Synthetic developments in host–guest chemistry

JEREMY D. KILBURN and HITESH K. PATEL

Department of Chemistry, University of Southampton, Southampton, SO9 5NH, UK

Reviewing the literature published between July 1992 and December 1993

1 Introduction

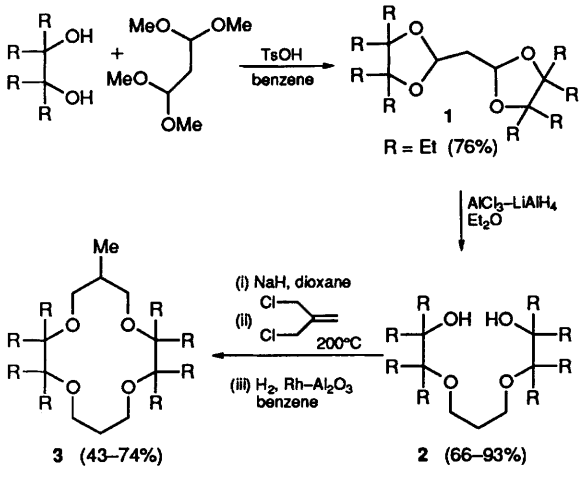
The discovery, by Pedersen in 1967,[1] of dibenzo-18-crown-6, and its ability to form stable complexes with alkali and alkaline-earth metals, effectively marks the beginning of synthetic host–guest chemistry. Since then research in this area has expanded dramatically, reflecting the important contribution that the study of artificial receptors can make to our understanding of molecular recognition phenomena in general, and pointing the way forward to the design and synthesis of supramolecular materials with tailored properties. Not surprisingly, much of the interest in this area focuses on the recognition properties of the receptors, a subject which is frequently reviewed in the literature.[2] However, before the properties of a new receptor can be investigated, the receptor must, of course, be synthesized. The importance of efficient synthesis in this area cannot be overstated if sufficient material is to be obtained for study, in a realistic time-span. Receptor synthesis is often far from trivial, particularly for the synthesis of large macrocyclic compounds, and can rival natural product synthesis in complexity and elegance. The purpose of this article, therefore, is to review developments in host–guest chemistry, over the period July 1992 to December 1993, with the emphasis on the synthetic aspects. The review is divided into sections using conventional categorization of the type of receptor concerned, but because, increasingly, receptors are being prepared with features of more than one structural type, these categorizations become somewhat arbitrary!

2 Crown ethers, cryptands, spherands, and podands

2.1 Crown ethers

More than 25 years after Pedersen's original discovery of dibenzo-18-crown-6, work continues to modify the many useful properties of crown ethers, by altering the various structural parameters. Consequently new syntheses of crown ethers are continually being published and reviewed.[3]

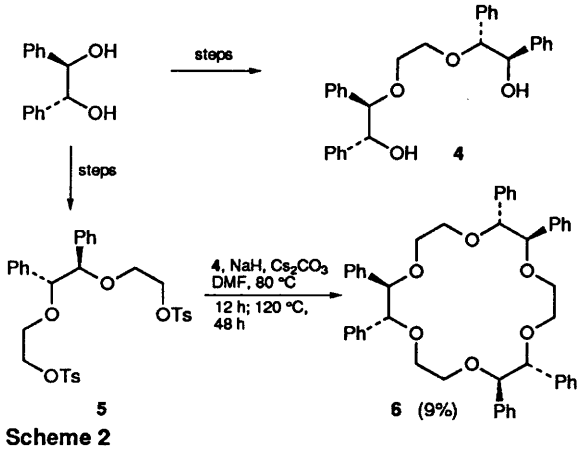
Because of its small size and high free energy of hydration, the lithium cation is difficult to bind selectively. A novel synthesis of highly substituted 14-crown-4 derivatives **3** (**Scheme 1**), from tertiary and neopentyl alcohols, gave gram quantities of these materials which showed high selectivity for Li^+ owing to the cylindrical cavity formed by the tertiary alkyl substituents.[4]



Scheme 1

Previous syntheses of such compounds were low yielding, probably because of the low nucleophilicity and high basicity of the tertiary alkoxides used in the syntheses. In this new work, reductive ring-opening of bis acetals **1** avoided the use of a Williamson ether synthesis, and gave the intermediate diols **2** in good yield. These were then condensed with methallyl dichloride at 200–250°C in a stainless-steel bomb.

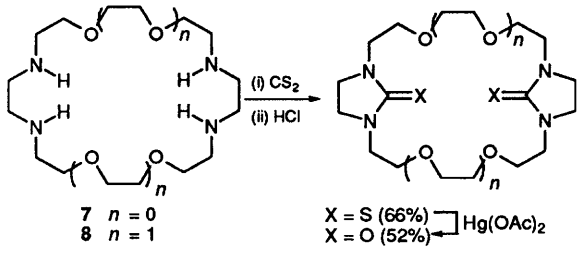
Chiral crown ethers are of considerable interest because of their ability to differentiate between enantiomers of racemic substrates and because they can be used as chiral reagents or catalysts for a number of transformations. The stereospecific synthesis of (*R,R,R,R,R,R*)-hexaphenyl-18-crown-6 **6**, and related crown ethers, has been reported by Stoddart (**Scheme 2**).[5]



Scheme 2

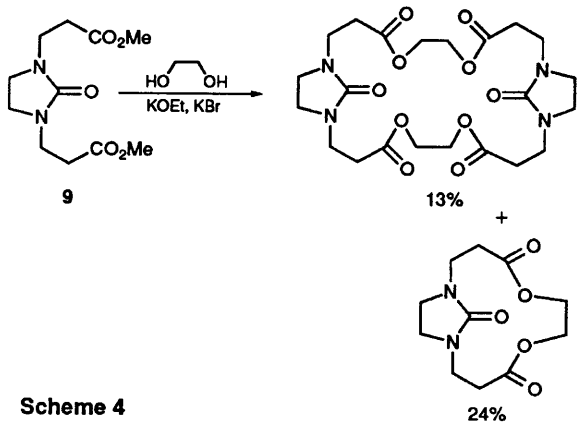
Starting from (*R,R*)-hydrobenzoin, the diol **4** and ditosylate **5** were prepared and condensed together using sodium hydride in the presence of caesium carbonate. These new crown ethers showed some ability to catalyse an asymmetric Michael addition between methyl phenylacetate and methyl acrylate. The synthesis of chiral crown ethers derived from D-mannitol,[6] and from various phenyl-substituted cyclohexane-1,2-diols, have also been described.[7]

A number of crown ether variants have been reported recently. Thus, Parker and co-workers have converted the tetraaza crown ethers **7** and **8** into macrocyclic thioureas, by reaction with carbon disulfide followed by treatment with HCl (**Scheme 3**).[8] The thiourea macrocycles were, in turn, transformed into macrocyclic ureas by treatment with mercuric acetate.



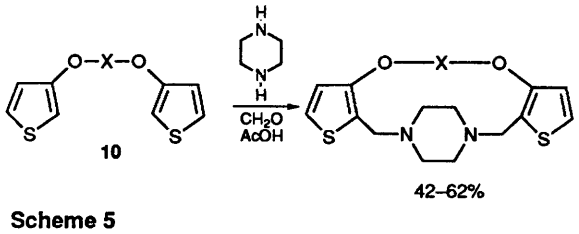
Scheme 3

Related macrocyclic ureas have also been synthesized, by transesterification of urea diester **9** with ethylene glycol (**Scheme 4**).[9]



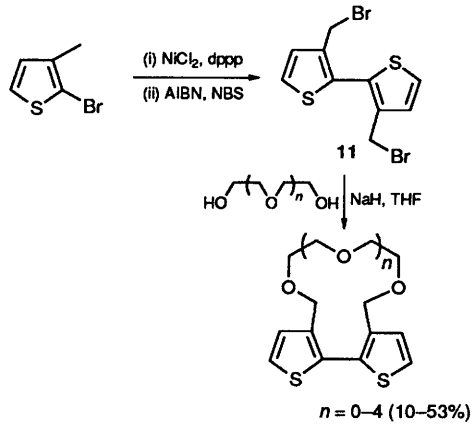
Scheme 4

Macrocycles containing two thiophene rings have been prepared by a double Mannich reaction between bis(thienyl)ethers **10**, formaldehyde, and either *N,N'*-dimethylethylenediamine or piperazine, in acetic acid (**Scheme 5**).[10] This reaction gave the macrocycles in good yields when the linking group between the thiophenes contained sulfur or oxygen atoms, rather than straight alkyl chains. Internal templating, by heteroatom stabilization of the iminium species generated in the Mannich reaction, is postulated to explain the better yields.



Scheme 5

A novel crown ether incorporating a 2,2'-bithiophene has been prepared, as a possible precursor for a conducting polymer by reaction of dibromide **11** with suitable dialkoxides (**Scheme 6**).[11]



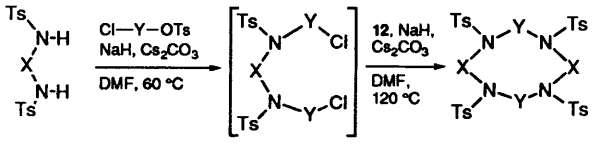
Scheme 6

2.2 Azacrowns and related compounds

Polyazamacrocycles and azacrowns have been popular because of their utility as ligands for a range of metal ions, and have found use in a number of contexts, including the removal of toxic metal ions from the

body, the transport of radioisotopes into cancer cells for radiotherapy, and as phase-transfer catalysts. An excellent review on methodology for the synthesis of azacrown macrocycles and cryptands has been published by Bradshaw *et al.*[12]

A general procedure for the synthesis of large tetraazamacrocycles, with 28- to 44-membered rings, has been described,[13] and involves the use of ω-chloroalkyl *p*-toluenesulfonates with the different leaving group abilities of the chloro and sulfonyl groups being used to advantage (**Scheme 7**).

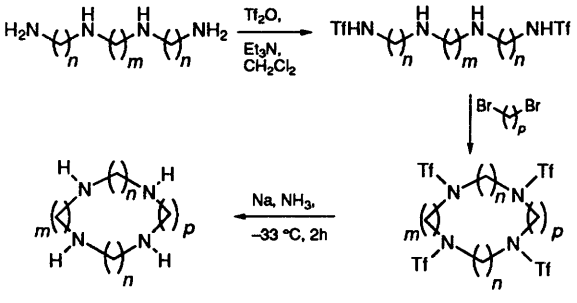


12 13 14 (25–42%)

Scheme 7

Thus bistoluenesulfonamides **12** are alkylated with ω-chloroalkyl *p*-toluenesulfonates (at 60°C), using NaH as base, to give the dichlorides **13** which are then added, without any purification, to a further equivalent of the dianion of **12** at a higher temperature (120°C), giving macrocycles **14** in 25–45% yield.

While the use of anions derived from toluenesulfonamides is a common approach in polyazamacrocycle synthesis, the ultimate removal of the tosylate group is often not trivial. A recent report describes the use of trifluoromethanesulfonyl derivatives of linear tetra-amines in macrocyclizations, with subsequent deprotection using sodium in liquid ammonia (**Scheme 8**).[14]



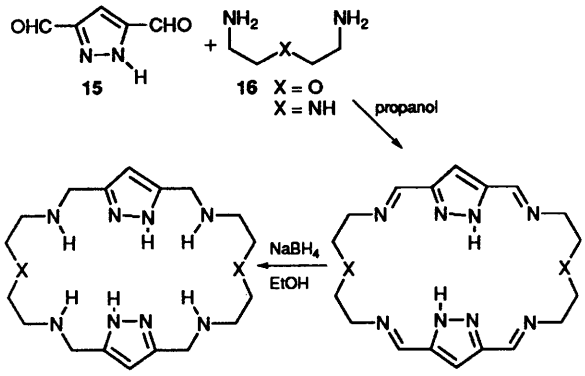
57–66% yield over 2 steps (except $m = n = p = 2$<5%)

$n = 2,3$ $m = 2,3,4$ $p = 2,3,4$

Scheme 8

Schiff base formation is another popular method for assembling polyazamacrocycles, and 26-membered macrocycles containing 3,5-disubstituted pyrazoles, which form dinuclear complexes with zinc cations, have been prepared by condensation of pyrazole dialdehyde **15** with diamine **16** and hydrogenation of the resulting Schiff base (**Scheme 9**).[15]

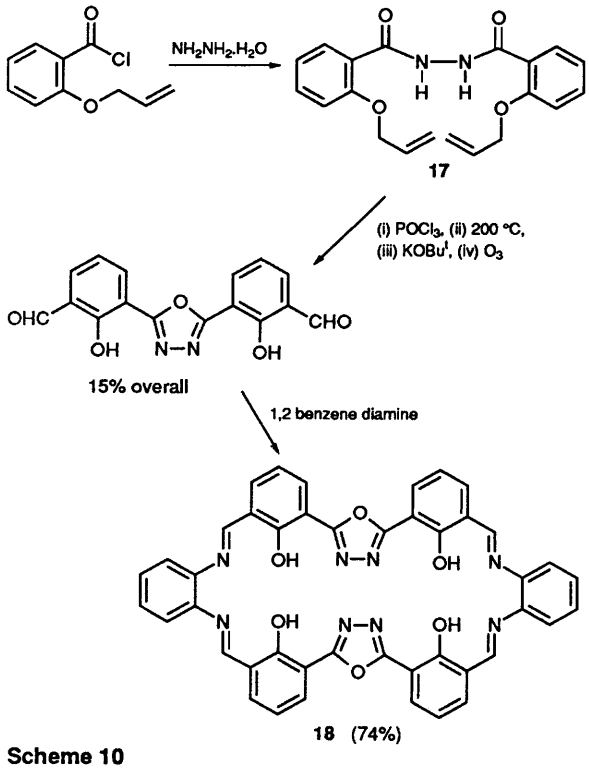
An unusual multidentate macrocycle containing 1,3,4-oxadiazole, imine, and phenol functionality has been prepared[16] by dehydration of bis(acyl)hydrazine **17** followed by Claisen rearrangement, isomerization of the allyl groups, and ozonolysis. Cyclization with



X = O (66% overall)
X = NH (30% overall)

Scheme 9

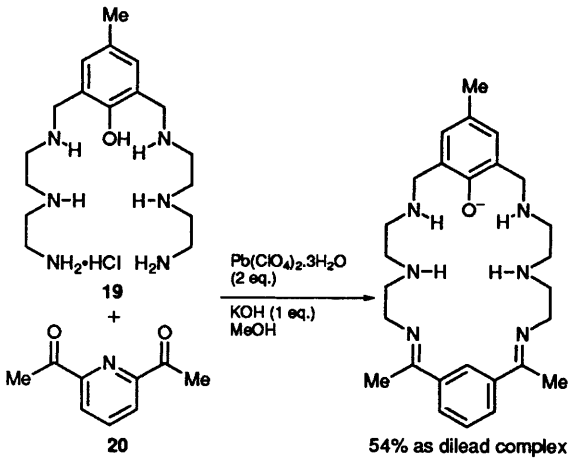
1,2-diaminobenzene gave the macrocycle **18** in 74% yield. Similarly, condensation with 1,2-diaminoethane gave the corresponding macrocycle in 82% yield (**Scheme 10**).



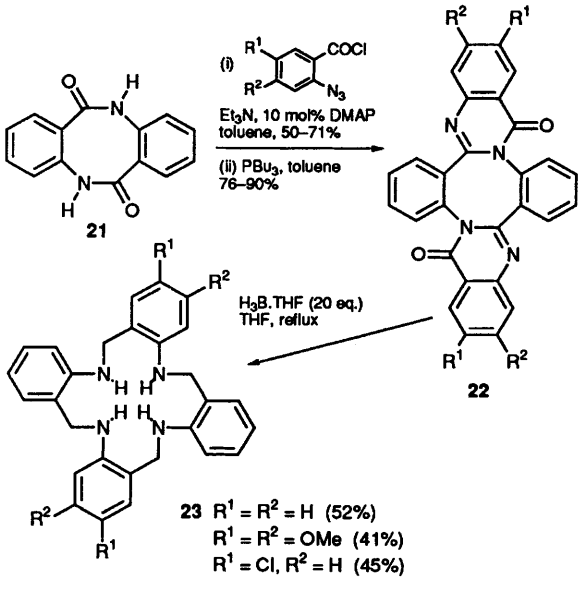
Scheme 10

A related macrocycle has been prepared by condensation of the partially neutralized diamine **19** with diketopyridine **20** templated by $Pb(ClO_4)_2$ (**Scheme 11**).[17] A route to tetrazole-containing macrocycles has also been reported.[18]

A novel route to benzopolyazamacrocycles involves a bisquinazoline annelation and reductive ring enlargement (**Scheme 12**).[19] Thus, readily available dianthranilide **21** was condensed with 2-azidobenzoyl chlorides, followed by a Staudinger reaction/aza-Wittig sequence to give bisquinazolines **22**. Reductive ring enlargement of **22** with 20 molar equivalents of $H_3B.THF$ gave macrocycles **23** in 41–52% yield.

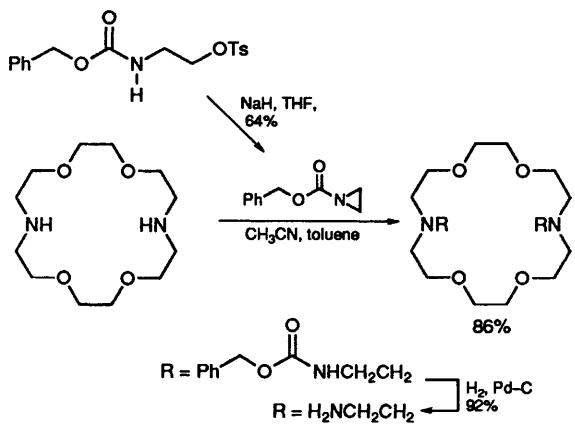


Scheme 11



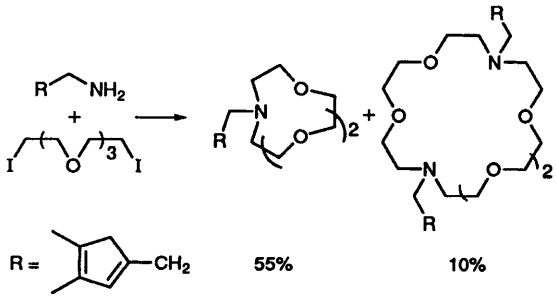
Scheme 12

Azamacrocycles are useful building blocks for larger structures since the nitrogen atoms can be readily functionalized. A simple strategy for the synthesis and purification of unsymmetrical *N,N'*-bis-substituted diaza-18-crown-6 has been reported, in which the purification of the highly polar intermediates was achieved by column chromatography, eluting first with acetone, and then with acetone/triethylamine.[20] The synthesis of a range of amide and amide-ester *N*-functionalized polyazamacrocycles has been described by Parker[21] while *N*-benzyloxycarbonylaziridine has been used as an efficient alkylating reagent for azacrowns in the preparation of 2-aminoethyl-armed lariat ethers (**Scheme 13**).[22] The use of an *N*-carbamoylaziridine, as opposed to the previously reported *N*-tosylaziridine, again allows a much easier deprotection to release the free aminoethyl crown ether derivative.



Scheme 13

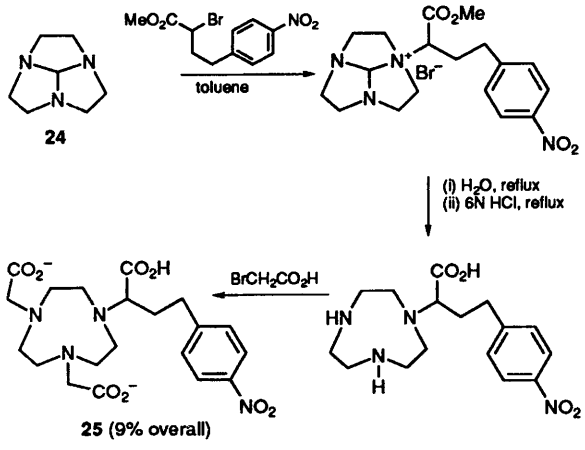
The attachment of spirobenzopyrans and spironaphthoxazins to azacrowns gave multifunctional receptors,[23] which rearranged to the coloured merocyanines in the presence of suitable alkali-metal cations, while attachment of 6-phenanthridinyl units led to new fluoroionophores.[24] Attachment of bis[(pyrazole)ethyl]amino units to azacrowns produced compounds capable of the simultaneous binding of copper and alkali-metal cations, and unusual redox properties were reported for these complexes.[25] The synthesis and redox properties of ferrocene-azacrown derivatives is described in detail in a full paper by Gokel.[26] Azacrowns with indene and cyclopentadiene side-arms have also been prepared and were designed to bind alkali-metal cations and transition metals simultaneously.[27] Although these azacrown derivatives could be synthesized by alkylation of the parent azacrown, they could also be prepared by the alternative strategy of condensing a suitable amine with a diiodide directly (**Scheme 14**). This method is, in principle, more economic than alkylation of the parent azacrown in situations where the parent azacrown is not readily available, and has itself to be synthesized.



Scheme 14

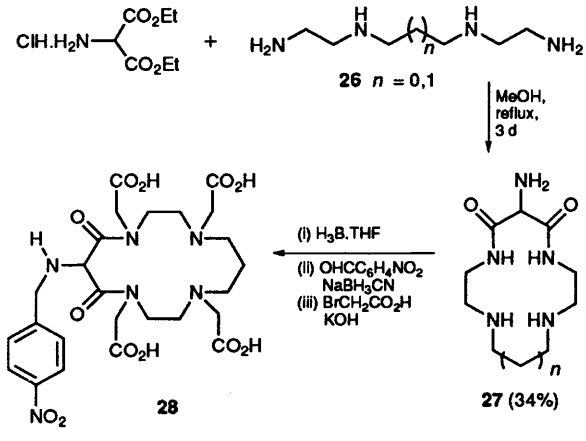
Bifunctional chelating agents (BCAs) are used for the chelation of radioisotopes, and possess extra functionality to allow them to be linked to monoclonal antibodies for use in radiotherapy. A novel synthesis of such a BCA began with the readily available orthoamide **24** (**Scheme 15**).[28] Monoalkylation and

hydrolysis gave the monoalkylated triamine, which was further derivatized with bromoacetic acid to give the ligand **25**.



Scheme 15

The synthesis of a related BCA began with the condensation of tetra-amine **26** with diethyl aminomalonate hydrochloride, to give **27** in 34% yield Scheme 16).[29] Reduction with $H_3B.THF$, reductive amination with 4-nitrobenzaldehyde, alkylation, and hydrolysis gave the desired ligand **28**.

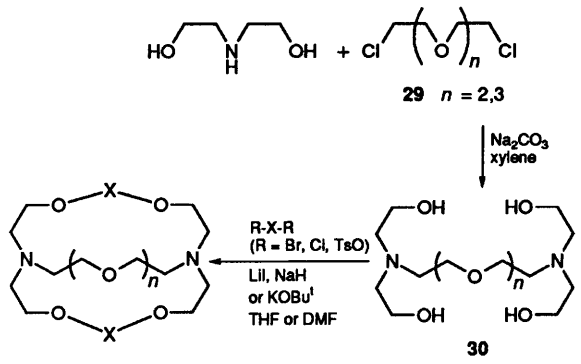


Scheme 16

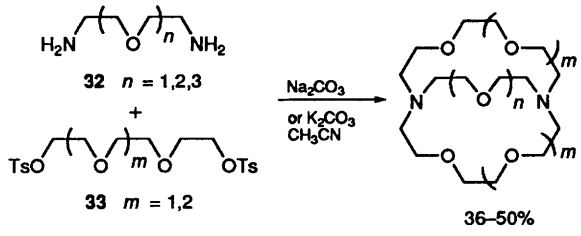
2.3 Cryptands

Syntheses of cryptands often require several steps, but a number of recent reports have described short routes to these important compounds. Bradshaw *et al.* started from diethanolamine which they condensed with dichlorides **29**, to give tetrols **30** in 90% yield (**Scheme 17**).[30] Ring-closure with a variety of aromatic or aliphatic dichlorides, dibromides, or ditosylates gave the cryptands **31** in yields of 20–55%.

The same group has published an improved procedure for the synthesis of aliphatic cryptands which involves simply condensing diamines **32** with ditosylates **33** (using sodium carbonate in refluxing acetonitrile) over six days (**Scheme 18**).[31] After work-up and chromatography the cryptands were obtained in yields of 36–50%.

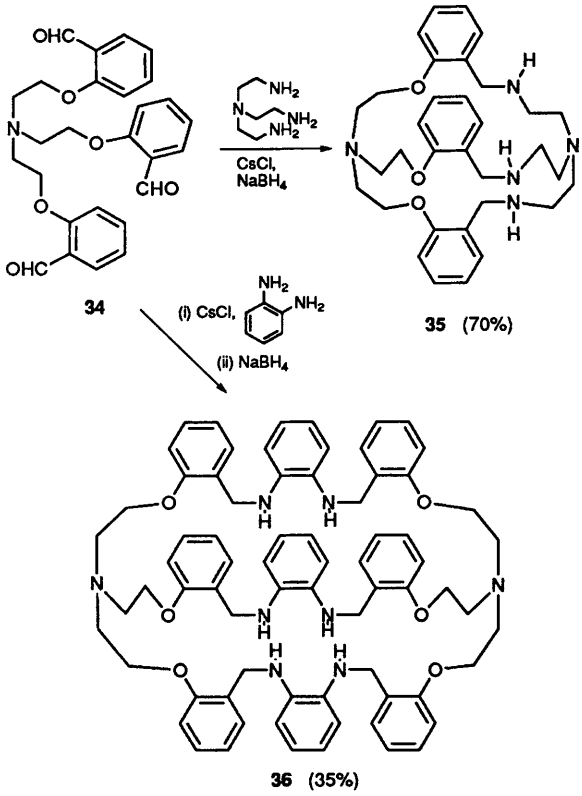


Scheme 17



Scheme 18

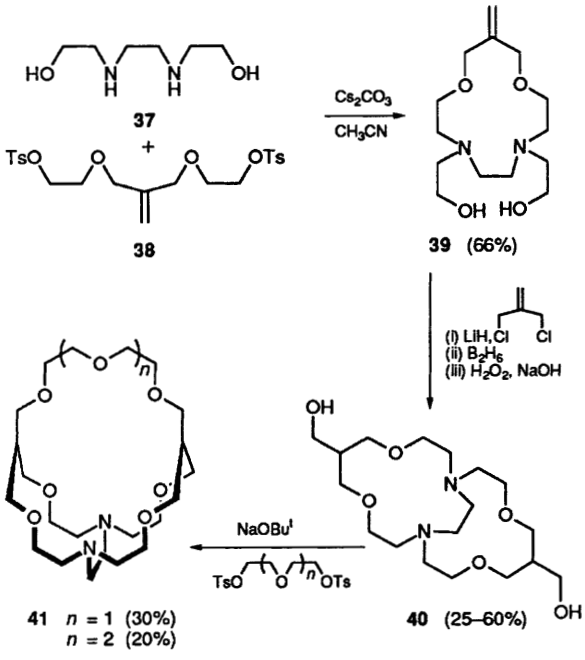
Short syntheses of rather different cryptands have been reported by Bharadwaj.[32] Thus tris(2-aminoethyl)amine and trialdehyde **34** were condensed, in the presence of caesium cations as a template, and reduced to give cryptand **35** in 70% yield (**Scheme 19**). Similarly, the tripodal trialdehyde



Scheme 19

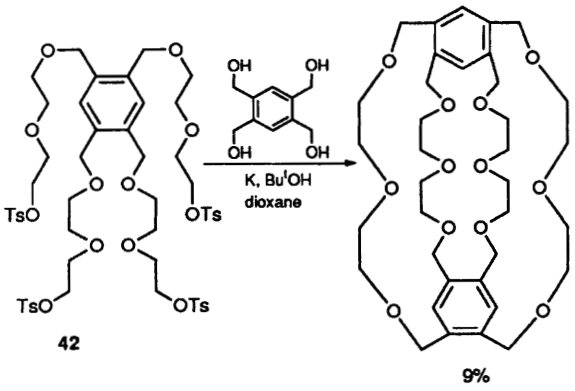
34 can be reductively aminated with 1,2-diaminobenzene, in the presence of caesium chloride, to give the product **36** in 35% yield (**Scheme 19**).[33]

A full paper has described in detail the synthesis of a number of macrobicyclic and macrotricyclic polyether ligands such as **41** (**Scheme 20**).[34] Typically, condensation of diamine **37** with ditosylate **38**, under weakly basic conditions, gave the crown ether derivative **39**, which was further reacted with methallyl dichloride, using lithium hydride as base, and converted into diol **40**. Cyclization of diol **40** with glycol ditosylates then gave the macrotricycles.



Scheme 20

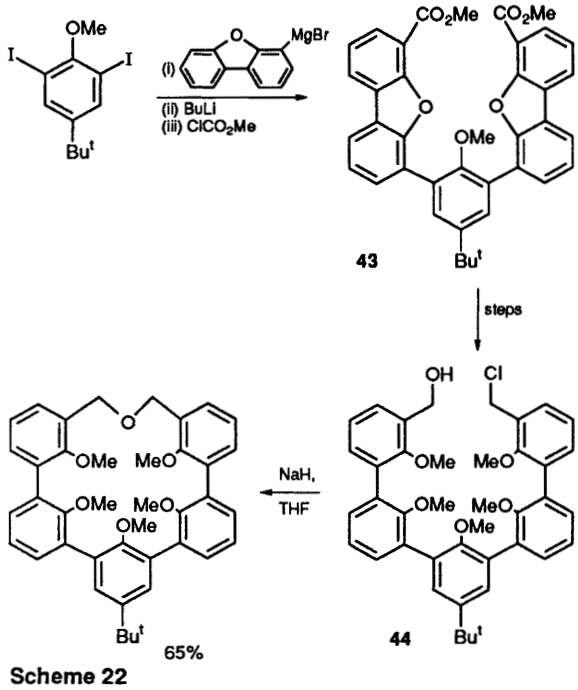
A series of benzene-bridged macropolycyclic polyethers has also been reported; the syntheses involve the condensation of tri- or tetra-tosylates, such as **42**, with a triol or a tetrol respectively, using potassium dissolved in t-butyl alcohol as base (**Scheme 21**).[35]



Scheme 21

2.4 Spherands

The requirement that a receptor should be preorganized in order to maximize the resulting binding energy upon complexation is firmly established, largely as a result of Cram's seminal work in this area.[36] In further work aimed at investigating the role of preorganization in the complexation of metal cations, Cram has reported the synthesis of a new spherand incorporating five anisyl units and one CH_2OCH_2 unit to compare with previously reported variations on this theme.[37] The synthesis began with a two-fold aryl–aryl coupling of 4-dibenzylfuranyl magnesium bromide with a diiodo anisole, followed by dimetallation and treatment with methyl-chloroformate, to give the diester **43** (**Scheme 22**). The diester was converted into chloroalcohol **44** and then cyclized, using NaH, in a reaction which appeared to be templated by Na^+. A number of related spherands were also prepared.

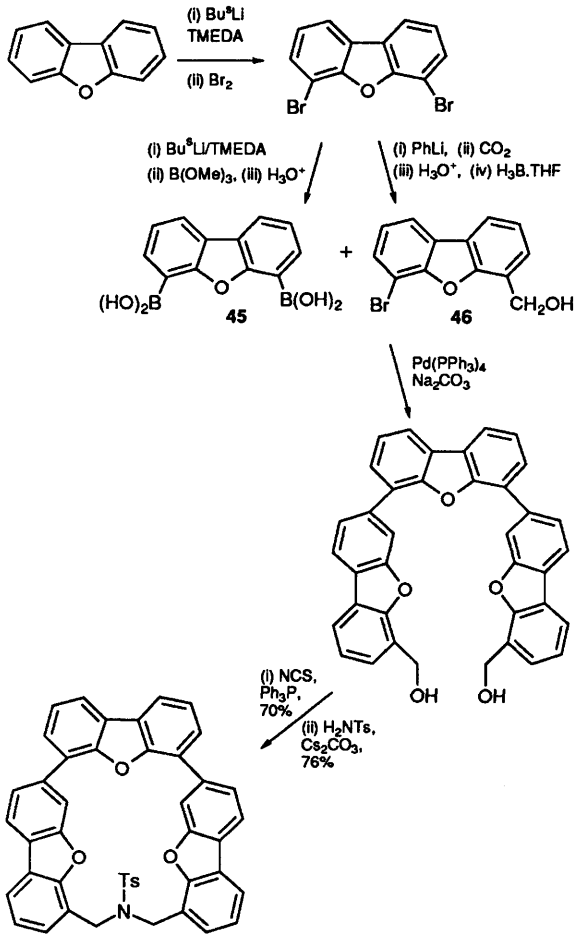


Scheme 22

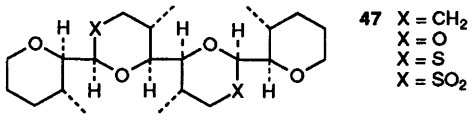
Cram has also reported on the synthesis of a series of saddle-shaped hosts based on fused dibenzofuran units.[38] In one such synthesis, benzofuran was converted into the diboronic acid **45** and into the bromo alcohol **46** (**Scheme 23**). A Suzuki coupling of these two, conversion into the corresponding dichloride, and cyclization with $TsNH_2$ gave the new macrocycle.

2.5 Podands

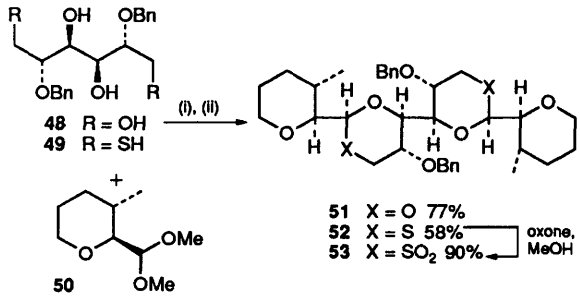
The requirement for preorganization has meant that receptor design tends to concentrate on macrocyclic structures. However, in the last few years Still has described the synthesis and binding properties of a number of non-macrocyclic podand ionophores of general structure **47** (**Scheme 24**), which by careful choice of the position of various alkyl substituents, can



Scheme 23



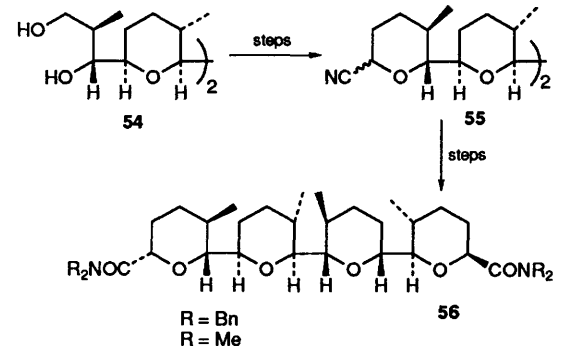
Scheme 24



Reagents: when R = OH (i) cat. CSA, THF; (ii) TsOH, CH_2Cl_2
when R = SH (i) $F_3B.OEt_2$

Scheme 25

Still has also sought to enhance the binding properties of these podands by adding suitable functional groups. Thus, the previously described tetrol **45** was converted into the bis(cyanohydrin)ether **55** and then partially hydrolysed, alkylated, and epimerized under basic conditions, to give the equatorial–equatorial bis(dialkylamide)podand **56** (**Scheme 26**).[40] The binding of alkali metal cations (Li^+, Na^+, K^+) by **56** was significantly enhanced compared with the parent podand **47** (X = CH_2) and approached that of macrocyclic crown ethers. Binding by the corresponding equatorial–axial isomer was approximately one order of magnitude lower and the axial–axial isomer showed a further drop in binding ability.



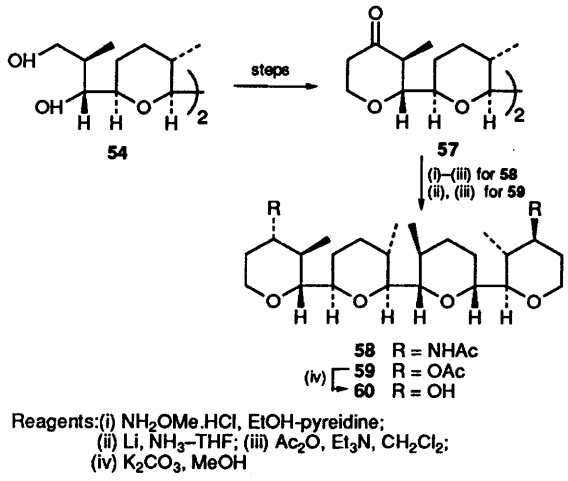
Scheme 26

The same tetrol **54** was taken through a series of steps to the diketone **57** which was then transformed to substituted podands **58**, **59**, and **60** (**Scheme 27**).[41] Acetamide **58** proved to be markedly more selective for the binding of α-amino acid methyl esters compared with the parent podand **47** (X = CH_2) or acetoxy podand **59**.

Hexacyclic podands **62** and **63** have also been synthesized (**Scheme 28**), again from tetrol **54** and acetal **50** (see **Scheme 25**).[42] These receptors align six oxygens in the same arrangement found in the crystal structure of potassium 18-crown-6 complex, and indeed were found to bind alkali metal cations with binding constants and selectivities closely matching those of dicyclohexyl 18-crown-6. However, they showed lower enantioselectivities for the binding of amino acid derivatives as compared with the corresponding tetracyclic podands **47**, which may be

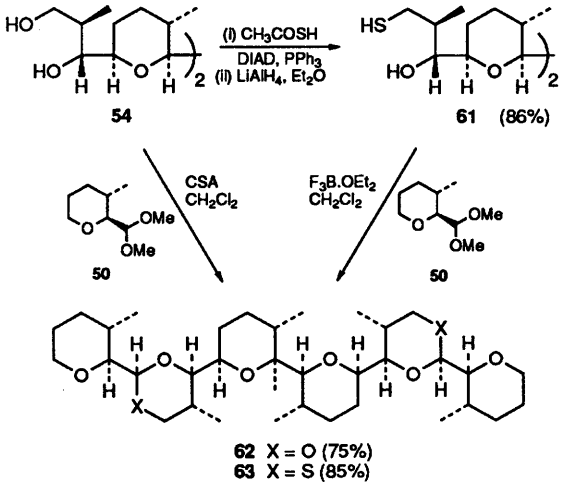
be locked into just one, or at most just a few, low energy conformations, and thus can be preorganized for highly selective binding.

In recent work a related podand has been prepared, with benzyloxy substituents to lock the conformation around the central inter-ring bond.[39] Thus, tetrol **48**, derived from D-mannitol, was coupled to acetal **50**, which was obtained from (+)-β-citrocellene, to give podand **51** as a mixture of diastereoisomers which could be equilibrated to pure **51** with further acid treatment (**Scheme 25**). The related thiopodand **52** was similarly prepared as a single stereoisomer by treatment of dithiol **49** with acetal **50** in the presence of catalytic $F_3B.OEt_2$. Oxidation then gave the sulfoxide podand **53**. These new podands bind various chiral ammonium ions enantioselectively, but, for instance, podand **53** is less enantioselective and less ionophoric than the analogous alkyl-substituted podand **47** (X = SO_2).



Reagents:(i) $NH_2OMe.HCl$, EtOH-pyreidine; (ii) Li, NH_3–THF; (iii) Ac_2O, Et_3N, CH_2Cl_2; (iv) K_2CO_3, MeOH

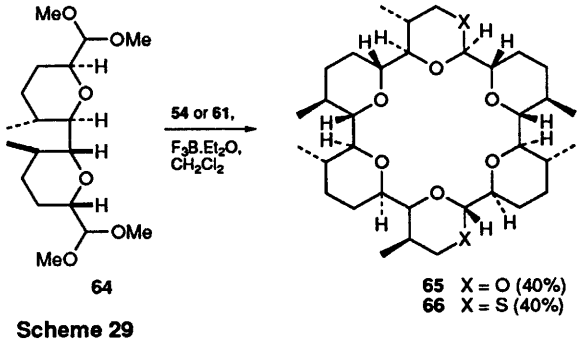
Scheme 27



Scheme 28

due to the gross conformation of **62** and **63** which is close to achiral D_{3d} symmetry.

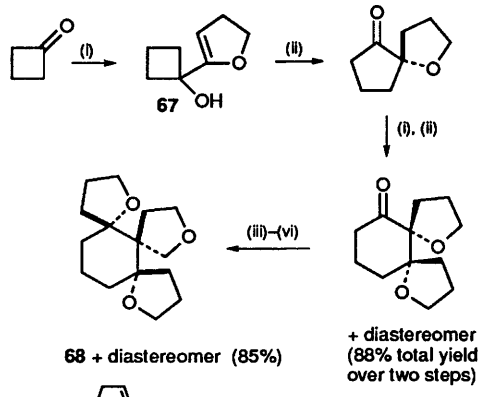
In a further paper in this series, the work has been taken full circle with the synthesis of the novel 18-crown-6 derivatives **65** and **66** (**Scheme 29**).[43] These were prepared by coupling either tetrol **54** (prepared from L-tartrate), or the derived thio-analogue **61**, with bisacetal **64** (prepared from D-tartrate). In the preparation of **65** a mixture of diastereoisomers resulted, but could be equilibrated to the desired diequatorial isomer using *p*-TsOH. These



Scheme 29

macrocycles have only one available conformation—again matching that of the potassium 18-crown-6 complex—and consequently **65** bound K^+ and Na^+ more tightly than 18-crown-6 itself.

In related work, Paquette and co-workers have synthesized di- and tri-spirocyclic tetrahydrofurans such as **68** using the acid-catalysed rearrangement of alcohols, such as **67**, as the key step (**Scheme 30**).[44] The *syn–syn* triether **68** was the most effective receptor for alkali-metal cations.



Reagents: (i)  THF, -78°C; (ii) Dowex-50x, CH_2Cl_2, r.t.; (iii) CH_2=$CHCH_2MgBr$; (iv) $H_3B.THF$; (v) H_2O_2, HO^-; (vi) TsOH, toluene, heat

Scheme 30

3 Calixarenes

Calixarenes are cavity-shaped cyclic molecules made up of phenol units linked *via* alkylidene groups.[45] Despite their attractive architecture, the host–guest chemistry of underivatized calixarenes has not been extensively developed, partly because calix[4]arene, in particular, has a rather small cavity. Calixarenes are, however, readily amenable to chemical modification on both the upper and lower rim, leading to molecules with selective binding properties. The easy accessibility of calix[4]arenes has made this member of the series increasingly popular as a building block or platform for assembling more elaborate structures with ligating side-arms. A timely review has been published which discusses many recent aspects of calixarene chemistry.[46]

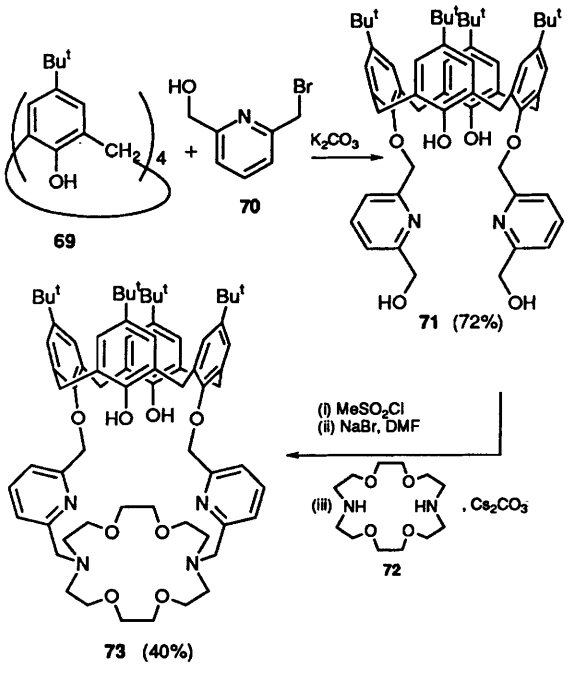
3.1 Calix[4]arenes

3.1.1 Modifications to the lower rim

The free hydroxyl groups in calix[4]arenes form strong intramolecular hydrogen bonds which favour the cone conformation. In tetra *O*-alkylated calixarenes, without such interactions, the cone conformation is no longer necessarily favoured. NaH has frequently been used as a base in the alkylation of calixarenes, but alkali-metal carbonates, M_2CO_3 (M = Na, K, Cs), when used as the base, can profoundly affect the conformer distribution of the resulting *O*-alkylated calixarenes, through metal template effects. Shinkai and co-workers have carried

out a systematic study involving the synthesis and classification of the many possible isomers which can be generated by partial or complete *O*-alkylation of calix[4]arenes, using a variety of synthetic methods, including the metal template method and the stepwise synthesis method.[47]

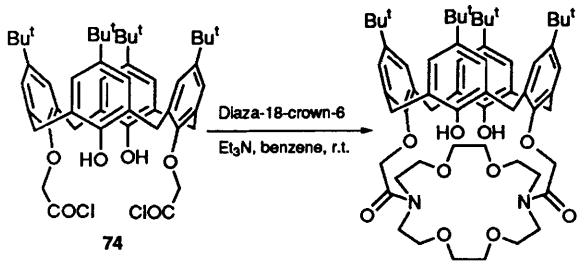
The lower ring of *p*-t-butylcalix[4]arene has been tetraalkylated to give a calix[4]arene tetraester containing anthracene moieties.[48] High Li^+ selectivity was found for these receptors which can be detected by the marked changes in the receptor's fluorescence spectrum upon complexation. Beer has selectively introduced substituents at the 1,3-distal hydroxy groups of calix[4]arenes and prepared 1,3-bis-pyridyl and 1,3-bis-alkylthioether calix[4]arenes designed to coordinate transition metal cations.[49] Adapting Reinhoudt's method[50] for the selective attachment of substituents at 1,3-distal hydroxy groups, alkylation of calix[4]arene **69**, with 2 equivalents of bromide **70**, using 1 equivalent of K_2CO_3, in refluxing CH_3CN, gave the 1,3-functionalized calix[4]arene **71** in 72% yield. The diol **71** was then converted into the corresponding dibromide, which was condensed with 1,10-diaza-18-crown-6 **72** to give the calixarene-cryptand **73** (**Scheme 31**). The syntheses of related 1,3-bipyridyl and 1,3-dialkylthioether calixarenes are also reported, along with the results of metal binding studies for these new receptors.



Scheme 31

Crown ethers have been similarly attached to the lower rim of calixarenes by the reaction of the 1,3-bis-(acid chloride) derivative **74** of *p*-t-butylcalix[4]arene with various diamines, including diaza-15-crown-5 and diaza-18-crown-6 (**Scheme 32**).[51]

Starting with a 1,3-bispropoxycalix[4]arene, Shinkai has functionalized the remaining hydroxyls on the lower rim to prepare a calix[4]arene, in the cone

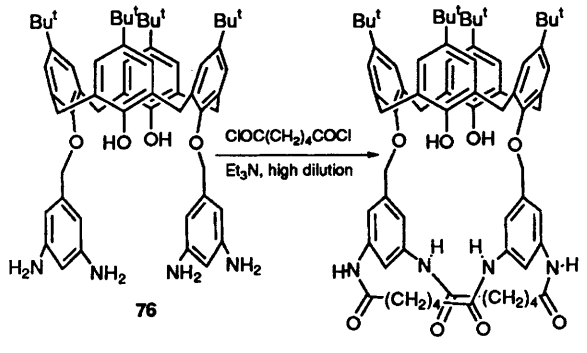


Scheme 32

conformation, with an ionophoric site near a hydrogen-bonding receptor site in the form of an amidopyridine unit.[52] Using an identical synthetic strategy, calix[4]arenes bearing diamidopyridine units at the lower rim have been synthesized,[53] and this has allowed the simultaneous binding of Na^+ and simple flavin guests to be monitored by fluorescence spectroscopy. A series of calix[4]arenes containing transition-metal Lewis acid binding-sites, in combination with amide NH groups, have been prepared, and these represent the first examples of calix[4]arene anion receptors.[54] The receptor was prepared by the condensation of the distal-(1,3) bis-(hydroxyacid chloride) **74** and 2 moles of 4-aminopyridine. The resulting transition-metal complexes all formed 1:1 solution complexes with chloride and bromide anions.

From 1,3-distal hydroxy-protected calix[4]arenes, mono- and di-phosphites have been prepared *via* the deprotonation of one or two phenol moieties and reaction with diphenylchlorophosphine.[55] Using Et_3N as the base afforded exclusively monophosphites, whereas the stronger base $LiNPr^i_2$ was required to introduce the second Ph_2P group.

More complex architectures have been produced by selective coupling of 3,5-dinitrobenzyl chloride, and related aromatic units, to the distal-(1,3) positions of *p*-t-butylcalixarene, followed by reduction to the tetraamine **76** and coupling with bis-(acid chlorides), to give 'doubly-spanned' calixarenes such as **77** (**Scheme 33**).[56]



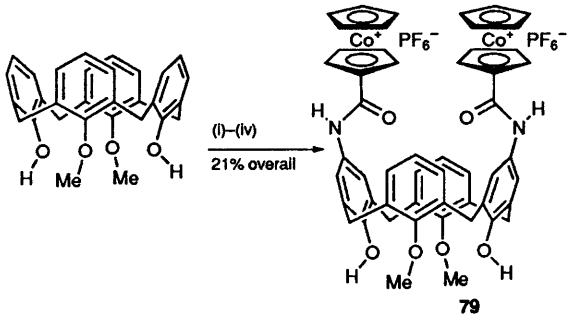
Scheme 33

Calix[4]arenes with proximal-(1,2) substitution have received less attention than the distal-(1,3) regioisomers, but Reinhoudt and co-workers have found that subtle changes in the functionality, and their regioselective positioning on these calixarenes, has considerable influence on the binding selectivity for

alkali-metal cations.[57] A general method for the preparation of proximal-(1,2) functionalized calix[4]arenes has been developed and used 4.2 equivalents of NaH and 2.2 equivalents of alkylating agent in DMF.[57] Further functionalization to give bis-proximally functionalized calix[4]arenes was best achieved using Cs_2CO_3 as the base.

3.1.2 Modifications to the upper rim

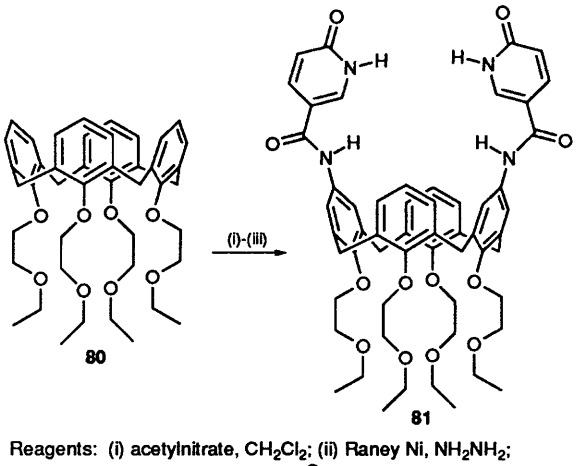
Beer has prepared a redox-responsive calix[4]arene ditopic anion receptor, which contains two cobalticinium moieties.[58] The receptor, which recognizes the adipate dicarboxylate dianion, was readily prepared from the reduction of the known dinitro-derivative using Raney nickel and hydrazine hydrate (**Scheme 34**). Condensation of the resulting diamine with dichloroacetyl cobaltacinium chloride **78** in DMF/CH_3CN, and treating the residue with sodium hexafluorophosphate, gave receptor **79** in 61% yield.



Reagents: (i) HNO_3, AcOH; (ii) Raney Ni, NH_2NH_2; (iii) chloroacetyl cobaltacinium chloride (**78**); (iv) $NaPF_6$

Scheme 34

Similarly, carefully controlled nitration of calix[4]arene **80** gives the diametrically substituted dinitrocalix[4]arene which was further derivatized to give calix[4]arene **81** (**Scheme 35**) in a rigid cone conformation, containing self-complementary α-pyridone moieties.[59] These compounds were found

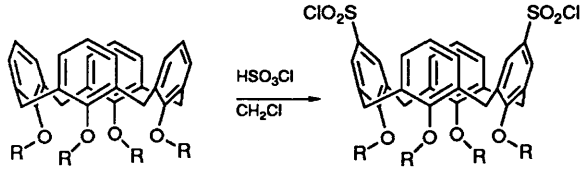


Reagents: (i) acetylnitrate, CH_2Cl_2; (ii) Raney Ni, NH_2NH_2;
(iii) $(Im)_2C{=}O$, HO_2C

Scheme 35

to form hydrogen-bonded aggregates in $CDCl_3$ solution, which could be denatured by the formation of a complex with urea derivatives. The same calix[4]arene has been used as a platform for the synthesis of a closely related receptor capable of recognizing phenobarbital.[60]

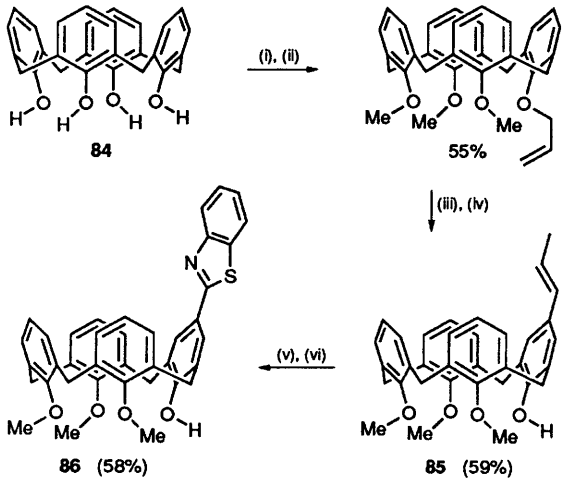
Chlorosulfonylation of the upper rim of a calixarene provides an alternative method for derivatizing calixarenes. Reaction of a series of calix[4]arenes with a large excess of chlorosulfonic acid generally gave tetrakis(chlorosulfonyl) calixarenes in good yields, but the amide-substituted calix[4]arene **82** gave calix[4]arene **83**, having just two SO_2Cl groups appended to the upper rim (**Scheme 36**).[61]



82 R = CH_2CONMe_2 **83** R = CH_2CONMe_2 (42 %)

Scheme 36

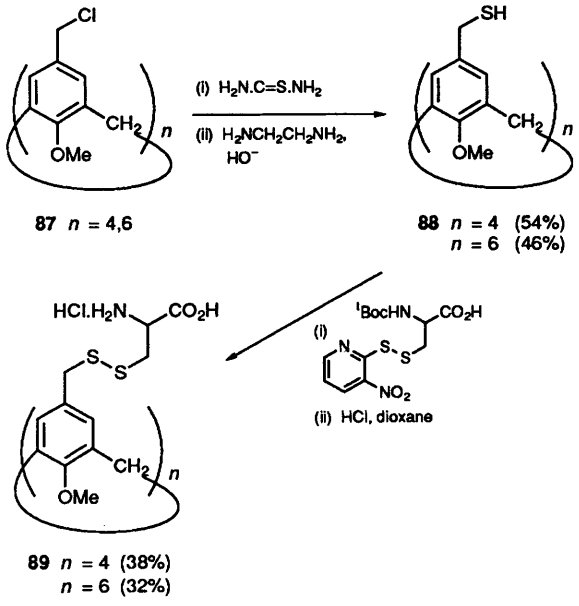
A novel fluorogenic calix[4]arene, functionalized at the upper ring with a benzothiazole chromophore, has been prepared *via* a Claisen rearrangement as the key step (**Scheme 37**).[62] Thus, calix[4]arene **84** was selectively trialkylated using Me_2SO_4 with BaO and $Ba(OH)_2.8H_2O$ in DMF, and the remaining free hydroxyl group was alkylated with allyl bromide. Refluxing in *N,N*-dimethylaniline brought about the Claisen rearrangement, and treatment with $KOBu^t$ gave the disubstituted alkene **85**, which was ozonolysed to the corresponding aldehyde and then condensed with *o*-aminothiophenol in acetic acid to give the fluorogenic calixarene **86**.



Reagents: (i) Me_2SO_4, BaO, $Ba(OH)_2.8H_2O$, DMF; (ii) $CH_2{=}CHCH_2Br$, NaH, THF; (iii) *N,N*-dimethylaniline, reflux; (iv) $KOBu^t$, THF; (v) O_3, $CHCl_3$; (vi) *o*-aminothiophenol, AcOH

Scheme 37

Shinkai has prepared calix[*n*]arenes (*n* = 4 and 6) modified with L-cysteines. These are water soluble, particularly at acidic and basic pH.[63] The chloromethyl groups on the upper rim of calixarene **87** were converted into mercaptomethyl groups by treatment with thiourea, followed by alkaline hydrolysis (**Scheme 38**).

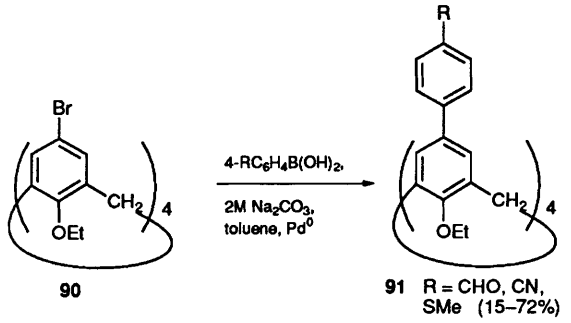


Scheme 38

The L-cysteine units were attached under anaerobic conditions, to avoid oxidation of **88** to unwanted disulfide products, and finally removal of the t-Boc groups gave water-soluble calixarenes **89** in moderate overall yields. These calixarenes were found to bind hydrophobic guests most effectively at pH 5–6. A water-soluble calixarene has also been prepared by the tetrasulfonylation of a tetraacid calixarene leading to a tetracarboxylate tetrasulfonated calix[4]arene.[64]

The conformation of a calix[4]arene has been locked by cross-linking the upper rim with catechol, resorcinol, or salycilic acid.[65] The cross-linked calixarenes were synthesized by reaction of calix[4]arene with catechol (or resorcinol) in refluxing acetone in the presence of M_2CO_3 (M = Na, K, Cs). The conformer distribution (cone, 1,2-alternate, or 1,3-alternate) was significantly affected by the metal cation present in the base. For example, the presence of Na^+ or K^+ favoured the formation of 1,3-alternate, whereas Cs^+ ions favour the formation of a proximal cross-link.

In an attempt to develop a new class of extended chromogenic calixarenes, Suzuki cross-couplings have been utilized to prepare upper rim functionalized cone conformers of donor–acceptor phenylcalix[4]arene.[66] To stabilize the cone conformation of the chromogenic calix[4]arene derivatives, in which all the chromophores are essentially oriented in the same direction, ethyl substituents on the phenolic oxygens were introduced using the conditions described by Reinhoudt.[67] Bromination of calix[4]arene tetraethyl ether with *N*-bromosuccinimide afforded bromide **90** in good yield (81%), and a Suzuki-type cross-coupling reaction between the bromide and appropriate boronic acids, catalysed by $Pd(OAc)_2.2P(o\text{-tol})_3$, gave the biphenyl derivatives **91** in reasonable yields (**Scheme 39**).



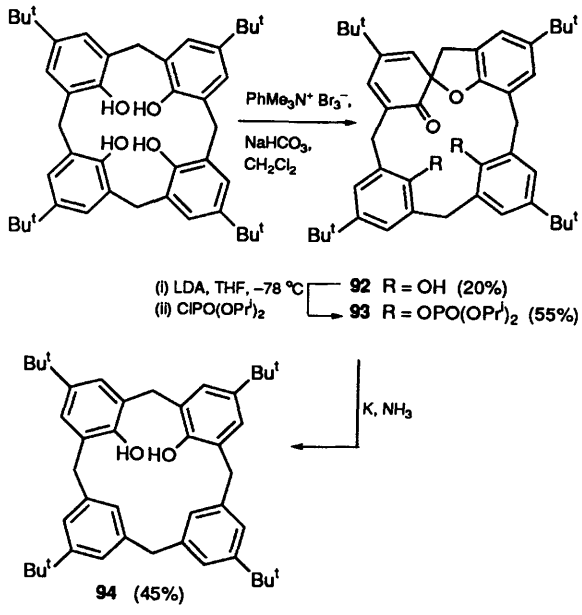
Scheme 39

3.1.3 Other modifications

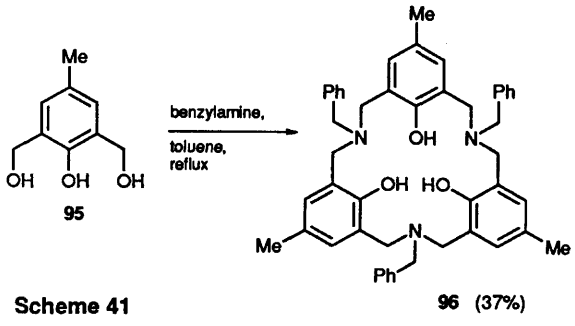
Calixquinones are of interest because of their potential as redox systems and as participants in the formation of charge-transfer complexes. Calix[4]quinones are readily accessible by the direct oxidation of *p*-t-butylcalix[4]arene as mono-, di-, tri-, or tetraquinones—depending upon the number of free phenolic groups in the calixarene. Gutsche has published a comprehensive study on 1,2-carbonyl additions and 1,4-conjugate additions with such calix[4]quinones to give a range of chiral calixarenes.[68] The oxidation of dialkyloxycalix[4]arenes with $Tl(NO_3)_3.3H_2O$ has been reported to give calix[4]arenediquinones, which are more flexible than the unoxidized parent calixarenes and can assume two partial cone conformations.[69] Biali has reported a method for the mild oxidation of calix[4]arenes using trimethylphenylammonium tribromide and a saturated solution of $NaHCO_3$, to yield the chiral mono(spirodienone) **92**.[70] Derivatization of this intermediate with diisopropyl chloroformate and LDA gave the bisphosphate ester **93**, which on treatment with potassium in liquid ammonia resulted in the reduction of the spirodienone moiety, and reductive cleavage of the phosphate groups, to afford didehydroxylated calixarene **94** (**Scheme 40**).

A new series of homoazacalixarenes has been described in which one or more of the methylene bridges of a calixarene are substituted by a dimethyleneaza bridge.[71] It is suggested that the cyclizations, for example, of bishydroxyphenol **95** with benzylamine in refluxing toluene to give the azacalixarenes such as **96** (**Scheme 41**), proceeded under the influence of a template effect provided by hydrogen-bonding between the hydroxyl groups and the nitrogen lone-pairs.

Similarly, a simple regioselective synthesis has been reported for a macrotricyclic receptor related to calix[4]arenes in which two of the methylene bridges are substituted by dimethyleneoxa bridges.[72] The two phenolic functions of **97** were linked with ditosylate **98**, and the resulting diol **99** was coupled with the corresponding dibromide **100**. The final Williamson

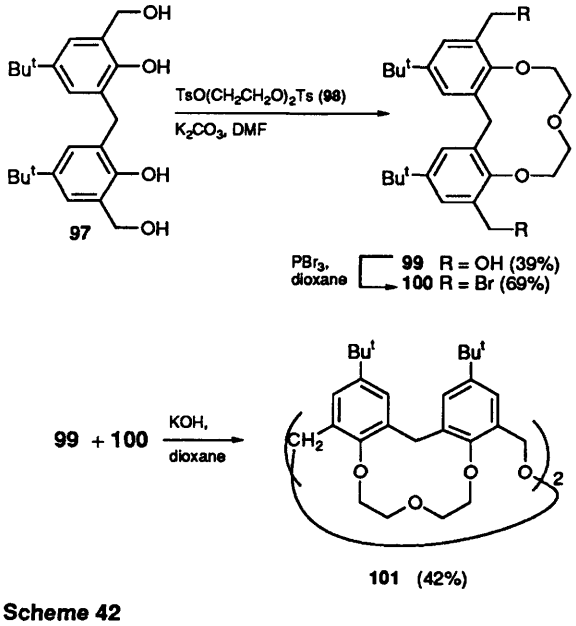


Scheme 40



Scheme 41

reaction was carried out by slow addition of **99** and **100** to a suspension of excess powdered KOH in dioxane, to give the modified calix[4]arene **101** in 42% yield and as a single geometric isomer (**Scheme 42**).

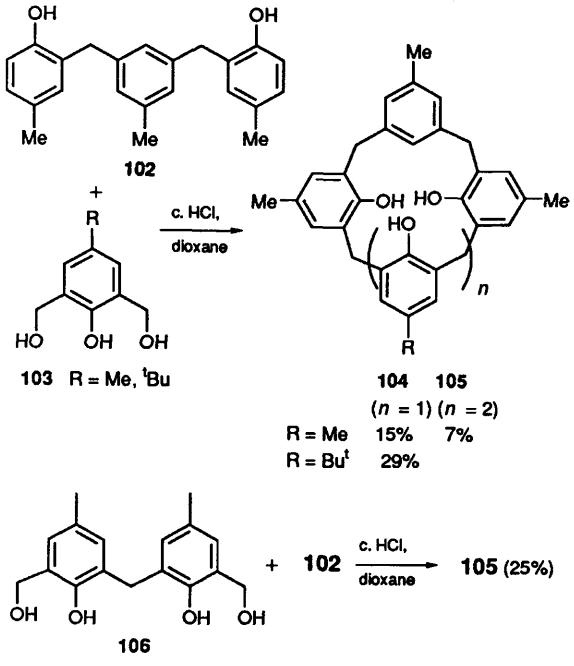


Scheme 42

The larger cavity of **101**, compared with an unmodified calix[4]arene, allows the complexation of several quaternary ammonium ions in chloroform solution.

3.2 Calix[5]arenes

A monodeoxycalix[5]arene has been synthesized by stepwise methods.[73] The treatment of diol **102** with phenol **103** (R = Me) under acidic conditions (conc. HCl in hot dioxane solution) gave the monodeoxycalix[5]arene **105** in low yield (7%), along with the previously described monodeoxycalix[4]arene **104**,[74] while reaction of **102** with **103** (R = Bu^t), under similar acidic conditions, gave only the monodeoxycalix[4]arene **104** in 29% yield (**Scheme 43**). An improved yield for the preparation of calix[5]arene **105** (25%) was obtained by condensing **102** directly with diol **106**. NOE experiments, along with crystal structures, suggested that these molecules adopt a partial cone structure in solution.



Scheme 43

The first examples of calixcrown compounds derived from calix[5]arenes have also been reported.[75] Alkylation of *p*-t-butylcalix[5]arene with oligoethylene glycol-ditosylates in the presence of CsF affords 1,3-bridged calix[5]arenes in 51–72% yield. These calixarenes were further modified by the alkylation of the remaining hydroxyl groups.

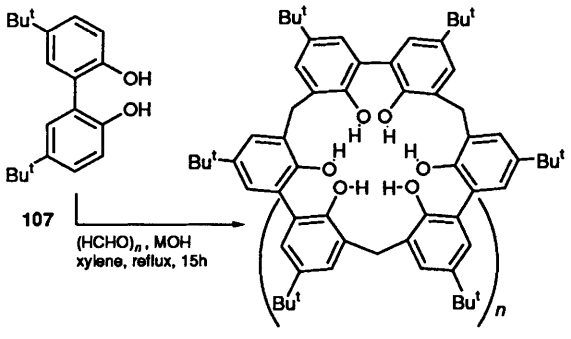
3.3 Calix[6]arenes

Compared with calix[4]arenes, much less is known about the chemistry of the more flexible calix[6]arenes, although in recent years the synthesis of several hexafunctionalized derivatives, and their corresponding complexing abilities with neutral molecules and cations, have been described.[76] In order to make calix[6]arenes available as molecular building

blocks, several approaches have been investigated for the selective functionalization of these molecules, and two recent papers have described the selective benzylation and aroylation of *p*-t-butylcalix[6]arene.[77] Modest regioselectivity in the methylation of calix[6]arenes on the lower rim can be achieved, the conditions for which have been described in detail.[78] Thus, for example, the 1,3,5-trimethylated compound was produced in 72% yield using 3 equivalents of potassium carbonate and 4 equivalents of methyl iodide, under 2 atmospheres of pressure. The same research group have also substituted the lower rim of *p*-t-butylcalix[6]arene with phosphate and thiophosphate groups, resulting in a restriction in the conformational freedom of the calix[6]arene.[79]

An extensive study of the base-catalysed alkylation of *p*-t-butylcalix[6]arene with 2-(chloromethyl)-pyridine in DMF, has led to the isolation and identification of 10 of the 12 possible pyridinium homologues of lower-rim-substituted calix[6]arenes.[80,81] The identity of the base, and the molar ratios of the reactants used, played a major role in determining the product distribution. Conformationally restricted calix[6]arenes have also been synthesized by transannularly bridging across the 1,4-position with several dihalides, using $KOSiMe_3$ as base.[82]

A spherand-type calix[6]arene has been prepared by condensation of biphenyl derivative **107** with formaldehyde.[83] Using NaOH as base gave the trimeric structure **108** in 52% yield, whereas the use of CsOH gave the tetrameric compound **109** in 66% yield (**Scheme 44**). The use of KOH gave a mixture of the two compounds and these results provide clear evidence of a metal templating effect.

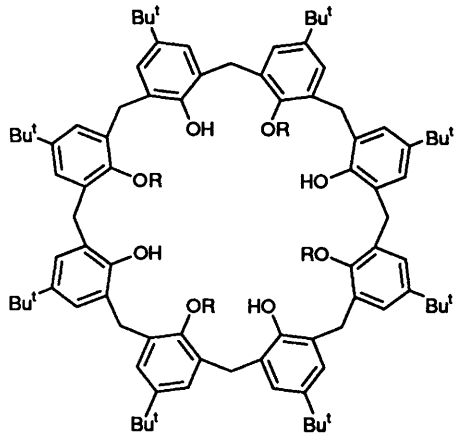


MOH	108 (n = 1)	109 (n = 2)
NaOH	52%	trace
KOH	32%	29%
CsOH	4%	66%

Scheme 44

3.4 Calix[8]arenes

Early attempts at the selective functionalization of the lower rim of calix[8]arene led to mixtures of regioisomers or structurally undefined di-, tetra-, and hexa-substituted derivatives. However, Neri has recently reported the synthesis of the first partially substitued calix[8]arenes **110** (**Scheme 45**) with defined structure,[84] having a 1,3,5,7-tetrasubstitution pattern and C_4 symmetry. The compounds were prepared in 20–41% yields by the treatment of calix[8]arene with various benzyl bromides (8 equivalents) and K_2CO_3 (16 equivalents) in THF/DMF (10:1 v/v).

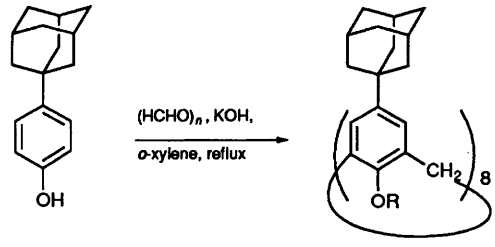


110

R = 4-$XC_6H_4CH_2$; X = H, Bu^t, Me, NO_2, CN

Scheme 45

Kovalev and co-workers have prepared *p*-1-adamantylcalix[8]arenes **111** in good yield (72%) by refluxing under N_2 an *o*-xylene solution of 4-(1-adamantyl)phenol, paraformaldehyde, and KOH in the ratio 45:85:1 (**Scheme 46**).[85] No other cyclic oligomers were found in the reaction mixture and **111** was further derivatized with various acylating or alkylating groups.



Scheme 46

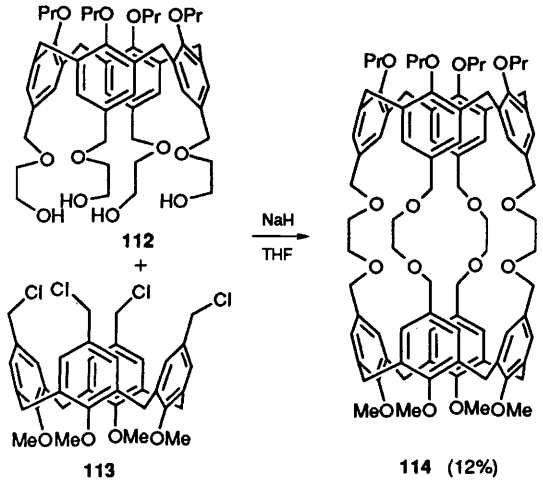
111 (72%)

3.5 Double calixarenes

The ease with which calix[4]arenes can be selectively derivatized had led to the synthesis of various double calixarenes, possessing large and well-defined molecular cavities. Progress in this area has been reviewed recently.[86]

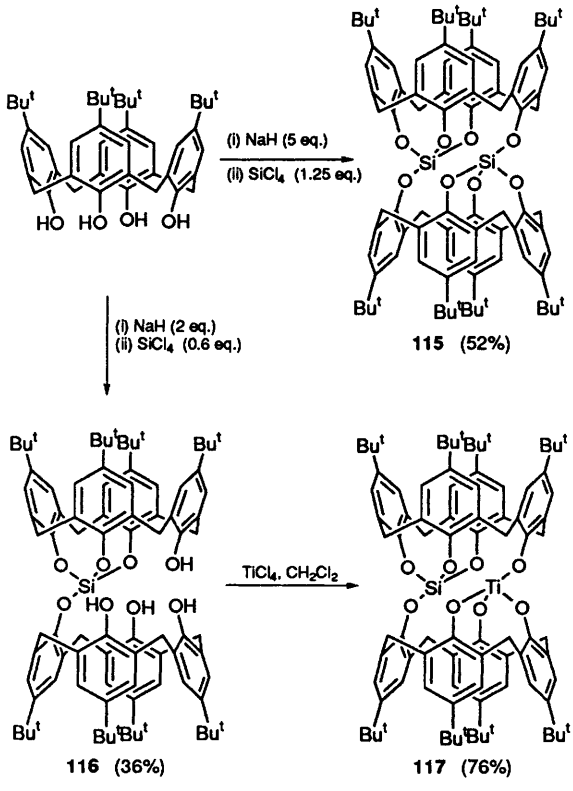
The biscalix[4]arene cage molecule **114** was prepared in 12% yield from **112** and **113**, under high-dilution conditions in THF, using NaH as the base (**Scheme 47**).[87]

The synthesis of a receptor possessing two divergent hydrophobic cavities was achieved by fusing two *p*-t-butylcalix[4]arene units in cone conformation using silicon atoms.[88] The reaction of *p*-t-butylcalix[4]arene with $SiCl_4$ in THF, in the



Scheme 47

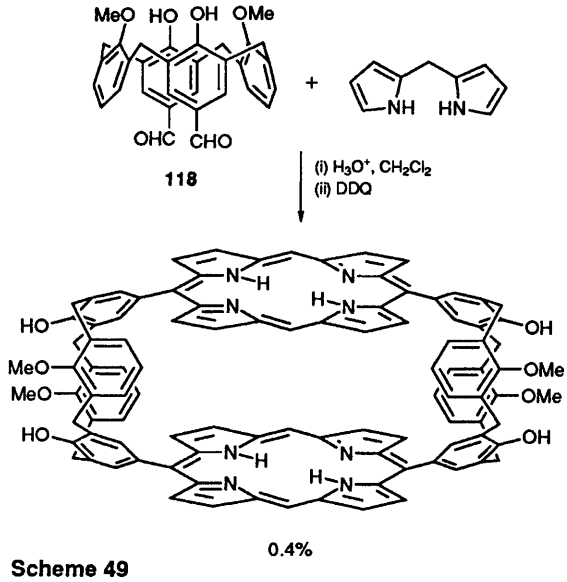
presence of NaH, at room temperature, afforded the double calixarene **115** in 52% yield (**Scheme 48**). This multicavitand has been shown to form specific interactions with iodine.



Scheme 48

Similarly, the synthesis and structural investigation of a non-centrosymmetric 'koiland' (hollow molecular unit), composed of two *p*-t-butylcalix [4] arenes fused by both silicon and titanium atoms has been reported.[89] Treatment of *p*-t-butylcalix[4]arene with 2 equivalents of NaH in THF followed by reaction with $SiCl_4$ afforded the mono-fused calixarene **116** in 36% yield. Since all four unreacted hydroxyl groups in **116** are disposed face-to-face, another atom requiring tetrahedral coordination can be accommodated and treatment of **116** with $TiCl_4$ in dichloromethane produced the heterobinuclear calixarene **117** in an almost instantaneous reaction, and in good yield (76%) (**Scheme 48**).

Finally, the condensation of dipyrryl methane and calix[4]arene-1,3-dialdehyde **118**, under dilute conditions, and in the presence of a catalytic amount of trifluoroacetic acid, gave a double porphyrin linked by two calix[4]arene units (**Scheme 49**).[90] The low yield of 0.4% was higher than the statistical yield (~ 0.01%) predicted for the random combination of 12 reactive centres located on 6 distinct molecules.



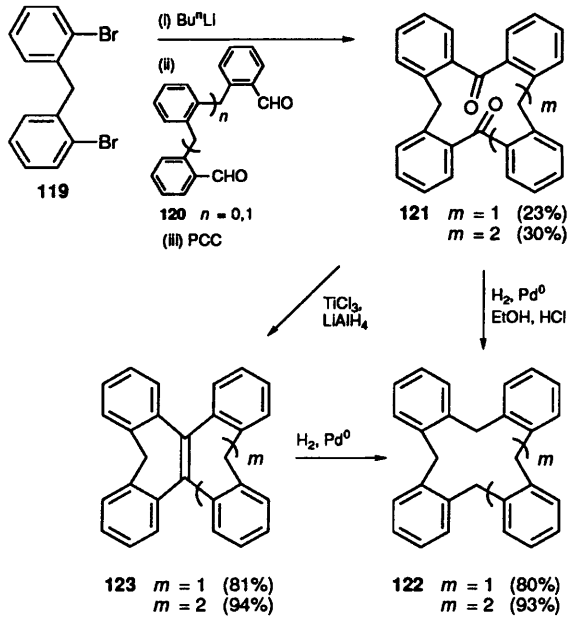
Scheme 49

4 Cyclophanes

Cyclophanes are broadly defined as 'bridged aromatic compounds' and as such most host–guest systems, including many crown ethers, cryptands, and spherands, can be termed cyclophanes, while calixarenes are simply meta-cyclophanes.[91] For the purposes of this review, the section on cyclophanes is intended to cover those compounds which do not fit into the earlier categories and for which the main structural feature are the aromatic units.

4.1 All-carbon cyclophanes

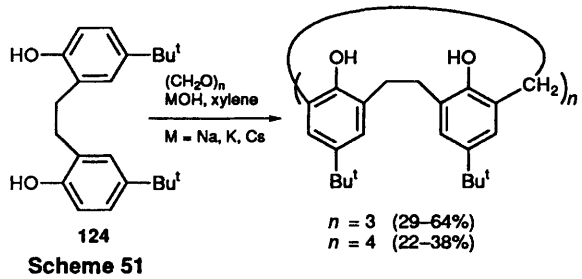
In spite of the extensive studies on cyclophanes, only a few [1_n] orthocyclophanes that contain more than three aromatic rings have been reported. Recently the first syntheses of [1_4] and [1_5] orthocyclophanes have been described.[92] Thus, dibromide **119** was lithiated with Bu^{n}Li and coupled with dialdehydes **120**, to give cyclic diols, which were oxidized with PCC to give the corresponding diketones **121** (**Scheme 50**). Palladium-catalysed reduction of **121** in EtOH/HCl afforded the deoxygenated cyclophanes **122** in good yield. Alternatively, reduction of the diketones with Zn(Hg)/HCl or with $TiCl_3/LiAlH_4$ gave the bicyclic coupled products **123** which could be hydrogenated to give the same monocyclic cyclophanes **122**.



119 120 n = 0,1 121 m = 1 (23%) m = 2 (30%) 123 m = 1 (81%) m = 2 (94%) 122 m = 1 (80%) m = 2 (93%)

Scheme 50

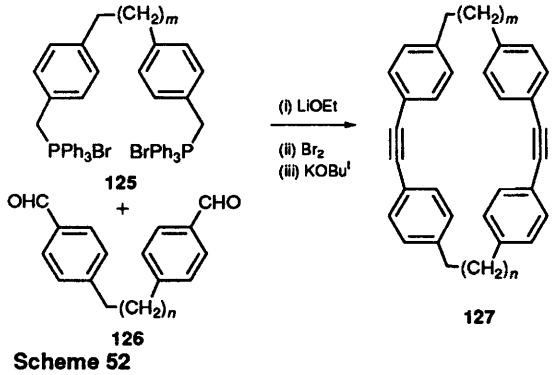
[$(2.1)_n$] Metacyclophanes have been prepared by condensation of the bisarylethane unit **124** with formaldehyde (**Scheme 51**).[93] This synthesis is very similar to the preparation of **109** and **110** described earlier, and product distribution was similarly affected by the templating effect of the base used in the reaction.



124 n = 3 (29–64%) n = 4 (22–38%)

Scheme 51

Vogtle has prepared a series of molecules ('tolanophanes'), such as **127**, which contain two acetylene units, by Wittig cyclization reactions of **125** with dialdehyde **126**, using lithium ethoxide as the base, followed by oxidation of the alkene units to alkynes (**Scheme 52**).[94]

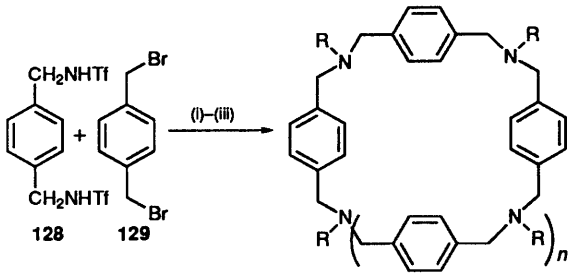


125 126 127

Scheme 52

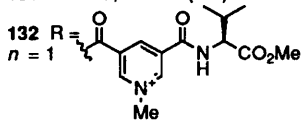
4.2 Heteroatom-containing cyclophanes

A simple method for the synthesis of tetraaza[3.3.3.3]paracyclophanes has been described.[95] Thus, alkylation of *N*-substituted trifluoroacetamides **128** with the corresponding bis(bromomethyl)benzenes **129**, followed by removal of the trifluoroacetyl group and *N*-methylation of the resultant amines, gave the cyclophanes **130** and **131** in yields of 21% and 5% respectively (**Scheme 53**). An identical route was used to prepare the corresponding tetraaza[3^4]metacyclophane along with diaza[3^2]metacyclophane.



128 129

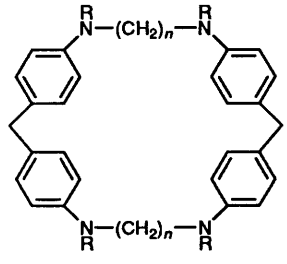
130 R = Me, n = 1 (21%)
131 R = Me, n = 3 (5%)
132 R = n = 1



Reagents: (i) NaH, DMF, 100°C; (ii) $NaBH_4$, EtOH; (iii) CH_2O, NaH_2PO_3, H_2O, dioxane

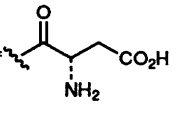
Scheme 53

Murakami has coupled L-valine methyl ester to the tetrakis(carboxynicotinoyl) derivative of **130**, followed by quarternization of the pyridine moiety to give **132** (**Scheme 53**), a water-soluble analogue of **130**.[96] Similarly, tetraazaparacyclophane **133** has been coupled with N^{α}-9-t-butoxycarbonyl-L-aspartic acid benzyl ester in the presence of DCC, followed by removal of the protecting groups, to give the water-soluble derivative **134** (**Scheme 54**), which exhibits marked pH-dependent binding of various organic guests.[97]



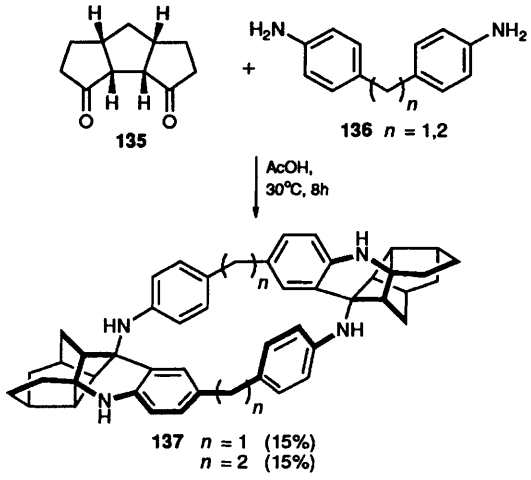
133, R = H

134, R =



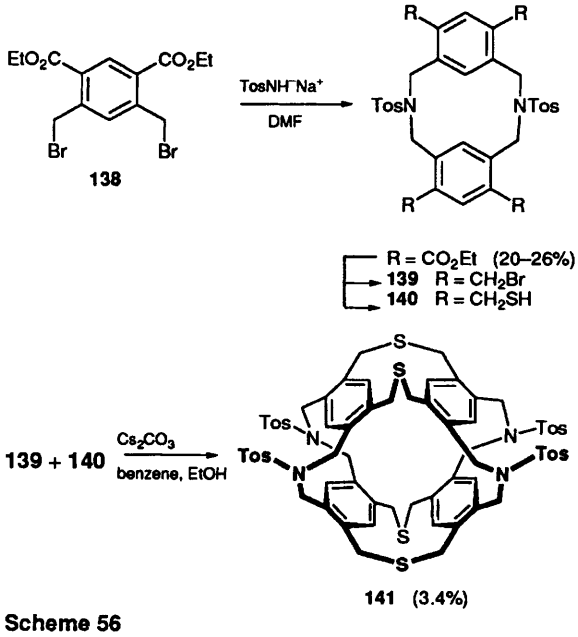
Scheme 54

Mehta has constructed some unusual cyclophanes by a one-pot reaction between a 1:3 mixture of triquinane dione **135** and dianilines **136**.[98] Cyclization is carried out in glacial acetic acid to give cyclophanes **137** in ~ 15% yield, with a simultaneous rearrangement of the triquinane system (**Scheme 55**).



Scheme 55

A series of four-fold functionalized 2,11-diaza[3.3]cyclophanes such as **139** and **140** have been prepared by condensation of *p*-toluenesulfonamide with dibromide **138** and subsequent functional group manipulation.[99] These cyclophanes were used to construct tube-shaped molecules such as **141**, albeit in low yield (**Scheme 56**).

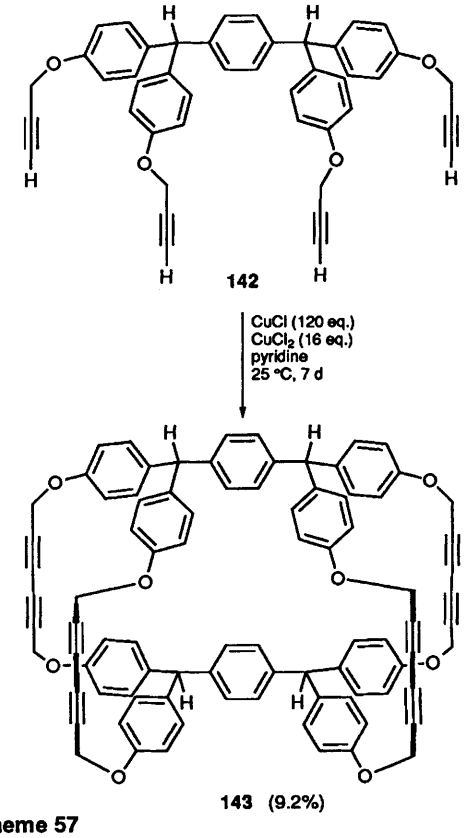


Scheme 56

Much larger dithiacyclophanes have also been prepared in good yields by condensation of dichlorides with xylenedithiols, and *m*-terphenyldithiol, using high dilution conditions,[100] and a biscatechol-derived tetrahydroxycyclophane has been prepared *via* the condensation of a suitable diamine and a bis-(acid chloride).[101,102] With its large cavity and *endo*-acidic functional groups, this receptor proved to be an ideal hydrogen bond receptor for piperazine-type guests in organic solution.

4.3 Cage-type cyclophanes

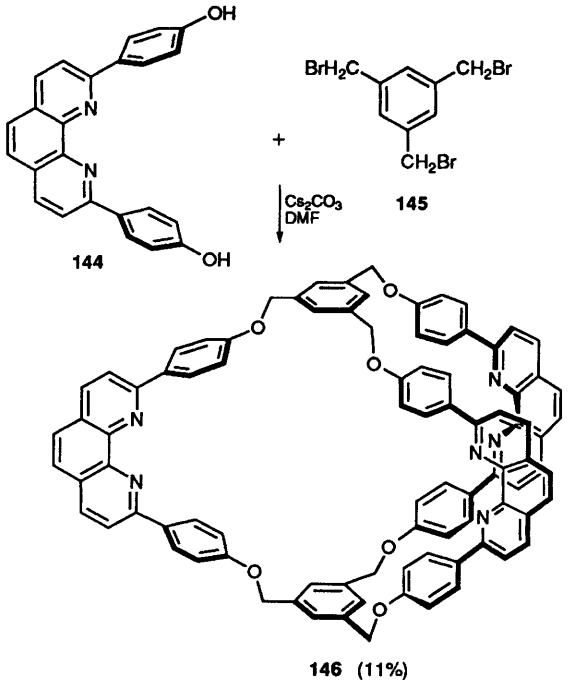
Vogtle has described the synthesis of a number of cage-type cyclophanes by bridging triphenylmethane units, using a three-fold acetylene dimerization reaction, to produce compounds with novel solvatochromic and halochromic properties.[103] This chemistry has also been used in the synthesis of a four-fold bridged macrocyclic compound **143** (**Scheme 57**).[104] The tetraalkyne **142** underwent an oxidative cyclodimerization in pyridine, containing 120 equiv. of CuCl and 16 equiv. $CuCl_2$, to afford macrocycles **143** in 9.2% yield.



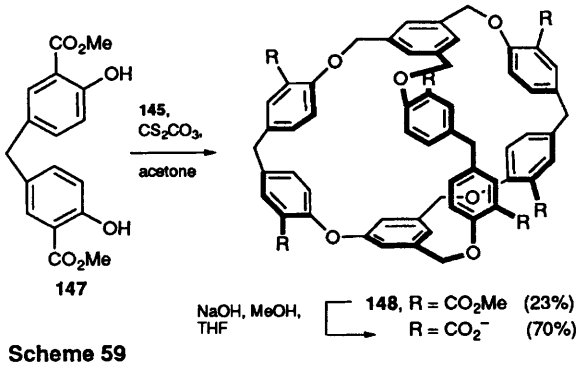
Scheme 57

Cyclophanes such as **146**, containing phenanthroline units, have been synthesized in a one-step cyclization procedure utilizing diol **144** and an appropriate tribromide, such as **145**, in DMF at 70°C with Cs_2CO_3 as the base (**Scheme 58**).[105] The rigid *endo*-preorganization of the nitrogen donors allows three 2,9-disubstituted 1,10-phenanthrolines to be complexed within the large cavity. Vogtle has also reported the synthesis of related cage structures containing azobenzene units.[106]

Using a similar strategy, Lehn has described the synthesis of receptor **148**, in 23% yield, by slow addition of an equimolar solution of 1,3,5-tris(bromomethyl)benzene and dimethyl methylenedisalicylate **147** to a suspension of caesium carbonate in refluxing acetone (**Scheme 59**).[107] Hydrolysis of **148** afforded a water-soluble hexacarboxylate macrocycle, which, for instance, bound to acetylcholine with a higher affinity than previously reported tetracarboxylate receptors.



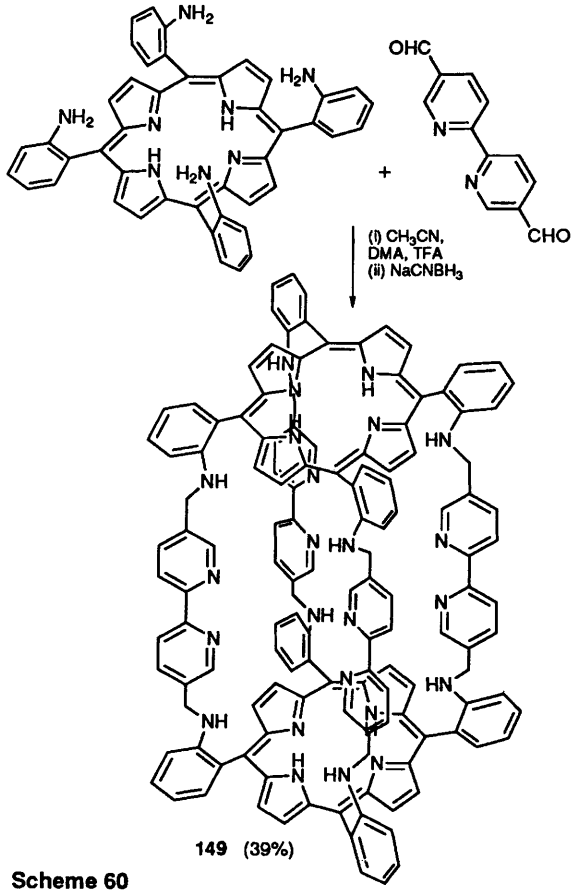
Scheme 58



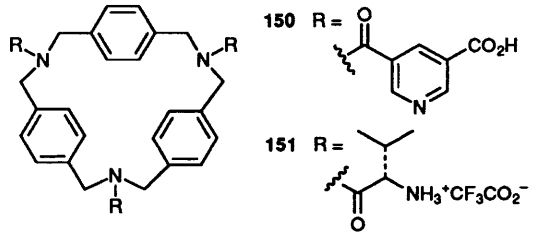
Scheme 59

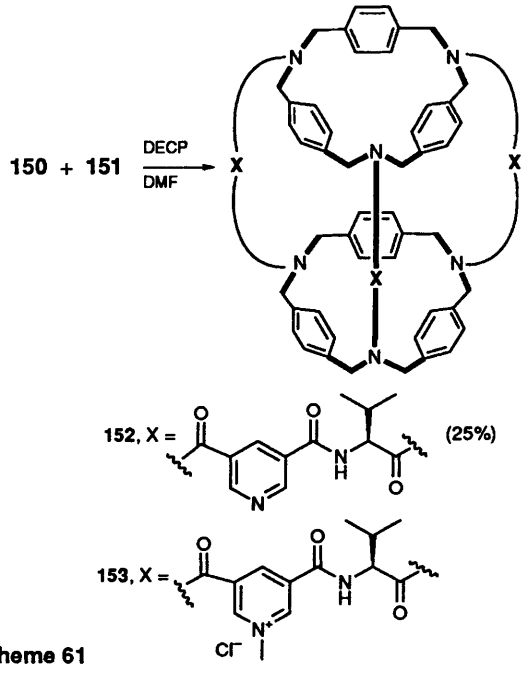
A one-pot reaction has also been used for the synthesis of a covalently linked cofacial bis(tetraphenylporphyrin) **149**.[108] Reaction of *meso*-tetra($\alpha,\alpha,\alpha,\alpha$-*o*-aminophenyl)porphyrin with 5,5′-diformyl-2,2′-bipyridine in acetonitrile/dimethyl acetamide, and *in situ* reduction with $NaBH_3CN$ gave the desired bisporphyrin (**Scheme 60**). Owing to the preorganization of the building blocks and their intermediates, the reduction proceeded without the application of high dilution conditions, to give **149** in overall 39% yield.

Murakami has recently described the preparation and asymmetric character of novel cage-type cyclophanes **152** and **153**, which are constructed with two rigid macrocyclic triaza[3.3.3]paracyclophanes, and three chiral bridging components.[109] Host **152** was synthesized in 25% yield by the condensation of substituted-triaza[3.3.3]paracyclophane **150** with **151**, in the presence of diethyl cyanophosphonate (DECP), and under high dilution conditions in DMF at 0°C (**Scheme 61**). The water-soluble version **153** of the cage-type cyclophane was derived from **152** by reaction with methyl iodide at room temperature over 7 days, followed by counter-ion exchange to give the chloride salt.



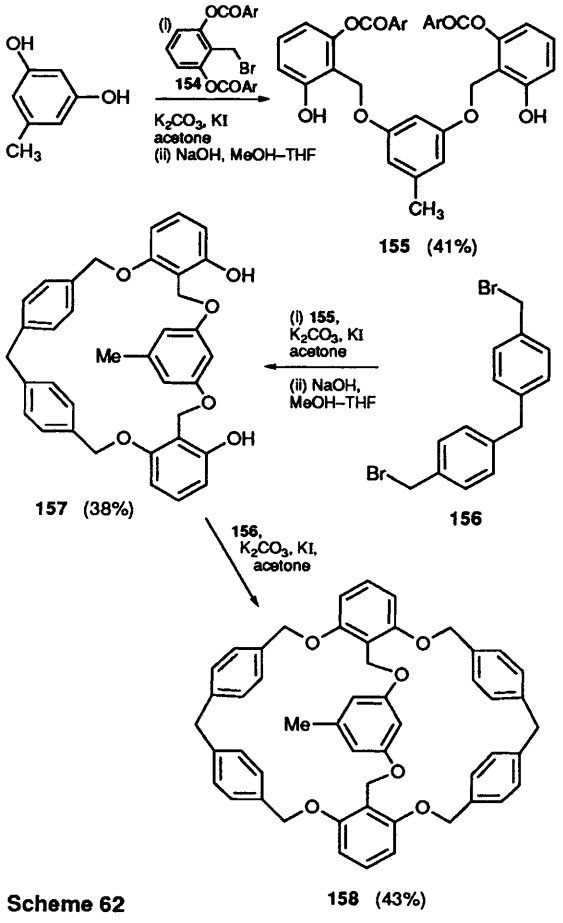
Scheme 60





Scheme 61

A bicyclic cyclophane **158**, with a molecular bowl structure, based on an aryl benzyl ether framework has been prepared.[110] The synthesis began with the construction of the central bridge, followed by stepwise cyclization. Thus, treatment of orcinol with the benzyl bromide **154** and hydrolysis, under dilute alkaline conditions, gave **155**, with the exclusive monodeprotection of each resorcinol unit (**Scheme 62**).

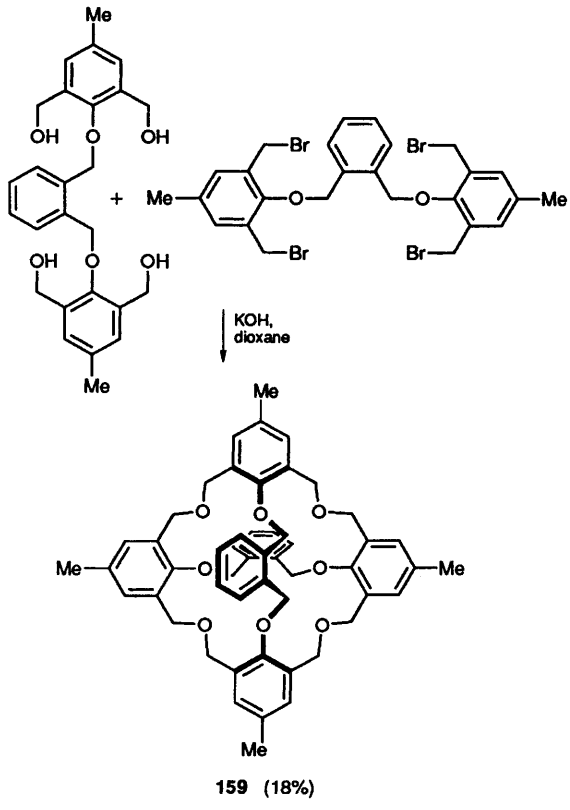


Scheme 62

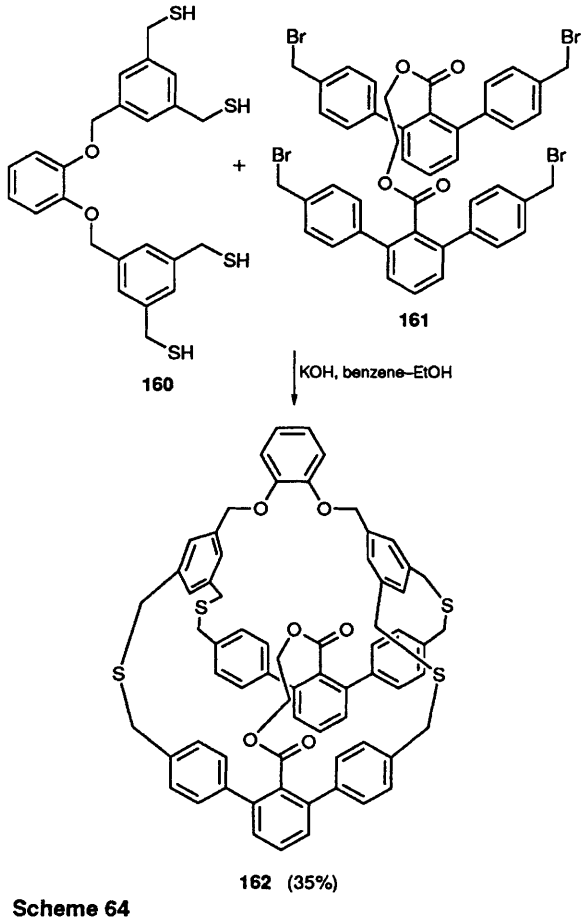
The reaction of **155** with dibromide **156**, under moderate dilution conditions, followed by further hydrolysis gave **157**. The oxacyclophane **158** was obtained in 43% yield by coupling **157** with **156** using K_2CO_3/KI in acetone.

Masci has reported the synthesis of macrocyclic and macropolycyclic ethers which are formally derived from the calix[4]arene family with the CH_2 groups replaced by CH_2OCH_2 groups.[111] The key step involves the reaction of suitable diols or tetrols with polybromides to give monocyclic, bicyclic, and tricyclic ether derivatives, as exemplified by the synthesis of **159** in 18% yield (**Scheme 63**).

A similar strategy has been used for the construction of a series of functionalized cyclophanes with cage structures, by the coupling of tetrathiol **160** with two equivalents of various dibromides, or with tetrabromide **161** (**Scheme 64**).[112] Under high dilution conditions, in the presence of KOH in benzene–ethanol, **162** was prepared in 35% yield.

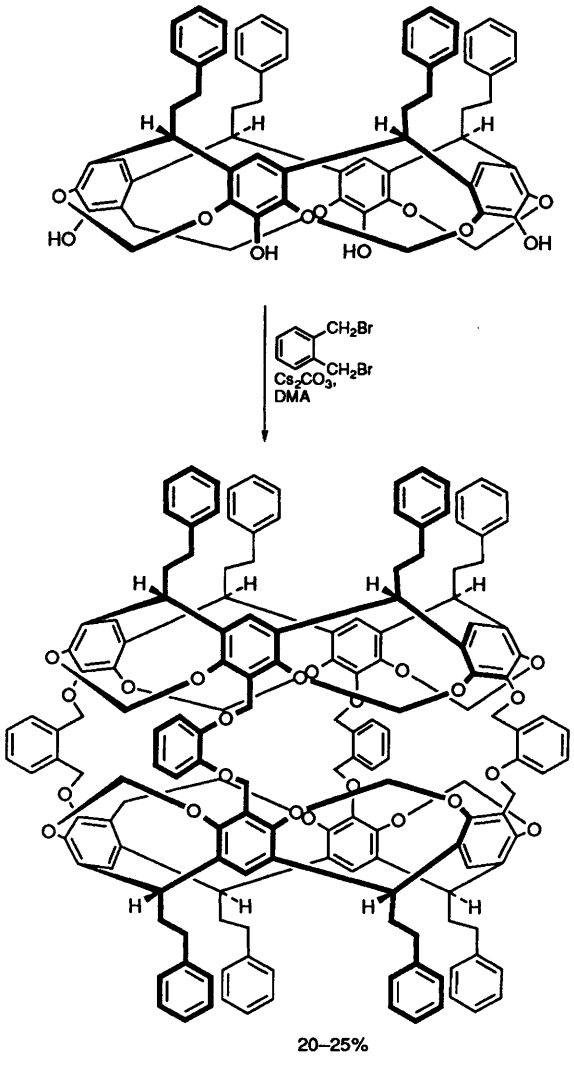


Scheme 63



Scheme 64

Cram has previously synthesized some remarkable globe-shaped hemicarcerands (highly sophisticated cyclophanes!) by linking two rigid bowl-like units, but previously the linking units were hydrolytically unstable. In more recent work the bowls have been linked by amide bonds using 1,3-phenylenediamine,[113] and by ether bonds using dibromo-*o*-xylene.[114] In the latter case the reaction is templated by dimethylacetamide, one molecule of which is encapsulated in the resulting cage, giving a yield of 20–25% for the reaction (**Scheme 65**).



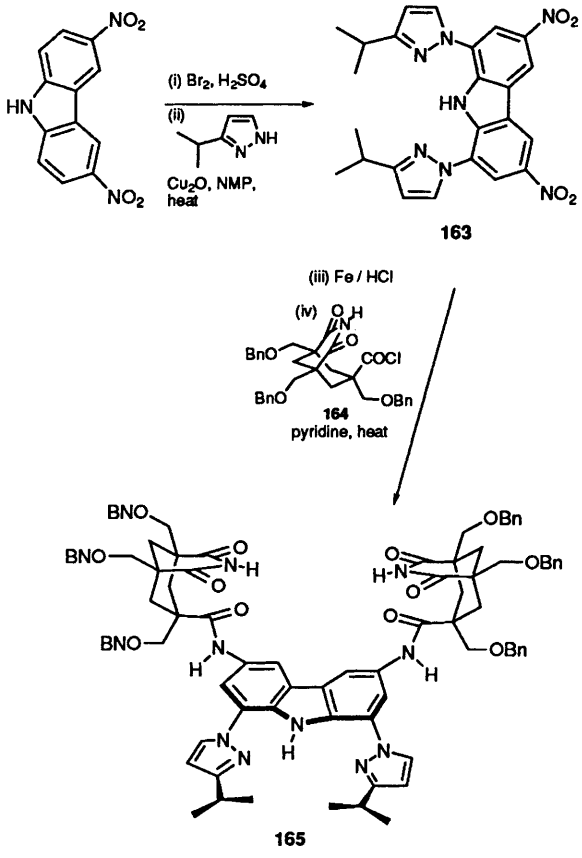
Scheme 65

5 Cleft receptors and molecular bowls

The receptors described in Sections 1–4 of this review have been classified as crown ethers or cyclophanes (including calixarenes), but a large range of other receptors are constantly being reported (some of which are also, strictly speaking, cyclophanes!). Broadly speaking these receptors are designed to arrange hydrogen-bonding functionality in suitable alignment to allow optimal interaction with chosen guests, although other binding interactions may also play an important role in the binding event. Such an arrangement of hydrogen bonds can be achieved using molecular clefts or macrocyclic structures with convergent functionality.

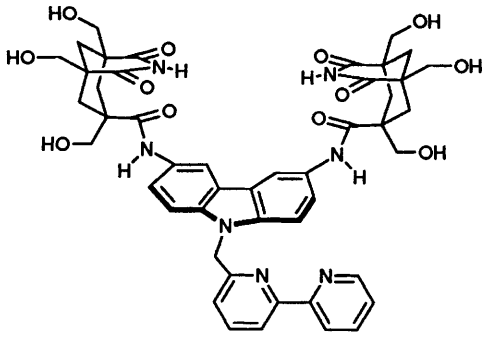
5.1 Cleft receptors

As remarked earlier, the requirement for preorganization to allow strong binding has meant that much receptor chemistry has concentrated on producing macrocyclic structures which are conformationally constrained. However, a number of groups have shown that molecular clefts with convergent functional groups can provide highly selective artificial receptors. Rebek has amply demonstrated this with the study of a range of receptors based largely upon the rigid architecture provided by Kemp's triacid derivatives. This work has recently been extended with the preparation of molecular clefts containing an adenine receptor portion and a metal binding site.[115] Thus, bromination of 3,6-dinitrocarbazole and an Ullmann coupling with 3(5)-isopropylpyrazole gave dinitro-compound **163**, which was reduced to the corresponding diamine and coupled with acid chloride **164** to give receptor **165** (**Scheme 66**).



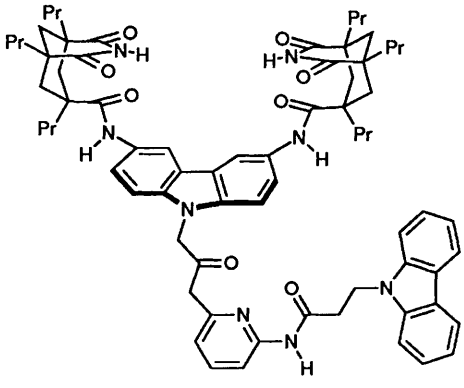
Scheme 66

A similar route was used to prepare a water-soluble receptor **166**, which bound to adenosine and 9-ethyladenosine in water. These clefts are prepared in short and highly modular syntheses, and with the inclusion of a metal-binding site, it is suggested that development of enzyme-like behaviour may be possible.



166

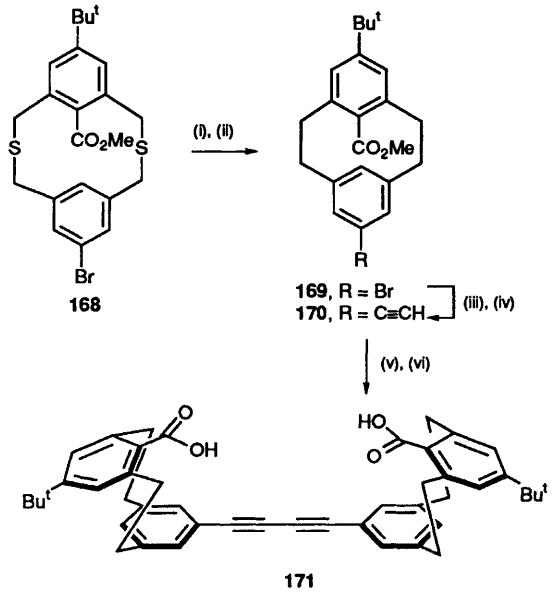
A similar strategy has been used for the synthesis of a 'scorpion-like' receptor **167** which binds adenosine derivatives by a combination of Watson–Crick and Hoogsteen base-pairing, further hydrogen-bonding interactions, and stacking interactions on both faces of the aromatic guest.[116]



167

Vogtle has prepared [2.2]metacyclophanes such as **171**, which provided a cleft with potentially two convergent carboxylic acid groups.[117] The cleft cyclophane **171** was synthesized (**Scheme 67**) from dithia[3.3]metacyclophane **168**, which was prepared in a few steps from 2,6-dimethylaniline and 5-t-butyl-1,3-dimethylbenzene. Oxidation of **168** led to the corresponding sulfone, and subsequent vacuum pyrolysis afforded the metacyclophane **169**. Palladium-catalysed ethynylation and silyl cleavage with K_2CO_3 gave **170**, which was directly coupled using CuI and Et_3N in 26% yield. Hydrolysis of the methyl groups afforded the desired cleft **171**, which was found to bind to pyrimidine and purine bases, with a preference for 2,6-diaminopurine over adenine or 2-aminopurine.

Zimmerman has previously described the synthesis and binding properties of 'molecular tweezers' which also provide hydrogen bonding and aromatic stacking interactions for the binding of the adenine skeleton.[118] Hashimoto has reported the synthesis of a water-soluble version of Zimmerman's tweezer, *via* coupling of these tweezers to a dextran polymer using a reductive amination.[119] These modified tweezers are readily purified by gel filtration column chromatography and show high affinity for adenosine in an aqueous buffer.



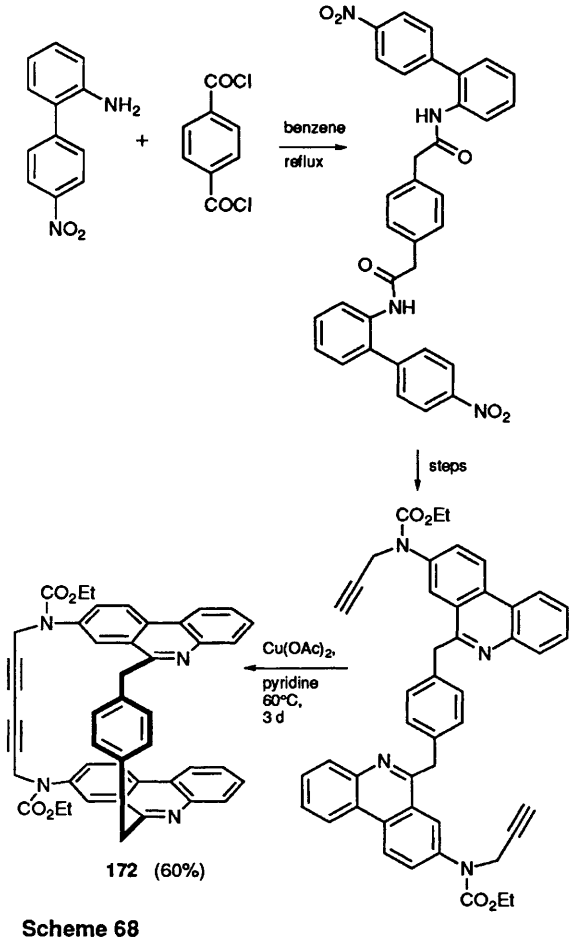
168 169, R = Br 170, R = C≡CH

Reagents: (i) H_2O_2, AcOH, C_6H_6; (ii) pyrolysis; (iii) $Me_3SiC{\equiv}CH$, $(Ph_3P)_2PdCl_2$, CuI, Et_3N, 26%; (iv) K_2CO_3, MeOH, 90%; (v) CuI, Et_3N, 58%; (vi) LiI, pyridine, reflux, 27%

171

Scheme 67

cyclo Bis-intercalands, such as **172**, containing two 8-amino-6-phenanthridinyl moieties, have been prepared by an intramolecular oxidative coupling of *N*, *N*-dipropargyl-bis-phenanthridines using copper(II) acetate (**Scheme 68**).[120] These clefts showed an

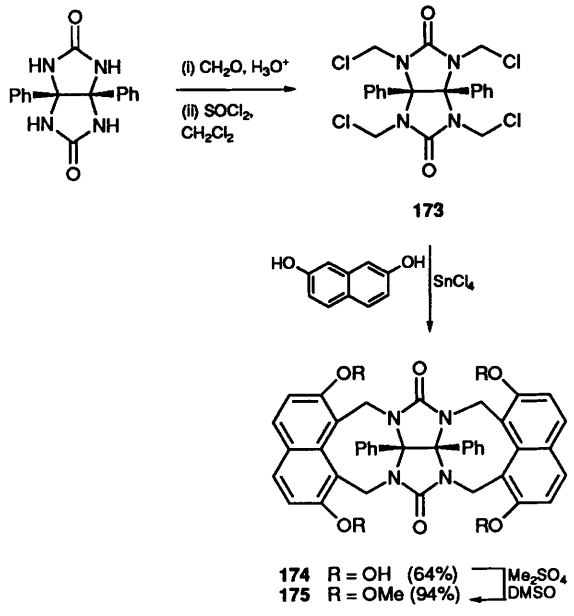


172 (60%)

Scheme 68

increase of the emission intensity in their fluorescence spectra compared with their acyclic bis-phenanthridine counterparts.

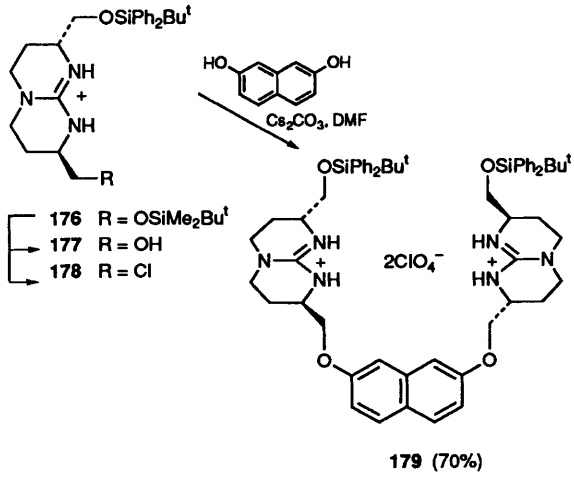
Glycoluril units have been used as building blocks for the development of 'molecular clip' receptors such as **175**, which bind aromatic guests by means of hydrogen bonding as well as π–π interactions. Crown ether derivatives also bind alkali salts and ammonium salts. Improved procedures for the synthesis of these molecules have been described in detail, with the most versatile method being the Lewis acid catalysed reaction of the tetrachloride **173** with appropriate benzene or naphthalene derivatives.[121] For instance, **173** was refluxed with 2,7-dihydroxynaphthalene, and $SnCl_4$ as catalyst, in 1,2-dichloroethane, to give **174** in 64% yield, and then alkylated with dimethyl sulfate to give **175** (**Scheme 69**). Compound **175** was an efficient receptor for aromatic guests, such as 1,4-dicyanobenzene, and binding occurred by an induced-fit mechanism.



Scheme 69

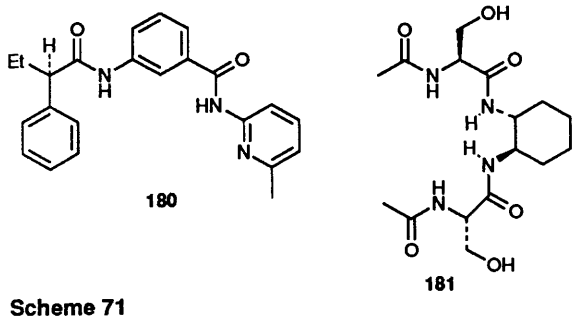
Schmidtchen has recently described an open-chain bis-guanidinium host **179** which bound dicarboxylate anions in competitive solvents such as methanol, despite the apparent lack of preorganization of binding sites.[122] Starting from the chiral guanidinium **176**, mild acid hydrolysis selectively removed the t-butyldimethylsilyl protecting group to give alcohol **177**, which was converted into the chloride **178** and coupled with 2,7-dihydroxynaphthalene to give **179** in yields of ~ 70% (**Scheme 70**). In related work, Diederich has used clefts formed by functionalized homochiral 9,9′-spirobifluorenes for the enantioselective complexation of dicarboxylic acids of *N*-protected derivatives of L-aspartic and L-glutamic acids, in chloroform.[123]

Hamilton has previously shown that amidopyridines serve as a convenient binding site for carboxylic acid functionality. In an extension of this work, acylamino acid carboxylates have been



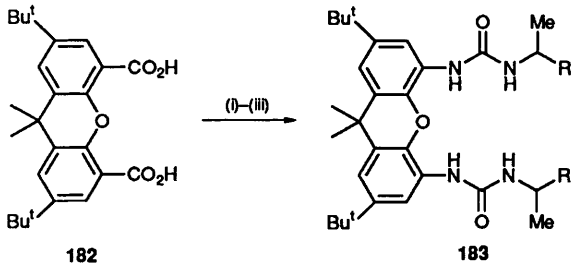
Scheme 70

recognized using receptors such as **180** (**Scheme 71**), which was derived from 6-methyl-2-aminopyridine.[124] Further work has led to the development of bis-ureas and bis-thioureas for the complexation of dicarboxylates in polar solvents,[125] while the synthesis of **181**, by coupling *N*-Cbz L-serine to (1*R*,2*R*)-*trans*-1,2-diaminocyclohexane, provided a receptor which showed a particularly large association constant for the complexation of tetrabutylammonium acetate, due to the multiple hydrogen bonding contacts available.[126]



Scheme 71

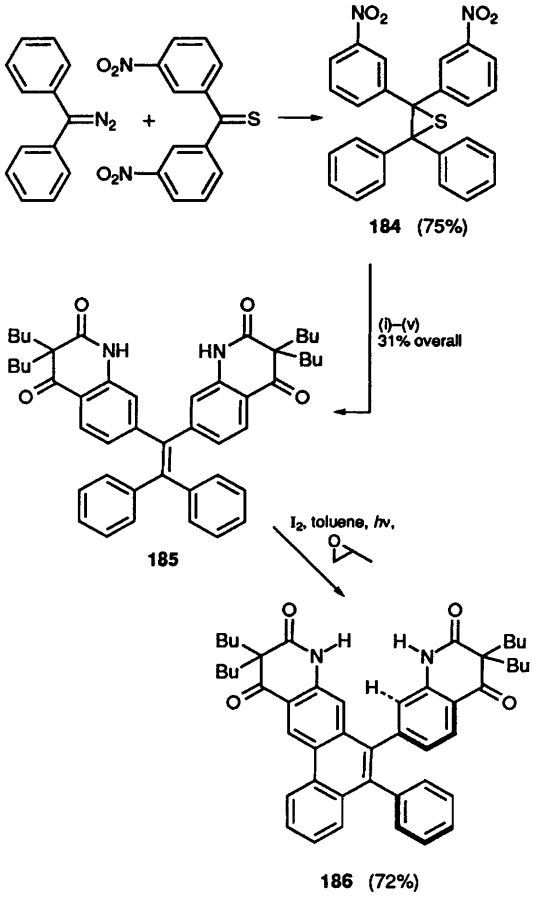
Rebek has also used convergent ureas as binding sites for carboxylate functionality and has described a neutral receptor **183**, which was prepared from xanthenedicarboxylic acid **182** *via* a Curtius rearrangement, followed by hydrogenolysis of the resulting carbamate, and coupling with the appropriate isocyanate (**Scheme 72**).[127]



Reagents: (i) DPPA, Et_3N BnOH, toluene 80 °C; (ii) H_2, Pd–C,EtOH; (iii) R–NCO (Me)

Scheme 72

Caballero has prepared receptor **186** by desulfurization of episulfide **184**, and subsequent derivatization, to give the tetrasubstituted alkene **185**. A photochemical cyclization, in toluene, with iodine oxidant, then gave the 9,10-diphenylphenanthrene skeleton (**Scheme 73**). These rigid receptors form strong complexes with malonic acid derivatives in chloroform, *via* a four-point hydrogen bonding array.[128]

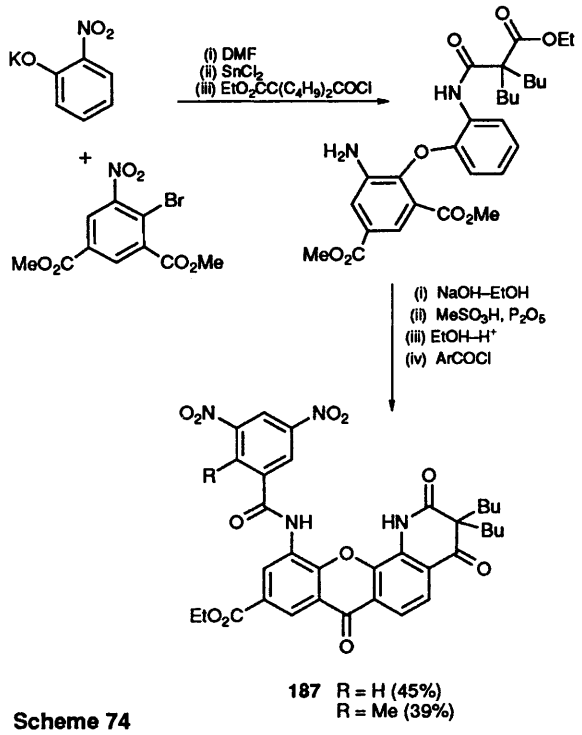


Reagents: (i) Ph_3P; (ii) Fe-AcOH; (iii) $Et_2OCC(C_4H_9)_2COCl$
(iv) NaOH/EtOH; (v) polyphosphoric acid

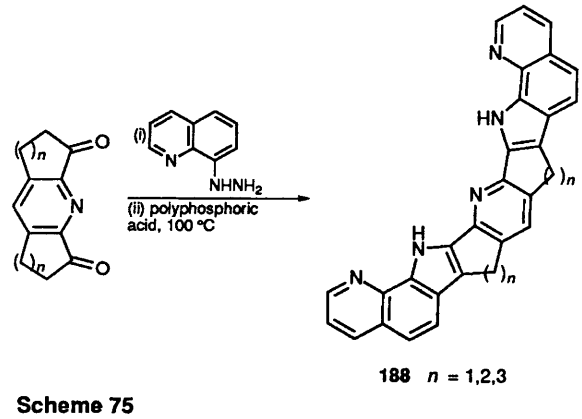
Scheme 73

A related receptor **187** has been prepared, starting from 4-bromo-5-nitrodimethylisophthalate and potassium nitrophenolate (**Scheme 74**).[129] The introduction of the dinitrotoluic residue provided strong aromatic interactions, as well as hydrogen-bonding interactions, for the binding of suitable aromatic acid and amide guests.

The Fischer cyclization of appropriate 8-quinolinylhydrazones has been employed for the preparation of a series of cavity-shaped hosts containing a central pyridine ring, appended on either the 2,6- or 3,5-positions by two pyrido[3,2-g]indole subunits.[130,131] Pyridyl diketones were treated with 8-hydrazinoquinoline to form the intermediate hydrazones, which cyclized directly to the desired host systems **188** when heated with polyphosphoric acid (PPA) at 100°C (**Scheme 75**). These receptors showed high affinity for imidazolidone and barbital guests.



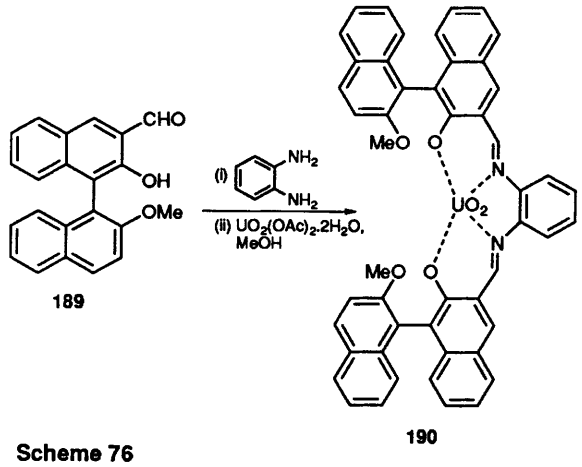
Scheme 74



Scheme 75

Reinhoudt has previously demonstrated that metalloreceptors containing an immobilized uranyl cation can be used as receptors for neutral and anionic guests. More recently, the binapthyl metallocleft **190** has been synthesized by the reaction of aldehyde **189** with 1,2-diaminobenzene, and subsequent addition of $UO_2(OAc)_2.2H_2O$, which afforded the hydrated complex **190**, in 38% yield (**Scheme 76**).[132]

These metalloclefts, containing the immobilized Lewis acidic uranyl cation, are excellent receptors for complexing neutral molecules, as nucleophilic groups (C=O, S=O) can coordinate to the uranyl cation, in addition to the available hydrogen-bonding and aromatic interactions. Simple modifications to the clefts have led to the recognition of anions with a high selectivity being shown for dihydrogen phosphate.[133] These clefts have also been converted into macrocyclic structures containing a 2,6-diaminopyridine unit, in addition to the metallocleft for the recognition of barbiturates.[134]



Scheme 76

5.2 Molecular bowls and other receptors

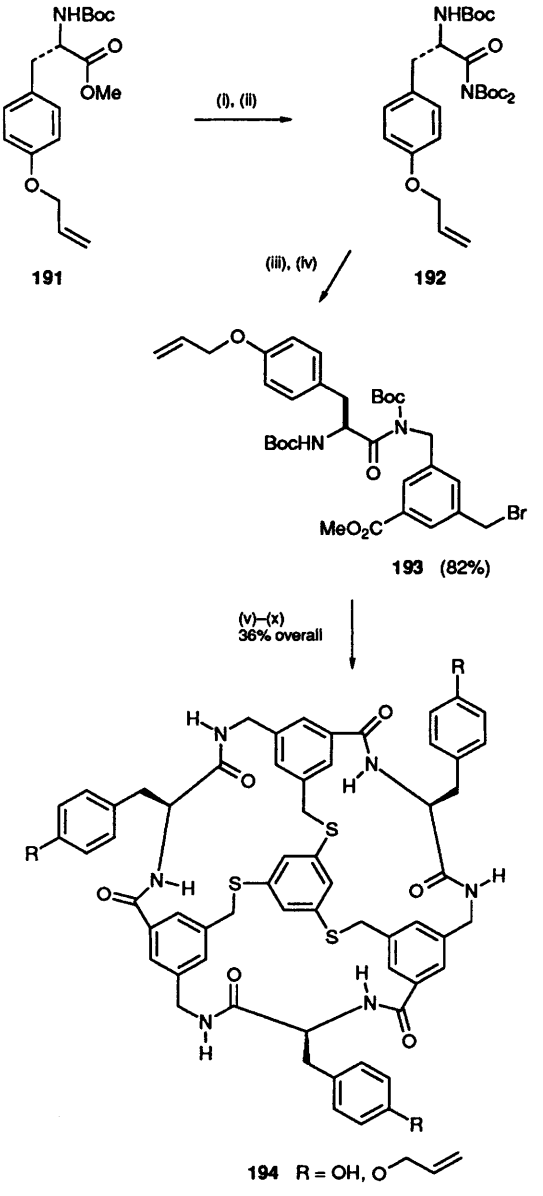
Still has previously described a novel C_3 symmetric receptor **194** (R = H), which binds to a variety of peptides and glycosides, displaying high selectivity for both the functionality and stereochemistry of the guest. An improved synthesis for this class of receptor has now been reported,[135] beginning with *O*-allyl-*N*-Boc-tyrosine methyl ester **191**, which was readily converted in two steps into amide **192** (**Scheme 77**). Deprotonation of **192** with sodium hexamethyldisilylazide in THF at −78°C led to rapid migration of one of the t-Boc groups, giving a t-Boc-stabilized amide anion which was alkylated with 1.2 equiv. of 3,5-bis(bromomethyl)benzoate to give **193** in 82% yield.

Bromide **193** was then used to triply alkylate trimercaptobenzene, and the synthesis was completed with a triple macrolactamization, using an activated tris(pentafluorophenyl ester), which proceeded in 78% yield. A closely related receptor has been prepared containing additional methylene groups built into the apolar base of the binding cavity, and additional binding studies and molecular modelling calculations have been carried out to test the effect of the increased conformational flexibility on binding selectivity.[136]

An efficient synthetic sequence has been described by Sanders for the preparation of a porphyrin-cyclocholate molecular bowl **197**.[137] Cholic acid was the starting point of the preparation of aldehyde **195**, which was converted, under Lindsey conditions, into a benzyl-protected tetrasteroidal porphyrin in 46% yield (**Scheme 78**).

Metallation of the porphyrin ring followed by hydrogenation of the benzyl esters afforded the corresponding tetraacid. Tetramacrolactonization to give **196** was achieved in 18% yield using Yamaguchi conditions. Removal of the trifluoroacetyl protecting groups and metallation gave the final product **197**.

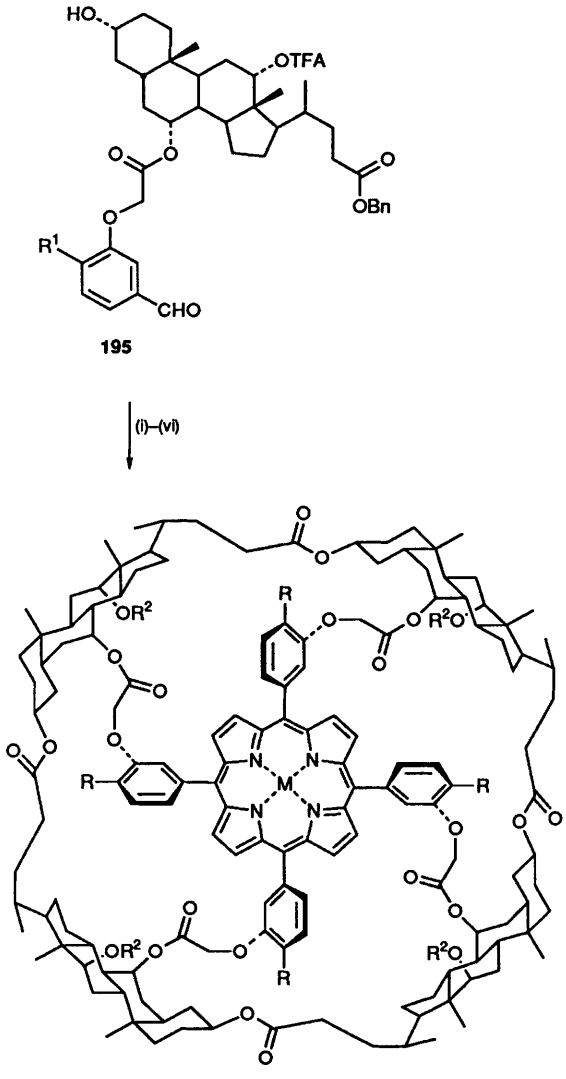
Davis has also used the readily available steroid cholic acid in the synthesis of cholophanes. Full papers now describe much of the synthetic work in detail, including the use of an arylmanganese reagent to introduce a 3β-(*p*-aminomethyl)phenyl unit into the structure, and the use of a novel 'benzostabase' *N*-protection methodology.[138,139] Using similar



Reagents: (i) MeOH, NH_3, r.t, 2 days; (ii) Boc_2O, pr^i_2NEt, 4-DMAP; (iii) NaN(TMS)$_2$, THF, -78 °C; (iv) tetra-n-butylammonium iodide and methyl 3,5-bis(bromomethyl)benzoate; (v) benzene-1,3,5-trithiol, pr^i_2NEt; (vi) TFA, anisole, CH_2Cl_2; (vi) Boc_2O, pr^i_2NEt, K_2CO_3; (vii) LiOH, THF, EtOH, H_2O; (viii) C_6F_5OH, EDC, THF; (ix) TFA, anisole, CH_2Cl_2; (x) pr^i_2NEt, THF

Scheme 77

methodology, a new cholophane framework has been prepared, with exocyclic functionality.[140] The synthesis involved condensation of ketone **198** with malononitrile, followed by equatorial-selective addition of an aryl cuprate to give **199**, which was then converted into the cholophane **200** (**Scheme 79**).

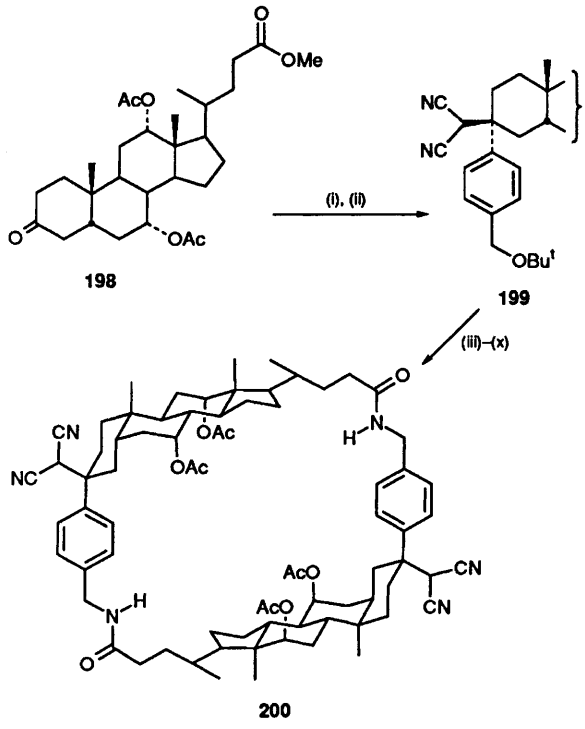


196 $R^1 = OC_{12}H_{25}$, $R^2 = CF_3CO$, M = H_2
197 $R^1 = OC_{12}H_{25}$, R^2 = H, M = Zn

Reagents: (i) pyrrole, $F_3B.OEt_2$, CH_2Cl_2; (ii) tetrachloroquinone; (iii) $Zn(OAc)_2$; (iv) H_2, Pd, C; (v) 2,6-dichlorobenzoyl chloride, Et_3N, 4Å sieves; (vi) DMAP, toluene, 100°C

Scheme 78

Still has reported the remarkable synthesis of the polycyclic receptor **202**, which displays similar enantioselectivities to the C_3 symmetric hosts **194** for the complexation of *N*-acylated and Boc-protected peptides.[141] Dimerization of oligomer **201**, derived from trimesic acid **204** and (*R*, *R*)-diaminocyclohexane **203**, gave the host **202** (**Scheme 80**). Direct treatment of free diamine **203** with the triacid chloride of trimesic acid **204**, gave receptor **202** in 13% yield in one step! The receptor forms 1:1 complexes with certain peptides (*e.g.* *N*-Ac-L-Val-NHBu^t is particularly well bound) and can even interact with peptides containing as many as three residues, as is the case for complexation with *N*-Boc-Gly-Val-Gly-NHBn.



Reagents: (i) $CH_2(CN)_2$, NH_4OAc, AcOH, benzene; (ii) $Bu^tOCH_2C_6H_4MgBr$, CuCN, THF; (iii) CF_3CO_2H, CH_2Cl_2, 50°C; (iv) NH_3 (aq), Et_2O; (v) CH_3SO_2Cl, Pr^i_2NEt, THF; (vi) $(Me_2N)_2CNH_2^+N_3^-$, $CHCl_3$; (vii) Ph_3P, THF, MeOH, H_2O; (viii) LiOH; (ix) aq HCl; (x) [$(EtO)_2P(O)CN$, DECP], $CHCl_3$–DMF, $KHSO_4$, 32%

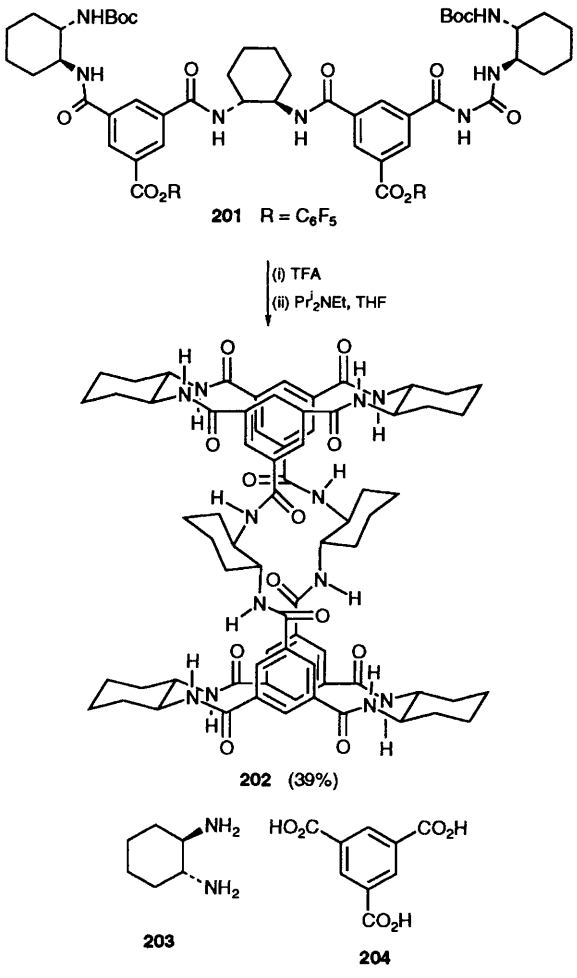
Scheme 79

6 Self-assembling receptors

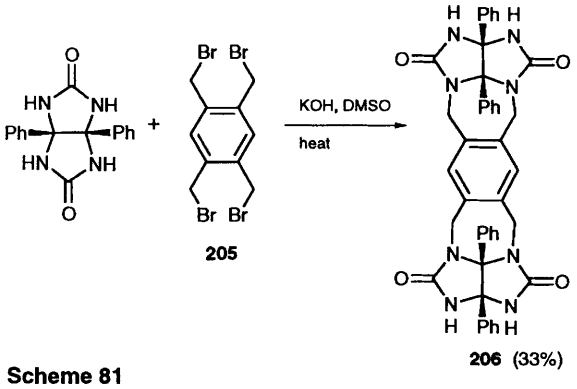
The rapid success of chemists in preparing artificial receptors has led to the new area of 'self-assembly' in which non-covalent interactions between individual molecules are used to allow the spontaneous assembly of complex supramolecular architectures such as catenanes, rotaxanes, and helices.[142] While self-assembly is not the subject of this review, it is exciting to find that examples of self-assembling receptors are appearing in the literature.

Thus, compound **206** has been synthesized by condensing two molecules of diphenyl glycoluril with durene tetrabromide **205** using KOH in hot DMSO (**Scheme 81**).[143] The lactam functionalities of **206** provide self-complementary hydrogen bonding groups, so that two molecules dimerize to form a closed-shell, three-dimensional surface through a network of hydrogen bonds, in a structure reminiscent of a tennis ball. More recently this dimer has been reported to encapsulate small hydrophobic guests, such as methane, ethane, and ethylene in a chloroform solution.[144]

Triamide cyclocholates such as **209** also self-associate strongly in CCl_4, forming molecules with short cylindrical shapes.[145] Starting from the readily available ketone **207**, the free hydroxy groups were esterified with dodecanoic acid, followed by a Beckman ring-expansion to afford lactam **208**



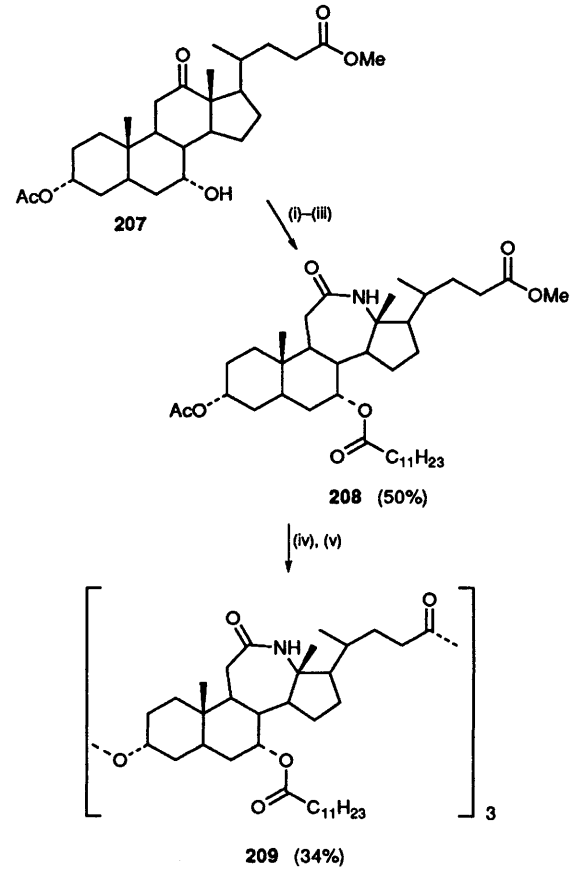
Scheme 80



Scheme 81

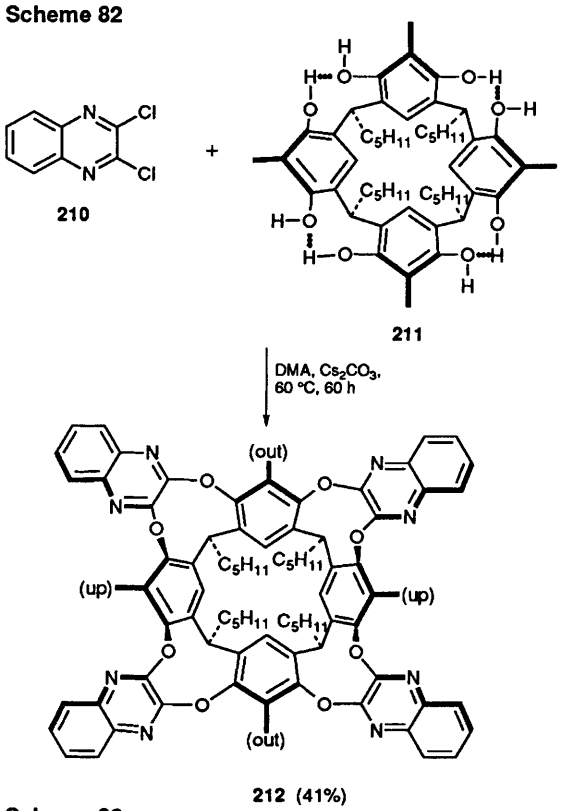
(**Scheme 82**). Selective hydrolysis of the terminal ester protecting groups, and then macrolactonization, under modified Yamaguchi conditions, afforded the cyclotrimer **209** in 34% yield.

Cram has also prepared molecules with large common surfaces which are capable of forming dimers.[146] Structure **212** (**Scheme 83**), when rotated through 90° about an axis perpendicular to the page, and then turned over and placed on top of **212**, forms a complex containing a large contact surface area with the four methyl groups on each half unit inserted into four cavities provided by the other. The absence of



Reagents: (i) dodecanoic acid, 2,6-dichlorobenzoyl chloride, DMAP; (ii) $NH_2OH.HCl$, NaOAc; (iii) *p*-TsCl, pyridine; (iv) aq NaOH; (v) 2,6-dichlorobenzoyl chloride, DMAP, 4Å sieves, CH_2Cl_2

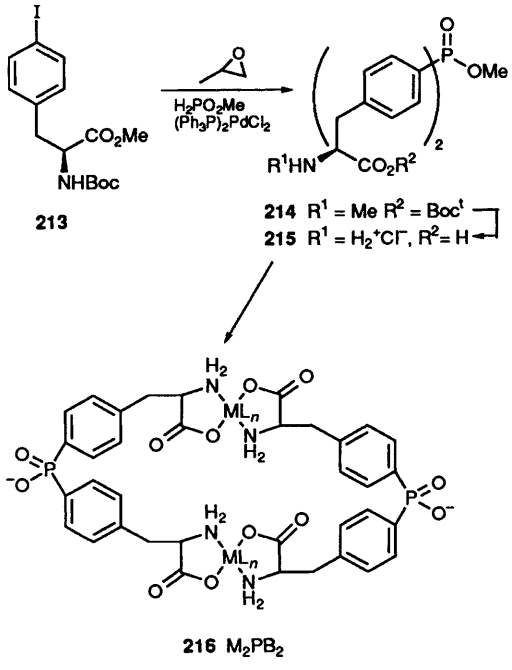
Scheme 82



Scheme 83

hydrogen bonds, ion pairs, or metal ligation sites leaves dipole–dipole, Van der Waals, and hydrophobic attraction as the major driving forces for complexation. The synthesis of molecules such as **212** involved the condensation of aromatic dihalides, such as **210**, with the octol **211** (for which an improved synthesis is described). Each reaction between dihalides and the octol involved the making and breaking of eight bonds, producing four new nine-membered rings. Remarkably high yields were obtained (50–86%) in this step of the synthesis.

Schwabacher has designed a new class of hydrophobic binding site **216**, with polar solubilizing functionality provided by connecting the aromatic rings with phosphonium functionality.[147] The self-assembly of this receptor occurred on addition of 4,4′-(hydroxyphosphinylidene)bis-L-phenylalanine (PBP) **215** to an equimolar solution of a metal such as Co^{2+}, in the presence of NaOH. The PBP was prepared in 4 steps by the conversion of protected iodophenylalanine **213** into protected PBP **214**, in 59% yield, using a palladium-catalysed coupling (**Scheme 84**). These receptors were able to transport pyrene from an isooctane layer across an aqueous phase.



Scheme 84

Current progress in host–guest chemistry, and in the more general area of supramolecular chemistry, is extremely rapid, as evidenced by the amount of new and varied chemistry reported in this review—which is far from comprehensive—and the frequent publication of articles dealing with the less synthetic aspects of this area of research. Molecules with ever more complex architectures are being designed and synthesized, and the incorporation of ideas of self-assembly and templating[148] will continue to provide new avenues for the synthetic chemist to explore.

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