Part I
General Characteristics of Calixarenes

Calixarenes and Resorcinarenes: Synthesis, Properties and Applications. W. Sliwa and C. Kozlowski

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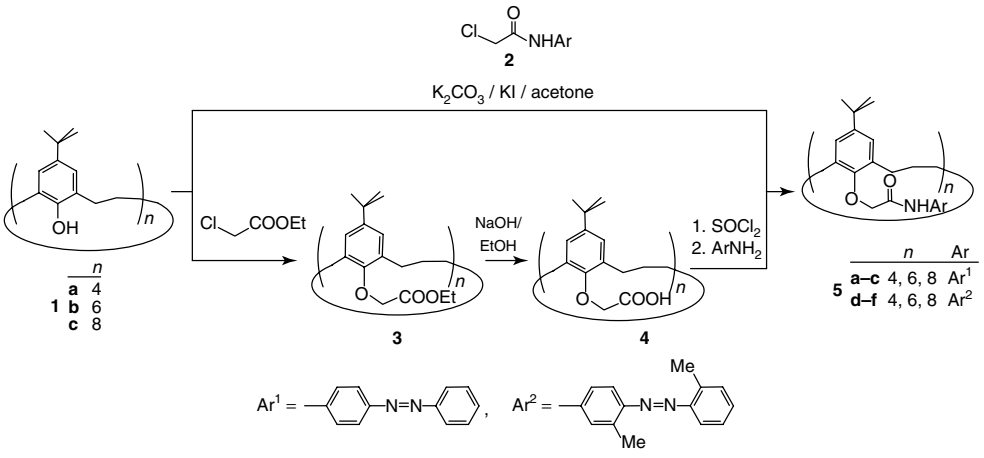
1
Reactivity of Calixarenes

Numerous reactions of calixarenes have been reported [1–14]; some examples of these are described here. To improve the properties of calixarenes, functionalization of the narrow [15–17] as well as of the wide rim is carried out [18–20]. In the first part, functionalization of the narrow rim of calixarenes is described, followed by functionalization of the wide rim. Then some examples of calixarene bridging are presented.

1.1
Functionalization of the Narrow Rim

A series of calixarenes bearing azo chromophores on the narrow rim were synthesized using two routes. The first one was a direct reaction of calixarenes **1a–c** with 4-chloroacetoaminoazobenzene **2** in the presence of K_2CO_3 and KI. In the second, indirect approach calixarenes reacted with ethyl chloroacetate affording esters **3** hydrolyzed to give acids **4**, which were treated with thionyl chloride, followed by *p*-aminoazobenzenes $ArNH_2$. Both procedures led to the formation of calixarenes **5** containing azo chromophores [21].



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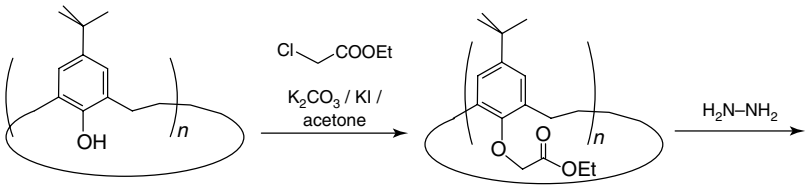
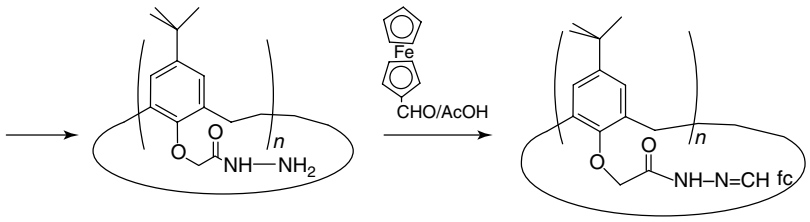
In order to introduce the ferrocenyl unit into calixarenes, the reaction of **1a–c** with ethyl chloroacetate affording esters **3** was performed. These compounds reacted with hydrazine to give hydrazides **6**, which upon treatment with ferrocenecarboxaldehyde yielded derivatives **7** [22].



		n
	a	4
1	**b**	6
	c	8

		n
	a	4
3	**b**	6
	c	8



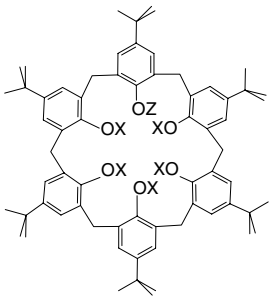
		n
	a	4
6	**b**	6
	c	8

		n
	a	4
7	**b**	6
	c	8

The reaction of calix[6]arene **8a** with (+)-camphor-10-sulfonyl chloride RCl **9** affords either the mono-*O*-sulfonylated product **8b** or the hexa-*O*-sulfonylated product **8c**, depending on the stoichiometry [23]. This rather unexpected result, i.e. the absence of di- to pentasubstituted products, is due to the structure of **8b** in which the camphor-sulfonyl unit covers the narrow rim of calixarene, thus forming a steric hindrance for substitution of the second hydroxyl group.

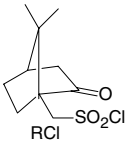
However, if the second hydroxyl group is sulfonylated, the two substituents repulse one another; therefore, other hydroxyl groups are exposed to reaction with excess sulfonyl chloride to give **8c**.

It was established that 1,3,5-trimethoxy-*t*-butylcalix[6]arene **10** reacts with phenylpyridines **11** and **12** and with fluorenylpyridine **13** to give calix[6]arenes **14**, **15**, and **16** respectively, functionalized at alternate rings on the narrow rim [24]. The ^{1}H NMR measurements show that **14–16** exist predominantly in the C_{3v} cone conformation and have unusually deep cavities.

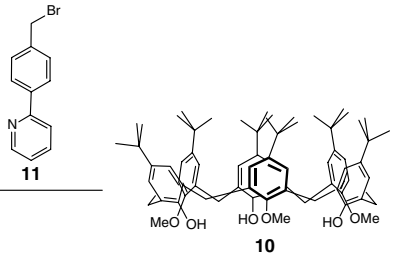


	X	Z
a	H	H
b	H	R
c	R	R

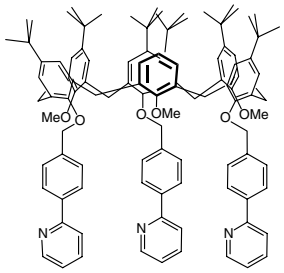
8



RCl
9



11 **10** **12**



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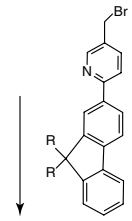

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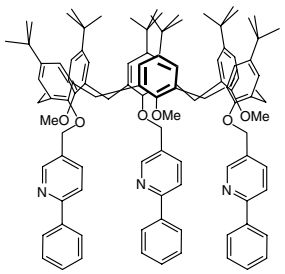

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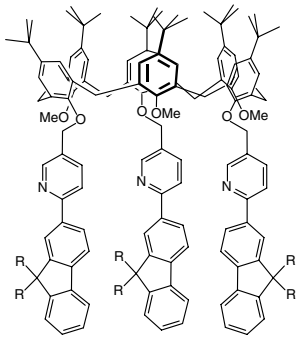
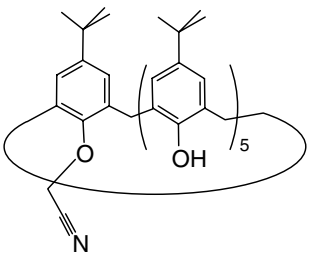


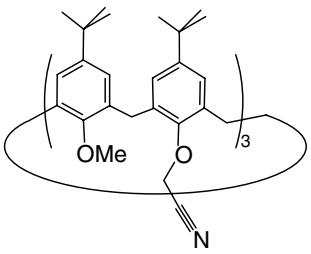
R = *n*-C_6H_{13}

16

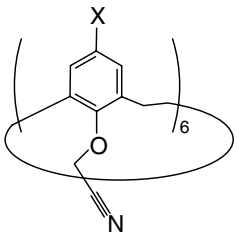
The restriction of the conformational flexibility of calix[6]arenes may be achieved by using the Ritter reaction. This procedure involves the reaction of calix[6]arenes bearing one, three, and six cyanomethoxy groups on the narrow rim i.e. **17**, **18**, and **19** respectively, with tertiary alcohols [25]. Functionalization of **17** and **18** with 1-adamantanol **20a** (R=H) or 3-substituted 1-adamantanol **20b** (R=CH_2COOH) yielded monoamides **21a**,**b** and triamides **22a**,**b** respectively, existing in rigid cone conformations.



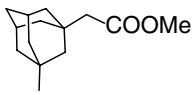
17

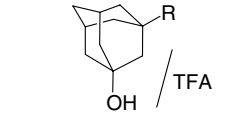


18



19

	X
a	*t*-Bu
b	
c	 COOMe

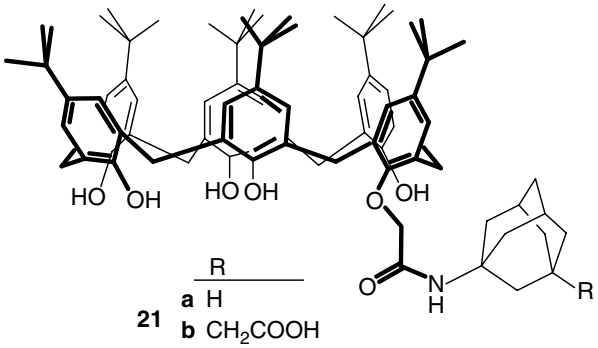


20

17 → **20**

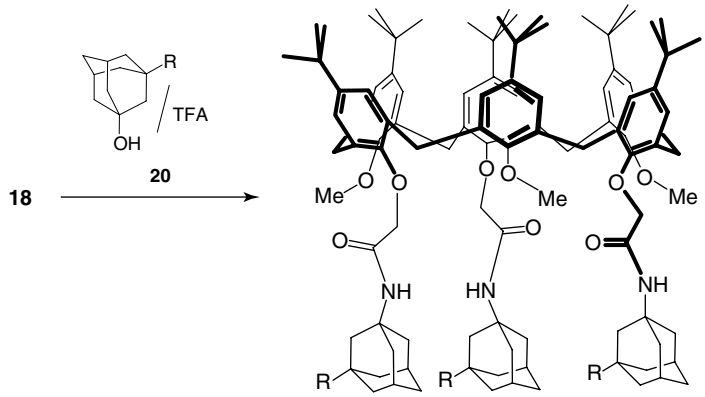
	R
a	H
b	CH_2COOH

20



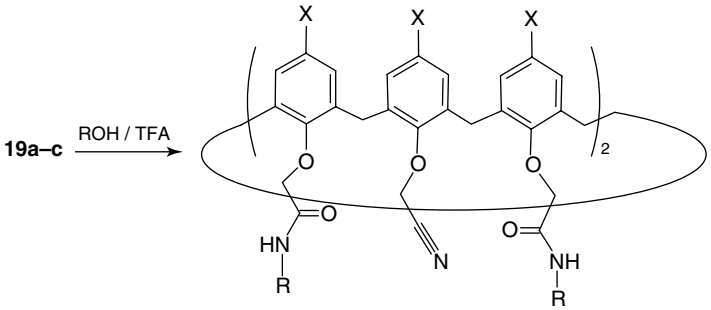
	R
a	H
b	CH_2COOH

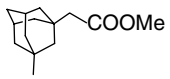
21



	R
a	H
b	CH_2COOH

22



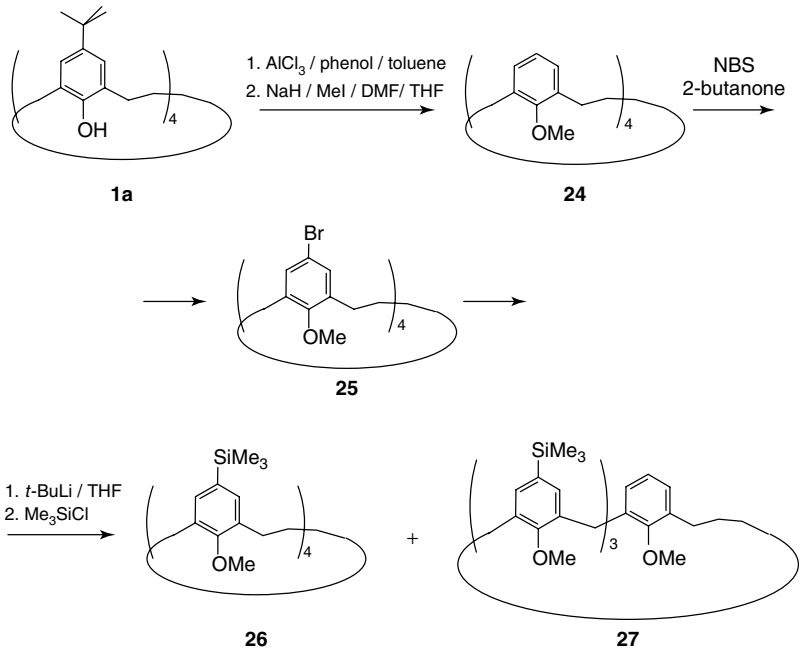
	R	X
a		*t*-Bu
b	*t*-Bu	*t*-Bu
c	*t*-Bu	
d	*t*-Bu	 COOMe

23

The reaction of **19a–c** bearing six cyanomethoxy groups showed an unexpected regioselectivity, since with adamantanol or *t*-butyl alcohol they afford tetramides **23**, adopting a flattened 1,2,3-alt conformation. This result, i.e. the selective functionalization of the narrow rim of calixarenes bearing exhaustively modified hydroxyl groups is rather surprising, because usually selective reactions occur in calixarenes with free hydroxyl groups.

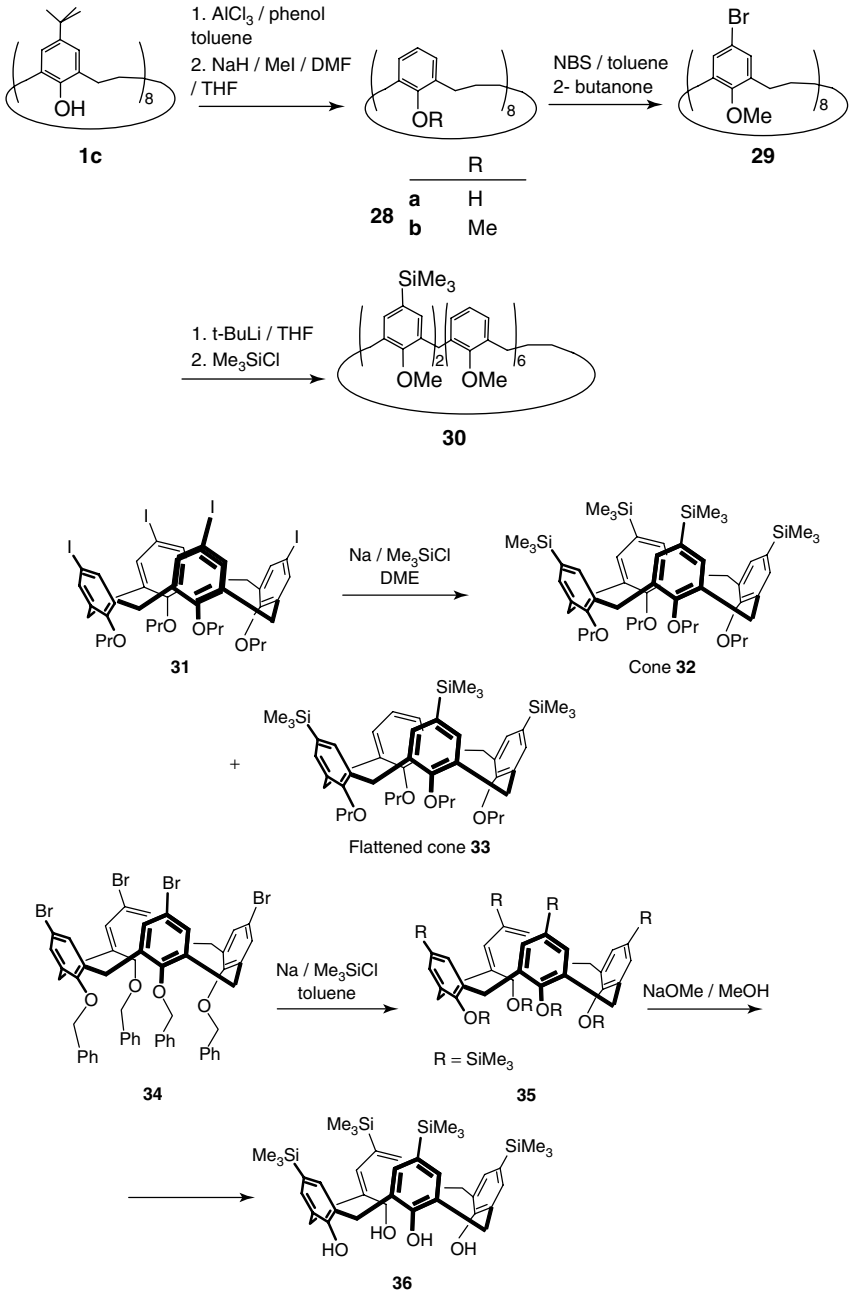
1.2
Functionalization of the Wide Rim

In order to obtain anion binding derivatives of calixarenes, syntheses of poly-Lewis-acid-based calixarenes have been studied. For this purpose, calix[4]arene **1a** was subjected to the removal of the *t*-butyl groups, followed by *O*-methylation to give **24**; its bromination afforded tetrabromocalix[4]arene **25**. The reaction of **25** with *t*-butyllithium gave the tetralithium salt, which without isolation was silylated with chlorotrimethylsilane affording tetrasilylated derivative **26** and the trisilylated derivative **27** [26]. However, the use of boron electrophiles after lithiation, e.g. boron trifluoride or boron trichloride instead of Me_3SiCl, resulted in only partial boronation.



In the next experiment, calix[8]arene **1c** was used. The removal of *t*-butyl groups from **1c** afforded **28a**, which was methylated to give **28b**. The subsequent bromination yielded **29**, which was lithiated, forming the octalithium salt; this without isolation was treated with Me_3SiCl, yielding **30**. It was shown that only partial silylation occurs, since only disilylated compound **30** was obtained [26].

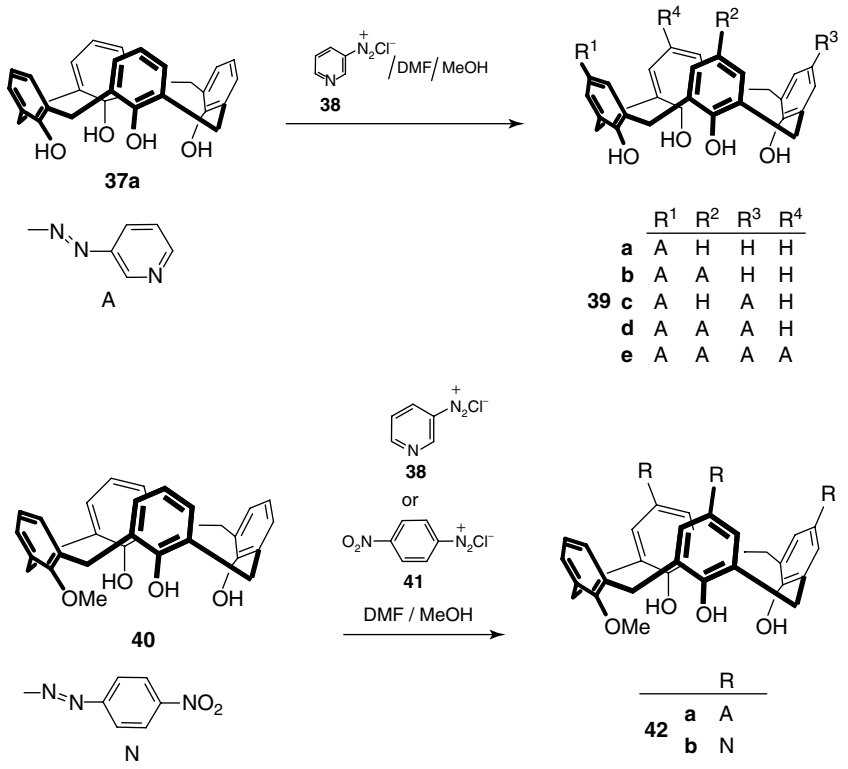
Tetraiodocalixarene **31** was subjected to the Wurtz–Fittig reaction with the use of Na/Me_3SiCl in 1,2-dimethoxyethane (DME), affording the mixture of tetrakis- and tris-silylated calixarenes cone **32** and flattened cone **33**, separated by chromatography. However, the reaction of tetrabromocalixarene **34** with Na/Me_3SiCl in toluene gave **35**, both C-silylated and O-silylated, which upon hydrolysis yielded tetrakis-silylated calixarene **36** [27].

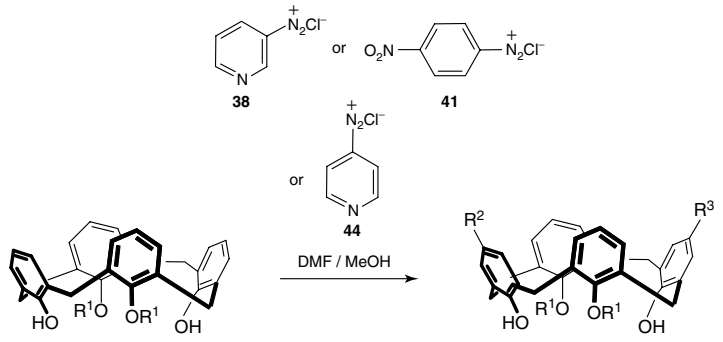


It should be noted that the above Wurtz–Fittig reactions are promising, since such large-scale processes are safer, cheaper, and easier to perform than those using *t*-butyllithium.

A series of calix[4]arenes with azo moieties containing four, three, two, and one free phenol groups, as well as those without free phenol groups, have been investigated in view of their conformational properties. Calixarenes with azo moieties, containing one to four free phenol groups were synthesized either by coupling calixarenes with corresponding diazonium salts or by reaction of calixarene diquinones with nitrosubstituted phenylhydrazines [28].

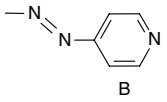
The coupling of calixarene **37a** with diazonium salt **38** [29] affords azosubstituted calixarenes containing four free phenol groups **39**; similarly, reactions of **40** with **38** and **41** yield azosubstituted calixarenes containing three phenol groups **42**. Similar reactions of calixarenes **43** with **38**, **41**, or **44** afford **45** containing two phenol groups. An alternative procedure, i.e. oxidation of **46** with ClO_2 leading to calix[4]arene diquinones **47**, subsequently treated with 4-nitro- and 2,4-dinitrophenylhydrazine, also gives rise to azosubstituted calixarenes containing two phenol groups **48**. The coupling of calixarenes **49** with diazonium salts **38** or **41** yields calixarenes **50a**,**b**, containing only one free phenol group.

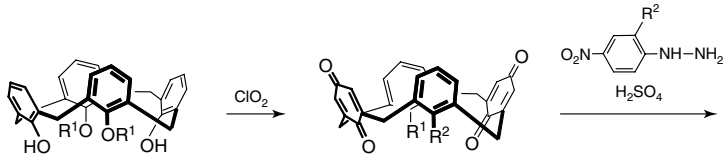




		R^1
43	**a**	CH_2COOEt
	b	Me
	c	COPh
	d	CH_2Ph

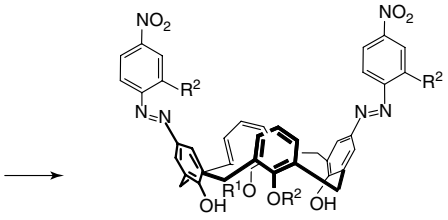
		R^1	R^2	R^3
45	**a**	CH_2COOEt	H	B
	b	CH_2COOEt	H	A
	c	CH_2COOEt	A	A
	d	Me	H	A
	e	Me	A	A
	f	COPh	N	N
	g	CH_2Ph	N	N



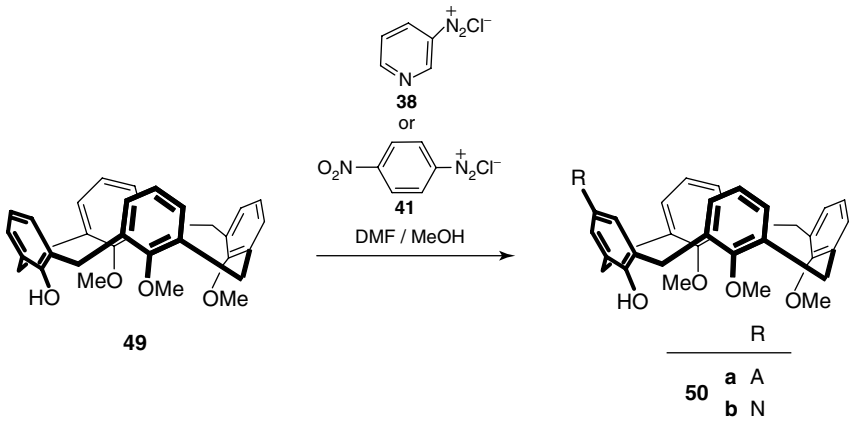


		R^1
46	**a**	COPh
	b	CH_2Ph

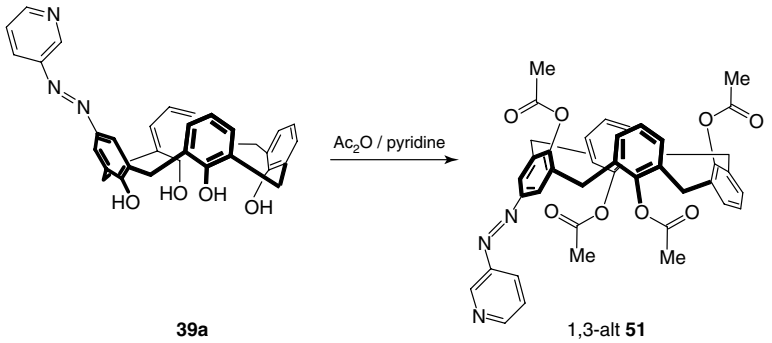
		R^1
47	**a**	COPh
	b	CH_2Ph

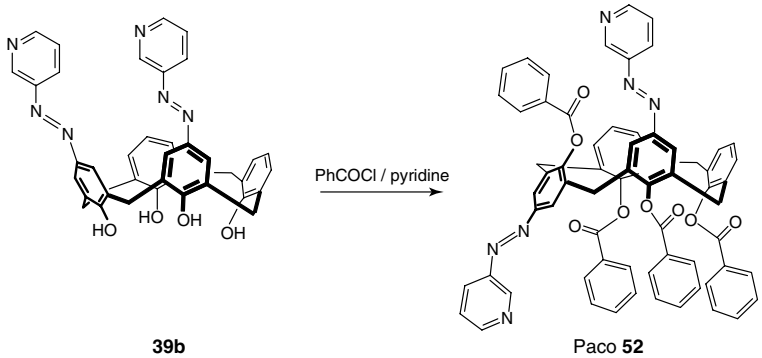


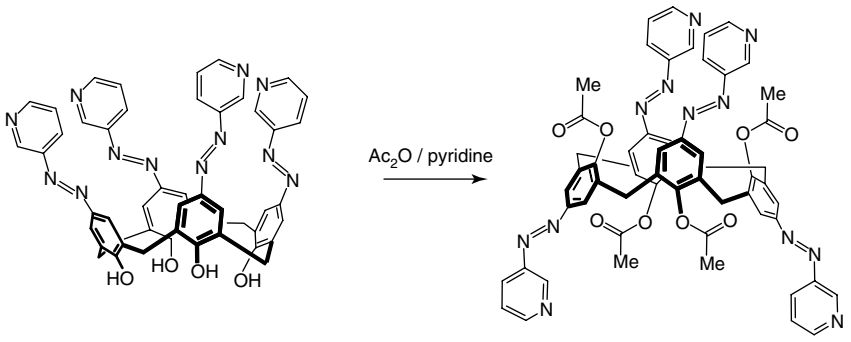
		R^1	R^2
48	**a**	COPh	H
	b	CH_2Ph	H
	c	COPh	NO_2
	d	CH_2Ph	NO_2



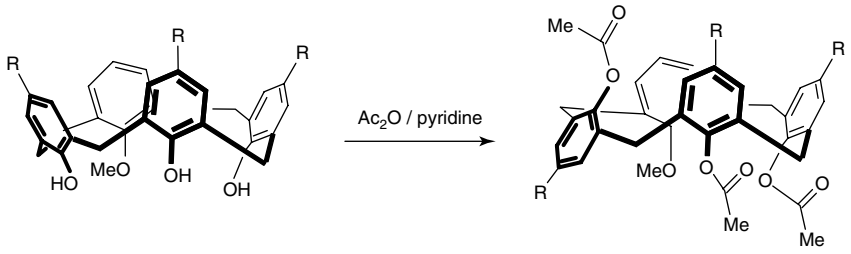
Acetylation and benzoylation of calixarenes bearing azo moieties were carried out for investigation of conformational changes that occur during these processes. In the study of calixarenes with four phenol groups, it was found that acetylation of cone **39a** affords 1,3-alt **51**, and benzoylation of **39b** gives rise to paco **52**. Acetylation of tetrasubstituted **39e** containing four phenol groups yields 1,3-alt **53** and acetylation of **42a,b** with three phenol groups leads to paco **54a,b**. Acetylation of **48a–d** containing two phenol groups affords calixarenes 1,3-alt **55**.





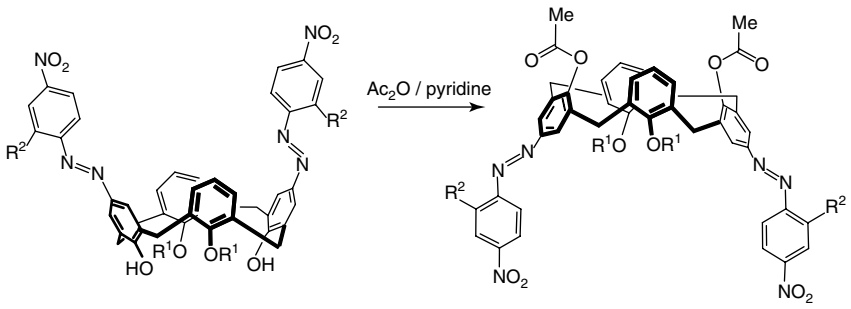


39e 1,3-alt **53**



		R
42	**a**	A
	b	N

		R
Paco **54**	**a**	A
	b	N



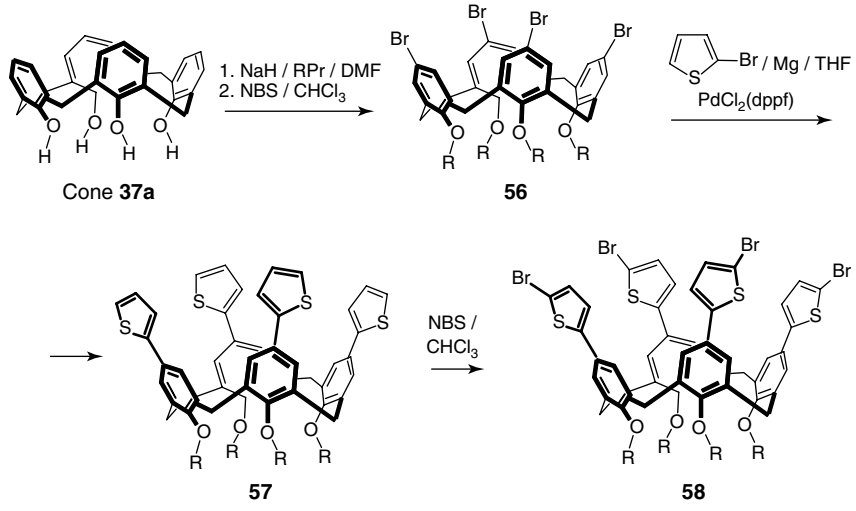
		R^1	R^2
48	**a**	COPh	H
	b	CH_2Ph	H
	c	COPh	NO_2
	d	CH_2Ph	NO_2

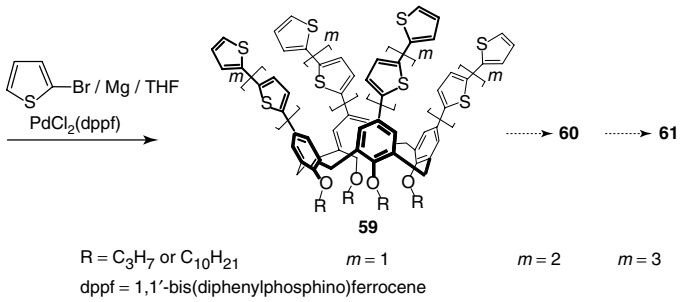
		R^1	R^2
1,3-alt **55**	**a**	COPh	H
	b	CH_2Ph	H
	c	COPh	NO_2
	d	CH_2Ph	NO_2

The conformational flexibility of calixarenes is usually explained by the presence of intramolecular hydrogen bonds, which is related to the number of free phenol groups. Accordingly, calixarenes containing four phenol groups **39a–e** exist as cone conformers.

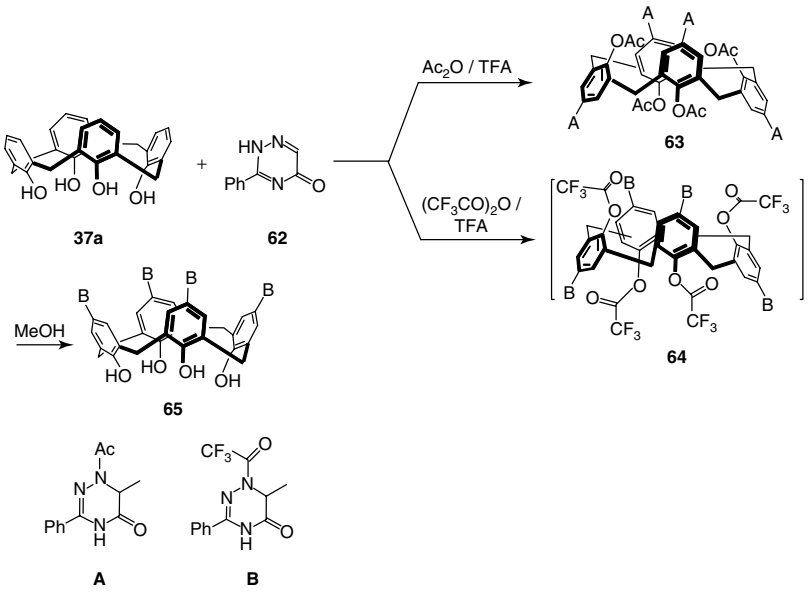
It could be expected that the conformational properties will be influenced by the decrease in the number of phenolic groups. However, it was shown that **42a**,**b** containing three phenol groups and **45a–g** containing two phenol groups also exist as cone conformers. One should note that calixarenes with two phenol groups, obtained by an alternate route via calix[4]arene diquinones **47a**,**b** present in their cone and paco conformations being in equilibrium with each other, afford **48a–d** as cone conformers. The results of single-crystal X-diffraction analysis of **50a**,**b** containing one phenol group indicate that they are present in a flattened cone conformation [28].

An efficient synthesis of oligothiophene-substituted calix[4]arenes was performed. The process begins with the stabilization of the cone conformation of cone **37a**, which involves the alkylation of calix[4]arene with bromopropane or bromodecane, followed by bromination with *N*-bromosuccinimide (NBS). The tetrabromoderivative **56** obtained was submitted to palladium-catalyzed Kumada cross coupling with thienylmagnesium bromide, prepared *in situ*, in the presence of $PdCl_2$(dppf) to give tetrathienyl calixarene **57**. The bromination of **57** with NBS yielded **58,** which, upon cross-coupling with thienylmagnesium bromide, afforded bisthienylcalixarene **59**. By repetition of such a sequence of bromination with NBS and cross-coupling reactions, tris(thienyl)- and tetra(thienyl)calixarenes **60** and **61** were obtained respectively [30]. The electrochemical and optical properties of synthesized oligothiophene-substituted calix[4]arenes **59–61** were determined. It should be noted that they show high thermal stability ($T_d > 400^\circ C$).

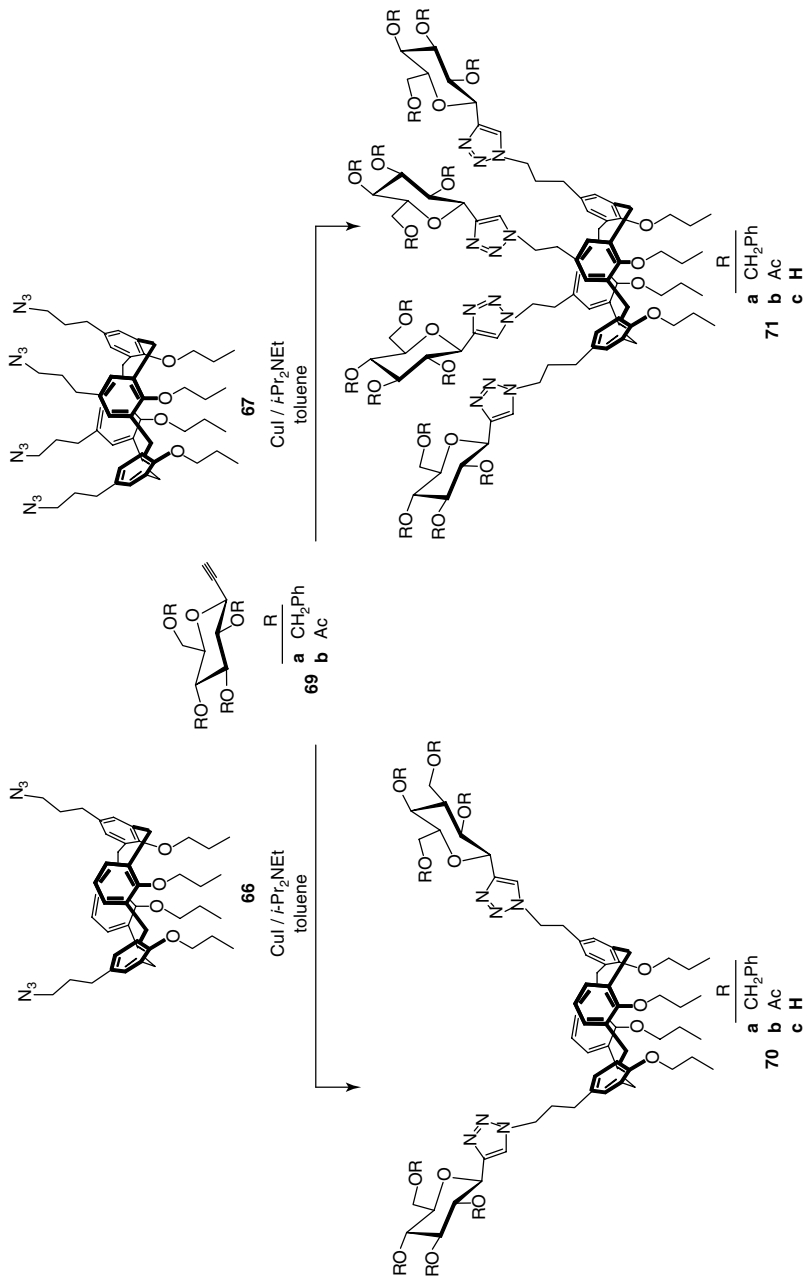




The heteroarylation of calix[4]arene **37a** at the wide rim was performed in a one-step procedure as an example of the direct C–C coupling of calixarene with electron-poor 1,2,4-triazinone **62** via the $S_N{}^H$ methodology. The reaction can be performed in trifluoroacetic acid (TFA) in the presence of acylating agents, such as acetic or trifluoroacetic anhydrides. Treatment of **62** with acetic or trifluoroacetic anhydride in TFA yields a protonated form of 2-acyl-1,2,4-triazinone. The process is accompanied by the rearrangement of the *N*(2)-acyl derivatives to those bearing the acyl group at the *N*(1) atom, adjacent to the reaction center [31].

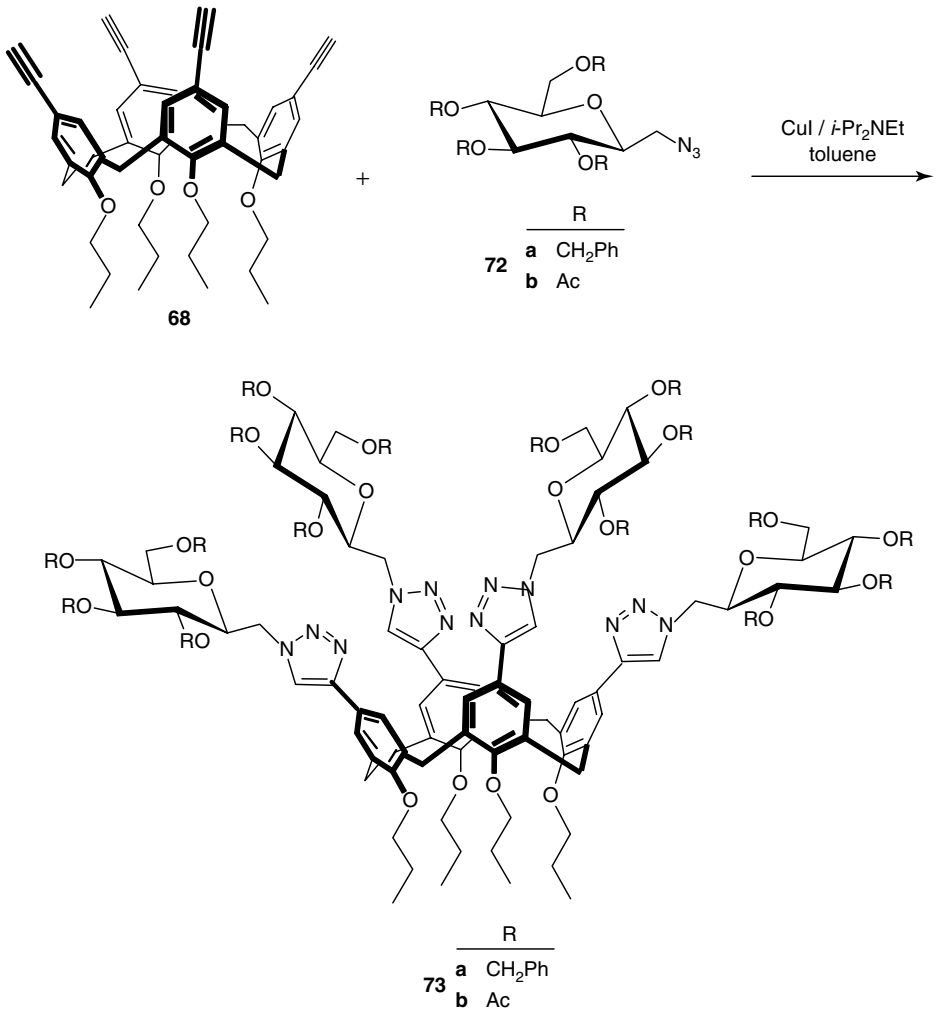


Organic anhydrides acylate hydroxyl groups of calixarene **37a** and change its conformation from cone into 1,3-alternate. The nature of the acylating agent influences the stereochemistry of the reaction of **37a** with **62**. Thus, in the presence of Ac_2O, the 1,3-alt calixarene **63** is formed, whereas reaction with $(CF_3CO)_2O$ and the subsequent recrystallization from MeOH gives, via the 1,3-alt intermediate **64**, the cone calixarene **65**. It is noteworthy that **63** and **65** effectively transport La^{3+} ions.


66
CuI / i-Pr2NEt
toluene
69 a CH2Ph
b Ac
67
CuI / i-Pr2NEt
toluene
70 a CH2Ph
b Ac
c H
71 a CH2Ph
b Ac
c H

The glycoside cluster effect exists in the carbohydrate–protein interaction, an important process in intercellular communication and in the adhesion of bacteria and viruses to the cell surface. For a better understanding of this effect, the glycocluster assemblies on calix[4]arene scaffold were synthesized.

The 1,2,3-triazole linkers have been formed via click chemistry, i.e. the copper (I)-catalyzed Huisgen 1,3-dipolar cycloaddition of azides to alkynes [32]. Calixarenes **66** and **67** bearing azido units, as well as calixarene **68** containing ethynyl groups, were used as starting materials. The reaction of **66** and **67** with ethynyl glycoside **69** afforded glycoclusters **70** and **71**. The reaction of **68** with azidomethylglucoside **72** yielded glycocluster **73**. It should be noted that the formation of 1,4-disubstituted triazole rings resulted in very high yield [33].

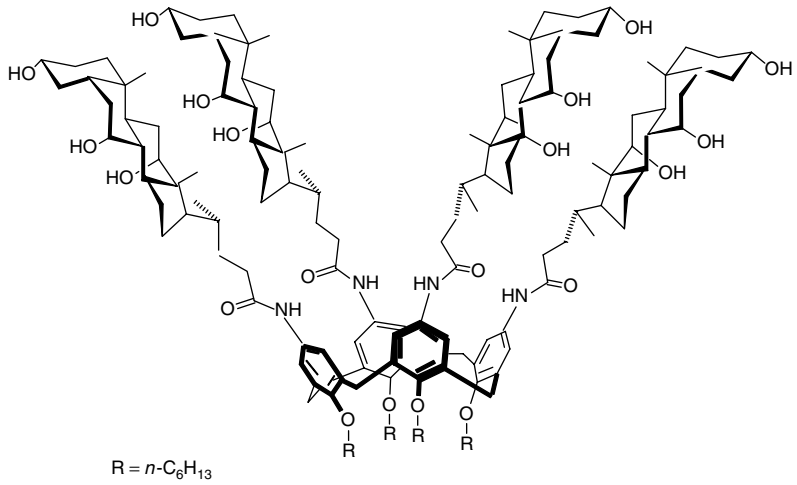


Cholic acid is being used as a building block for the construction of conformationally controllable foldamers [34] and nonfoldamers [35]. It was established that calixarene **74** can reversibly switch between a micelle-like conformation (with the hydrophilic faces of cholates pointing outward) in polar environments and a reversed-micelle-like conformation in nonpolar environments [36]. As a result of the conformational change, **74** can act as a tunable supramolecular host to bind polar guests in nonpolar solvents and nonpolar guests in polar solvents.

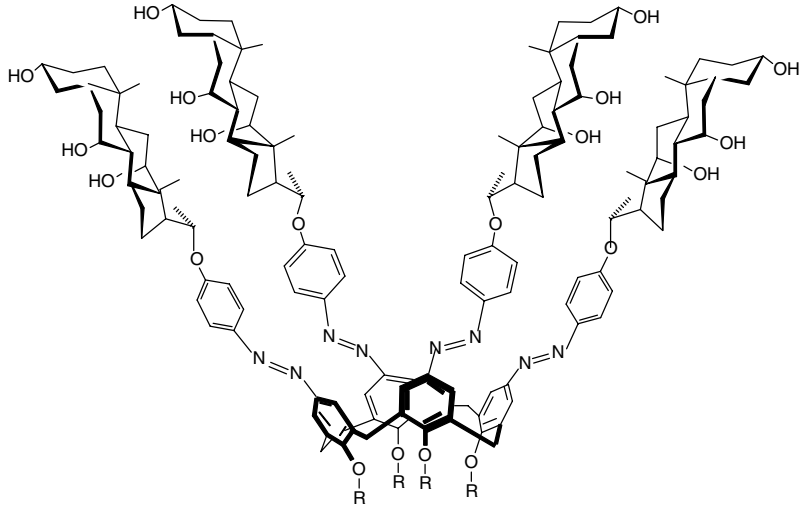
The amphiphilic calixarene **75** containing cholate units linked by azobenzene spacers was synthesized. It was sensitive both to solvent changes (due to cholate units) and ultraviolet (UV) irradiation (due to azobenzene units). In nonpolar solvents, **75** turns its polar faces inward to bind polar guests, e.g. sugar derivatives. In polar solvents, **75** turns its nonpolar faces inward to bind hydrophobic guests, e.g. pyrene. Calixarene **75** can also respond to UV irradiation, resulting in the trans – cis isomerization of azobenzene units; it should be noted that the response toward both kinds of solvents and UV light is fully reversible [37].

Many calixarenes bearing azobenzene units on the wide rim are known [38]. The synthesis of **75** begins with the diazotization of calixarene **76** followed by coupling with phenol to give calixarene **77**, which upon reaction with brominated cholate **78** affords **75**.

In the study of guest-binding properties of **75**, it was observed that, in 5% CD_3OD/CCl_4, i.e. a mostly nonpolar mixture, **75** binds phenyl β-D-glucopyranoside **79**. The binding of polar guests in a nonpolar mixture shows that **75** can adopt reversed-micelle-like conformations similar to that of **74**.

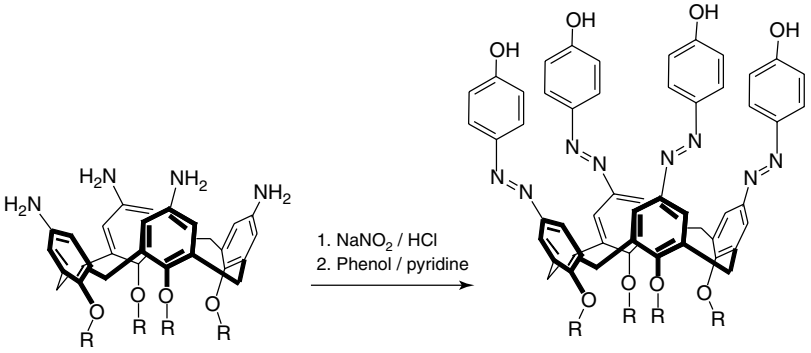


74



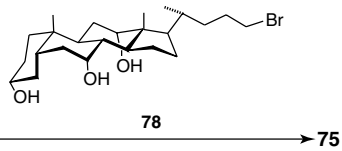
R = *n*-C_6H_{13}

75

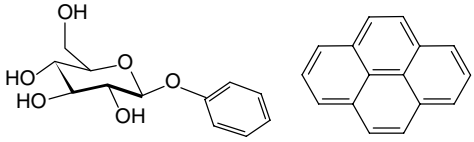


R = *n*-C_6H_{13}

76 **77**



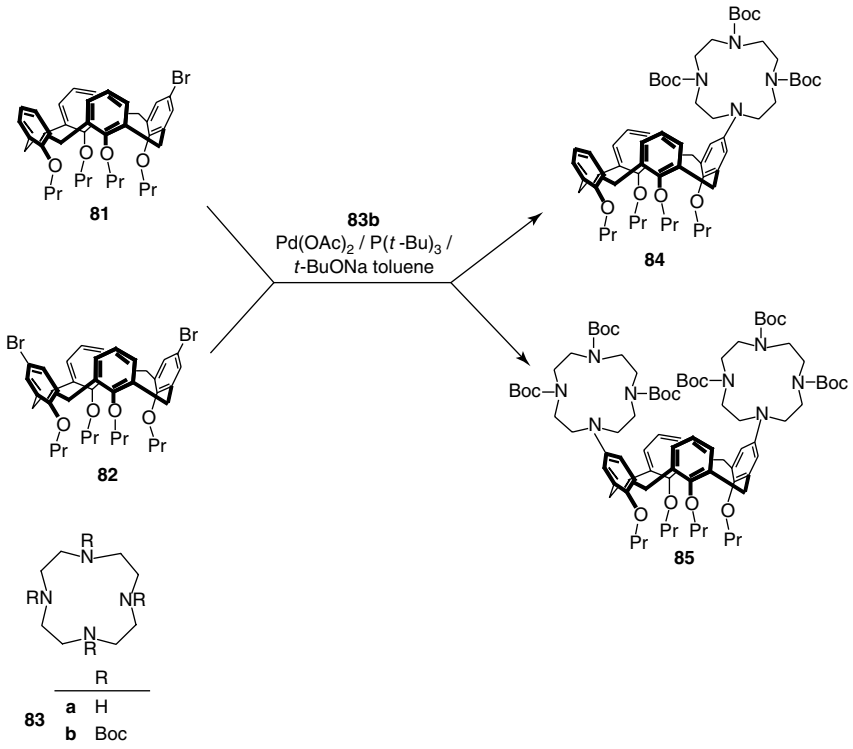
78 → **75**

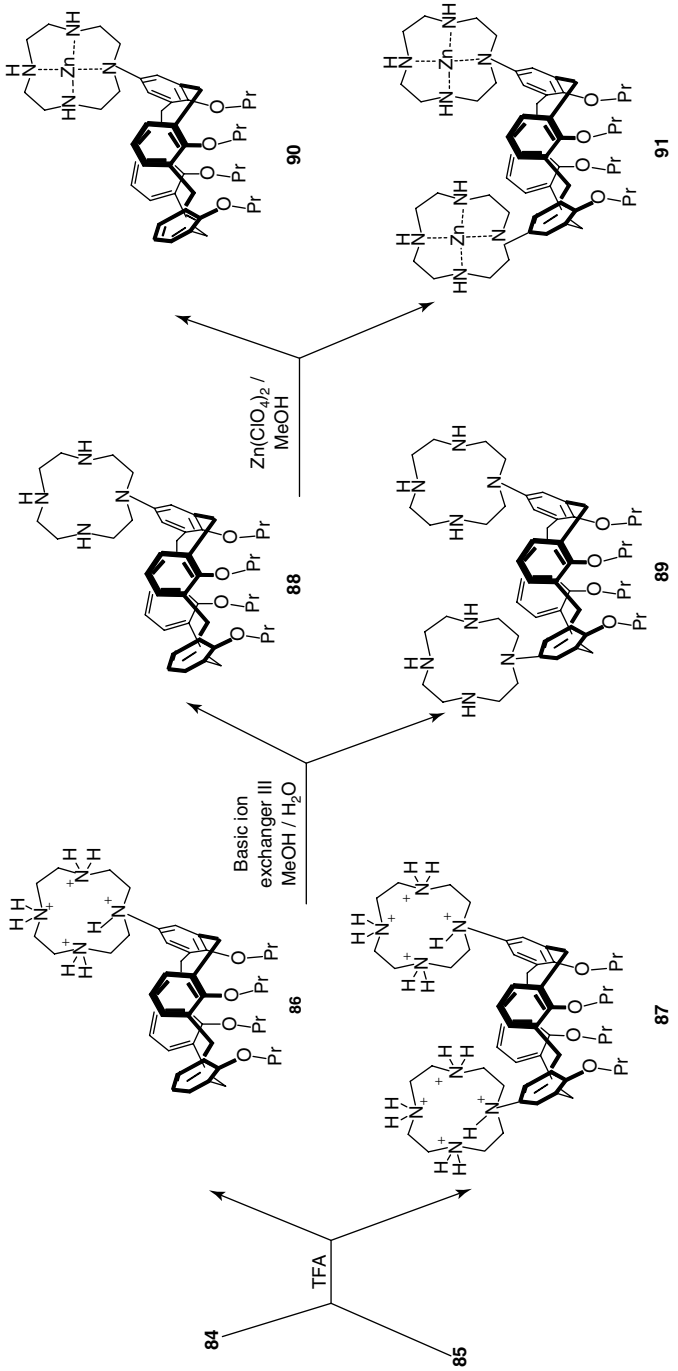


79 **80**

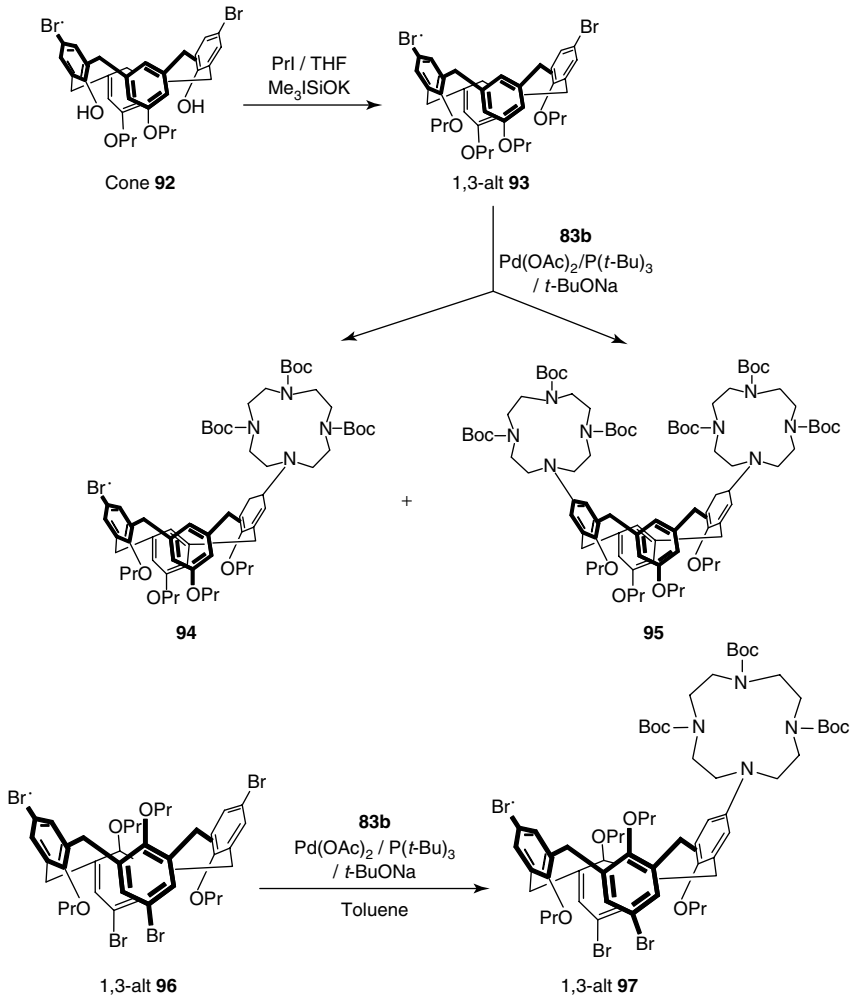
It was found that pyrene **80** is a suitable guest for the micelle-like conformer. In methanol, **74** and **75** bind with pyrene through the hydrophobic faces of cholates, supporting the formation of micelle-like conformations in polar solvents. The above experiments combining the solvent-induced conformational changes and photoisomerization of **75** show their dual responsive properties.

The palladium-catalyzed Buchwald–Hartwig procedure was used for the synthesis of cyclenylcalixarenes [39]. Monobromo- and dibromocalixarenes **81** and **82** reacted with threefold Boc-protected cyclen **83b** in the presence of catalytic amount of $Pd(OAc)_2$ and tris(*t*-butyl)phosphine affording mono- and biscyclenylcalixarenes **84** and **85** respectively. It should be mentioned that cyclen **83a** was Boc-protected to give **83b** in order to avoid the connection of more calixarene units on its molecule. The Boc-protective groups were removed from **84** and **85** in the presence of TFA to give *N*-protonated mono- and biscyclenylcalixarenes **86** and **87**. They were basified with a basic anion exchanger affording mono- and biscyclenylcalixarenes **88** and **89**, which upon treatment with $Zn(ClO_4)_2 \cdot 6H_2O$ yielded metallated compounds **90** and **91** [39].




TFA
Basic ion exchanger III MeOH / H2O
Zn(ClO4)2 / MeOH
84
85
86
87
88
89
90
91

In order to investigate the influence of conformation of starting materials on the Buchwald–Hartwig process, cone dibromocalixarene **92** was alkylated with 1-iodopropane in tetrahydrofuran (THF) using Me_3SiOK as a base to give 1,3-alt **93**, which was treated with **83b**. This reaction afforded mono- and biscyclenylcalixarenes **94** and **95**, both as 1,3-alt conformers.



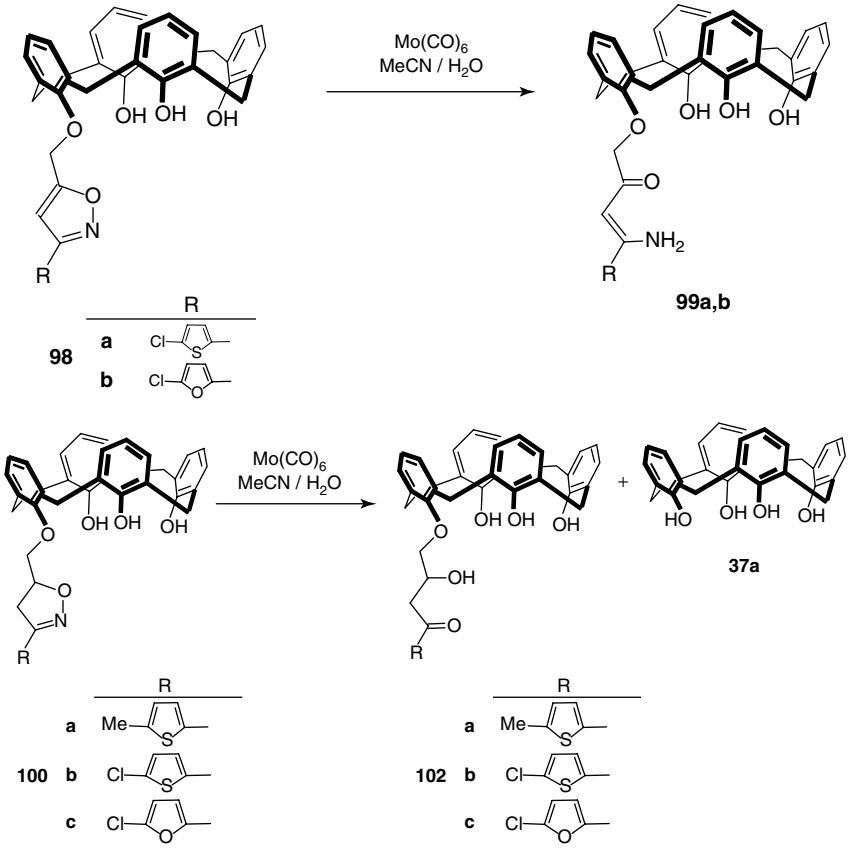
It is worth noting that the 1,3-alt tetrabromocalixarene **96** does not form calixarene containing four cyclen units, but the reaction of **96** with **83b** leads to 1,3-alt monocyclenylcalixarene **97**. This fact results from the increased steric hindrance of the 1,3-alt system, since the presence of one bulky tri(Boc)cyclen unit at the wide rim of calixarene molecule causes the outstretching of two of its neighboring propoxy groups. As a consequence, two bromine atoms present at the narrow rim are located closer to each other, making their substitution impossible. This

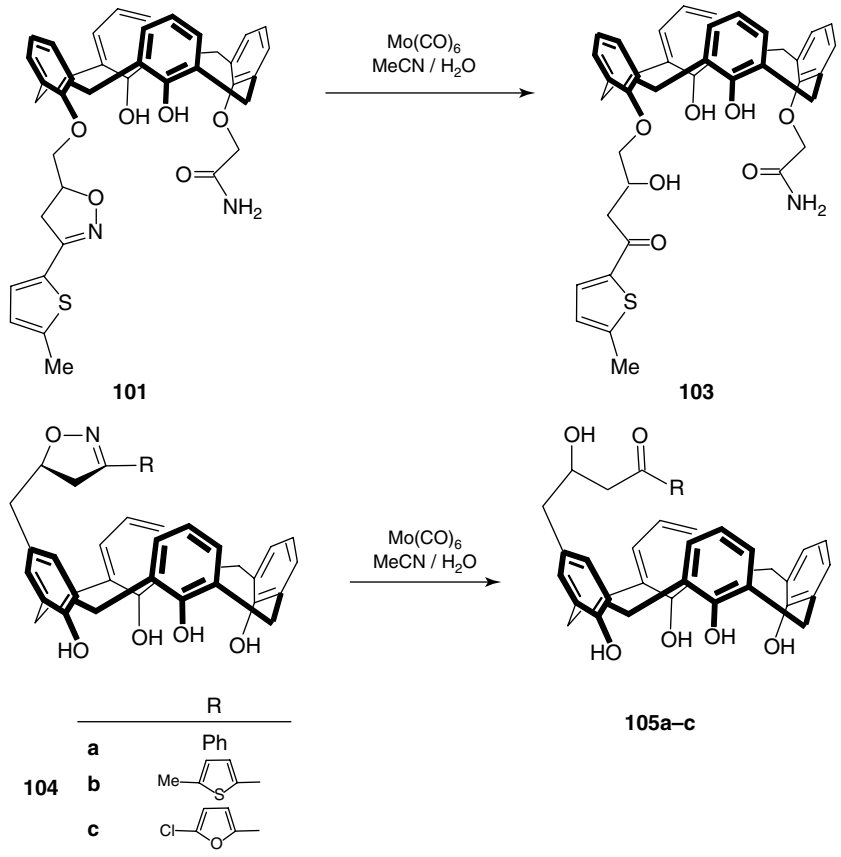
behavior resembles a complexation-induced negative allosteric effect observed in some 1,3-alt calixarenes. It should be noted that calixarene **90** shows binding affinity to chloride, acetate, and benzoate anions, forming 1:1 complexes with them.

1.3
Functionalization of Both Rims

Calixarenes bearing isoxazole or isoxazoline substituents undergo $Mo(CO)_6$-mediated opening of the heterocyclic ring to give calixarene derivatives containing α, β-unsaturated β-aminoketone or β-hydroxyketone units respectively [40, 41].

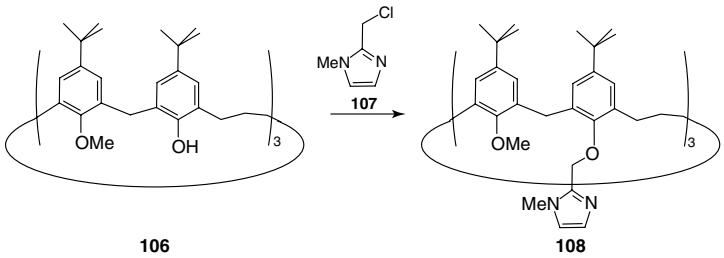
Calixarenes **98** bearing isoxazole units at the narrow rim afford compounds **99**. Calixarenes **100** and **101** bearing isoxazoline units at the narrow rim yield products **102** and **103** respectively; in the former case also, the cleaved calixarene **37a** is obtained. Calixarenes **104a–c** bearing isoxazoline moiety at the wide rim undergo a similar reaction, leading to **105a–c**. The ^{1}H NMR results have shown the cone conformation for all calixarenes studied.





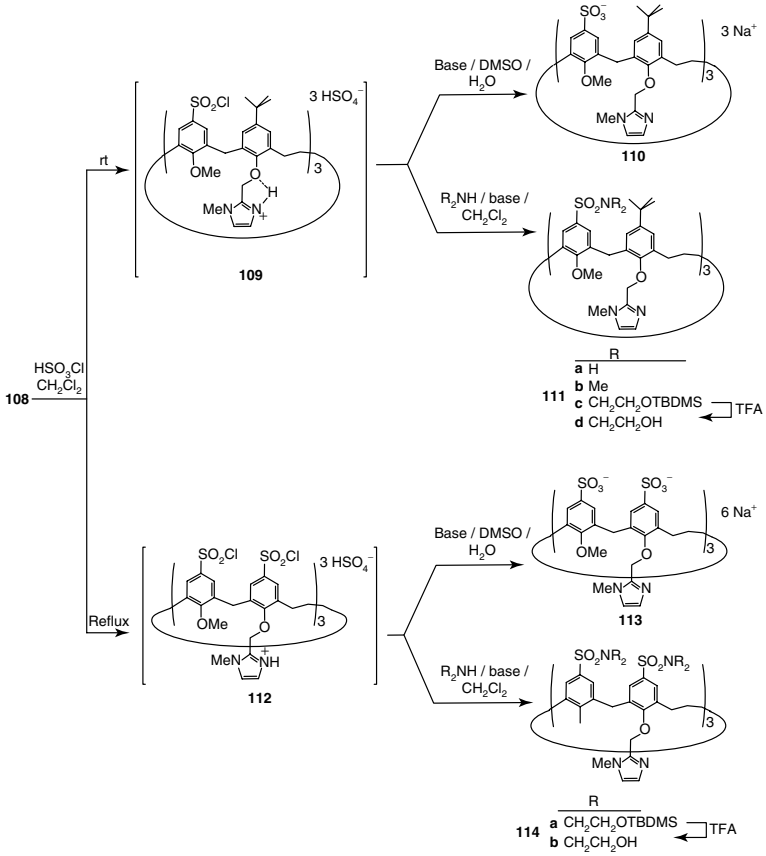
By investigating models of metalloenzymes, it was found that calixarene **106** treated with imidazole **107** affords derivative **108** containing three imidazolyl arms at the narrow rim, which mimics the coordination core encountered in enzymes. Upon binding a transition-metal ion, such calixarenes are constrained to a cone conformation, thus mimicking the enzyme funnel that controls the access to the metal center [42].

In the search for supramolecular models of metalloenzyme sites, the replacement of *t*-butyl groups by electrophilic substituents has been performed on the basis of an example of *ipso*-chlorosulfonylation [42]. When aromatic rings were *O*-substituted by a protonable imidazole units, they became deactivated toward an electrophilic attack, and therefore the anisole rings could be selectively *ipso*-chlorosulfonylated under mild conditions at room temperature. The regioselectivity was controlled by the presence of protonable imidazole units at the narrow rim. The process is selective and highly efficient.



106 **108**

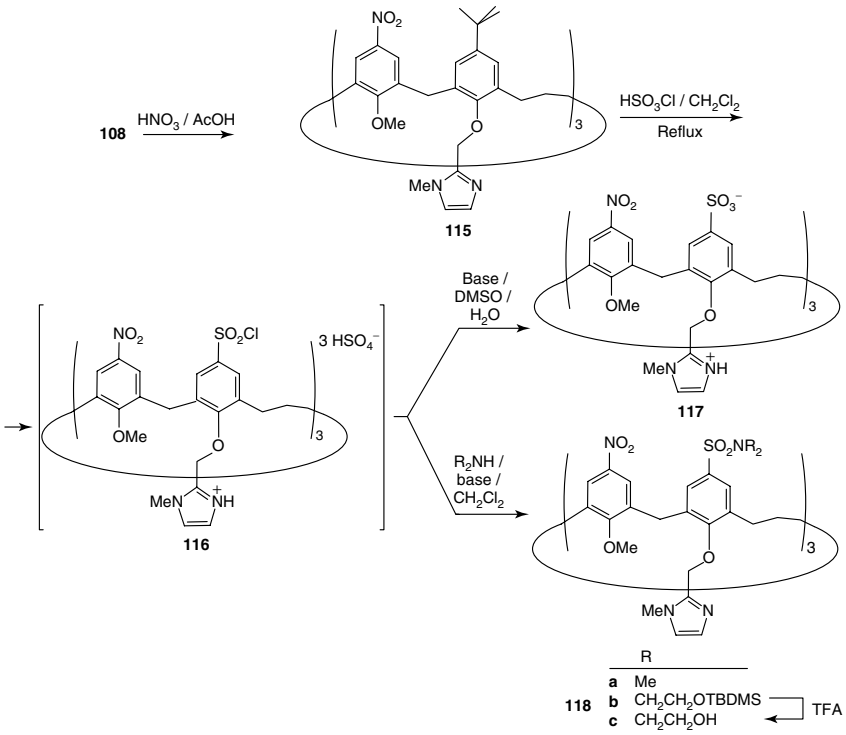
It was established that treatment of **108** with chlorosulfonyl acid at room temperature leads to the formation of the intermediate **109**, which upon hydrolysis yields the sulfonate derivative **110**, and gives sulfonamide derivatives **111a–d** with amines. The reactions of **109** were performed with NH_3, $NHMe_2$, and *t*-butyldimethylsilyl (TBDMS)-protected diethanolamine; in the latter case, the deprotection with TFA was necessary to obtain **111d** [42]. The above reactions of **108** are useful for the synthesis of calixarenes selectively functionalized at the wide rim, and cause water solubilization of obtained products.

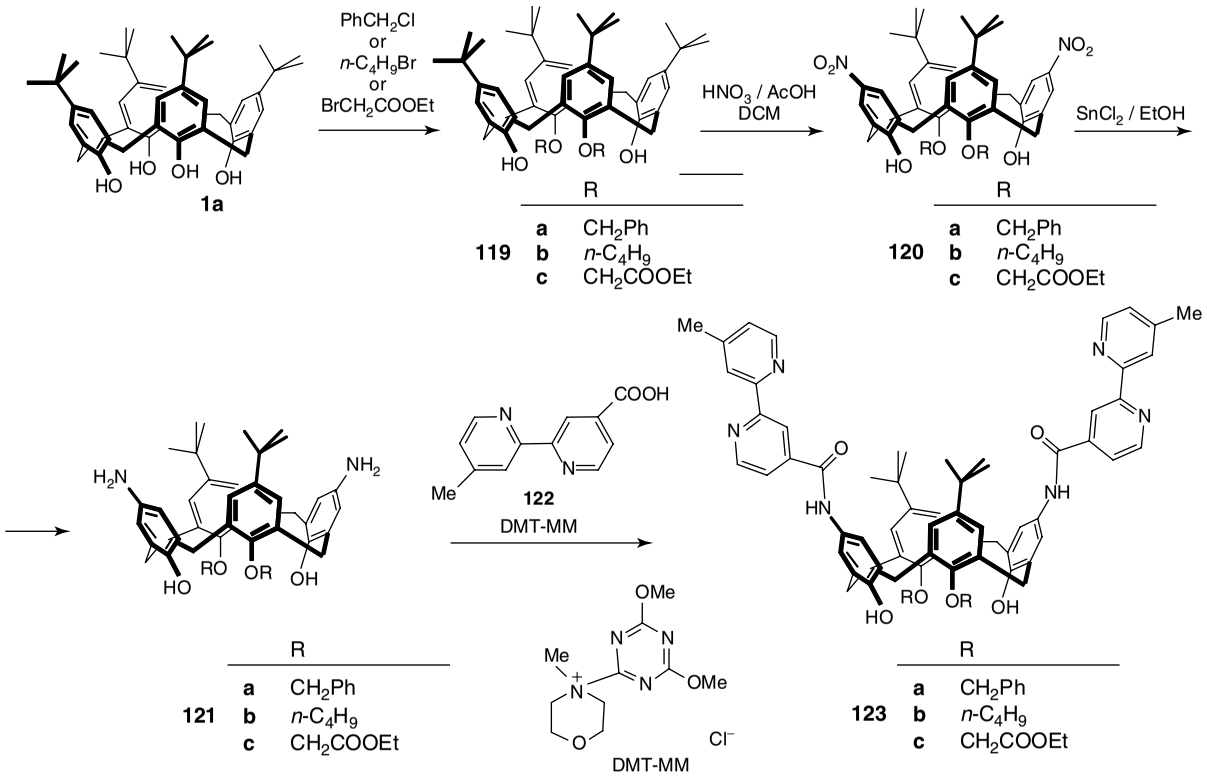


When reaction of **108** with chlorosulfonyl acid is carried out at a higher temperature (reflux of CH_2Cl_2), perchlorosulfonylation, leading to hexachlorosulfonyl calixarene **112**, takes place. Similarly, hydrolysis of **112** affords the hexaanion **113**, and reaction with TBDMS-protected diethanolamine leads to **114a**, deprotected to **114b**.

It should be noted that hexaanion **113** cannot be constrained to the desired cone conformation due to the strong repulsion at the wide rim. In order to avoid perchlorosulfonation, in the synthesis of **110** and **111** only three benzene rings were sulfonated by carrying out the reaction at room temperature.

The reaction of **108** with HNO_3 in the presence of AcOH yields the product of *ipso*-nitration **115**. This process may be combined with chlorosulfonylation of **115**, leading to the *ipso*-chlorosulfonylation product **116**. Hydrolysis of **116** afforded tris-sulfonate derivative **117**, and the reaction of **116** with $NHMe_2$ and TBDMS-protected diethanolamine gave tris-sulfonamides **118** [42].




PhCH2Cl
or
n-C4H9Br
or
BrCH2COOEt
HNO3 / AcOH
DCM
SnCl2 / EtOH
1a
119
120
121
123
R
a CH2Ph
b n-C4H9
c CH2COOEt
122
DMT-MM
DMT-MM
Cl−

The functionalization of narrow and wide rims of calixarene **1a** has been performed. Reaction of **1a** with benzyl chloride, 1-bromobutane, or ethyl bromoacetate affords calixarenes **119**, substituted on the narrow rim, which upon nitration yield dinitro calixarenes **120**.

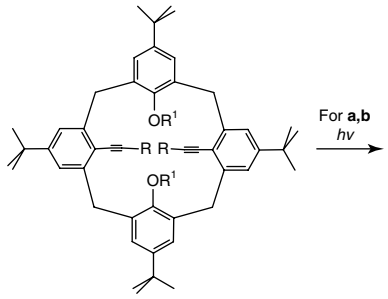
Reduction of **120** with $SnCl_2$ leads to the formation of diaminocalixarenes **121**. These compounds were treated with 2,2′-bipyridine **122** in the presence of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM) as condensing agent to give calixarenes **123** substituted on the wide rim [43].

1.4 Bridging of Calixarenes

In the study of photochemical reactions of calixarenes [44, 45], the photochemical cycloisomerizations of calixarenes containing phenylethynyl groups have been investigated. Calixarenes **124** serve as an example. they undergo photochemical cycloisomerization to give **125**. It was found that the attempted second photochemical reaction, which should have led to **126a,b,** did not occur; instead **127a,b** was formed [46]. One should mention that molecular mechanics modeling has shown that **126a,b** are highly strained.

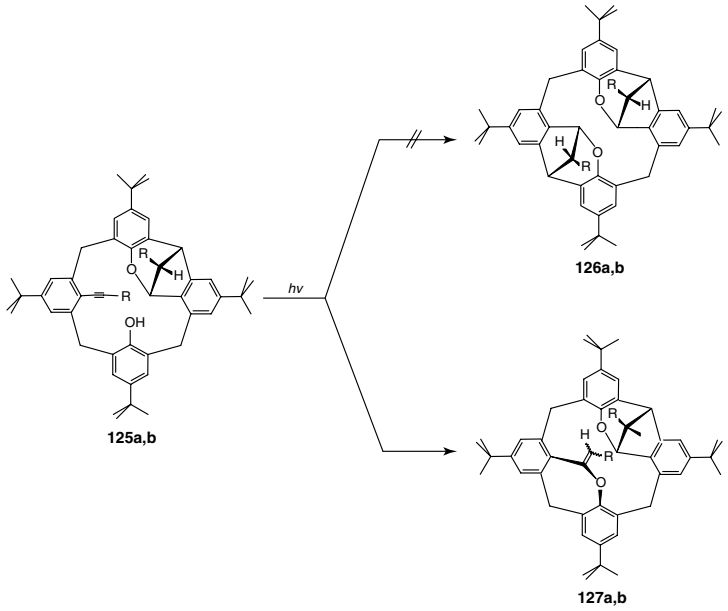
It was observed that the presence of hydroxyl groups in starting compounds is necessary for the above photocyclization/rearrangement reactions. This was confirmed by the fact that the photoirradiation of **124c,d** containing *O*-propyl groups instead of hydroxyl groups did not result in the formation of desired products.

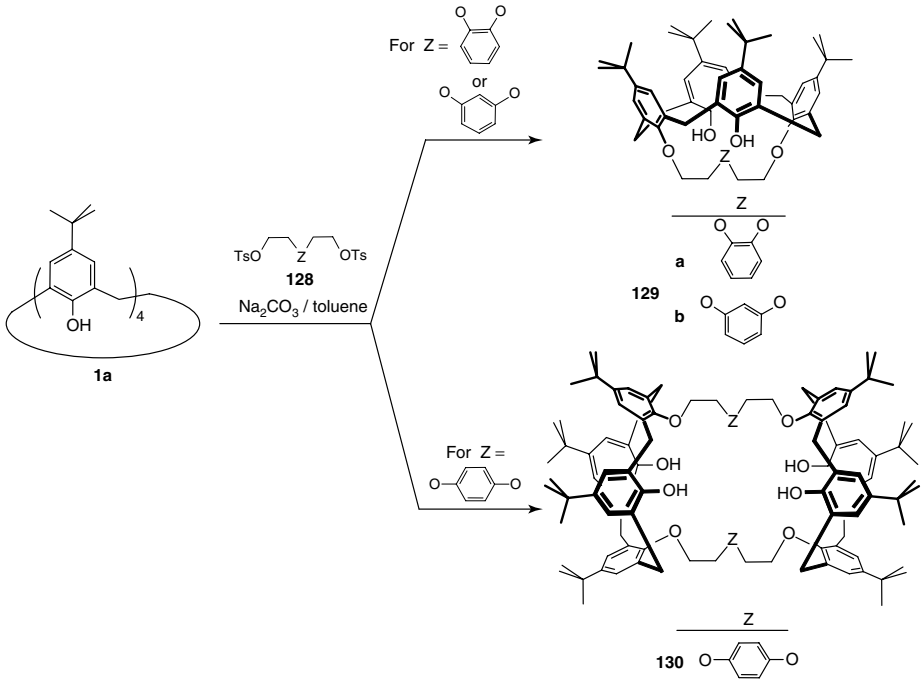
The above reactions are assisted by the templating effect of the calixarene scaffold; their mechanism is proposed. It should be noted that these reactions are rare examples of intramolecular cyclizations of calixarenes containing alkynyl groups.



124

	R	R^1
a	Ph;	H
b	4-C_6H_4-CF_3	H
c	Ph	*n*-Pr
d	4-C_6H_4-CF_3;	*n*-Pr

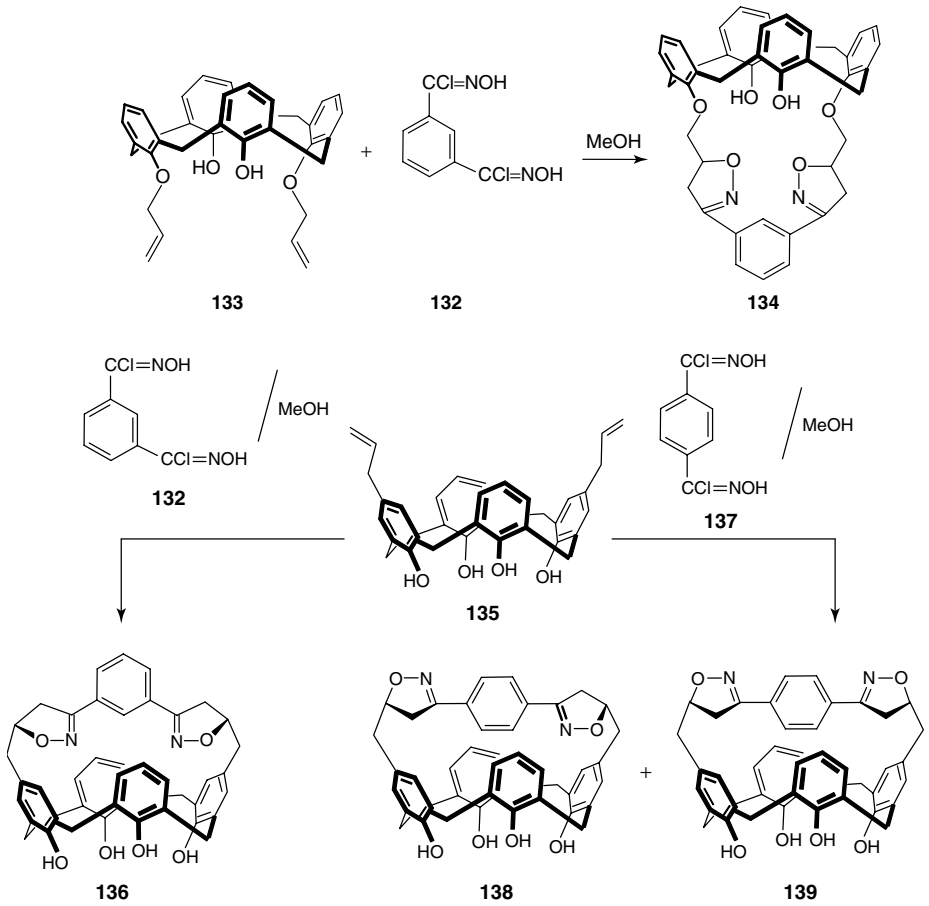

R
O
H
R
OH
hv
125a,b
126a,b
127a,b

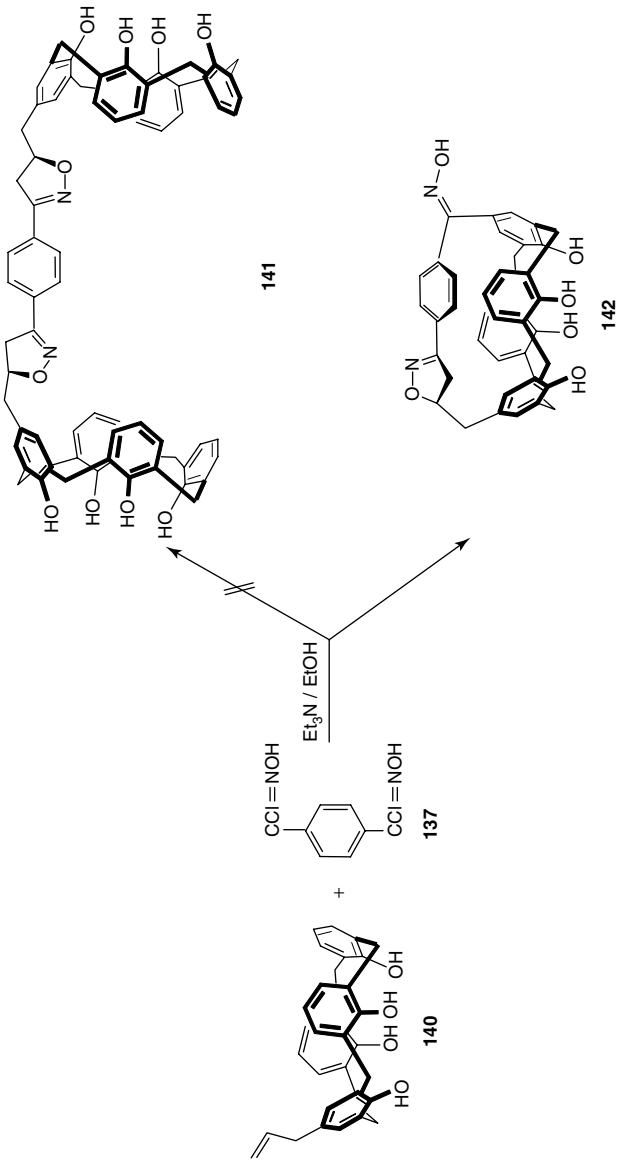

For Z =
or
OH
4
1a
TsO
Z
OTs
128
Na2CO3 / toluene
HO
OH
Z
129
a
b
For Z =
130

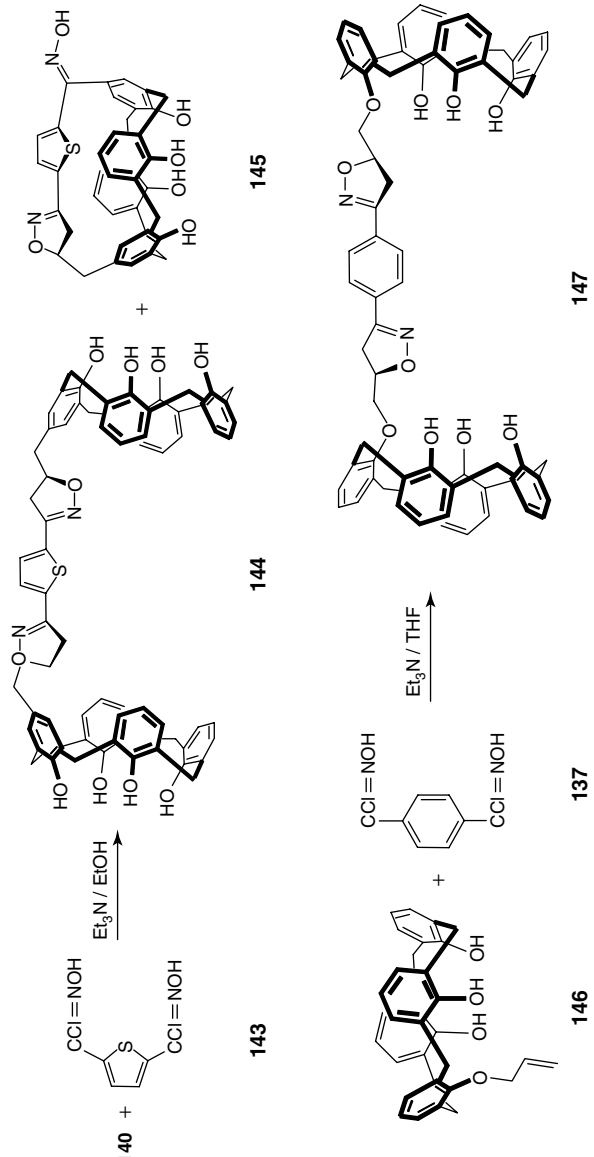
Calixarene **1a** reacts with bis(tosylethoxy)benzenes **128** to give intramolecularly bridged calixcrowns **129a**,**b**, and intermolecularly bridged biscalixcrown **130**. Calixcrowns **129a** and **129b** of 1:1 stoichiometry are formed from ortho and meta isomers of **128**, while **130** of 2:2 stoichiometry is obtained from the para isomer of **128** [47].

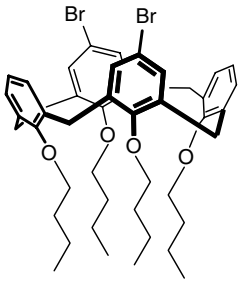
The bridging of calixarenes bearing allyl substituents on narrow or wide rims has been reported. This process occurs by 1,3-dipolar cycloaddition reactions, with benzodinitrile oxides **131** serving as bis-1,3-dipoles; benzodinitrile oxides are formed *in situ* from benzodihydroximoyl chlorides e.g. **132** [48].

In the study of diallylcalixarenes, it was observed that the reaction of **133** with isophthaldinitrile oxide (in the form of **132)** affords calixarene **134** bridged at the narrow rim; a similar reaction of **135** with **132** yields calixarene **136**, bridged at the wide rim. When **135** reacted with terephthaldinitrile oxide (in the form of **137**), the diastereomers **138** and **139** were obtained.



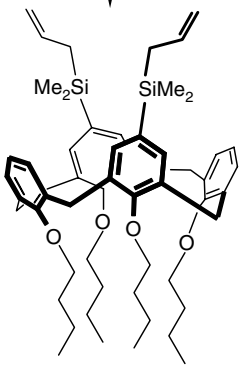

OH
OH
OH
OH
O
N
O
N
HO
HO
HO
HO
141
N
OH
OH
OH
OH
HO
142
Et3N / EtOH
CCl=NOH
CCl=NOH
137
+
OH
OH
OH
HO
140


Et3N / EtOH
Et3N / THF
CCl=NOH
CCl=NOH
140
143
144
145
137
146
147



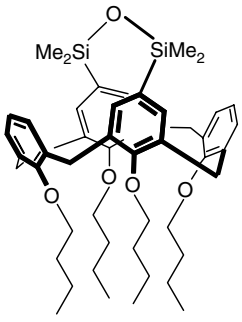
148

1. *t*-BuLi / THF
2. (Allyl)Me_2SiCl / Et_3N



149

TBAF / THF

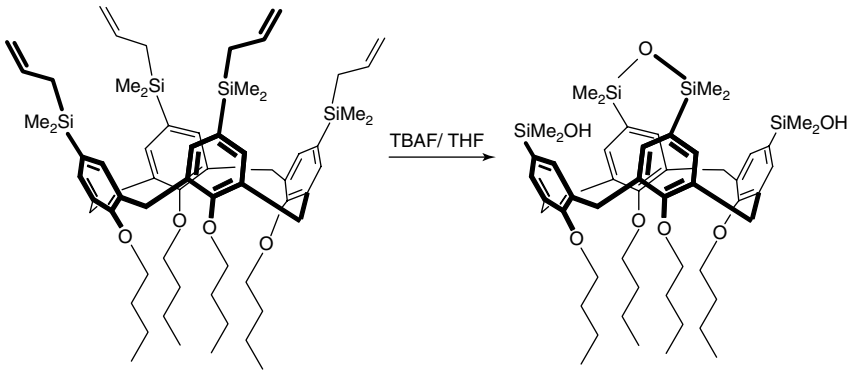


150

By investigating monoallylcalixarenes, it was found that the reaction of **140** bearing the allyl group at the wide rim with terephthaldinitrile oxide **137** did not give the expected biscalixarene **141**; instead the asymmetric calixarene **142** bearing isoxazoline and oxime moiety was formed.

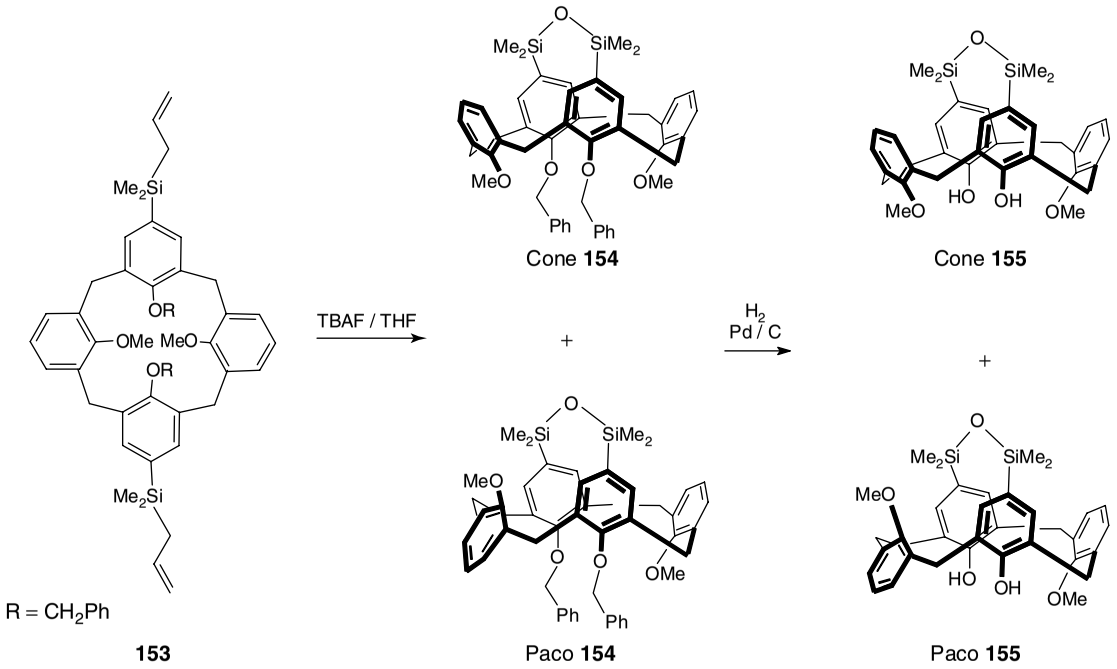
However, the reaction of **140** with thiophene-2,5-dinitrile oxide (in the form of **143**) afforded the desired biscalixarene **144** along with isoxazoline-oxime compound **145**. The reaction of monoallylcalixarene **146**, bearing the allyl group at the narrow rim yielded biscalixarene **147**, as expected.

Bridging of allyldimethylsilylated calixarenes, which leads to the formation of a Si–O–Si siloxane link, was investigated [49]. The reaction of **148** with *t*-BuLi, followed by (allyl)Me_2SiCl, afforded calixarene **149** bearing two allyldimethylsilyl groups; **149** upon treatment with tetrabutylammonium fluoride (TBAF) in THF yielded bridged calixarene **150**. Calixarene **151** containing four allyldimethylsilyl groups afforded the bridged compound **152** via a similar reaction with TBAF. Both bridged products **150** and **152** have the flattened cone conformation.



151 **152**

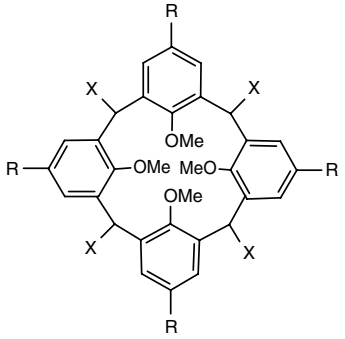
The reaction of calixarene **153** with TBAF gave rise to bridged compounds **154** obtained as a mixture of cone and paco conformers. Removal of benzyl groups by hydrogenation in the presence of Pd/C yielded dihydroxycalixarenes **155**, also as a mixture of cone and paco conformers. This result was unexpected because usually the presence of hydroxyl groups, allowing the hydrogen bonding, favors the formation of the cone conformer exclusively; in this case, however, presumably the presence of the siloxane bridge increased the barrier of the conformational change. Both cone and paco **155** were separated by chromatography [49].


Me2Si
OR
OMe MeO
OR
Me2Si
R = CH2Ph
153
TBAF / THF
O
Me2Si
SiMe2
MeO
OMe
O
O
Ph
Ph
Cone 154
+
Paco 154
H2
Pd / C
HO
OH
Cone 155
+
Paco 155

1.5
Other Reactions of Calixarenes

Contrary to many modifications of narrow and wide rims of calixarenes, the monofunctionalization of four methylene bridges of calixarenes is rather rare [50]; the following reactions of **156a**,**b** may serve as examples. For this purpose, calixarenes **156a**,**b** were brominated with NBS to give **156c**,**d**, respectively, which were used as starting materials for functionalization.

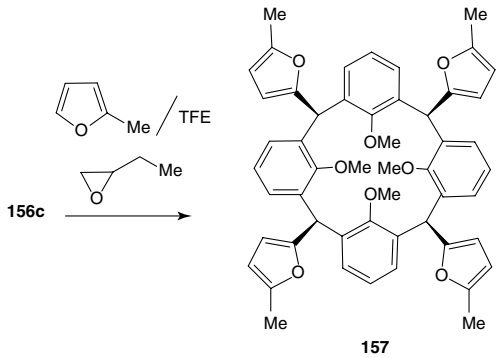
The solvolysis of **156d** in trifluoroethanol (TFE) under S_N1 conditions yielded calixarene **156e** containing four trifluoroethyl groups. In order to obtain the tetraethoxy-substituted product **156f**, the solvolysis of **156d** in EtOH/TFE (1:1) mixture was carried out. The reaction of **156d** with NaN_3 in TFE leads to **156g** of paco conformation. The above reactions gave rise to products containing C–O bonds in the case of TFE and EtOH, and C–N bonds in the case of azide [51].



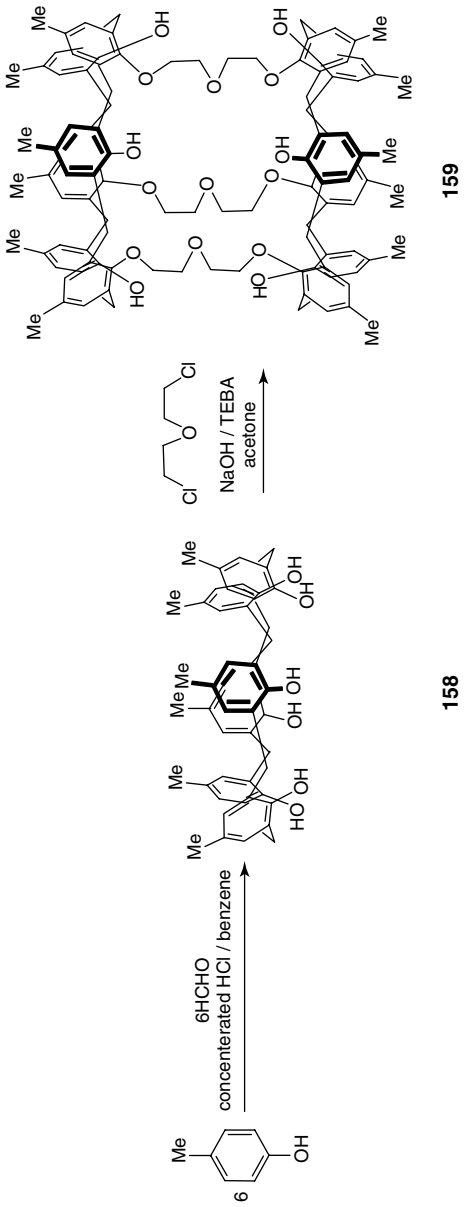
156

	R	X
a	H	H
b	*t*-Bu	H
c	H	Br
d	*t*-Bu	Br
e	*t*-Bu	OCH_2CF_3
f	*t*-Bu	OEt
g	*t*-Bu	N_3

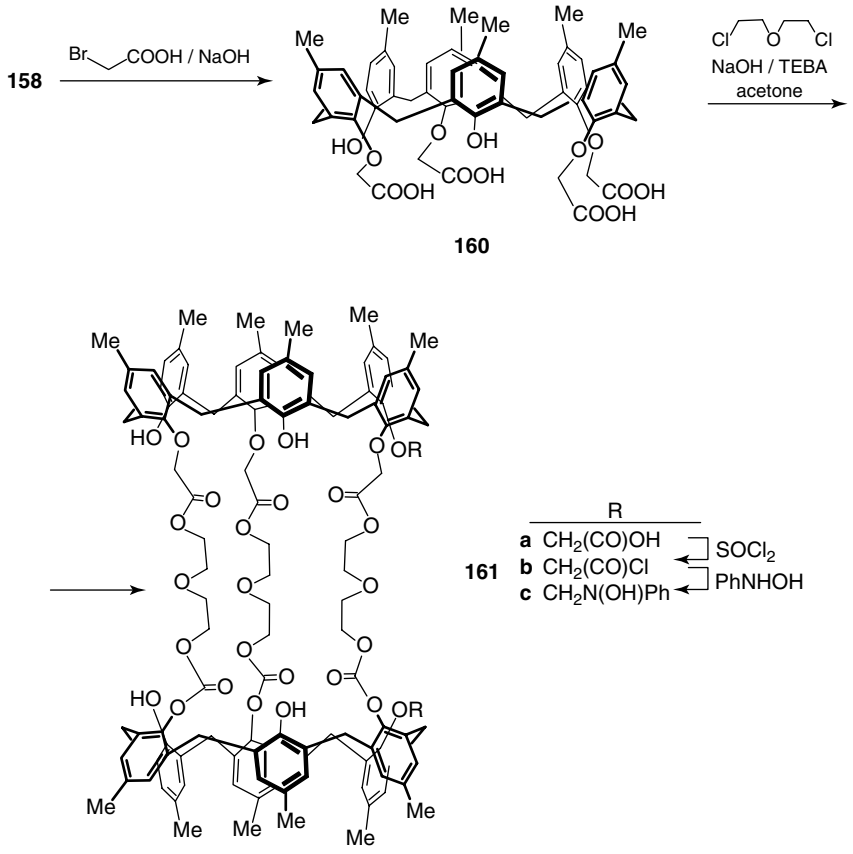
In order to synthesize products with C–C bonds, the solvolytic Friedel–Crafts reaction of **156c** with 2-methylfuran was performed in TFE using 1,2-butylene oxide as a scavenger of HBr; calixarene **157** was obtained as the sole product. The X-ray analysis results have shown its pinched cone conformation with all furanyl substituents situated at equatorial positions of the macrocycle and the furanyl oxygen atoms pointing toward the narrow rim [51].



157


Me
OH
6
6HCHO
concenterated HCl / benzene
158
NaOH / TEBA
acetone
159

Synthesis of biscalixarenes joined tail to tail via ether linkages was carried out. Biscalixarenes have interesting recognition abilities; they are promising in the design of redox active chromophores, ditopic receptors, and ion selective electrodes [52]. The acid-catalyzed condensation of *p*-cresol with formaldehyde leads to calix[6]arene **158** in a single step. The reaction of **158** with bis(2-chloroethyl)ether in the presence of NaOH and triethylbenzylammonium chloride (TEBA) as a phase-transfer catalyst (PTC) affords biscalix[6]arene **159**.



In order to obtain other biscalixarenes, **158** was treated with bromoacetic acid to give calixarene **160**, which reacted with bis(2-chloroethyl)ether in the presence of NaOH and TEBA, yielding biscalix[6]arene **161a**. The reaction of **161a** with thionyl chloride gives rise to **161b**, which upon condensation with *N*-phenylhydroxylamine affords biscalixarene **161c** bearing hydroxamic acid moieties.

In the above syntheses, a phase-transfer catalyst was used; a large amount of solvents and a longer reaction time would have been required without the use of the catalyst [52].