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The Synthesis of Tricyclic Cryptands[1]

Ryszard Ostaszewski[a] and Janusz Jurczak[a,b,*]

[a]Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warszawa

[b]Department of Chemistry, University of Warsaw, 02-093 Warszawa, Poland

Abstract: General methods for the synthesis of tricyclic cryptands are discussed. A new and efficient method for the synthesis of both symmetric and nonsymmetric tricyclic cryptands, based on the high-pressure technique, is designed and its practical application is shown on three examples.
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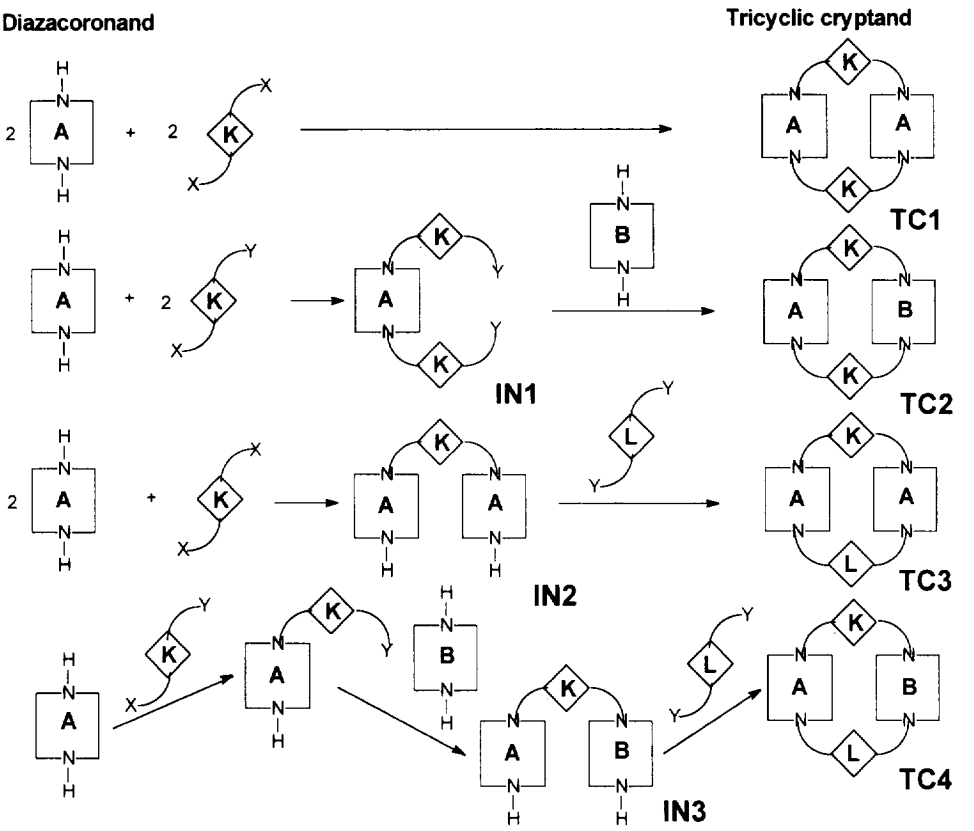
Ionophores of cryptand-like structure are a very important class of host molecules due to their interesting complexing properties.[2] They can effectively complex cations,[3] anions,[4] and even neutral molecules.[5,6] In most cases, stabilities as well as selectivities of complexes formed from cryptands are higher as compared with monomacrocyclic receptors.[3] Unfortunately, their synthesis is difficult and cumbersome[7]. The synthesis of these compounds can be realized using various methods, and application of a particular method is strongly influenced by the structure of the desired product.

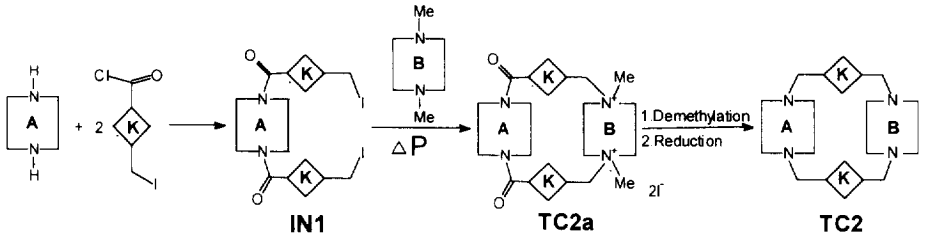
In the case of tricyclic cryptands four different chemical structures are conceivable, as shown in Scheme 1. Structure of the tricyclic cryptand (**TC**) may be fully symmetric (**TC1**), crown-ether rings may be different (**TC2**) or spacers connecting rings may be different (**TC3**). The last, fully nonsymmetric structure consists of two different crown-ether rings and two different spacers (**TC4**). The synthesis of nonsymmetric cryptands **TC2**, **TC3**, and **TC4** requires preparation of intermediate compounds **IN1**, **IN2**, and **IN3**, respectively.

The synthesis of macrocyclic compounds is based on several methods which are used with different results. Our high-pressure method was successfully used for the synthesis of simple and chiral bicyclic cryptands and diazacoronands.[8] The superiority of this method over the standard high-dilution method has been demonstrated.[9]



Scheme 1

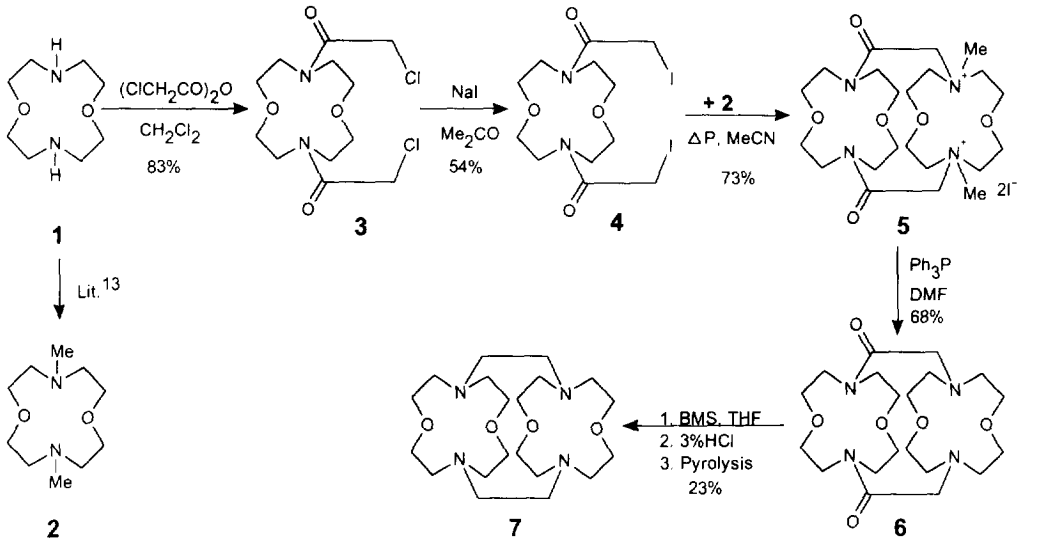
In the course of extensive synthetic studies we were interested in the synthesis of ionophores capable of complexing two identical or different cations. The structure of the desired compound (**TC2** in Scheme 1) implies preparation of intermediate product **IN1.** For this synthesis we decided to apply the high-pressure method according to the general idea presented in Scheme 2.



Scheme 2

Intermediate **IN1**, prepared from diazacoronand **A** and two molecules of spacer **K**, reacts with the N,N'-dimethyl diazacoronand **B** to yield the quaternary salt **TC2a**. Demethylation, followed by reduction of carbonyl groups, leads to the desired tricyclic cryptand **TC2**. Thus the protection-deprotection reaction sequence is avoided which simplifies the synthesis and raises the overall yield. Studies on the high-pressure preparation of bicyclic cryptands showed its high selectivity. Only the lowest molecular weight products were formed.[10-12] This paper deals with the extension of the high-pressure technique to the synthesis of tricyclic cryptands.

Two symmetric cryptands containing two 18- or two 12-membered rings, and one nonsymmetric cryptand containing 18- and 12-membered rings were selected as target molecules. The smallest tricyclic cryptand **7** was obtained according to Scheme 3.

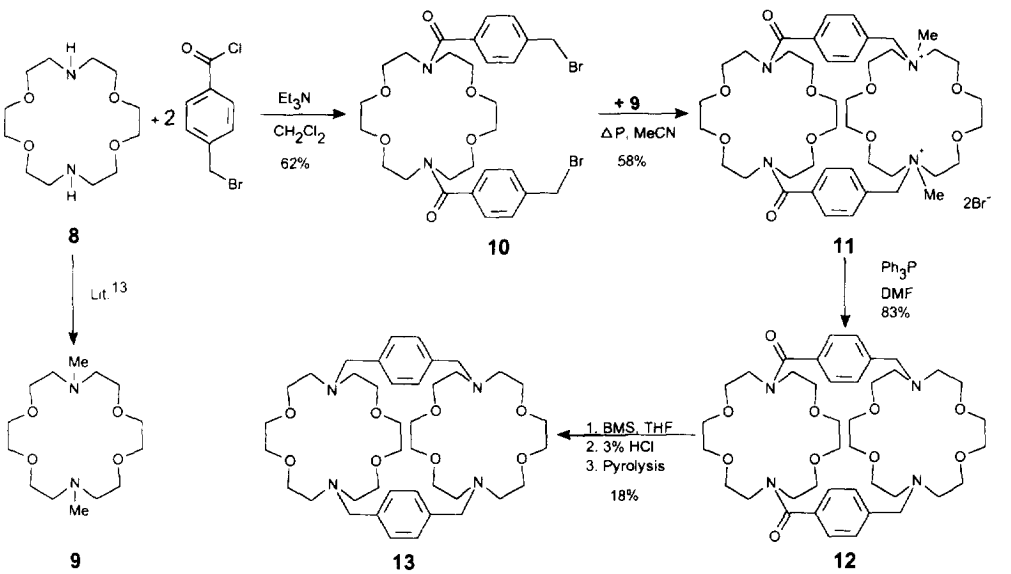


Scheme 3

Chloroacetyl derivative **3** was obtained in 83% yield from diazacoronad **1** and chloroacetyl anhydride. Since this compound was not reactive enough in the Menshutkin reaction, even under high-pressure conditions, the chlorine atoms were exchanged for iodine using sodium iodide in acetone. The resulting compound **4** was very unstable, and was used in the next step without purification. The macrocyclization reaction of **4** with with N,N'-dimethyldiazacoronand **2**[13] was performed in an acetonitrile solution, under high-pressure conditions, to afford 73% of the desired macrotricyclic salt **5**. The NMR spectrum of this compound shows broad signals of a complex structure which indicates that its conformational mobility is completely frozen. In the next step, the quaternary methyl groups were removed, and precursor of tricyclic cryptand **6** was obtained in 68% yield. Reduction of the amide function was very difficult. Commonly used reducing agents resulted in decomposition or no reaction occurred. After many trials, we found that diborane-dimethyl sulfide complex was capable of reducing the amide function. Unfortunately, the reaction led to the BH_3 complex of the desired cryptand. This

complex was decomposed with dilute hydrochloric acid, and after base treatment final purification was achieved by high-vacuum pyrolysis, giving tricyclic cryptand **7** in 23% yield. The properties of cryptand **7** are in accordance with published data.[14] The overall yield based on diazacoronand **1** was 5.1%; the yield is substantially reduced by the chemical instability of amide **4** which readily decomposes, even when stored in a refrigerator under argon, as well as by a low efficiency of the reduction of amide **6**.

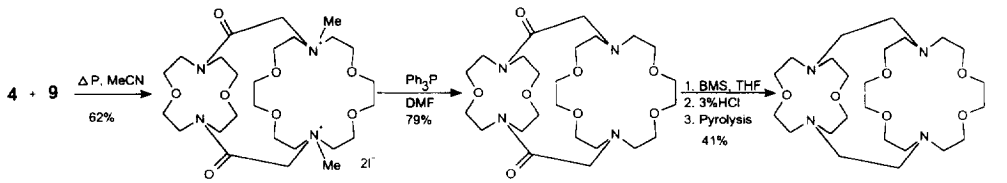
The synthesis of symmetric tricyclic cryptand **13** containing 18-crown-6 rings was achieved according to Scheme 4.



Scheme 4

In the first step amide **10** was obtained in the reaction between diazacoronand **8** and 4-bromomethylbenzoyl chloride in 62% yield. Then, the high-pressure reaction of **10** with N,N'-dimethyldiazacoronand **9**[13] leads to formation of the highly hygroscopic salt **11** in 58% yield. This salt was treated with triphenylphosphine in boiling DMF to yield 83% of the desired precursor **12**. Final reduction of compound **12** was performed similarly to the previous synthesis; hydrolysis and pyrolysis of the resulting sodium complex led to formation of cryptand **13** in 18% yield. Its properties are in accordance with published data.[15]

Synthesis of symmetric tricyclic cryptands, performed according to our concept, gave desired products in a four-step reaction sequence. From the same intermediates the synthesis of nonsymmetric tricyclic cryptands can be completed. This was performed according to Scheme 5.



14 **15** **16**

Scheme 5

Starting from diamide **4** and N,N'-dimethyldiazacoronand **9**,[13] the expected salt **14** was obtained under high-pressure conditions in 62% yield. Demethylation of this salt led to formation of derivative **15** in 79% yield. Reduction of amide functions, followed by hydrolysis and pyrolysis of the complex formed, afforded the nonsymmetric tricyclic cryptand **16** in 41% yield. The overall yield in this synthesis is above 20%, based on amide **4**. This new compound forms stable complexes with alkali metal cations which are directly observed in mass spectrometry (*vide infra*).

Application of high-pressure techniques to the synthesis of supramolecular assemblies usually gave the desired compounds in high yield. A new concept based on the high-pressure synthesis of tricyclic cryptands was very successful and promising for future studies. The key reaction between iodo- or bromoamides and N,N'-dimethyldiazacoronands, performed under high-pressure conditions, leads to formation of expected tricyclic quaternary ammonium salts in very good yield. Preorganization of substrates resulted in highly specific reaction in which only one product was formed. Unfortunately, the next reaction step, reduction of the amide function, is inefficient and reduces the overall yield.

The same concept can be extended to the synthesis of more elaborated structures, e.g. tricyclic chiral cryptands.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AMX (500 MHz) or Varian Gemini (200 MHz) with TMS as internal standard. Coupling constants *J* are given in Hz. IR spectra were taken with a Perkin-Elmer FT-IR-1600 spectrophotometer and only noteworthy absorptions are listed. Mass spectra (electron impact, 70 eV and L-SIMS Cs^+, 7 keV) were obtained on an AMD 604 (AMD Intestra GmbH, Germany).

General procedure for the preparation of diazacoronand diamides:

To a stirred solution of 2 mmol of a diazacoronand in 20 mL of methylene chloride cooled to 5°C, 4.6 mmol of chloroacetyl anhydride or 4-(bromomethyl)benzoyl chloride was added, and the reaction mixture was stirred at room temperature for 18 h; then 10 mL of aqueous sodium bicarbonate was added and phases were

separated. The organic layer was washed with water (2x10 mL) and dried over $MgSO_4$. The solvent was removed and the residue was crystallized from chloroform-diethyl ether.

Diamide **3:** yield 83%; m.p. 120-123°C; ^{1}H NMR, δ ($CDCl_3$): 3.46 (t, J=4.8, 3H), 3.50-3.53 (m, 5H), 3.68-3.71 (m, 4H), 3.70 (t, J=5.1, 1H), 3.85 (t, J=4.9, 3H), 4.11 (s, 2H), 4.17 (s, 2H); IR [cm^{-1}] ($CHCl_3$): ν(COC) 1155-1145, ν(CON) 1615-1640; Elemental analysis for $C_{12}H_{20}N_2O_4Cl_2$: calcd. C, 44.0; H 6.2; N 8.6; Cl 21.7%; found C 43.9; H 6.3; N 8.7; Cl 21.8%.

Diamide **10:** yield 83%; m.p. 144-145°C; ^{1}H NMR δ ($CDCl_3$): 3.50-3.66 (m, 16H), 3.77-3.80 (m, 8H), 4.48 (s, 4H), 7.35 (d, J= 8.0, 4H), 7.40 (d, J=8.0, 4H); IR [cm^{-1}] ($CHCl_3$): ν(COC) 1075-1085, ν(CON) 1620-1640; MS $[M]^+$ m/z (%): 655 (M^+, 1), 577 (13), 575 (11), 118 (100); Elemental analysis for $C_{28}H_{36}N_2O_6Br_2$: calcd. C 51.2; H 5.5; N 4.4%; found C 51.1; H 5.9; N 4.0%.

Preparation of diiodo crown 4:

To a solution of sodium iodide (1.5 g, 10mmol) in acetone (100 mL), diazacoronand **3** (0.245g, 0.75 mmol) was added and the reaction mixture was stirred at room temperature in darkness for 1 day. Solids were removed by filtration and solvent was evaporated. The crude product was dissolved in methylene chloride (25 mL) and washed with water (10 mL), sodium thiosulfate solution (2x10 mL, 10%), water (10 mL) and dried over $MgSO_4$. Diazacoronand **4** was obtained after evaporation of solvent and dried under high vacuum in darkness. Due to its high chemical unstability, this compound was used in next reaction without further purification.

General procedure for high-pressure reactions, preparation of tricyclic cryptands:

In a Teflon ampoule were placed solutions of 0.3 mmol of diazacoronand **4** or **10** and 0.3 mmol of the respective N,N'-dimethyldiazacoronand in 2.5 mL of acetonitrile. High-pressure (11 kbar) was applied for 20 h at room temperature. Then the solution was transferred into 100 mL glass flask and 30 mL of diethyl ether was added. The precipitated crystalline powder was filtered off, washed with diethyl ether and dried.

Quaternary salt **5:** yield 73%; ^{1}H NMR δ (D_2O): 3.40-3.84 (m, 38H), 4.20-4.23 (m, 4H); Elemental analysis for $C_{22}H_{42}N_4O_6I_2$: calcd. C 36.9; H 5.9; N 7.8%; found C 36.7; H 6.2; N 8.2% .

Quaternary salt **11:** yield 58%; ^{1}H NMR δ (D_2O): 3.27-3.75 (m, 54H), 3.93 (m, 4H), 7.28-7.47 (m, 8H); Elemental analysis for $C_{42}H_{66}N_4O_{10}Br_2 + H_2O$: calcd. C 52.3; H 7.1; N 5.8%; found C 51.9; H 7.5; N 5.9%.

Quaternary salt **14:** yield 62%; ^{1}H NMR δ (D_2O): 3.27-3.75 (m, 46H), 3.93 (m, 4H); Elemental analysis for $C_{26}H_{50}N_4O_8I_2 + 0.5H_2O$: calcd. C 38.6; H 6.3; N 6.9%; found C 39.0; H 6.0; N 7.1%.

General procedure for demethylation of quaternary ammonium salts:

To a solution of triphenylphosphine (0.071 g, 0.37 mM) in dimethylformamide (5 mL), quaternary cryptand salt (about 0.18 mM) was added and this reaction mixture was refluxed for 18 h under argon, then cooled to room temperature and solvent was evaporated *in vacuo*. Products **6**, **12**, and **15** were separated

from impurities (mainly methyltriphenylphosphonium iodide or bromide) *via* flash chromatography (basic Al_2O_3, eluent CH_2Cl_2) and were directly used for the next reactions. These intermediates were not subjected to elemental nor to HRMS analysis.

Crude amide **6:** yield ~68%; ^{1}H NMR δ ($CDCl_3$): 3.40 (t, J=4.5, 4H), 3.42-3.45 (m, 14H), 3.52-3.71 (t, J=5.5, 2H), 3.67-3.69 (m, 6H), 3.73 (t, J=5.1, 2H), 3.84 (t, J=4.9, 4H), 4.13 (s, 2H), 4.15 (s, 2H); IR [cm^{-1}] ($CHCl_3$): ν(COC) 1105-1140, ν(CON) 1640-1670.

Crude amide **12:** yield ~83%; ^{1}H NMR δ ($CDCl_3$): 3.50-3.70 (m, 36H), 3.75-3.80 (m, 8H), 3.97-4.01 (m, 4H), 4.93 (s, 4H), 7.30-7.45 (m, 8H); IR [cm^{-1}] ($CHCl_3$): ν(COC) 1115-1135, ν(CON) 1645-1670.

Crude amide **15**: yield ~79%; ^{1}H NMR δ ($CDCl_3$): 3.42 (t, J=4.6, 4H), 3.40-3.82 (m, 36H), 4.14 (m, 4H); IR [cm^{-1}] ($CHCl_3$): ν(COC) 1115-1150, ν(CON) 1635-1660.

General procedure for reduction, hydrolysis and pyrolysis of tricyclic amides:

To a solution of the tricyclic cryptand amide (0.5 mmol) in tetrahydrofuran BMS solution (1 mL) was added under argon and the reaction mixture was stirred under reflux. After 1 hour, the reaction mixture was cooled to room temperature and excess of the reducing reagent was destroyed by addition of methanol (10 mL) and solvents were evaporated. Residue was dissolved in 3% hydrochloric acid and heated under reflux for 30 min. The solution was cooled to room temperature and adjusted to pH 10 by addition of 5% potassium hydroxide solution. The aqueous phase was extracted with methylene chloride (5x20 mL), organic phases were combined, dried ($MgSO_4$) and solvent was evaporated. The oily residue was purified by vacuum pyrolysis (125-150°C/0.001 Torr) in a Kugelrohr apparatus.

Tricyclic cryptand **7**: yield 23%; m.p. 140-149 °C, Lit.[14], m.p. 144-149 °C; ^{1}H NMR δ ($CDCl_3$): 2.87-2.93 (m, 8H), 3.42-3.79 (m, 32H); IR [cm^{-1}] ($CHCl_3$): ν(COC) 1150-1100.

Tricyclic cryptand **13**: yield 18%; m.p. 120-125 °C, Lit.[15], m.p. 116 °C; ^{1}H NMR δ ($CDCl_3$): 3.10-3.11 (m, 16H), 3.50-3.84 (m, 40H), 7.22-7.47 (m, 8H); IR [cm^{-1}] ($CHCl_3$): ν(COC) 1145-1110.

Tricyclic cryptand **16**: yield 41%; m.p. 116-117 °C; ^{1}H NMR δ ($CDCl_3$): 2.81-2.91 (m, 24H), 3.55-3.89 (m, 24H); IR [cm^{-1}] ($CHCl_3$): ν(COC) 1160-1110; HR-MS $[M]^+$ calcd. for $C_{24}H_{48}N_4O_6$ 488.357, observed 488.360: MS m/z (%): 511 ($[M+Na]^+$, 68), 489 ($[M+H]^+$, 100), 488 (M^+, 30); Elemental analysis for $C_{24}H_{48}N_4O_6$: calcd. C 59.0; H 9.9; N 11.5%; found C 59.2; H 9.7; N 11.3%.

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References

1. Preliminary communication: Jurczak, J.; Ostaszewski, R. *Polish J. Chem.* **1996,** *66,* 2885.
2. For recent reviews on the cryptands complexation, see: Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1995,** *95,* 2529; Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1991,** *91,* 1721.
3. Arnaud-Neu, F.; Sanchez, M.; Yahya, R.; Schwing-Will, M. J.; Lehn, J. M. *Helv. Chim. Acta* **1985**, *68*, 456; Arnaud-Neu, F.; Almasio, M. C.; Spiess, B.; Schwing-Will, M. J.; Sullivan, S. A.; Lehn, J. M. *Helv. Chim. Acta* **1985**, *68*, 831; Lehn, J. M.; Simon, J.; Moradpour, A. *Helv. Chim. Acta* **1978**, *61*, 2407; Boudon, C.; Gross, M.; Kotzyba-Hilbert, F.; Lehn, J. M; Saigo, K. *J. Electroanal. Chem. Interfacial Electrochem.* **1985**, *191*, 201.
4. Lehn, J. M.; Sonveaux, E.; Willand, A. K.; *J. Am. Chem. Soc.* **1978**, *100*, 4914; Schmidtchen, F. P. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 720; Graf, E.; Lehn, J. M. *J. Am. Chem. Soc.* **1976**, *98*, 6403.
5. Golovkova, L. P.; Telyatnik, A. I.; Bidzilya, V. A.; Akhmetova, N. E.; Konovalova, V. I. *Theor. Exp. Chem. (Engl. Transl.)* **1985**, *21*, 238.
6. Golovkova, L. P.; Telyatnik, A. I.; Bidzilya, V. A.,;Akhmetova, N. E.; Konovalova, V. I. *Theor. Exp. Chem. (Engl. Transl.)* **1988**, *24*, 716.
7. For recent reviews on the synthesis of cryptands, see: An, H.; Bradshaw, J. S.; Izatt, R. M. *Chem. Rev.* **1992,** *92,* 543; Lindsey, J. S. *New. J. Chem.* **1992,** *15*, 153.
8. Jurczak, J.; Ostaszewski, R. *J. Coord. Chem.* **1992,** *27*, 201.
9. Pietraszkiewicz, M.; Jurczak, J. *J. Carbohydr. Chem.* **1985,** *4,* 429.
10. Pietraszkiewicz, M.; Salanski, P.; Jurczak, J. *Bull. Pol. Ac.: Chem.* **1985**, *33*, 433.
11. Pietraszkiewicz, M.; Salanski, P.; Jurczak, J. *Heterocycles*, **1985**, *23*, 547.
12. Pietraszkiewicz, M.; Salanski, P.; Ostaszewski, R., Jurczak, J. *Heterocycles* **1986**, *24*, 1203.
13. Jurczak, J.; Ostaszewski, R. *Tetrahedron Lett.* **1988**, *29*, 959.
14. Calvery, M. J.; Dale, J. *J. Chem. Soc., Chem. Commun.* **1981,** 1084.
15. Kintzinger, J. P.; Kotzyba-Hilbert, F.; Lehn, J. M.; Pagelot, A.; Saigo, K. *J. Chem. Soc., Chem. Commun.* **1981,** 883.

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