Synthetic developments in host–guest chemistry

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Reviewing the literature published between January and December 1995
Continuing the coverage in *Contemporary Organic Synthesis*, 1995, **2**, 289

1 Introduction

Nature's host–guest systems achieve very impressive levels of selectivity and utility. Since the discovery of dibenzo-18-crown-6 and its ability to form stable complexes with alkali metals by Pedersen in 1967,[1] the synthesis and testing of the properties of artificial receptors have become regular features in the literature. While, not surprisingly, most emphasis is placed upon the actual recognition properties of these receptors, the development of efficient syntheses is always an important consideration. The transfer of a receptor from a figment of its designer's imagination to reality often involves far from trivial work and so the dissemination of the tricks of the synthetic supramolecular chemist's trade is a necessary task. The purpose of this article is to review synthetic developments in host–guest chemistry over the period January 1995 to December 1995.[2] As before, the review is divided into sections using the conventional categories of receptor type but due to the increasing 'cross-pollination' between these subspecies with features of one occurring in another, the categorization can be somewhat arbitrary.

2 Crowns, cryptands and podands

Two general reviews have appeared this year dealing with the design and synthesis of macrocyclic structures. One concentrates on the use of Schiff bases as linking moieties,[3] and the other on hosts for lanthanides and actinides.[4]

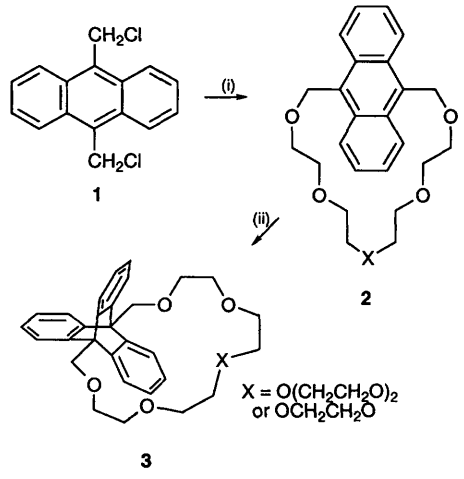
2.1 Crown ethers

One of the constant problems in the synthesis of crown ethers and macrocycles in general is the macrocyclization step. One method of obtaining high yields of cyclic oligomers in preference to polymer is to use a template. Tris(2-methoxyphenyl)bismuthane has been reported to work as both a mild dehydrating agent and a good template in macrocyclic ester synthesis.[5] The synthesis of macrocyclic esters has previously been reported to proceed in only low yields (1–30%) using high-dilution condensations of diacid dichlorides and glycols. The bismuthane templated the reaction of dicarboxylic acid anhydride and glycols at higher concentration, giving higher yields of the 1:1 adduct (13–83%).

Preorganization of reactants is also a common strategy for efficient macrocyclization. Using this idea, Jenneskens and co-workers have reported the formation and isolation of huge cyclic oligomers from an untemplated ester polycondensation in *ca.* 30% overall yield.[6] The reaction of 1,5-bis-(1-hydroxy-3,6,9-trioxanonyl)naphthalene and terephthaloyl chloride gave crownophanes with $30n$ ($n = 1$–5) atom perimeters. The authors suggest favourable pre-orientation of the rigid diol as the reason for the relatively high degree of intramolecular ring closure.

If triptycene is used as a structural component of crown ethers, there is the possibility of it acting not only as a rigid spacer but also as a donor for cation-π-interactions with guests. The synthesis of the first triptycenocrown ethers **3** was achieved in a two-step

procedure which comprised condensation of 9,10-bis(chloromethyl)anthracene **1** with polyethylene glycols to yield intermediate 9,10-anthracenocrown ethers **2** followed by cycloaddition of benzyne to the anthracene moiety (**Scheme 1**).[7]



1 2 3

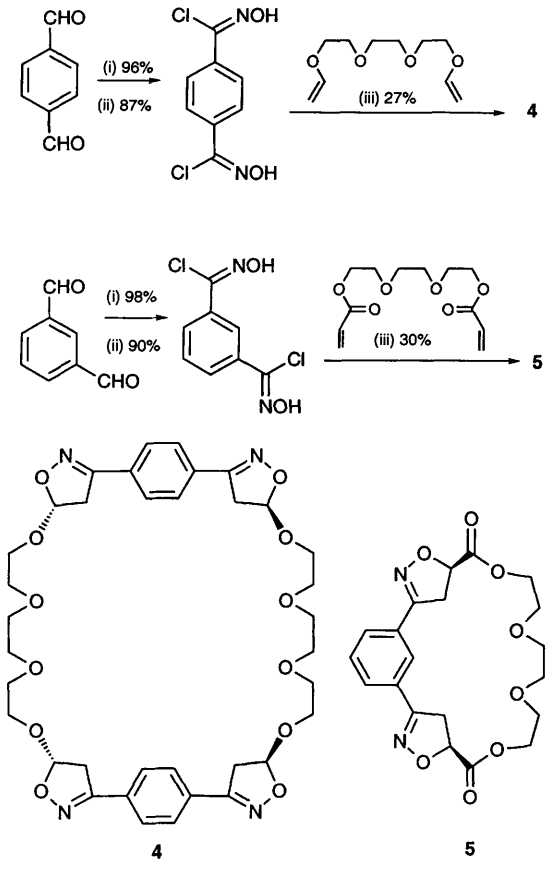
Reagents: (i) $HO(CH_2CH_2O)_nH$ (n = 5 or 6), KOH, Bu^{t}OH, reflux 6–8 h; (ii) o-$H_2NC_6H_4COOH$, $(CH_3)_2CHCH_2CH_2ONO$, CH_2Cl_2, reflux 6 h

Scheme 1

Crown-type cavities can be prepared by metal-assisted organization of linear oligo(oxyethylene). Both tropolonoid moieties[8] and β-diketones[9] have been used at the terminal, metal-binding ends of the prehost.

Two groups have reported the use of double or quadruple cycloadditions as a method of macrocyclization of crown ethers. Thus the reactions of alkyne dipolarophiles with azides have been described,[10] and Kim and co-workers have reacted dihydroximoyl chlorides prepared from dialdehydes with divinyl ethers or acrylates.[11] When using tetraethylene glycol diacrylate as dipolarophile, a *para*-related bifunctional dipole provided the [2+2] cycloadduct **4**, and a *meta*-related bifunctional dipole yielded the [1+1] cycloadduct **5** (**Scheme 2**).

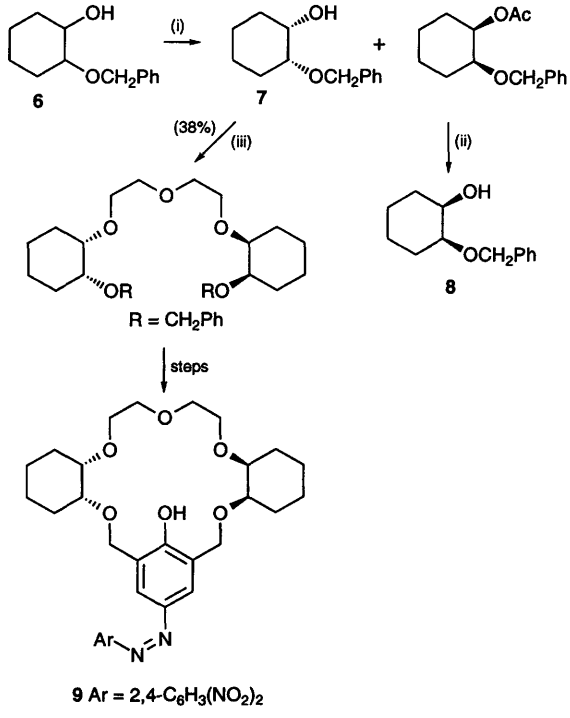
Chiral crown ethers are of interest because of their potential as enantioselective hosts. An optically active crown ether that relies solely on *cis*-cyclohexane-1,2-diol for its chirality has been reported.[12] This diol was desymmetrized by conversion of one of the hydroxy groups to a benzyloxy group and the resulting racemate **6** was enantioselectively acylated by lipase YS (from *Pseudomonas fluorescens*) with vinyl acetate as acylating agent. The two products of this reaction could be separated by chromatography providing easy access to large quantities of both 2-benzyloxycyclohexanol enantiomers **7** and **8** and, after several steps, both enantiomers of the azophenolic crown ether e.g. **9** (**Scheme 3**). Chiral crown ethers have also been prepared using D-glucose as structural units, for instance the bis-gluco-crown ether **10** (**Scheme 4**).[13]



4 5

Reagents: (i) NH_2OH•HCl; (ii) NCS; (iii) Et_3N, EtOH (10 mM)

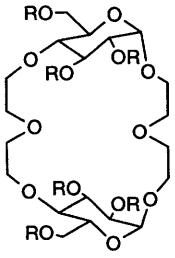
Scheme 2



9 Ar = 2,4-$C_6H_3(NO_2)_2$

Reagents: (i) lipase YS, CH_2=CHOAc; (ii) conc HCl, MeOH; (iii) $MeSO_2OCH_2CH_2OCH_2CH_2OSO_2Me$, NaH

Scheme 3



10 R = OCH_2Ph

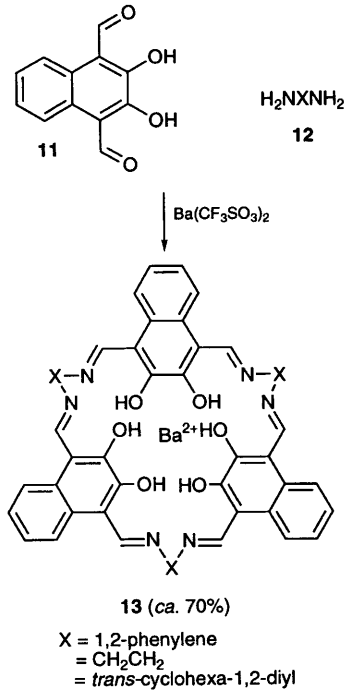
Scheme 4

The palladium-catalysed Heck arylation of alkenes has proved a valuble synthetic method for the elaboration of moieties on the periphery of a crown ether though removal of homogeneous catalyst can some times be problematic. The use of polymeric palladium catalysts however has been reported to effect the vinylation of 4′-iodobenzo-crown ethers in good yields (45–85%) with the catalyst being completely removed by filtration.[14]

2.2 Azacrown ethers and related compounds

There are several common, general procedures for the synthesis of azacrowns and the use of tosylated synthons in azacrown construction is a popular one. Such tosylated synthons played a pivotal role in the first unequivocal syntheses of 1- and 8-*N*-mono-substituted 1,4,8,12-tetraazacyclopentadecane which has been reported by Granier and Guilard.[15] Gu and Bowman-James have used a tosylated synthon strategy to prepare a series of new macrocycles containing four pendant arms and ranging in size from 18- to 24-membered rings.[16] Their strategy, which also entails the [1 + 1] addition of two different halves, enables the construction of symmetrically and asymmetrically *N*-substituted polyazaoxamacrocycles. Wu and co-workers have reported the use of 1,3-dichloropropan-2-ol with bis-*N*-tosylamides with sodium ethoxide in ethanol acting as base, as a facile method for the preparation of hydroxyl-*N*-tosylcyclams in moderate yields (31–57%).[17] New conditions for rapid and high-yielding detosylation of linear and macrocyclic tosylamides have been described by Lázár.[18] The use of 50% concentrated sulfuric acid solution at 170–180 °C produced detosylated product in only five to eight minutes. This compares favourably with the common conditions involving the use of 10% sulfuric acid solutions at 100–110 °C which require reaction times of the order of days.

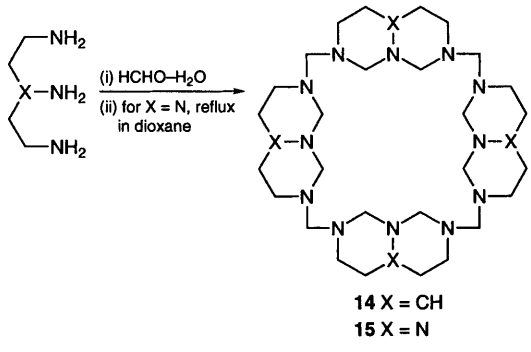
Picard and co-workers have described methods for construction of polyoxa- and polyaza-macrocycles *via* tetralactam formation using stepwise amide bond-forming reactions[19] while Reinhoudt and co-workers have used Schiff-base formation for the synthesis of host **13** which combines a crown ether-like interior with linking salen units.[20] Cyclization of the dialdehyde **11** with diamine **12** in the presence of barium cations as



Scheme 5

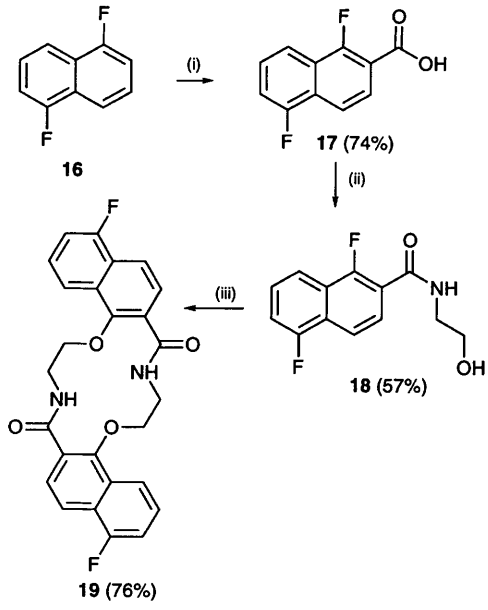
templates gave **13** in approximately 70% yield (**Scheme 5**).

The syntheses of the two nonacyclic structures **14** and **15** were reported by Dale and co-workers.[21] These interesting structures were formed in one-pot procedures, **14** by reaction of an aqueous solutions of pentane-1,3,5-triamine with formaldehyde, and **15** by reaction of 1,1-bis(2-aminoethyl)hydrazine and formaldehyde under similar conditions followed by reflux in dioxane. Macrocyclic **14** precipitated from the reaction mixture in 100% yield (**Scheme 6**).



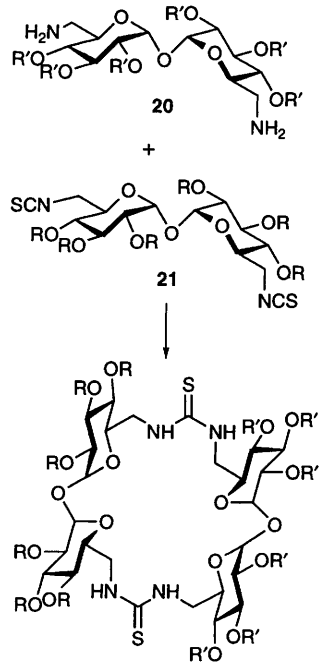
Scheme 6

A bimolecular cyclization process using nucleophilic substitution of an aryl fluoride has been used to form naphtho- and biaryl-fused 1,8-diaza-14-crown-4 macrocycles.[22] The ability of fluoride to direct *ortho*-metallation enabled preparation of, for instance, 1,5-difluoronaphthalene-2-carboxylic acid **17** from 1,5-difluoronaphthalene **16** in 74% yield. Acid **17** was then converted to hydroxyamide **18** and bimolecular cyclization with NaH in DMF at



Reagents: (i) (*a*) TMEDA, Bu^{s}Li, –78 °C; (*b*) solid CO_2, Et_2O, –78 °C; (ii) (*a*) $SOCl_2$, reflux; (*b*) $H_2NCH_2CH_2OH$, CH_2Cl_2, NaOH, H_2O; (iii) NaH, DMF

Scheme 7



R = Ac or TMS
R′ = H, Ac or TMS

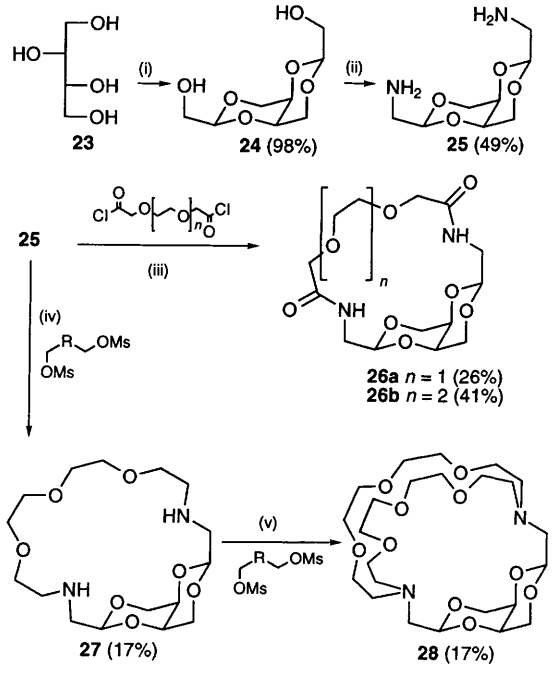
Scheme 8

ambient temperature provided the bis-naphtho-fused macrocycle **19** (**Scheme 7**) in good yield.

An interesting series of macrocycles which provide a rigid ring of oxygen- and nitrogen-containing functionality analogous to azacrowns are the cyclic oliogosaccharides **22** which were constructed from two α,α′-trehalose units connected by thiourea bridges.[23] These macrocycles were assembled by reaction of 6,6′-diamino derivative of α,α′-trehalose **20** with a 6,6′-diisothiocyanate derivative **21** in 40–65% yield (**Scheme 8**). Fuchs and co-workers have built receptors using the 1,3,5,7-tetraoxadecalin diacetal system.[24] The synthesis begins with the condensation of *rac*- or D-threitol **23** with hydroxyacetalaldehyde, and the conversion of the bis(hydroxymethyl) derivative **24** so produced to the diamine **25**. This precursor was then used to form macrocyclic dilactams **26** using tri- and tetra-glycolic acid dichloride, and diaza-crown **27** and cryptand **28** using respectively one and two equivalents of triethyleneglycol bis(trifluoro-methanesulfonate) (**Scheme 9**).

The intramolecular coupling of aromatic diimines has been shown to be an effective method for the synthesis of a variety of nitrogen-containing macrocycles.[25] Electroreduction or chemical reduction with zinc has produced various ring sizes of 1,4-diazacrown ethers from bis(iminoethers)(e.g. **29**→**30**), macrocyclic bislactones from bis(imino-esters) (e.g. **31**→**32**) and macrocyclic bislactams from bis(iminoamides) (e.g. **33**→**34**) in mostly good yields (26–90%) (**Scheme 10**).

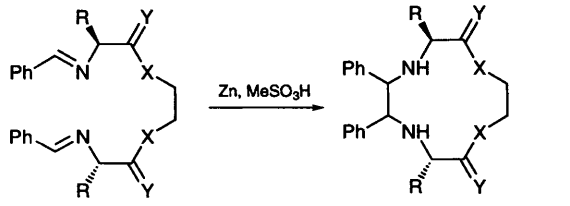
Yoon and co-workers have shown that photocyclization reactions of *N*-[(ω-trimethylsilyl-methoxy)polyoxalkyl]phthalimides **35** gave azacrown



R = $[CH_2OCH_2]_3$

Reagents: (i) $HOCH_2CHO$, HCl 1 M, 15 min; (ii) (*a*) CH_2SO_3Cl, NEt_3, DMF; (*b*) DMF, NaN_3; (*c*) MeOH, Pd/C, H_2; (iii) DMF, K_2CO_3, 90 °C, 7 d; (iv) CH_3CN, K_2CO_3, 80 °C, 5 d; (v) CH_3CN, K_2CO_3, 80 °C

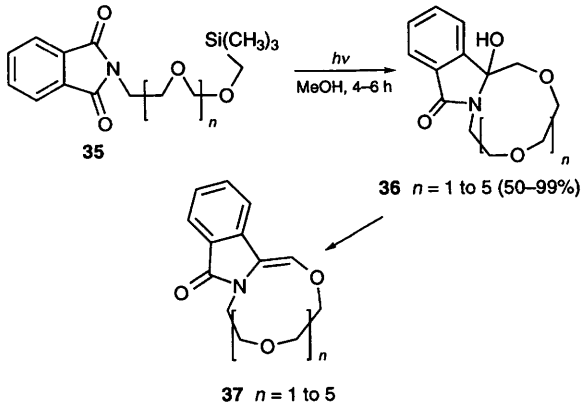
Scheme 9



29 R = H, Y = H_2, X = O
31 R = Pr^i, Y = O, X = O
33 R = H, Y = O, X = NH

30 R = H, Y = H_2, X = O, (90%)
32 R = Pr^i, Y = O, X = O, (53%)
34 R = H, Y = O, X = NH, (41%)

Scheme 10



35

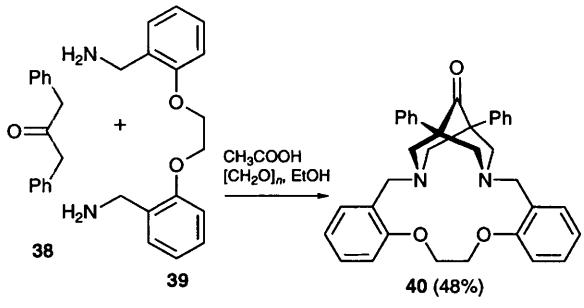
36 *n* = 1 to 5 (50–99%)

37 *n* = 1 to 5

Scheme 11

ethers.[26] Irradiation of compounds **35** in methanol solution (3–9 mM) by Pyrex glass-filtered light for up to six hours provided cyclized products **36** in 50–99% yield. Compounds **36** underwent slow dehydration in solution to generate unsaturated azacrown ethers **37** (**Scheme 11**).

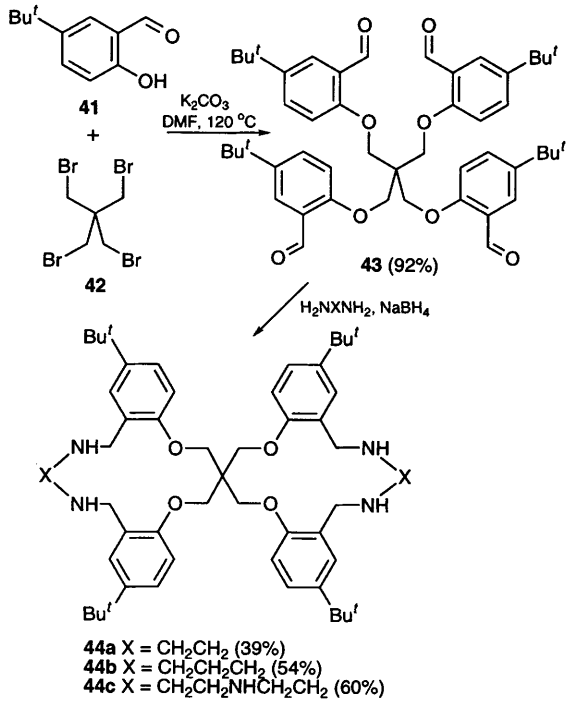
Black and co-workers have proposed that 3,7-diazabicyclo[3.3.1]nonan-9-one or 'bispidinone' may be useful as structural elements of receptors.[27] Symmetrically *N*-substituted bispidinones can be readily prepared by Mannich condensations between a propanone, formaldehyde and primary amine. The initial substituents on the bispidinone can be controlled by varying the amine or propanone employed. For instance, a reaction between ketone **38**, diamine **39** and formaldehyde gave the macrocycle **40** in 48% yield (**Scheme 12**).



38 **39** **40** (48%)

Scheme 12

Linked macrocycles that bind two cations in close proximity provide the potential for generating unusual physical and chemical properties. Lindoy and co-workers have prepared spiro-linked receptors using a pentaerythrityl core.[28] The reaction of a salicylaldehyde derivative **41** with pentaerythrityl bromide **42** produced linking unit **43**. Schiff base formation followed by reduction yielded two-ring receptors such as **44a–c** (**Scheme 13**).



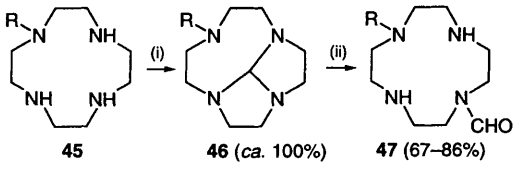
41 **42** **43** (92%)

44a X = CH_2CH_2 (39%)
44b X = $CH_2CH_2CH_2$ (54%)
44c X = $CH_2CH_2NHCH_2CH_2$ (60%)

Scheme 13

While the complexation properties of polyaza-macrocycles are fundamentally determined by ring size, *N*-functionalization can be used to 'tune' selectivity. Sherry has reported the addition of phosphonic and phosphinic moieties in efficient syntheses of 1,4,7-triazacyclononane-tris(methylene-phosphonic acid) and -tris(methylenephosphinic acid) ester derivatives from the unsubstituted azacrown.[29] Direct attachment of aromatic rings to the nitrogens of azacrowns using high pressure S_NAr reactions has been described.[30] The synthesis of azacrown hosts with a pattern of *N*-functionalization is commonly achieved by the selective addition of *N*-substitution of pre-formed macrocycles. The metal complexes of 1,4,7,10-tetraazacyclododecanes and its derivatives are widely used in diagnostic and therapeutic medicine and so the regioselective *N*-functionalization of the parent azacrown has received some attention. Kovacs and Sherry have reported a general synthesis of 1,7-disubstituted derivatives which relies on the regiospecific addition of chloroformates in acid solution to give 1,7-diprotected compounds (yields ranging from 66 to 98%).[31] The same authors have reported a general synthesis of mono- and di-substituted 1,4,7-triaza-

cyclononanes.[32] Their method relies on the fact that the unsubstituted macrocycle reacts with exactly two equivalents of Boc-ON or Z-ON in anhydrous chloroform to form the appropriate disubstituted derivatives in over 90% yields. The reaction of 1,4,7,10-tetraazacyclododecane with methyltrichlorosilane was reported to produce a hypervalent silicon bonded to the four azacrown nitrogens and its methyl group.[33] This structure was then used in high-yielding synthesis of *N*-monoalkylated and N^1,N^7-symmetrically and dissymmetrically dialkylated compounds (yields 60–85%). The regioselective preparation of 7-substituted 1,4,7,10-tetraazacyclododecane-1-carbaldehydes **47** (in yields 67–86%) has been described, and used ring opening of orthoamide protected derivatives **46** prepared by reaction of the mono-*N*-substituted compound **45** with dimethylformamide diethyl acetal (**Scheme 14**).[34]

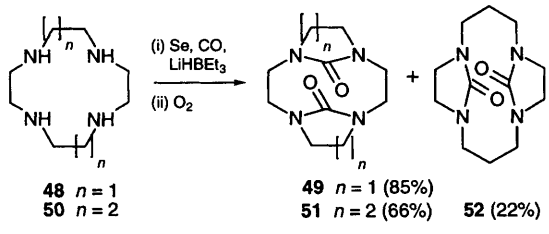


Reagents: (i) $Me_2NCH(OEt)_2$, C_6H_6, reflux 2–4 h; (ii) EtOH–H_2O or THF–H_2O

Scheme 14

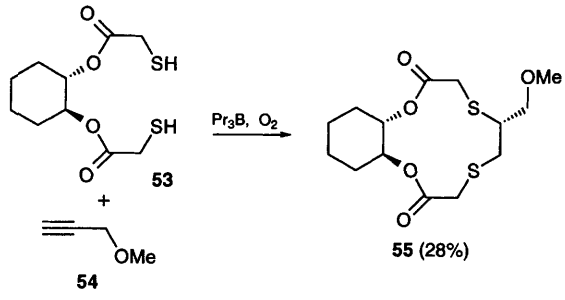
Mono-*N*-alkylation and -*N*-acylation of two tetraazacrowns has also been achieved in 35–90% yield by reaction of either their chromium or molybdenum tricarbonyl complexes with enolisable aldehydes or acid chlorides.[35]

The conversion of azacrowns 1,4,7,10-tetraazacyclododecane **48** and 1,4,8,11-tetraazacyclotetradecane **50** to macrocyclic diureas has been reported.[36] The azacrown, selenium and $LiHBEt_3$ were suspended in THF, in an atmosphere first of carbon monoxide then of oxygen. Thus **48** produced **49** in 85% yield and **50** gave the two isomers **51** and **52** in 66% and 22% respectively (**Scheme 15**).



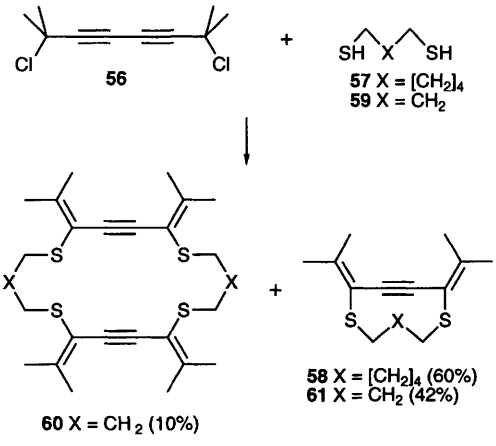
Scheme 15

Thiacrown ethers are an important variation on crown ethers due to the 'soft' nature of their ligating sites. Troyansky and colleagues have reported a stereoselective free radical cycloaddition–macrocyclization which enables the facile synthesis of *trans*-cyclohexane-fused 12-membered crown thioethers.[37] Their method involved the one-step cycloaddition of α,ω-dithiols to alkynes initiated by a tripropylborane–oxygen system. Using the *trans*-dithiol **53**, cycloaddition of **54** afforded a mixture of stereoisomeric *trans*-cyclohexane-fused crown thialactones with a significant predominance of the isomer **55** shown (3.1 : 1, overall yield 28%) (**Scheme 16**). In contrast use of the *cis*-dithiol resulted in equal quantities of the two possible stereoisomers in 21% yield.



Scheme 16

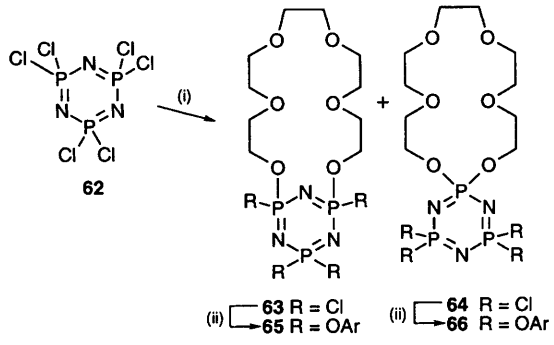
Gleiter and co-workers have produced a range of strained, conjugated thiacrowns.[38] Reacting 2,7-dimethyl-2,7-dichloroocta-3,5-diyne **56** with aliphatic and α,ω-dithiols gives 1 : 1 or 2 : 2 products with the proportions of each macrocycle dependent on the chain length of the dithiol. The reaction is proposed to occur *via* a S'_N reaction with a reactive [4]cumulene as an intermediate. Thus hexane-1,6-dithiol **57** formed the [1 + 1] product **58**, while propane-1,3-dithiol **59** gave the [2 + 2] and [1 + 1] products **60** and **61** (**Scheme 17**). Aromatic dithiols yielded solely a [2 + 2] product.



Scheme 17

Another heteroatom used in the construction of crown ether analogues is phosphorus and Majoral and co-workers have extended their work on the synthesis of phosphorus-containing macrocycles[39] and multimacrocycles[40] by the reaction of

functionalized phosphodihydrazides with dialdehydes. Novel diphosphazacrown **65** and phosphacrown **66** have been prepared from hexachlorocyclotriphosphazatriene **62** after reaction with oligo(ethylene glycols) (producing **63** and **64**) and subsequent reaction with phenol or 2-naphthol (sodium hydride acting as base in both reactions) (**Scheme 18**).[41]



Reagents: (i) $HO[CH_2CH_2O]_5H$, NaH; (ii) NaH, ArOH

Scheme 18

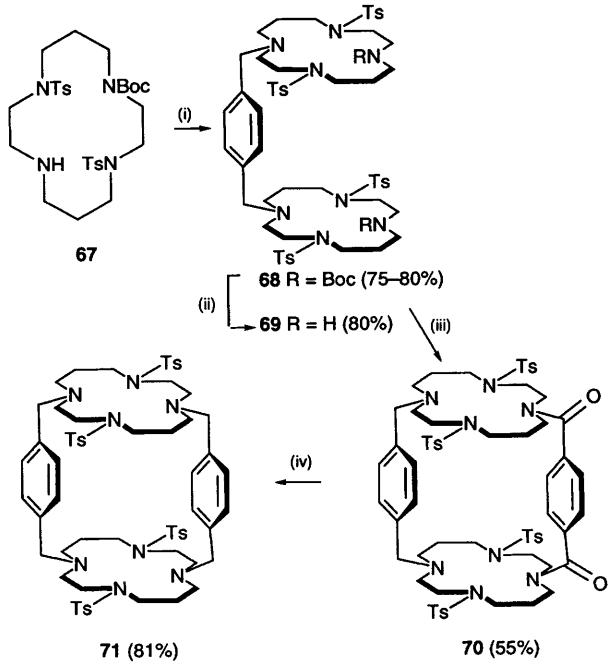
Finally, silicon-containing macrocycles have been prepared using a catalytic amount of bis(*tert*-butyl isocyanide)palladium(0) to induce oligomerization of 1,1,2,2-tetramethyl-1,2-disilacyclopentane through Si–Si bond metathesis. Cyclic oligomers up to the 40-membered octamer were prepared using this methodology.[42]

2.3 Cryptands

Guilard and co-workers have reported the synthesis of the tricyclic host molecule **71**.[43] The tris-protected azacrown **67** was reacted with a dibromo-aromatic linker to form **68**. After the removal of the Boc protection, the bimacrocycle **69** was reacted with an aromatic diacid dichloride at high dilution. The amide bonds in the resulting compound **70** were then reduced with diborane to yield host **71** (**Scheme 19**). A similar reaction sequence produced the *m*-phenylene-linked variant.

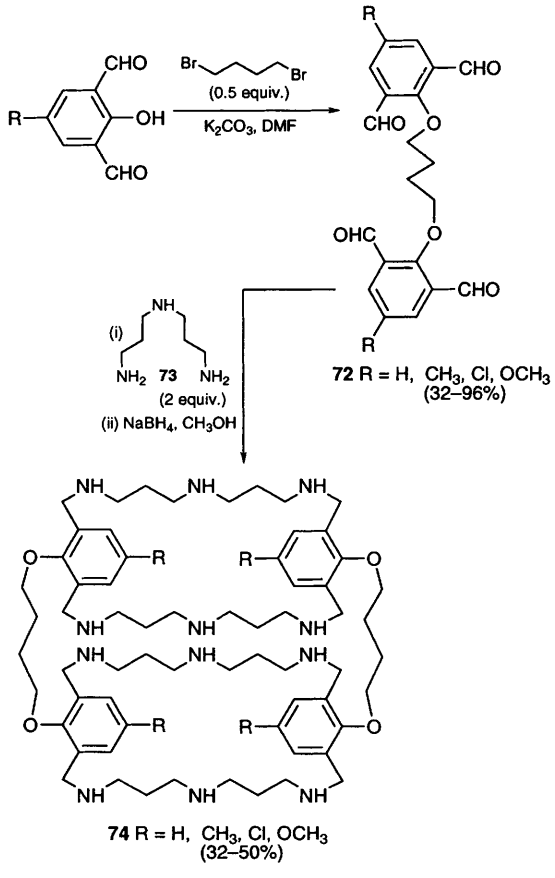
Due to the multi-bridged nature of cryptands, stepwise syntheses of this type of compound can become a lengthy process. Clark and co-workers have described a remarkable one step condensation, requiring neither high dilution conditions nor a metal template, which assembled six fragments in a tetrapode capping reaction.[44] Two moles of tetraaldehyde **72** and four moles of triamine **73** formed eight imine links which, after reduction of these bonds by sodium borohydride, gave the cryptands **74** in 32 to 50% yield (**Scheme 20**).

Supercryptands have been defined as spherical macrotricyclic ligands with at least ten ligating atoms. Krakowiak and Bradshaw have reported an efficient six-step synthesis of these relatively



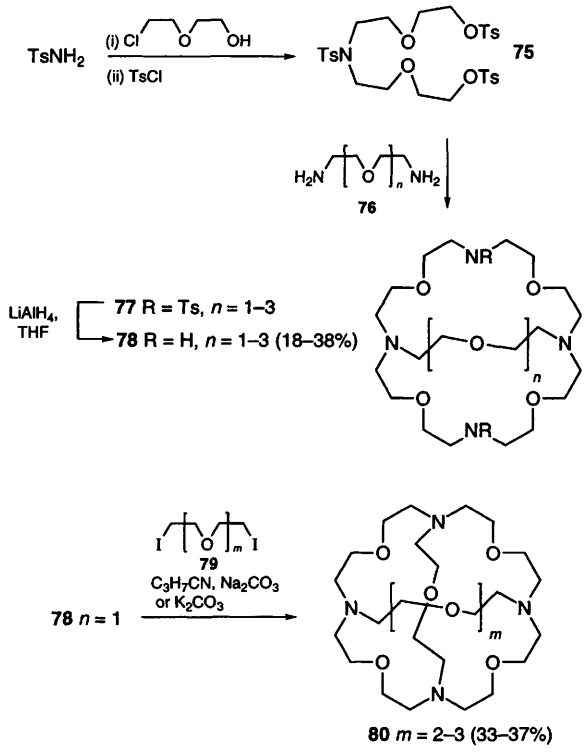
Reagents: (i) p-$BrCH_2C_6H_4CH_2Br$, K_2CO_3, CH_3CN, reflux; ii) TFA–H_2O; (iii) p-$ClCOC_6H_4COCl$, NEt_3, THF; (iv) $LiAlH_4$

Scheme 19

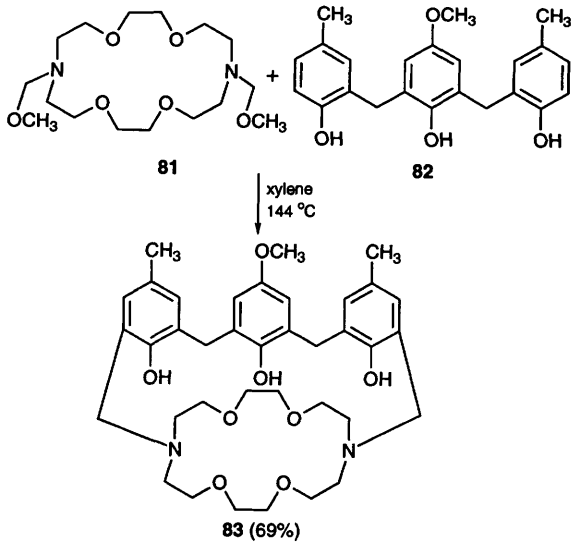


Scheme 20

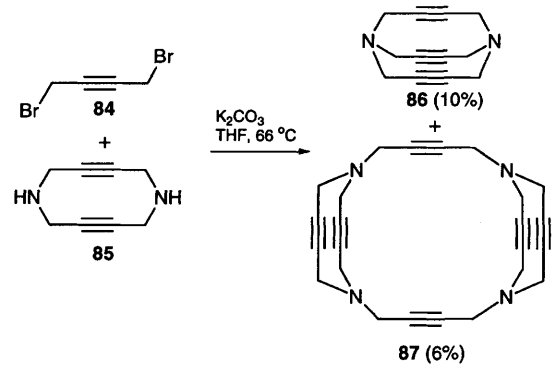
inaccessible hosts starting from toluene-*p*-sulfonamide.[45] The appropriate diamino ether **76** was treated with bis(toluene-*p*-sulfonate) **75** (2.1 equiv.) to give the cryptand **77**. The toluene-*p*-sulfonyl protecting groups were removed using $LiAlH_4$, and the resulting cryptand **78** reacted with an excess of the appropriate diiodo compounds **79** to form supercryptands **80** in yields of 30 to 40% (**Scheme 21**).



Scheme 21



Scheme 22



Scheme 23

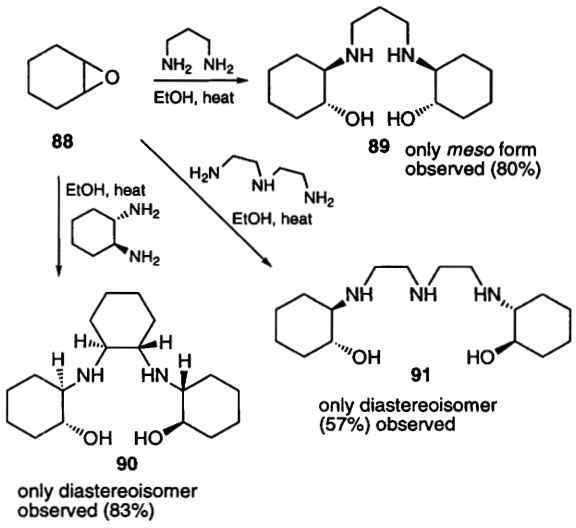
Bradshaw and co-workers have also published a paper detailing a one-step method for the synthesis of new phenol-containing cryptands and cryptohemispherands by coupling *N,N'*-bis(methoxymethyl)diazacrowns with the appropriate bis- and tris-phenols,[46] using a Mannich-type reaction. Reaction of **81** with trisphenol **82**, for instance, gave cryptohemispherand **83** in 61% yield (**Scheme 22**).

A rigid cryptand which incorporates alkynes and thus offers the possibility of establishing π–π interactions with potential guests, has been described by Gleiter.[47] The reaction of 1,4-dibromobut-2-yne **84** with diazacyclodecadiyne **85** resulted in bicyclic triyne **86** (10%) and macrotricycle **87** (6%) (**Scheme 23**).

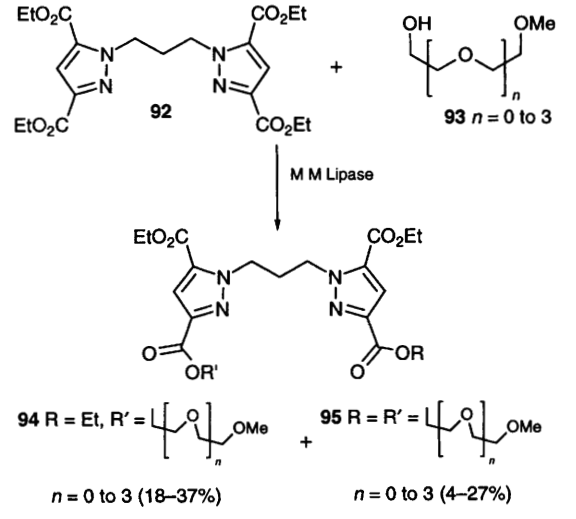
2.4 Podands

A macrocyclic structure is not necessarily a prerequisite for host properties as the required degree of preorganization can be obtained from an acyclic podand morphology. De Sousa and Hancock have shown that cyclohexene oxide **88** reacted diastereoselectively with polyamines to give good yields of podands such as **89**, **90** and **91** (**Scheme 24**).[48] Rodríguez-Franco and colleagues have synthesized podands **94** and **95** which include 1,3-bis(1*H*-pyrazol-1-yl)propane units.[49] The key step in their synthesis was a regioselective lipase-catalysed transesterification of the dipyrazolic tetraethyl ester **92** with monomethyl ether polyethylene glycols **93** (**Scheme 25**). Hovorka and co-workers have reported that binapthols **96** and **98** reacted with poly(ethylene glycols) using chlorinated silica gel as a Lewis acid to afford podands **97** and **99** respectively in good to excellent yields (37–99%) (**Scheme 26**).[50]

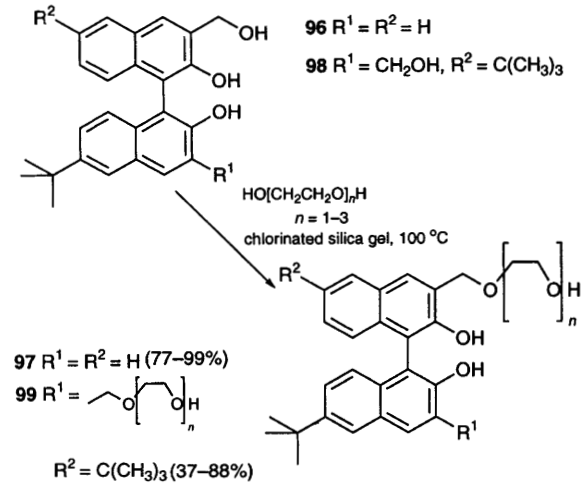
Several tripodal receptors have been described. Three squarimide moieties supported by a triaryl benzene spacer were used to provide a receptor for polyalkylammonium salts,[51] and Morán and co-workers have reported tripodal receptors comprising three chromenone fragments on a cyclohexane support[52] and three ureas or chromenone units arranged on tris(2-aminoethyl)amine.[53] Polypodands comprising a cyclophosphazenic ring and six *N,N'*-bis[oligo(oxyalkylene)] amine chains have also been synthesized.[54]



Scheme 24



Scheme 25



Scheme 26

3 Calixarenes

3.1 Calix[4]arenes

Böhmer has published a very comprehensive review of calixarene chemistry.[55] Takeshita and Shinkai have reviewed recent topics on functionalization and recognition ability of calixarenes[56] and a review has also been published on calixcrowns and related molecules.[57]

3.1.1 Modifications to the lower rim

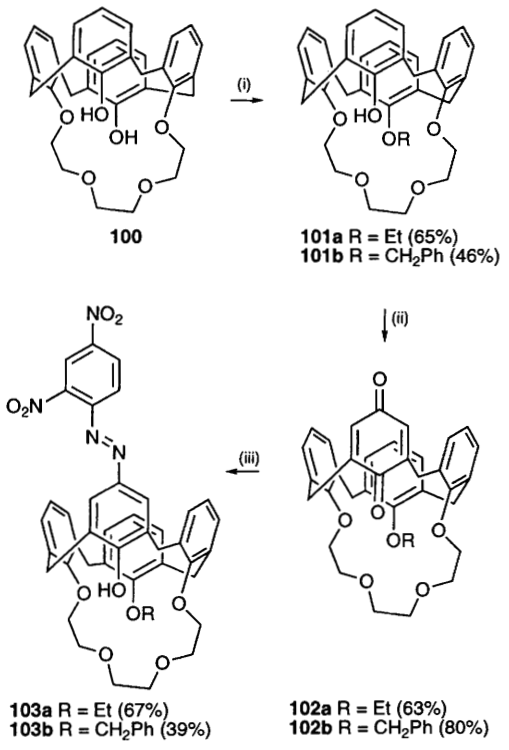
Modifications to the phenolic hydroxy groups of calixarenes by alkylation are well known. One drawback to this functionalization is that it removes the intramolecular hydrogen bonding which favours the cone conformation and as a result tetraalkylated calix[4]arenes tend to be formed as a mix of different conformers. However, Bitter and co-workers have described a set of liquid–liquid phase-transfer catalysis conditions which afford calix[4]arene tetraethers in the cone conformation in good yield.[58] Gutsche has also published a full paper describing selective arylmethylation, arylmethenylation and aroylation of mono- and tetra-*p*-cyanomethylcalix[4]arene.[59]

Alkylation can also be used to put a strap across the lower rim of the calixarene. Examples of this reported include a 1,3 distal link consisting of a 1,8-bis(ethyleneoxy)anthraquinone bridge,[60] and a 1,3 distal link containing a bithiophene (which enabled the manufacture of a polythiophene functionalized with calix[4]arene ionophores).[61] Shinkai and co-workers have synthesized a chromogenic Na^+ selective ionophore from a 1,3 distal crown strapped calix[4]arene **100**.[62] Alkylation of one of the remaining hydroxy groups to form **101** was followed by the conversion of the last phenol unit of the calix[4]arene to a quinone, making **102**. Finally condensation of **102** with 2,4-dinitrophenylhydrazine produced the receptor **103** with a remarkably high selectivity for Na^+ over K^+ ions (**Scheme 27**).

De Mendoza and colleagues found that the 1,3-bis(trifluoromethanesulfonate) and 1,3-bis(methanesulfonate) derivatives of calix[4]arene underwent a facile intermolecular rearrangement of sulfonyl groups in the presence of both a palladium catalyst and chloride anion, leading to 1:1 mixtures of the mono- and tri-substituted derivatives that cannot be prepared directly from calix[4]arene by sulfonylation reactions.[63]

Employment of the Newman–Kwart method to replace the phenolic hydroxy groups of calixarenes with thiol groups has been used by Hosseini and co-workers in the synthesis of a 1,3-dihydroxy-2,4-disulfonylcalix[4]arene[64] and Gutsche and co-workers have published a detailed account of the use of the Newman-Kwart method to produce tetrathiol, trithiol, 1,3-dithiol and the monothiol derivatives of calix[4]arene.[65]

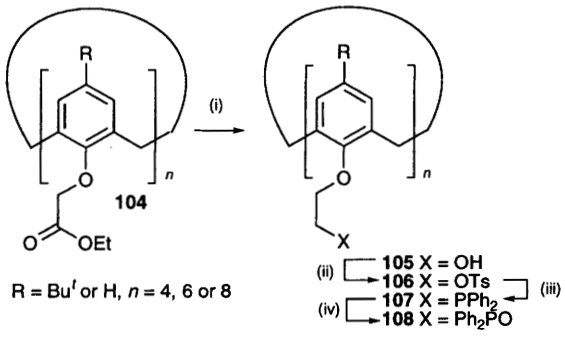
The attachment of phosphorus to the lower rim gives a calixarene novel properties and the synthesis



Reagents: (i) RBr (1 equiv.), NaH, DMF, 0 °C, 4 h; (ii) $Tl(NO_3)_3.3H_2O$, MeOH, EtOH, $CHCl_3$, 10 min; (iii) $2,4\text{-}(NO_2)_2C_6H_3NHNH_2$, H_2SO_4, EtOH, $CHCl_3$, rt, 2 h

Scheme 27

of calixarene phosphine oxides has been reported.[66] Reduction of the known ethyl acetates **104** to primary alcohols **105**, conversion to toluene-*p*-sulfonates **106**, introduction of diphenylphosphino residues through reaction with sodium diphenylphosphide and oxidation of the resulting phosphines **107** using dimethyldioxirane or hydrogen peroxide in acetone produced phosphine oxides **108** (**Scheme 28**). These compounds were shown to be highly efficient in extraction of actinides from simulated nuclear waste.



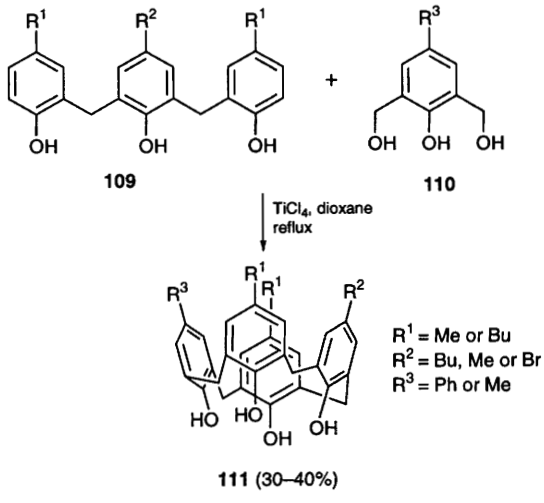
Reagents: (i) DIBAL in toluene; (ii) TsCl in pyridine; (iii) $NaPPh_2$ in dioxane–THF; (iv) dimethyldioxirane or H_2O_2 in acetone

Scheme 28

Phosphine groups have been attached indirectly to the lower rim so that the calixarene provides a scaffold for novel transition metal catalysts.[67,68] The reaction of the lower rim hydroxy groups with various chlorophosphorinanones has also been used to produce a bifunctional ligand for metal coordination[69] and metals such as molybdenum have also been connected directly to the hydroxy groups of the lower rim.[70] Other phosphorus-containing calixarenes formed by reaction of the calixarene hydroxy groups which have been reported this year include monofluorophosphites and mono- and bis-difluorophosphites.[69]

3.1.2 Modifications to the upper rim

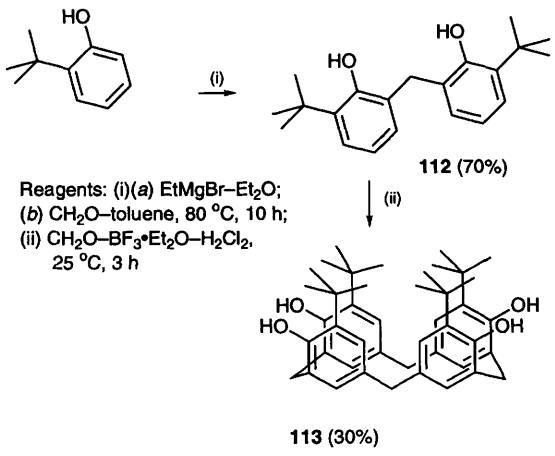
One method of obtaining a particular pattern of substituents on the upper rim of a calixarene is by condensation of the appropriate calixarene fragments. No and co-workers have reported a synthesis of calixarenes with substituents in an ABAC pattern.[71] This was achieved by a {3+1} condensation reaction between a trimer of *para*-substituted phenol **109** (the ABA segment) and a 2,6-bishydroxymethylated *para*-substituted phenol **110** (the C fragment) to give calix[4]arenes **111** in 30–40% yield (**Scheme 29**).



Scheme 29

Sartori and co-workers have synthesized the *o*-(*tert*-butyl)phenol-derived calixarene **113**, which has the hydroxyls arranged in an extraannular fashion, by condensation of 2,2′-dihydroxy-3,3′-di-*tert*-butyldiphenylmethane **112** with formaldehyde using $BF_3 \cdot Et_2O$ catalysis (**Scheme 30**).[72]

Kanamathareddy and Gutsche have reported the syntheses of a variety of calix[4]arenes carrying two types of functional groups on the upper rim.[73] This pattern of functionality was achieved by selective aroylation of a tetraol followed by removal of *tert*-butyl groups *para* to the phenol groups and subsequent use of the quinomethane procedure to effect substitution. The same publication described the use

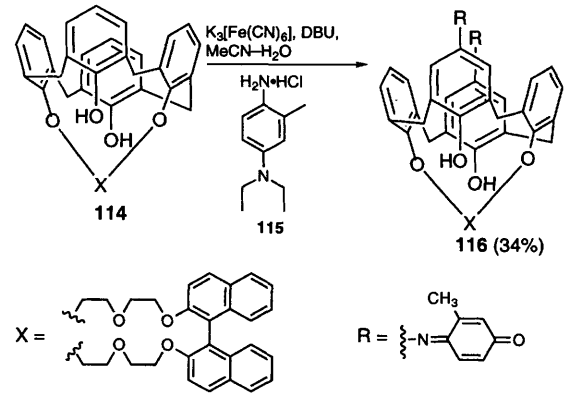


Scheme 30

of intramolecular oxidative coupling of prop-2-ynyl substituents to yield bridged calixarenes.[73] Pochini and co-workers have also described the synthesis of calix[4]arenes diametrically bridged with a hexa-2,4-diynyl moiety.[74]

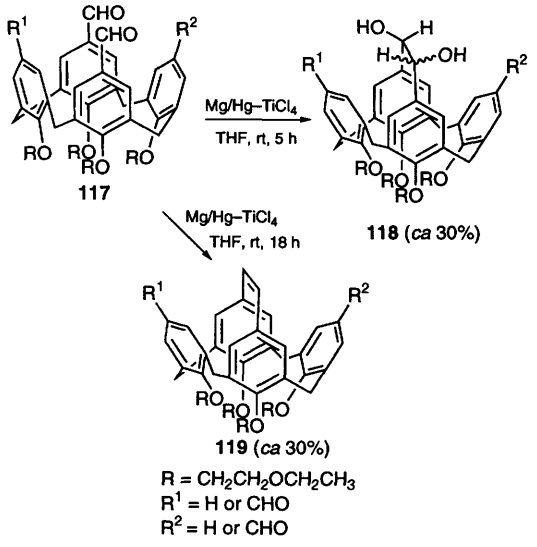
The selective chloromethylation of a diol dimethoxy calix[4]arene has been reported and involved nucleophilic substitution with, for instance, alcohols or thiols, to give calixarenes with ether and thioether moieties *para* to their lower-rim hydroxy groups. Attachment of a hydrophilic cyclodextrin to the calix[4]arene's upper rim has been used to produce a water-soluble calix[4]arene.[76] Kubo and colleagues have introduced a chromogenic function to the upper rim of a calix[4]arene,[77] by effecting a condensation of aniline derivative **115** with calix-crown **114** in an alkaline solution of 1,8-diazo-bicyclo[5.4.0]undecene (DBU) and potassium hexacyanoferrate, to give receptor **116** in 34% yield, capable of recognition of butylamines (**Scheme 31**).

Pochini and co-workers have reported the regio-selective formylation of tetraalkoxycalix[4]arenes in the cone formation, including conditions for mono-, di-, tri- and tetra-formylation.[78] The 1,3-dialdehyde was used in the preparation of highly distorted cone calix[4]arenes using a McMurry coupling reaction.[79]



Scheme 31

The cross coupling of calix[4]arene dialdehydes **117** using low-valent titanium produced highly distorted calixarenes in approximately 30% yield bridged by either a $(CHOH)_2$ unit (as in **118**) or a CH=CH unit (as in **119**) depending on the reaction time (**Scheme 32**).



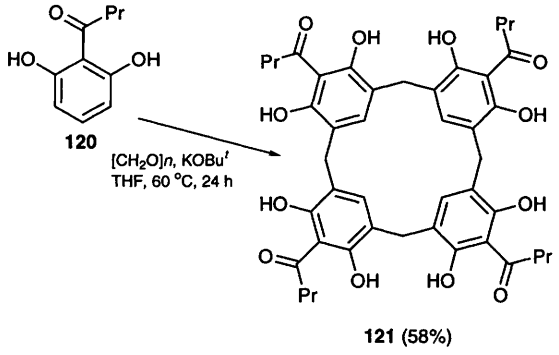
Scheme 32

The persubstitution of the *meta*-position of calix-arenes has the effect of radically reducing their conformational freedom. Mascal and co-workers perbrominated the *meta*-position of calix[4]- and calix[8]-hydroquinone using a variety of conditions for electrophilic bromination in 32–67% yields.[80] Reinhoudt and co-workers have monosubstituted the *meta*-position of mono(acetamido)calix[4]arenes to give inherently chiral calix[4]arenes. Thus, bromination or nitration selectively introduced a substituent adjacent to the acetamido moiety in 58–98% yield.[81] Chiral calix[4]arenes were also produced by dibromination or dinitration of bis(acetamido)calix[4]arenes in 10 and 53% yields respectively.

3.1.3 Calix[4]resorcinarenes and other 'calix' tetramers

Calix[4]resorcinarenes are readily synthesized by acid-catalysed cyclocondensation of resorcinols with aliphatic or aromatic aldehydes. However the presence of an electron-withdrawing group on the 2-position of the resorcinol deactivates it towards electrophilic attack. Konishi and Iwasaki have discovered that deactivated 2-butyrylresorcinol **120** formed a calix[4]resorcinarene **121** with para-formaldehyde under basic conditions in 58% yield (**Scheme 33**).[82]

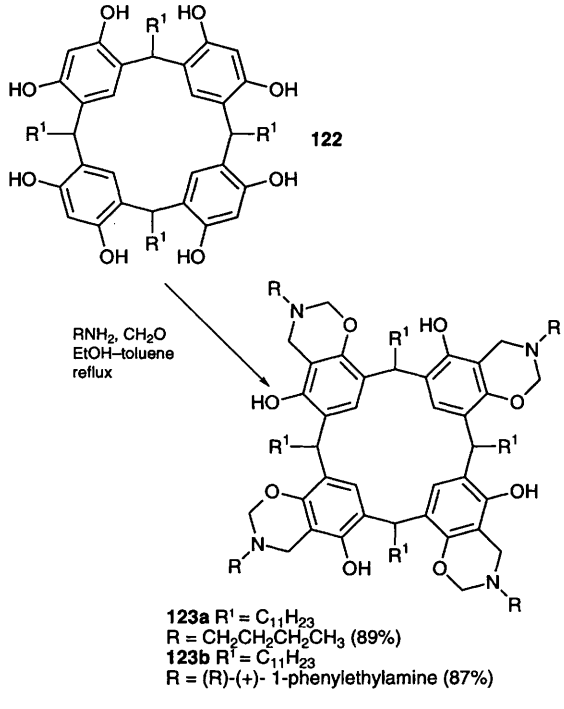
There are several positions on the calix[4]-resorcinarene skeleton where derivatization is possible. The hydroxy groups can be used to add further functionality and have been selectively



Scheme 33

acylated to give a tetrasubstituted compound (yields 30–50%).[83] All eight phenolic hydroxy groups have been used to form four dioxaphosphocine rings, the different diastereoisomers of which were separated by chromatography (total isolated yields 50–80%).[84]

Linnane and Shinkai have used a Mannich reaction to add aza-18-crown-6 to the 2-position to form calix-azacrowns in 99% yield.[85] The use of the Mannich reaction to effect a regio- and diastereoselective addition of primary amines to calix[4]-resorcinarene (e.g. **122**→**123**) has also been widely reported (**Scheme 34**),[86–88] and using α-amino alcohols rather than primary amines led to the formation of 1,3-oxazolidine moieties rather than 1,3-oxazine rings.[89]

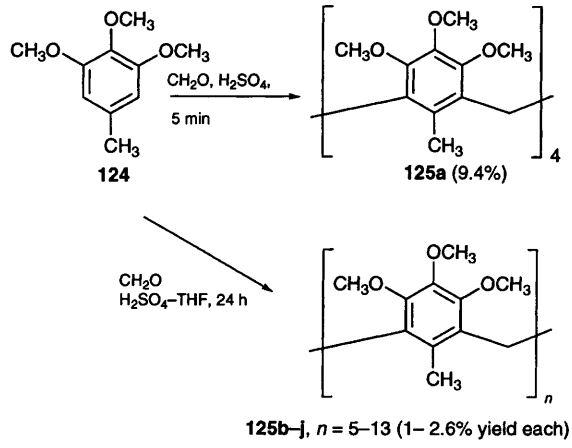


Scheme 34

Novel lantern-shaped molecules with large cavities and shielded intra-cavity functionality were synthesized by Okazaki and colleagues by combining a *m*-terphenyl fragment and a calix[4]resorcinarene.[90] The link was *via* a substituted benzyloxy ether appended to the 2-position of the resorcinol units.

Another position for calix[4]resorcinarene elaboration is at the methine linker between the aryl units. Reinhoudt and co-workers reported the synthesis of calix[4]resorcinarenes which self-assemble on a gold surface *via* four bis(decyl sulfide) chains attached to the methine linker.[91]

Schilling and co-workers have reported the synthesis of persubstituted calix[n]arenes **125** comprising 4 to 13 aryl units by acid-catalysed reaction of 3,4,5-trimethoxytoluene **124** with para-formaldehyde (**Scheme 35**).[92] Separation of the different oligomers was accomplished by chromatography. The substitution of calix[*n*]arenes **125** was adopted to force what the authors term an 'inverse' conformational behaviour wherein the alkyl groups formed the base of the calix shape rather than the rim.



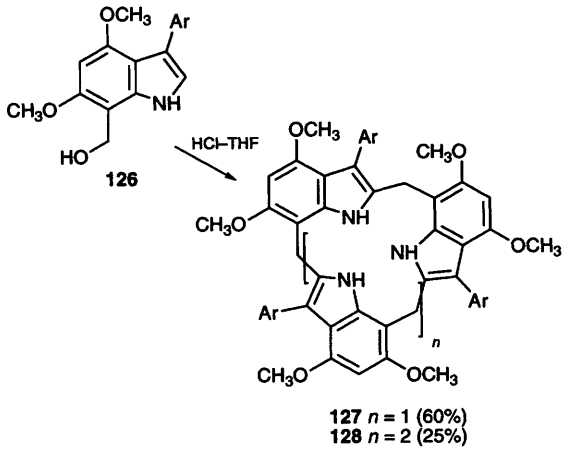
Scheme 35

Other aromatic units have been used to construct calix-type structures. Syntheses of four isomeric calix[4]naphthalenes from 1-naphthol have been described providing four novel supramolecular building blocks with different cavity morphologies.[93] The monosodium salt of 4-amino-5-hydroxynaphthalene-2,7-disulfonic acid has been used to form a cyclic tetramer which was water-soluble and provided a hydrophobic binding cavity able to bind polyaromatic hydrocarbons.[94] Black and co-workers have reported the formation of calix[4]indoles **128** in 25% yield from the reaction of the 7-hydroxymethylindole **126** in hydrochloric acid as the minor component to a trimer **127** (**Scheme 36**).[95]

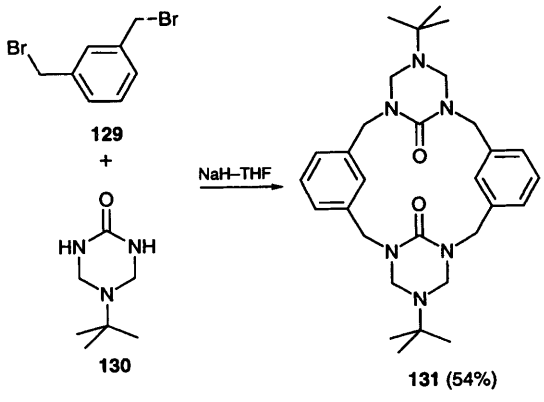
An analogue of calix[4]arene, **131**, has been prepared by the reaction of dibromo compound **129** with triazinone **130** (**Scheme 37**) and its conformational behaviour compared to that of calix[4]arene.[96]

3.2 Calix[5]arenes

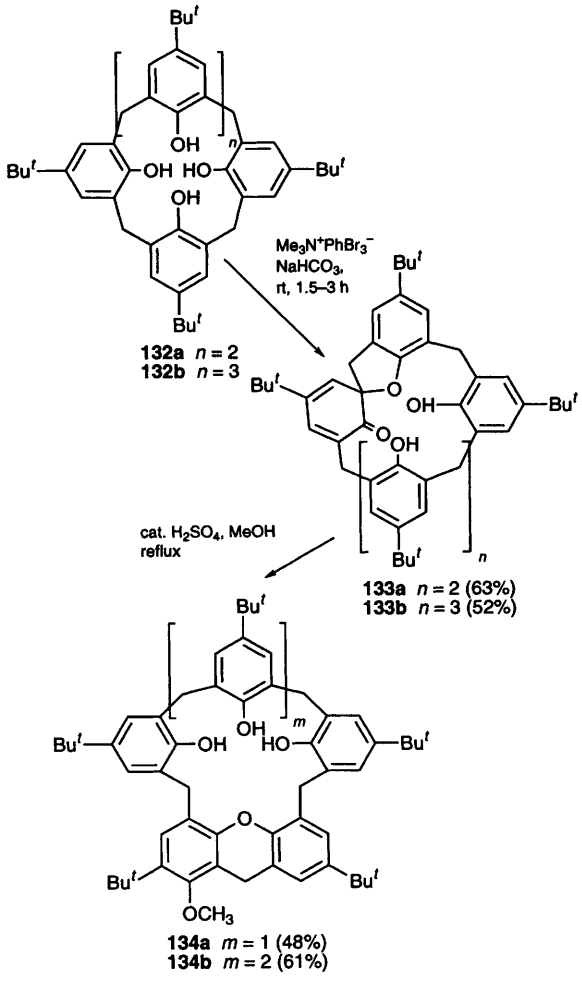
Gutsche and co-workers have synthesized a variety of ethers and esters of *p-tert*-butylcalix[5]arene, and assessed their conformational behaviour, deter-



Scheme 36



Scheme 37



Scheme 38

mining those derivatives with limited or no conformational mobility.[97] Beer and colleagues have reported the preparation of a 1,3,4-trisferrocenoyl ester of *p-tert*-butylcalix[5]arene[98] which exhibited an interesting change in redox activity on addition of potential guests which may reflect host–guest association.

In an extension to their work on calix[4]arenes, Biali and co-workers reported a method for intra-annular incorporation of an amino group, or an azo group, in a calix[5]arene skeleton by reaction of amino nucleophiles with the monospirodienone derivatives **133a** of calix[5]arene.[99] The monospirodienones **133a** and **133b** were formed by the reaction of the appropriate calixarene **132a** or **132b** with a mild oxidizing agent, $Me_3N^+PhBr_3^-$. In addition, both the monospirodienone derivatives **133a** and **133b** underwent an acid-catalysed rearrangement leading to calixarene systems **134a** and **134b** incorporating a xanthene unit (**Scheme 38**).[99]

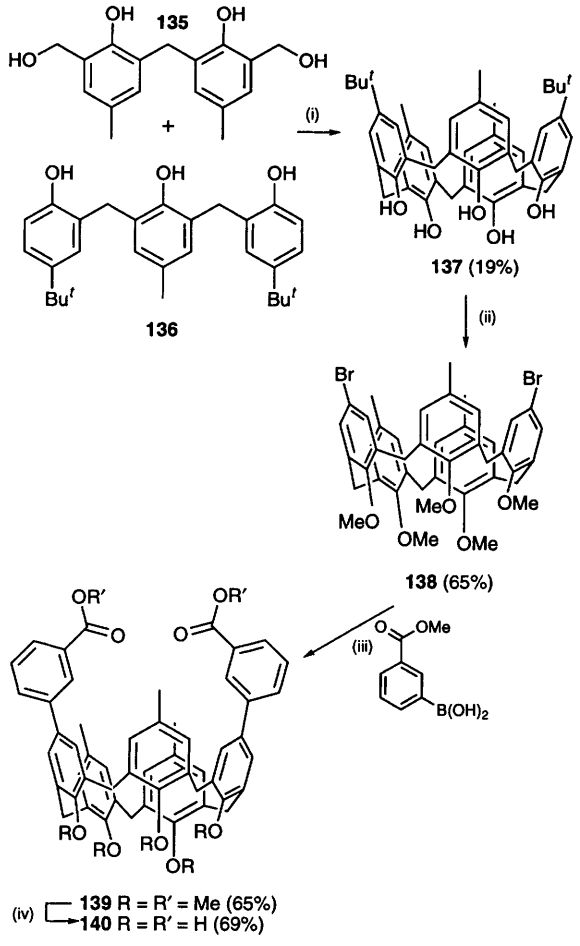
Derivatization of the upper rim of calix[5]arenes has followed developments in calix[4]arene chemistry.

Böhmer and co-workers have reported the synthesis of a bis(arylazo)calix[5]arene crown in 36% yield from the starting unsubstituted calix[5]arene.[100] The calix[5]arene receptor **140** which bears two benzoic acid moieties was shown to bind imidazolium ions.[101] The initial calix[5]arene superstructure with two types of upper-rim functionality was synthesized by a [1 + 1] cyclization of **135** and **136**. After removal of the *tert*-butyl groups under retro-Friedel–Crafts conditions from **137**, protection of its hydroxy groups and bromination, the calix[5]arene **138** underwent a Suzuki coupling reaction to produce **139**. Removal of protecting ether and ester functionality yielded the target molecule **140** (**Scheme 39**).

Yamato and co-workers reported the synthesis of novel ethylene-bridged analogues of calix[5]- and calix[6]-arene resulting from the base-catalysed condensation of suitable tetrahydroxyphenyl fragments.[102]

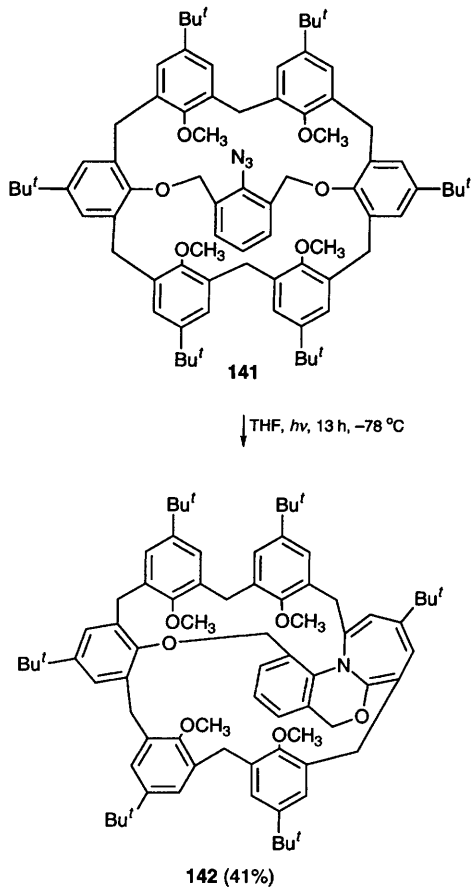
3.3 Calix[6]arenes

The larger cavity dimensions of calix[6]arenes are of increasing interest because of their use in receptors for larger guests. Most work in this area has been based around functionalization of the lower rim. Thus, Shinkai and co-workers have reported the syntheses of all the possible calix[6]arene derivatives



Reagents: (i) xylene, reflux; (ii) (*a*) phenol, $AlCl_3$–toluene; (*b*) CH_3I, Bu^{t}OK; (*c*) NBS, butan-2-one; (iii) $Pd(PPh_3)_4$, Na_2CO_3; (iv) (*a*) LiOH–MeOH–H_2O; (*b*) BBr_3–CH_2Cl_2

Scheme 39



Scheme 40

with MeO and $EtOCOCH_2O$ substituents,[103] as well as syntheses of calix[6]arenes bridged with a xylenyl unit or capped with a mesitylenyl group.[104] Reinhoudt and co-workers have added pendant ureas from the lower rim of a calix[6]arene to form a receptor for anions[105] while Ungaro and co-workers have synthesized 1,4-calix[6]crown ethers from the parent calix[6]arene and tetraethylene glycol bis(toluene-*p*-sulfonate) in 36–42% yield,[106] and Ross and Lüning have added 1,4-pyridine-containing bridges which create concave reagents for base-catalysed reactions.[107] The calix[6]arene **141** bridged by *m*-phenylene supporting an azide group underwent an unusual reaction in which the azide was converted to a nitrene by photolysis followed by a transannular addition reaction to produce the fused azepine **142** (41% yield) as the major product (**Scheme 40**).[108]

The partial functionalization of the upper rim by selective nitration, formylation, halogenation, chloromethylation and Claisen rearrangement has been reported,[109] and the same paper described the formation of di- and tri-quinones of calix[6]arene.

Konishi and co-workers have described the synthesis of the first examples of calix[6]resorcinarenes.[110] Refluxing 2-propylresorcinol and 1,3,5-trioxane in ethanol–conc. HCl (4:1 v/v) for three hours, produced the hexamer (as a minor product to the tetramer) in 22% yield.

3.4 Calix[7]arenes and calix[8]arenes

A one-step synthesis of *p-tert*-butylcalix[7]arene has been described.[111] The optimum conditions for base-catalysed cycloaddition of *p-tert*-butylphenol were established and gave an isolated 11% yield of *p-tert*-butylcalix[7]arene.

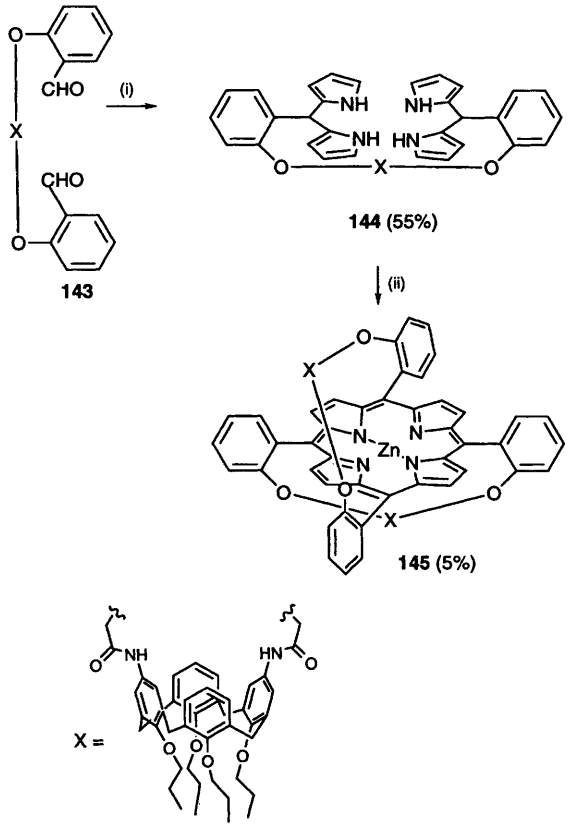
Neri and co-workers have studied the alkylation of *p-tert*-butylcalix[8]arene by *p*-methylbenzyl bromide in the presence of weak bases.[112] They have determined that substitution proceeds by an 'alternate alkylation' mechanism, *i.e.* the reaction path goes mainly *via* mono-, 1,3-di-, 1,3,5-tri-, 1,3,5,7-tetra-, 1,2,3,5,7-penta-, 1,2,3,4,5,7- and 1,2,3,5,6,7-hexa- and hepta-substitution. They have also described a synthesis of 1,3,5,7-tetramethyl ether of *p-tert*-butylcalix[8]arene (previously unreported as synthesis by standard alkylation reactions was very much hampered by the target compound being insoluble in most organic

solvents),[113] and of doubly-crowned *p-tert*-butylcalix[8]arenes.[114]

3.5 Multiple calixarene structures

One strategy to obtain larger cavities is to form a receptor from several calixarene units. Shinkai and co-workers have described a biscalix[4]arene which, though formed by a single methylene connection between the upper rims of the constituent calixarenes, is conformationally-immobile and serves as a receptor for *N*-methylpyridinium iodide.[115] Reinhoudt and colleagues have synthesized a biscalix[4]arene **145** which incorporated a zinc–porphyrin moiety between its two calixarene units.[116] The calixarene **144** was used to template the synthesis of the porphyrin unit in the product **145** (**Scheme 41**). The same research group has also continued its studies into receptors built from upper-rim-functionalized calix[4]arenes and partly bridged resorcinarenes,[117] and have described a novel calix[4]arene-based carceplex.[118]

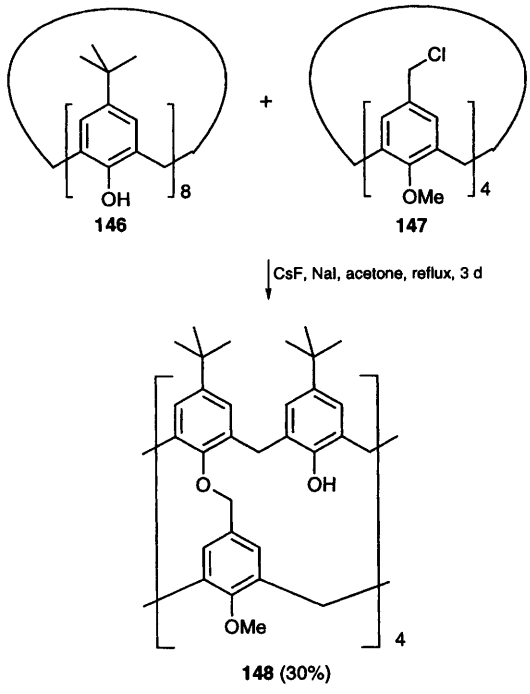
Beer and co-workers have reported the synthesis of a neutral fluoride ion selective biscalix[4]arene receptor in which the upper rim of one calix[4]arene segment was linked by amide bonds to the lower rim of the other.[119] Ether links formed between lower rim phenolic oxygens have been used to assemble



Reagents: (i) pyrrole, TFA, 0.5 h, rt; (ii) (*a*) **143**, $BF_3{\cdot}Et_2O$, $CHCl_3$, 1 h, rt; (*b*) DDQ, $CHCl_3$, 1 h, rt; (*c*) $Zn(OAc)_2{\cdot}2H_2O$, $CHCl_3$–MeOH (2:1) reflux, 3 h

Scheme 41

biscalixarenes joined by calixarene-type segments,[120] and oligocalixarenes (containing up to five monomers) linked by aliphatic chains,[121] while Pochini and co-workers have reported the synthesis of the macrocavitand **148**[122] by the head-to-tail four-point capping of *p-tert*-butylcalix[8]arene **146** with tetramethoxy-*p*-tetrakis(chloromethyl)calix[4]arene **147**. In the presence of CsF and NaI, in refluxing acetone, at high dilution, the reaction gave a 30% yield of biscalixarene **148** (**Scheme 42**).



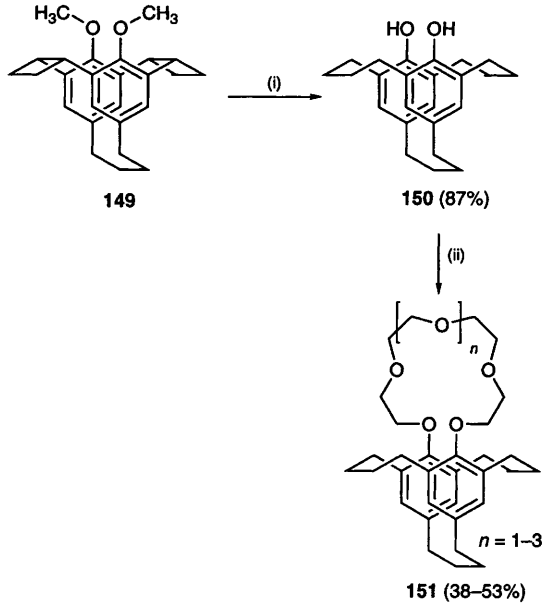
Scheme 42

4 Cyclophanes

4.1 All-carbon cyclophanes

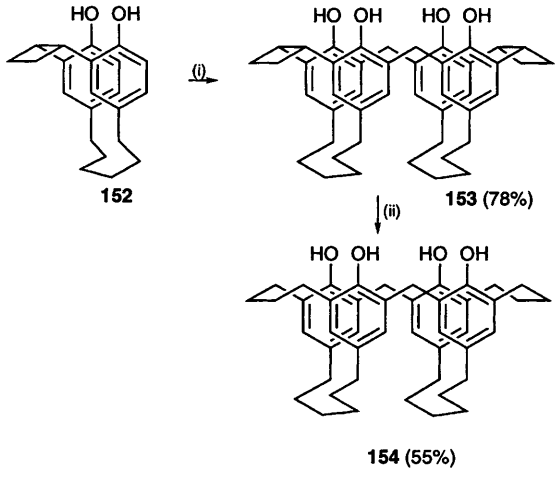
An ionophore which is selective for the larger alkali metals has been prepared by incorporating an oligo(oxyethylene) bridge into a rigid 'paddlane' unit.[123] The dihydroxycyclophane **150** was prepared by Birch reduction of **149** followed by ether cleavage with HBr–AcOH (**Scheme 43**) and the crownophane **151** was then synthesized by standard Williamson ether methodology.

Nishimura and co-workers have also developed a new calix[4]arene-type cyclophane using *syn*-dihydroxy[2.*n*]metacyclophane **152** as the building block.[124] Dimerization of **152** using CsOH and paraformaldehyde yielded cyclophane **153**. The cyclobutane rings of **153** could be opened by Birch reduction producing cyclophane **154** (**Scheme 44**) and the phenolic hydroxy groups of **153** and **154** were derivatized to produce a variety of pendant ethers. Related cyclophanes with ether substituents bearing chiral pendants were shown to selectively extract and transport amino acids.[125]



Reagents: (i) (*a*) liq. NH_3, Na, Bu^{t}OH–THF, –60 °C to rt; (*b*) HBr–AcOH, reflux; (ii) $TsO(CH_2CH_2O)_mTs$ (m = 4–6), NaH–THF, reflux

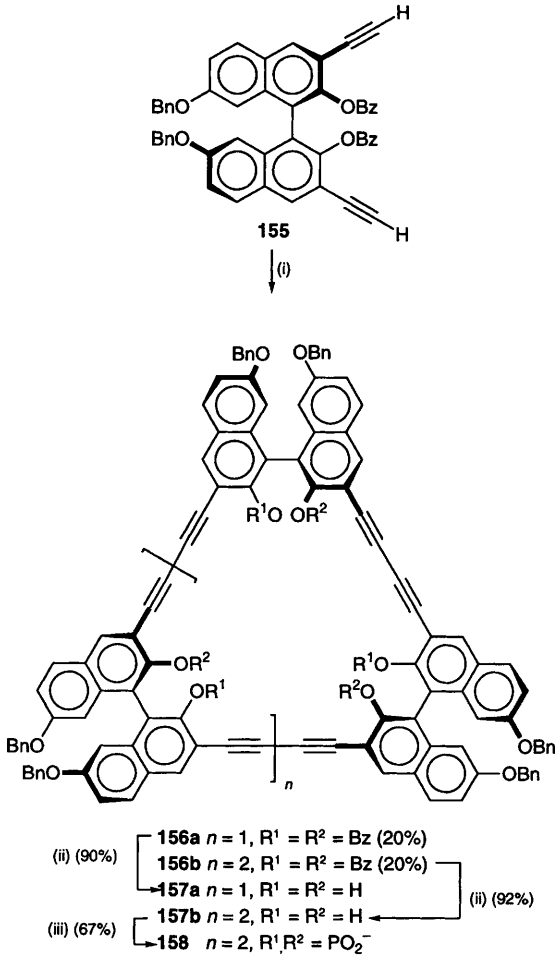
Scheme 43



Reagents: (i) CH_2O, CsOH, diglyme 140–150 °C, 12 h; (ii) (*a*) $ClCH_2OCH_3$, NaH, THF–DMF; (*b*) Na, EtOH, liq. NH_3, THF; (*c*) aq. HCl-dioxane

Scheme 44

The use of diyne units to give rigidity to cyclophanes is common. Höger and Enkelmann have prepared large ambiphilic macrocycles by coupling of oligo(arylalkyne) units.[126] Sanders and co-workers have published several full papers detailing their syntheses of various porphyrin cyclophanes which use diyne[127] and even tetrayne[128] links with the aim of creating spacious cavities able to bind two or more substrate molecules in such a manner that homogeneous catalysis could occur. A related platinum-linked porphyrin trimer has also been reported.[129] Diederich and co-workers have made a series of chiral receptors (**157a**, **157b** and **158**) for pyranosides derived from a 3,3′-diethynyl-1,1′-binaphthyl-2,2′-diol spacer **155**.[130] The monomer **155** was cyclized by oxidative Glaser–Hay coupling to give trimer **156a** and tetramer **156b**, both in 20% yield. Removal of benzyl protection (giving **157a** and **157b**) and conversion of **157b** to tetraphosphate **158** were accomplished in good yield (**Scheme 45**).



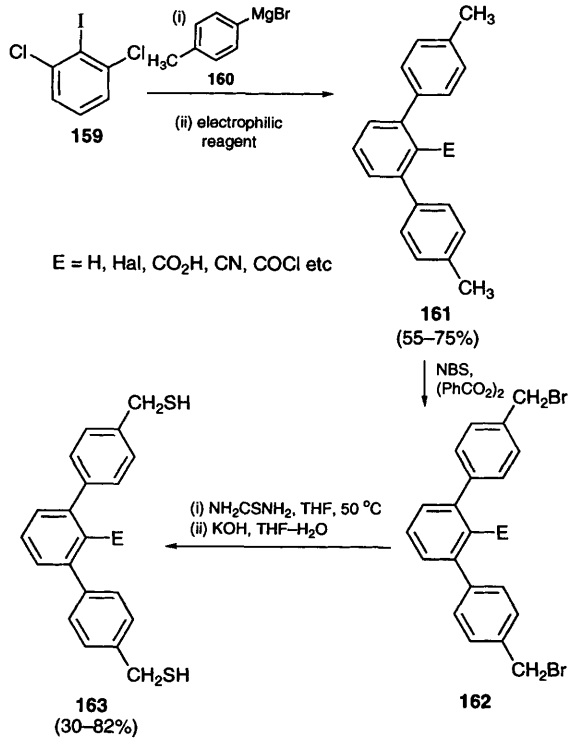
Reagents: (i) air, $CuCl_2$, TMEDA; (ii) KOH, MeOH–THF; (iii) (*a*)$POCl_3$, NEt_3, CH_2Cl_2; (*b*)THF–H_2O, 12 h, 40 °C

Scheme 45

4.2 Heteroatom-containing cyclophanes

A simple method of formation of [3.3] azacyclophanes by dialkylation of cyanamide has been described by Shinmyozu and colleagues.[131] In the presence of a phase-transfer catalyst, in a mixture of toluene or CH_2Cl_2 and water, in mildly alkaline conditions, the addition of cyanamide to a range of bromomethyl compounds produced *N,N′*-dicyano[3.3]azacyclophanes and their higher homologues in good to moderate yields. Molina and

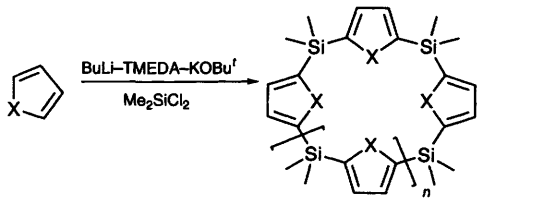
co-workers have reported a method of preparation of macrocyclic bis(guanidines) using the high yielding reaction (74–98%) of readily available bis(carbodiimides) with ammonia, primary or secondary amines and α,ω-diamines.[132] Hart, Rajakumar and co-workers have used the tandem aryne reaction of aryl Grignard reagents **160** with 1,2,3-trihalobenzenes **159** followed by electrophilic quenching to produce *m*-terphenyl units **161** with the electrophile attached to the 2′-position (**Scheme 46**). Substitution on the outer aryl groups of the terphenyl provided linking moieties *e.g.* bromination of **161** gave **162** followed by displacement to form dithiol **163**. Structures of this type have been used to build a variety of oxa-and thia-cyclophanes with intraannular functionality.[133–135]



Scheme 46

Inouye and colleagues have used a sterically similar terpyridine moiety to provide an intra-annular hydrogen bonding functionality in their macrocyclic receptor for β-ribofuranosides,[136] while Shinkai and co-workers have continued their research on oxacyclophanes describing a triamide ionophoric derivative[137] and a C_3-symmetrically-capped host for primary ammonium ions.[138]

König and co-workers have described the synthesis of silicon-bridged macrocycles such as **164** and **165**.[139,140] Furan, thiophene and *N*-methylpyrrole were deprotonated at the 2- and 5-positions with two equivalents of BuLi–TMEDA–KOBu^t (1 : 1 : 1) in hexane and after slow addition of Me_2SiCl_2, macrocyclic tetramers **164** and hexamers **165** were formed in yields up to 35% (**Scheme 47**).[139] The

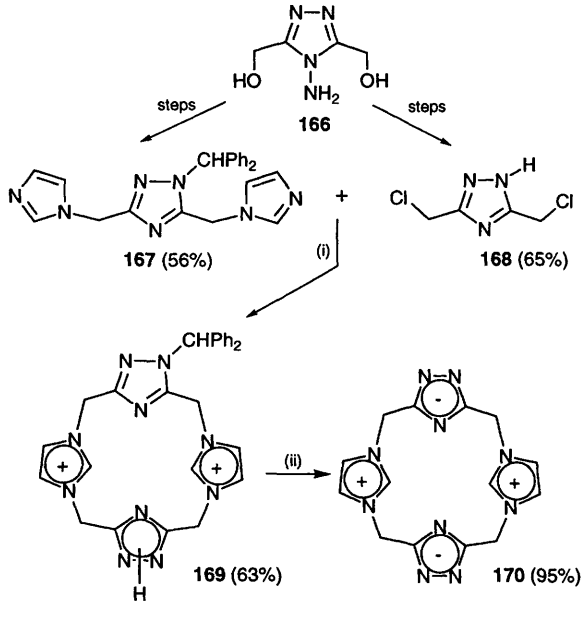


164 n = 1, X = O, S, NMe (12–18%)
165 n = 3, X = O, S (10–17%)

Scheme 47

same group has also used the addition of dianions to biselectrophiles to form silicon-substituted derivatives of calix[4]arene, an octamethoxysila-[1.1.1.1]paracyclophane and tin or phosphorus analogues of **164** and **165** by using Me_2SnCl_2 or $PhPCl_2$ rather than Me_2SiCl_2.[140]

Heterophanes have also been constructed using heterocyclic betaine units.[141,142] The trisheterocyclic fragment **167** was obtained by a three-step procedure from 1,2,4-triazole **166**. Condensation of **167** with bis(chloromethyl) derivative **168** afforded the macrocycle **169** in 63% yield. After reflux of **169** with trifluoroacetic acid (TFA) and phenol for an hour, the resultant compound was treated with an anion exchange resin producing **170** in 95% yield from **169** (**Scheme 48**). Other novel, charged heterophanes assembled by reaction of alkyl halide with amine include Xie and co-workers' imidazolium cyclophane,[143] Menger and Catlin's octacationic 1,4-diazabicyclo[2.2.2]octane (DABCO)-based macrocycle[144] and Skog and Wennerström's macrocyclic host constructed with four nicotinamide subunits.[145]



Reagents: (i) dry MeCN, reflux, 48 h; (ii) (*a*) TFA, phenol, reflux, 1 h; (*b*) anion exchange resin IRA-401(OH$^-$ form)

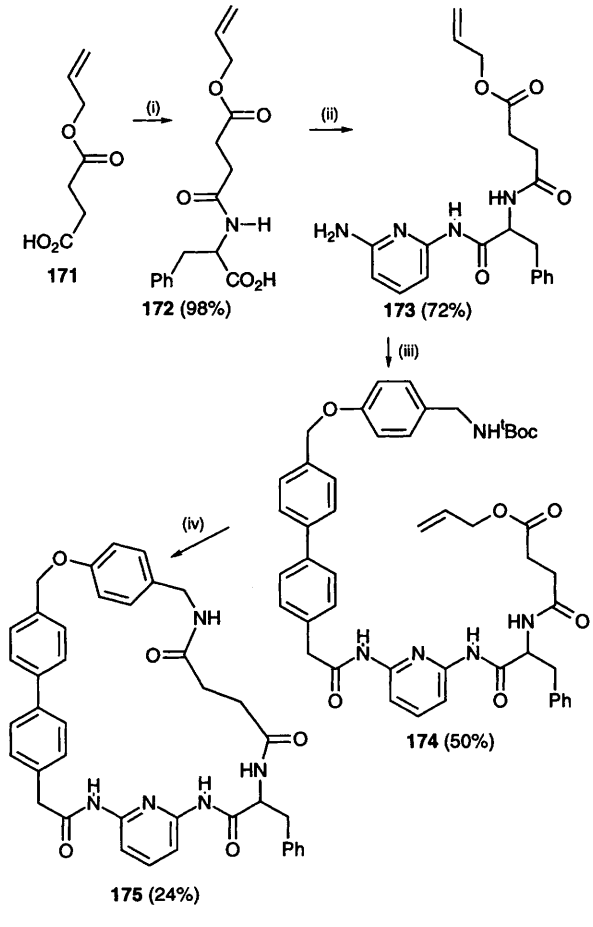
Scheme 48

Amino acids are useful 'building blocks' for molecular receptors. Ishida and co-workers have synthesized a series of neutral cyclic hexapeptides containing the non-natural amino acid 3-amino-benzoic acid which serves to orient the amide groups correctly for interaction with phosphoester guests.[146] Flack and Kilburn's macrocyclic receptor for peptides was assembled from a diaminopyridine unit, succinic acid, phenylalanine and a non-natural amino acid spacer unit with the formation of four amide bonds (**Scheme 49**).[147] First, monoprotected succinic acid **171** was reacted with *N*-phenylalanine *via* the formation of the acid chloride, giving **172** which was coupled with 2,6 diaminopyridine using 1,3-dicyclohexylcarbodiimide–4-dimethylamino-pyridine (DCC–DMAP) forming **173**. Addition of a large spacer unit using ethyl 1,2-dihydro-2-ethoxy-quinoline-1-carboxylate (EEDQ) created **174** which, after deprotection and activation, was cyclized to form **175**.

4.3 Cage-type cyclophanes

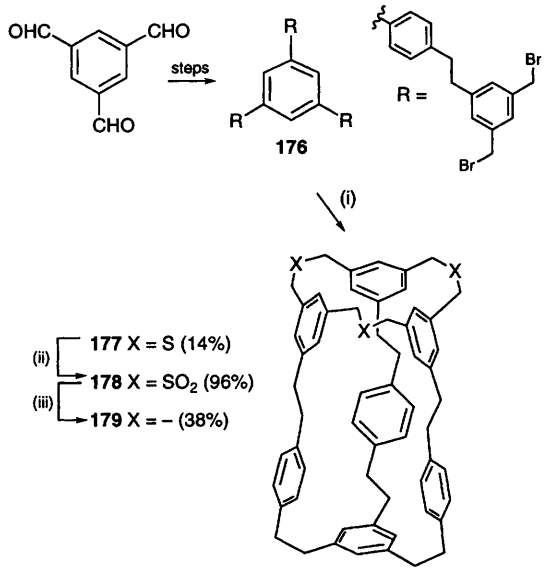
Diederich and colleagues have described the first examples of 'dendrophanes' which are composed of a [6.1.6.1] paracyclophane embedded in first-, second- and third generation dendritic poly(ether amide) shells.[148]

The construction of spherical hydrocarbons which can act as silver ion receptors has been described by Vögtle and co-workers.[149] For instance, the tripodal unit **176** was reacted with sodium sulfide at high dilution, to produce the thia-bridged compound **177**. Subsequent oxidation to **178** and pyrolytic desulfurization gave hydrocarbon host **179** in overall 5% yield from **177** (**Scheme 50**).



Reagents: (i) (*a*) $(COCl)_2$, cat. DMF, CH_2Cl_2; (*b*) L-phenylalanine, Na_2CO_3, H_2O; (ii) 2,6-diaminopyridine, DCC, DMAP, CH_2Cl_2; (iii) non-natural amino acid spacer unit, EEDQ, THF; (iv) (*a*) $Pd(PPh_3)_4$, H_2O, dioxan; (*b*) C_6F_5OH, DCC; (*c*) 20% HCl, dioxane; (*d*) DMAP, Et_3N, DMF

Scheme 49



Reagents: (i) $Na_2S{\cdot}9H_2O$, Cs_2CO_3, benzene–EtOH, reflux; (ii) MCPBA, $CHCl_3$; (iii) 10^{-6} Torr, 580 °C

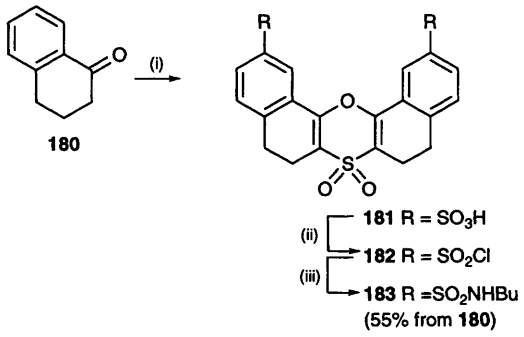
Scheme 50

Cram has continued his programme of study on hemicarcerands and carcerands and their complexes[150] and has described new linking elements such as a diphenylmethane derivative which provides hemicarcerands with large interiors of the same scale as [60]fullerene,[151] and the synthesis and properties of a hemicarcerand-corand able to complex both a cation and an anion simultaneously.[152] Sherman has reviewed the field of carceplexes and hemicarceplexes,[153] and has also described the templated synthesis of both covalently-linked and self-assembled carceplexes.[154]

5 Clefts, bowls and other morphologies

5.1 Cleft-type receptors

The cleft is an attractive overall design for a receptor as it can generate a high degree of pre-organization of binding moities in a relatively short synthesis. For instance, cleft **183** was produced in three steps from α-tetralone **180** in 55% yield (**Scheme 51**).[155] The cleft **181** was synthesized by heating **180** in sulphuric acid at 100 °C for 4–5 h. Chlorination of the sulfonates with chlorosulfonic



Reagents: (i) H_2SO_4, 100 °C, 4–5 h; (ii) HSO_3Cl, rt; (iii) $BuNH_2$, EtOAc

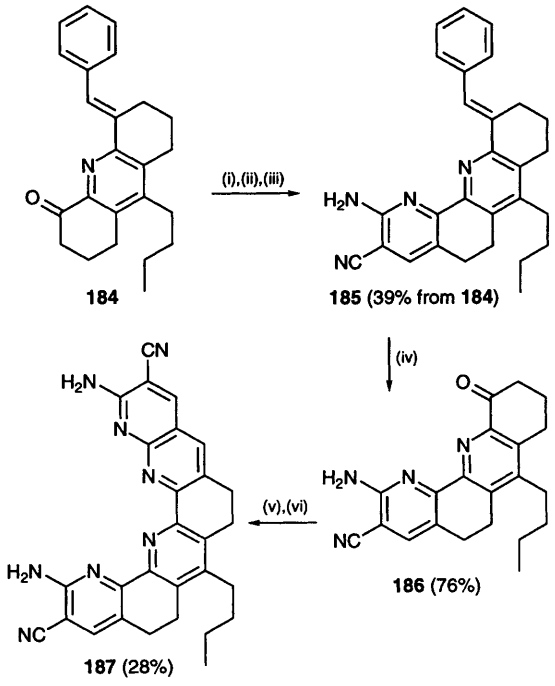
Scheme 51

acid yielded **182** and then reaction with butylamine gave **183**.

A synthetically accessible cleft has been reported by Hamilton and co-workers and consists of a rigid bicyclo[3.3.0]octane framework holding two guanidinium units parallel and 4–5 Å apart. It has proved capable of selectively binding aspartate residues separated by two amino acids on an α-helical peptide.[156] Zimmerman and co-workers have published a full paper describing the syntheses of heterocyclic compounds containing three contiguous hydrogen bonding sites in all the possible arrangements of donor and acceptor.[157] These heterocycles can be used as modules in the construction of more specific clefts. For instance, the fused pyridine framework of receptor **187** was built up from benzylidene ketone **184**.[158] Construction of the lower pyridine ring was achieved through addition to $CH_3CH_2OCH{=}C(CN)_2$ and cyclization, giving **185**. After removal of the benzylidene group by ozonolysis, addition of the upper naphthyridine unit to **186** was achieved by a Friedländer addition of 4-aminopyrimidine-5-carbaldehyde, acid hydrolysis of the resultant pyrimidine ring and reaction with malononitrile (**Scheme 52**). The resultant cleft **187** has an arrangement of hydrogen bond donors and acceptors which tightly docks with guanine derivatives. The related syntheses of highly preorganized polyheterocyclic hosts for creatinine has also been described.[159]

Porphyrin analogues of Tröger's base have been synthesized (in 70% yield from 2-aminoporphyrin derivatives) to produce chiral clefts with large cavities containing two metal centres for binding guests.[160] Chiral clefts have also been fabricated using 9,9-spirobi[9*H*-fluorene],[161] 1,1′-binaphthyl[162] and 2,6-diarylbenzoic acid units.[163]

The use of peptides as a source of chirality in clefts or tweezer-like molecules has been reported by Kelly who has constructed a host by coupling dibenzofuran-2,8-dipropanoic acid with two tetrapeptides.[164] The two peptides are hence arranged such that a peptide guest can bind between them in a three-stranded antiparallel β-sheet. Related tweezer-like receptors for peptides have also been



Reagents:
(i) pyrrolidine, benzene, reflux, 24 h; (ii) $CH_3CH_2OCH{=}C(CN)_2$, THF, –20 °C, 30 min; (iii) conc. aq. NH_3, THF, reflux, 4 h; (iv) CH_2Cl_2–CH_3OH, O_3, –78 °C; (v) 4-amino-1,3-pyrimidine-5-carbaldehyde, CH_3OH–toluene, KOH, reflux, 30 h; (vi) (*a*) 0.2 M HCl, reflux, 12 h; (*b*) $CH_2(CN)_2$, CH_3OH–toluene, piperidine, reflux, 24 h

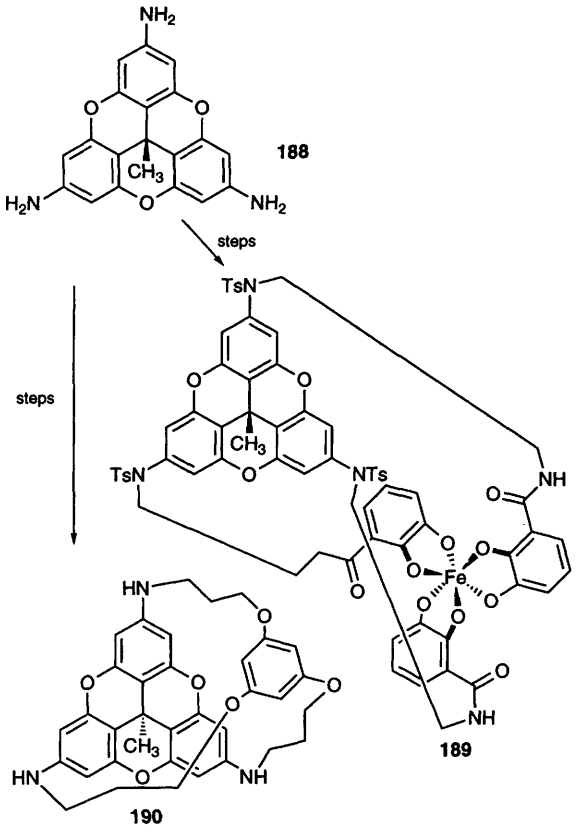
Scheme 52

constructed with two vinylogous sulfonyl peptides arrayed on a benzene-1,3,5-tricarboxylate spacer, the third position on this unit being used to attach a dye molecule to facilitate screening with a library of potential guests.[165] The use of peptidic frameworks as the basis of molecular receptors has been reviewed by Voyer and Lamothe.[166]

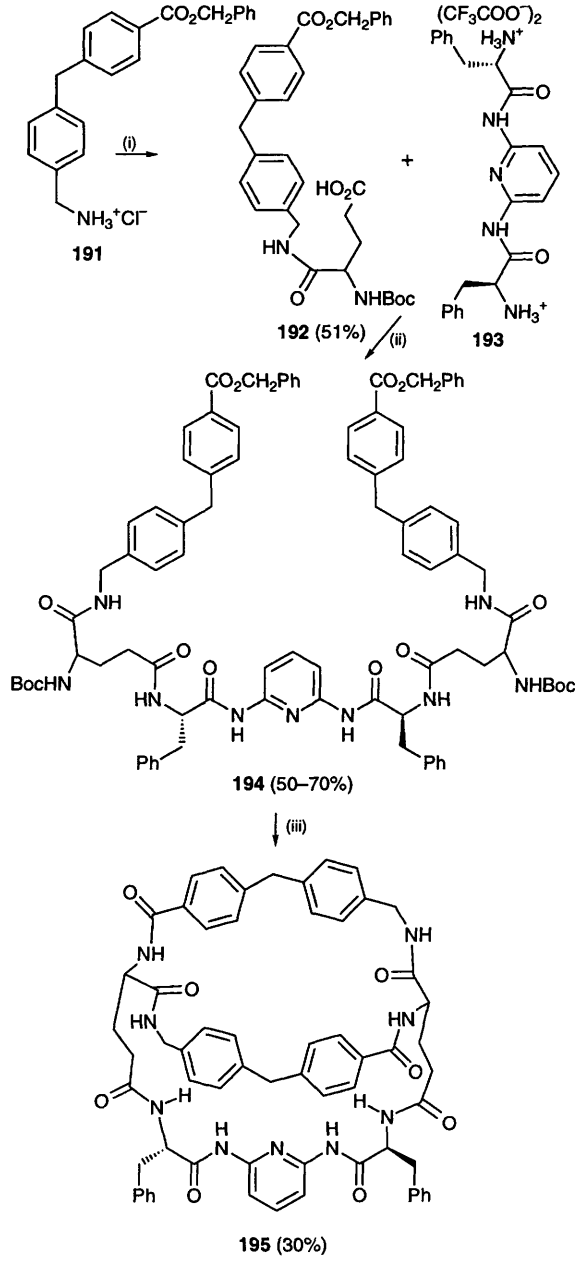
5.2 Molecular bowls and other receptors

The use of 2,6,10-triaminotrioxatricornan **188** as a C_3-symmetric, bowl-shaped keystone for the construction of cyclophanes has been reported.[167,168] A (metallo)macrocyclophane **189** assembled with a ferric tris(catecholamide) unit[167] and a cage cyclophane **190** capped with a phloroglucinol unit[168] have been described (**Scheme 53**).

Kilburn and co-workers have constructed a series of macrobicyclic receptors for amino acid derivatives which have a bowl-like shape.[169–171] They used amino acid subunits to impart chirality and incorporated either thiourea or diamidopyridine units as carboxylic acid binding sites. The macrobicycles were generally assembled by stepwise formation of amide bonds with a double macrocyclization as the key step. For instance,[169] the biarylmethane unit **191** (prepared by a Suzuki coupling) which rigidifies the upper rim was coupled with DCC–HOBt to a suitably protected glutamic acid. After removal of



Scheme 53



Reagents; (i)(*a*) Boc-L-glutamic acid γ-allyl ester, DCC, HOBt, DIPEA, DMF; (*b*) $Pd(PPh_3)_4$, pyrrolidine, CH_2Cl_2; (ii) PyBOP, Pr^i_2NEt, DMF; (iii) (*a*) 10%Pd/C, NH_4CO_2H, DMF; (*b*) C_6F_5OH, DCC, DMAP, THF; (*c*) 50% TFA, CH_2Cl_2; (*d*) syringe pump addition to DIPEA, CH_3CN.
HOBt = 1-hydroxybenzotriazole; PyBOP = benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
DIPEA = Pr^i_2NEt

Scheme 54

the allyl protecting group, two equivalents of **192** were reacted with bis(L-phenylalanine)-derived amidopyridine unit **193** yielding macrocycle precursor **194**. The benzyl esters of **194** were hydrolysed and the resulting diacid converted to a bis(pentafluorophenyl ester). Removal of the amine protecting groups with trifluoroacetic acid and slow addition of the resulting bis(trifluoroacetate salt) to a solution of DIPEA in acetonitrile gave the desired macrobicycle **195** in ~30% yield (**Scheme 54**).

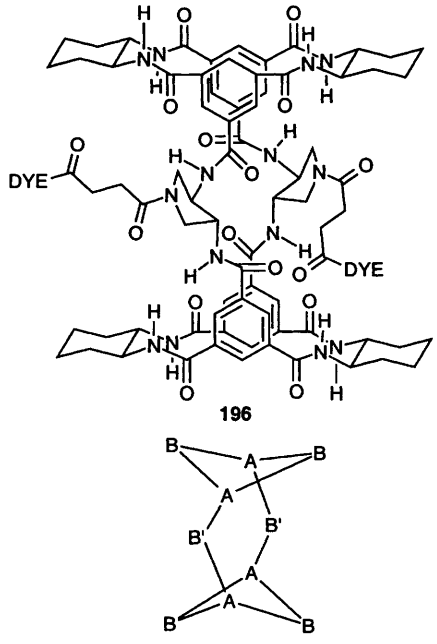
Still and his group have extended their studies of peptide-binding A_4B_6 macrotricycles. The synthesis of an $A_4B'_2B_4$ variant **196** (**Scheme 55**) and Still's method of ascertaining its binding selectivity for di- and tri-peptide sequences using an encoded combinatorial library has been the subject of a full paper.[172]

They have also reported a water soluble analogue **197** which exhibited sequence-selective binding of peptides in water.[173] It was constructed with trimesic acid for the A motif and two derivatives of a chiral diaminocycloazaheptane for the B portions; a hydrophilic ammonium salt as B and a rhodamine dye-substituted azaheptane as B′ (**Scheme 56**).

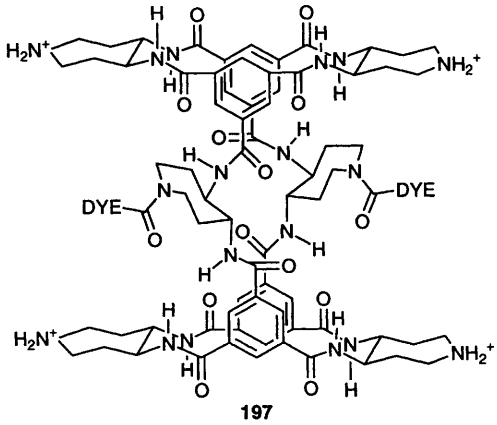
Further research has been aimed at finding the minimal structural element of the $A_2B'_2B_4$ receptor system which functions as a sequence-selective binding host.[174] Interestingly, whilst fragments **198** and **199** show no evidence of binding, partial receptor **200** showed greater selectivity than the parent structure **196** (**Scheme 57**).

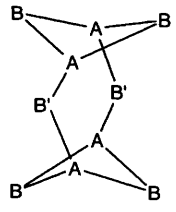
6 Self-assembling receptors

The use of non-covalent bonds to construct host molecules is an increasingly popular and easy method of receptor manufacture because the greater the degree of self-assembly in the host, the less work for the synthetic chemist, in theory at least! A review on self-assembling supramolecular complexes has appeared,[175] and the self-assembly of

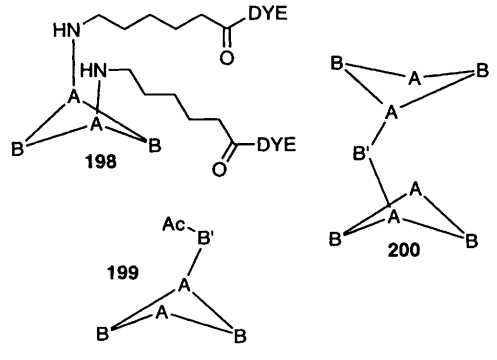


Scheme 55

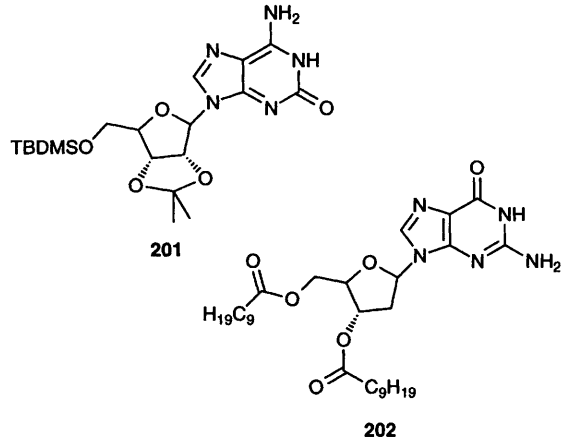




Scheme 56



Scheme 57



Scheme 58

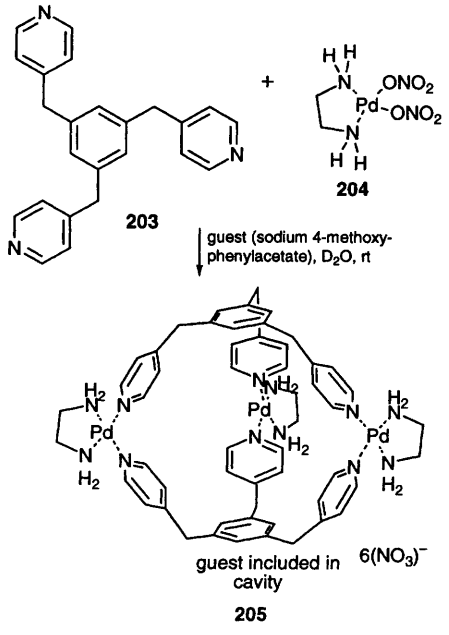
molecular-sized boxes has been reviewed by Hunter.[176]

Metal chelation has been used to provide the driving force for the self assembly of receptors. Self-assembling ionophores based on isoguanosine[177] and deoxyguanosine[178] have been reported. Isoguanosine mononucleoside **201** (**Scheme 58**) formed cyclic tetramers in nonpolar organic solvents which on addition of metal ion guest could be either stabilized, destabilized so that monomer was favoured or even further assembled into octamers, all depending on the identity of the metal ion. Deoxyguanosine derivative **202** formed a receptor able to extract alkali metal picrates by a similar mode of self assembly.

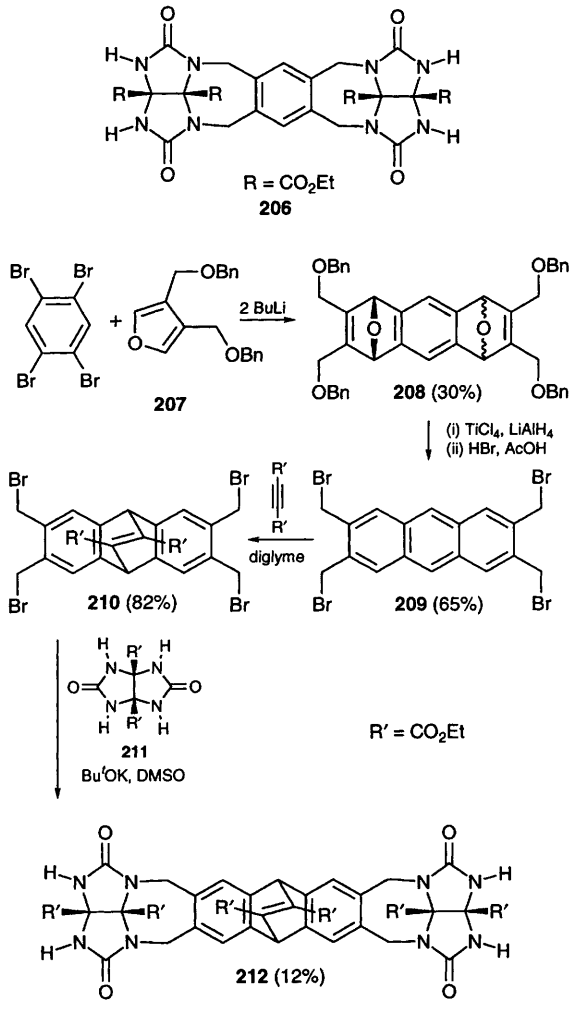
Hamilton and his group have published further work on metal-templated receptors[179,180] and they have described the preparation of a small library of bifunctional receptors using such an assembly procedure.[181] Thus terpyridyl ligands substituted at the 5-position with binding moieties such as a thiourea or a crown ether were prepared and coordinated to a Ru^{II} centre to form a library of fifteen receptors. These were then assessed for their selectivity towards various bifunctional guests. Stang and his group have published further work on macrocyclic squares assembled with either metal or iodonium corner pieces.[182]

The use of guest-induced assembly to create a host has been described by Ogura and co-workers.[183] Thus, a three-dimensional cage **205** was formed when the tridentate ligand **203** and $Pd(en)(NO_3)_2$ **204** were mixed in the presence of sodium 4-methoxyphenylacetate, in water (**Scheme 59**). Without the correct guest present, only oligomers were formed. Bilyk and Harding have described the guest-induced assembly of a chiral [2+2] metallomacrocycle.[184]

Rebek and his group have continued their research into self-complementary molecules that assemble into dimeric capsules using hydrogen bonding and can act as size-selective hosts. For instance, **206** dimerized to encapsulate xenon (**Scheme 60**).[185] Other monomer units have been synthesized generally by reaction of an appropriate



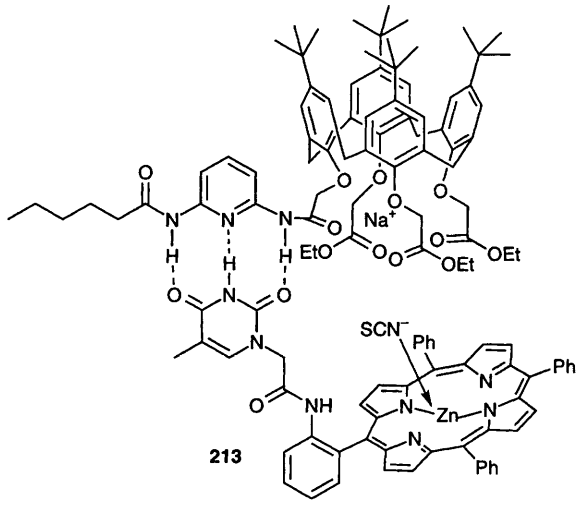
Scheme 59



Scheme 60

tetrabromide with a glycoluril.[186,187] One of the new monomers **212** has a bridged anthracene spacer which was synthesized *via* tandem benzyne additions to furan **207**. The reaction produced a mixture of isomeric *syn*- and *anti*-endoxides **208** which were both reduced with Ti^0 and after replacement of the benzyl oxyether groups with bromides gave **209**. A subsequent Diels–Alder reaction with diethyl acetylenedicarboxylate yielded the ethenoanthracene tetrabromide **210**. Reaction of **210** with glycoluril **211** produced a mixture of **212** and two stereoisomers. However the target compound **212** was the only isomer soluble in nonpolar organic solvents and could be separated by extraction with chloroform (Scheme 60).

Reinhoudt and co-workers have reported a self-assembled bifunctional receptor which uses hydrogen bonding in its construction.[188] The receptor **213** contained a calix[4]arene unit to recognize sodium cations and a tetraphenylporphyrin unit to coordinate to anions such as thiocyanate. The two halves of the receptor **213** assembled *via* a diamidopyridine–thymine interaction (**Scheme 61**).



Scheme 61

7 References

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