_f: 0.91 (9:1 hexane/EtOAc). Mp: decomposed >240 °C. IR (KBr) ν_{max}: 3172, 2960, 2862, 1814, 1258, 1050 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.21 (s, OH, 4H), 7.06 (m, ArH, 4H), 6.93 (m, ArH, 5H), 6.63 (s, ArH, 2H), 4.23 (d, J=13.3 Hz, $ArCH_2Ar$, 4H), 3.43 (d, J=14.4 Hz, $ArCH_2Ar$, 4H), 1.22 (s, *t*-Bu, 18H), 1.19 (s, *t*-Bu, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.6 (C–OH), 146.7, 145.1, 144.6, 144.4, 132.6, 129.7, 128.1, 127.6, 125.9, 125.3, 119.9, 119.1, 114.7 (Ar–C), 34.0, 32.6, 32.5, 31.4, 29.3 ($ArCH_2Ar$, *t*-Bu). Anal. Calcd for $C_{46}H_{50}I_2O_5$: C, 58.98; H, 5.38. Found: C, 59.12; H, 5.47.

*4.2.12. 11,23-Di-tert-butyl-5,17-di-O-(2,4-diiodo)phenylcalix[4]arene (**5f**).* Yield: 6% as white solid. R_f: 0.83 (9:1 hexane/EtOAc). Mp: decomposed >240 °C. IR (KBr) ν_{max}: 3172, 2958, 2860, 1813, 1256, 1044 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.07 (s, OH, 4H), 7.26 (m, ArH, 4H), 7.12 (m, ArH, 6H), 6.76 (s, ArH, 4H), 4.23 (d, J=13.2 Hz, $ArCH_2Ar$, 4H), 3.46 (d, J=12.7 Hz, $ArCH_2Ar$, 4H), 1.25 (s, *t*-Bu, 18H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.5 (C–OH), 149.6, 146.5, 144.6, 143.3, 131.6, 129.7, 128.8, 126.8, 125.6, 118.2, 117.4, 114.3 (Ar–C), 34.1, 32.0, 31.4, 30.8, 29.4 ($ArCH_2Ar$, *t*-Bu). Anal. Calcd for $C_{48}H_{44}I_4O_6$: C, 47.08; H, 3.62. Found: C, 47.14; H, 3.71.

*4.2.13. 11,17,23-Tri-tert-butyl-5-O-(4-phenyl)phenylcalix[4]arene (**4g**).* Yield: 30% as white solid. R_f: 0.89 (9:1 hexane/EtOAc). Mp: decomposed >240 °C. IR (KBr) ν_{max}: 3173, 2960, 2858, 1800, 1259, 1053 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.29 (s, OH, 4H), 7.83 (m, ArH, 2H), 7.53 (m, ArH, 5H), 7.05 (m, ArH, 8H), 6.75 (s, ArH, 2H), 4.25 (d, J=13.0 Hz, $ArCH_2Ar$, 4H), 3.48 (d, J=14.0 Hz, $ArCH_2Ar$, 4H), 1.22 (s, *t*-Bu, 18H), 1.20 (s, *t*-Bu, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.4 (C–OH), 146.6, 146.4, 145.0, 144.4, 144.1, 138.0, 129.7, 128.8, 127.9, 127.7, 127.6, 127.5, 127.3, 126.9, 126.7, 126.6, 126.0, 125.8, 125.7, 119.0, 118.2 (Ar–C), 34.0, 33.9, 32.5, 32.3, 31.4, 31.3, 29.630 ($ArCH_2Ar$, *t*-Bu). Anal. Calcd for $C_{52}H_{56}O_5$: C, 82.07; H, 7.42. Found: C, 82.02; H, 7.39.

4.3. General procedure for the reaction of calix[4]bis (spirodienone) with thiols

A mixture of bis(spirodienone) **1** (50 mg, 0.08 mmol), thiol (4.0 equiv), and *p*-TSA (5.0 equiv) in toluene was taken in a 50 ml R. B. flask and was stirred at 70 °C. The reaction was continued till it was complete as shown by TLC (~6 h). The solvent was removed under reduced pressure. The reaction mixture was worked up using dichloromethane/water mixture and the solid mass obtained was purified by column chromatography.

*4.3.1. 11,17,23-Tri-tert-butyl-5-S-pentylcalix[4]arene (**7**).* Yield: 36% as a pasty mass. R_f: 0.78 (9:1 hexane/EtOAc). IR (KBr) ν_{max}: 3170, 2956, 2860, 1784, 1058 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 10.21 (s, OH, 4H), 7.02 (m, ArH, 6H), 6.55 (s, ArH, 2H), 4.23 (d, J=12.3 Hz, $ArCH_2Ar$, 4H), 3.77 (t, J=6.0 Hz, CH_2, 2H), 3.46 (d, J=13.5 Hz, $ArCH_2Ar$, 4H), 1.68 (m, CH_2, 2H), 1.34, 1.23, 1.19 (m, CH_2, *t*-Bu, 31H), 0.89 (m, CH_3, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.4 (C–OH), 146.9, 146.3, 144.4, 144.2, 142.3, 129.2, 127.8, 127.6, 127.2, 125.9, 125.8, 125.7, 115.5 (Ar–C), 43.5 ($-SCH_2$), 34.0, 32.6, 31.5, 31.4, 29.2, 28.1, 22.6, 14.9 ($ArCH_2Ar$, *t*-Bu). MALDI-TOF MS: calcd for $C_{46}H_{58}O_4S$, $(M+Na)^+$: 717.40. Found: 717.86.

*4.3.2. 11,17,23-Tri-tert-butyl-5-S-(4-methyl)phenylcalix[4]arene (**8**).* Yield: 42% as white solid. R_f: 0.75 (9:1 hexane/EtOAc). Mp: decomposed >240 °C. IR (KBr) ν_{max}: 3172, 2958, 2860, 1790, 1259, 1053 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.19 (s, OH, 4H), 7.06 (s, ArH, 4H), 6.98 (s, ArH, 2H), 6.83 (m, ArH, 4H), 6.67 (s, ArH, 2H), 4.23 (d, J=13.5 Hz, $ArCH_2Ar$, 4H), 3.42 (s, $ArCH_2Ar$, 4H), 2.13 (s, CH_3, 3H), 1.22 (s, *t*-Bu, 18H), 1.19 (s, *t*-Bu, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.9 (C–OH), 150.3, 146.7, 145.1, 144.6, 144.4, 144.2, 132.5, 129.8, 127.7, 127.6, 126.9, 126.2, 125.9, 125.8, 119.9, 119.3, 115.1, 114.7 (Ar–C), 57.2 ($-CH_3$), 34.0, 32.7, 32.5, 34.4, 31.5, 30.8, 29.7, 22.6 ($ArCH_2Ar$, *t*-Bu). Anal. Calcd for $C_{47}H_{54}O_4S$: C, 78.95; H, 7.61; S, 4.48. Found: C, 78.92; H, 7.59, S, 4.50.

4.4. Procedure for the synthesis of 5,17-dihydroxycalix[4] arene (12)

11,23-Di-*tert*-butyl-5,17-dimethoxycalix[4]arene, **10** (50 mg, 0.09 mmol) dissolved in 10 ml dry dichloromethane in a two necked R.B, was cooled in ice-salt mixture, BBr_3 (87 mg, 0.35 mmol) was added to it over a period of half-an-hour and the reaction mixture was allowed to stir under argon for 3 h (0 °C). The completion of the reaction was tested by TLC. The product was obtained using column chromatography [petroleum ether/ethyl acetate (90:10)] as a colorless mass **12** (34 mg, 72%).

*4.4.1. 11,23-Di-p-tert-butyl-5,17-dihydroxycalix[4]arene (**12**).* Yield: 72% as a pasty mass. R_f: 0.60 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 3172, 2960, 2860, 1786, 1060 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 10.14 (s, OH, 4H), 7.06 (s, ArH, 4H), 6.52 (s, ArH, 4H), 4.22 (d, J=13.8 Hz, $ArCH_2Ar$, 4H), 3.45 (broad s, $ArCH_2Ar$, 4H), 1.24 (s, *t*-Bu, 18H), two of the OH protons could not be detected. ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.7 (C–OH), 147.2, 144.0, 143.4, 142.6, 132.4, 130.8, 129.8, 129.2, 128.8, 128.3, 128.1, 127.3, 125.7, 114.1 (Ar–C), 34.1, 32.3, 31.5, 30.6, 29.7, 27.7, 21.6, 19.2 ($ArCH_2Ar$, *t*-Bu). MALDI-TOF MS: calcd for $C_{36}H_{40}O_6$, $(M+Na)^+$: 591.28. Found: 591.77.

4.5. Procedure for the synthesis of calix[4]monoquinone (13)

To 5-hydroxycalix[4]arene **11** (25 mg, 0.04 mmol) dissolved in minimum amount of dichloromethane, CH_3CN (8 mL)/H_2O (2 mL) mixture was added and cooled to 0 °C. CAN (45 mg, 0.08 mmol) dissolved in CH_3CN (6 mL)/H_2O(4 mL) mixture was added over a period of 1 h, stirred at 0 °C for 12 h. The completion of the reaction was checked using TLC. The color of the reaction mixture turned from light yellow to dark red. Solvent was removed under reduced pressure. The solid mass obtained was extracted with dichloromethane and dried over anhydrous sodium sulfate. The residue obtained after removal of the solvent was purified by column chromatography [petroleum ether/ethyl acetate (90:10)] to afford **13** as a red crystalline solid (24 mg, 98%).

*4.5.1. 11,17,23-Tri-p-tert-butylcalix[4]monoquinone (**13**).* Yield: 98% as a dark red solid. R_f: 0.69 (7:3 hexane/EtOAc). Mp: 330–334 °C. IR (KBr) ν_{max}: 3259, 2956, 1647, 1485 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 9.13 (s, OH, 1H), 8.88 (s, OH, 2H), 7.10 (d, J=2.0 Hz, ArH, 2H), 7.03 (s, ArH, 2H), 6.89 (d, J=2.0 Hz, ArH, 2H), 6.68 (s, quinone H, 2H), 3.86 (s, $ArCH_2Ar$, 4H), 3.76 (s, $ArCH_2Ar$, 4H), 1.21 (s, *t*-Bu, 18H), 1.20 (s, *t*-Bu, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.5, 187.4, 148.2, 148.0, 147.2, 144.3, 144.1, 134.2, 129.6, 127.5, 127.1, 125.5, 123.2, 34.1, 34.0, 32.4,

31.5, 31.4, 30.7. Anal. Calcd for $C_{40}H_{46}O_5$: C, 78.19; H, 7.64. Found: C, 78.34; H, 7.91.

4.6. Procedure for the synthesis of calix[4]diquinone (14)

To 11,23-di-*tert*-butyl-5,17-dimethoxycalix[4]arene **10** (25 mg, 0.04 mmol) dissolved in minimum amount of dichloromethane, CH_3CN (8 mL)/H_2O (2 mL) mixture was added and cooled to 0 °C. CAN (45 mg, 0.08 mmol) dissolved in CH_3CN (6 mL)/H_2O(4 mL) mixture was added over a period of one hour, stirred at 0 °C for 12 h. The completion of the reaction was checked using TLC. The color of the reaction mixture turned from light yellow to dark red. Solvent was removed under reduced pressure. The solid mass obtained was extracted with dichloromethane and dried over anhydrous sodium sulfate. The residue obtained after removal of the solvent was purified by column chromatography [petroleum ether/ethyl acetate (90:10)] to afford **14** as a red crystalline solid (17 mg, 72%).

*4.6.1. 11,23-Di-p-tert-butylcalix[4]diquinone (**14**).* Yield: 72% as a red solid. R_f: 0.71 (7:3 hexane/EtOAc). Mp: 330–334 °C. IR (KBr) ν_{max}: 3259, 2956, 1647, 1485 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.31 (s, OH, 2H), 6.89 (s, ArH, 4H), 6.68 (s, quinone H, 4H), 3.72 (s, $ArCH_2Ar$, 8H), 1.14 (s, *t*-Bu, 18H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.0, 187.5, 149.4, 148.8, 144.4, 133.3, 126.4, 125.4, 34.1, 31.9, 31.5, 30.9. Anal. Calcd for $C_{36}H_{36}O_6$: C, 76.57; H, 6.48. Found: C, 76.53; H, 6.45.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.04.021. This data include MOL files and In ChiKeys of the most important compounds described in this article.

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