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A Concise, Modular Synthesis of Chiral Peraza-Macrocycles Using Chiral Aziridines

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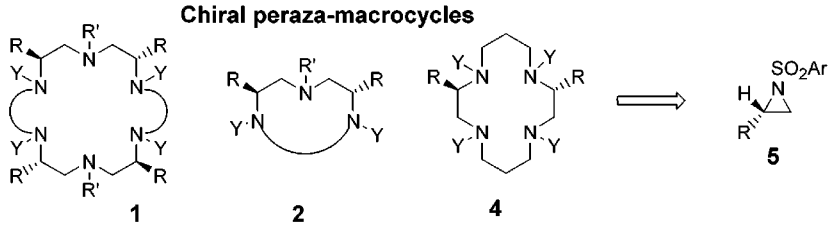
ABSTRACT



Novel chiral peraza-macrocycles were synthesized from chiral aziridines as a common building block. Efficient syntheses of chiral [26]-N_6, [12]-N_4, [9]-N_3, and [14]-N_4 systems were accomplished.

Aza-crown macrocycles[1] had been reported even before the advent of crown ethers and continued to be the subject of intense research.[2] Peraza-crown macrocycles containing transition metals have been utilized as artificial enzyme models.[3] In particular, the synthesis and application of cyclam and cyclen derivatives have been the focus of much interest due to their ability to bind transition and lanthanide metal ions.[4] Application of 1,4,7-triazacyclononane derivatives has also been reported as redox metalloenzyme mimics for oxidative organic transformations and artificial metallohydrolases for the cleavage of DNA or RNA.[3b,h,m,n,4b,c,i] Therefore, the development of efficient synthesis for peraza-

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macrocycles has received much attention. However, there are only a handful of chiral aza-macrocycles reported to date, mostly in the form of oxaza-macrocycles, which have been derived from naturally occurring oxygen-containing optically active starting materials such as amino alcohols and carbohydrates.[5] For the synthesis of achiral peraza-macrocycles such as cyclen and cyclam derivatives, a modular approach has been successfully adopted.[1] However, conventional modular approaches cannot be applied to the synthesis of chiral peraza-macrocycles, unless proper chiral building blocks are available. Toward this goal, we have previously reported an efficient, modular synthesis of chiral peraza-macrocycles **1** and **2** as shown in Figure 1.[6] Compounds **1**

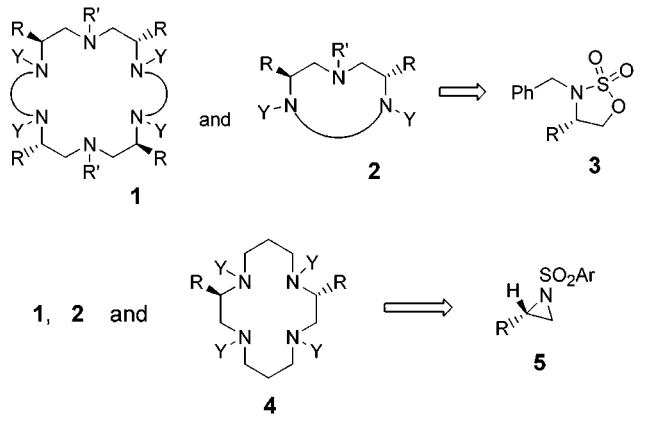
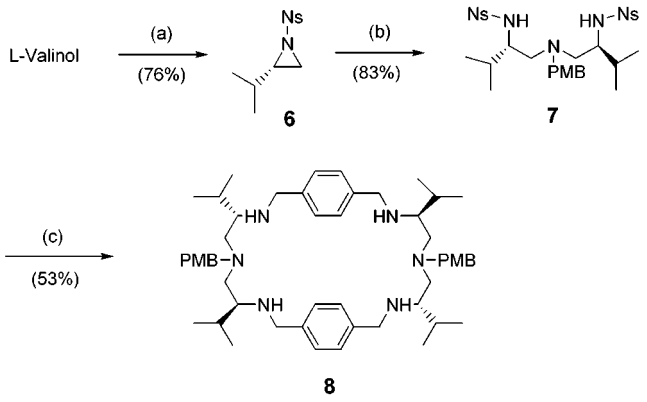


Figure 1.

and **2** (R = CO_2R', Y = CH_2Ar) were prepared from a common building block, cyclic sulfamidate **3**.[7]

In this case, the chiral sulfamidate **3** was an effective "alanine β-cation synthon". We envisioned that chiral aziridine derivatives **5** could be used as yet another alanine β-cation synthon in place of the cyclic sulfamidate **3** for the preparation of various chiral peraza-macrocycles such as **1**, **2**, and **4**. Chiral aziridines can be easily prepared from the corresponding chiral amino alcohols and have been employed as convenient starting materials for various chiral ligands.[8] Indeed this new aziridine-based methodology could be extended to the construction of a variety of chiral peraza-macrocycles. Herein we report on the highly efficient synthesis of chiral peraza-macrocycles equipped with various R groups and having a variety of ring sizes such as [26]-N_6, [12]-N_4, [9]-N_3, and [14]-N_4, Synthesis of chiral [26]-N_6 system (**1**) could be achieved in five steps from the chiral aziridine derivative as shown in Scheme 1. *p*-Nitroben-

Scheme 1[a]



[a] (a) NsCl, TEA, CH_3CN; (b) $PMBNH_2$, CH_3CN; (c) (i) α,α'-dibromo-*p*-xylene, CH_3CN, K_2CO_3, (ii) *n*-propane thiol, CH_3CN, $LiOH\cdot H_2O$.

zenesulfonyl (nosyl)-protected chiral aziridine **6** was prepared from (*S*)-valinol according to a known method.[8a,c]

Opening of the chiral aziridine **6** with 0.5 equiv of *p*-methoxybenzylamine provided the triamine unit **7** in a remarkably good (83%) yield. For the construction of compound type **1**, a proper bridging unit, which would facilitate a 2 + 2 Richman−Atkins-type coupling,[9] would be required for connecting the two chiral triamine units.

Synthesis of macrocycle **8** was accomplished from the coupling reaction between triamine **7** and α,α'-dibromo-*p*-xylene in a dilute solution in CH_3CN followed by removal of the nosyl protecting groups employing *n*-propanethiol[10] in 53% overall yield. Construction of chiral, conformationally constrained cyclen analogues is of much interest since the

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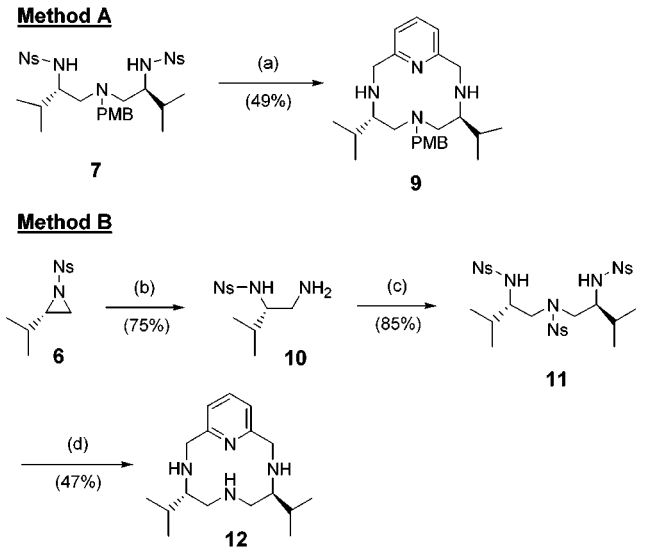
cyclen derivatives have been often employed in the design of artificial hydrolytic enzymes.[3] As shown in Scheme 2,

Scheme 2[a]



[a] (a) (i) 2,6-Pyridine dimethanol (bismethanesulfonate), CH_3CN, K_2CO_3, (ii) *n*-propanethiol, CH_3CN, $LiOH·H_2O$; (b) (i) LiN_3, CH_3CN, (ii) PPh_3, H_2O, THF; (c) (i) **6**, CH_3CN, (ii) NsCl, TEA, CH_2Cl_2; (d) (i) 2,6-pyridinedimethanol (bismethanesulfonate), CH_3CN, K_2CO_3, (ii) *n*-propane thiol, CH_3CN, $LiOH·H_2O$.

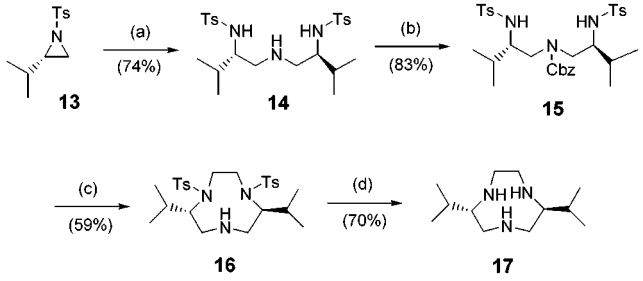
[12]-N_4 systems **9** and **12** containing a pyridine ring were synthesized from the triamine intermediate **7** and **11**, respectively. For the construction of compound **9**, a 1:1 cyclization process was utilized between **7** and 2,6-pyridine dimethanol bismethanesulfonate to furnish the desired compound in 49% yield after deprotection of the nosyl groups (Method A). However, with possible foreseeable complication in the removal of the PMB group on the nitrogen in mind, we decided to prepare unprotected compound **12** through a different route as depicted in Scheme 2 (Method B).

The chiral aziridine **6** was treated with lithium azide to provide a ring-opened product, which was reduced by PPh_3 to give compound **10** in 75% overall yield.[11] Using compound **10** as a nucleophile for the opening of the aziridine **6**, another triamine unit **11** was obtained in 85% yield. This route opens up a possibility of preparing unsymmetrically substituted chiral peraza-macrocycles of compound **12** type.

From coupling of triamine **11** with 2,6-pyridine dimethanol bismethanesulfonate followed by deprotection of all nosyl groups, we were able to obtain the unprotected compound **12** in 47% yield.

A chiral triamine unit could be used as yet another building block for the synthesis of a chiral [9]-N_3 peraza-macrocycle from *N*-*p*-toluenesulfonylated (*N*-tosyl) chiral aziridine (**13**)[12] as depicted in Scheme 3. Bistosylated chiral triamine **14** was

Scheme 3[a]



[a] (a) (i) LiN_3, CH_3CN, (ii) H_2, Pd/C, MeOH, (iii) **13**, CH_3CN; (b) CbzCl, TEA, CH_2Cl_2; (c) (i) 1,2-ethanediol bis(*p*-toluenesulfonate), DMF, Cs_2CO_3, (ii) H_2, Pd/C, MeOH; (d) concentrated H_2SO_4, heat.

obtained in the same way as shown in Scheme 2 in good yield through opening with azide, reduction, and aziridine opening in 74% overall yield. Protection of the free amine of **14** with a carbobenzyloxy (Cbz) group was accomplished to give **15** in 83% yield. Construction of chiral peraza-macrocycle **16** using ethylene diol bistosylate according to the Richman−Atkins protocol was accomplished in 59% yield under high dilution conditions.

Deprotection of the tosyl groups from **16** yielded the chiral cyclic triamine **17** in 70% yield. The structure of **17** was confirmed through X-ray crystallographic analysis of its nickel complex.[13] An X-ray structure of a Ni cation and two molecules of **17** ($[Ni·(\mathbf{17})_2]Cl_2·H_2O$) was obtained as de-

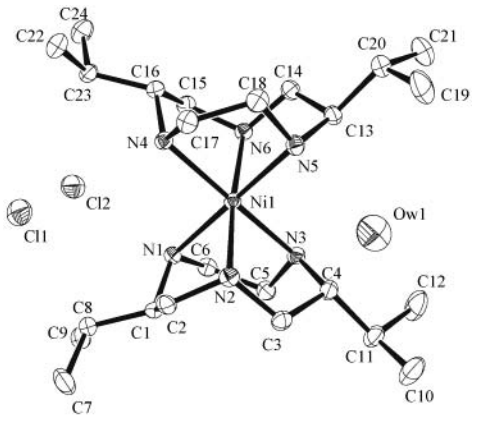


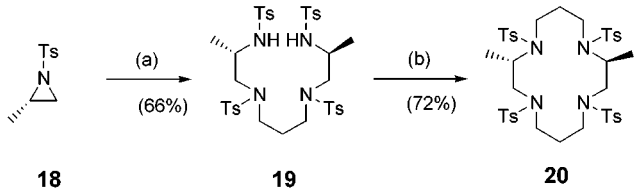
Figure 2. X-ray structure of $[Ni·(\mathbf{17})_2]Cl_2·H_2O$

(11) Boger, D. L.; Patane, M. A.; Zhou, J. *J. Am. Chem. Soc*. **1994**, *116*, 8544.

(12) The synthesis of chiral aziridines from *N*-tosyl-2-amino alcohols was reported: (a) Barry, M. B.; Craig, D. *Synlett* **1992**, 42. (b) Preparation of (*S*)-*N*-tosyl-2-alkylaziridine (**13**, **18**) from free amino alcohols: To a solution of L-amino alcohol (8 mmol) and TEA (3.5 equiv) in dry CH_3CN (80 mL) was slowly added *p*-TsCl (2 equiv) and DMAP (0.1 equiv) at 0 °C with stirring for 30 min. The reaction mixture was stirred at room temperature for 4−5 h. The solvent was removed under reduced pressure and dissolved with EtOAc (100 mL). The organic layer was washed with brine (40 mL × 2). The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified on a silica gel column chromatography to give white solid **13** (1.62 g, 82% yield) and **18** (1.21 g, 73% yield).

picted in Figure 2. Complexes of a metal and achiral 1,4,7-triazacyclononane have been well-studied, and numerous metal complexes of this and related macrocyclic ligands have been synthesized.[14] In the X-ray structure, the constrained ligand imposes a trigonal distortion since the ethylene bridge is not large enough to allow the Ni(II)-linked nitrogen atoms to span idealized 90° bond angles. For that reason, the structure is observed to be an octahedral-like Ni(II) complex of rigid tridentate chiral ligand **17**.

Scheme 4[a]



18 **19** **20**

[a] (a) (i) 1,3-Diaminopropane, DMF, (ii) TsCl, TEA, CH_2Cl_2; (b) 1,3-propanediol bis(*p*-toluenesulfonate), DMF, Cs_2CO_3.

Utilization of 0.5 equiv of α,ω-diamines in the opening of chiral aziridine **18**[12] followed by tosylation successfully led to the preparation of chiral tetraamine **19** in 66% overall yield. Construction of a chiral cyclam derivative **20** was accomplished in 72% yield through reaction of **20** with 1,3-dielectrophile under high dilution conditions.

(13) See Supporting Information for the crystal data of $[Ni\cdot(\mathbf{17})_2]Cl_2\cdot H_2O$.

In conclusion, we have developed a novel and concise synthetic methodology for the construction of chiral peraza-macrocycles through efficient opening of chiral aziridine derivatives. By the judicious choice of dielectophiles, we were able to obtain 1:1 or 2:2 cyclization products. We are currently investigating the scope of this synthetic method for the preparation of other classes of chiral peraza-macrocycles and the utilization of the chiral peraza-macrocycles in the context of chiral artificial metalloenzymes and molecular recognition.

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Supporting Information Available: Experimental procedures, spectral characterization of all new compounds, and crystallographic data for $[Ni\cdot(\mathbf{17})_2]Cl_2\cdot H_2O$. This material is available free of charge via the Internet at http://pubs.acs.org.

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