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STRATEGY FOR THE SYNTHESIS OF UNSYMMETRICAL N-SUBSTITUTED POLYAZAMACROCYCLES

Kunjian Gu, Kristin Bowman Mertes,[#] Mathias P. Mertes[*]

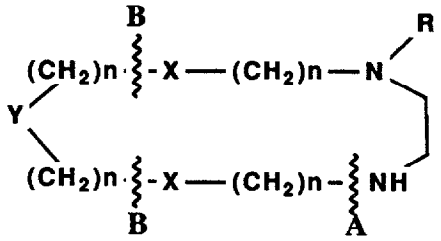
Departments of Medicinal Chemistry and Chemistry[#],University of Kansas, Lawrence, Kansas, 66045, USA

Summary: A convergent route is described for the preparation of unsymmetrical N-substituted polyammonium macrocycles that is potentially applicable for the synthesis of a wide variety of macrocycles of differing ring size and heteroatom substitution.

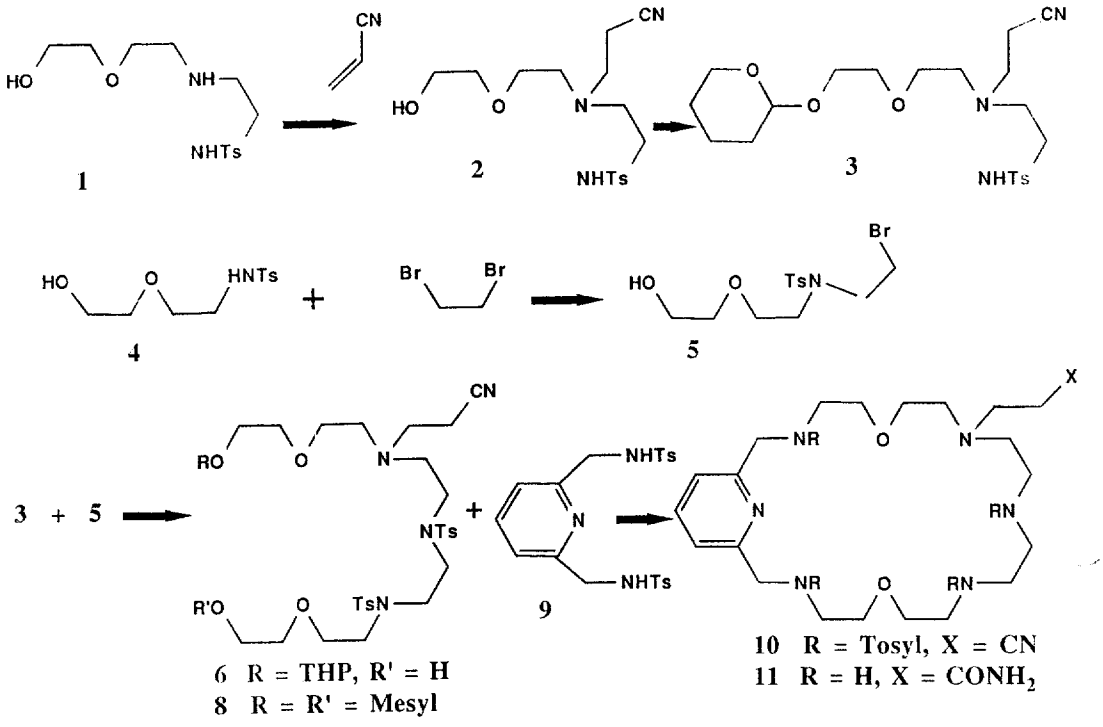
Polyammonium macrocycles specifically designed for the complexation of anions have been found to form high affinity supramolecular complexes that, in some cases, lead to unique chemical transformations.[2] Catalysis within the supramolecular complex has been particularly useful in exploring phosphoryl transfer reactions and in modeling enzymatic reactions that catalyze such reactions.[3] In an effort to explore the effect of additional catalytic sites on polyammonium macrocycles the synthesis of a series of symmetrically substituted 24-membered hexaazamacrocycles containing pendant functionality was recently described.[4] This report describes a facile approach found to be useful in the preparation of unsymmetrically N-substituted polyazamacrocycles.

Advances in the application of macrocyclic and macropolycyclic receptor molecules in the study of the complexation of metal ions and other substrates has relied on versatile methods of synthesis. Of contemporary interest is the development of synthetic routes that have allowed for the introduction of pendant functionality in azacrown ethers,[5] calixarenes,[6] and in the study of convergent functional groups by Rebek and co-workers.[7] The preparation of symmetrically substituted polyazamacrocycles generally employs selective protection, functionalization, cyclization, and deprotection reactions.[8] Relatively rare, however, are examples of unsymmetrical substitution of polyazamacrocycles. Two such examples are highlighted in the chiral macrocyclic analogue of spermine[9] and monofunctionalized N-substituted tetraazamacrocycles.[10] However, the latter approach is limited by the lack of selectivity in the N-alkylation reaction and the inherent problems in separation of the mono- and polysubstituted products.

Two regiospecific strategies were examined for a general route for the synthesis of unsymmetrically substituted polyazamacrocycles, and it was found that the convergent route described was most versatile. The bond disconnection shown in the structure highlights two advantages of the method. The western half of the macrocycle can be varied in the cyclization step B leading to a variety of ring sizes and substituents (X). The eastern half is prepared conveniently in a convergent sequence (A) that employs, in the examples given, the cyanoethyl group as the pendant functionality. However, the sequence is sufficiently general such that any substituent stable under the conditions of the reactions can be used. Furthermore, the length of the eastern synthon can be readily varied to give different ring sizes and heteroatom substitutions (Y).

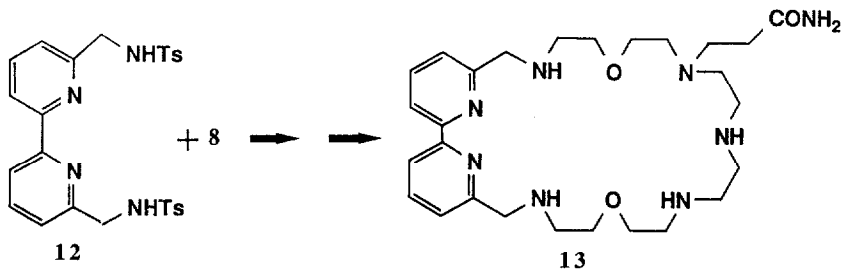


An example of this approach is described for the synthesis of the pyridyl 24-membered hexaazamacrocycle **11** which contains an N-substituted moiety in an unsymmetrical position on the eastern half of this ditopic receptor. The starting secondary amine **1** was prepared in 93% yield through the reaction of aminoethoxyethanol with N-tosylaziridine[8a,11] in acetonitrile. Cyanoethylation of **1** using a 10-fold excess of acrylonitrile in refluxing benzene was essentially quantitative in the formation of **2.** The next step in the sequence required protection of the hydroxy group; using dihydropyran, the protected product **3** that can be isolated in quantitative yield also can be used without purification. The intermediate **4** was prepared at room temperature by treatment of 4 equivalents of aminoethoxyethanol with 1 equivalent of tosyl chloride (93% yield based on tosyl chloride). Conversion of **4** to **5** represented one of the three limiting steps in the sequence in that treatment of the anion of **4** (NaH) in DMF with a five-fold excess of 1,2-dibromoethane and heating 100 ^{o}C for 24 hours afforded a 33% isolated yield of **5**. The low yield of this reaction does not present a problem since this step is early in the sequence and the reaction can be run in large scale. The synthesis of **6** was accomplished in 28% yield by treatment of the bromo derivative **5** with the anion (NaH) of **3** in DMF at 100 ^{o}C for 12 hr.



Activation of the intermediate **6** prior to the cyclization reaction required deprotection (HCl, MeOH, methylene chloride) to give the diol **7** that was used without purification in the next reaction. Treatment of the diol **7** with methanesulfonyl chloride in methylene chloride containing five equivalents of triethylamine at room temperature gave the dimesyl derivative **8** that again was used without purification. The second reactant in the cyclization reaction, the bis(tosylaminomethyl)pyridine **9** was prepared from the diamine[12] and tosyl chloride (75%). The addition of the dimesyl derivative **8** to a DMF solution of the disodium salt (NaH) of **9** in the presence of a 15-fold excess of cesium carbonate gave the cyclized product **10** in 25% isolated overall yield for the three steps from compound **6**. Detosylation of 70 mg of **10** by treatment with 50 mg of phenol in 1 mL of 32% HBr-HOAc in a sealed vial at 60 °C for 48 hours was accompanied by conversion of the nitrile to the amide **11** in 83% yield.

Using the method described the 27-membered ring bipyridyl derivative **13** was prepared in a two step reaction by cyclization of the dianion of the bis-tosylamide[13] **12** and compound **8** (35% yield) followed by deprotection and hydrolysis of the nitrile to the amide by treatment with phenol and HBr/HOAc (55% yield).[14]



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References and Notes.

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13. Compound **12** was prepared from the bis-dichloromethyl derivative using the procedures of Newkome et al; a) Newkome, G. R.; Puckett, W. E.; Kiefer, G. E.; Gupta, V. K.; Xia, Y.; Coreil, M.; Hackney, M. A. *J. Org. Chem.* **1982**, *47*, 4116-4120; b) Newkome, G. R.; Pappalardo, S.; Gupta, V. K.; Fronczek, F. R. *J. Org. Chem.* **1983**, *48*, 4848-4851.
14. All new compounds described in this work were fully characterized by ^{1}H and ^{13}C NMR, mass spectroscopy, and elemental analysis for all numbered compounds except **11** and **13** which were verified as the amides by infrared and high resolution mass spectroscopy.

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