Synthetic developments in host–guest chemistry

JAMES DOWDEN, JEREMY D. KILBURN, and PAUL WRIGHT

Department of Chemistry, University of Southampton, Southampton, SO17 1BJ, UK

Reviewing the literature published between January and December 1994
Continuing the coverage in *Contemporary Organic Synthesis*, 1994, **1**, 259

1 Introduction

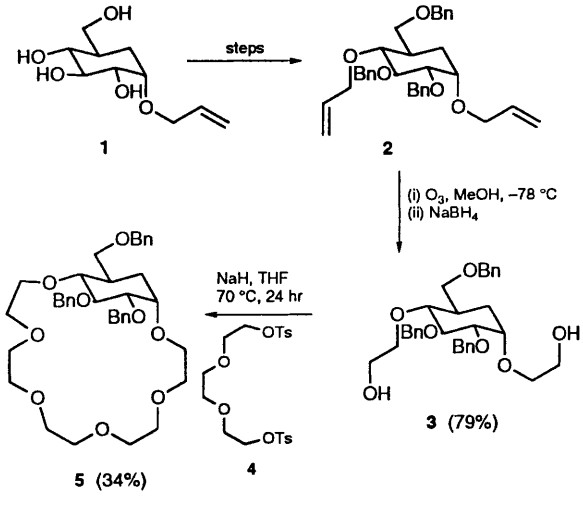
The study of artificial receptors is critical to our understanding of molecular recognition phenomena, and leads to the design and synthesis of supramolecular materials with tailored properties. Not surprisingly, much of the interest in this area focuses on the recognition properties of the receptors, a subject which is frequently reviewed in the literature. 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 is to review developments in host–guest chemistry, over the period January to December 1994, with the emphasis on the synthetic aspects. As before,[1] 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 and cryptands

2.1 Crown ethers

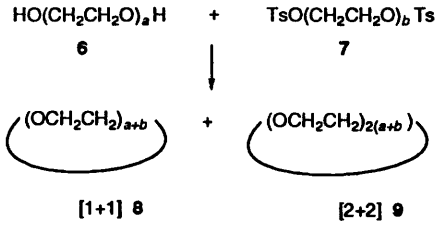
Two reviews on crown ethers have appeared this year dealing with bis- and oligo-(benzocrown ethers)[2] and metallomacrocycles based on, and incorporating, crown ethers.[3]

Chiral crown ethers are of interest because of their enantioselective binding properties. A crown ether incorporating a glucose unit has been synthesized in six steps from α-allyl glucopyranoside **1** (**Scheme 1**).[4] The diallyl derivative **2** was subjected to ozonolysis followed by reductive work-up to give diol **3** in 79% yield. The macrocycle **5** was then formed in 34% yield by reaction of **3** with triethylene glycol ditosylate **4** and sodium hydride in refluxing tetrahydrofuran.



Scheme 1

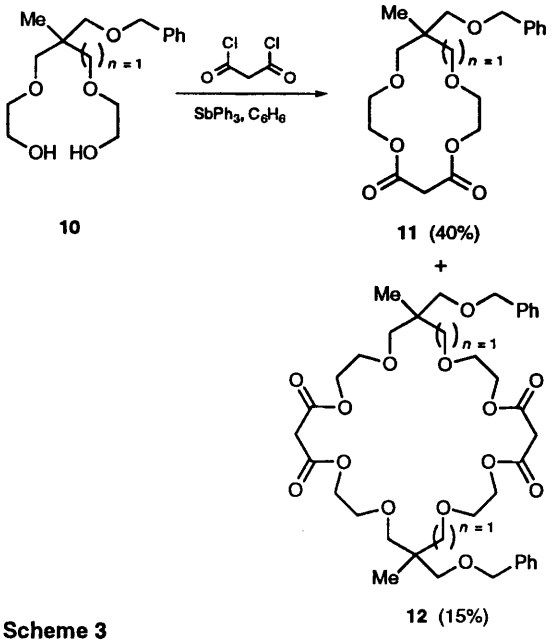
The synthesis of large crown ethers can be problematic, but Gibson has reported[5] full details of an approach to the synthesis of 30–72 membered crown ethers by combining oligo(ethylene glycols) and oligo(ethylene glycol) ditosylates to give the [1+1] or [2+2] condensation products **8** or **9** (**Scheme 2**). In order to maximize the yield of the



Scheme 2

[2+2] product **9**, 0.5 equivalents of ditosylate was added slowly to the dialkoxide before dilution of the mixture and addition of a further 0.5 equivalents of ditosylate. The readily available starting materials and the ability to optimize the reaction conditions allow the preparation of large crown ethers on a 100 g scale.

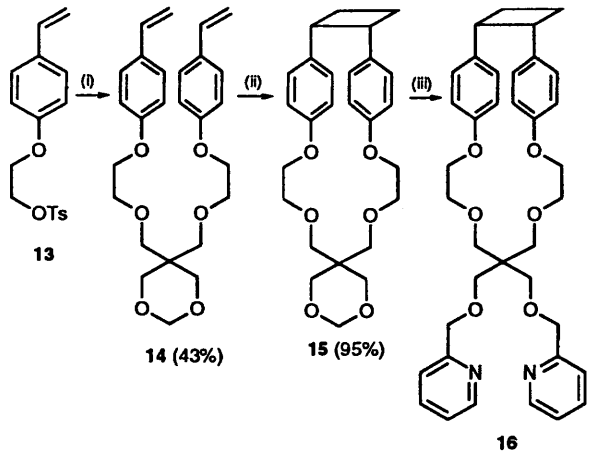
Armed crown ethers **11** and **12** have been synthesized by reaction of malonyl chloride with the corresponding diol (**Scheme 3**).[6] Triphenyl antimony was used to template the preferred formation of the [1+1] product **11** relative to the [2+2] product **12**.



Scheme 3

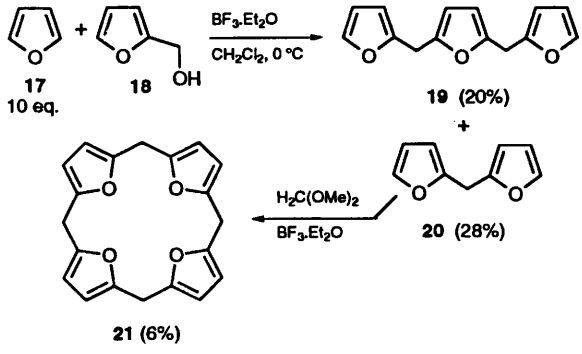
A [2+2] intramolecular cyclization reaction was used to prepare a novel crown ether derivative with two cation ligating side-chains (**Scheme 4**).[7] The key [2+2] cyclization gave the 'crownophane' intermediate **15** in 95% yield and was subsequently converted into **16**, which displayed a particular selectivity for Ag^+ ions.

Cyclic oligofurans have been prepared by reaction of furan with hydroxymethylfuran, in the presence of boron trifluoride etherate, giving the trifuran **19** and difuran **20** in 20 and 28% yields respectively.[8] The difuran could then be cyclized by treatment with boron trifluoride etherate and dimethoxymethane to give the 'calixfuran' **21** in 6% yield (**Scheme 5**).



Reagents: (i) 1,3-dioxane-5,5-methanol, NaH, THF;
(ii) hν (>280nm), MeCN, N_2;
(iii) steps

Scheme 4

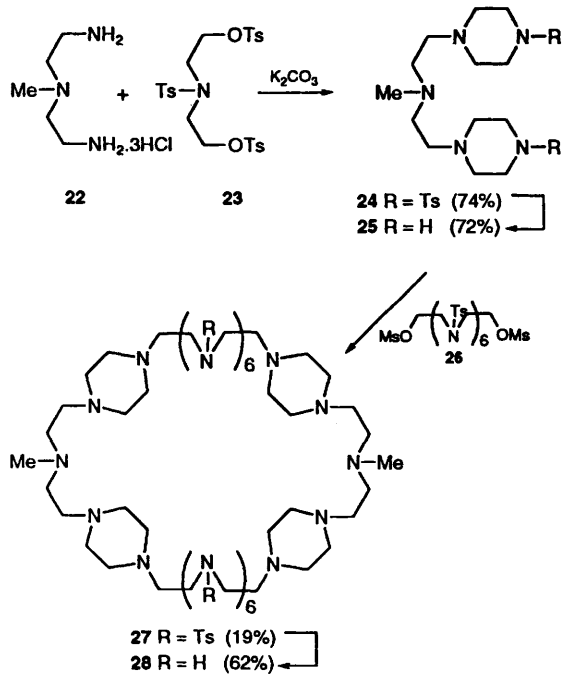


Scheme 5

Other functionalities have been incorporated within the ring of the crown system, including thiophene[9] and disulfide bonds,[10] the latter being synthesized by closure of the S–S bond using benzyltriethylammonium tetrathiomolybdate $(C_6H_5CH_2NEt_3)_2MoS_4$. The synthesis of a series of perfluoro crown ether based macrocycles[11] and crowns with pendant sugars[12] have also been reported.

2.2 Azacrown ethers and related compounds

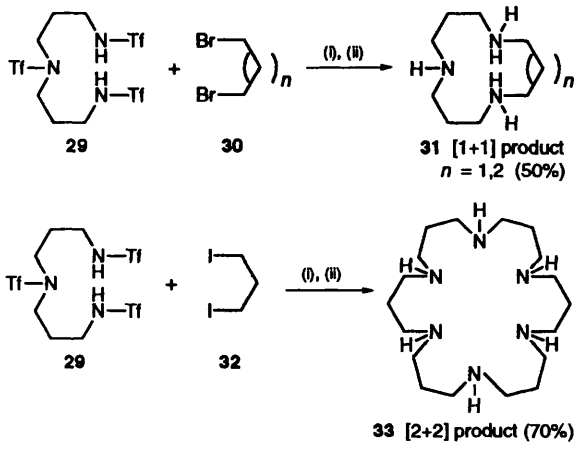
Simple azacrowns may be regarded as nitrogen analogues of crown ethers with the potential for incorporating additional functionality on the nitrogen atoms. As with large crown ethers, the synthesis of large azamacrocycles can be difficult. To overcome the unfavourable entropy associated with large ring formation, relatively rigid six-membered rings have been incorporated within the macrocycle.[13,14] Thus, reaction of triamine **22** with ditosylate **23** forms the intermediate **24**, containing two piperazine rings, which can then be incorporated into the macrocycle **27** by standard methodology, giving a reasonable yield of 19% for the final cyclization (**Scheme 6**).



Scheme 6

Using more flexible precursors, the combination of a dihalogenoalkane with an *N*-pertriflated polyamine gave either the [1+1] or the [2+2] cyclization products **31** and **33**, depending on the nature and concentration of reactants.[15] Using potassium carbonate and the ω,ω'-dibromoalkanes at a concentration of 0.05 M in DMF, reaction with the *N,N'*-triflated amines gave the [1+1] product **31**. However, reaction with ω,ω'-diodoalkanes, at higher concentrations (0.2 M), gave predominantly the [2+2] product **33**. Subsequent deprotection with lithium/liquid ammonia gave the corresponding azamacrocycles in good yield (55–70%) (**Scheme 7**).

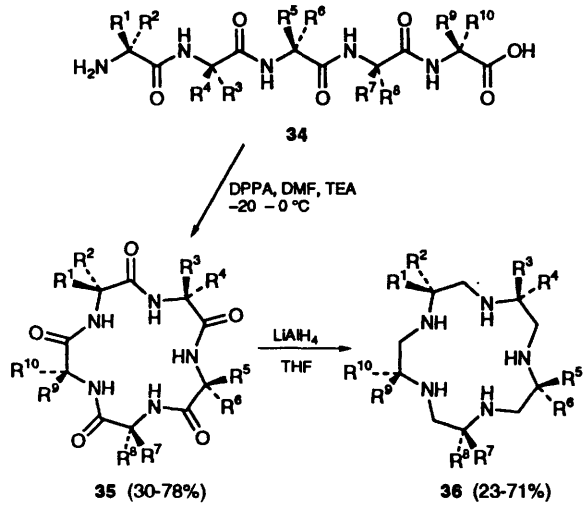
A novel approach to azamacrocycles with substitution on the carbon backbone involves the complete reduction of polypeptide macrocycles.[16]



Reagents: (i) K_2CO_3, DMF, Δ; (ii) Li, $NH_{3(l)}$

Scheme 7

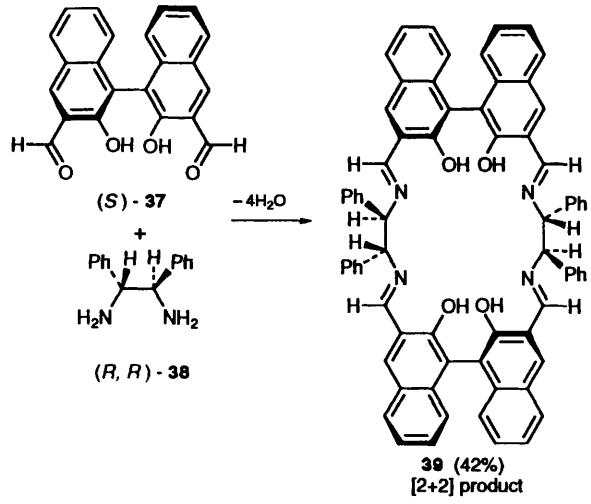
Peptide synthesis is well established and allows straightforward preparation of the linear precursor **34** which can be cyclized with diphenylphosphoryl azide in yields ranging from 30–78%, depending on the nature of the substituents (amino acids that have been used in this approach include glycine, alanine, *O*-benzyltyrosine and *O*-benzylserine) (**Scheme 8**). Reduction with lithium aluminium hydride then gave the desired azamacrocycles **36** with yields generally greater than 55%.



Scheme 8

In related work, also relying on amide bond formation and subsequent reduction, Lennon *et al.*[17] have prepared azamacrocycles by condensation of bis(chloroacetamides) of chiral diamines with tris(*N*-tosyl)diethylenetriamine dianion.

Macrocycle **39** has been synthesized from the binaphthyl derivative (*S*)-**37** and (*R,R*)-1,2-diamino-1,2-diphenylethylene **38** using imine formation (**Scheme 9**).[18] (*R*)-**37** reacted with **38**, under the same conditions, to give polymeric material. This result was attributed to the ends of the growing

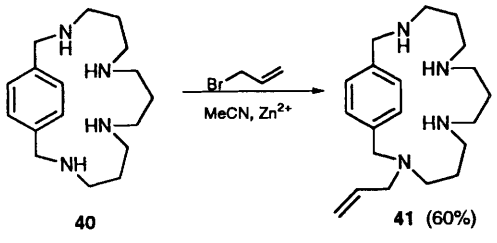


Scheme 9

chain being far apart in the case of (*R*)-**37**, but close enough together to close the macrocycle in the case of (*S*)-**37**.

Azamacrocycles can, of course, be readily substituted on the nitrogen atoms as well as the carbon backbone. This is most generally achieved by simple alkylation or acylation followed by reduction as exemplified recently by the incorporation of catechols onto diaza-18-crown-6.[19] Anthraquinone substituted crown ethers have been prepared in reasonable yield by reaction of fluoro-anthraquinones with monosubstituted diaza-crowns.[20]

Monofunctionalization of polyamine compounds can, however, be difficult due to the potential for multiple alkylation. Luis[21] has reported the selective monoalkylation of the polyamine heterophane **40**, with a stoichiometric amount of allyl bromide. In the presence of one equivalent of Zn^{2+}, the coordination of three of the nitrogens to the zinc leaves one of the benzylic nitrogen atoms free to react with the allyl bromide, giving a 60% yield of the monoalkylated product **41** (**Scheme 10**).

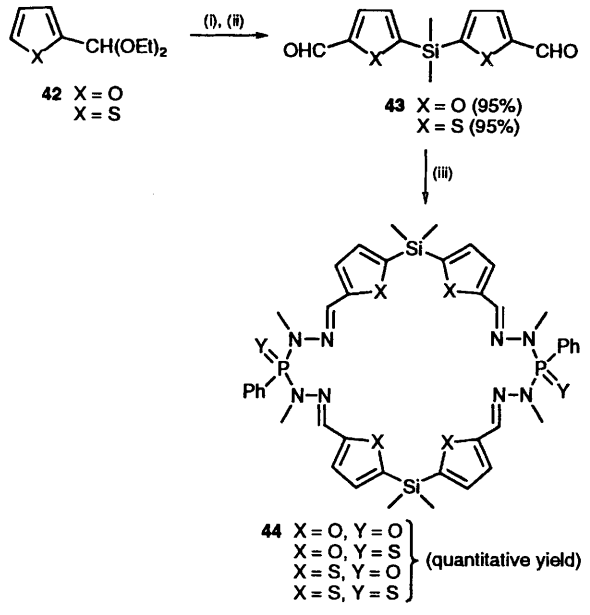


40 **41** (60%)

Scheme 10

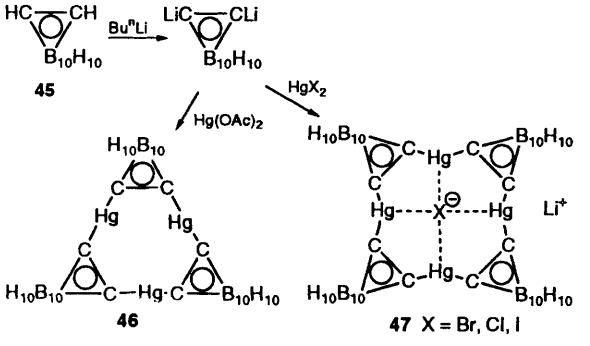
Phosphorus containing receptors are rare but a review covering a wide range of macrocycles based on phosphorus has been published.[22] New macrocycles containing a combination of nitrogen, phosphorus, and silicon have been prepared, beginning with the lithiation of heterocycles **42** and coupling with appropriate silanes. Subsequent acetal hydrolysis gave the bis(heteroaryl)silanes **43** in 95% yield, which on reaction with phosphono-dihydrazides gave the [2+2] macrocycles **44** in quantitative yield (**Scheme 11**).[23]

Metallic analogues of the classic crown ethers have also been reported, comprised of electrophilic mercury centres supported by a carborane skeleton. Icosahedral carborane *closo*-1,2-$C_2B_{10}H_{12}$ **45** was lithiated at the vertices by treatment with two equivalents of butyl lithium. Reaction with mercury halides gave tetrameric **47**, while reaction with mercury acetate gave the trimer **46** (**Scheme 12**).[24] The charge-reversed analogues of crown ethers were able to bind halide anions, and indeed the synthesis of **47** appeared to be templated by the iodide anion.



Reagents: (i) (a) Bu^nLi (1.2 eq.), Et_2O, –15 °C – r.t.; (b) $Me_2Si(OEt)_2$; (c) H_2O; (ii) 6 N HCl, Et_2O, reflux; (iii) $PhP(Y)[NMeNH_2]_2$, $CHCl_3$, r.t., 24 hr

Scheme 11



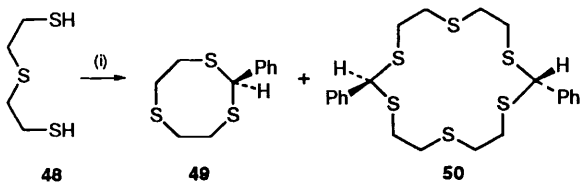
Scheme 12

2.3 Thiacrown ethers

Thiacrown ethers are of interest because of the soft character of the ligating sites and there have been several reports of new strategies for the synthesis of such compounds this year.

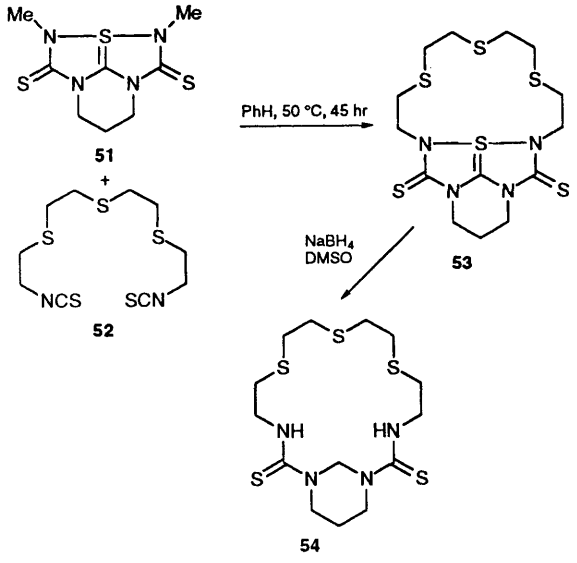
Condensation of dithiols **48** with aldehydes has been used to prepare sulfur crowns containing thioacetal units.[25] Under appropriate conditions the [2+2] products **50** can be obtained in reasonable yields (**Scheme 13**). The same authors have described the synthesis of larger macrocyclic sulfur crown ethers (up to 24-membered rings), in good yields, using the conventional condensation of caesium dithiolates with appropriate dibromides.[26]

An unusual approach to azathiocrown ethers (and azacrown ethers) has been developed based upon condensation of the hypervalent sulfur-containing tetraazapentalene **51** with suitable isothiocyanates.[27] For example, condensation of **51** with diisothiocyanate **52** gave the thiocrown ether **53** in 45% yield. The hypervalent sulfur could be removed by treatment with sodium borohydride giving **54**,

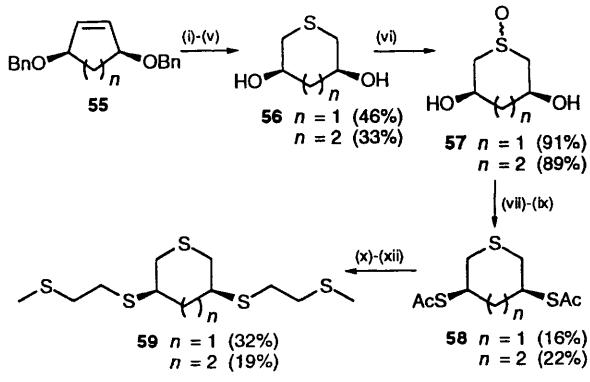


Reagents: (i)PhCHO, C_6H_6, TsOH, 80 °C, 8 hr; or → **49** (2%) + **50** (62%)
PhCHO, MeOH, HCl, 50–55 °C, 50 hr → **49** (85%) + **50** (3%)

Scheme 13



Scheme 14



Reagents: (i) O_3, $NaBH_4$; (ii) TsCl, py, CH_2Cl_2;
(iii) Bu^n_4NBr, $NaHCO_3$, butan-2-one, reflux, 4 hr;
(iv) Na_2S, aq. EtOH, reflux; (v) Na, NH_3; (vi) O_3;
(vii) TsCl, DMAP, CH_2Cl_2; (viii) AcSK, DMF;
(ix) Me_3SiCl, NaI, MeCN; (x) NaOEt, $ClCH_2CH_2OH$;
(xi) $SOCl_2$; (xii) MeSNa, EtOH, MeCN

Scheme 15

incorporating two thiourea moieties, in 57% yield. (**Scheme 14**).

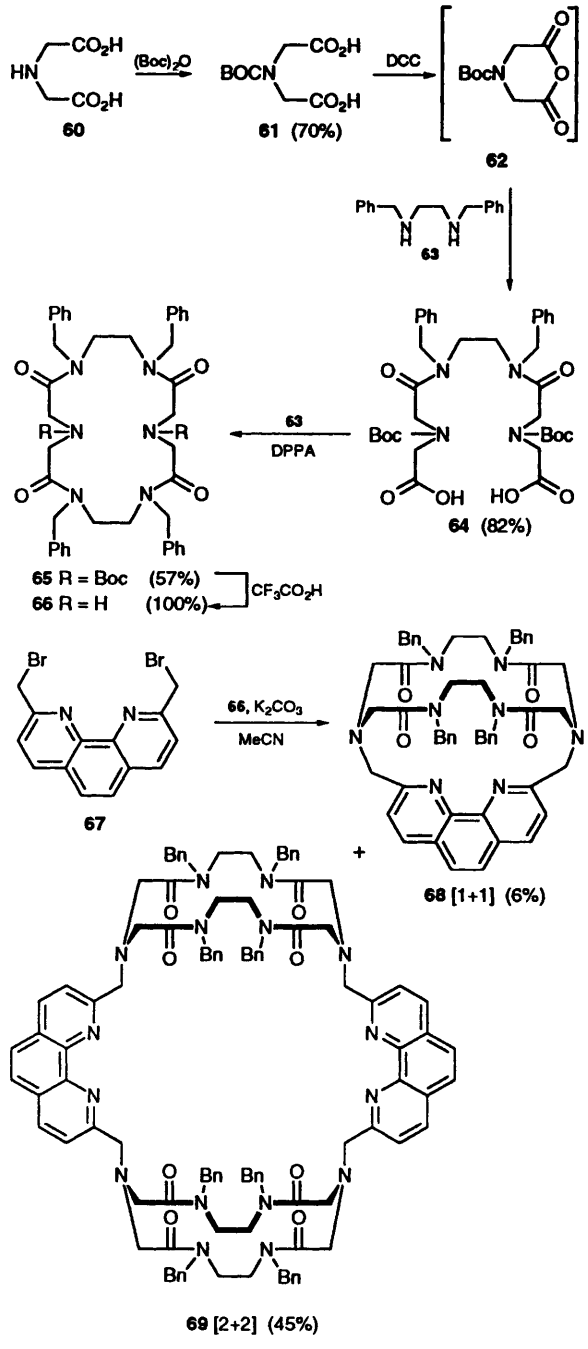
A stereospecific synthesis of non-macrocyclic thioether ligands **59** (strictly thiopodands) has been reported.[28] Protected *cis*-dihydroxycycloalkenes **55** were converted into thiopyrans **56** (**Scheme 15**). Activation of the secondary hydroxy groups of **56** was not practical with the ring sulfur atom in the reduced form because of rearrangements that are known to occur in such systems. Temporary oxidation to the sulfoxide **57** allowed the preparation of the required *cis*-ditosylates. Subsequent displacement with thioacetate gave the core structure with three sulfur atoms and the required configuration. After reduction of the sulfoxide the synthesis of **59** was completed in a straightforward manner.

2.4 Cryptands

Novel cryptands have been prepared by bridging azacrowns **66** with the 1,10-phenanthroline moiety **67** (**Scheme 16**).[29] Starting from iminodiacetic acid, conversion into a cyclic anhydride followed by opening with dibenzylethylenediamine gave **64** in 82% yield. Reaction with a further equivalent of dibenzylethylenediamine and DPPA, followed by deprotection gave the azacrown **66**. Further reaction with 2,9-bis(bromomethyl)-1,10-phenanthroline **67** then gave the sodium bromide complexes of the [1+1] cryptand **68** (6%) and the [2+2] cryptand **69** (45%).

A novel cryptand has been reported which exhibits selective binding of calcium and strontium cations with associated changes in the absorbance spectrum resulting from isomerization of the host on binding.[30] Reduction of lactone **70** and functionalization gave hydroxyaldehyde **72** which was condensed with iodide **73** to give **74** (**Scheme 17**). Reaction of **74** with diazacrown ethers then gave cryptands such as **75**, by a combination of amine and amide formation, in 18% yield.

Chelators for tribasic cations, such as Fe^{3+} and In^{3+}, have possible use in treatment of iron overload disease, as NMR contrast agents, and for radioimaging. The novel cryptand **81**, incorporating hydroxamate functionality, has been synthesized by Hider, and the formation of 1:1 complexes with Fe^{3+} and In^{3+} has been studied.[31] Monoprotected **76** was coupled to the bis acid chloride **77** at high dilution in 50% yield (**Scheme 18**). Deprotection and acylation of the pendant nitrogen with 6-chlorohexanoyl chloride was followed by cyclization (at high dilution) to give the macrobicycle **80** in 40% yield. Removal of the benzyl

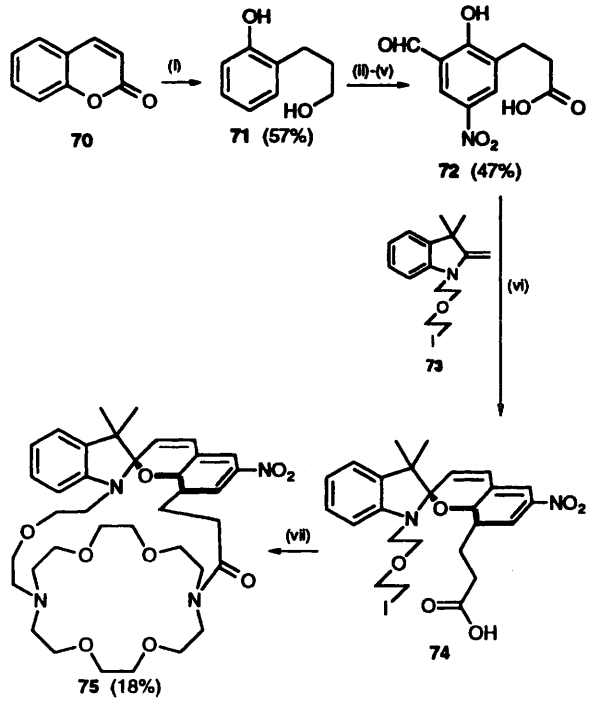


Scheme 16

groups required a two-step procedure. Reaction with dimethyl boron bromide followed by hydrogenation over palladium gave host **81** with free hydroxamate donor groups.

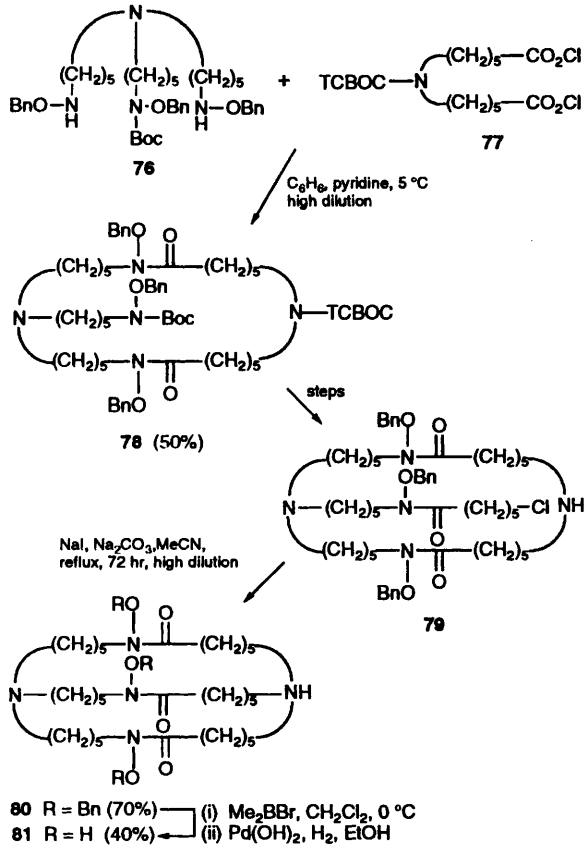
A polyazacryptand has been prepared, templated by Co^{3+}. Stereospecific sequential condensation of paraformaldehyde and propionaldehyde with a tripodal bis(triamine), in the presence of Co^{3+}, led to intermediate **83** with encapsulation of the metal (**Scheme 19**). Subsequent reduction of the imines gave the hexaazabicycle **84** which had unusual structural and chromophore electron properties.[32]

Derivatization of the known polyazacryptand **85** with boron–tetrahydrofuran gave the adduct **86** in

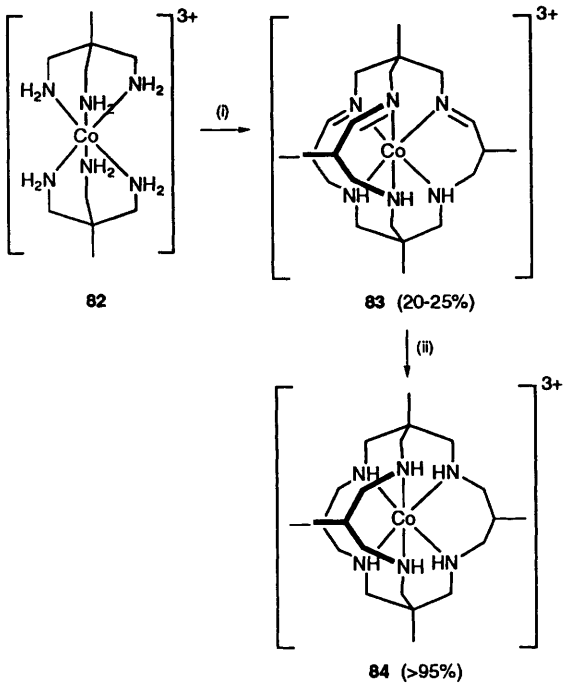


Reagents: (i) $LiAlH_4$, THF, reflux, 48 hr; (ii) Bu^nLi, $ClCH_2OMe$; (iii) Bu^tLi, Me_2NCHO; (iv) HCl, MeOH; (v) HNO_3; (vi) EtOH, 3 hr; (vii) 1,10-diaza-[18]crown-6, 2-chloro -1-methylpyridinium iodide, Et_3N, CH_2Cl_2, reflux, 3 hr

Scheme 17



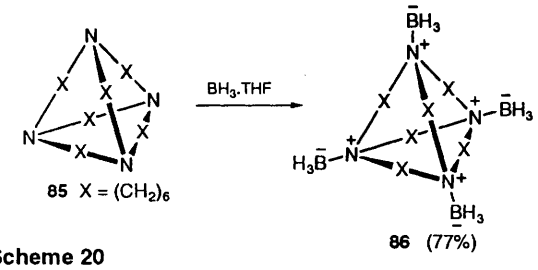
Scheme 18



Reagents: (i) EtCHO, $(CH_2O)_n$, MeCN, Et_3N, 2 hr, r.t.; (ii) $NaBH_4$, pH 9-10, 20 min, r.t.

Scheme 19

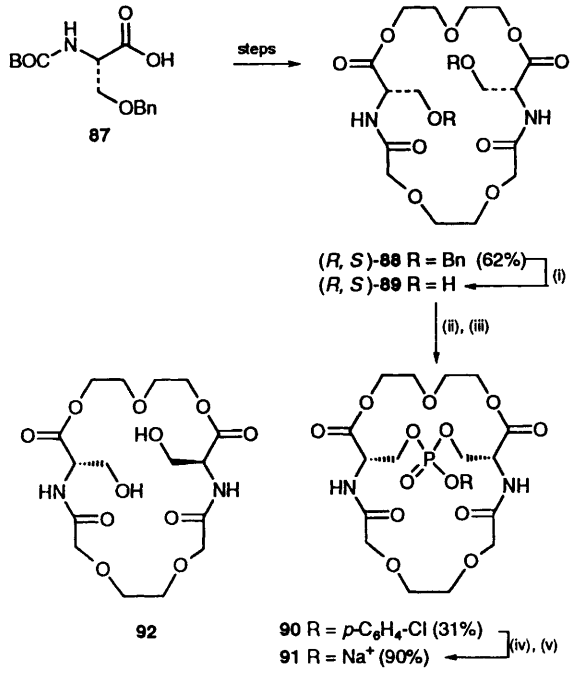
77% yield (**Scheme 20**).[33] The novel host **86** was found to bind small anionic guests (such as chloride and cyanide) by ion–dipole interactions. The selective complexation of anions by neutral receptors carries its own challenges and has been the subject of a recent review.[34]



Scheme 20

Novel cryptands based on amino acids with a phosphodiester linkage have been described.[35] Thus, Boc-L-Ser(Bn)-OH **87** was coupled with an excess of diethylene glycol, followed by a second coupling with Boc-D-Ser(Bn)-OH, and the product carried through to the (*R,S*)-macrocycle **88** (**Scheme 21**). Deprotection and subsequent reaction of **89** with a phosphorodichlorite linked the two serine side-chains. Oxidation at phosphorus with *meta* chloroperbenzoic acid gave cryptand **90** (31% yield) which could be converted into the water soluble sodium salt **91**. The corresponding (*S,S*)-macrocycle **92** could not, however, be cross-linked in the same way.

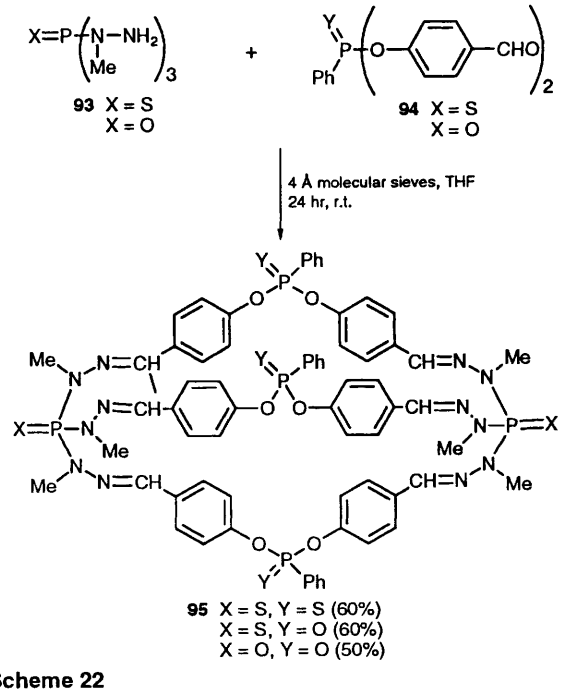
A somewhat different cryptand containing phosphorus has been synthesized by a [2+3]



Reagents: (i) H_2, 10% Pd/C; (ii) DIPEA, *p*-$ClC_6H_4CH_2OPCl_2$; (iii) m-CPBA; (iv) 10%Pd/C, H_2, NaOAc, Bu^tOH, H_2O; (v) Sephadex LD-20

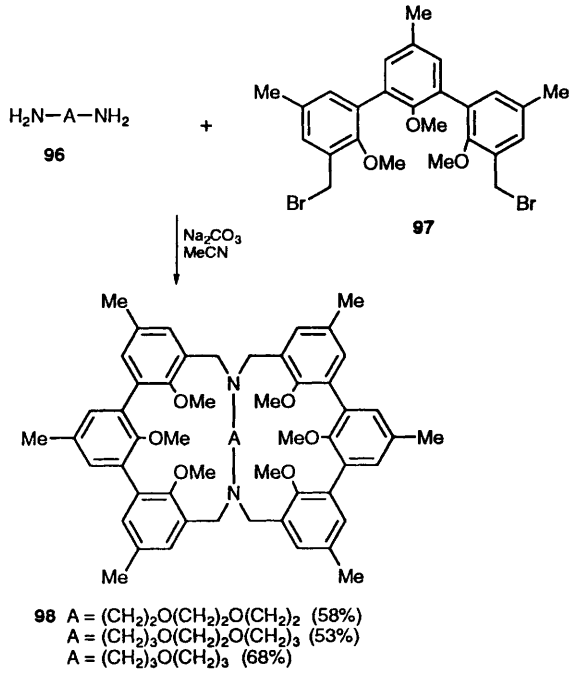
Scheme 21

cyclocondensation between the phosphotrihydrazides **93** and the dialdehydes **94**.[36] The reaction gave good yields of the cryptands **95** (**Scheme 22**) when carried out in tetrahydrofuran with 4 Å molecular sieves. This methodology has been developed further to give a range of similar compounds.[37]



Scheme 22

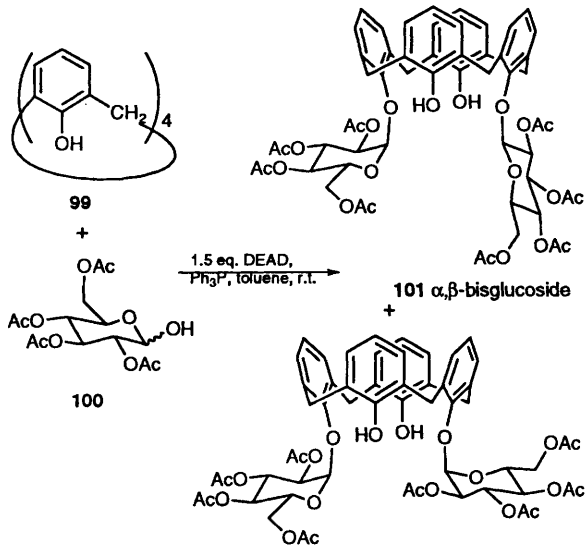
Relatively rigid 'cryptaspherands' **98** have been prepared by treating the appropriate dioxa- or oxa-alkanediamine **96** with two equivalents of 2,6-bis[3-(bromomethyl)-2-methoxy-5-methyl-phenyl]-4-methylanisole **97** and sodium carbonate in acetonitrile (**Scheme 23**).[38]



98 A = $(CH_2)_2O(CH_2)_2O(CH_2)_2$ (58%)
A = $(CH_2)_3O(CH_2)_2O(CH_2)_3$ (53%)
A = $(CH_2)_3O(CH_2)_3$ (68%)

Scheme 23

Water-soluble, non-ionic calixarenes are of interest as potential molecular receptors for highly polar organic molecules, such as amino acids and carbohydrates, in water. With this in mind Dondoni and Ungaro have introduced sugar moieties to both the lower and upper rim of calix[4]arenes. Lower rim functionalization was achieved by Mitsonobu glycosylation, for example reaction of calix[4]arene **99** with tetraacetyl-α,β-D-glucoside **100** in toluene gave a 1:1 mixture of α,β-bisglucoside **101** and α,α-bisglucoside **102** in 50% overall yield (**Scheme 24**).[42]



101 : 102 1 : 1 (50% overall)

Scheme 24

3 Calixarenes

3.1 Calix[4]arenes

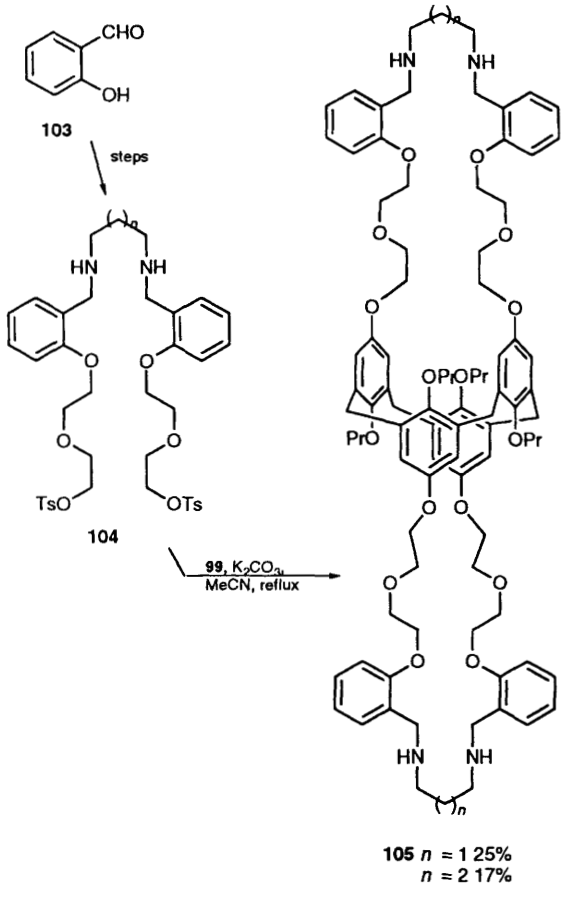
3.1.1 Modifications to the lower rim

Modification of the lower rim of calixarenes is particularly attractive since it can be achieved by straightforward alkylation of the phenolic oxygens. The complete and partial alkylation of the free phenolic oxygens has already been examined in great detail and procedures for selective alkylation have been established. Pappalardo has now published an extensive study on the mixed alkylation of calix[4]arenes using a range of alkylating agents to generate chiral binding environments.[39] Other recent work has focused on extending these ideas by alkylating with other reagents; for example, tetra *O*-alkylation of *p*-t-butylcalix[4]arene with 4-bromobutyronitrile, followed by reduction and reaction with alkyl and aryl (thio)isocyanates gave a series of thiourea derivatives that could form hydrogen bonds with spherical anions.[40] Grigg has developed a luminescent pH sensor by *O*-alkylation of one or two of the free phenolic oxygens with bromomethylbipyridine, and subsequent formation of a trisbipyridylruthenium(II) complex to act as the luminophore. The remaining free phenolic oxygens act as the acid–base sites.[41]

Another popular method for the introduction of functional variety at the lower rim has been to convert known calix[4]arene carboxylic acid derivatives into acid chlorides, and to introduce novel moieties by amide or ester formation. Shinkai has used this approach to develop ditopic ligands that can bind both hard metal cations such as Na^+, and soft metal cations such as Ag^+. Functionalization of the lower rim was achieved by formation of the tetra(acid chloride) from *p*-t-butyltetrakis-(carboxymethoxy)calix[4]arene and subsequent reaction with $EtS(CH_2)_nNH_2$.[43] Similarly, reaction of 2-hydroxy-5(4′-nitrophenylazo)benzyl alcohols with a calixarene tetraacid chloride gave a tetraphenylazophenol derivative in 80% yield, which could be used as a visual indicator for gaseous amines.[44]

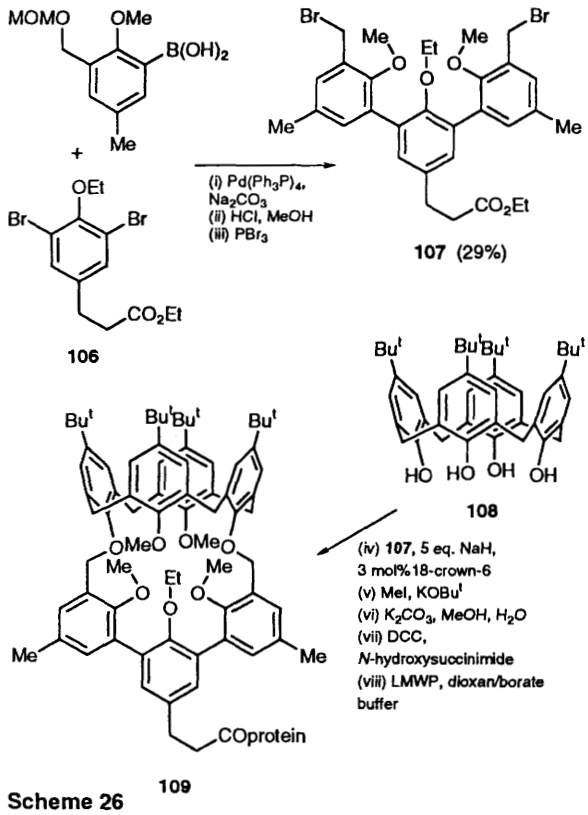
It has been shown that exceptional selectivity for binding sodium over potassium metal ions can be accomplished by bridging calix[4]arenes with polyether chains.[45] To this end Shinkai has carried out a thorough study of the product distribution for the reaction of calix[4]arene tetrol and 3,6-dioxocatane-1,8-ditosylate. Weak bases such as M_2CO_3 (where M = K, Na) lead to 1,3-bridging in agreement with previous findings for general *O*-

alkylations. However, a strong template effect was observed for alkali metal hydrides. LiH led to 1,3-bridging while NaH and KH encouraged reaction at the proximal phenolic oxygen, giving rise to 1,2-bridging.[46] Related to this work, Vicens has described the synthesis of doubly bridged calixarenes **105** in the 1,3-alternate conformation by alkylation of calix[4]arene **99** with bistosylate **104** (**Scheme 25**).[47]

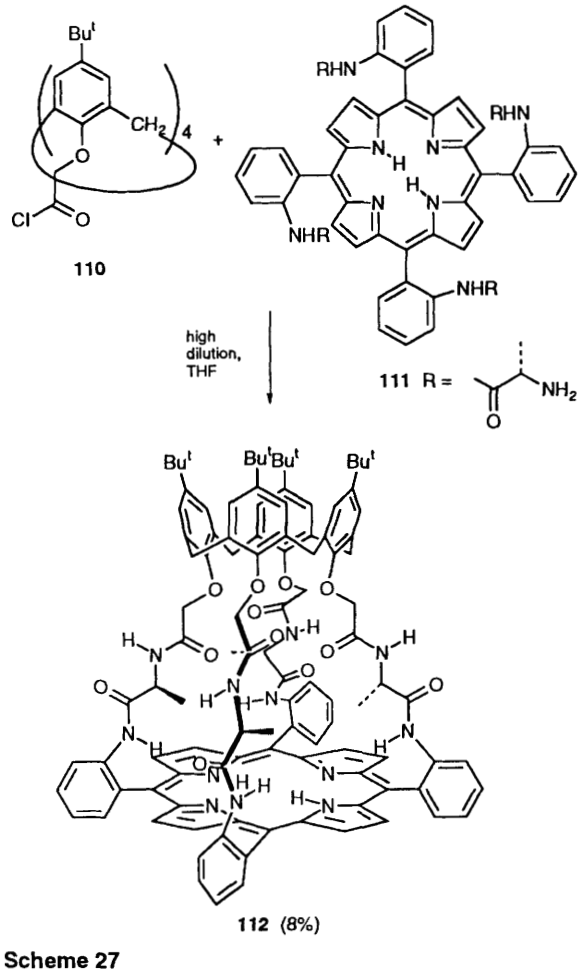


Scheme 25

Reinhoudt has prepared a series of calixpherands, that form kinetically stable complexes with alkali metal ions, by bridging *p*-t-butylcalix[4]arene with *m*-terphenyl units. Previous attempts at synthesis using high dilution techniques only gave poor yields, but addition of a solution of the *m*-terphenyl dibromide, without high dilution, to the polyanion of *p*-t-butylcalix[4]arene, formed using five equivalents of sodium hydride, gave the diametrically bridged molecule in an improved 80% yield. The second, bridge-forming alkylation is only possible with the distal phenol, since alkylation on the more reactive proximal phenol is prevented by the rigidity of the *m*-terphenyl. It is thought that sodium acts as a metal template in the reaction since, with potassium hydride as base to generate the polyanion, the resulting calixspherands were produced in very low yields.[48] A Suzuki cross-coupling was used to prepare *m*-terphenyl **107** which



Scheme 26



Scheme 27

was then linked to calix[4]arene **108** using the above methodology (**Scheme 26**). After protection of the phenols and ester hydrolysis the resulting calixpherand could be coupled to low molecular weight proteins (LMWP) to give **109** in good yield. By attaching egg-white lysozyme the calixspherand and entrapped Rb^+ (or the radioactive isotope) could be delivered to a specific organ, in this case kidney, in an approach to tracing bloodflow through specific organs.[49]

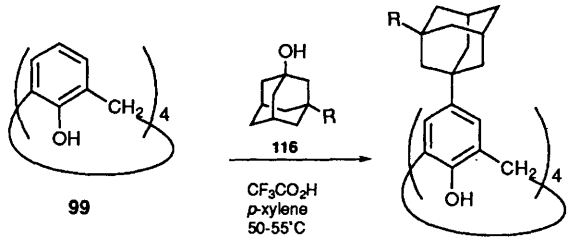
Shinkai has formed a calix[4]arene-capped tetraphenylporphyrin, **112** (**Scheme 27**), by functionalization of 5,10,15,20-tetrakis (2-aminophenyl)porphyrin with L-alanine and subsequent coupling, under high dilution conditions, to the calix[4]arene tetraacid chloride **110**. The chiral, C_4 symmetric receptor **112** with a hard–soft ditopic binding site was obtained in 8% yield.[50]

3.1.2 Modifications to the upper rim

Structural extension of the upper rim provides calixarenes with much deeper pockets, and functionalization that can be further developed into binding sites. Thus, Lin has isolated all the possible derivatives of the diazo-coupling reaction between calix[4]arene and the diazonium salts of 6-amino-1,3-benzodioxin — a reaction that showed little selectivity.[51]

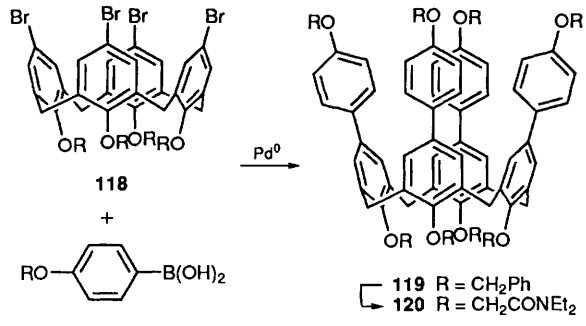
Gutsche has made a thorough study of the 'quinonemethide' route to upper-rim substituted calix[4]arenes. Aminomethylation of calix[4]arene **99**, followed by quarternization with MeI and treatment with various nucleophiles, gives a flexible route to *para*-substitution at the upper rim (**Scheme 28**). If the aminomethylation was carried out in THF/HOAc reaction took place at all available positions giving **114**. However, with no HOAc present, aminomethylation occurred at just one position, giving **115**.[52] When CN^- was the nucleophile, *p*-cyanomethyl calix[4]arene was formed, and subsequent reaction with strong base and benzyl halides gave rise to a variety of heavily substituted calix[4]arenes with deep pockets. Both cone and 1,3 alternate conformations could be obtained depending on the synthetic protocol employed.[53] The synthetic utility of these compounds has been further extended by using aromatic aldehydes in aldol condensations with the *p*-cyanomethyl calix[4]arenes.[54]

Kovalev has described the synthesis of adamantyl substituted upper rim calix[4]arenes **117** (**Scheme 29**). Direct reaction of various 1-hydroxy-adamantanes **116** with calix[4]arene **99** in trifluoroacetic acid gave the tetraadamantyl calix[4]arene in 75% yield. The low nucleophilicity but high solvating ability of TFA made it an excellent medium for this reaction.[55]



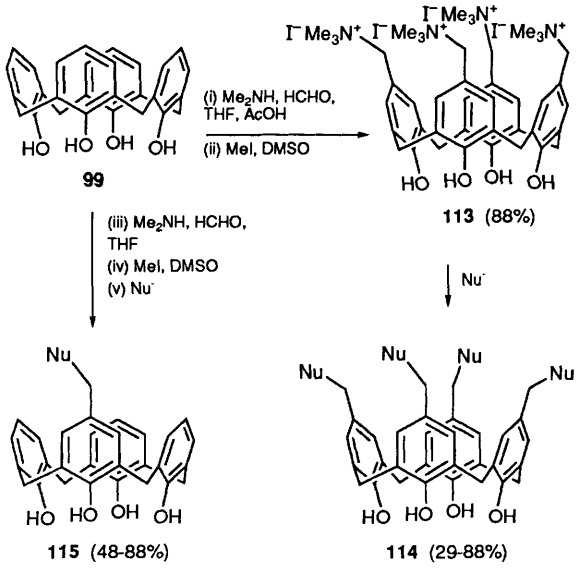
Scheme 29

Sutherland has prepared a calix[4]arene derivative with cation binding sites at both the upper and lower rim, giving rise to strong co-operativity in the binding of alkali metal cations. Bromination of the cone conformer of the known tetrabenzylether of calix[4]arene, followed by Suzuki-arylation with benzyloxyboronic acid gave **119**. Debenzylation, and alkylation of all eight hydroxy groups with *N,N*-diethylchloroacetamide in the presence of sodium iodide, gave the novel derivative **120** (**Scheme 30**).[56]



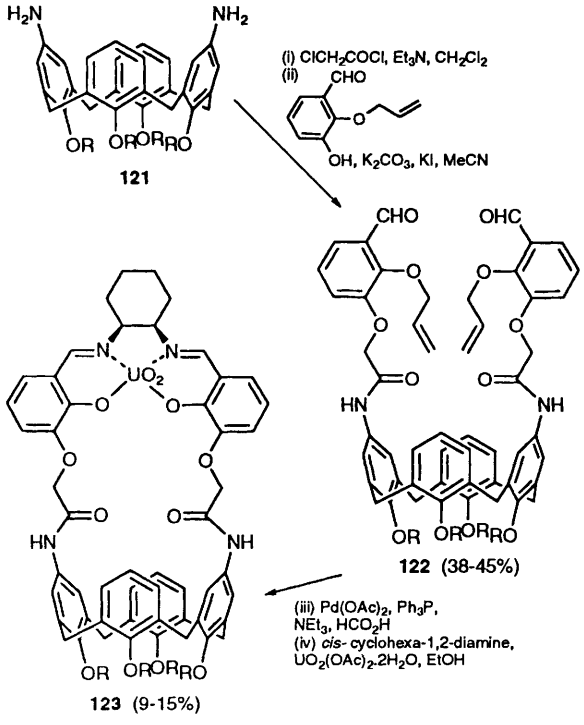
Scheme 30

Reinhoudt has synthesized calix[4]arene salenes **123** that act as neutral bifunctional receptors for NaH_2PO_4. The receptors contain an immobilized Lewis acidic UO_2-centre as well as amido units that



Scheme 28

can act as hydrogen bonding sites for anions, and showed a high selectivity for dihydrogen phosphate, with the calix[4]arene unit providing a binding site for a sodium cation. 1,3-Diaminocalix[4]arene **121** was reacted with chloroacetylchloride, followed by alkylation with 2-(2-allyloxy)-3-hydroxybenzaldehyde in the presence of K_2CO_3. Palladium-catalysed deallylation of **122** gave a bis-aldehyde which on reaction with *cis*-1,2-diaminocyclohexane and UO_2-$(OAc)_2.H_2O$ gave the receptor **123** in 15% yield (**Scheme 31**).[57]



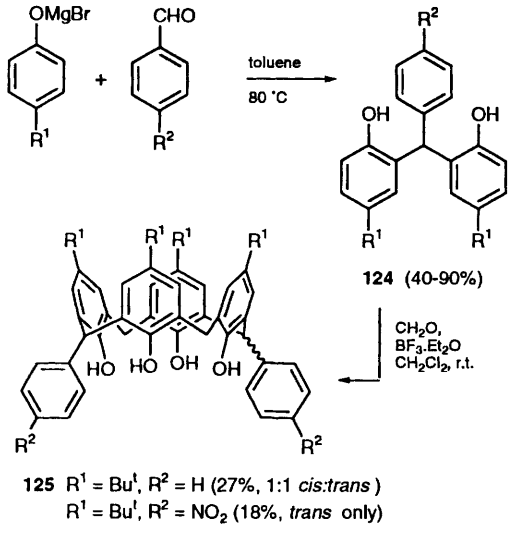
Scheme 31

3.1.3 Other modifications

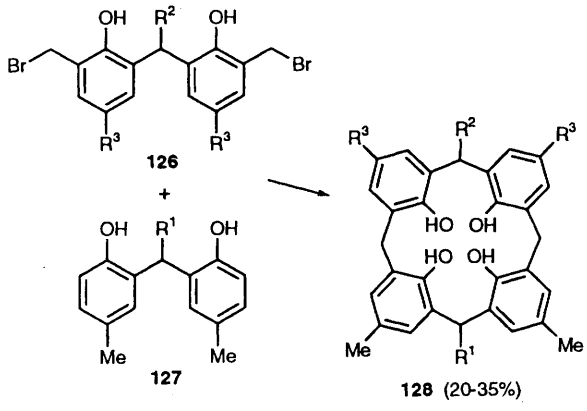
An alternative method for obtaining novel calixarenes is to go back to the synthesis of the calixarene itself. Thus calix[4]arenes **125** have been prepared bearing aryl groups on the methylene bridges, in diametrical positions, starting from 2,2′ dihydroxytriphenylmethanes **124**. The triphenylmethanes are readily produced by the directed *ortho*-regioselective alkylation of bromomagnesium phenolates with various aromatic aldehydes (**Scheme 32**). Acid-promoted macrocyclization of **124** with formaldehyde gave calix[4]arenes **125** in moderate yields.[58]

A related strategy has been recently reported by Böhmer using a 2+2 condensation of a bisbromomethylated biaryl fragment **127** with a second biaryl unit **126**, although reaction conditions were not described (**Scheme 33**).[59]

Calix[4]resorcinane octamethyl ethers have been synthesized in almost quantitative yield by treatment of 2,4-dimethoxybenzylalcohol with 5% TFA/$CHCl_3$.[60] A novel route, that offers considerable

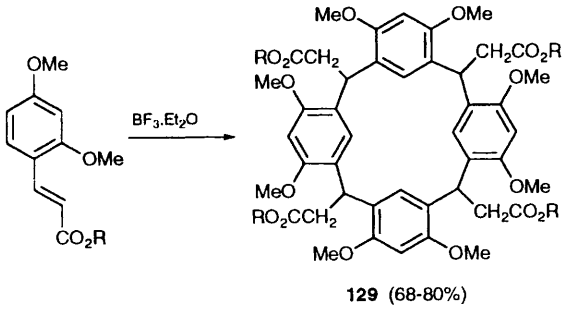


Scheme 32



Scheme 33

flexibility in the variation of the functionality at the methylene bridge, has been developed for calix[4]resorcinanes. The reaction of 2,4-dimethoxycinnamates with $BF_3.Et_2O$ gave good yields of the calix[4]resorcinanes **129**, as a mixture of stereoisomers (**Scheme 34**).[61]



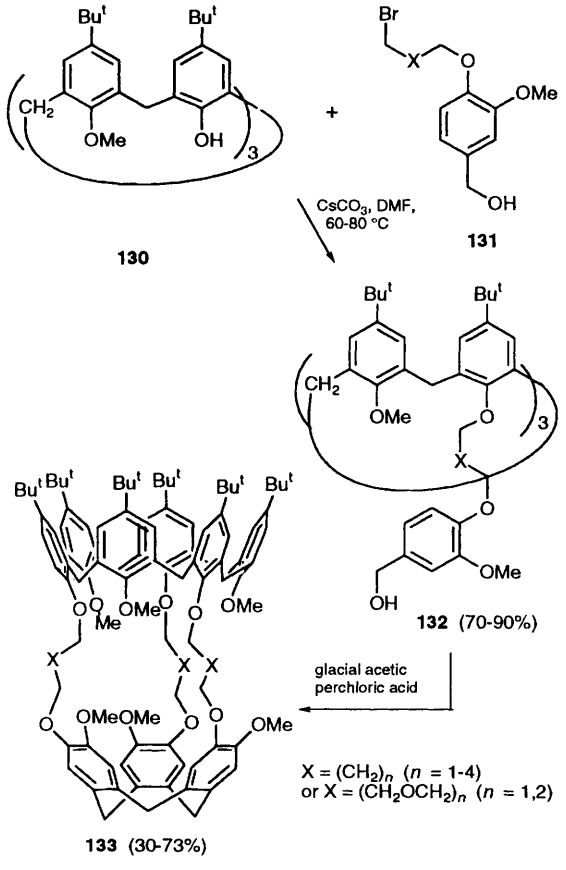
Scheme 34

3.2 Calix[6]arenes

In comparison with calix[4]arenes, much less attention has been paid to the calix[6]arenes, although larger ions can be bound within the cavity

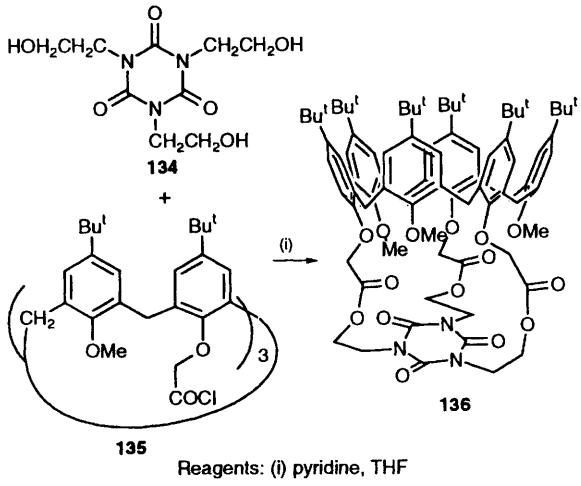
of the latter. The controlled derivatization of the calix[6]arenes is vital for their development as molecular building blocks. 1,3,5-regioselective *O*-alkylation provides C_3 symmetric points of attachment but, previously, only methyl iodide gave good yields for such alkylations. This has now been successfully extended to other alkyl iodides and *para*-substituted benzyl bromides, by reaction with *p*-t-butylcalix[6]arene in the presence of a weak base such as K_2CO_3 or CsF.[62] Shinkai has completed a thorough study on the synthetic strategies, including direct methylation and protection–deprotection methods, leading to all possible *O*-methylated derivatives of hexa-t-butylcalix[6]arene hexol.[63]

The greater flexibility of calix[6]arenes discourages their use as platforms for binding arrays, but capping of the lower or upper rim restricts conformational freedom and provides necessary preorganization. Such capped calixarenes can provide derivatives with C_6 or C_3 symmetry, suitable for the recognition of ammonium cations. Reinhoudt has developed a three point capping between *p*-t-butylcalix[6]arene and a cyclotriveratrylene to form a crypto-calix[6]arene **133**. Coupling various veratryl units **131** to 1,3,5-trimethoxy-*p*-t-butylcalix[6]arene **130**, using Cs_2CO_3 in DMF, gave the precursors **132** in 70–90% yields (**Scheme 35**). Slow addition of a 0.1 M solution of **132**, in glacial acetic acid, to an ice-cooled mixture of glacial acetic acid and perchloric acid (2:1, v/v) gave the capped products **133** in yields varying from 30–73%, after purification.[64]



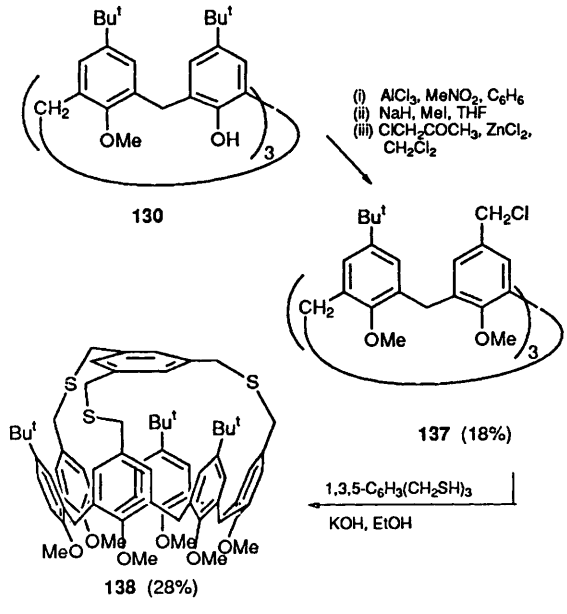
Scheme 35

Shinkai has also capped the lower rim by high dilution esterification of calix[6]arene tris(acid chloride) **135** with tris(2-hydroxyethyl)isocyanurate, to give **136** (**Scheme 36**).[65]



Scheme 36

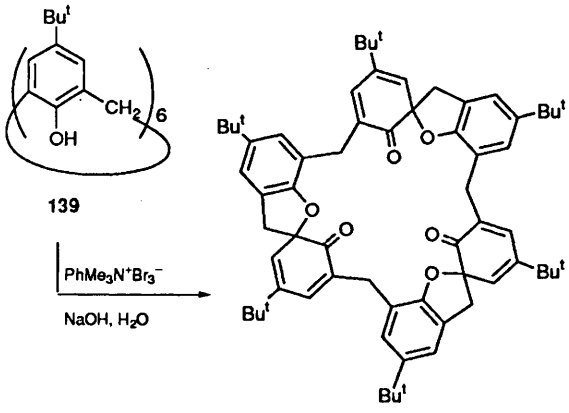
The same group has successfully capped the upper rim. Treatment of 1,3,5-trimethoxy-*p*-t-butylcalix[6]arene **130** with $AlCl_3$, in the presence of nitromethane in benzene, gave selective di-t-butylation of the free phenols, which were then protected by methylation. Chloromethylation at the free *para*-positions, and high dilution intramolecular coupling with 1,3,5-tris(sulfanylmethyl)benzene gave the capped calix[6]arene **138** in 28% yield (**Scheme 37**).[66]



Scheme 37

Other modifications to calix[6]arenes include the formation of a mono(indoaniline) derivative by reaction of calix[6]arene with 4-diethylamino-

2-methylaniline hydrochloride, in the presence of $K_3Fe(CN_6)$, to give a UO_2^+ sensitive chromophore in 53% yield.[67] Complete removal of the six hydroxy groups of calix[6]arene has been successfully achieved by phosphorylation, followed by reduction with K/NH_3, to give the corresponding metacyclophane.[68] Biali has extended his work, on the oxidation of calix[4]arenes, to calix[6]arenes, and has described the synthesis of trisspirodienones **140** (**Scheme 38**). Mild oxidation of calix[6]arene **139** with phenyl trimethylammonium tribromide and aqueous NaOH gave the major chiral spirodienone derivatives **140** in 44% overall yield providing a potential route to calix[6]arenes selectively functionalized in intra- or extra-annular positions.[69]

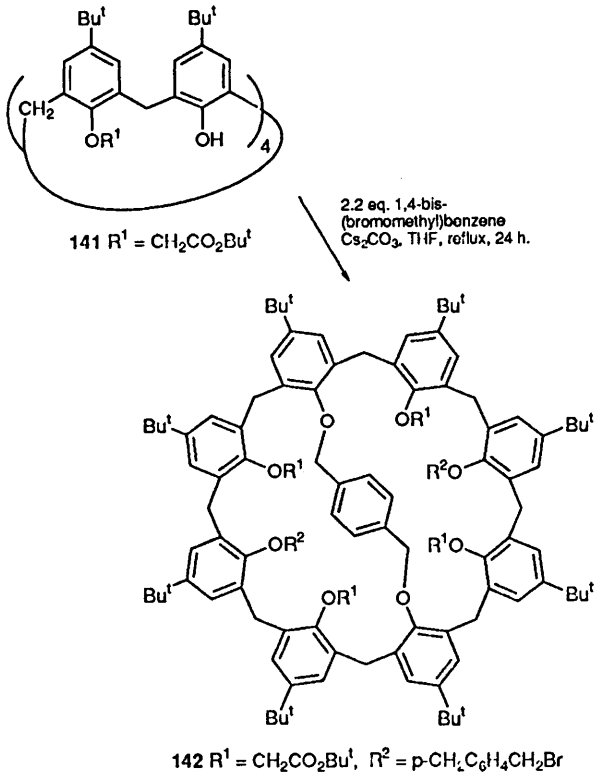


Scheme 38

3.3 Calix[8]arenes

The calix[8]arenes bear all the same challenges as the calix[6]arenes. Neri has completed a thorough study of the substitution patterns obtained from *O*-alkylation reactions. Strong base-mediated reactions give rise to good yields of octa-substituted calix[8]arenes while weak base gives more complex mixtures from which 1,3,5,7-tetraethers with C_4 symmetry were generally obtained in up to 49% yield. However, when MeI was the electrophile, no C_4 symmetric tetraethers were detected, instead the 1,2,4-trimethoxy and 1,2,3,4-tetramethoxy derivatives were isolated as the main products.[70] The same group has synthesized the first example of a 1,5 intramolecularly bridged calix[8]arene **142** by reaction of **141** with 1,4-bis(bromomethyl)benzene using Cs_2CO_3 as base (**Scheme 39**). The products are conformationally frozen into a double conical shape.[71]

Calix[8]arene has also been capped with 4,4′-diazophenyls potentially leading to novel chromogenic calix[8]arenes, although the regioselectivity of the capping is unclear from this work.[72,73] A water soluble *p*-t-butylcalix[8]arene has been prepared by reaction with ethylene oxide, resulting in functionalization of the lower rim with polyoxyethylene chains.[74]

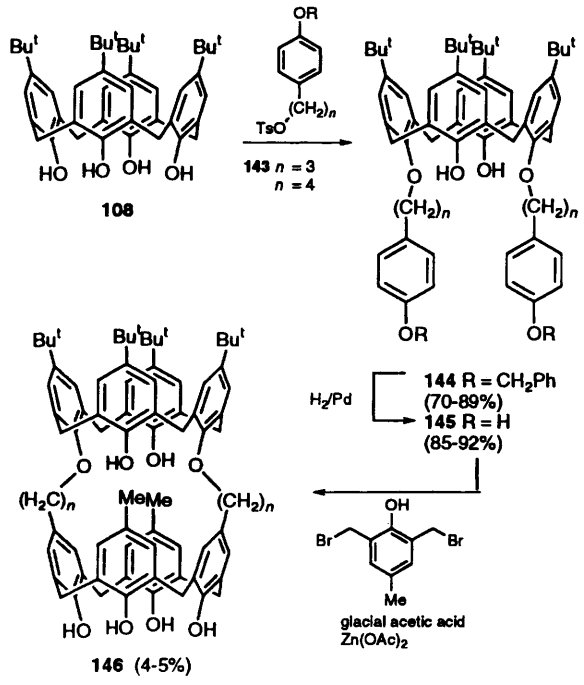


Scheme 39

3.4 Double calixarenes

Calixarenes can be linked together to form bis-calixarenes that provide large, rigid cavities. An octathio-bis-calixarene, for example, was generated by replacement of the t-butyl groups with thiomethyls and bridging by reaction with CH_2I_2 under high dilution conditions, with yields between 26–30% for the final step.[75] Ziessel has prepared a family of calix[4]arene podands and bis-calix[4]arenes by selective alkylation of *p*-t-butyl-calix[4]arene with 5,5′-substituted-2,2′-bi-pyridine building blocks in the search for lanthanide receptors.[76] The first examples of 'head-to-tail' linked bis-calixarenes **146** have been synthesized, with the dipole moments of the two calixarene units linked up in an additive manner.[77] 1,3-Dialkylation of *p*-t-butylcalix[4]arene **108** with two equivalents of tosylate **143** gave **145** after deprotection. Condensation of **145** with bis-bromomethyl *p*-cresol in glacial acetic acid gave the head-to-tail linked calixarene **146** in 4–5% yield (**Scheme 40**).

In a single experiment Reinhoudt has generated two large calixarene-based receptors resulting from an intramolecular cyclization and a dimerization. Coupling of calix[4]arene **147** with **148** gave the 1:1 adduct **149** exclusively as the *endo*-isomer shown (**Scheme 41**). Reduction of the nitro groups and condensation of the resulting amines with chloroacetylchloride gave **150**. Removal of the silyl protecting groups and stirring for 48 hours with Cs_2CO_3 and KI then led to two products. The first,



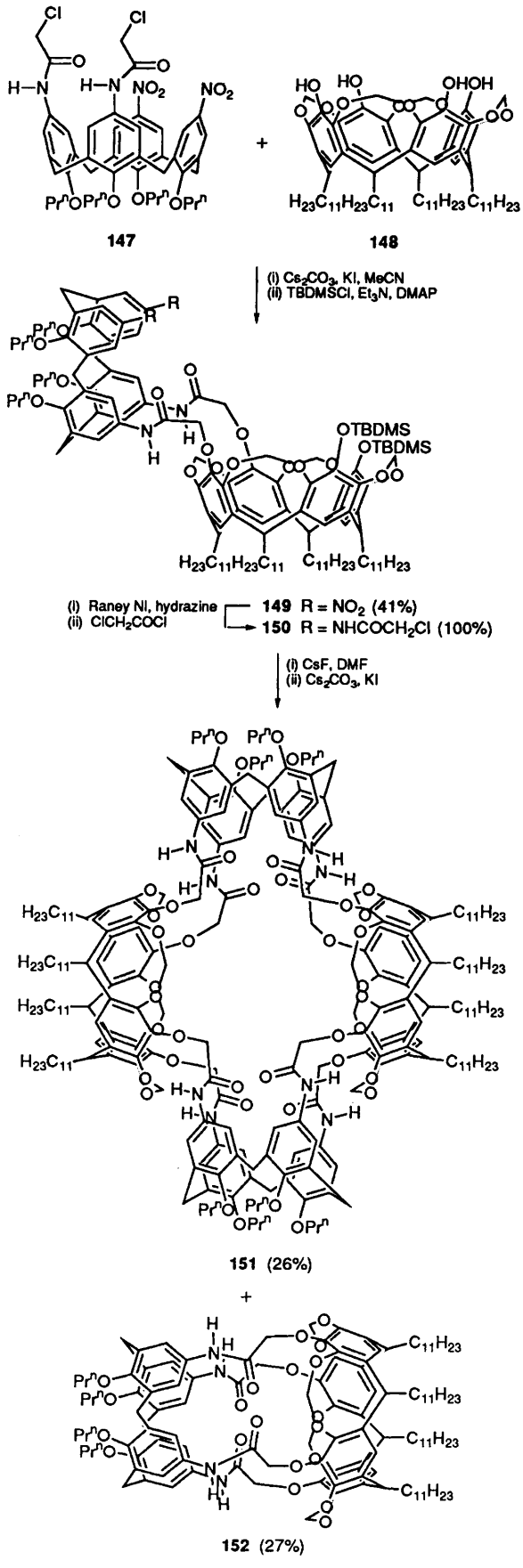
Scheme 40

obtained in 26% yield, was the highly symmetrical 'holand' **151**, comprised of two opposed calix[4]arene and two cavitand moieties, which produces a cavity of nanometre proportions.[78] The second product, in 27% yield, was a calix[4]arene based cancerand **152**. Complexes with this carcerand showed novel stereoisomerism ('carceroisomerism') as a result of hindered rotation of guest molecules in the carcerand cavity.[79]

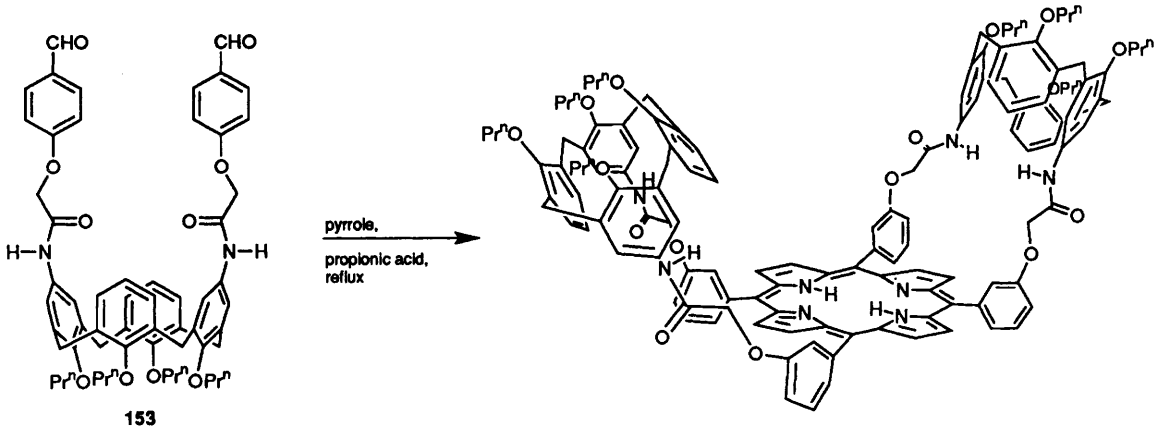
The same group has also reported the formation of a biscalix[4]arene–tetraarylporphyrin **154**, by refluxing 1,3-bisaldehyde calix[4]arenes **153** with pyrrole in propionic acid, in a reaction which gave just one of the possible rotational isomers in 3–5% yield (**Scheme 42**).[80]

1,3-Alternate conformers of calix[4]arenes lend themselves to the construction of materials by formation of rods and tubes. The observation of metal tunnelling through calix[4]arenes[81] has led Shinkai to synthesize π-basic 'nano-tubes' by linking 1,3-alternate calix[4]arene units.[82] Chloromethyl substitution at the *para*-positions of a 1,3-alternate conformer of calix[4]arene provided the basic building block **155**. Reaction of **155** with a bisphenol provided the linking unit **157**, while terminal units **156** were prepared by capping **155** with catechol. Controlled capping and linking of these units provided the 'nano-tube' **158** in 17% yield (**Scheme 43**).

Finally, a triscalix[4]arene has been prepared by linking three *p*-t-butylcalix[4]arene units with two silicon atoms. Reaction of *p*-t-butylcalix[4]arene **108** with 1.2 equivalents of $SiCl_4$ and five equivalents of NaH in THF for 1 hour gave a tridirectional multicavity receptor in 69% yield.[83] (Biscalixarenes linked by non-covalent interactions are described in the final section of this review.)



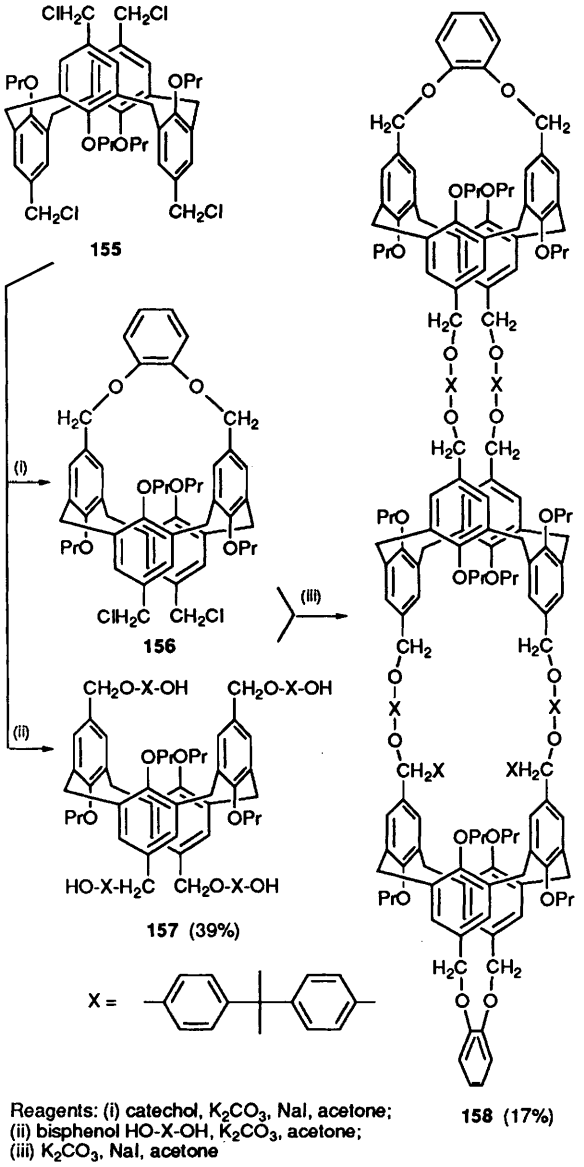
Scheme 41



153

154 (4%)

Scheme 42



155

156

157 (39%)

158 (17%)

Reagents: (i) catechol, K_2CO_3, NaI, acetone; (ii) bisphenol HO-X-OH, K_2CO_3, acetone; (iii) K_2CO_3, NaI, acetone

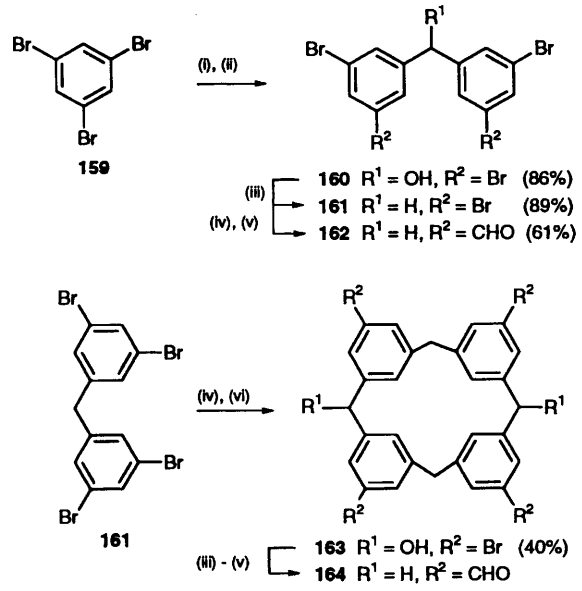
Scheme 43

4 Cyclophanes

Several reviews on the subject of cyclophanes have appeared in the literature recently, dealing with the chemistry of $[1_n]$orthocyclophanes,[84] the synthesis of small cyclophanes,[85] and the intramolecular [2+2] photocycloaddition of vinylarenes to give cyclophanes.[86]

4.1 All carbon cyclophanes

Some new work has been reported in this area this year, including synthesis of metacyclophanes which incorporate crown ether-type functionality.[87] Rajca has described a novel route to [1.1.1.1]meta-cyclophanes, such as **164**, starting from 1,3,5-tribromo-benzene (**Scheme 44**).[88] Mono lithiation of tribromobenzene and condensation with ethyl



159

160 R^1 = OH, R^2 = Br (86%)
161 R^1 = H, R^2 = Br (89%)
162 R^1 = H, R^2 = CHO (61%)

161

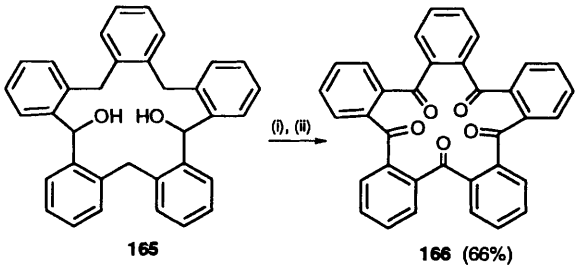
163 R^1 = OH, R^2 = Br (40%)
164 R^1 = H, R^2 = CHO

Reagents: (i) Bu^nLi, Et_2O (ii) HCO_2Me; (iii) red P, I_2, AcOH; (iv) Bu^tLi, THF; (v) PhMeNCHO; (vi) **162**

Scheme 44

formate gave **160** which was transformed, again by partial lithiation, to give **162**. A similar sequence coupled **161** and **162** to give **163** and subsequently **164** after a final lithiation.

Polyoxo[1_n]orthocyclophanes ('ketonands') have been synthesized by exhaustive oxidation of all the methylenes in odd numbered [1_n]orthocyclophanes.[89] Thus, treatment of **165** with pyridinium chlorochromate, followed by further oxidation with ceric ammonium nitrate in hot acetic acid gave ketonand **166** in 66% yield (**Scheme 45**).



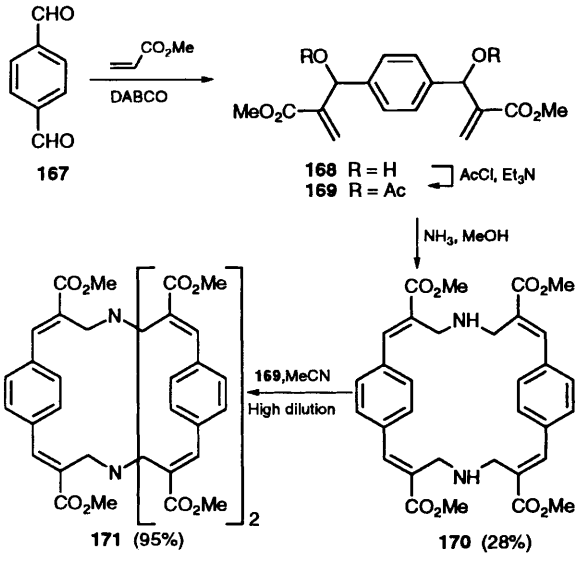
165 **166** (66%)

Reagents: (i) Pyridinium chlorochromate
(ii) Ceric ammonium nitrate, AcOH, 80 °C, 1 day

Scheme 45

4.2 Heteroatom-containing cyclophanes

Two syntheses of cyclophanes incorporating carbamate functionality have been described using the condensation of appropriate diols with diisocyanates.[90,91] Azacyclophanes such as **170** and **171** have been prepared using a Baylis–Hillman reaction (**Scheme 46**).[92] Dialdehyde **167** was reacted with methyl acrylate in the presence of DABCO, or 3-quinuclidinol, for 1–14 days at room temperature, to give **168** which was subsequently acylated. The resulting diacetate **169**, on treatment with ammonia

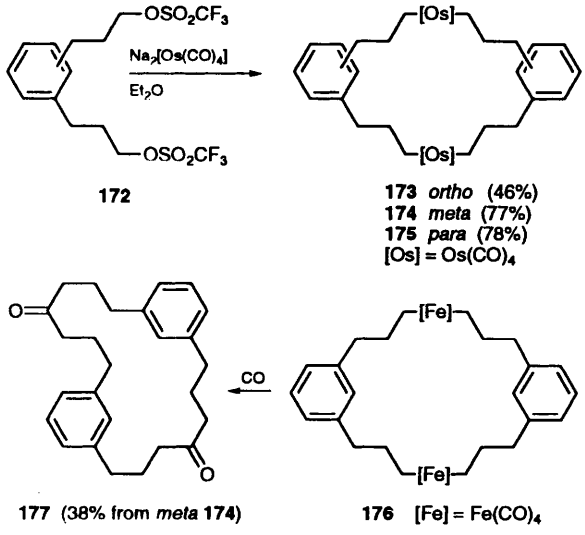


167 **168** R = H, R = Ac **169** **171** (95%) **170** (28%)

Scheme 46

in methanol, gave the cyclophane **170** in 28% yield. Further reaction of **170** with another equivalent of **169** in reluxing acetonitrile (high dilution) led to the macrobicyclic cryptophane **171** in 95% yield. An extensive study on the conformation of this and other cyclophanes was reported.

Novel metallocyclophanes have been reported by Lindner. Thus, reaction of bistriflates **172** with $Na_2[Os(CO)_4]$ gave the *ortho*-, *meta*-, and *para*-diosmacyclophanes **173–175** in reasonable yields (**Scheme 72**). Thermolabile diferracyclophanes, such as **176**, could be obtained in the same way, and reacted with CO to give the corresponding cyclic diketones **177**.[93]



172 **173** *ortho* (46%) **174** *meta* (77%) **175** *para* (78%) [Os] = $Os(CO)_4$

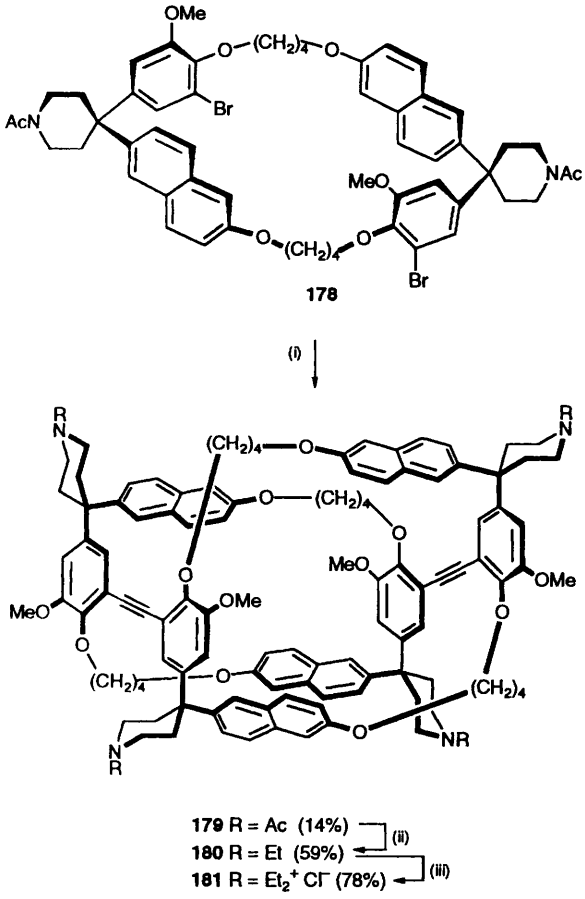
177 (38% from *meta* **174**) **176** [Fe] = $Fe(CO)_4$

Scheme 47

4.3 Cage-type cyclophanes

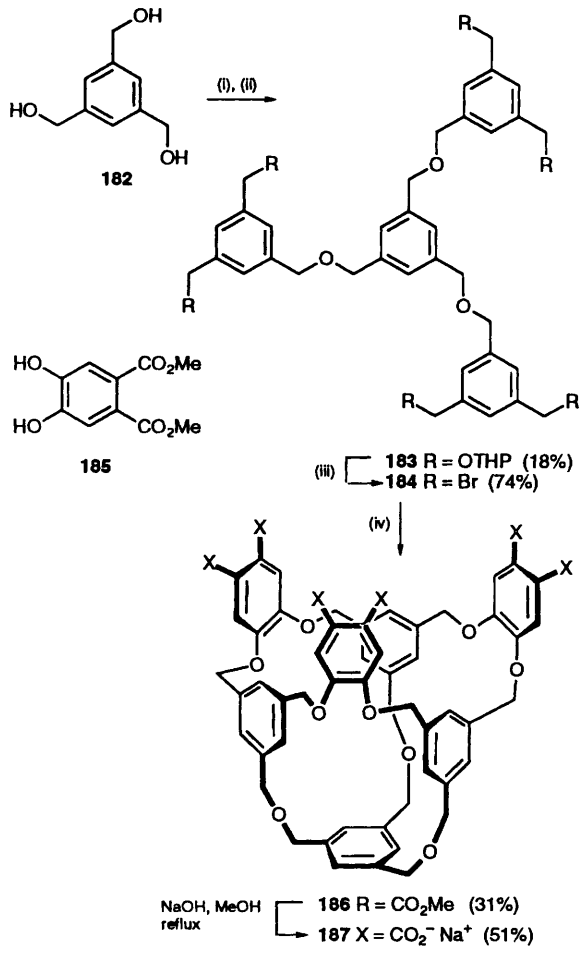
A tricyclic cyclophane able to selectively bind cholesterol in water has been reported by Diederich. The key step was the Pd^0-catalysed Stille coupling of equimolar amounts of bis(tributylstannyl)acetylene and dibromocyclophane **178**, which can be prepared in multigram quantities starting from 2-bromo-6-ethoxynaphthalene (**Scheme 48**).[94] The reaction produced the chiral D_2-symmetrical macrotricycle **179** selectively in 14% yield and none of the possible achiral isomer with C_{2h} symmetry. Reduction of **179** with lithium aluminium hydride, followed by quaternization with ethyl iodide and ion exchange chromatography, afforded the water-soluble receptor **181** (**Scheme 48**).

A basket like macrotricyclic cyclophane **187** has been synthesized via a triple condensation of hexabromide **184** with catechol derivative **185** (**Scheme 49**).[95] Double protection of **182** as the THP ether, followed by reaction with 1,3,5-tris(bromomethyl)benzene gave **183**. The protected alcohols were converted into bromides and the resulting hexabromide **184** was then reacted to give **186** using $CsCO_3$ as base. Subsequent ester hydrolysis gave receptor **187**.



Reagents: (i) $Bu_3SnC{\equiv}CSnBu_3$, $[Pd(PPh_3)_4]$, 2,6-di-t-butyl-*p*-cresol, DMF, 110 °C, pressure bottle, 2 days; (ii) $LiAlH_4$, Et_2O, 20 °C, 12 hr.; (iii) (a) EtI, $CHCl_3$, 20 °C, 4 days, (b) Dowex resin (Cl^-) eluent H_2O/MeOH (1:1)

Scheme 48



Reagents: (i) THP, pyridinium *p*-toluene sulphonate; (ii)1,3,5-tris(bromo-methyl)benzene, NaH, THF–DMF, –2 °C, 20 hr.; (iii) PPh_3, CBr_4; (iv) Cs_2CO_3, **185**, acetone, reflux, high dilution

Scheme 49

5 Cleft receptors and molecular bowls

Among the most interesting host–guest molecules are receptors that have novel structures designed to possess the preorganization required for the recognition of specific guest molecules. These structures often bear only a passing resemblance to those already discussed in this review.

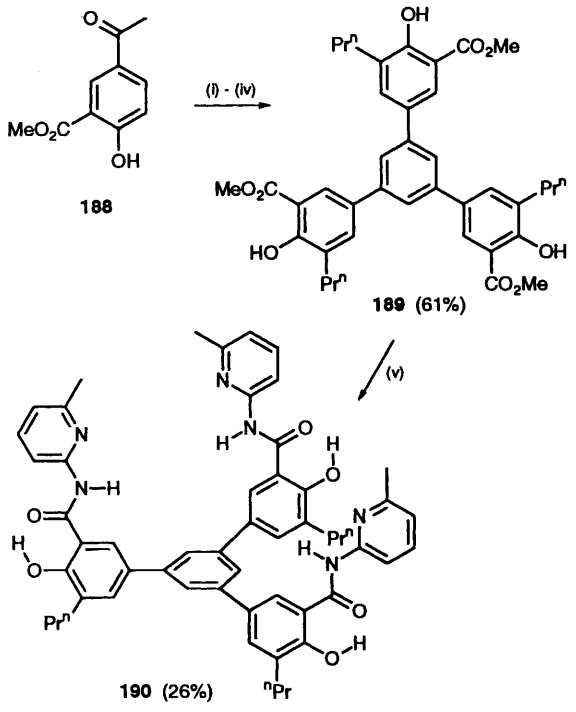
5.1 Cleft receptors

One of the most important concepts in the design of a receptor is the preorganization of binding groups. The synthetically most accessible means is to generate a cleft in which convergent binding sites are constrained by a rigid spacer. The strategy often results in strong and highly selective binding. A good example is the C_3-symmetric cleft **190**, constructed to bind *cis*-1,3,5-cyclohexane tri(carboxylic acid). The desired three point recognition was provided by three amido pyridine units attached, by an adaptation of the Weinreb procedure, to the C_3-symmetric base **189**, which, in turn, was synthesized from 4-acetylmethylsalicylate **188** in four steps (**Scheme 50**).[96]

Rebek has previously demonstrated the usefulness of his rigid receptors and this family has since been extended further by condensation of xanthine derivatives with aromatic dianhydrides, to give cleft receptors that provide a deeper cavity with restricted internal rotation, and are straightforward to derivatize.[97] Nolte has expanded the scope of his molecular clip receptors, by functionalization of the basic clip receptor with two bispyrazole ligands, to give a dicopper(II) pyrazole complex which could selectively oxidize benzylic alcohols.[98]

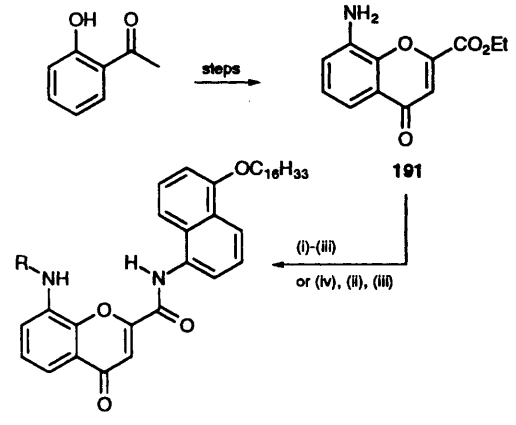
Morán has recently generated a family of receptors that bind *N*-benzyloxyaminoacids, based on the chromenone derivative **191**, which is easily prepared from the nitro derivative of 2-hydroxy-acetophenone. Thus, for example, the phosphoramide **192** and the sulfonamide **193** were each prepared in three steps in reasonable yields (**Scheme 51**).[99,100]

Very similar structures were employed in the generation of lactone receptors that were able to catalyse the nucleophilic addition of pyrrolidine to 2-(5*H*)-furanone.[101] The same group has also



Reagents: (i) $SiCl_4$/EtOH; (ii) $BrCHCH{=}CH_2$, Cs_2CO_3, DMF, acetone, reflux; (iii) N,N-dimethylaniline, reflux; (iv) H_2, Pd/C 10%; (v) 3 eq. Me_3Al, then Me_3Al/2-amino-6-methylpyridine complex, benzene, reflux

Scheme 50

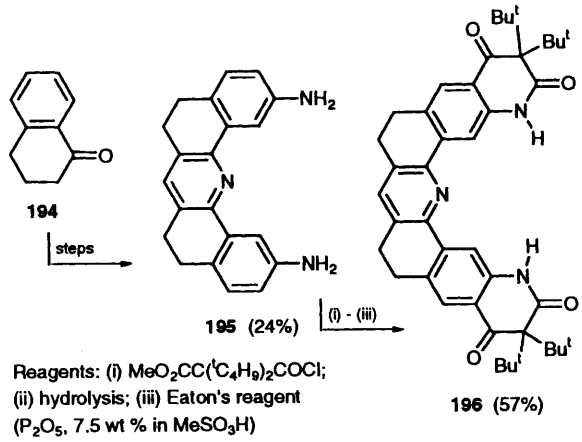


192 R = $(EtO)_2PO$ (77%)
193 R = $H_{11}C_6NHSO_2$ (64%)

Reagents: (i) $(EtO)_2POCl$; (ii) NaOH, EtOH; (iii) 5-hexadecyloxy -1- naphthylamine, CMC; (iv) $H_{11}C_6NHSO_2Cl$, pyridine

Scheme 51

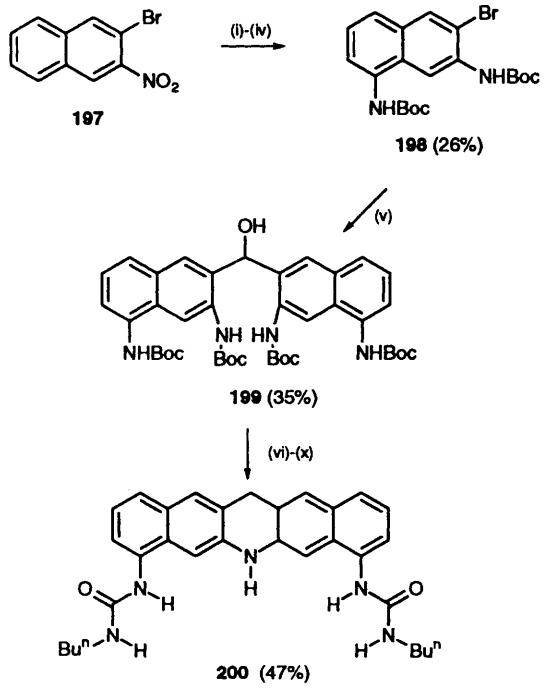
developed a novel receptor for dibutylmalonic acid. α-Tetralone was converted into diamine **195**, which served as the core unit for a series of highly preorganized receptors. The most effective of these was formed by acylation of the amine groups with the chloride of dibutylmalonic acid mono-methylester, hydrolysis, and final treatment with Eaton's reagent (phosphorus pentoxide, 7.5 wt% in methane sulfonic acid) to produce the symmetric bislactam **196** in 57% total yield (**Scheme 52**).[102]



Reagents: (i) $MeO_2CC(^tC_4H_9)_2COCl$; (ii) hydrolysis; (iii) Eaton's reagent (P_2O_5, 7.5 wt % in $MeSO_3H$)

Scheme 52

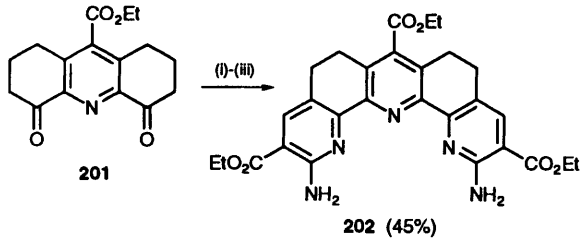
Related structures have been devised by Kelly[103] and showed high affinity for isophthalate and $1,3\text{-}C_6H_4[P(OH)O_2]^-$. The 2,3-substituted naphthalene **197** was reduced, nitrated, and reduced again to give **198**, after protection of the amine groups (**Scheme 53**). Lithiation and reaction with methyl formate gave the bisnaphthyl derivative **199**, which, after oxidation and deprotection, underwent tin tetrachloride mediated ring closure in 93% yield, and led ultimately to the highly preorganized bisurea **200**.



Reagents: (i) H_2, Raney Nickel; (ii) HNO_3, H_2SO_4; (iii) H_2, Raney Nickel; (iv) $(Boc)_2O$; (v) (*a*) 3 eq. MeLi; (*b*) 4 eq. BuLi; (*c*) methyl formate; (vi) PDC; (vii) TMSI; (viii) $SnCl_4$; (ix) BH_3; (x) Bu^nNCO.

Scheme 53

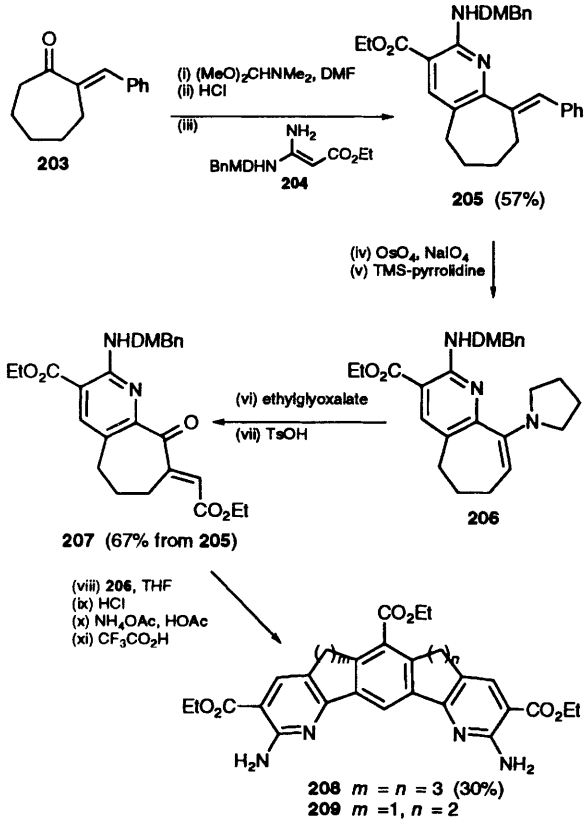
Polycyclic pyridines have also been the basis of a series of receptors developed by Anslyn, and designed to recognize cyclitols and phosphodiesters. For example, diketone **201** was diformylated and condensed with ethyl 2,2-diaminopropenoate to give receptor **202** in 45% yield (**Scheme 54**).[104]



Reagents: (i) $(MeO)_2CHNMe_2$, DMF; (ii) HCl, H_2O; (iii) ethyl 2,2-diaminopropenoate

Scheme 54

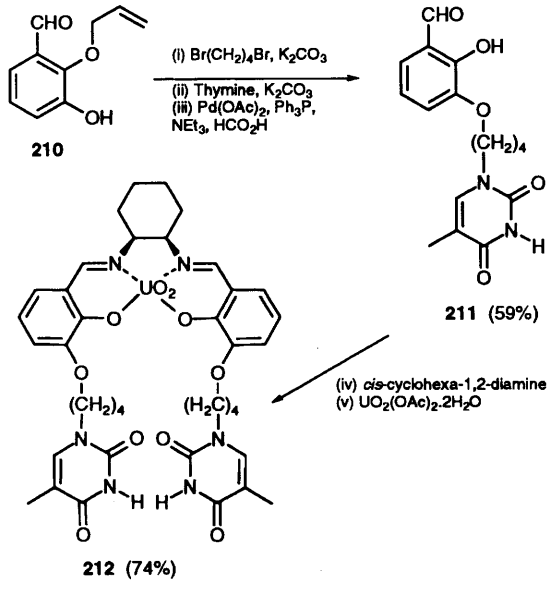
A modified receptor **208** was also synthesized using a lengthier route. Thus, cycloheptanone derivative **203** was formylated and condensed with the 2,2-diaminopropenoate derivative **204**, to give the bicyclic pyridine **205**, in 57% yield. Oxidative cleavage of the alkene and enamine formation, followed by treatment with ethylglyoxalate, gave **207**. Reaction of **207** with a further equivalent of enamine **206** in THF, and cyclization of the central pyridine ring with ammonium acetate in acetic acid gave, after deprotection, the receptor **208** in moderate yield (**Scheme 55**).[104] This linear route



Scheme 55

also allowed the synthesis of a related unsymmetrical cleft **209**.[105]

Reinhoudt has developed metalloreceptors such as **212**[106–108] for the recognition of phosphates. The metalloreceptors were obtained by derivatization of key precursor **210** with various pendant amides, by alkylation of the hydroxy function. Deallylation and reaction with 1,2-diaminocyclohexane or diaminobenzene, and subsequent addition of $UO_2(OAc)_2.2H_2O$, gave the metalloclefts in good yields. In one example a ditopic receptor **212** was constructed by functionalization of **210** with thymine (**Scheme 56**). The molecule showed strong association with adenosine monophosphate in d_6-DMSO.



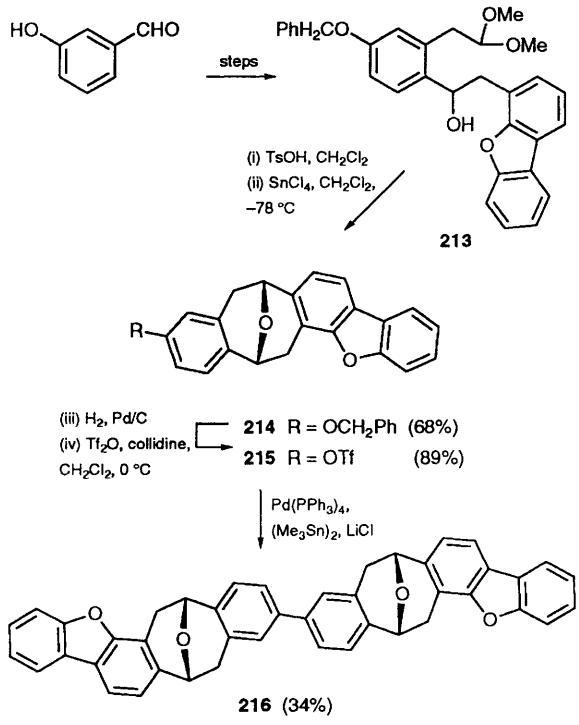
Scheme 56

Molecular tweezers are of interest as mimics of antitumour antibiotics, and Harmata has developed a novel, chiral tweezer based upon Kagan's ether. *m*-Hydroxybenzaldehyde was converted in six steps into the dibenzofuran derivative **213**. Treatment with tosic acid, followed by $SnCl_4$, gave the Kagan ether **214** in 68% yield. Conversion into the triflate ester **215** and homocoupling, using a Stille protocol, gave the biaryl **216** in 34% yield (**Scheme 57**).[109]

5.2 Molecular bowls

Cram has continued his studies of hemicarcerands.[110] Thus, hemicarcerand **218** was prepared by reaction of the tetrol **217** with $TsOCH_2C{\equiv}CCH_2OTs$ in 2–10% yield (**Scheme 58**). Reaction of *cis*-$ClCH_2CH{=}CHCH_2Cl$ with tetrol **217** gave the corresponding hemicarcerand in 25% yield. Trapped guest solvent molecules were not released on reduction of the unsaturated bonds around the equator.[111]

Still has continued to synthesize an impressive range of receptors for the recognition of peptide

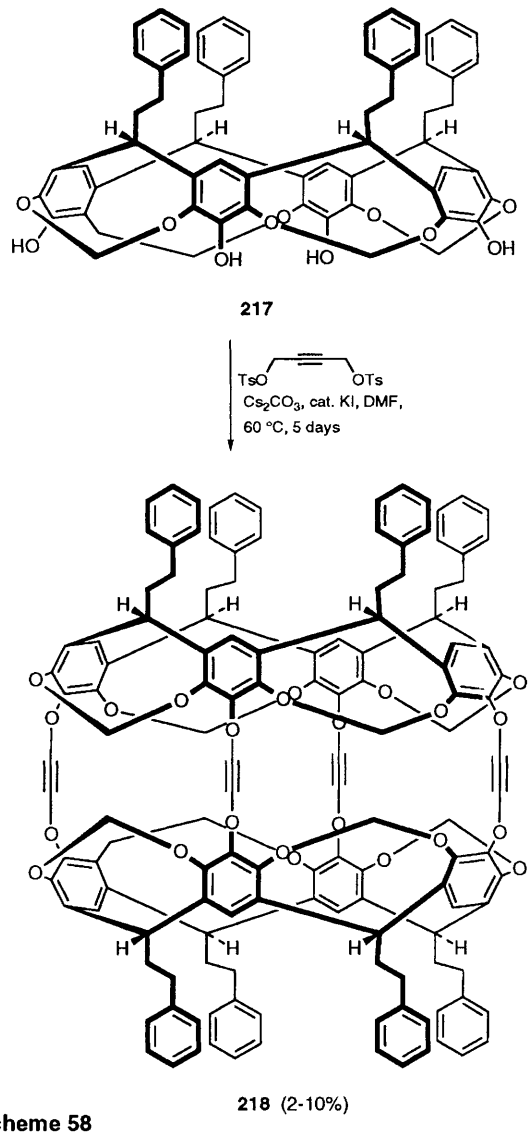


Scheme 57

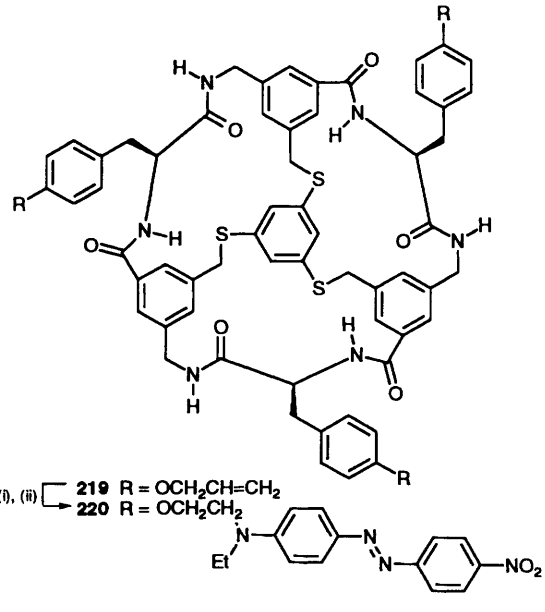
sequences. The previously reported receptor **219** has now been functionalized with a dye molecule (**Scheme 59**) and the resulting coloured host molecule **220** was introduced to a binary encoded combinatorial library of ~50000 tripeptides. The most tightly bound tripeptide beads became brightly coloured, allowing easy identification and thus provided an extremely efficient assay for the binding characteristics of such receptors, and, in this case, uncovered unexpectedly selectivity for binding certain peptide sequences.[112]

This technique has also been employed in the elucidation of the peptide binding preferences of a new receptor **224**. The molecule is closely related to receptor **220**, differing by the introduction of naphthyl groups in place of benzyl aromatic spacers, around the rim of the receptor, thus widening the binding site, and again providing a highly selective receptor for tripeptides, particularly those with an internal L-Pro unit. The synthesis began with a Friedel–Crafts cyclization of the Stobbe derived half-ester **221** to give the naphthyl unit which was elaborated to **222** (**Scheme 60**). Macrolactamization with Pr^i_2NEt gave **223** in 50% yield, which was then tagged with a dye molecule to give **224**.[113]

Related C_3-symmetric 'cup-shaped' receptors have also been prepared by much shorter routes than those described above. Coupling three equivalents of pentafluorophenyl dimethyl trimesate **226** to one equivalent to 1,3,5-tri(aminomethyl)-benzene **225** gave **227** in 78% yield. After conversion into the activated ester, **228**, three-fold coupling with (3*R*, 4*R*)-3,4-diaminopyrrolidine **229** (linked to the Dye Disperse Red by a succinyl

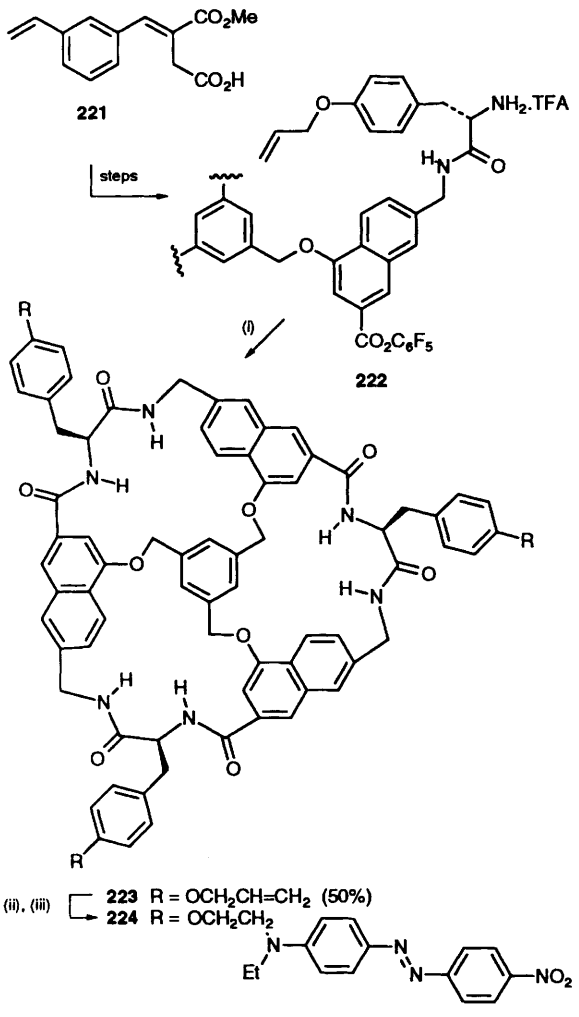


Scheme 58

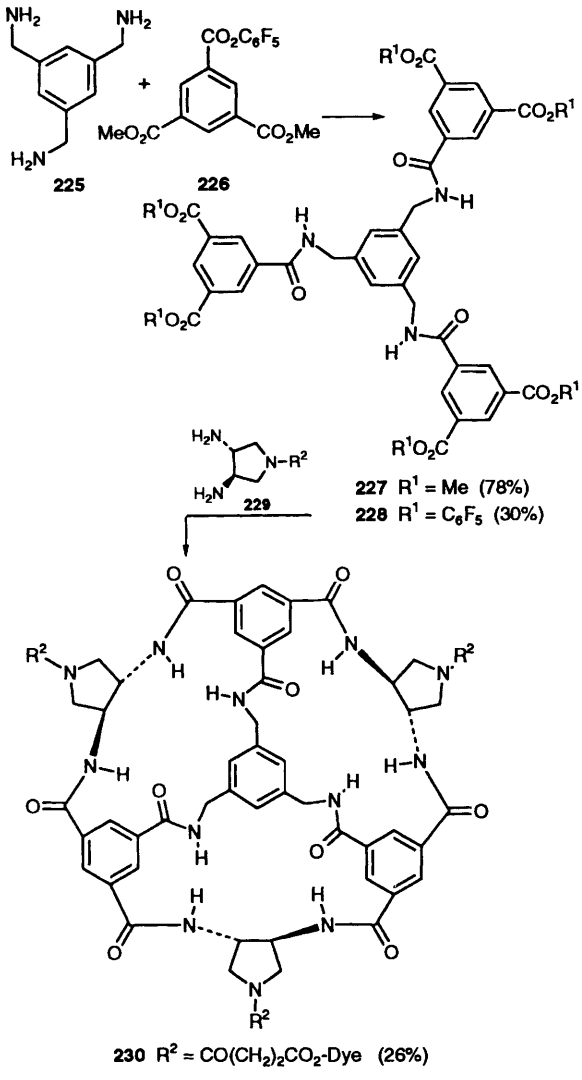


Reagents: (i) $Pd(Ph_3P)_4$, dimedone; (ii) Bu_4NF, RMs

Scheme 59



Scheme 60

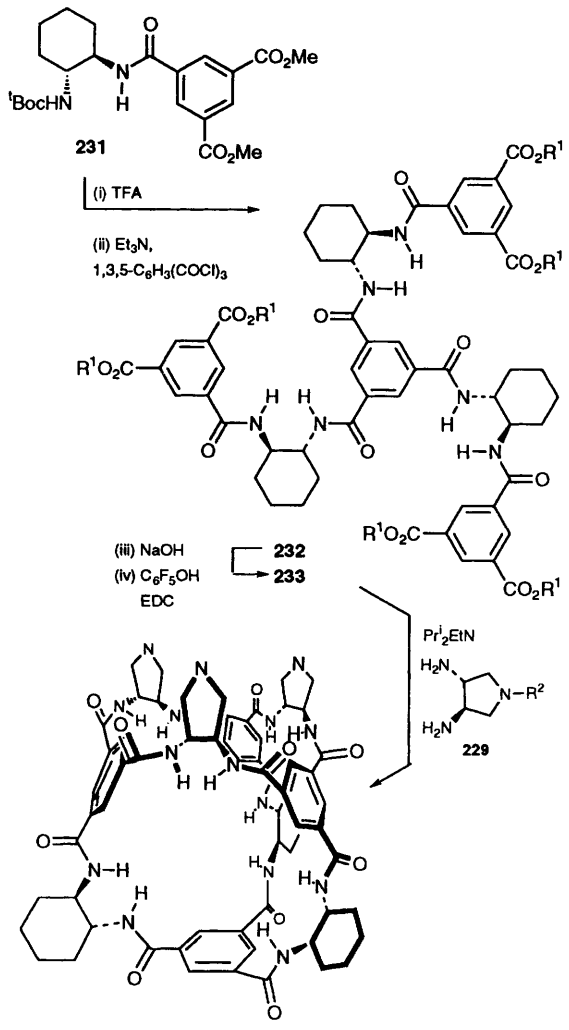


Scheme 61

spacer) gave the receptor **230** in 26% yield (**Scheme 61**).[114]

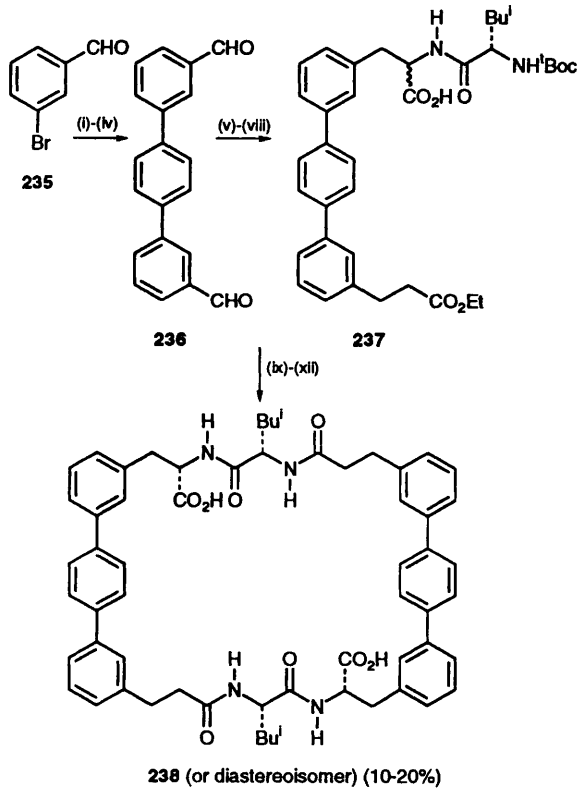
Still has extended his work on A_4B_6 macrotricycles, previously prepared in a remarkable one-step synthesis by reaction of the tris(acid chloride) of trimesic acid (A) with diaminocyclohexane (B). Similar reaction of the tris(acid chloride) or trimesic acid with a series of diamines gave a number of novel receptors structures with subtle variations in their binding selectivities.[115] A structurally distinct A_4B_6 system — a tetrahedral receptor — has now been synthesized, using a strategy very similar to that in **Scheme 61**. Trimesic acid dimethyl ester was coupled (DCC) with monoprotected 1,2-diaminocyclohexane to give **231**. Three equivalents of deprotected **231** were then coupled with one equivalent of trimesic acid tris(acid chloride) yielding **232** (**Scheme 62**). Conversion into the hexapentafluorophenyl ester **233** and then treatment with three equivalents of the diamine **229** gave the desired dye-tagged, macrotricyclization product **234** in 51% yield. This new receptor also showed selectivity in the binding of certain tripeptides.[116] Still has also used the combinatorial technique to generate a library of $\sim 10^4$ receptors based on a peptidosteroid structure. This library could then be assayed for binding activity with arbitrarily selected dye-tagged substrates.[117]

Chamberlin has also synthesized novel macrocycles designed to bind to peptides, and the chiral C_2 macrolactams **238** did bind cyclic dipeptides enantioselectivity (**Scheme 63**). Starting from bromo aldehyde **235**, the terphenyl **236** could be prepared on large-scale via an aryl lithium addition to benzoquinone. Terphenyl **236** was further elaborated using Horner–Emmons chemistry and hydrogenation of the resulting olefins, to give the precursor **237** as a 1:1 mixture of (*S*,*S*)- and (*R*,*S*)-diastereoisomers. The first olefination reaction of **236** with phosphonate **239** gave a greater than statistical yield (75%) of mono-alkene product. The diastereoisomers of **237** could be separated by column chromatography, after manipulation of the protecting groups, and were separately subjected to



234 $R^2 = CO(CH_2)_2CO_2$-Dye (51%)

Scheme 62



238 (or diastereoisomer) (10-20%)

Reagents: (i) MeOH, H^+; (ii) Bu^nLi, THF, –78 °C; (iii) 1,4 benzoquinone; (iv) 47% HI, THF, 0 °C; (v) NaOMe, THF, Boc-Val-NHCH(CO_2Me)$PO(OEt)_2$ (**239**); (vi) LiOH, MeOH, H_2O; (vii) $EtO_2CCH_2PO(OEt)_2$, DBU, CH_2Cl_2; (viii) H_2, 5% Rh/C, 2 atm.; (ix) Me_2NH, Et_3N, HOBT, EDC; (x) TFA, CH_2Cl_2, flash chromatography; (xi) LiOH, MeOH; (xii) BOP, Pr^i_2EtN, THF, 0 °C, 1 mmol concentration

Scheme 63

macrolactamization which was successfully carried out using the BOP coupling reagent in yields of 10–20%.[118]

A crown ether based peptide receptor **245** has also been synthesized, using an adapted Stille procedure to bring about 4,4′-biaryl formation in the ring-closing step. 1,10-Diaza-18-crown-6 **243** was first monoalkylated with an aryl stannane **240**. A second alkylation with bromide **242**, generated from *p*-bromobenzyl alcohol **241** in five steps, gave the cyclization precursor **244**. Macrocyclization using $Pd(PPh_3)_4$ and potassium carbonate in DMF gave **245** in 15% yield (**Scheme 64**).[119]

6 Self-assembling receptors

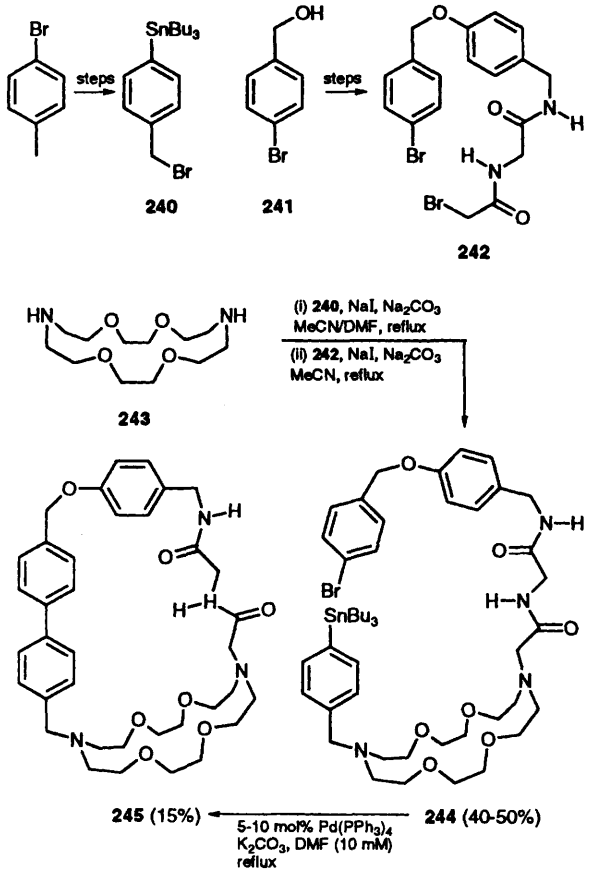
Complex assemblies can be achieved by employing non-covalent interactions. This aspect of molecular design is called self-assembly and can significantly reduce the number of synthetic steps required to develop a receptor.

The hydrogen bond has been used by Gokel for the preparation of molecular boxes and results of this work are described in detail.[120] Complementary adenine and thymine nucleotide bases were attached by flexible spacers to 1,10-diaza-18-crown-6. An induced fit ternary complex **246** was formed between these fragments with suitable diammonium salts as guests (**Scheme 65**).

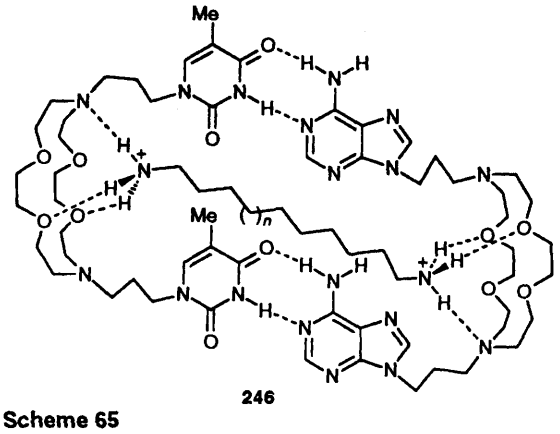
Hydrogen bonding interactions between carboxylic acid and pyridyl groups have been used to assemble a molecular capsule **250** from two calix[4]arenes. The two calixarenes, **248** and **249**, were both prepared from the formyl calix[4]arene **247** (**Scheme 66**) and formed a dimeric structure involving four hydrogen bonds.[121]

A biscalix[4]arene has also been assembled using metal co-ordination. Calix[4]arene **251** was bisfunctionalized at distal positions of the upper rim, using established procedures. Complexation of **252** with copper(II) gave the dimerized complex **253** in 50% yield (**Scheme 67**).[122]

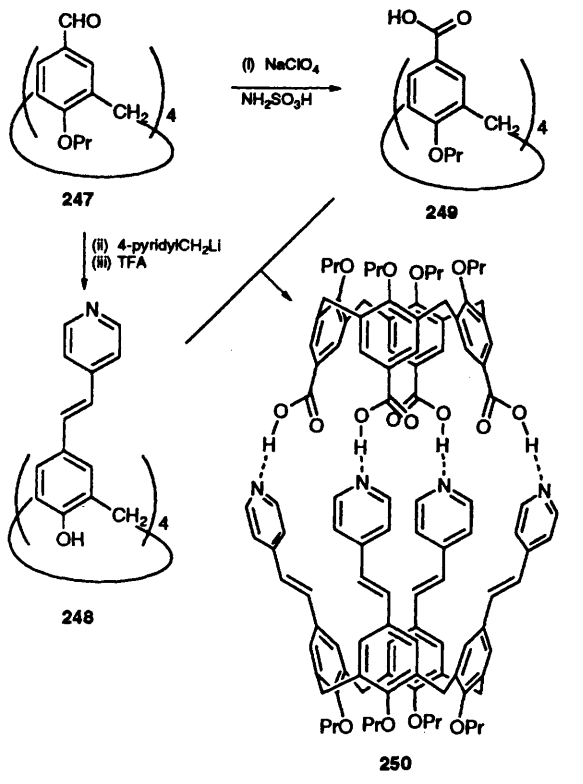
Hunter has exploited the co-ordination of pyridine ligands perpendicular to zinc porphyrins to generate a dimeric receptor **256**. The cavity defined by the dimer has inwardly directed hydrogen bond recognition sites which were used to bind terephthallic acid derivatives. Incorporation of a



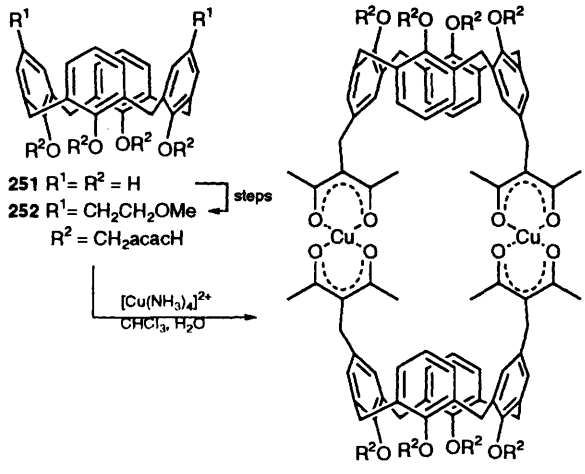
Scheme 64



Scheme 65



Scheme 66

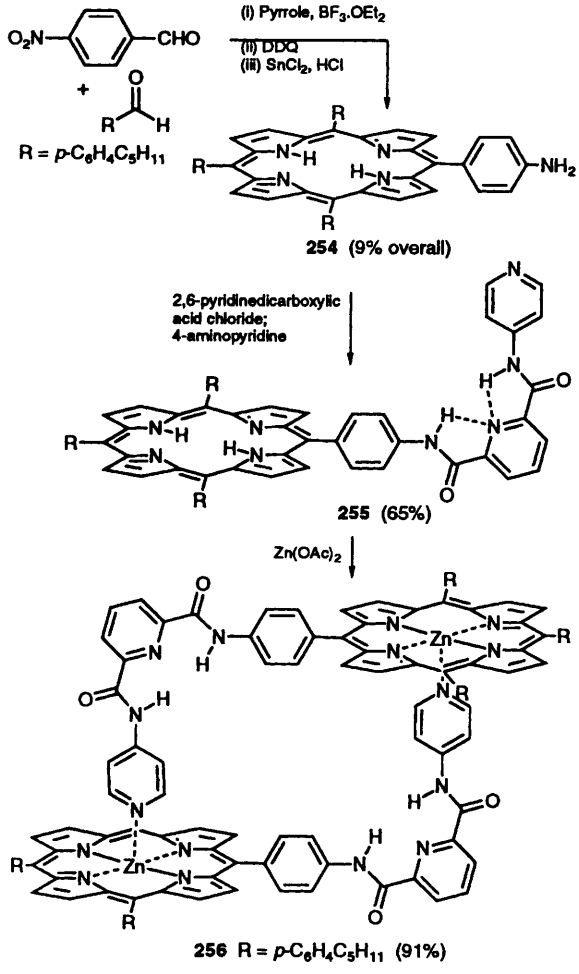


Scheme 67

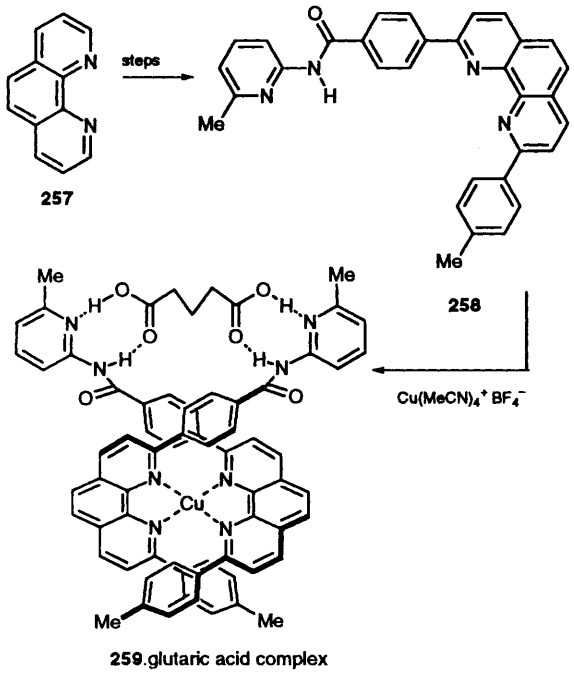
2,6-pyridinedicarboxylamide moiety into monomeric unit **255** orientates the covalently linked pyridine and porphyrin at the approximately 90° angle necessary for dimerization, using internal hydrogen bonds to stabilize such a conformation. Reaction of the porphyrin derived amine **254** with pyridine-2,6-dicarbonyl chloride, and 4-aminopyridine, gave **255** in 65% yield (**Scheme 68**). Complexation with Zn^{II} gave **256** in 91% yield which exists as a self-assembled dimer at concentrations 10^{-7}–10^{-2} M, at room temperature, in chlorinated organic solvents.[123]

Hamilton has coupled two units of simple phenanthroline derivative **258** by coordination with Cu^{I}. The resulting distorted tetrahedral bisphenanthroline complex **259** is chiral, and places the acylaminopyridine moieties in the appropriate orientation for binding dicarboxylic acids. The key subunit **258** was prepared by double arylation of 1,10-phenanthroline **257** (**Scheme 69**).[124]

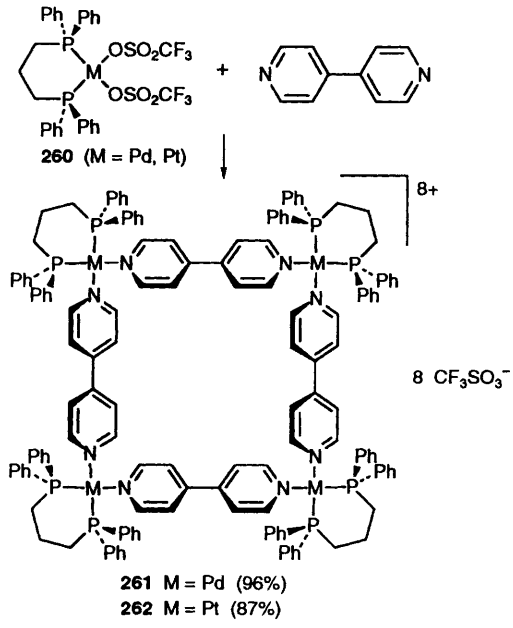
The structural role of metals has been extended even further, allowing preparation of macrocyclic receptors with a minimal amount of organic synthesis.[125] For example, tetranuclear cationic molecular boxes have been assembled from 4,4′-bipyridine and square-planar platinum(II) and palladium(II) complexes **260**. The assembly process



Scheme 68



Scheme 69



Scheme 70

gave **261** and **262**, which were soluble in most organic solvents, in excellent yields (**Scheme 70**).

7 References

1 J.D. Kilburn and H.K. Patel, *Contemp. Org. Synth.*, 1994, **1**, 259.
2 H. An, J.S. Bradshaw, R.M. Izatt, and Z. Yan, *Chem. Rev.*, 1994, **94**, 939.
3 F.C.J.M. van Veggel, W. Verboom, and D.N. Reinhoudt, *Chem. Rev.*, 1994, **94**, 279.
4 N.S. Mani and P.P. Kanakamma, *Tetrahedron Lett.*, 1994, **35**, 3629.
5 H.W. Gibson, M.C. Bheda, P. Engen, Y.X. Shen, J. Sze, H. Zhang, M.D. Gibson, Y. Delaviz, S.-H. Lee, S. Liu, L. Wang, D. Nagvekar, J. Rancourt, and L.T. Taylor, *J. Org. Chem.*, 1994, **59**, 2186.
6 Y. Habata, F. Fujishiro, and S. Akabori, *J. Chem. Soc., Chem. Commun.*, 1994, 2217.
7 S. Inokuma, T. Yasuda, S. Araki, S. Sakai, and J. Nishimura, *Chem. Lett.*, 1994, 201.
8 R.M. Musau and A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2881.
9 Y.Q. Li, T. Thiemann, T. Sawada, and M. Tashiro, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2323.
10 A.R. Ramesha and S. Chandrasekaran, *J. Org. Chem.*, 1994, **59**, 1354.
11 T.-Y. Lin, W.-H. Lin, W.D. Clark, R.J. Lagow, S.B. Larson, S.H. Simonsen, V.M. Lynch, J.S. Brodbelt, S.D. Maleknia, and C.-C. Liou, *J. Am. Chem. Soc.*, 1994, **116**, 5172.
12 Y. Takai, Y. Okumura, T. Tanaka, M. Sawada, S. Takahashi, M. Shiro, M. Kawamura, and T. Uchiyama, *J. Org. Chem.*, 1994, **59**, 2967.
13 C. Bazzicalupi, A. Bencini, V. Fusi, M. Micheloni, P. Paoletti, and B. Valtancoli, *J. Org. Chem.*, 1994, **59**, 7508.
14 C. Bazziclupi, A. Bencini, V. Fusi, M. Micheloni, and B. Valtancoli, *J. Chem. Soc., Chem. Commun.*, 1994, 1119.

15 V. Panetta-Le Mer, J.J. Yaouanc, and H. Handel, *Tetrahedron Lett.*, 1994, **35**, 2337.
16 K.W. Aston, S.L. Henke, A.S. Modak, D.P. Riley, K.R. Sample, R.H. Weiss, and W.L. Neumann, *Tetrahedron Lett.*, 1994, **35**, 3687.
17 P.J. Lennon, H. Rahman, K.W. Aston, S.L. Henke, and D.P. Riley, *Tetrahedron Lett.*, 1994, **35**, 853.
18 H. Brunner and H. Schiesling, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 125.
19 E. Graf, M.W. Hosseini, and R. Ruppert, *Tetrahedron Lett.*, 1994, **35**, 7779.
20 L. Echegoyen, R.C. Lawson, C. Lopez, J. de Mendoza, Y. Hafez, and T. Torres, *J. Org. Chem.*, 1994, **59**, 3814.
21 M.I. Burguete, B. Esuder, S.V. Luis, J.F. Miravet, and E. Garcia-Espana, *Tetrahedron Lett.*, 1994, **35**, 9075.
22 A.-M. Caminade and J.P. Majoral, *Chem. Rev.*, 1994, **94**, 1183.
23 N. Launay, F. Denat, A.-M. Caminade, J.-P. Majoral, and J. Dubac, *Bull. Soc. Chim. Fr.*, 1994, **131**, 758.
24 X. Yang, C.B. Knobler, Z. Zheng, and M.F. Hawthorne, *J. Am. Chem. Soc.*, 1994, **116**, 7142.
25 H. Xianming, R.M. Kellogg, and F. van Bolhuis, *J. Chem. Soc., Perkin Trans. I*, 1994, 707.
26 J.J.H. Edema, J. Buter, and R.M. Kellogg, *Tetrahedron*, 1994, **50**, 2095.
27 N. Matsumura, R. Hirase, and H. Inoue, *Tetrahedron Lett.*, 1994, **35**, 899.
28 J.M. Desper and S.H. Gellman, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 319.
29 B. Cathala, L. Cazaux, C. Pricard, and P. Tisnès, *Tetrahedron Lett.*, 1994, **35**, 1863.
30 M. Inouye, Y. Noguchi, and K. Isagawa, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1163.
31 S.S. Chana and R.C. Hider, *Tetrahedron Lett.*, 1994, **36**, 9455.
32 R.J. Geue, A. Höhn, S.F. Ralph, A.M. Sargeson, and A.C. Willis, *J. Chem. Soc., Chem. Commun.*, 1994, 1513.
33 K. Worm, F.P. Schmidtchen, A. Schier, A. Schäfer, and M. Hesse, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 327.
34 D.E. Otten and A. Kaufmann, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1832.
35 A.H. van Oijen, N.P.M. Huck, J.A.W. Kruijtzer, C. Erkelens, J.H. van Boom, and R.M.J. Liskamp, *J. Org. Chem.*, 1994, **59**, 2399.
36 J. Mitjaville, A.-M. Caminade, and J.-P. Majoral, *J. Chem. Soc., Chem. Commun.*, 1994, 2161.
37 J. Mitjaville, A.-M. Caminade, and J.-P. Majoral, *J. Am. Chem. Soc.*, 1994, **116**, 5007.
38 K.E. Krakowiak, J.S. Bradshaw, C. Zhu, J.K. Hathaway, N.K. Dalley, and R.M. Izatt, *J. Org. Chem.*, 1994, **59**, 4082.
39 G. Ferguson, J.F. Gallagher, L. Giunta, P. Neri, S. Pappalardo, and M. Parisi, *J. Org. Chem.*, 1994, **59**, 42.
40 J. Scheerder, M. Fochi, F.J. Engbersen, and D.N. Reinhoudt, *J. Org. Chem.*, 1994, **59**, 7815.
41 R. Grigg, J.M. Holmes, S.K. Jones, and W.D.J.A. Norbert, *J. Chem. Soc., Chem. Commun.*, 1994, 185.
42 A. Marra, M.-C. Scherrmann, A. Dondoni, A. Casnati, P. Minari, and R. Ungaro, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2479.
43 K.N. Koh, T. Imada, T. Nagasaki, and S. Shinkai, *Tetrahedron Lett.*, 1994, **35**, 4157.
44 M. McCarrick, S.J. Harris, and D. Diamond, *J. Mater. Chem.*, 1994, **4**, 217.
45 H. Yamamoto and S. Shinkai, *Chem. Lett.*, 1994, 1115.
46 H. Yamamoto, T. Sakaki, and S. Shinkai, *Chem. Lett.*, 1994, 469.
47 S. Wenger, Z. Asfari, and J. Vicens, *Tetrahedron Lett.*, 1994, **35**, 8369.
48 W.I.I. Bakker, M. Haas, C. Khoo-Beattie, R. Ostaszewski, S.M. Franken, H.J. den Hertog, Jr., W. Verboon, D. de Zeeuw, S. Harkema, and D.N. Reinhoudt, *J. Am. Chem. Soc.*, 1994, **116**, 123.
49 W.I.I. Bakker, M. Haas, H.J. den Hertog, Jr., W. Verboom, D. de Zeeuw, A.P. Bruins, and D.N. Reinhoudt, *J. Org. Chem.*, 1994, **59**, 972.
50 T. Nagasaki, H. Fujishima, and S. Shinkai, *Chem. Lett.*, 1994, 989.
51 M. Yeh, F. Tang, S. Chen, W. Liu, and L. Lin, *J. Org. Chem.*, 1994, **59**, 754.
52 I. Alam, S.K. Sharma, and C.D. Gutsche, *J. Org. Chem.*, 1994, **59**, 3716.
53 S.K. Sharma and C.D. Gutsche, *J. Org. Chem.*, 1994, **59**, 6030.
54 S.K. Sharma and C.D. Gutsche, *Tetrahedron*, 1994, **50**, 4087.
55 A.N. Khomich, E.A. Shokova, and V.V. Kovalev, *Synlett*, 1994, 1027.
56 C.A. Gleave and I.O. Sutherland, *J. Chem. Soc., Chem. Commun.*, 1994, 1873.
57 D.M. Rudkevich, W. Verboom, and D.N. Reinhoudt, *J. Org. Chem.*, 1994, **59**, 3683.
58 G. Sartori, R. Maggi, F. Bigi, A. Arduini, A. Pastorio, and C. Porta, *J. Chem. Soc., Perkin. Trans. 1*, 1994, 1657.
59 C. Grüttner, V. Böhmer, W. Vogt, I. Thondorf, S.E. Biali, and F. Grynszpan, *Tetrahedron Lett.*, 1994, **35**, 6267.
60 O.N. Falana, E. Al-Farhan, P.M. Keehn, and R. Stevenson, *Tetrahedron Lett.*, 1994, **35**, 65.
61 B. Botta, M.C. Di Giovanni, G. Delle Monache, M.C. De Rosa, E. Gacs-Baitz, M. Botta, F. Corelli, A. Tafi, A. Santini, E. Benedetti, C. Pedone, and D. Misiti, *J. Org. Chem.*, 1994, **59**, 1532.
62 P. Neri, G.M.L. Consoli, F. Cunsolo, and M. Piatelli, *Tetrahedron Lett.*, 1994, **35**, 2795.
63 H. Otsuka, K. Araki, and S. Shinkai, *J. Org. Chem.*, 1994, **59**, 1542.
64 R.G. Janssen, W. Verboom, J.P.M. van Duynhoven, E.J.J. van Velzen, and D.N. Reinhoudt, *Tetrahedron Lett.*, 1994, **35**, 6555.
65 K. Araki, K. Akao, H. Otsuka, K. Nakashima, F. Inokuchi, and S. Shinkai, *Chem. Lett.*, 1994, 1251.
66 M. Takeshita, S. Nishio, and S. Shinkai, *J. Org. Chem.*, 1994, **59**, 4032.
67 Y. Kubo, S. Maeda, M. Nakamura, and S. Tokita, *J. Chem. Soc., Chem. Commun.*, 1994, 1725.
68 J.-B. Regnouf de Vains, S. Pellet-Rostaing, and R. Lamartine, *Tetrahedron Lett.*, 1994, **35**, 8147.
69 F. Grynszpan and S.E. Biali, *J. Chem. Soc., Chem. Commun.*, 1994, 2545.
70 P. Neri, E. Battocolo, F. Cunsolo, C. Geraci, and M. Piatelli, *J. Org. Chem.*, 1994, **59**, 3880.
71 F. Cunsolo, M. Piattelli, and P. Neri, *J. Chem. Soc., Chem. Commun.*, 1994, 1917.
72 H.M. Chawla and K. Srinivas, *Tetrahedron Lett.*, 1994, **35**, 2925.
73 H.M. Chawla and K. Srinivas, *J. Chem. Soc., Chem. Commun.*, 1994, 2593.
74 Y. Shi and Z. Zhang, *J. Chem. Soc., Chem. Commun.*, 1994, 375.
75 M.T. Blanda and K.E. Griswold, *J. Org. Chem.*, 1994, **59**, 4313.
76 G. Urich and R. Ziessel, *Tetrahedron Lett.*, 1994, **35**, 6299.

77 W. Wasikiewicz, G. Rokicki, J. Kielkiewicz, and V. Böhmer, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 214.
78 P. Timmerman, W. Verboom, F.C.J.M. van Veggel, W.P. van Hoorn, and D.N. Reinhoudt, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1292.
79 P. Timmerman, W. Verboom, F.C.J.M. van Veggel, J.P.M. van Duynhoven, and D.N. Reinhoudt, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2345.
80 D.M. Rudkevich, W. Verboom, and D.N. Reinhoudt, *Tetrahedron Lett.*, 1994, **35**, 7131.
81 A. Ikeda and S. Shinkai, *J. Am. Chem. Soc.*, 1994, **116**, 3102.
82 A. Ikeda and S. Shinkai, *J. Chem. Soc., Chem. Commun.*, 1994, 2375.
83 X. Delaigue, M.W. Hossieni, R. Graff, J.-P. Kintzinger, and J. Raya, *Tetrahedron Lett.*, 1994, **35**, 1711.
84 W.Y. Lee, *SynLett*, 1994, 765.
85 V.V. Kane, W.H. De Wolf, and F. Bickelhaupt, *Tetrahedron*, 1994, **50**, 4575.
86 J. Nishimura, Y. Okada, S. Inokuma, Y. Nakamura, and S.R. Gao, *SynLett*, 1994, 884.
87 Y. Okada, K. Hoshina, J. Aida, and J. Nishimura, *SynLett*, 1994, 786.
88 A. Rajca, R. Padmakumar, D.J. Smithhisler, S.R. Desai, C.R. Ross, II, and J. Stezowski, *J. Org. Chem.*, 1994, **59**, 7701.
89 W.Y. Lee, C.H. Park, H.-J. Kim, and S. Kim, *J. Org. Chem.*, 1994, **59**, 878.
90 S. Abramson, E. Ashkenazi, I. Goldberg, M. Greenwald, H. Jatzke, M. Vardi, S. Weinman, and B. Fuchs, *J. Chem. Soc., Chem. Commun.*, 1994, 1611.
91 S. Irie, M. Yamamoto, I. Iida, T. Nishio, K. Kishikawa, S. Kohmoto, and K. Yamada, *J. Org. Chem.*, 1994, **59**, 935.
92 P. Bauchat, N. Le Bras, L. Rigal, and A. Foucaud, *Tetrahedron*, 1994, **50**, 7815.
93 E. Lindner, W. Wassing, R. Fawzi, and M. Steimann, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 321.
94 B.R. Peterson and F. Diederich, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1625.
95 R. Méric, J.-M. Lehn, and J.-P. Vigneron, *Bull. Soc. Chim. Fr.*, 1994, **131**, 579.
96 P. Ballester, A. Costa, P.M. Deyà, J.F. González, M.C. Rotger, and G. Deslongchamps, *Tetrahedron Lett.*, 1994, **35**, 3813.
97 K.D. Shimizu, T.M. Dewey, and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1994, **116**, 5145.
98 C.F. Martens, R.J.M. Klein Gebbink, and R.J.M. Nolte, *J. Am. Chem. Soc.*, 1994, **116**, 5667.
99 C. Raposo, M. Martín, M.L. Mussons, M. Crego, J. Anaya, Ma.C. Caballero, and J.R. Morán, *J. Chem. Soc., Perkin. Trans. 1*, 1994, 2113.
100 M. Crego, A. Partearroyo, C. Raposo, M.L. Mussons, J.L. López, V. Alcázar, and J.R. Morán, *Tetrahedron Lett.*, 1994, **35**, 1435.
101 C. Raposo, M. Almaraz, M. Crego, M.L. Mussons, N. Pérez, M.C. Caballero, J.R. Morán, *Tetrahedron Lett.*, 1994, **35**, 7065.
102 M.L. Mussons, C. Raposo, M. Crego, J. Anaya, M.C. Caballero, J.R. Morán, *Tetrahedron Lett.*, 1994, **35**, 7061.
103 T.R. Kelly and M.H. Kim, *J. Am. Chem. Soc.*, 1994, **116**, 7072.
104 C.-Y. Huang, L.A. Cabell, and E.V. Anslyn, *J. Am. Chem. Soc.*, 1994, **116**, 2778.
105 F. Chu, L.S. Flatt, and E.V. Anslyn, *J. Am. Chem. Soc.*, 1994, **116**, 4194.
106 D.M. Rudkevich, W. Verboom, Z. Brzozka, M.J. Palys, W.P.R. Stauthamer, G.J. van Hummel, S.M. Franken, S. Karkema, J.F.J. Engbersen, and D.N. Reinhoudt, *J. Am. Chem. Soc.*, 1994, **116**, 4341.
107 D.M. Rudkevich, Z. Brzozka, M. Palys, H.C. Visser, W. Verboom, and D.N. Reinhoudt, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 467.
108 S.M. Lacy, D.M. Rudkevich, W. Verboom, and D.N. Reinhoudt, *Tetrahedron Lett.*, 1994, **35**, 5953.
109 M. Harmata, C.L. Barnes, S. Rao Karra, and S. Elahmad, *J. Am. Chem. Soc.*, 1994, **116**, 8392.
110 T.A. Robbins, C.B. Knobler, D.R. Bellew, and D.J. Cram, *J. Am. Chem. Soc.*, 1994, **116**, 111.
111 C.N. Eid, Jr., C.B. Knobler, D.A. Gronbeck, and D.J. Cram, *J. Am. Chem. Soc.*, 1994, **116**, 8506.
112 A. Borchardt and W.C. Still, *J. Am. Chem. Soc.*, 1994, **116**, 373.
113 A. Borchardt and W.C. Still, *J. Am. Chem. Soc.*, 1994, **116**, 7467.
114 S.S. Yoon and W.C. Still, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2458.
115 W.C. Still and S.S. Yoon, *Tetrahedron Lett.*, 1994, **35**, 2117.
116 W.C. Still and S.S. Yoon, *Tetrahedron Lett.*, 1994, **35**, 8557.
117 R. Boyce, G. Li, H.P. Nestler, T. Suenaga, and W.C. Still, *J. Am. Chem. Soc.*, 1994, **116**, 7955.
118 M.F. Cristofaro and A.R. Chamberlain, *J. Am. Chem. Soc.*, 1994, **116**, 5089.
119 H.K. Patel, J.D. Kilburn, G.J. Langley, P.D. Edwards, T. Mitchell, and R. Southgate, *Tetrahedron Lett.*, 1994, **35**, 481.
120 O.F. Schall and G.W. Gokel, *J. Am. Chem. Soc.*, 1994, **116**, 6089.
121 K. Koh, K. Araki, and S. Shinkai, *Tetrahedron Lett.*, 1994, **35**, 8255.
122 K. Fulimoto and S. Shinkai, *Tetrahedron Lett.*, 1994, **35**, 2915.
123 C.A. Hunter and L.D. Sarson, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2313.
124 M.S. Goodman, J. Weiss, and A.D. Hamilton, *Tetrahedron Lett.*, 1994, **35**, 8943.
125 P.J. Stang and D.H. Cao, *J. Am. Chem. Soc.*, 1994, **116**, 4981.