ORGANIC LETTERS

2011
Vol. 13, No. 24
6540–6543

# Modular Synthesis of Functionalized Bis-bispidine Tetraazamacrocycles

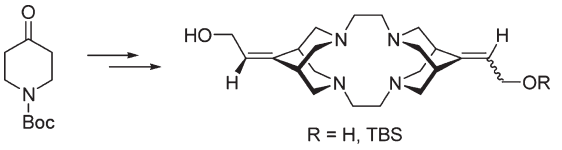
**Zhuo Wang,* Erin J. Miller, and Samantha J. Scalia**

*Department of Chemistry and Biochemistry, University of Windsor, Windsor, Ontario, Canada N9B 3P4*

*zhuowang@uwindsor.ca*

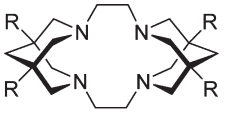
**Received October 20, 2011**

## ABSTRACT




**An effective synthesis is reported for the construction of highly rigid and preorganized bis-bispidine tetraazamacrocycles bearing either identical or different functionalities. Using essential building blocks derived from *N*-Boc-*N*′-allylbispidinone, the modular approach facilitates independent incorporation of the functional groups to the macrocyclic framework as well as selective derivatization of one functionality in the presence of another.**

Macrocyclic compounds are capable of forming stable complexes with selected metal ions of unusual oxidation states.[1] This is particularly the case for highly rigid and preorganized frameworks such as bis-bispidine tetraazamacrocycles (**1**) (Figure 1).[2−6] Due to the high rigidity of the structure and the steric hindrance around the cavity, the macrocycle is considered to have unprecedented ligand field strength for a tetramine donor and has been used to encapsulate metal ions to form highly stable complexes which exhibit interesting optical and electronic properties.[2,3]




**1** (R = H, Me, Ph)

**Figure 1.** Bis-bispidine tetraazamacrocycle.

As part of our research interest to construct polymacrocycles which can be used to selectively bind metal ions with interesting oxidation and electronic states, it was necessary to incorporate the rigid tetraazamacrocycles into a polymer framework.[7,8] This requires that the macrocycle possess suitable functional groups which can be utilized in a polymerization reaction. For this purpose, we found that

(1) (a) Constable, E. C. *Coordination Chemistry of Macrocyclic Compounds*; Oxford Science Publications: New York, 1999. (b) Ribas Gispert, J. *Coordination Chemistry*; Wiley-VCH: Weinheim, 2008. (c) Dietrich, B.; Viout, P.; Lehn, J.-M. *Macrocyclic Chemistry: Aspects of Organic and Inorganic Supramolecular Chemistry*; VCH Weinheim: New York, 1993. (d) *Coordination Chemistry of Macrocyclic Compounds*; Melson, G. A., Ed.; Plenum Press: New York, 1979. (e) *Synthetic Multidentate Macrocyclic Compounds*; Izatt, R. M., Christensen, J. J., Eds.; Academic Press, Inc.: New York, 1978.

(2) For recent reviews, see: (a) Comba, P.; Schiek, W. *Coord. Chem. Rev.* **2003**, *238*−*239*, 21. (b) Barefield, E. K. *Coord. Chem. Rev.* **2010**, *254*, 1607. (c) Hancock, R. D.; Melton, D. L.; Harrington, J. M.; McDonald, F. C.; Gephart, R. T.; Boone, L. L.; Jones, S. B.; Dean, N. E.; Whitehead, J. R.; Cockrell, G. M. *Coord. Chem. Rev.* **2007**, *251*, 1678.

(3) Comba, P.; Pritzkow, H.; Schiek, W. *Angew. Chem., Int. Ed.* **2001**, *40*, 2465.

(4) Miyahara, Y.; Goto, K.; Inazu, T. *Chem. Lett.* **2000**, 620.

(5) Miyahara, Y.; Goto, K.; Inazu, T. *Tetrahedron Lett.* **2001**, *42*, 3097.

(6) Galasso, V.; Goto, K.; Miyahara, Y.; Kovac, B.; Klasinc, L. *Chem. Phys.* **2002**, *277*, 229.

(7) For metal-containing polymers, see: (a) Manners, I. *Synthetic Metal-Containing Polymers*; Wiley-VCH Verlag: Weinheim, 2004. (b) Abd-El-Aziz, A. S. *Macromol. Rapid Commun.* **2002**, *23*, 995. (c) *Metal-Containing and Metallosupramolecular Polymers and Materials*; Schubert, U. S., Newkome, G. R., Manners, I., Eds.; ACS Symposium Series 928; American Chemical Society: Washington, D.C., 2006.

(8) For polymacrocycles, see, for example: (a) Zhan, H.; Lamare, S.; Ng, A.; Kenny, T.; Guernon, H.; Chan, W.-K.; Djurisic, A. B.; Harvey, P. D.; Wong, W.-Y. *Macromolecules* **2011**, *44*, 5155. (b) Delaviz, Y.; Gibson, H. W. *Macromolecules* **1992**, *25*, 4859. (c) Huang, X.; Zhu, C.; Zhang, S.; Li, W.; Guo, Y.; Zhan, X.; Liu, Y.; Bo, Z. *Macromolecules* **2008**, *41*, 6895.

10.1021/ol202840s 
**Published on Web 11/15/2011**

the existing literature methods developed for the construction of **1** could not be successfully adapted to the synthesis of functionalized bis-bispidine macrocycles due to a lack of tolerance for the functional groups, inefficient transformation, and/or generation of byproducts which were difficult to remove by conventional purification methods.[3−5,9,10] In this communication, we report an effective synthetic pathway which provides access to functionalized bis-bispidine tetraazamacrocycles. The modular approach allows independent incorporation of the functionalities to the highly rigid macrocycle as well as selective derivatization of one functional group in the presence of another.

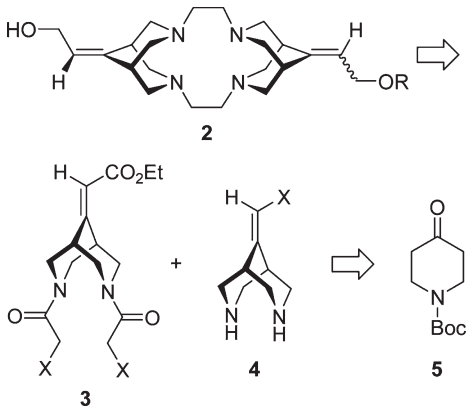
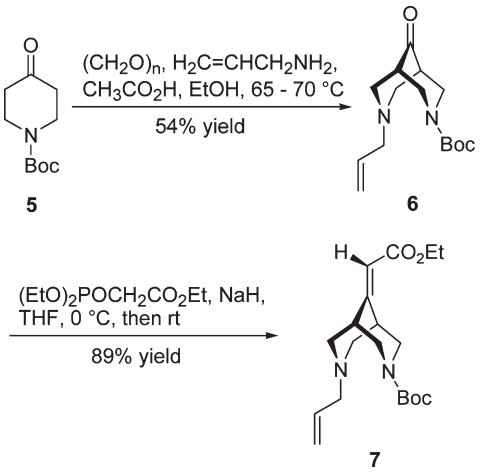



**Figure 2.** Retrosynthetic plan.

The target macrocycle would be constructed via cyclization of functionalized bispidine derivatives **3** and **4** (Figure 2). Both building blocks could be prepared from *N*-Boc-4-piperidone (**5**) via double Mannich reaction. Thus, reaction of **5** with paraformaldehyde and allylamine under acidic conditions afforded *N*-Boc-*N*′-allylbispidinone (**6**) in 54% yield (Scheme 1).[11,12] Deprotonation of triethyl phosphonoacetate followed by nucleophilic addition of the resulting carbanion to bispidinone **6** under Horner−Wadsworth−Emmons conditions generated the desired bispidine ester **7** in excellent yield.[13]

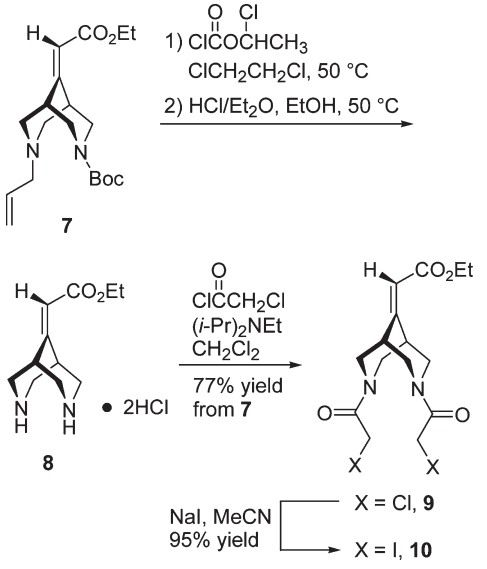
Besides **6**, *N*,*N*′-diallylbispidinone and *N*-Boc-*N*′-benzylbispidinone had also been investigated as possible substrates for the construction of the tetraazamacrocycles. Both compounds were prepared in good yields via a double Mannich reaction in a similar fashion to the synthesis of **6**, with the former generated from *N*-allyl-4-piperidone and allylamine, and the latter from *N*-Boc-4-piperidone (**5**) and benzylamine. However, the diallyl substituents in *N*,*N*′-diallylbispidinone and the benzyl substituent in

**Scheme 1.** Synthesis of Bispidine Ester **7**




*N*-Boc-*N*′-benzylbispidinone were difficult to remove cleanly in subsequent reactions. Bispidinone **6** was found to be much superior in this regard.

**Scheme 2.** Synthesis of Bis(iodoacetamide) **10**



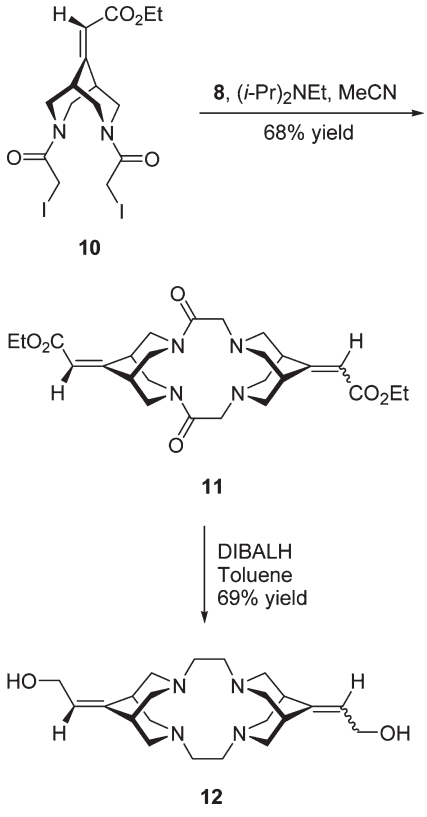

The allyl group on bispidine ester **7** was removed cleanly upon treatment with 1-chloroethyl chloroformate (Scheme 2).[14,15] The resulting 1-chloroethyl carbamate was cleaved efficiently together with the Boc protective group under acidic conditions to give bispidine hydrochloride **8**. Acetylation of **8** with chloroacetyl chloride provided bis(chloroacetamide) **9** in 77% overall yield from bispidine

(9) Miyahara, Y.; Goto, K.; Inazu, T. *Synthesis* **2001**, 364.
(10) Black, D. S. C.; Deacon, G. B.; Rose, M. *Tetrahedron* **1995**, *51*, 2055.
(11) Ruenitz, P. C.; Smissman, E. E. *J. Heterocycl. Chem.* **1976**, *13*, 1111.
(12) Huttenloch, O.; Laxman, E.; Waldmann, H. *Chem.—Eur. J.* **2002**, *8*, 4767.
(13) Wadsworth, W. *Org. React.* **1977**, *25*, 73.
(14) Olofson, R. A.; Martz, J. T.; Senet, J.-P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081.
(15) Tidwell, J. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11797.

ester **7**. Further conversion of **9** to bis(iodoacetamide) **10** was achieved in high yield.

Macrocyclization of bispidine hydrochloride **8** with bis(iodoacetamide) **10** proceeded smoothly at room temperature to afford bisamide **11** in 68% yield (Scheme 3). In comparison, cyclization of **8** with the chloro substrate **9** did not proceed after a prolonged reaction at reflux. The bromo substrate, which can be prepared from **8** and bromoacetyl bromide in a similar way to the synthesis of **9**, was also unsuitable as its reaction with **8** was very sluggish.

**Scheme 3.** Formation of Dihydroxy Tetraazamacrocycle **12**



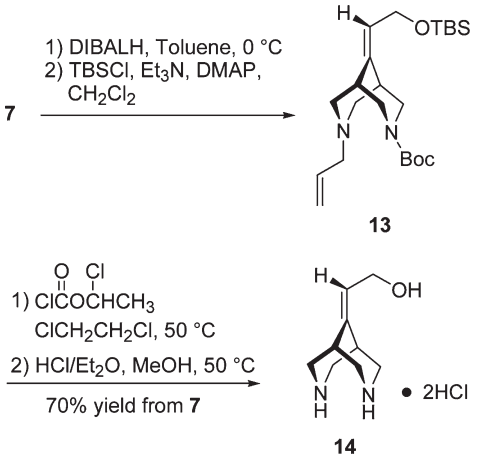

The $^{1}H$ and $^{13}C$ NMR spectra of the macrocyclic bisamide **11** are unusually complex.[16] Similar results have been obtained for bisamide **15**. However, upon DIBALH reduction of **11**, the resultant tetraazamacrocycle **12** demonstrates straightforward NMR data in accordance with the proposed structure. Likewise, tetraazamacrocycle **16** displays clear-cut spectra. These results seem to suggest that bisamide **11** (and **15**) possesses different conformations which may not interconvert quickly on the NMR time scale due, in part, to a significant restriction to bond rotations imposed by the bispidine rings and the amide groups. As each conformer may exhibit distinctive resonance peaks, it is possible that the $^{1}H$ and $^{13}C$ NMR spectra represent a collection of resonances produced by the different conformers.

(16) See Supporting Information.

The tetraazamacrocyclic diol **12** possesses two primary hydroxyl groups that extend away from the ring system. This is expected to render them sterically favorable for further reactions and functionalizations. However, derivatization seems to be limited to the generation of identical functionalities as our attempt to monosilylate **12** led to a mixture of mono- and diprotected products as well as unprotected diols.[17,18]

In order to incorporate different functional groups on each end of the tetraazamacrocylic framework, it is more straightforward to introduce the functionalities to the bispidine building blocks prior to macrocyclization. To this end, DIBALH reduction of bispidine ester **7** followed by TBS-protection afforded silyl ether **13** (Scheme 4).[19] Subsequent removal of the allyl, Boc, and TBS groups provided hydroxybispidine **14** in 70% overall yield.

**Scheme 4.** Synthesis of Hydroxybispidine **14**




Macrocyclization of **14** and **10** generated bisamide **15** which was then reduced to give the desired monoprotected hydroxy tetraazamacrocycle **16** (Scheme 5). In the DIBALH reduction of **15**, it was found that solvents played an important role. At ambient temperature, reduction of the amide groups in **15** proceeded sluggishly in THF. When toluene was used, the amide groups could be successfully reduced.[20] However, the TBS protective group was also completely cleaved. The best solvent system for this reduction seems to be a mixture of toluene and diethyl ether which facilitated the reduction of the amide and ester groups while keeping the TBS group intact.[21]

The tetraazamacrocycles **12** and **16** possess a highly basic tetramine core which can bind readily to normal-phase silica gel and therefore could not be purified on a

(17) McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388.

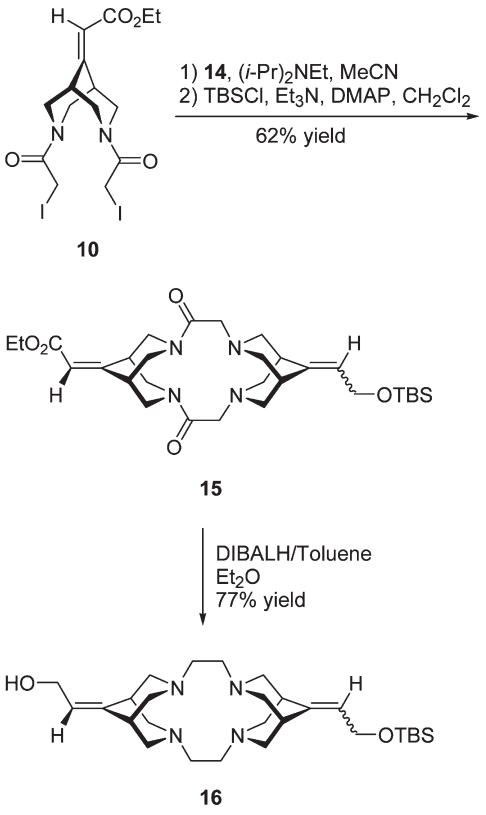
(18) Yu, C.; Liu, B.; Hu, L. *Tetrahedron Lett.* **2000**, *41*, 4281.

(19) TBS protection was necessary as the hydroxyl group can react with 1-chloroethyl chloroformate and interfere with the allyl group removal in the next step.

(20) Yoon, N. M.; Gyoung, Y. S. *J. Org. Chem.* **1985**, *50*, 2443.

(21) Taniguchi, T.; Ogasawara, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 1136.

**Scheme 5.** Formation of Hydroxy Tetraazamacrocycle **16**




conventional column. Sublimation of the compounds was unsuccessful due, in part, to strong intermolecular hydrogen bonding. However, they can be purified without difficulty by column chromatography using commercially available reversed-phase silica gel.

It should be noted that the hydroxyl group in the monoprotected macrocycle **16** can be selectively transformed in the presence of the silyl ether group when further derivatization is desired. This will enable independent introduction of various functionalities to either side of the tetraazamacrocyclic structure if necessary.

In summary, an effective synthetic pathway has been developed for the construction of functionalized bis-bispidine tetraazamacrocycles. Using essential building blocks derived from bispidinone **6**, the modular approach facilitates independent incorporation of either identical or different functionalities to the highly rigid and preorganized macrocycle. The synthesis offers the opportunity for further derivatization after the formation of the tetraazamacrocyclic framework, including selective transformation of one functional group in the presence of another. This makes it possible to introduce a variety of functional groups, in particular those which may be labile throughout the macrocycle formation, onto the ring system. Currently, this synthetic approach is being employed in the preparation of polytetraazamacrocycles which will be reported in due course.

**Acknowledgment.** We thank the Natural Science and Engineering Research Council (NSERC) of Canada for funding. We also thank Dr. Jiaxi Wang at Queen's University, Canada, for HRMS analysis.

**Supporting Information Available.** Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.