Syntheses and reactivity of calixarenes functionalized at *meso* positions

Wanda Sliwa and Malgorzata Deska

Jan Dlugosz University , Institute of Chemistry, Environmental Protection and Biotechnology, 42-200 Czestochowa, Armii Krajowej 13/15 Street, Poland
E-mail: w.sliwa@ajd.czest.pl

DOI: http://dx.doi.org/10.3998/ark.5550190.0013.106

Abstract

In this paper the syntheses and reactivity of calixarenes functionalized at their *meso* positions are reviewed. First the calixarenes substituted at one, two and all *meso* positions are described; they are followed by presentation of ketocalixarenes.

Keywords: Calixarene, conformation, functionalization, *meso* position, substitution

Table of Contents

1. Introduction
2. Calixarenes Substituted at One *meso* Position
   2.1. Calix[4]arenes
   2.2. Calix[6]arenes
3. Calixarenes Substituted at Two *meso* Positions
4. Calixarenes Substituted at All *meso* Positions
5. Ketocalixarenes
6. Conclusion
7. Acknowledgement
8. References

1. Introduction

Calixarenes are widely investigated due to their valuable properties, as well as due to their relatively simple syntheses and functionalization.[1-4] Among various applications of calixarenes

one should point out that they may serve as fluorescent sensors[5,6] and form complexes with metal ions,[7-9] allowing detection of metals; also they find applications in chromatography,[2,10] and some calixarene derivatives show biological activity.[11]

Calixarenes can be functionalized at their wide[12-14] and narrow[15-17] rims, and the present review deals with functionalization of the *meso* positions of calixarenes. It is noteworthy that functionalization of the *meso* positions of calixarenes has not been as intensively studied as that of the wide and narrow rims. The paper is a continuation of our work concerning calixarenes.[18-22]

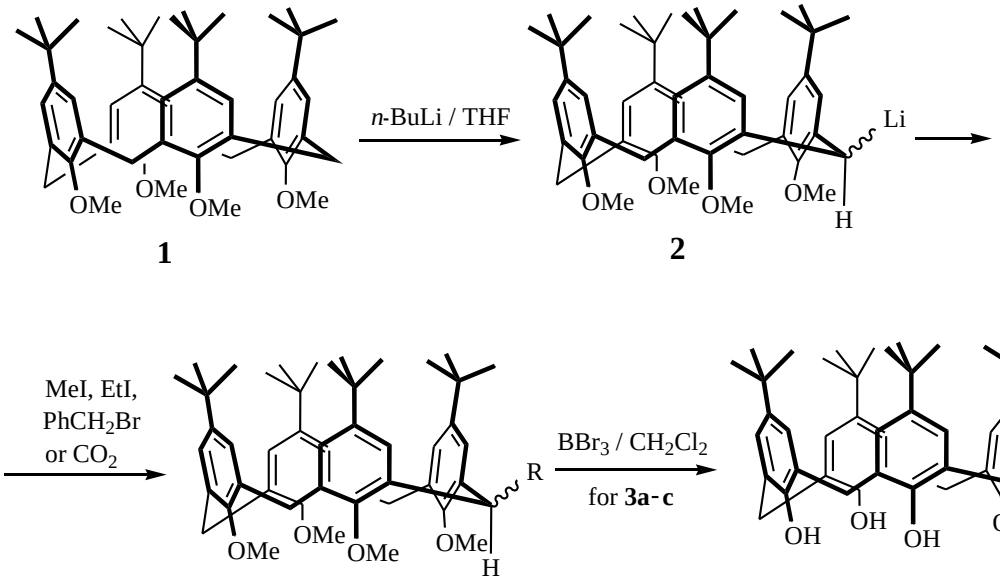
The text consists of four parts, showing calixarenes substituted at one, two, and all *meso* positions, then ketocalixarenes are briefly described.

2. Calixarenes Substituted at One *meso* Position

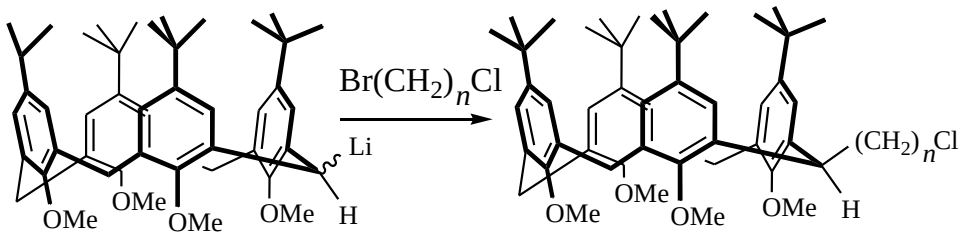
Selected examples of calix[4]arenes and calix[6]arenes substituted at one *meso* position are described, showing their syntheses, reactivity and results of conformational analyses.

2.1.Calix[4]arenes

For the synthesis of calix[4]arenes substituted at one *meso* position, the reaction of calixarene **1** with *n*-butyllithium was used. The formed monolithiated intermediate **2** upon treatment with alkyl or benzyl halides, or carbon dioxide, affords *meso* monosubstituted calixarenes **3a-d**. The substituted tetramethoxycalixarenes **3a-c** react with boron tribromide to give the corresponding tetrahydroxycalixarenes **4a-c**.[23]

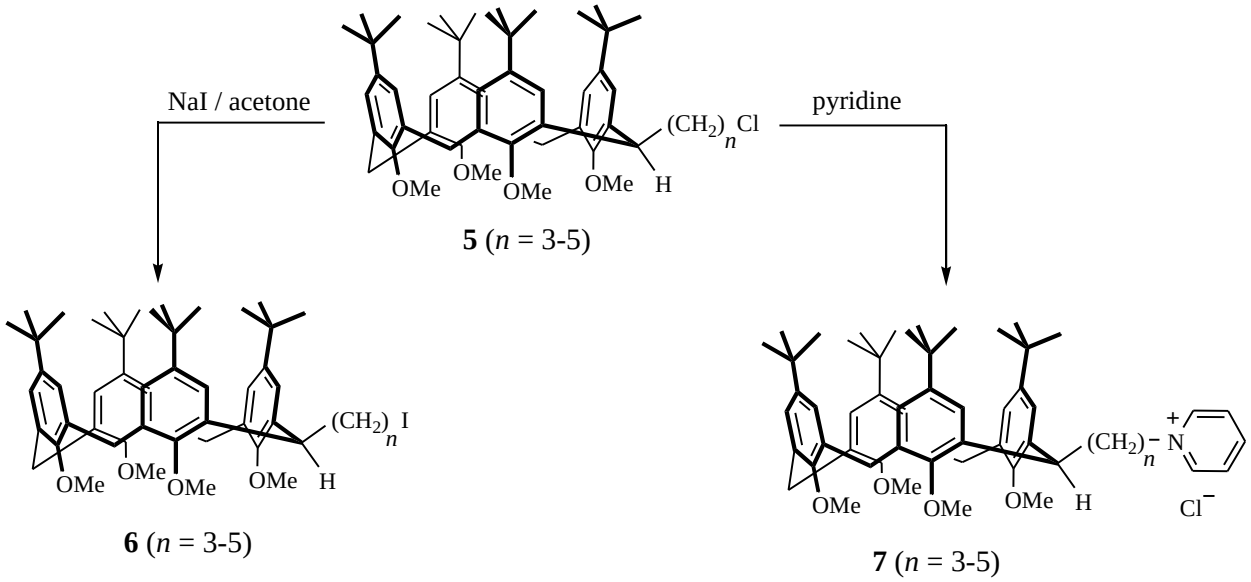


The same procedure leading to **2** served for subsequent attachment of chloro or iodo, pyridinium and amino moieties at the end of the alkyl tether of 3-6 carbon atoms at a single *meso* position of calixarene **1**.[24] The reaction of **2** with 1-bromo-ω-chloroalkanes containing 3-6 carbon atoms, gave **5**.



2 **5**

It was found that **5** (*n* = 3-5) treated with NaI afforded iodo derivatives **6** (*n* = 3-5), while the reaction with pyridine yielded pyridinium salts **7** (*n* = 3-5).

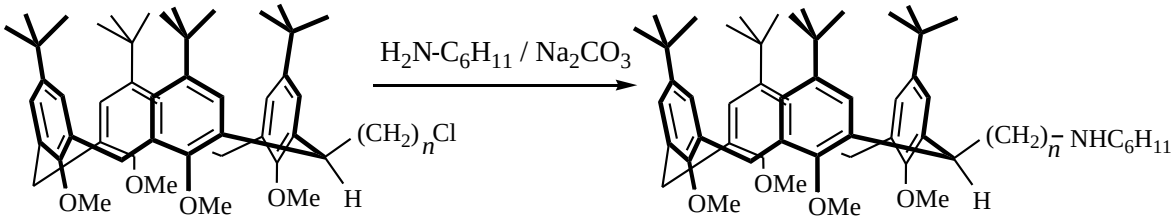


5 (*n* = 3-5)

6 (*n* = 3-5)

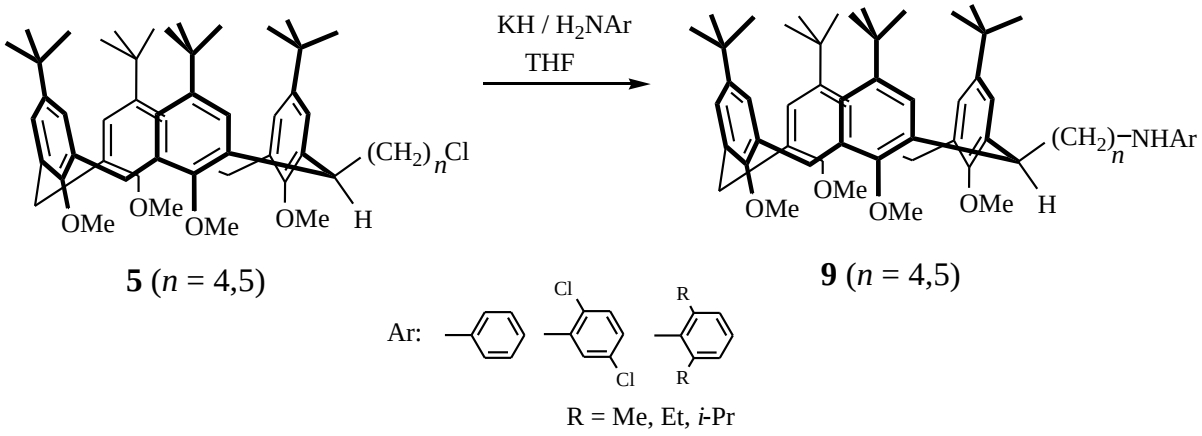
7 (*n* = 3-5)

For attachment of amines to the *meso* position of calixarenes, as an example, the reaction of **5** (*n* = 3 or 5) with cyclohexylamine leading to derivatives **8** is shown:



3 (*n* = 3 or 5) **8** (*n* = 3 or 5)

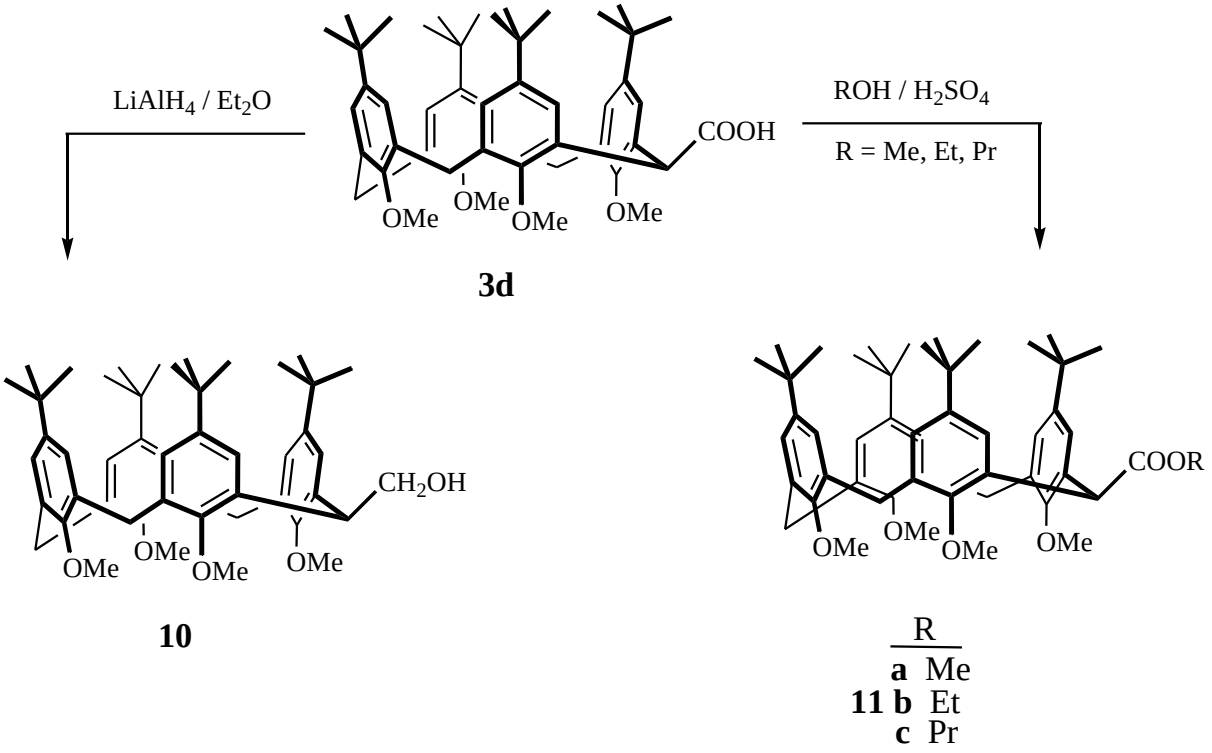
The attachment of aniline or its derivatives required their conversion into their potassium salts. Thus, calixarene **5** (*n* = 4,5) was treated with previously prepared potassium salts of aniline or its derivatives to give compounds **9** (*n* = 4,5).



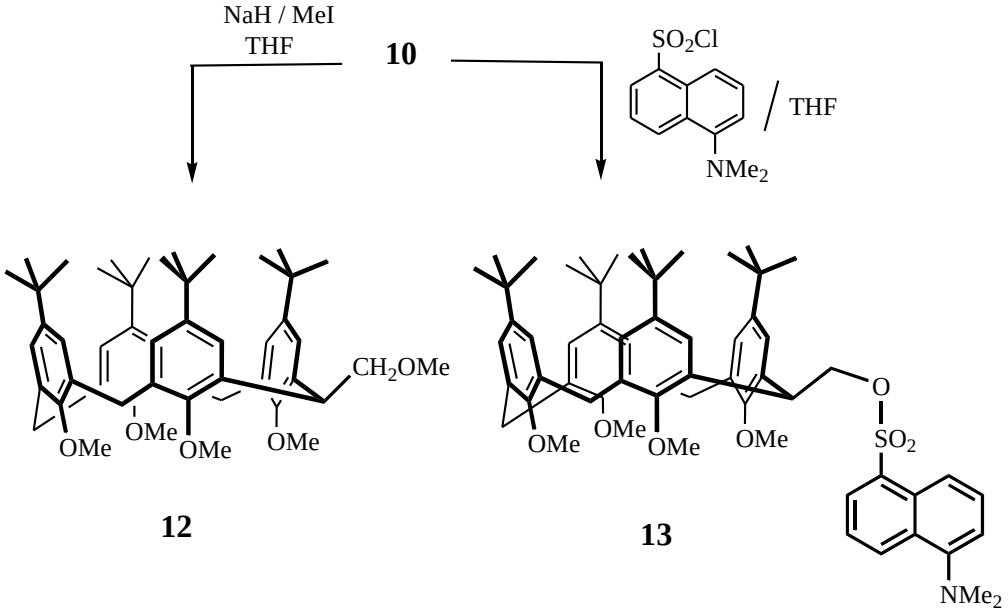
5 (*n* = 4,5) **9** (*n* = 4,5)

It should be noted that the above syntheses of amine-functionalized calixarenes enable their metallation or binding to solid supports.[24]

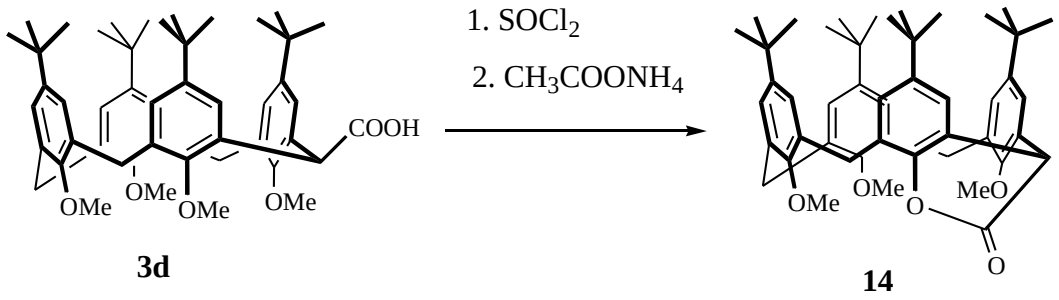
In the study of calixarenes, substituted at a single *meso* position[25,26] compound **3d** was reduced to give the alcohol **10**, and was esterified to give esters **11a-c**.[27]



Alcohol **10** was methylated with MeI affording the ether **12** and was dansylated using dansyl chloride to give the fluorescent sulfonate ester **13** which is sensitive to Cu(II) ions.



However the attempted conversion of **3d** to an amide unexpectedly afforded lactone **14**.



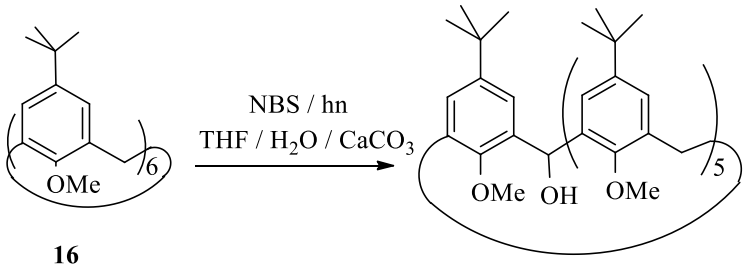
3d **14**

The conformational analysis of calixarene **3d** has been performed in solution and in crystalline state. It was found that calixarene **3d** in $CDCl_3$ undergoes a fast interconversion of phenyl units. The steric crowding of *t*-butyl groups on the wide rim exists, therefore the less symmetrical *paco* conformers prevail, while the more symmetrical *cone* and 1,2-*alt* are not favored. The existence of a special monomeric *paco*-1 conformation of **3d** with an intramolecular hydrogen bond in apolar solvents was confirmed by DOSY NMR measurements and MM calculations; it was found that *cone*, *paco*-2 and 1,2-*alt* conformers of **3d** form aggregates.[28]

The crystal structures of unsolvated **3d** as well as of two mixed solvent complexes **15a**, *i.e.* **3d**•EtOH•H_2O (1:1:1) and **15b**, *i.e.***3d**•EtOH•THF (1:1:1) are reported. It is of interest that in *paco* **3d** the carbon atom of the CH_2 group, bearing the carboxyl group becomes a centre of chirality due to the asymmetric geometry of the calixarene; this is a rare conformational chirality isomerism. The above investigation of **3d** is promising for use of similarly substituted calixarenes in design of nanostructures [29] and of immobilized devices.[30]

2.2.Calix[6]arenes

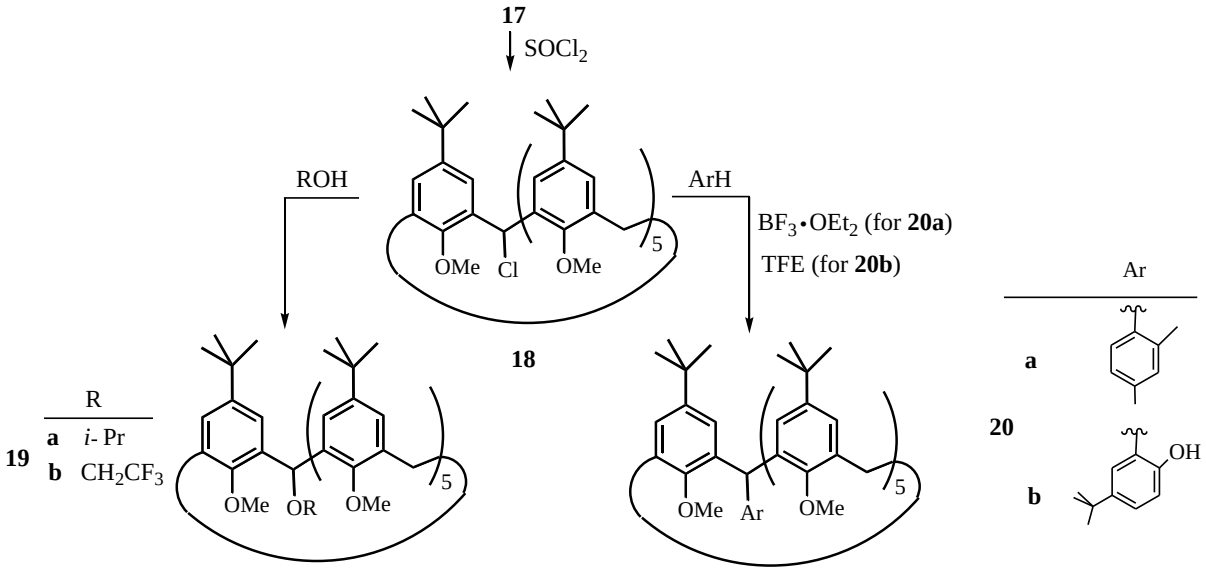
In order to obtain calix[6]arenes substituted at one *meso* position, the photochemical reaction of calixarene **16** with NBS was performed. The resulting bromination of a single *meso* position, followed by hydrolysis afforded the desired calixarene **17** which is hydroxylated at a single *meso* position.



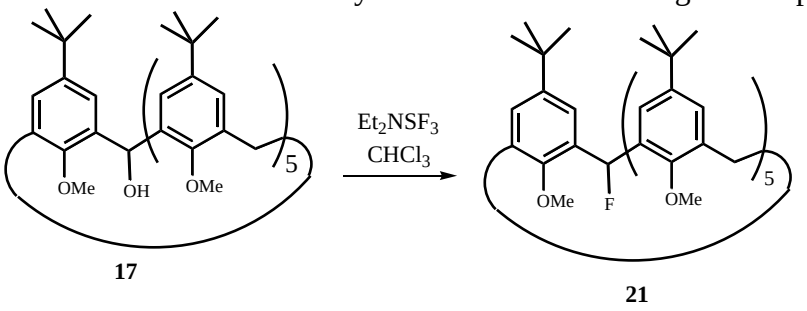
16 **17**

Calixarene **17** is a starting material for synthesis of a wide range of calixarenes functionalized at a single *meso* position. Thus the treatment of **17** with thionyl chloride yields

calixarene **18** which upon reaction with 2-propanol or with TFE gives calixarenes **19a**,**b**, and upon reaction with *m*-xylene or with *p*-*t*-butylphenol yields **20a**,**b**, respectively.[31]



It was found also that **17** reacts with Et_2NSF_3 (deoxofluorinating agent DAST) *via* replacement of the hydroxyl group by fluorine, affording **21**; one should mention that **21** is the first example of a calixarene functionalized by fluorine atom at the single *meso* position.



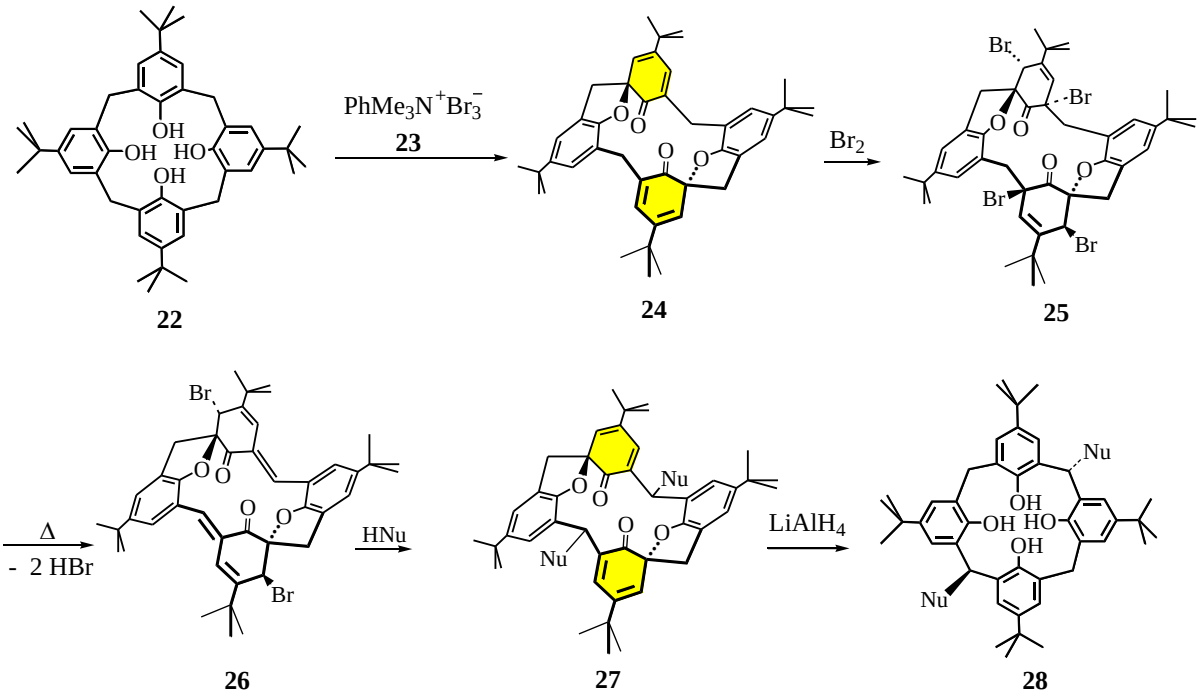
The above investigation has shown that easily available hydroxy- and chloro-functionalized calixarenes **17** and **18** are valuable starting materials for a variety of calixarenes substituted at one *meso* position. [31]

3. Calixarenes Substituted at Two *meso* Positions

In the first part of this section, calixarenes *meso* disubstituted by various nucleophiles are shown; then the functionalization of *meso* positions of calixarenes by ortho-Fries rearrangement is described.

It was established that calixarene **22** upon mild oxidation with phenyl trimethylammonium tribromide **23** affords bis(spirodienone)calix[4]arene **24**, which by a bromination/debromination sequence, *via* compound **25** yields dibromoderivative **26**. Reaction of **26** with nucleophiles leads

to *trans*-disubstituted bis(spirodienone)calixarenes **27** which upon reduction with $LiAlH_4$ give *trans*-disubstituted calixarenes **28**. [32]



22 **24** **25**

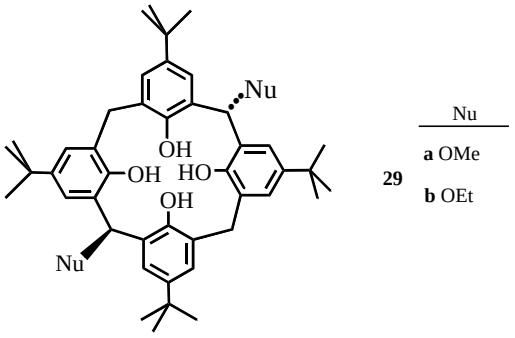
26 **27** **28**

Nu = OEt, SMe, NHPh, $CH(COOEt)_2$

Calixarene **26** reacts with oxygen, sulfur, nitrogen and carbon nucleophiles, [33] these processes are presented below.

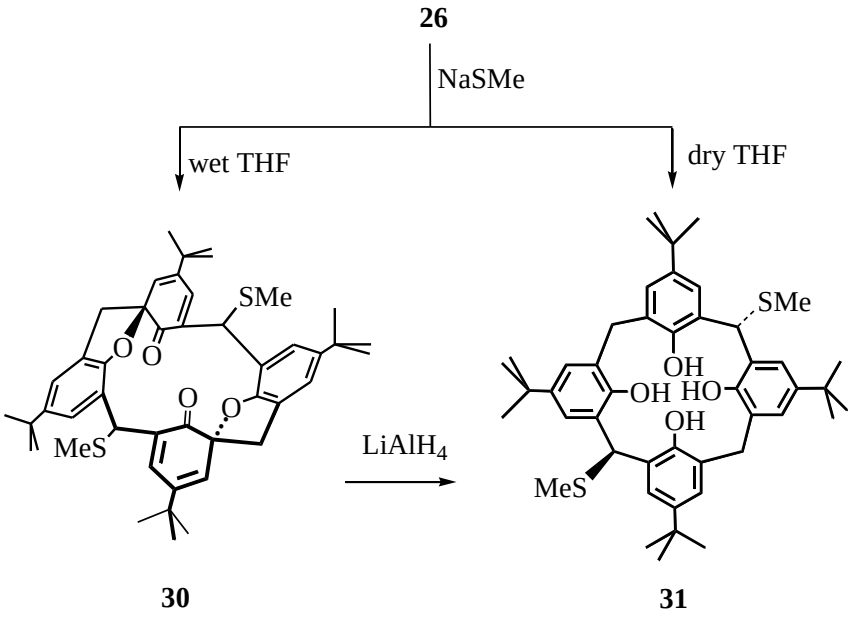
● Oxygen nucleophiles

For oxygen nucleophiles, MeO^- and EtO^- were used affording **29a**,**b**.



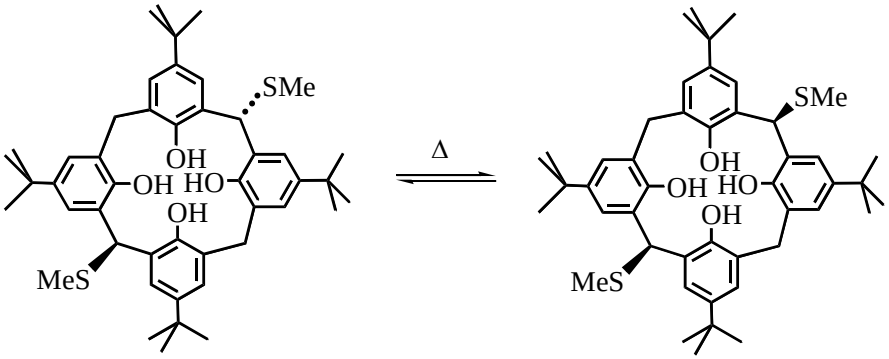
● Sulfur nucleophile

The reaction of **26** with NaSMe was performed using THF as a solvent; it was found that the results depend upon the dryness of THF. The reaction made in "wet" THF yielded the expected disubstituted bis(spirodienone)calixarene **30**, while in dry THF the *meso trans*-disubstituted calixarene **31** was formed. The $LiAlH_4$ reduction of **30** may also afford calixarene **31**.



30 **31**

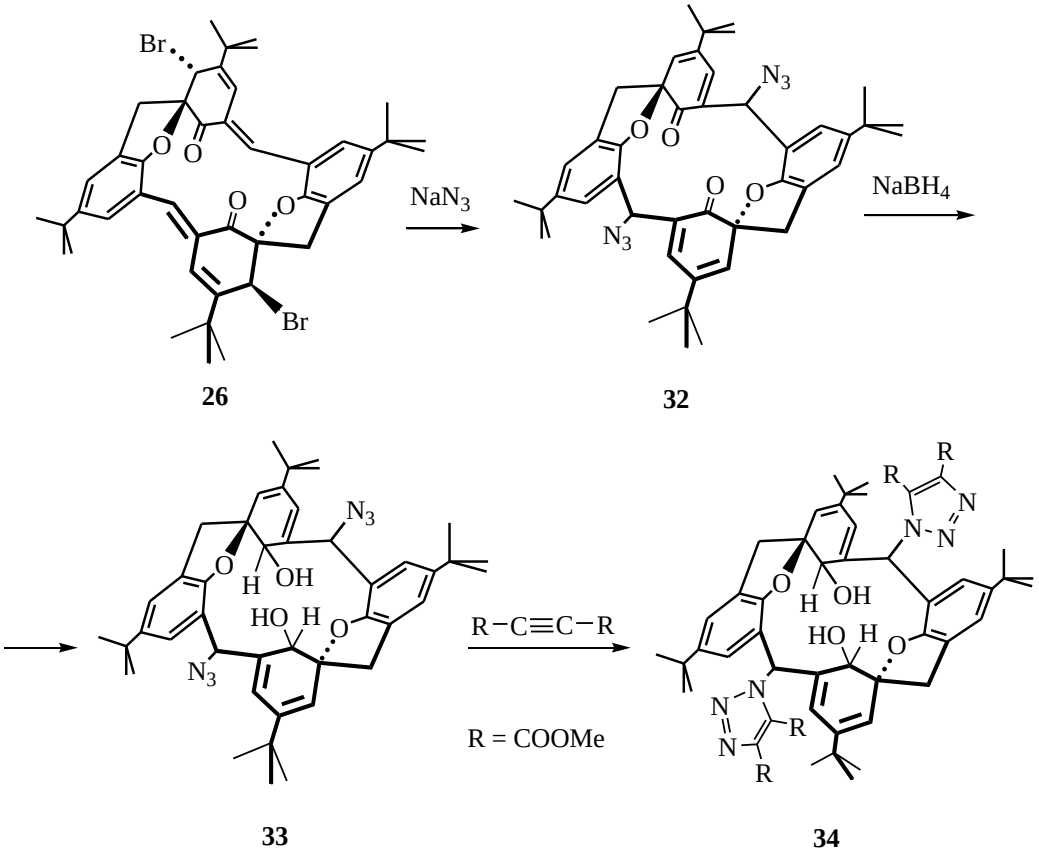
The obtained *trans* **31** undergoes a thermal isomerization to give more stable *cis* **31**.



trans **31** *cis* **31**

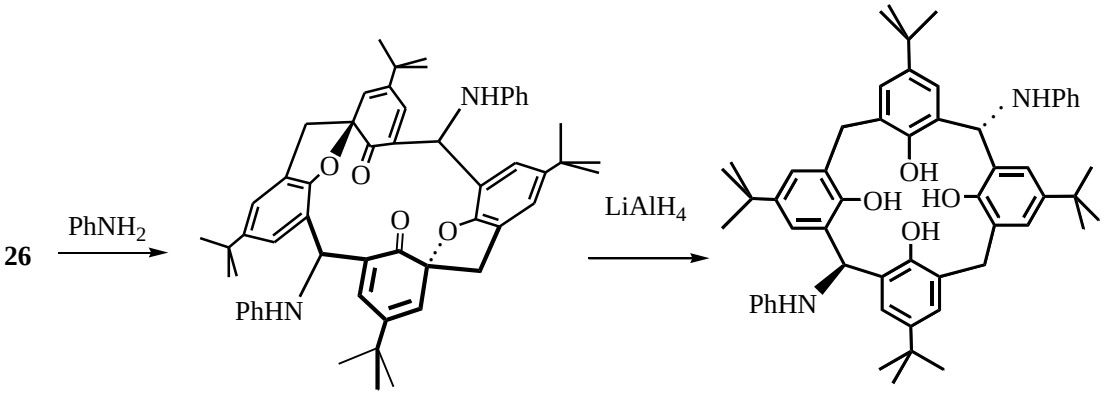
● Nitrogen nucleophiles

a) The reaction of **26** with sodium azide affords **32**. One may confirm this result by using Huisgen click reaction with an alkyne, however in order to avoid the concomitant Diels-Alder reaction of alkyne with the two diene systems of **32**, the $NaBH_4$ reduction of **32**, leading to **33**, was made. Treatment of **33** with dimethyl acetylenedicarboxylate yielded the desired **34** bearing two 1,2,3-triazole units.



26 **32** **33** **34**

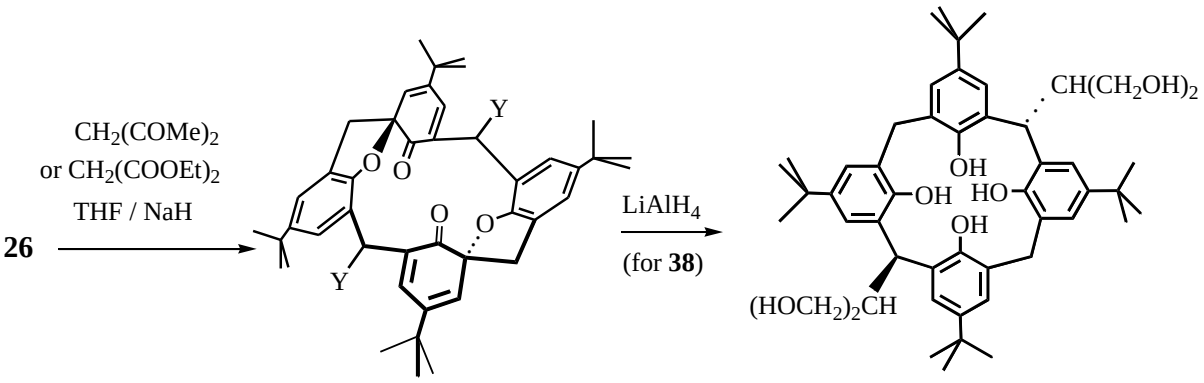
b) The reaction of **26** with aniline afforded **35** which was reduced with $LiAlH_4$ to give calixarene **36**.



35 **36**

●Carbon nucleophiles

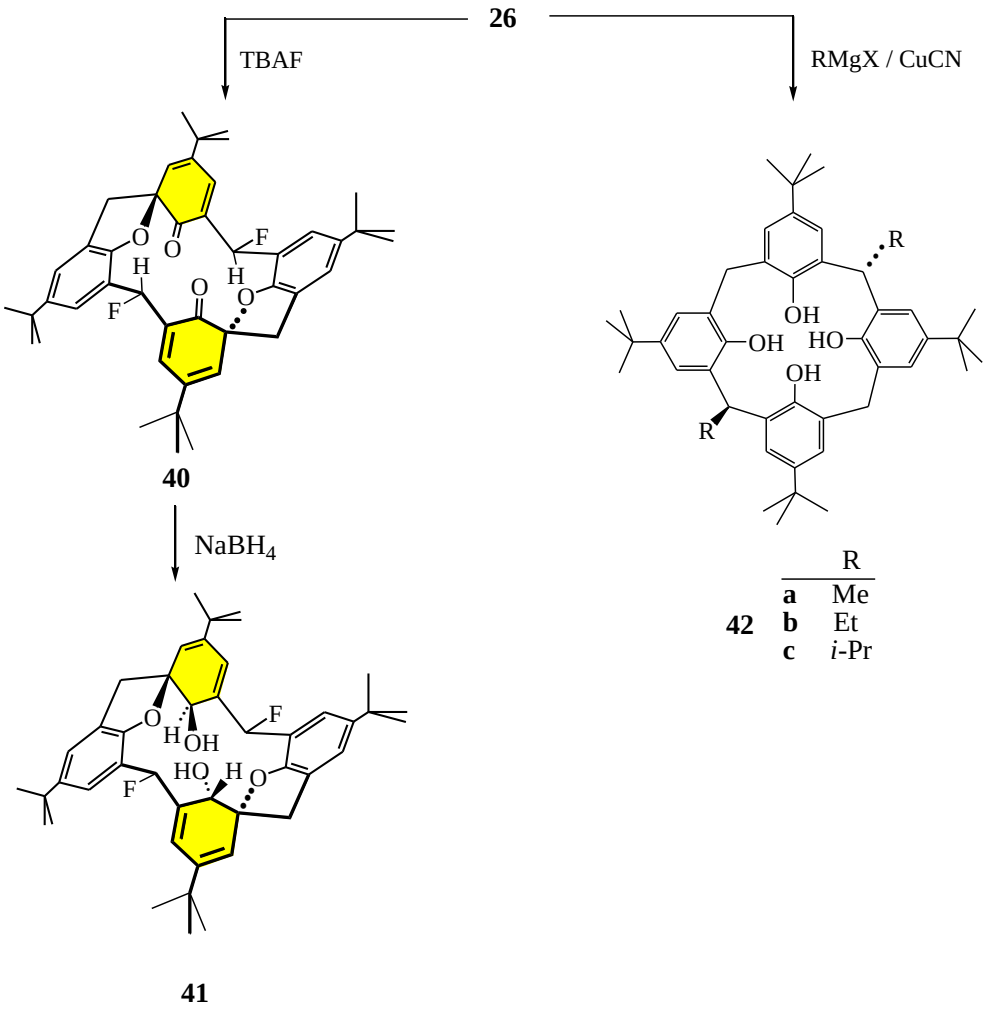
The reaction of **26** with sodium enolates of acetylacetone or diethyl malonate yielded **37** and **38**, respectively. The subsequent $LiAlH_4$ reduction of **38** gave calixarene **39**.



	Y
37	$CH(COMe)_2$
38	$CH(COOEt)_2$

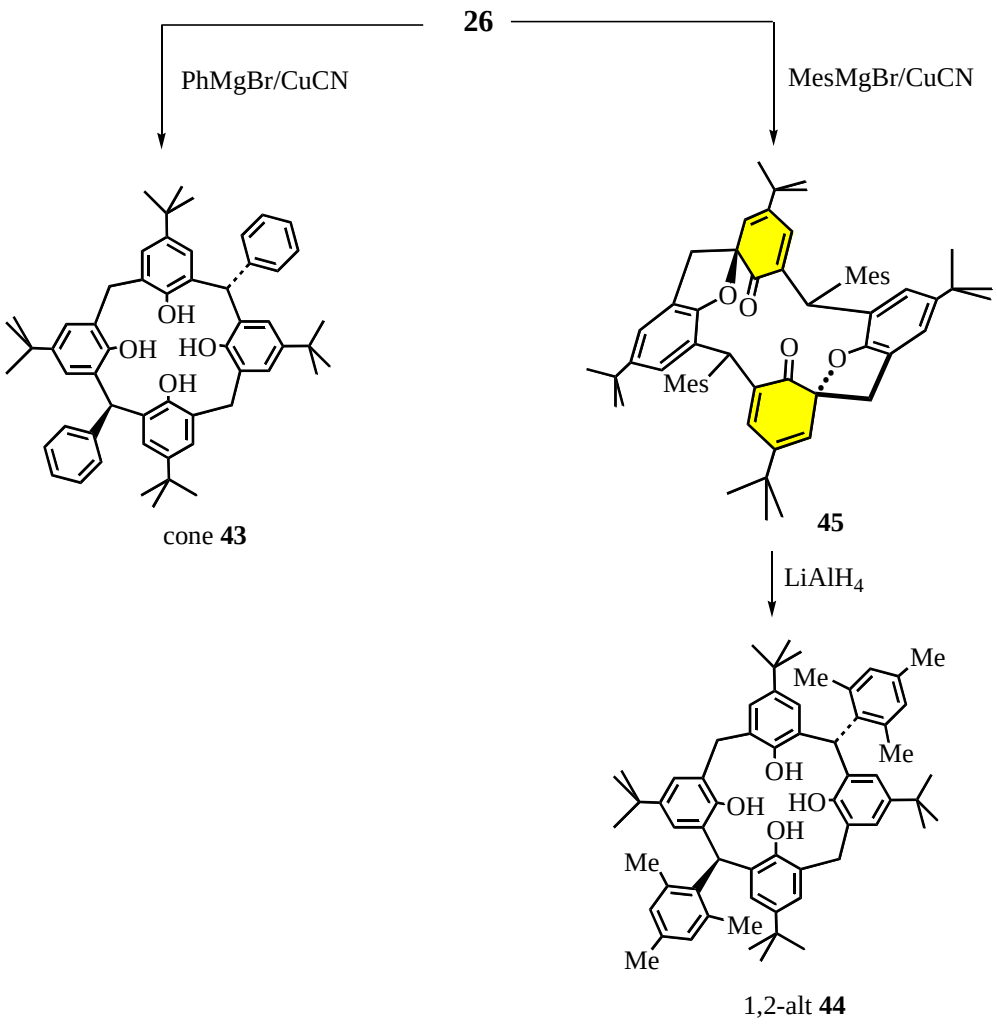
39

It was observed that **26** reacts with tetrabutylammonium fluoride (TBAF) to give difluorinated bis(spirodienone)calixarene **40** which upon reduction afforded *trans*-difluorinated compound **41**. In order to substitute *meso* positions with alkyl groups, the reactions of **26** with RMgX/ CuCN (for R = Me or Et, X = Br; for R = *i*-Pr, X= Cl) were carried out to give *trans*-disubstituted calixarenes **42a**–**c**.[32]



Compound **26** is also the starting material for synthesis of calixarenes *meso trans*-disubstituted by phenyl and mesityl groups, **43** and **44**, respectively; the reaction of **26** with PhMgBr/CuCN affords **43**, while the reaction of **26** with MesMgBr/CuCN leads to formation of bis(spirodienone)calixarene **45** which upon reduction with $LiAlH_4$ yields **44**.

The *cone* conformation of parent calixarene **22** is stabilized by the existence of the circular array of hydrogen bonds between hydroxyl groups. It was observed that *meso* diphenyl calixarene **43** also adopts the *cone* conformation, whereas *meso* dimesityl calixarene **44** has the 1,2-*alt* conformation due to the presence of bulky mesityl substituents.[34]

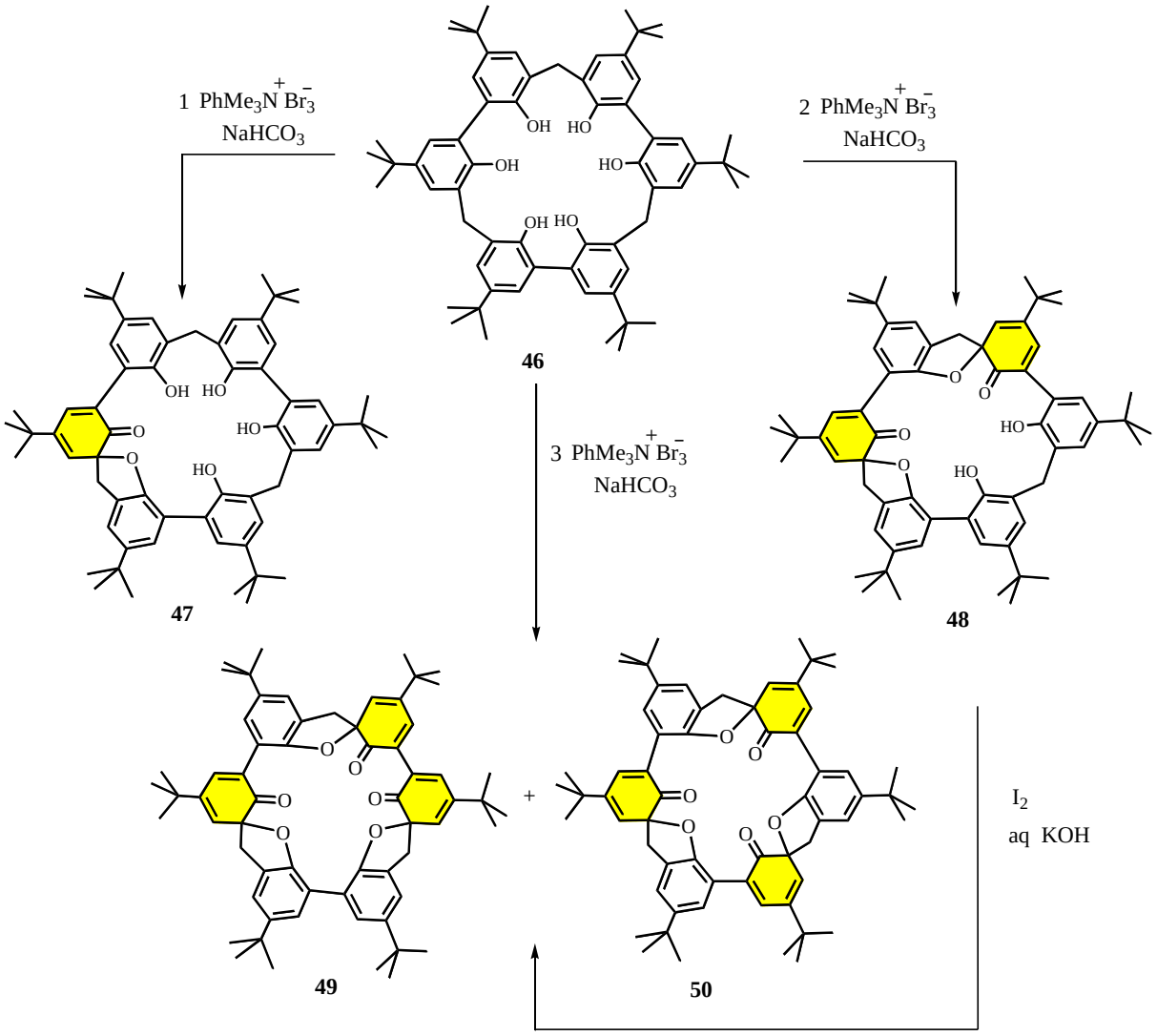


cone **43**

45

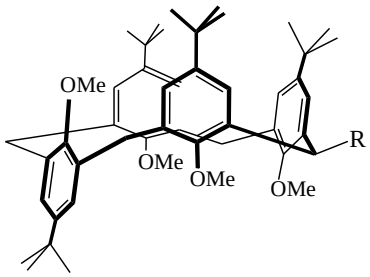
1,2-alt **44**

In order to obtain compounds related to spirodienonecalix[6]arenes, the mild oxidation of the macrocycle **46**, joining structural features of calixarenes and spherands, was performed with **23** in a similar way as for calix[4]arene **22**. It was found that the reaction result depends on the amount of used **23**: the oxidation with one or two **23** equivalents leads to products **47** and **48** containing one or two spirodienone units, respectively, whereas the use of three **23** equivalents affords two isomeric compounds **49** and **50** containing three spirodienone units. It was observed that the oxidation of **48** with iodine in aqueous KOH solution also yields **49** and **50**.[35]



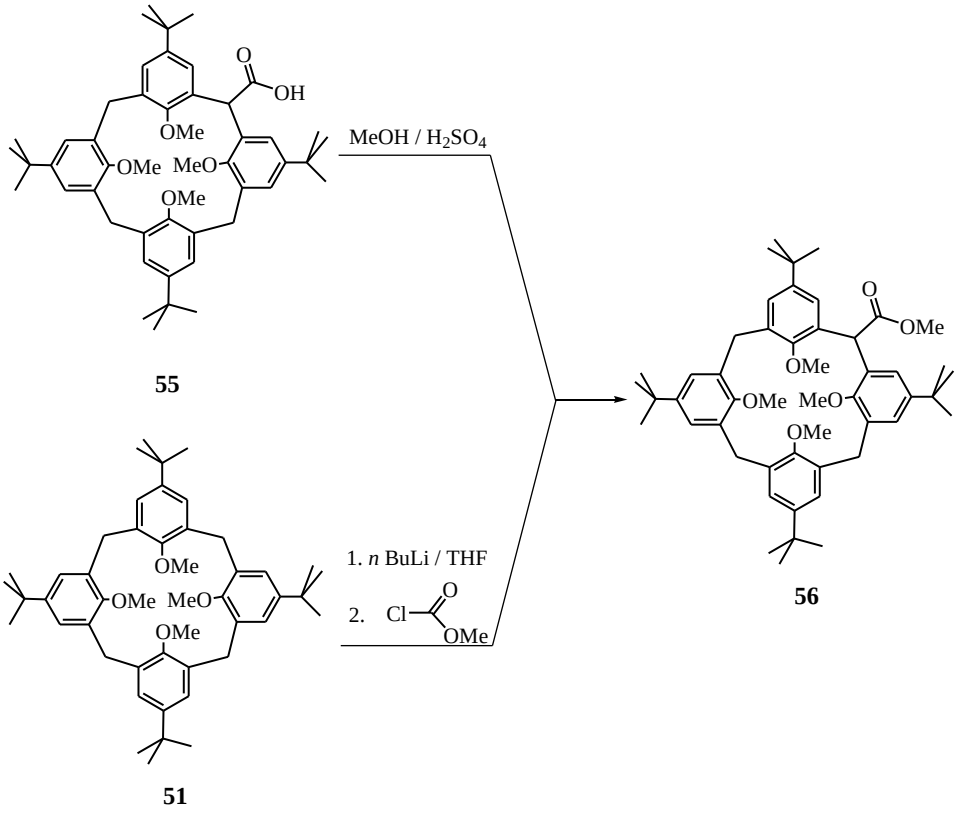
Compounds **49** and **50** isomerize upon heating in the solid state and in benzene solution; in equlibrium mixture **49** is the major component.[35]

Calixarenes *meso trans* disubstituted by alkyl, allyl, *p*-bromobenzyl and carboxyl groups have been obtained *via* a simple two-step procedure.[36] The first step involves lithiation of one *meso* position of **51** followed by reaction with bromoderivatives RBr (R=Me, Et, allyl) or with CO_2. The obtained monosubstituted products **52-55** adopt a *paco* conformation in $CDCl_3$ solution, however addition of small amounts of NaI and acetonitrile-d_3 leads to their *cone* conformation, this behavior being due to complexation of the sodium ion with the methoxy group.

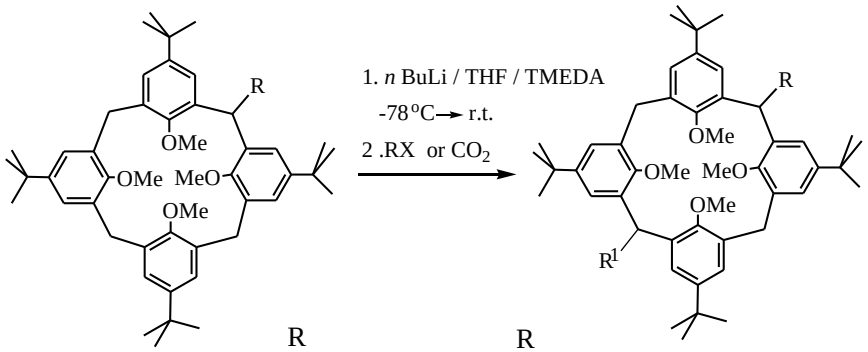


	R
51	H
52	Me
53	Et
54	$CH_2CH=CH_2$
55	COOH

One should mention that the calixarene **55** bearing carboxyl group may be converted into its methyl ester **56** by esterification with methanol; this compound may be also obtained from calixarene **51** by lithiation and subsequent treatment with methyl chloroformate.



The second step leads to conversion of monosubstituted calixarenes **52-55** into calixarenes **57-64** containing two equal or different substituents at *meso trans* positions; this second step involves lithiation followed by substitution with use of RX. To avoid side processes with the first substituent, these reactions were conducted at – 78°C. It was found that **52** reacts with MeBr or CO_2 to give **57** or **58**, respectively; similarly **54** reacts with allyl bromide or CO_2 affording **63** or **64**.

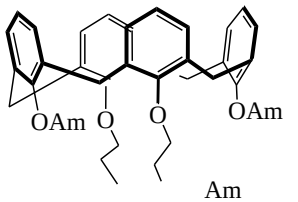


	R		R
52	Me	**57**	Me
	Me	**58**	COOH
53	Et	**59**	Me
	Et	**60**	$CH_2CH{=}CH_2$
	Et	**61**	H_2C–C$_6$H$_4$–Br
	Et	**62**	COOH
54	$CH_2CH{=}CH_2$	**63**	$CH_2CH{=}CH_2$
	$CH_2CH{=}CH_2$	**64**	COOH

The obtained calixarenes **57**-**64**, adopting rare 1,2-*alt* conformation in solution and in the solid state are promising for design of supramolecular receptors.[36]

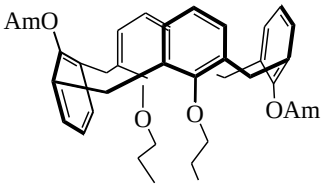
The functionalization of *meso* positions of calixarenes may be achieved using ortho-Fries rearrangement of calixarene bis-*O*-carbamates. In these experiments *cone*, *paco* and 1,3-*alt* calixarenes **65a**,**b**-**67a**,**b** were reacted with LDA in THF to give products **68**-**77**. The rearrangement was made from starting materials substituted by *O*-C(O)NEt$_2$ groups; for synthesis of **68b**, **69b**, **72b** and **73b** the starting materials substituted by *O*-C(O)NMe$_2$ groups were used.[37]

starting calixarene *O*-carbamates



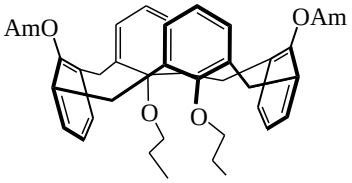
	Am
65 **a**	C(O)NEt$_2$
b	C(O)NMe$_2$

cone



66 **a** Am = C(O)NEt$_2$
b Am = C(O)NMe$_2$

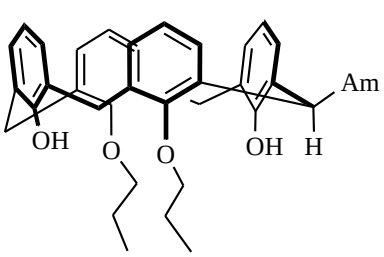
paco



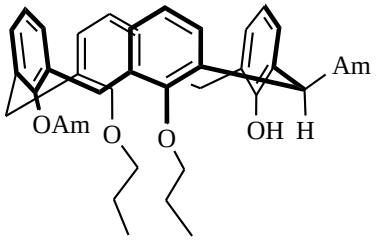
67 **a** Am = C(O)NEt$_2$
b Am = C(O)NMe$_2$

1,3-*alt*

mono-rearranged products



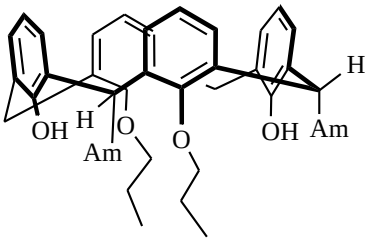
eq **68a**,**b**



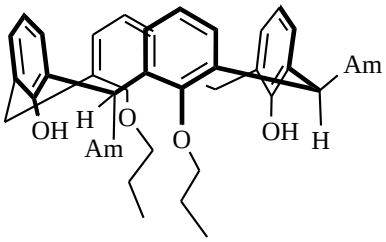
eq **69a**,**b**

bis-rearranged products

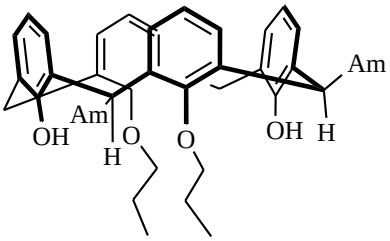
▪proximal:



ax,ax **70a**

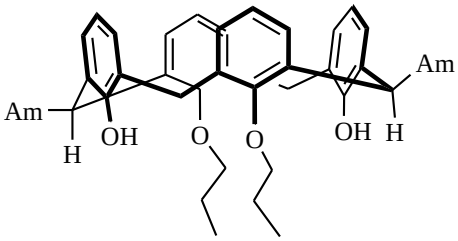


ax,eq **71a**



eq,eq **72a**,**b**

▪distal



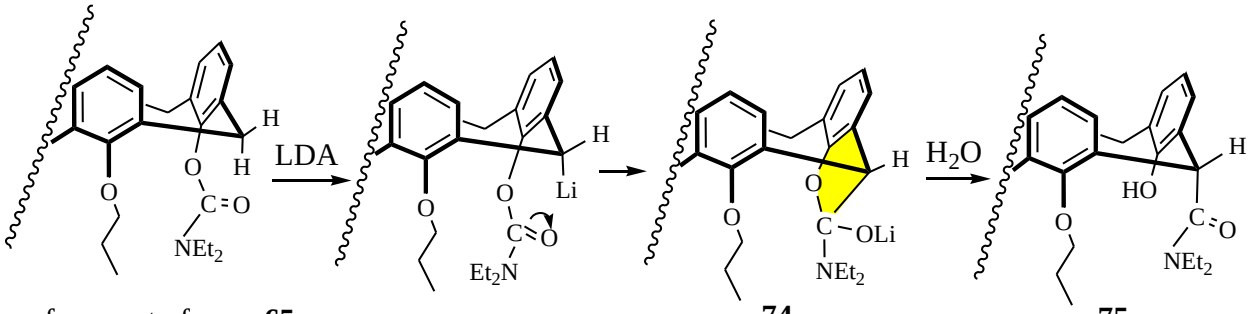
eq,eq **73a**,**b**

The reactions afforded rearranged *cone* calixarenes **68**-**73**, namely mono-rearranged: **68a**,**b** (equatorial) and **69a**,**b** (equatorial) and bis-rearranged: proximal **70a** (ax,ax); **71a** (ax,eq) and **72a**,**b** (eq,eq) and distal **73a**,**b** (eq,eq).

All products adopt a *cone* conformation, even when the starting calixarenes were not in *cone* conformations (as **65a**,**b**), but were in *paco* (as **66a**,**b**) or 1,3-*alt* conformation (as **67a**,**b**). In the

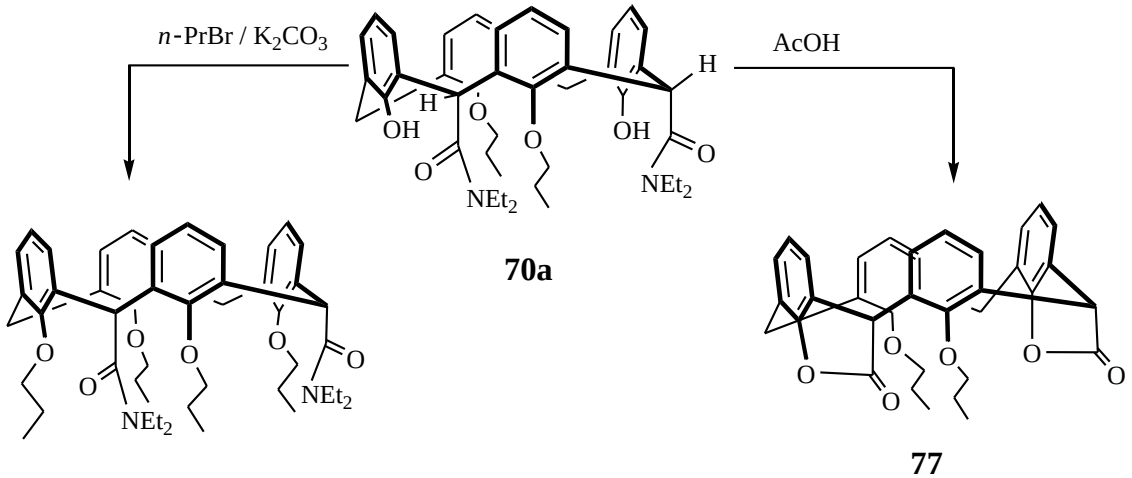
case of mono-rearranged products, the remaining *O*-carbamate group is stable (as in **69a**,**b**) or may undergo hydrolysis to form the hydroxyl group (as in **68a**,**b**).

The rearrangement proceeds *via* an intermediate five-membered ring. In the case of mono-rearrangement, the deprotonation by LDA affords a carbanion, which attacks the carbonyl of the *ortho* (adjacent) *O*-carbamate group, to form a five-membered ring. The subsequent quenching of the reaction mixture completes the migration, affording compound bearing at one *meso* position the amide group. For *cone* **65a**, the formation of five-membered ring in the intermediate **74**, leading to axial mono-rearranged product **75**, is presented. The bis-rearrangement proceeds *via* two five-membered intermediates.

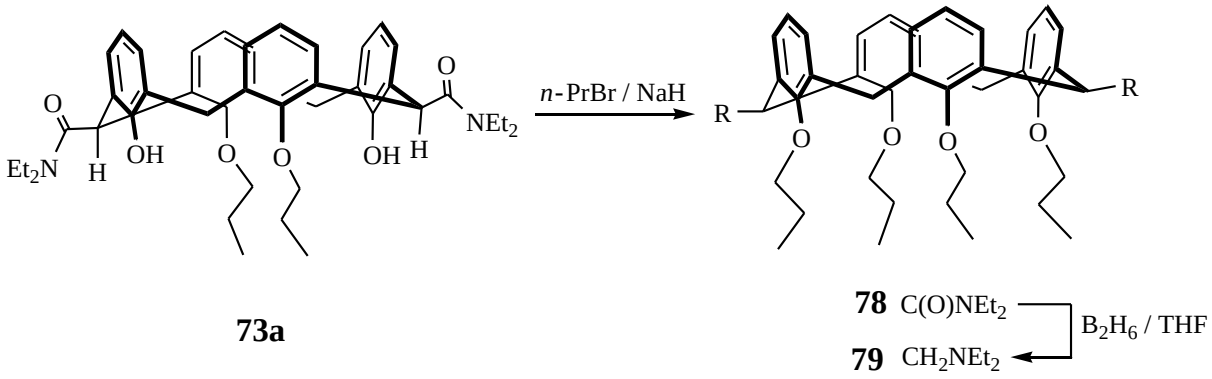


It should be pointed out that the above Fries rearrangement proceeds readily and the obtained calixarenes containing amide groups at *meso* positions undergo further reactions; as examples those of **70a** and **73a** are shown.

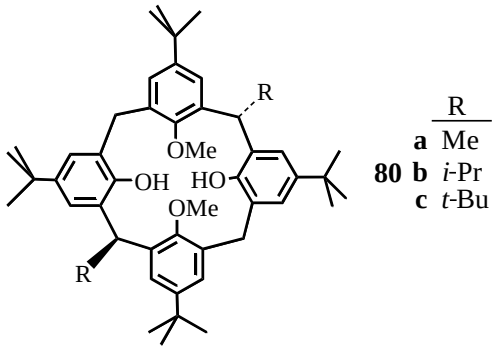
In **70a** the existence of two axial amide groups in proximal positions allows the reaction with *n*-propyl bromide in the presence of K_2CO_3 affording **76**, and the reaction with acetic acid yielding bis-lactone **77**. This behavior of **70a** results from the close proximity of two axial amide groups, which increases the acidity of the hydroxyl groups.



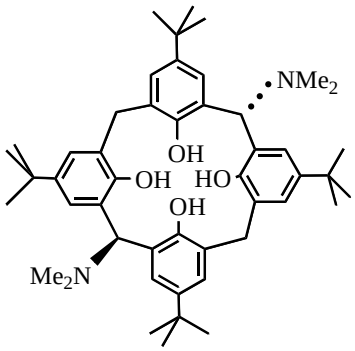
It is noteworthy that in **73a**, bearing two equatorial amide groups in distal positions, the propylation in the presence of K_2CO_3 would be impossible, instead NaH is required. The propylation of **73a** in the presence of NaH affords **78** which by reduction with diborane yields the diamine **79**.[37]



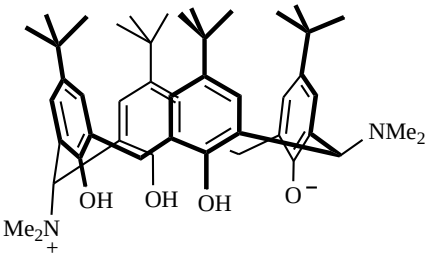
The conformational analysis of *trans*-disubstituted calixarenes **80a-c** has shown that in **80a** (R = Me) the *cone* and 1,2-*alt* conformations coexist in $CDCl_3$, however in calixarenes **80b** and **80c** bearing more bulky substituents (R = *i*-Pr and *t*-Bu, respectively) the 1,2-*alt* conformation is preferred.[38]



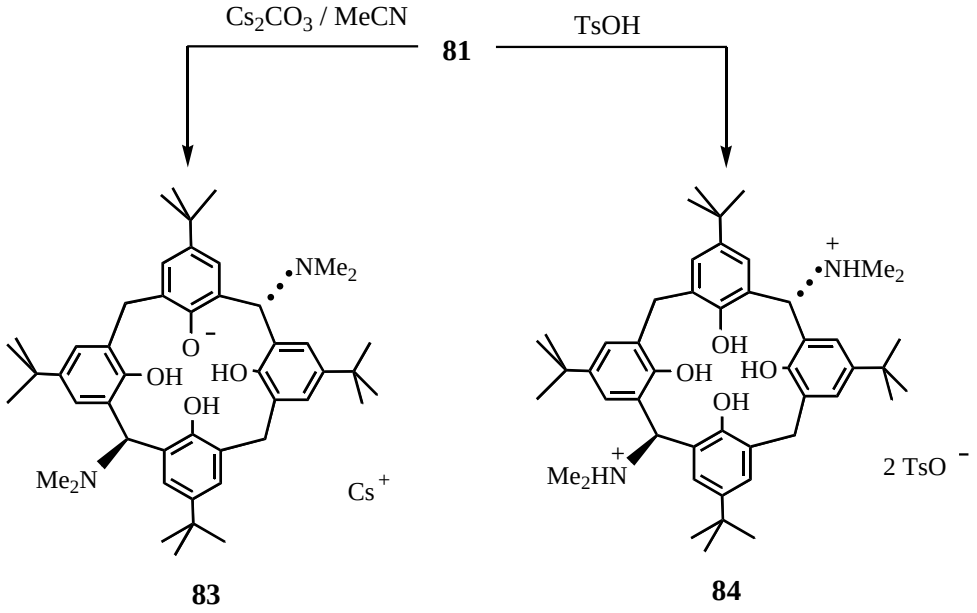
A single crystal of **81**, grown from acetonitrile was investigated by X-ray diffraction. Calixarene **81** crystallizes with two MeCN molecules, one of them being situated inside the cavity. It was found that **81** adopts a *cone* conformation and exists in the crystal and in polar solvents as a zwitterion **82**, with the axial dimethylamino group protonated and one hydroxyl group deprotonated. [39]



81



82



83 **84**

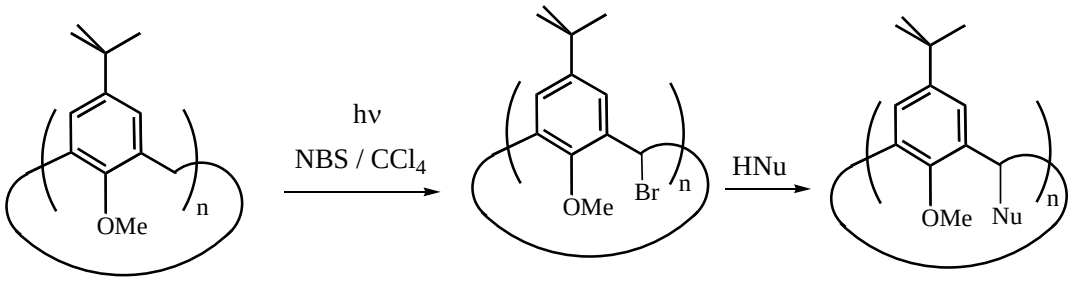
For ^{1}H NMR examination of **81**, the model compounds **83** (with both dimethylamino groups nonprotonated) and **84** (with both dimethylamino groups protonated) have been synthesized. The reaction of **81** with Cs_2CO_3 in acetonitrile afforded **83**, and reaction with *p*-toluenesulfonic acid yielded **84**. The measurement of ^{1}H NMR spectra has confirmed the existence of **81** as a zwitterion **82** in THF.[39]

4.Calixarenes substituted at all *meso* positions

The functionalization reactions of calixarenes proceeding at all *meso* positions will be described for calix[*n*]arenes, where *n* = 4, 5 and 6. Then the direct synthesis of chiral *meso* substituted calixarenes will be shown.

It was found that calix[*n*]arenes (*n* = 4,5,6), **85a–c**, upon photochemical bromination afford calixarenes **86a**–**c** substituted at all *meso* positions by bromine atoms.[40-42] Reactions of calixarenes **86a**–**c** with O-, N- and C- nucleophiles involve replacement of bromine atoms by

nucleophiles, leading to calixarenes **87a**–**c** functionalized at all *meso* positions. These reactions proceed in alcohols used as solvents or may require ionizing solvents, such as 2,2,2-trifluoroethanol (TFE) or hexafluoro-2-propanol (HFIP).[40-42]



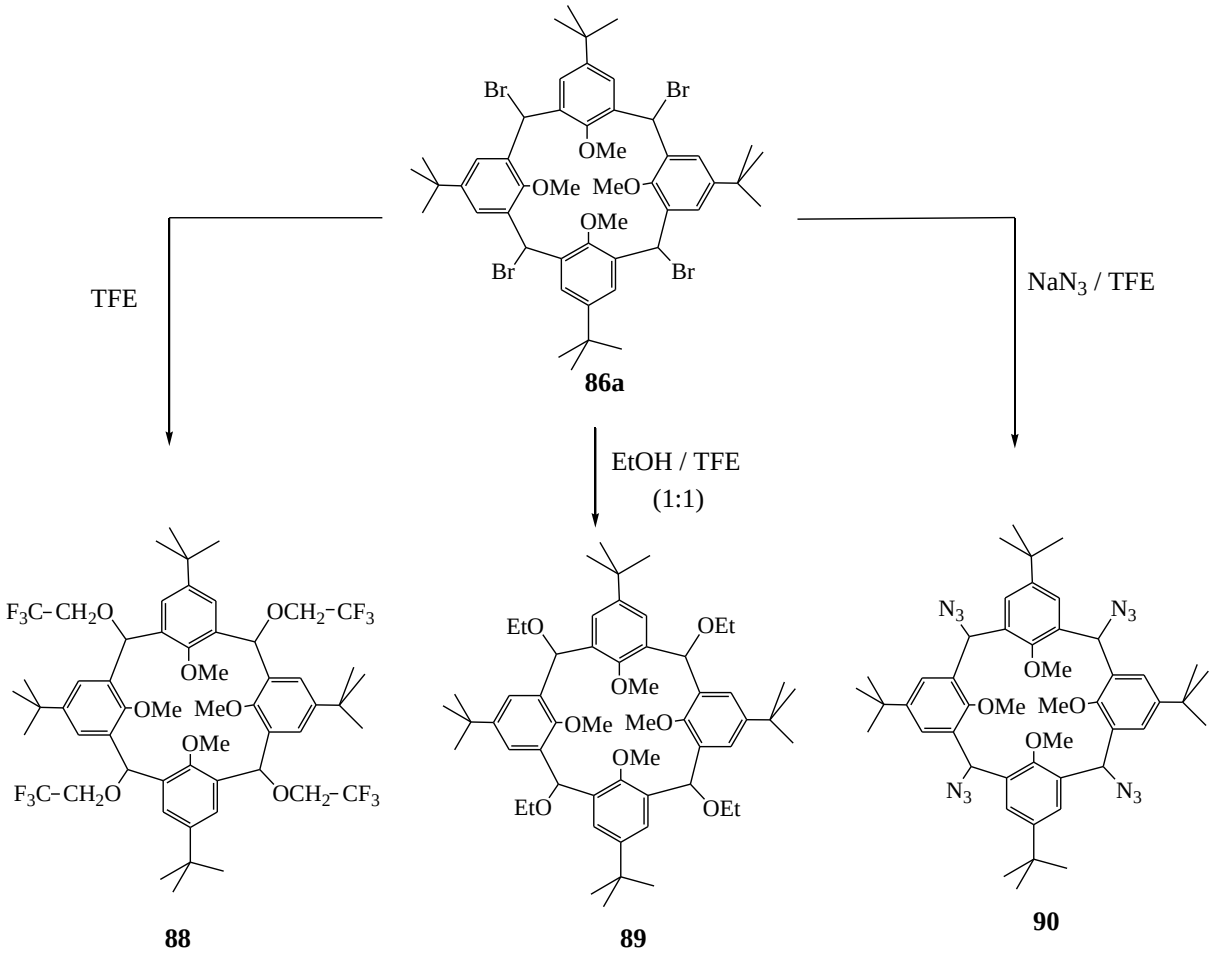
	n
a	4
85 b	5
c	6

	n
a	4
86 b	5
c	6

	n
a	4
87 b	5
c	6

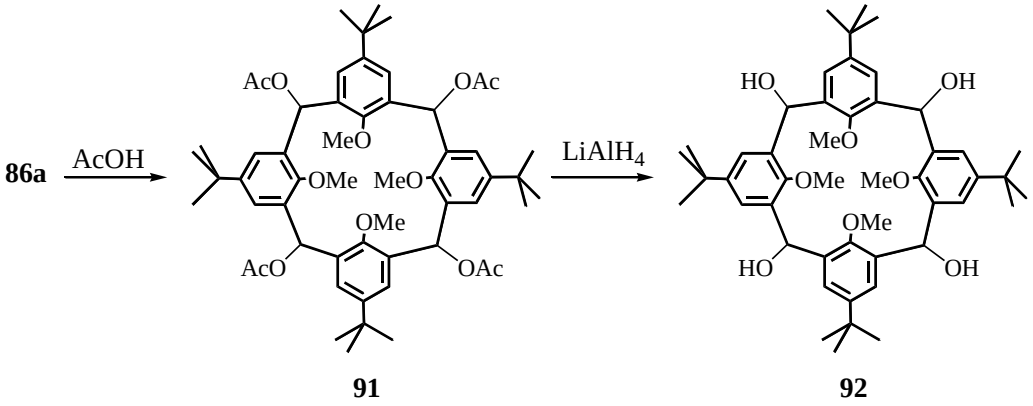
● Functionalization of calix[4]arenes at all *meso* positions

The solvolysis of **86a** with TFE (=2,2,2-trifluoroethanol), performed in the absence of an additional nucleophile or a Lewis acid, yielded **88**, and when carried out with EtOH/TFE 1:1 mixture, gave **89**. The reaction of **86a** with NaN_3 in the presence of TFE or HFIP yielded **90**.[43]

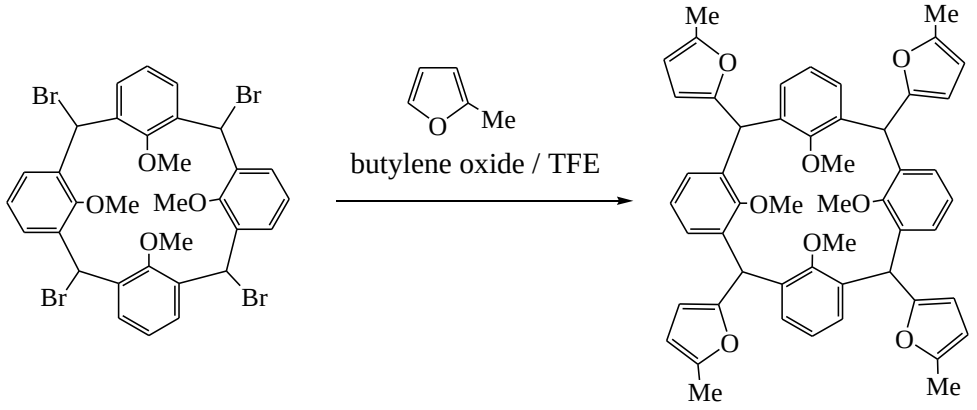


In a similar procedure **86a** reacted with *n*-PrOH, *i*-PrOH and ethylene glycol.

Solvolysis of **86a** in AcOH yielded **91** which upon reduction of acetoxy groups gave calixarene **92** bearing hydroxyl groups at all *meso* positions.[40]



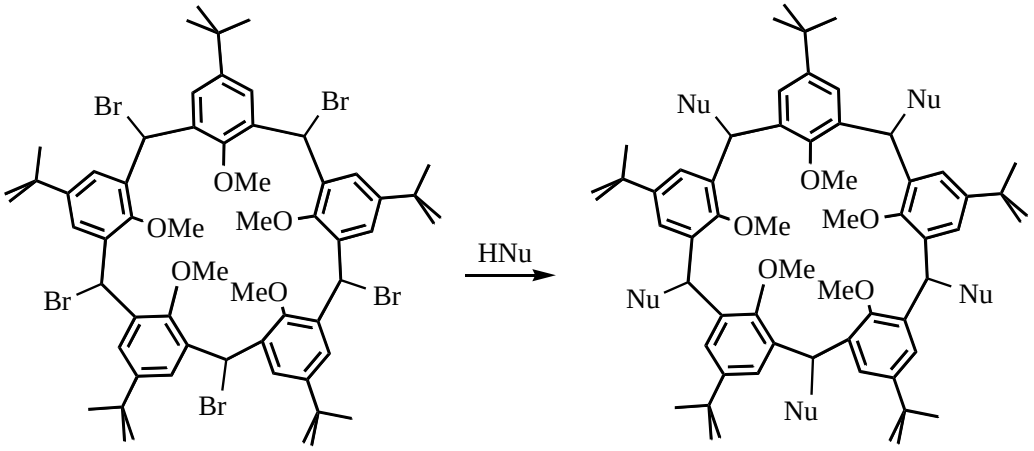
The solvolytic Friedel-Crafts reaction of **93** (obtained from the corresponding calixarene by similar bromination with NBS) with 2-methylfuran, performed with the use of 1,2-butylene oxide as a HBr scavenger, afforded **94**.[43]



93 **94**

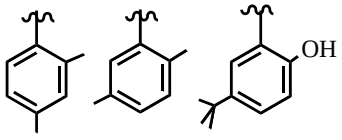
● Functionalization of calix[5]arenes at all *meso* positions

Replacement of bromine atoms in **86b** by nucleophiles affords calixarenes **87b**. It was found that the reactions with TFE and 2-propanol proceed by refluxing **86b** with these alcohols, however in the case of propargyl alcohol, *m*- and *p*-xylenes and *p*-*t*-butylphenol, the use of HFIP is necessary.[41]



86b **87b**

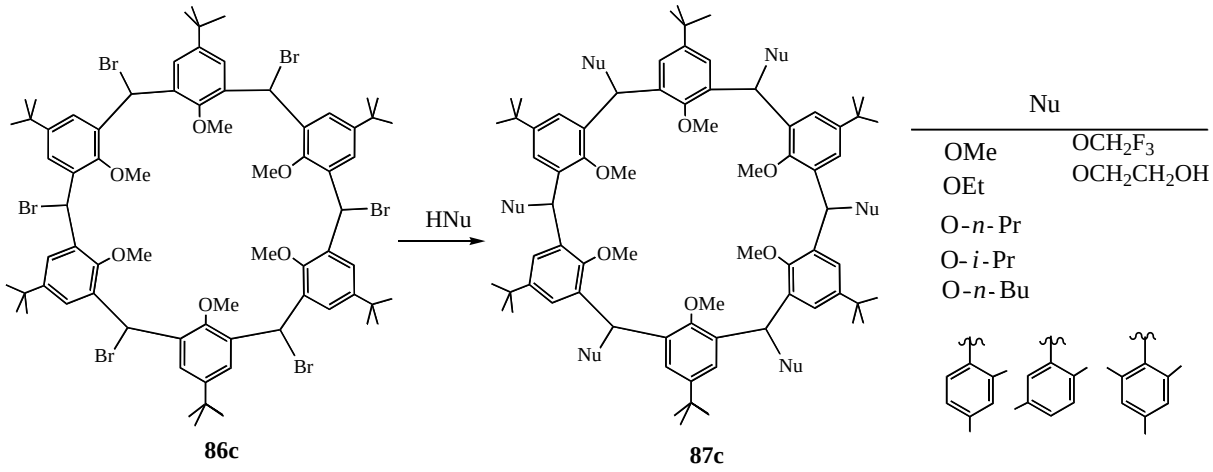
Nu
OCH_2CF_3
O–*i*-Pr
OCH_2–C≡CH



One should point out the importance of calix[5]arene derivatives functionalized at *meso* positions; their cavity is larger than that of functionalized calix[4]arenes, but in contrast to larger calixarenes they still adopt nearly symmetric *cone* conformations.

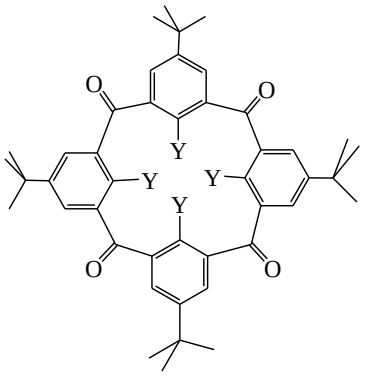
● Functionalization of calix[6]arenes at all *meso* positions

Calixarene **86c** was refluxed in alcohols MeOH, EtOH, *n*-PrOH, *i*-PrOH, *n*-BuOH to give products **87c** substituted at all *meso* positions by alkoxy groups. Refluxing of **86c** in TFE yielded **86c** (Nu = OCH_2CF_3), and refluxing of **86c** with ethylene glycol in TFE afforded **87c** (Nu= OCH_2CH_2OH). [42] Reactions of **86c** with *m*- and *p*-xylenes and with mesitylene leading to products **87c** substituted at all *meso* positions by aryl groups were carried out in HFIP.



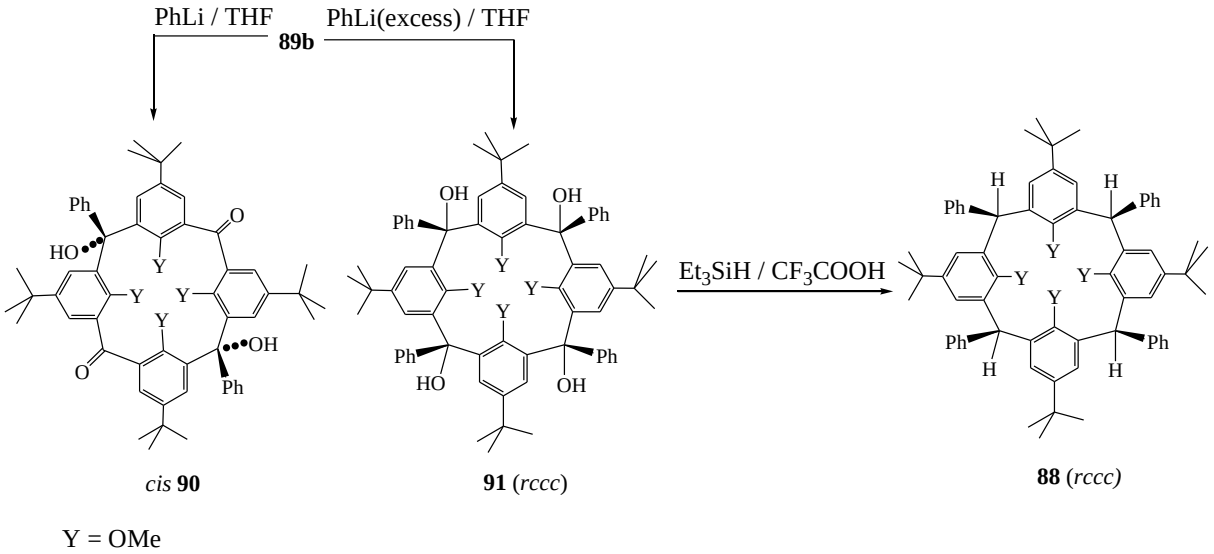
Reactions of **86c** with sodium azide and with aniline performed in TFE, lead to calixarenes **87c** (Nu = N_3) and **87c** (Nu = HNPh), respectively. Acetolysis of **86c** afforded **87c** (Nu = OAc) which upon $LiAlH_4$ reduction yielded **87c** (Nu= OH). It is worth noting that the presence of substituents at *meso* positions of **87c** rigidifies the calixarene structure.

Calixarene **88** with all four meso positions monosubstituted by phenyl groups has been obtained from tetraketocalixarene **89b**.[44] The synthesis begins with the reaction of **89b** with PhLi. The starting tetraketocalixarene 1,3-*alt* **89b** was obtained by methylation of **89a**; this protection of the hydroxyl groups of **89a** was necessary to avoid the acid–base reactions of these hydroxyl groups with PhLi.



	Y
89 **a**	OH
b	OMe

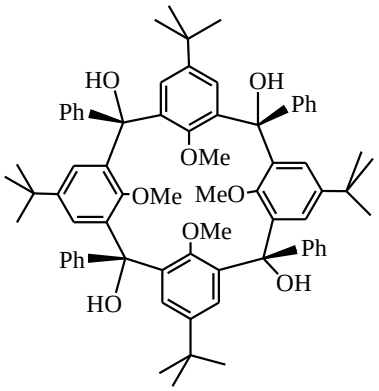
The reaction of **89b** with PhLi in THF afforded *trans* di-addition product **90**; with the excess of PhLi, the tetra-addition product **91** was obtained as a mixture of four isomers *rccc*, *rcct*, *rctt* and *rtct*, which upon recrystalization gave one product, **91** (*rccc*). The next step was the reduction of the four hydroxyl groups in **91**, performed with Et_3SiH/CF_3COOH to give **88**.[44]



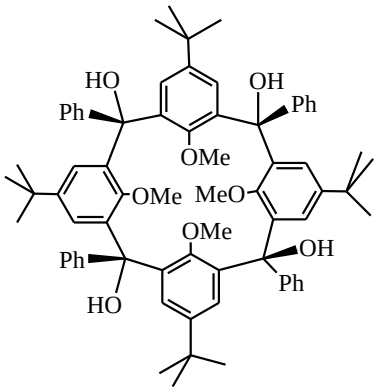
cis **90** **91** (*rccc*) **88** (*rccc*)

Y = OMe

It was found that **88** has *all cis*, *i.e.* the *rccc* form; **88** in the crystal adopts the 1,3-*alt* conformation. Calixarene **92** which is an isomer of **88** has the *rcct* form; **92** in the crystal also adopts the 1,3-*alt* conformation. Examination of the X-ray structures of **88** and **92** shows that in the 1,3-*alt* conformation their methoxy groups, intramolecularly hydrogen bonded to neighboring hydroxyl groups are pointing toward the cavity (orientation "in").[44]



88 (*rccc*)

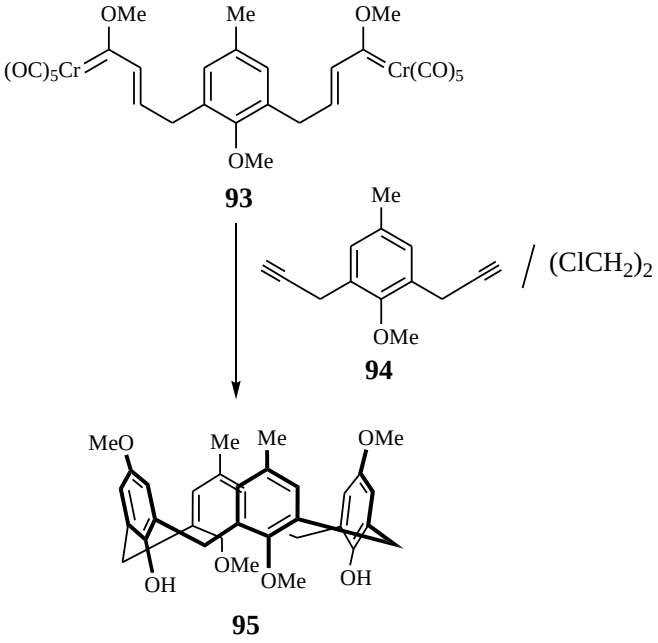


92 (*rcct*)

When **88** is dissolved in acetone-d_6, the hydroxyl protons exchange with the deuterium atoms present in residual water of the solvent. The analysis of the ^{1}H NMR (400 MHz) spectrum of **88** in acetone-d_6 differs from that in $CDCl_3$. This behavior results from isotopic perturbation of the conformational equilibrium in **88**. Several species (isotopomers) of a different number and positions of the OD groups are possible for **88**.[45]

An attention should be paid also to the method allowing a direct construction of *meso*-substituted chiral calixarenes in which the chirality results from the substitution of *meso* positions.[46] This method is highly valuable, having in mind that among syntheses of calixarenes substituted at *meso* positions, the approach to chiral species is rare.

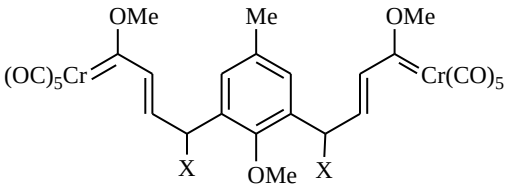
The synthetic procedure is similar to the shown below annulation of the biscarbene complex **93** with diyne **94**, leading to calixarene **95**; in this reaction new rings of the product were built.[47-50]



95

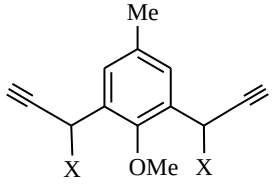
The formed calixarene **95** is *meso*-unsubstituted, however the substitution of one or both methylene groups in **93** and/or **94** allows to obtain the desired *meso*-functionalized calixarenes.[46]

Biscarbene complexes: unsubstituted **96a**, (X=H) and disubstituted **96b** (X=OMe) and diynes: (*R*,*R*)-**97** (X=OMe), (*S*,*S*)-**97** (X=OMe) and (*R*,*R*)-**98** (X=OTBS) served as starting compounds.

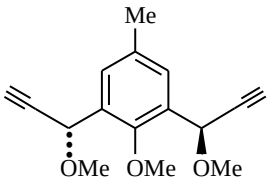


biscarbene complexes

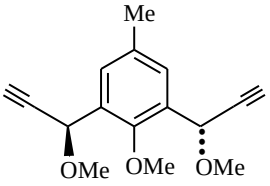
	X
96 **a**	H
b	OMe



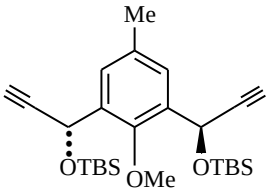
diynes **97**



(R,R)-**97** (X=OMe)



(S,S)-**97** (X=OMe)

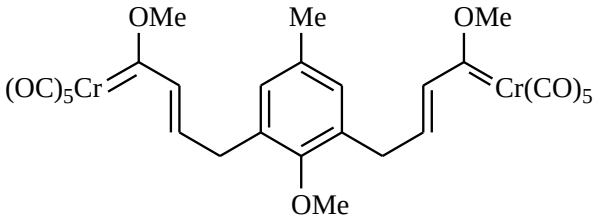


(R,R)-**98** (X=OTBS)

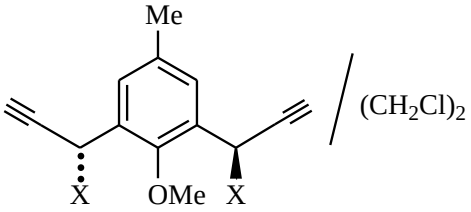
TBS = *t*-BuMe_2Si–

Synthesis of calixarenes, substituted at two *meso* positions:

The reaction of **96a** with diyne (*R*,*R*) **97** (X=OMe) afforded the mixture of *cone* and *paco* conformers of calixarene **99**, substituted at two *meso* positions, the major species being *cone* **99.** Similarly the reaction of **96a** with diyne (*R*,*R*) **98** (X=OTBS) afforded the mixture of *cone* and *paco* conformers of calixarene **100**, the major product being *cone* **100**. Upon removal of the TBS group from **100**, the calixarene (*S*,*S*) **101**, substituted at two *meso* positions, existing exclusively as *cone* conformer was obtained.

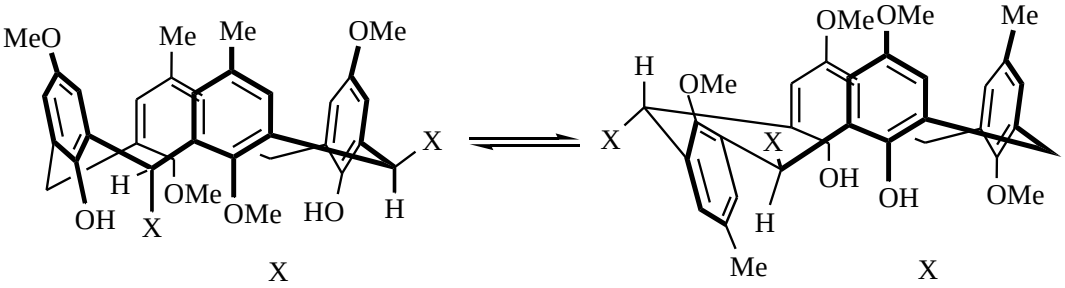


96a



(*R*,*R*) **97** OMe

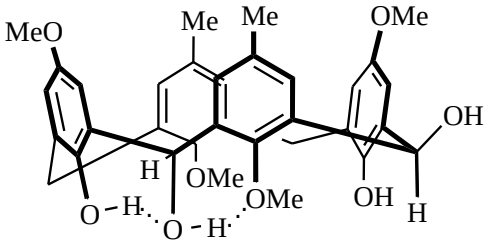
(*R*,*R*) **98** OTBS



	X
cone **99**	OMe
cone **100**	OTBS

	X
paco **99**	OMe
paco **100**	OTBS

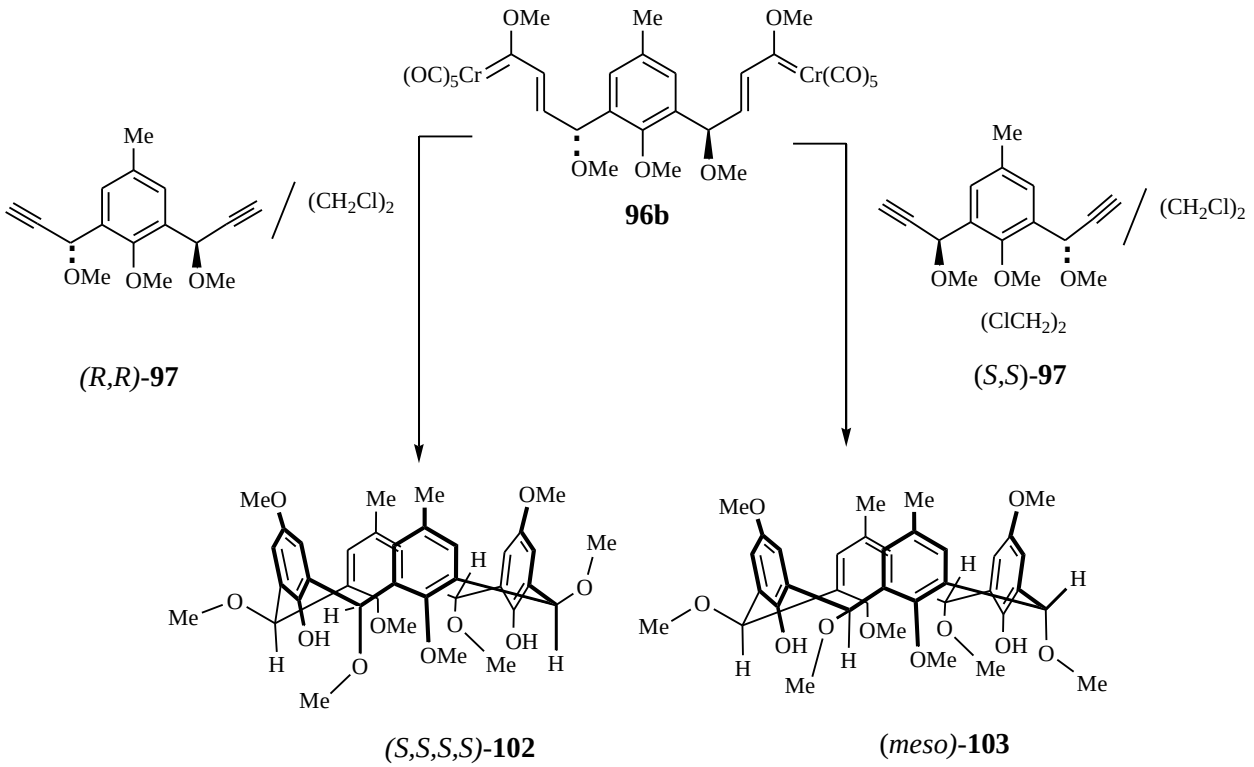
TBAF
(for X = OTBS)



(*S*,*S*)-**101**

Synthesis of calixarenes substituted at four *meso* positions:

The biscarbene complex **96b** reacts with diyne (*R*,R)-**97** to give *meso* tetrasubstituted calixarene (*S*,*S*,*S*,*S*) **102** existing as a single *cone* conformer and reacts with diyne (*S*,*S*)-**97** affording, as expected, optically inactive (*meso*)-**103**.



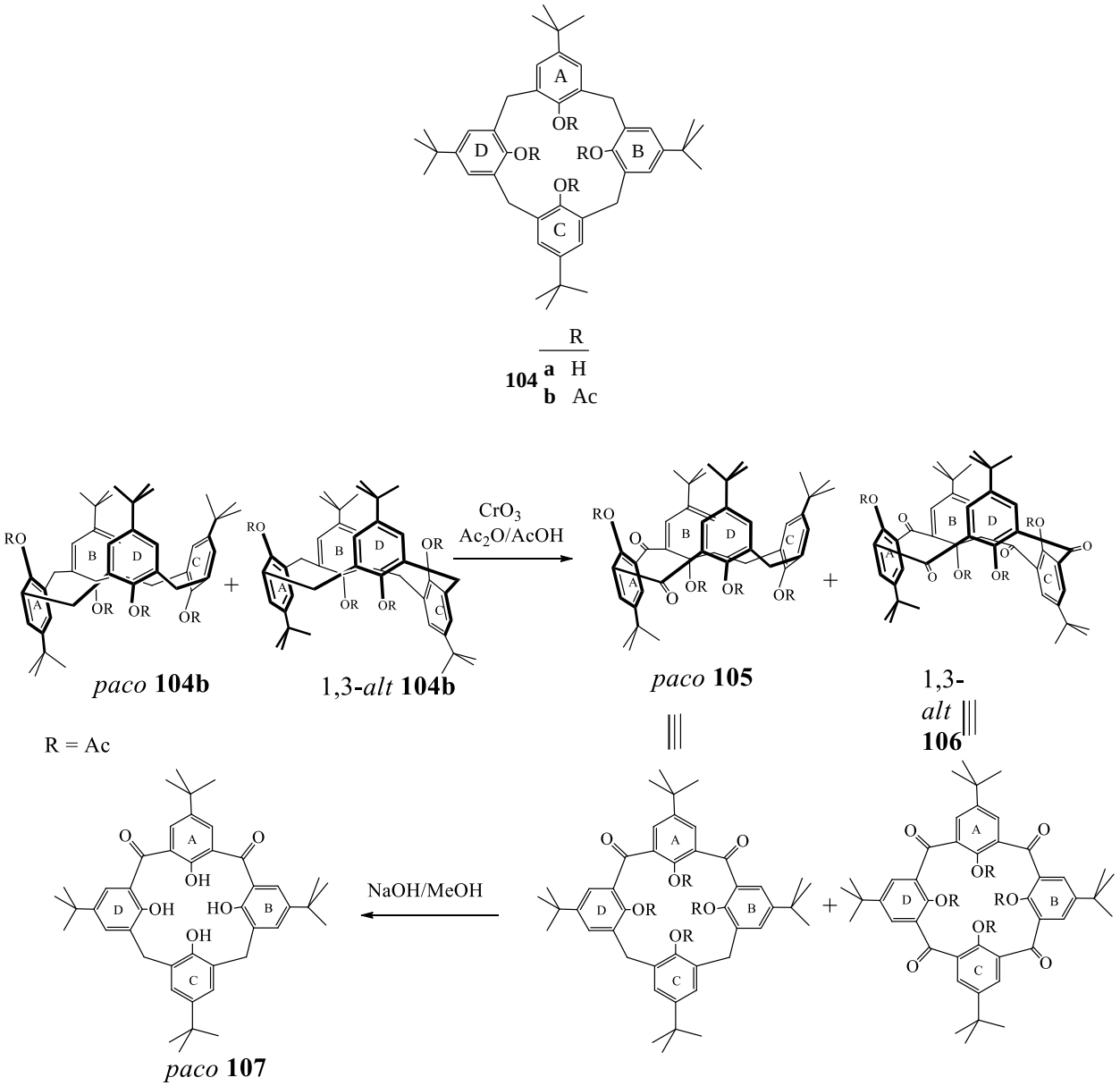
In conclusion, the above syntheses are an interesting approach to chiral calixarenes substituted at two and at all *meso* positions.[46]

5. Ketocalixarenes

Ketocalixarenes are a class of compounds which may be regarded as calixarenes functionalized by carbonyl groups situated at their *meso* positions; they are interesting as synthons for various target products, among them *meso*-substituted calixarenes. Selected examples of syntheses and reactivity of ketocalixarenes are described below.

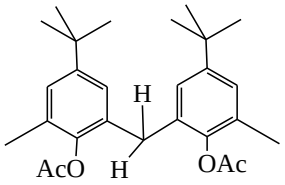
The synthesis of ketocalixarenes may be achieved by oxidation of calixarene **104b** at the *meso* positions using CrO_3. In contrast to **104a**, the starting calixarene **104b** containing four acetate groups is conformationally rigid, because the rotation of the rings through the annulus is blocked by the bulky acetate substituents. Therefore **104b** exists as different atropoisomers rather than the usual types of conformers.

The acetylation of **104a** afforded the starting calixarene **104b** as a mixture of *paco* **104b** and 1,3-*alt* **104b**. This atropoisomeric mixture upon treatment with CrO_3 in boiling Ac_2O/AcOH yielded a mixture of *paco* **105** (from *paco* **104b**) and 1,3-*alt* **106** (from 1,3-*alt* **104b**), which could be separated by fractional crystallization. The basic hydrolysis of *paco* **105** afforded *paco* diketocalixarene **107** with the carbonyl groups in *cis* positions.[51]

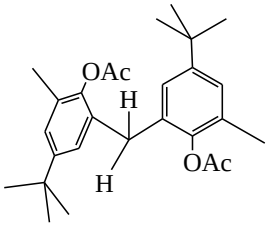


During CrO_3 oxidation it was found that the rotation of the aryl rings through the annulus does not occur, and that only *meso* positions connected to geminal rings anti, *i.e.* rings pointing to opposite directions can be oxidized; the *meso* positions which are between rings *syn*, *i.e.* rings pointing out to the same direction, cannot be oxidized.

Therefore, *paco* **104b**, in which only two methylene groups connected with the ring **A** are located between *anti* rings, are oxidized to give diketocalixarene *paco* **105**, whereas 1,3-*alt* **104b**, in which all methylene groups are located between rings *anti*, is oxidized to tetraketocalixarene 1,3-*alt* **106**.[51]

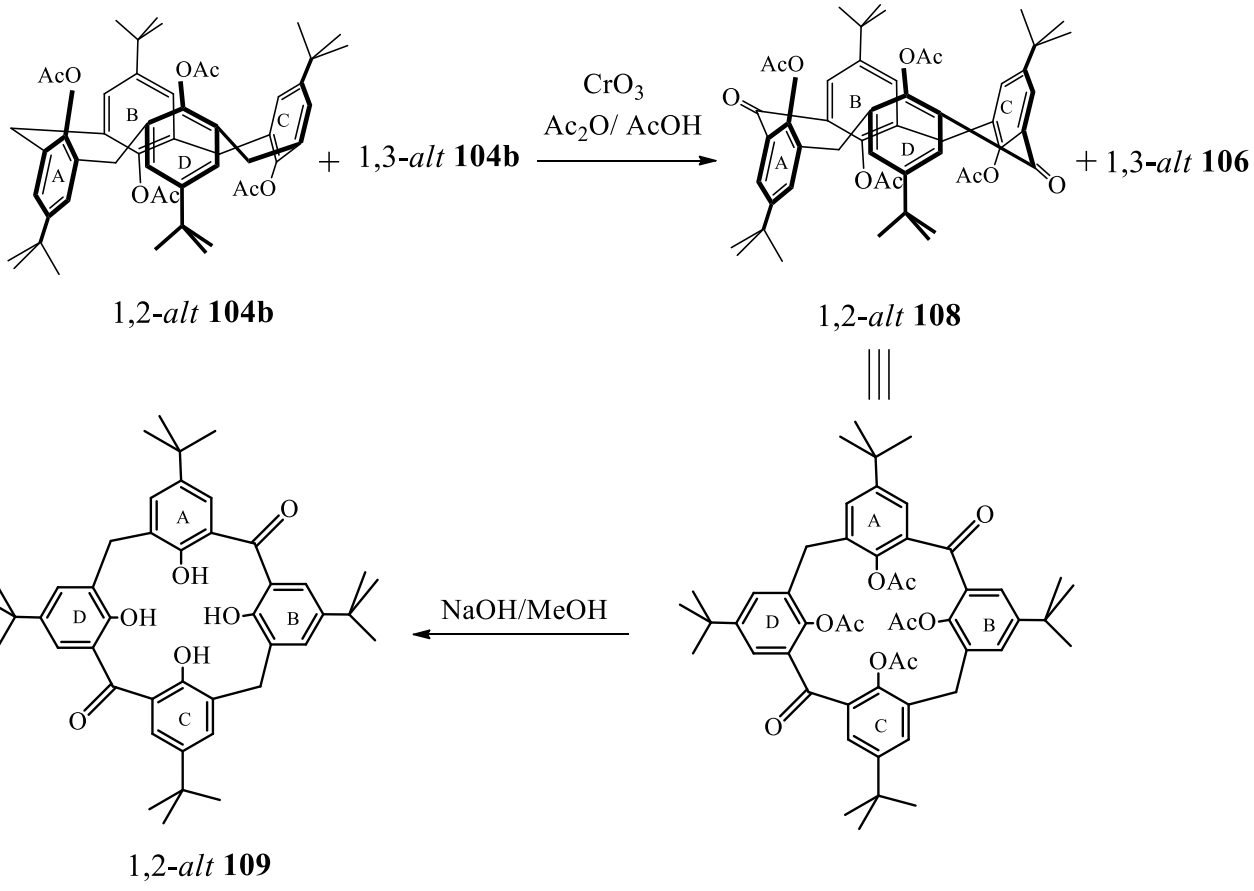


syn
(no oxidation)

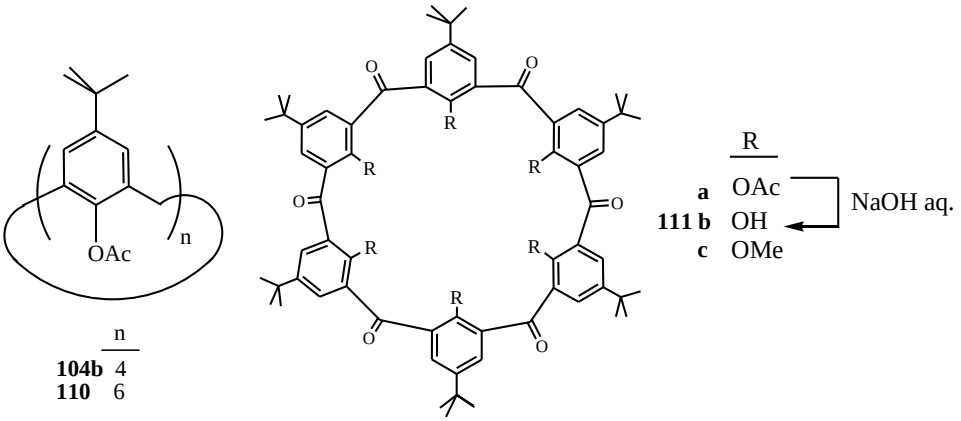


anti
(oxidation occurs)

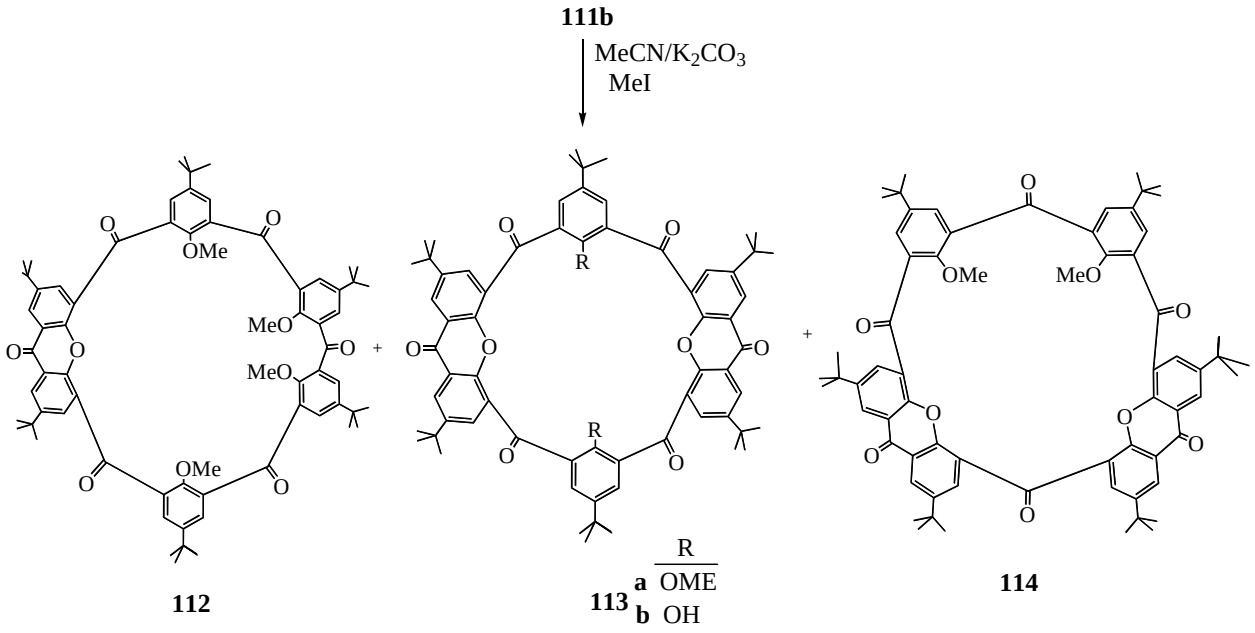
In order to obtain diketocalixarene with carbonyl groups in *trans* positions, the mixture of 1,2-*alt* **104b** and 1,3-*alt* **104b** (9:1) was oxidized with CrO_3 to give 1,2-*alt* **108** (from 1,2-*alt* **104b**) and 1,3-*alt* **106** (from 1,3-*alt* **104b**). The basic hydrolysis of 1,2-*alt* **108** yielded 1,2-*alt* **109**.[51]



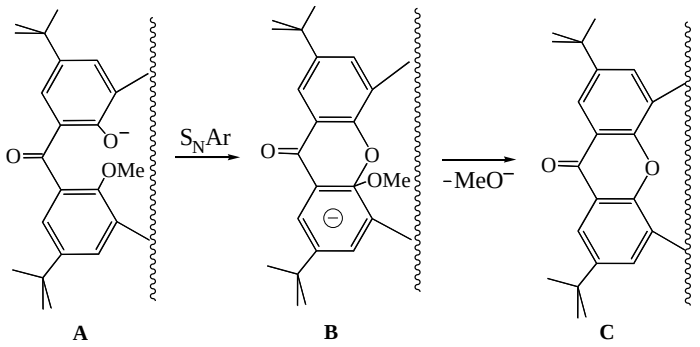
Calixarene **110** was oxidized with CrO_3 to give ketocalix[6]arene **111a** which upon basic hydrolysis afforded ketocalix[6]arene **111b**. This experiment was followed by the base-catalyzed methylation of **111b** in order to obtain the ketocalixarene **111c**.



However, reaction of **111b** with MeI in MeCN in the presence of K_2CO_3 as a base did not give the expected **111c**, instead the monoxanthone calixarene **112** and three calixarenes **113a,b** and **114** containing two xanthone moieties were obtained.[52]



In the above process the formation of xanthone groups under methylation conditions is facilitated by the activating influence of the carbonyl groups which enables the intramolecular S_NAr reaction between a methylated benzene ring and a neighboring phenolate serving as a nucleophile (**A→B→C**). It should be pointed out that **111b** is able to form such xanthone derivatives, whereas for lower calixarenes it would be impossible, since the large calixarene can better accomodate the increased strain resulting from the presence of the rigid xanthone group.

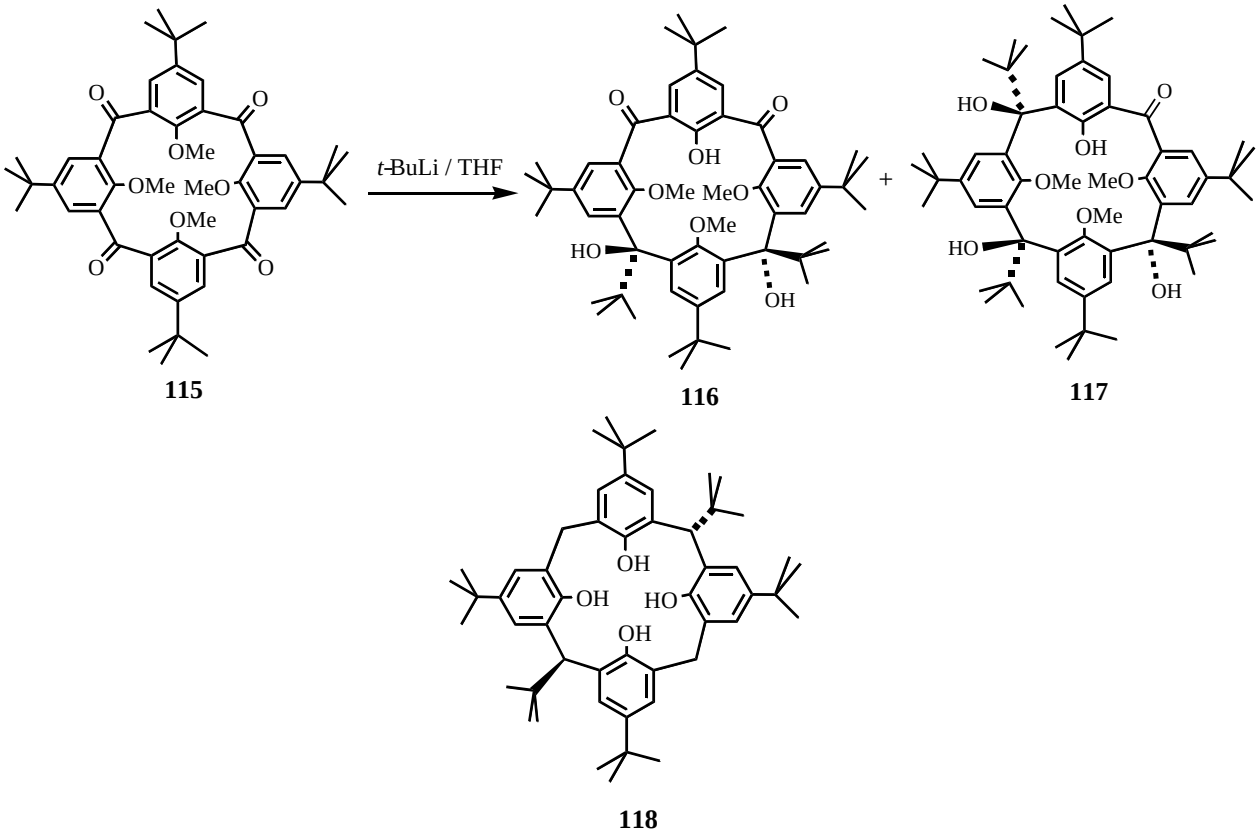


A **B** **C**

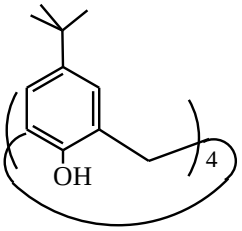
Using a large excess of MeI, dimethylacetamide as a solvent, and Cs_2CO_3 as a base, **111b** could be converted into desired **111c**.[52]

Studying the reactivity of ketocalixarenes it was found that tetraketocalixarene **115** upon treatment with excess *t*-BuLi yielded a complex mixture, with **116** as a major product. Recrystalization of the crude product from $CHCl_3$/acetone afforded a mixture of **116**, di-*t*-butylated at two bridges, and **117**, tri-*t*-butylated at three bridges. It should be emphasized that **116** and **117** are rare examples of calixarenes containing two different functionalities at the *meso* bridges. In the above reaction, one of the four methoxy groups of **115** was cleaved; compounds **116** and **117** bear only three methoxy groups at the narrow rim. Rotation of the *t*-butyl groups situated at the *meso* bridges in calixarenes **116** and **117** is restricted due to steric hindrance.[53]

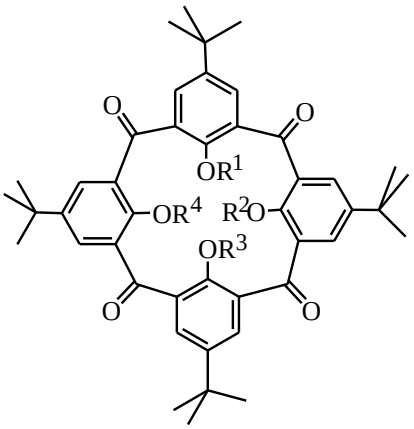
By way of contrast, the rotation of *t*-butyl groups is not restricted in the *cone* calixarene **118** in which two opposite bridges are substituted by *t*-butyl groups.



Investigation of the dimethylation and dibenzylation reactions of tetraketocalixarene **119a** has shown that they afford proximal (*i.e.* disubstituted in neighboring rings) products **119c** and **119f**.[54] The result of these processes is other than in the case of the parent **22** which upon the same reactions affords distal, (*i.e.* disubstituted in opposite rings) products.

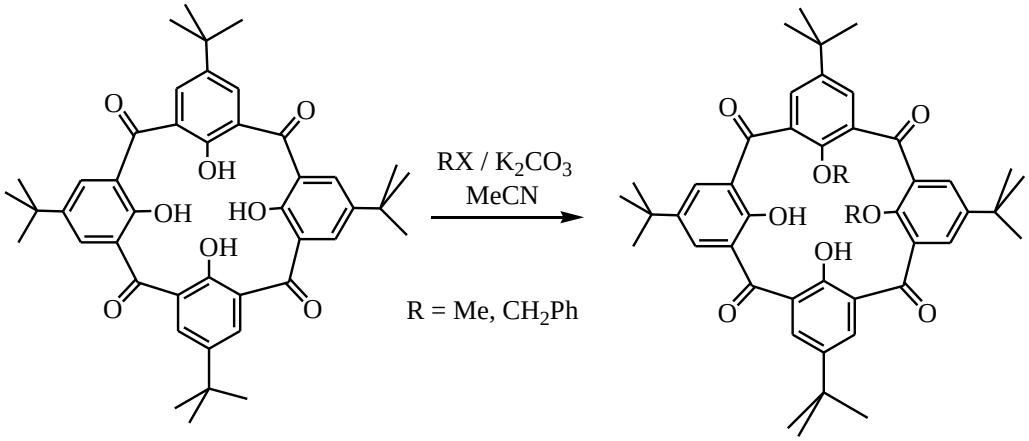


22



		R^1	R^2	R^3	R^4
119	**a**	H	H	H	H
	b	Me	H	H	H
	c	Me	Me	H	H
	d	Me	Me	Me	H
	e	Me	Me	Me	Me
	f	Bz	Bz	H	H
	g	Bz	Bz	Bz	Bz

119a-g



119a

	R
119 **c**	Me
f	Bz

The methylation products were mono- and di-substituted tetraketocalixarenes **119b** and **119c**, respectively; the increased amount of a base gave rise to formation of tri- and tetramethylated compounds **119d** and **119e**. The benzylation afforded di- and tetrasubstituted products **119f** and **119g**, respectively.

In contrast to parent calixarene **22** which has the *cone* conformation, the tetraketocalixarene **119a**, along with its substituted products **119b-g** adopts the 1,3-*alt* conformation.[54]

6. Conclusion

Calixarenes functionalized at their *meso* positions have been studied in order to achieve new products having desired properties. Since the investigation of calixarenes dealing with their syntheses, reactivity and a large variety of applications is very intense, [55-70] only selected examples of considered compounds are described in this review.

There are relatively few reports concerning functionalization of calixarenes at *meso* positions, compared to reports on modification of their wide and narrow rims, therefore it seemed of interest to review works on substitution of their *meso* positions, and to pay attention to the usefulness of obtained species for further reactions, which are often difficult to perform using other methods.

7. Acknowledgement

The financial support of this work provided by Polish Science Foundation (Grant NN 209441539) is gratefully acknowledged.

8. References

1. Gutsche, C.D. Calixarenes: An Introduction, Monographs in Supramolecular Chemistry, Royal Soc. Chem.: Cambridge, 2008.
2. Mokhtari, B.; Pourabdollah, K.; Dalali, N. *Chromatographia* **2011**, *73*, 829.
3. Joseph, R.; Rao, C. P. *Chem. Rev.* **2011**, *111*, 4658.
4. Vicens, J.; Harrowfield, J., Eds.; Calixarenes in the Nanoworld, Springer Verlag: Dordrecht, 2007.
5. Maity, D.; Chakraborty, A.; Gunupuru, R.; Paul, P. *Inorg. Chim. Acta* **2011**, *372*, 126.
6. Matvieiev, Y.; Karpenko, I.; Kulinich, A.; Ryabitskii, A.; Pivovarenko, V.; Shishkina, S.; Shishkin, O.; Kalchenko, V. *Tetrahedron Lett.* **2011**, *52*, 3922.
7. Makrlik, E.; Vanura, P.; Selucky, P. *J. Radioanal. Nucl. Chem.* **2011**, *287*, 899.
8. Qazi, M. A.; Qureshi, I.; Memon, S. *J. Fluoresc.* **2011**, *21*, 1231.
9. Yang, Y.; Lee, E. K.; Zhou, H.; Surowiec, K.; Bartsch, R. A. *J. Incl. Phenom. Macrocycl. Chem.* **2011**, *70*, 197.
10. Hu, K.; Zhao, W.; Wen, F.; Liu, J.; Zhao, X.; Xu, Z.; Niu, B.; Ye, B.; Wu, Y.; Zhang, S. *Talanta* **2011**, *85*, 317.
11. Goodworth, K.; Hervé, A.-C.; Stavropoulos, E.; Hervé, G.; Casades, I.; Hill, A. M., Weingarten, G. G.; Tascon, R. E.; Colston, M. J.; Hailes, H. C. *Tetrahedron* **2011**, *67*, 373.
12. Solovyov, A. V.; Cherenok, S. O.; Kalchenko, O. I.; Atamas, L. I.; Kazantseva, Z. I.; Koshets, I. A.; Tsymbal, I. F.; Kalchenko, V. I. *J. Mol. Liquids* **2011**, *159*, 117.
13. Düker, M. H.; Gómez, R.; Vande Velde, C. M. L.; Azov, V. A. *Tetrahedron Lett.* **2011**, *52*, 2881.
14. Hudecek, O.; Curinova, P.; Budka, J.; Lhoták, *Tetrahedron* **2011**, *67*, 5213.
15. Maji, P. *Inorg. Chim. Acta*, **2011**, *372*, 120.
16. Makrlik, E.; Ćajan, M.; Budka, J.; Vañura, P. *Monatsh. Chem.* **2011**, *142*, 5.
17. Sayin, S.; Yilmaz, M. *Desalination* **2011**, *276*, 328.

18. Sliwa, W.; Kozlowski, C. Calixarenes and Resorcinarenes. Synthesis, Properties and Applications, Wiley-VCH, Weinheim, **2009**.
19. Sliwa, W.; Deska, M. *Arkivoc* **2011**, *1*, 496.
20. Deska, M.; Sliwa, W. Covalently and noncovalently bound assemblies of calixarenes, Nova Science Publishers, Inc.: New York, 2011.
21. Sliwa, W.; Girek, T. *J. Incl. Phenom. Macrocycl. Chem.* **2010**, *66*, 15.
22. Sliwa, W.; Deska, M. *Arkivoc* **2008**, *1*, 87.
23. Scully, P. A.; Hamilton, T. M.; Bennett, J. L. *Org. Lett.* **2001**, *3*, 2741.
24. Hertel, M. P.; Behrle, A. C.; Williams, S. A.; Schmidt, J. A. R.; Fantini, J. L. *Tetrahedron* **2009**, *65*, 8657.
25. Gruner, M.; Fischer, C.; Gruber, T.; Weber, E. *Supramolecular Chem.* **2010**, *22*, 256.
26. Fischer, C.; Seichter, W.; Weber, E. *Struct. Chem. Commun.* **2010**, *1*, 43.
27. Fischer, C.; Gruber, T.; Seichter, W.; Weber, E. *Org. Biomol. Chem.* **2011**, *9*, 4347.
28. Gruber, T.; Gruner, M.; Fischer, C.; Seichter, W.; Bombicz, P.; Weber, E. *New. J. Chem.* **2010**, *34*, 250.
29. Atwood, J.L.; Steed, J.W. *Eds, Organic Nanostructures,* Wiley-VCH: Weinheim, 2008.
30. Ozcan, F.; Sahin, O.; Yilmaz, M. *J. Inclusion Phenom. Macrocycl. Chem.* **2009**, *63*, 123.
31. Itzhak, N.; Biali, S. E. *J. Org. Chem.* **2010**, *75*, 3437.
32. Simaan, S.; Biali, S. E. *J. Org. Chem.* **2003**, *68*, 3634.
33. Simaan, S.; Agbaria, K.; Biali, S. E. *J. Org. Chem.* **2002**, *67*, 6136.
34. Simaan, S.; Biali, S. E. *J. Org. Chem.* **2004**, *69*, 95.
35. Agbaria, K.; Aleksiuk, O.; Biali, S. E.; Böhmer, V.; Frings, M.; Thondorf, I. *J. Org. Chem.* **2001**, *66*, 2891.
36. Fischer, C.; Lin, G.; Seichter, W.; Weber, E. *Tetrahedron* **2011**, *67*, 5656.
37. Middel, O.; Greff, Z.; Taylor, N. J.; Verboom, W.; Reinhoudt, D. N.; Snieckus, V. *J. Org. Chem.* **2000**, *65*, 667.
38. 38 Simaan, S.; Biali, S. E. *J. Org. Chem.* **2003**, *68*, 7685.
39. Simaan, S.; Biali, S. E. *Org. Lett.* **2005**, *7*, 1817.
40. Columbus, I.; Biali, S. E. *J. Org. Chem.* **2008**, *73*, 2598.
41. Kogan, K.; Biali, S. E. *J.Org. Chem.* **2009**, *74*, 7172.
42. Kogan, K.; Columbus, I.; Biali, S. E. *J. Org. Chem.* **2008**, *73*, 7327.
43. Columbus, I.; Biali, S. E. *Org. Lett.* **2007**, *9*, 2927.
44. Kuno, L.; Seri, N.; Biali, S. E. *Org. Lett.* **2007**, *9*, 1577.
45. Kuno, L.; Biali, S. E. *J. Org. Chem.* **2009**, *74*, 48.
46. Gopalsamuthiram, V.; Predeus, A. V.; Huang, R. H.; Wulff, W. D. *J. Am. Chem. Soc.* **2009**, *131*, 18018.
47. Waters, M. L.; Wulff, W. D. *Org. React.* **2008**, *70*, 121.
48. Gopalsamuthiram, V.; Wulff, W. D. *J. Am. Chem. Soc.* **2004**, *126*, 13936.
49. Wang, H.; Huang, J.; Wulff, W. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **2003**, *125*, 8980.
50. Moore, D.; Pu, L. *Org. Lett.* **2002**, *4*, 1855.

51. Seri, N.; Thondorf, I.; Biali, S. E. *J. Org. Chem.* **2004**, *69*, 4774.
52. Kogan, K.; Biali, S. E. *Org. Lett.* **2007**, *9*, 2393.
53. Kuno, L.; Biali, S. E. *Org. Lett.* **2009**, *11*, 3662.
54. Seri, N.; Biali, S. E. *J. Org. Chem.* **2005**, *70*, 5278.
55. Genorio, B.; Subbaraman, R.; Strmcnik, D.; Tripkovic, D.; Stamenkovic, V. R.; Markovic, N. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 5468.
56. Kulesza, J.; Bocheńska, M. *Eur. J. Inorg. Chem.* **2011**, 777.
57. Mačková, M.; Himl, M.; Minářová, L.; Lang, J.; Lhoták, P. *Tetrahedron Lett.* **2011**, *52*, 2543
58. Chen, M.; Shang, T.; Liu, J.; Diao, G. *J. Chem. Thermodynamics* **2011**, *43*, 88.
59. Maffei, F.; Betti, P.; Genovese D.; Montalti, M.; Prodi, L.; De Zorzi, R.; Geremia, S.; Dalcanale, E. *Angew. Chem. Int. Ed.* **2011**, *50*, 4654.
60. Ho, I.-T.; Chu, J.-H.; Chung, W.-S. *Eur. J. Org. Chem.* **2011**, 1472.
61. Solangi, I. B.; Bhatti, A. A.; Kamboh, M. A.; Memon, S.; Bhanger, M. I. *Desalination* **2011**, *272*, 98.
62. Bonvallet, P. A.; Mullen, M. R.; Evans, P. J.; Stoltz, K. L.; Story, E. N. *Tetrahedron Lett.* **2011**, *52*, 1117.
63. Fang, L.; Wang, C.; Fahrenbach, A. C.; Trabolsi, A.; Botros, Y. Y.; Stoddart, J. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 1805.
64. Memon, S.; Memon, N.; Memon, S.; Latif, Y. *J. Hazardous Materials* **2011**, *186*, 1696.
65. da Silva, D. L.; do Couto Tavares, E.; de Souza Conegero, L.; de Fatima, A.; Pilli, R. A.; Fernandes, S. A. *J. Incl. Phenom. Macrocycl. Chem.* **2011**, *69*, 149.
66. Chennakesavulu, K.; Raviathul Basariya, M.; Sreedevi, P.; Bhaskar Raju, G.; Prabhakar, S.; Rao, S.S. *Termochimica Acta* **2011**, *515*, 24.
67. Kim, S.-H.; Hwang, I.-J.; Gwon, S.-Y.; Burkinshaw, S. M.; Son, Y.-A. *Dyes and Pigments* **2011**, *88*, 84.
68. Morales, A.; Santana, A.; Althoff, G.; Melendez, E. *J. Organomet. Chem.* **2011**, *696*, 2519.
69. Monnereau, C.; Rebilly, J.-N.; Reinaud, O. *Eur. J. Org. Chem.* **2011**, 166.
70. Gharib, F.; Hajmalek, M.; Alamoti, R. A.; Farajtabar, A. *J. Mol. Liquids* **2011**, *159*, 161.

