Synthesis of Conformationally Tailored Pentaazacyclopentadecanes.
Preorganizing Peptide Cyclizations.

William L. Neumann,* Gary W. Franklin, Kirby R. Sample, Karl W. Aston,

Randy H. Weiss, and Dennis P. Riley.

Contribution from the Monsanto Company, St. Louis, Missouri 63167

Abstract: A general method for the preparation of rigidified pentaazamacrocycles using *trans*-(1R,2R)-diaminocyclohexane as the conformational controller element. High macrocyclization yields have been obtained by strategic placement of the diamino-cyclohexane group within the pseudopeptide backbone. © 1997, Elsevier Science Ltd. All rights reserved.

As part of our ongoing program aimed at the discovery and pharmaceutical development of small molecule transition metal complexes which mimic the actions of the macromolecular superoxide dismutase (SOD) enzymes,[1] we required general synthetic strategies that could access many types of macrocyclic ligand systems. We have previously reported the asymmetric synthesis of functionalized 1,4,7,10,13-pentaazacyclopentadecanes, ([15]aneN₅), via hydride reduction of cyclic peptide precursors.[2] The strength of the method lies in the ability to generate macrocyclic ligands for metal chelation which incorporate stereogenic centers to a degree that has been previously unattainable. We now report a pseudopeptide approach for the synthesis of further rigidified pentaazamacrocycles containing fused-cyclohexane rings.

Commercially available *trans*-(1R,2R)-diaminocyclohexane **1** was converted to the pseudodipeptide building block **2** in three steps by monotosylation, Boc-protection and alkylation of the sulfonamide anion with methyl bromoacetate. Pseudodipeptide **2** has been inserted directly into standard solution-phase synthesis protocols[3] and serves as a typical lipophilic residue for coupling reactions. Thus, **2** has been incorporated into a number of pseudopentapeptides with the diaminocyclohexane group as the central "residue" (Table 1). As the central "residue", *trans*-diaminocyclohexane behaves as a configurationally stable *cis*-amide bond surrogate,[4] affording a rigid reverse turn of the pseudopeptide.[5] In this way, most of the entropic cost associated with preorganizing the C- and N-termini for macrocyclization have been paid for by the diaminocyclohexane group. Thus, very efficient macrocyclizations are observed which generally fall in the range of 60 - 90% yield. We have conducted variable temperature NMR studies of the Boc-ethyl ester precursor of **3a** in the cyclization solvent (14mM in DMF-d₇) to probe for the existence of intramolecular hydrogen bonding which may result from and/or contribute to the preorganization in these systems.[5,6] Indeed, a low temperature coefficient ($\Delta\delta/\Delta t$ = -2.59

Scheme 1

R_1, R_2, R_3 = H or CH_3
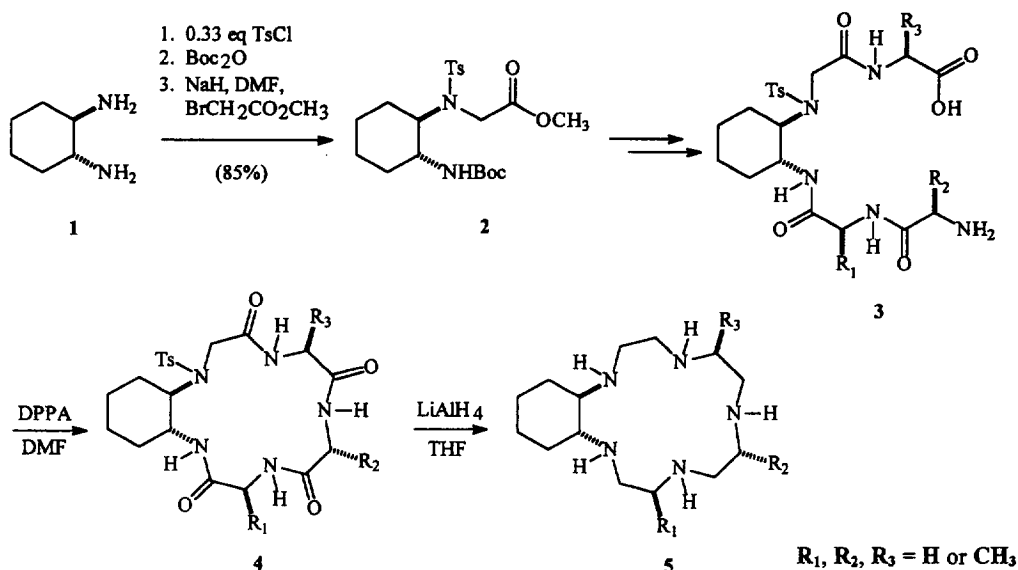
Table 1. Cyclization and Reduction of *trans*-Diaminocyclohexane-Containing Pseudopeptides

| Linear "Peptide"[a]	Cyclization Product / Yield (%)	Cyclo-Dimer (%)	Reduction Yield (%)	Product
Gly-Gly-Cyc-TsGly-Gly, **3a**	**4a** / 90	none	76	**5a**
D-Ala-Ala-Cyc-TsGly-Ala, **3b**	**4b** / 85	none	72	**5b**
D-Ala-Ala-Cyc-TsGly-D-Ala, **3c**	**4c** / 88	<5[b]	83	**5c**

a. Cyc = Cyclohexanediamine

b. By mass spectroscopic analysis

ppb/°C) for the cyclohexyl-NH was observed over a large temperature range (-50 to 90°C). Moreover, in the cyclization temperature window (-15 to 25°C) the cyclohexyl-NH displays very little temperature dependence of chemical shift ($\Delta\delta/\Delta t$ = -0.46 ppb/°C) indicating a high degree of shielding from the hydrogen bond-accepting solvent DMF-d_7. We propose that this cyclohexyl-NH is hydrogen bonded to the N-tosylglycine carbonyl (Figure 1). This affords an eight-membered hydrogen bonded ring resembling a δ-type turn.[7]

As an example from this series, a 29g sample of **3b** (as the TFA salt) was cyclized in 85% yield using diphenylphosphoryl azide (DPPA) in DMF to afford 19.1g of pure cyclic pseudopeptide **4b**.[2,3a] As is evident from the high cyclization yields in Table 1, the preorganization afforded by the *trans*-diaminocyclohexane group is not disrupted by heavier substitution patterns. Compound **3b** contains alternating peptide residues of opposite

Figure 1. Proposed Intramolecular Hydrogen Bonding.
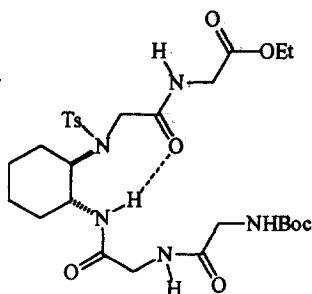
configuration and may actually help to further enforce the reverse-turn conformation.[3c] In addition, this stereochemistry should ultimately afford a pentaazacyclopentadecane ligand **5b** that is highly preorganized for chelation.[1b] Reduction of 5.20g of **4b** afforded, after recrystallization from acetonitrile, 2.26g (72% yield) of analytically pure ligand **5b**. Due to the use of peptide-like intermediates, we were concerned by the potential for racemization upon extended exposure to the lithium aluminum hydride reduction conditions. However, in nearly all cases we recovered single isomers that are diastereomerically clean by NMR spectroscopy.
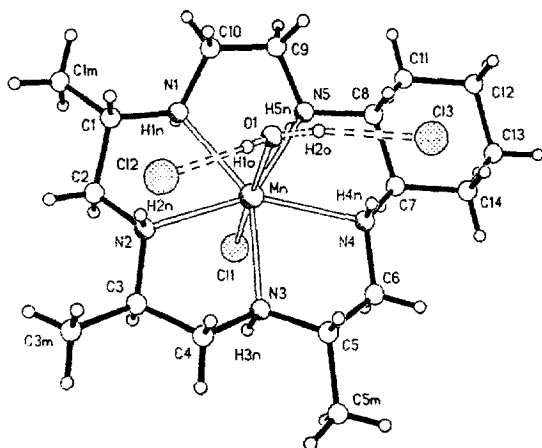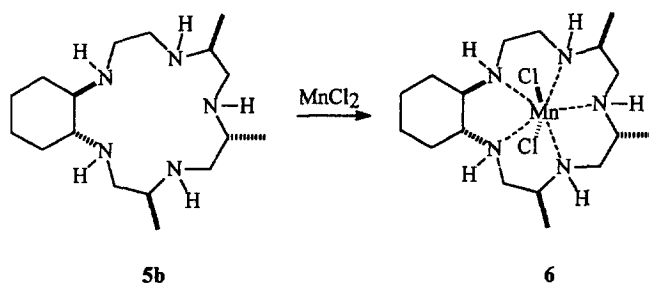

5b   **6**

Figure 2. Perspective plot for complex **6**. Hydrogen bonding interactions involving the coordinated water and Cl⁻ ions are represented by dashed open bonds.

Based upon the X-ray crystal structure of the parent [Mn([15]andN$_5$)Cl$_2$] complex,[1a] we theorized that the three methyl groups of **5b** would occupy equatorial positions relative to their individual chelate rings in the resulting Mn(II) complex. X-ray crystallographic analysis of complex **6** confirms the absolute stereochemistry of the ligand system (Figure 2). As planned, the methyl groups, which are equatorial to their respective chelate rings are also "equatorial" to the overall complex due to the rigidified planar nature of the macrocyclic ligand. Subtle conformational control of the ligand on the metal center by the use of alternate substituent configurations has enormous implications with respect to SOD catalysis.[1b] Extensive studies concerning Mn(II) complexes with folded forms of these macrocyclic ligands and their performance as SOD mimics will be reported elsewhere.

1. (a) Riley, D.P.; Weiss, R.H. *J. Am. Chem. Soc.* **1994**, *116*, 387. (b) Riley, D.P.; Henke, S.L.; Lennon, P.J.; Weiss, R.H.; Neumann, W.L.; Rivers, W.J.; Aston, K.W.; Sample, K.R.; Rahman, H.; Ling, C.-S.; Shieh, J.-J.; Busch, D.H.; Szulbinski, W. *Inorg. Chem.* **1996**, *36*, 5213. (c) Weiss, R.H.; Flickinger, A.G.; Rivers, W.J.; Hardy, M.M.; Aston, K.W.; Ryan, U.S.; Riley, D.P. *J. Biol. Chem.* **1993**, *268*, 23049.

2. Aston, K.W.; Henke, S.L.; Modak, A.S.; Riley, D.P.; Sample, K.R.; Weiss, R.H.; Neumann, W.L. *Tetrahedron Lett.* **1994**, *35*, 3687.

3. (a) Veber, D.; Brady, S.F.; Varga, S.L.; Freidinger, R.M.; Schwenk, D.A.; Mendlowski, M.; Holly, F.W. *J. Org. Chem.* **1979**, *44*, 3101. (b) Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*; Springer-Verlag: Berlin, 1984. (c) Kopple, K.D. *J. Pharm. Sci.* **1972**, *61*, 1345. (d) Davies, J.S.; Enjalbal, C.; Wise, C.J.; Webb, S.E.; Jones, G.E. *J. Chem. Soc., Perking Trans. 1* **1994**, 2011. (e) Bogusky, M.J.; Brady, S.F.; Sisko, J.T.; Nutt, R.F.; Smity, G.M. *Int. J. Pept. Protein Res.* **1993**, *42*, 194.

4. Rose, G.D.; Gierasch, L.M.; Smith, J.A. *Adv. Protein Chemistry* **1985**, *37*, 1.

5. (a) Dyson, H.J.; Rance, M.; Houghton, R.A.; Lerner, R.A.; Wright, P.E. *J. Mol. Biol.* **1988**, *201*, 161. (b) Balaram, P.; Sakol, D. *Biochemistry* **1986**, *25*, 6004. (c) Gellman, S.; Dado, G.P.; Liang, G.-B.; Adams, B.R. *J. Am. Chem. Soc.* **1991**, *113*, 1164.

6. (a) For example of a *cis*-amide bond surrogate see: Abell, A.D.; Hoult, D.A.; Jamieson, E.J. *Tetrahedron Lett.* **1992**, *33*, 5831. (b) For numerous references concerning the incorporation of conformationally rigid molecules into peptides to stabilize a single conformation and for the design and synthesis of β-turn mimetics see: Tsang, K.Y.; Diaz, H.; Graciani, N.; Kelly, J.W. *J. Am. Chem. Soc.* **1994**, *116*, 3988.

7. Stroup, A.N.; Rockwell, A.L.; Rhiengold, A.L.; Gierasch, L.M. *J. Am. Chem. Soc.* **1988**, *110*, 5157 and references cited therein.