Syntheses of novel types of calix[6]bis-crowns and related compounds

Yuanyin Chen* and Haibing Li

Department of Chemistry, Wuhan University, Wuhan 430072, P. R. China.
E-mail: yychen@whu.edu.cn

Received (in Montpellier, France) 6th September 2000, Accepted 24th October 2000
First published as an Advance Article on the web 21st December 2000

The syntheses of novel types of *p-tert*-butylcalix[6]bis-crowns and related compounds is described. By reacting *p-tert*-butylcalix[6]-1,4-crown-4 with ethylene glycol ditosylate or polyethylene glycol ditosylates using NaH as a base in DMF, *p-tert*-butylcalix[6]-2,3-ethylene-1,4-crown-4, *p-tert*-butylcalix[6]-1,4-crown-4-2,6-crown-3, monotosyloxyethoxyethyl-*p-tert*-butylcalix[6]-1,4-crown-4, *p-tert*-butylcalix[6]-1,4-crown-4-2,5-benzocrown-4 and *p-tert*-butylcalix[6]-1,4-crown-4-2,6-crown-5 were obtained in reasonable yields under selective conditions.

Calixcrowns comprise a family of calixarenes in which the phenolic oxygens are linked intramolecularly *via* flexible poly(oxyethylene) chains.[1] As they possess preorganized structures and more rigid binding sites in comparison with calixarenes and crown ethers, they exhibit superior recognition ability toward alkali metal ions and other ions by the cooperative effects of calixarene and crown moieties. In particular, calix[4]arene crown-6 hosts have been investigated for the sequestration and removal of radioactive ^{137}Cs from aqueous waste mixtures.[2] At present, as calix[4]crown chemistry approaches maturity not only many types of calix[4]monocrowns, but also many types of calix[4]bis-crowns have been synthesized.[3–9] Their recognition properties toward Cs^+, K^+, *etc.* have been studied as well.[10–14] However, in contrast to the extensive investigations on calix[4]bis-crowns, very little is known about calix[6]bis-crowns.

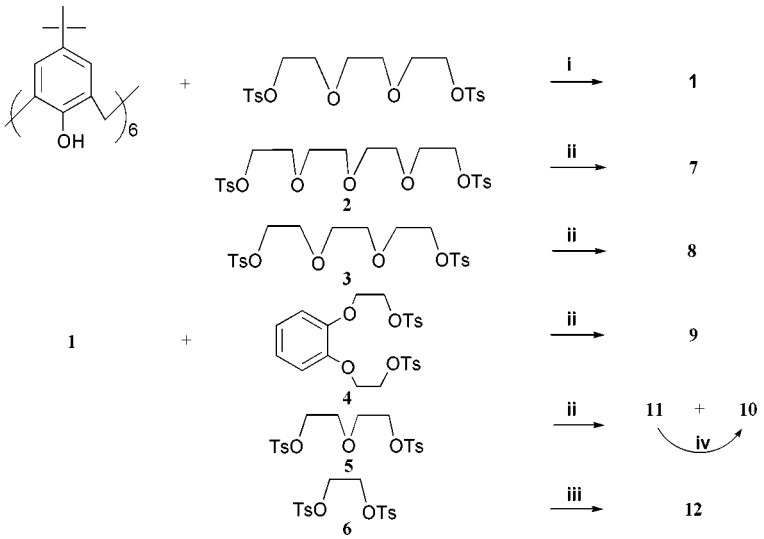
Just recently, Blanda *et al.* reported the first examples of calix[6]bis-crowns: 1,4-diallyloxycalix[6]-2,6-3,5-bis-crown-4s,[15] as shown in Fig. 1. Meanwhile, Chen *et al.* have also synthesized *p-tert*-butylcalix[6]-1,4-2,5-bis-crown-4, **8**, and *p-tert*-butylcalix[6]-1,4-benzocrown-4-2,5-crown-4, **9**, from *p-tert*-butylcalix[6]-1,4-crown-4, **1**, or *p-tert*-butylcalix[6]-1,4-benzocrown-4 by reacting them with triethylene glycol ditosylate, **3**.[16] As an extension of the above work, we report here a systematic investigation on the condensation of *p-tert*-butylcalix[6]-1,4-crown-4, **1**, with ethylene glycol ditosylate, **6**, diethylene glycol ditosylate, **5**, 1,2-bis(tosyloxyethoxy)benzene, **4**, and tetraethylene glycol ditosylate, **2**. Under selected conditions, a series of positional isomers of calix[6]bis-crowns and related compounds have been prepared in reasonable yields as outlined in Scheme 1.

Results and discussion

Syntheses and characterization

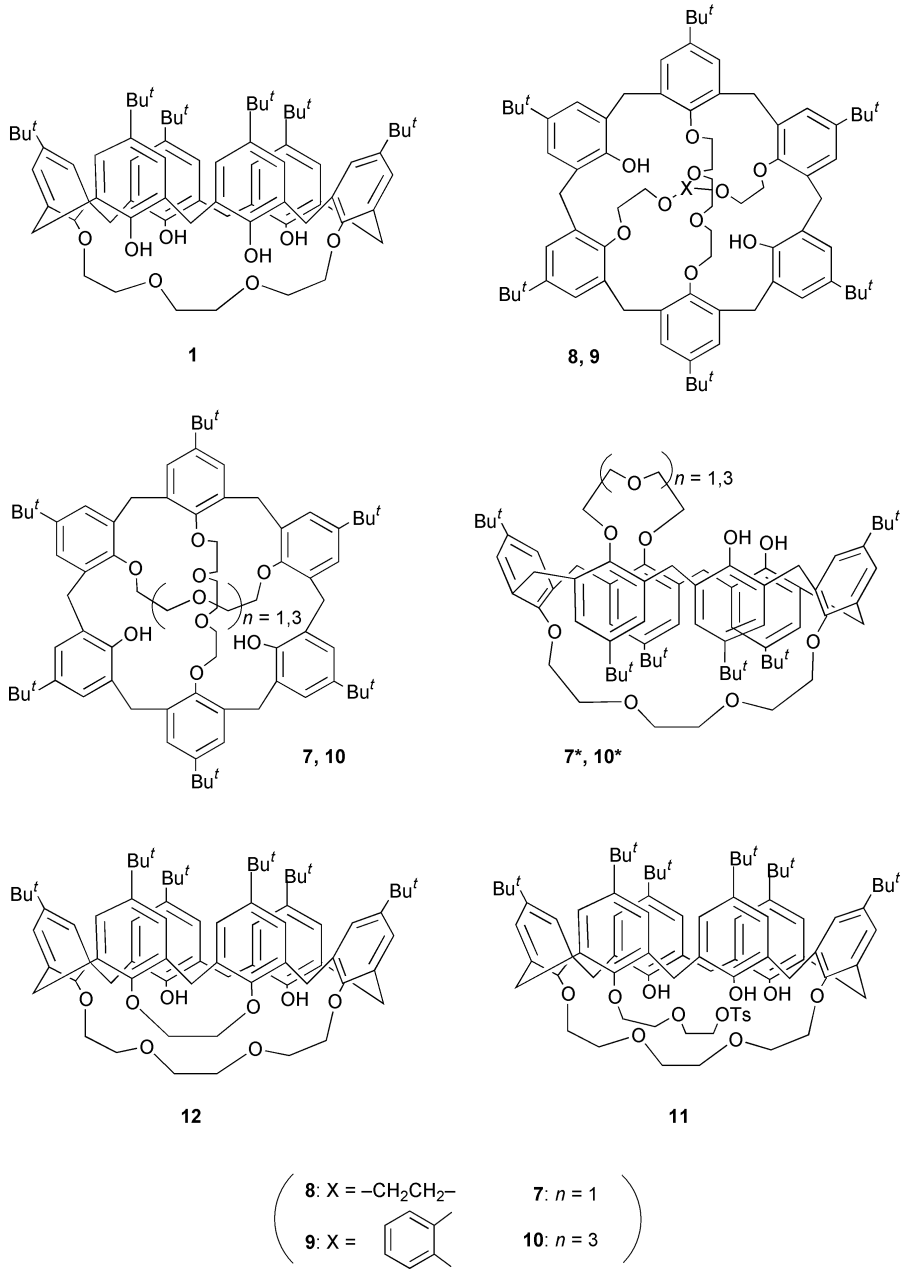
The synthetic route is depicted in Scheme 1. *p-tert*-Butylcalix[6]-1,4-crown-4, **1**, has been obtained by reacting *p-tert*-butylcalix[6]arene with triethylene glycol ditosylate in K_2CO_3–CH_3CN as a mixture of *p-tert*-butylcalix[6]-1,4-crown-4 and *p-tert*-butylcalix[6]-1,3-crown-4 in yields of 20 and 11% respectively.[17] However the yield of **1** can be increased to nearly 40% by using toluene as the solvent instead of MeCN, and the work-up was simplified in comparison with the original method.[16]

Further treatment of **1** with diethylene glycol ditosylate, **5**, 1,2-bis(tosyloxyethoxy) benzene, **4**, or tetraethylene glycol ditosylate, **2**, in the presence of NaH as a base in DMF gave **11** plus **10**, **9** and **7** in yields of 35, 16, 60 and 32% respectively. No separable product has been obtained from **1** with



Scheme 1 *Reagents and conditions*: (i) K_2CO_3 (9.0–10.0 equiv.), toluene, reflux, 24 h. (ii) NaH, DMF, 60 °C, 7–12 h. (iii) NaH, THF-DMF (10 : 1 v/v), reflux, 24 h. (iv) NaH, THF, reflux, 2 days.

 DOI: 10.1039/b007408j



Scheme 2 **7*** and **10*** are the possible conformers of **7** and **10**, respectively.

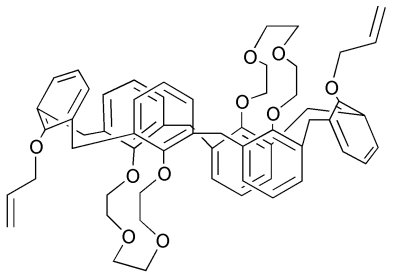
ethylene glycol distosylate, **6**, under the above conditions. After much effort, we found finally that by using THF–DMF (10 : 1 v/v), instead of DMF alone, the reaction product was easily separated and the desired product **12** was obtained in 23% yield.

Compound **9** has been synthesized by a different route from *p-tert*-butylcalix[6]-benzocrown-4 before.[16] The structures of **7**, **10**, **11** and **12** (shown in Scheme 2) were confirmed by ^{1}H NMR FAB-MS and elemental analysis. The ^{1}H NMR spectrum of **7** shows four singlets (ratio 1 : 2 : 2 : 1) for the *tert*-butyl groups, three pairs of doublets (one is mixed with ethylene protons) for the methylene protons, and one singlet for the hydroxyl protons. This is in accord with the structure of *p-tert*-butylcalix[6]-1,4-crown-4-2,6-crown-5, **7**. Compound **10** gives satisfactory elemental analysis results and shows the expected molecular ion peak in the mass spectrum. The ^{1}H NMR spectrum of **10** shows four singlets (ratio 1 : 2 : 2 : 1) for the *tert*-butyl groups, three pairs of doublets (two are mixed with ethylene protons) for the methylene protons, and one singlet for the hydroxyl protons. This is in accord with the structure of *p-tert*-butylcalix[6]-1,4-crown-4-2,6-crown-3, **10**. It is worth noting that most of the above mentioned spectral features of **10** are very similar to those of **7**. However, as the (u,d,d,u,d,d) and (u,d,u,u,u,d) conformations will both give similar NMR data for methylene protons, it is not possible to assign the conformation, although we believe the former is more plausible (as shown in Scheme 2).

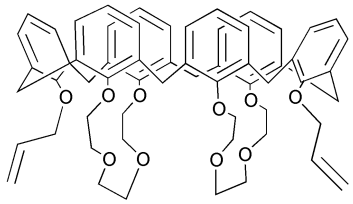
The ^{1}H NMR spectrum of **11** shows one singlet at δ 2.44 and a pair of doublets at δ 7.25 and 7.80 for the tosyloxy group, and six singlets for the *tert*-butyl groups, obviously indicating that the structure of **11** is asymmetrical. It is hard to confirm the conformation of **11** at ambient temperature due to the overlapping signals in the region of δ 3.50–4.15.

The fact that compounds **10** and **11** were isolated in the condensation of **1** and **5** suggests that **11** may be a possible intermediate for **10**. Refluxing **11** in THF in the presence of NaH for two days, a small amount of **10** could be isolated. This can be considered as indirect evidence for the structure of **11**.

The elemental analysis data of **12** are in accordance with the molecular formula $C_{74}H_{96}O_8$. The FAB-MS spectrum shows the expected molecular ion peak at *m/z* 1112. The ^{1}H NMR spectrum of **12** shows three singlets (1 : 1 : 1) for *tert*-butyl groups as well as the aromatic protons, one singlet for



1,2,3-Alternate conformation



Cone conformation

Fig. 1 1,2,3-Alternate conformation and cone conformation calix[6]bis-crowns.

the hydroxyl protons, and four pairs of doublets (ratio 1 : 2 : 2 : 1) for the methylene protons in the calixarene skeleton (one of which is perturbed by superposition with the peaks of the spacers). The data support that **12** is *p-tert*-butylcalix[6]-2,3-ethylene-1,4-crown-4 and **12** adopts the (u,u,u,u,u,u) cone conformation at ambient temperature.

Extraction abilities

Examination of the CPK molecular models reveals that compounds **12**, **10**, **9**, **8** and **7** are well preorganized to extract cations. *p-tert*-Butylcalix[6]1,4-crown-4, **1**, is used as the reference compound. The percentage extraction of seven picrate salts by these six hosts from water into $CHCl_3$ at 25 ± 1 °C was determined; the arithmetic mean of several experiments is shown in Table 1; the standard deviation on the mean is $\sigma_{N-1} \leqslant 1$. Comparing with compound **1**, the extraction levels of **12**, **10**, **9**, **8** and **7** are higher, especially **12**. This can be attributed to the beneficial influence of a second oxyethylene bridge, which increases the rigidity of the calix[6]arene framework, as compound **12** adopts a cone conformation at room temperature. It is worthy of note that **10** shows high selectivity towards $Me_2NH_2^+$. To the best of our knowledge, **10** may be the first example of an ionophore with high $Me_2NH_2^+$ selectivity in calixarene chemistry.

Comment

The syntheses of a series of calix[6]bis-crowns is reported here and the work may promote the syntheses of new types of calix[6]bis-crowns and their application in supramolecular chemistry.

Experimental

Melting points were recorded on a Gallenkamp melting point apparatus in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Mercury VX300 instrument at ambient temperature. TMS was used as an internal standard for NMR. FAB-MS spectra was obtained from a Kratos MS80RF mass spectrometry service, with *m*-nitrobenzyl alcohol as a matrix. Elemental analyses were performed by the Analytical Laboratory of the Department of Chemistry, Wuhan University. All solvents were purified by standard produres. Petroleum ether refers to the fraction with bp 60–90 °C. All other chemicals were analytically pure and used without further purification.

Syntheses

Improved procedure for the synthesis of 1,4-*p-tert*-butylcalix[6]crown-4, 1.[16] A mixture of *p-tert*-butylcalix[6]arene (5 mmol), triethylene glycol ditosylate (5.5 mmol), and anhydrous K_2CO_3 (50 mmol) in toluene (500 ml) was stirred and refluxed under N_2 for 24 h. After the solvent was removed under reduced pressure, the residue was treated with HCl (10%, v/v) and extracted with $CHCl_3$. The organic layer was separated, dried by $MgSO_4$ and filtered. The organic phase was evaporated again. The crude product was subjected to recrystallization from $CHCl_3$ and petroleum ether (60–90 °C) to afford **1** in 40% yield. Its spectra are the same as those reported in ref. 17.

General procedure for the synthesis of compounds 7, 9, 10 and 11. A solution of *p-tert*-butylcalix[6]-1,4-crown-4, **1**, in freshly distilled DMF was treated with NaH at room temperature for 30 min. Diethylene glycol ditosylate, **5**, tetraethylene glycol ditosylate, **2**, or 1,2-bis(tosyloxyethoxy)-benzene, **4**, (1.2 equiv. in each case) was added. The reaction mixture was then stirred at 60 °C for 7–12 h and the excess NaH was destroyed by addition of a minimal quantity of methanol (**caution!**). The mixture was evaporated to dryness and the residue was treated with a solution of HCl (10% v/v) and extracted with ethyl acetate. After purification by column chromatography, compounds **7, 9, 10** and **11** were isolated as white solids in yields of 32, 60, 16 and 35%, respectively.

7. Mp: 314–6 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 [s, 9H, $C(CH_3)_3$], 1.24 [s, 18H, $C(CH_3)_3$], 1.26 [s, 18H, $C(CH_3)_3$], 1.32 [s, 9H, $C(CH_3)_3$], 2.35 (t, 4H, $J = 9.0$, OCH_2CH_2), 2.70

Table 1 Percentage extraction (%*E*) of picrate salts from water into $CHCl_3$ at 25 °C.[a] %*E* is the arithmetic mean of several experiments. The standard deviation on the mean is $\sigma_{N-1} \leqslant 1$

	%*E*						
Host	Li^+	Na^+	K^+	NH_4^+	$Me_2NH_2^+$	$Et_2NH_2^+$	*n*-$PrNH_3^+$
7	2.4	6.9	5.9	7.6	12.8	11.4	12.1
8	1.4	5.2	18.9	16.2	4.8	6.4	12.0
9	0.3	1.2	9.5	12.4	24.1	3.6	6.5
10	4.3	7.8	5.6	2.3	19.3	3.6	4.4
11	1.1	3.5	10.5	6.3	7.8	15.3	14.3
12	15.3	11.0	25.5	28.2	31.4	40.7	32.3
1	2.6	6.5	4.5	4.0	2.9	3.8	5.6

[a] 1.00 ml of a 0.0025 mol dm^{-3} receptor solution in $CHCl_3$ was shaken (20 min) with 1.00 ml of 0.005 mol dm^{-3} picrate salt solution in triply distilled H_2O and the percentage extraction was measured from the resulting absorbance at 380 nm. Control experiments showed that no picrate extraction occurred in the absence of the calixarene derivative.

(d, 2H, $J = 10.8$, OCH_2CH_2), 2.88 (q, 4H, $J = 10.5$, OCH_2CH_2), 3.16 (q, 4H, $J = 10.5$, OCH_2CH_2), 3.31 (t, 4H, $J = 9.0$, OCH_2CH_2), 3.44 (d, 2H, $J = 10.2$, $ArCH_2Ar$), 3.53–3.64 (m, 12H, OCH_2CH_2 and $ArCH_2Ar$), 3.87 (d, 2H, $J = 10.2$, $ArCH_2Ar$), 4.08 (d, 2H, $J = 13.5$, $ArCH_2Ar$), 4.17 (d, 2H, $J = 13.5$, $ArCH_2Ar$), 4.47 (d, 2H, $J = 17.7$, $ArCH_2Ar$), 6.54 (d, 2H, $J = 2.7$, ArH), 6.72 (d, 4H, $J = 2.7$, ArH), 6.95 (d, 4H, $J = 2.7$, ArH), 7.14 (s, 2H, ArOH), 7.34 (d, 2H, $J = 2.7$ Hz, ArH). MS(FAB) m/z: 1244 (M^+). Anal calc. for $C_{80}H_{108}O_{11}$: C, 77.13; H, 8.74; found: C, 77.15; H, 8.71%.

9. The spectra of **9** are the same as those reported in ref. 16.

10. Mp: 276 °C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 [s, 9H, $C(CH_3)_3$], 1.24 [s, 18H, $C(CH_3)_3$], 1.26 [s, 18H, $C(CH_3)_3$], 1.34 [s, 9H, $C(CH_3)_3$], 2.36 (t, 4H, $J = 8.7$, OCH_2CH_2), 2.75 (t, 4H, $J = 9.0$, OCH_2CH_2), 3.00 (q, 4H, $J = 10.5$, OCH_2CH_2), 3.19–3.58 (m, 12H, OCH_2CH_2 and $ArCH_2Ar$), 3.84 (d, 2H, $J = 10.5$, $ArCH_2Ar$), 4.04 (d, 2H, $J = 13.5$, $ArCH_2Ar$), 4.13 (d, 2H, $J = 13.5$, $ArCH_2Ar$), 4.42 (d, 2H, $J = 17.1$, $ArCH_2Ar$), 6.50, 6.87, 6.93, 7.06, 7.21, 7.35 (d, each 2H, $J = 2.4$ Hz, ArH), 7.14 (s, 2H, ArOH); MS(FAB) m/z: 1157 (MH^+). Anal. calc. for $C_{76}H_{100}O_9$: C, 78.86; H, 8.71; found: C, 78.89; H, 8.69%.

11. Mp: 212–4 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16, 1.21, 1.24, 1.26, 1.31, 1.34 [s, each 9H, $C(CH_3)_3$], 2.25 (t, 4H, $J = 9.0$ Hz, OCH_2CH_2), 2.44 (s, 3H, $ArCH_3$), 2.71 (d, 2H, $J = 10.2$, OCH_2CH_2), 2.84 (q, 4H, $J = 9.0$, OCH_2CH_2), 3.20–3.34 (m, 6H, OCH_2CH_2), 3.42 (br s, 1H, $ArCH_2Ar$), 3.50–4.15 (m, 14H, OCH_2CH_2 and $ArCH_2Ar$), 4.41 (d, 1H, $J = 15.3$, $ArCH_2Ar$), 6.43, 6.82, 6.85, 7.09, 6.88, 7.18 (s, each, 2H, ArH), 7.15 (br s, 2H, ArOH), 7.25 (d, 2H, $J = 8.4$, ArH), 7.80 (d, 2H, $J = 8.4$ Hz, ArH), 8.04 (br s, 1H, ArOH); MS(FAB) m/z: 1330 (MH_2^+). Anal. calc. for $C_{83}H_{108}O_{12}S$: C, 74.97; H, 8.19; found: C, 74.95; H, 8.23%.

Synthesis of compound 12. *p-tert*-Butylcalix[6]-1,4-crown-4, **1**, was dissolved in THF–DMF (10 : 1). To this solution, NaH was added and the mixture was stirred for 30 min at room temperature. Ethylene glycol ditosylate, **6** (1.2 equiv.), was added *via* a syringe and the reaction mixture was heated to reflux for 24 h. The solvent was removed under reduced pressure; the residue was redissolved in $CHCl_3$ and washed with 1 N HCl and brine. The organic layer was dried over $MgSO_4$, filtered, concentrated, and then purified by column chromatography on silica gel (CH_2Cl_2–Et_2O 5 : 3 v/v).

12. Mp: 244–6 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 [s, 18H, $C(CH_3)_3$], 1.18 [s, 18H, $C(CH_3)_3$], 1.26 [s, 18H, $C(CH_3)_3$], 2.54 (t, 2H, $J = 9.0$, OCH_2CH_2), 2.73 (q, 4H, $J = 10.2$, OCH_2CH_2), 3.11 (t, 2H, $J = 9.0$, OCH_2CH_2), 3.24–3.55 (m, 9H, OCH_2CH_2 and $ArCH_2Ar$), 3.70 (d, 1H, $J = 10.2$, $ArCH_2Ar$), 3.85 (d, 1H, $J = 10.2$, $ArCH_2Ar$), 4.03 (d, 2H, $J = 17.1$, $ArCH_2Ar$), 4.10 (d, 2H, $J = 13.5$, $ArCH_2Ar$), 4.16 (d, 1H, $J = 12.9$, $ArCH_2Ar$), 4.34 (d, 2H, $J = 13.5$, $ArCH_2Ar$), 4.43 (d, 2H, $J = 17.1$ Hz, $ArCH_2Ar$), 6.73 (s, 4H, ArH), 7.05 (s, 4H, ArH), 7.26 (s, 4H, ArH), 8.15 (s, 2H, ArOH); MS(FAB) m/z: 1112 (M^+). Anal. calc. for $C_{74}H_{96}O_8$: C, 79.82; H, 8.69; found: C, 79.85; H, 8.65%.

Acknowledgement

Financial support from the Natural Science Foundation of China is gratefully acknowledged.

References

1 H. Yamamoto and S. Shinkai, *Chem. Lett*., 1994, 1115.
2 Z. Asfari, B. Pulpoka, M. Saadioui, S. Wenger, M. Nierlich, P. Thuery, N. Reynier, J.-F. Dozol and J. Vicens, *J. Mol. Inclusion, Recognit. Proc. 9th Int. Symp*., 1998, 173.
3 A. Arduini, A. Casnati, L. Dodi, A. Pochini and R. Ungaro, *J. Chem. Soc., Chem. Commun*., 1990, 1597.
4 Z. Asfari, R. Abidi, F. Arnaud and J. Vicens, *J. Inclusion Phenom. Mol. Recognit. Chem*., 1992, **13**, 163.
5 Z. Asfari, S. Wenger and J. Vicens, *Pure Appl. Chem*., 1995, **67**, 1037.
6 A. Arduini, L. Domiano, A. Pochini, R. Ungaro, F. Ugozzoli, O. Struck, W. Verboom and D. N. Reinhoudt, *Tetrahedron*, 1997, **53**, 3767.
7 G. Ferguson, A. J. Lough, A. Notti and S. Pappalardo, *J. Org. Chem*., 1998, **63**, 9703.
8 Z. Asfari, V. Lamare, J. F. Dozol and J. Vicens, *Tetrahedron Lett*., 1999, **40**, 691.
9 L. Nicod, S. Pellet–Rostaing, F. Chirtry, M. Lemaire, H. Barnier and V. Federici, *Tetrahedron Lett*., 1998, **39**, 4993.
10 V. Lamare, J. F. Dozol, S. Fuangswassdi, F. Arnaud-Neu, P. Thuery, M. Nierlich, Z. Asfari and J. Vicens, *J. Chem. Soc., Perkin Trans. 2*, 1999, 271.
11 Z. Asfari, V. Lamare, J. F. Dozol and J. Vicens, *Tetrahedron Lett*., 1999, **40**, 691.
12 P. Thuery, M. Nierlich, J. C. Bryan, V. Lamare, J. F. Dozol, Z. Asfari and J. Vicens, *J. Chem. Soc., Dalton Trans*., 1997, 4191.
13 H. H. Zeng and B. Dureault, *Talanta*, 1998, **46**, 1485.
14 J. S. Kim, W. K. Lee, D. Y. Ra, Y. I. Lee, W. K. Choi, K. W. Lee and W. Z. Oh, *Microchem. J*., 1998, **59**, 464.
15 M. T. Blanda, D. B. Farmer, J. S. Brodbelt and B. J. Goolsby, *J. Am. Chem. Soc*., 2000, **122**, 1486.
16 Y. Y. Chen, F. F. Yang and X. R. Lu, *Tetrahedron Lett*., 2000, **41**, 1571.
17 J. S. Li, Y. Y. Chen and X. R. Lu, *Tetrahedron*, 1999, **55**, 10653.