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# Asymmetric Synthesis of Highly Functionalized Polyazamacrocycles via Reduction of Cyclic Peptide Precursors.

Karl W. Aston, Susan L. Henke, Anil S. Modak, Dennis P. Riley, Kirby R. Sample, Randy H. Weiss, and William L. Neumann*

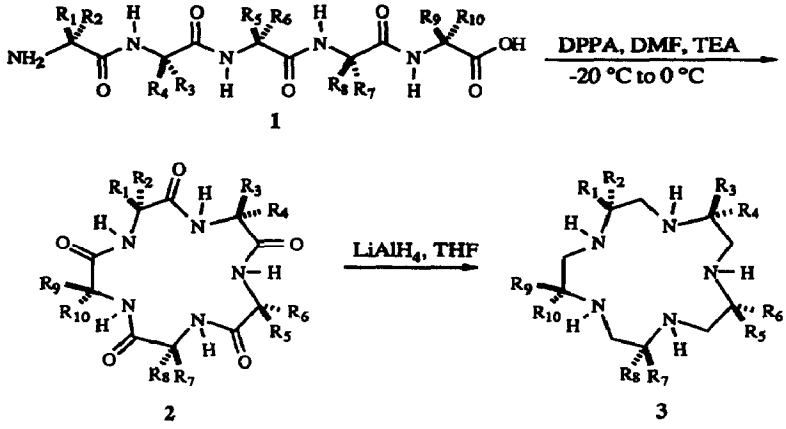
Contribution from the Monsanto Company, St. Louis, Missouri 63167

*Abstract:* A general synthetic method for the preparation of carbon-functionalized polyazamacrocycles from the corresponding cyclic peptides is described.

Polyazamacrocycles, a diverse class of molecules which contain three or more nitrogen atoms within a cyclic carbon backbone, are highly preorganized ligand systems for metal coordination.[1] From the standpoint of designing and synthesizing biologically stable metalloenzyme mimetics we have found that polyazamacrocycles afford not only excellent ligand environments but also suitable platforms for building in functionality capable of directing and/or enhancing programmed modes of catalysis. These features have been particularly useful for the development of superoxide dismutase mimetics based upon polyazamacrocyclic complexes of manganese(II).[2] While a large number of reports have appeared detailing the synthesis of nitrogen substituted polyazamacrocycles, carbon backbone functionalized versions are less common.[3]

We report herein a general method for the asymmetric synthesis of carbon-functionalized pentaazacyclopentadecane systems by complete hydride reduction of the corresponding cyclic pentapeptide precursors. The key strategic advantage offered by this methodology is that the macrocyclic ring systems can be assembled through well-known peptide synthesis and peptide cyclization chemistry[4] with a wide variety of natural and/or unnatural amino acid side-chain functionality present. Thus, one is able to take advantage of the extensive arsenal of very mild reagents and methods that have been developed for peptide synthesis for the ultimate goal of preparing highly functionalized *non-peptide* polyazamacrocycles.[5]

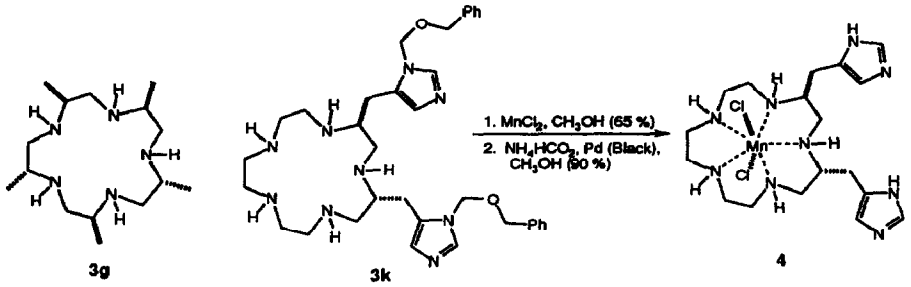
Scheme I illustrates the general synthetic route for preparing functionalized pentaazamacrocycles from cyclic pentapeptides. The requisite linear pentapeptides were assembled through standard solution-phase peptide synthesis and cyclized according to the method of Veber using diphenylphosphoryl azide (DPPA) as the coupling agent.[6] The cyclization yield was found to vary with the degree of side-chain substitution and stereochemistry (see Table I) and was optimized for substitution patterns which further stabilize ß-turn conformation of the linear peptide (such as opposite stereochemical configuration of side chain substituents on adjacent residues).[6] For pentasubstituted cases it was found that optimal




1 2 3

Scheme I

yields were obtained when macrocyclizations were designed via coupling of N-terminus and C-terminus residues of opposite configurations. The resulting cyclic pentapeptides were routinely prepared on 10 to 20 g scale and reduced to the corresponding pentaazacyclopentadecane systems with lithium aluminum hydride in THF. Most of the more hydrophilic cyclic peptides could be solubilized in THF by carefully controlling the stoichiometry of the lithium aluminum hydride added. For example, when a suspension of *cyclo*-(Gly-Ala-Gly-D-Ala-Gly-) (2c) in THF was treated with 12 equivalents of lithium aluminum hydride (2.4 equivalents per amide group), *a completely homogeneous solution resulted!*[7] This type of inorganic additive-assisted peptide solubilization in non-polar organic solvents has been




3g 3k 4

Fig 1.

documented by Seebach.[8] However, to our knowledge this is the first time lithium aluminum hydride has been employed as the "additive". In general, the solutions were heated at reflux over night to insure complete reduction during which time they became heterogeneous again. The products were isolated by

standard methods and purified by recrystallization.[9] Cyclization and reduction results are summarized in Table I.

Using this methodology a wide variety of amino acid side-chain functionality can be incorporated onto the carbon framework of the polyazamacrocycle. For example compound **3g**, with a methyl group (derived from alanine) on each chelate ring, is highly preorganized ligand for metal chelation. Additionally, the bis-imidazolylmethyl complex **4** is representative of the types of functionalized metal complexes that can be prepared from these ligand systems. In this example, the manganese(II) complex was prepared from the protected bis-benzyloxymethyl ligand **3k** and the protecting groups were removed hydrogenolytically in a "post- chelate" operation (Fig. 2).[10] Therapeutic applications of the manganese(II) complexes of the functionalized ligands described herein as synthetic superoxide

**Table I. Preparation of Functionalized Pentaazacyclopentadecanes**

| Entry | Linear Peptide[a] | Cyclization yield (%) | Reduction yield (%)[b] | Product[c] |
|---|---|---|---|---|
| 1 | Gly-Ala-D-Ala-Gly-Gly | 60 | 56 | **3a** ($R_3$, $R_6 = CH_3$) |
| 2 | Gly-Ala-Ala-Gly-Gly | 52 | 65 | **3b** ($R_3$, $R_5 = CH_3$) |
| 3 | Gly-Ala-Gly-D-Ala-Gly | 67 | 39 | **3c** ($R_3$, $R_8 = CH_3$) |
| 4 | Gly-Ala-Gly-Ala-Gly | 35 | 63 | **3d** ($R_3$, $R_7 = CH_3$) |
| 5 | Gly-Ala-D-Ala-Ala-Gly | 23 | 71 | **3e** ($R_3$, $R_6$, $R_7 = CH_3$) |
| 6 | Gly-Ala-D-Ala-Ala-D-Ala | 48 | 70 | **3f** ($R_3$, $R_6$, $R_7$, $R_{10} = CH_3$) |
| 7 | Ala-Ala-D-Ala-Ala-D-Ala | 54 | 44 | **3g** ($R_1$, $R_3$, $R_6$, $R_7$, $R_{10} = CH_3$) |
| 8 | Gly-Gly-Ppg[d]-Gly-Gly | 30 | 23 | **3h** ($R_5$ or $R_6 = CH_2C{\equiv}CH$)[d] |
| 9 | Gly-Gly-Tyr(OBzl)[e]-Gly-Gly | 62 | 57 | **3i** ($R_5 = CH_2C_6H_4OBzl$) |
| 10 | Ser(OBzl)-D-Ser(OBzl)-Ser(OBzl)-D-Ser(OBzl)-Gly | 49 | 69 | **3j** ($R_1$, $R_4$, $R_5$, $R_8 = CH_2OBzl$) |
| 11 | Gly-His(Bom)[f]-D-His(Bom) Gly-Gly | 78 | 25 | **3k** ($R_3$, $R_6$, = (N-π-Bom)-imidazolylmethyl |

[a] Linear peptides were prepared as either TFA or HCl salts. [b] Unoptimized yields. [c] All other R groups are H. [d] Racemic α-propargyl glycine. [e] Bzl = Benzyl. [f] Bom = Benzyloxymethyl.

dismutase mimetics with improved catalytic activities and/or tailored biophysical properties will be the subject of future reports. Synthetic studies extending this method to other ring sizes, substitution patterns and carbon functionality are in progress.

***References and Notes***

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2. For a preliminary account describing the design and synthesis of functional mimics of manganese superoxide dismutase based upon the parent [15]aneN$_5$ ligand system see: Riley, D.P.; Weiss, R.H. *J. Am. Chem. Soc.* **1994**, *116*, 387-388.
3. (a) It has been shown that C-alkylated ethylene diamine-based ligands (such as EDTA or DTPA) form metal complexes with higher thermodynamic and kinetic stabilities relative to their unsubstituted counterparts due primarily to restricted rotation and thus preorganization of the ethylenediamine units: Martell, A. E.; Hancock, R. D. *Chem. Rev.* **1989**, *89*, 1875. Desper, J.M.; Gellman, S.H.; Wolf, Jr., R.E.; Cooper, S.R. *J. Am. Chem. Soc.* **1991**, *113*, 8663. (b) For the synthesis of some of these types of ligand systems see: McMurray, T.J.; Brechbiel, M.; Wu, C.; Gansow, O. *Bioconjugate Chem.* **1993**, *4*, 236 and references cited therein.
4. (a) Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*; Springer-Verlag: Berlin, 1984. (b) Koppel, K.D. *J. Pharm. Sci.* **1972**, *61*, 1345.
5. For related work in the tetraazamacrocycle area which does not make use of cyclic peptides as penultimate intermediates see: Meares, C.F.; Renn, O. *Bioconjugate Chem.* **1992**, *3*, 563.
6. 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.
7. All of the glycine/alanine-based peptides reported in this paper appear to be virtually insoluble in THF alone. In general addition of less than or greater than ~2 equivalents of lithium aluminum hydride per amide function resulted in heterogeneous mixtures.
8. Seebach, D.; Thaler, A.; Beck, A.K. *Helv. Chim. Acta* **1989**, *72*, 857.
9. Typical procedure: **(2*S*,5*R*)-Dimethyl-1,4,7,10,13-pentaazacyclopentadecane.** An oven-dried 500 mL flask containing a glass stir-bar was allowed to cool to RT under argon flow and charged with *cyclo*-(Gly-Ala-DAla-Gly-Gly-) **2a**, (5.10 g, 16.3 mmol) and THF (74.0 mL). To this stirred suspension was added 1.0 M LAH in THF (196 mL, 196 mmol) dropwise over 10 min. The suspension was stirred for 1 h at RT and became homogeneous during this time. The mixture was then refluxed for 48 h. The mixture was cooled to ~-20 °C and quenched (cautiously) with saturated sodium sulfate (50 mL). The resulting mixture was concentrated in vacuo to a dry white powder, and this mixture was triturated with methylene chloride* (3 x 100 mL). The combined triturates were concentrated in vacuo and the resulting residue was recrystallized from acetonitrile and then from hexanes to afford 2.23 g (56 % yield) of the pure product **3a** as a white solid: mp = 114-116 °C; $[\alpha]_d^{20}$ = -4.76 (0.008, methanol); $^1$H NMR (300 MHz, $CDCl_3$) δ 2.95 - 2.45 (obs m, 16 H, NC*H*$_2$C*H*$_2$N of ethylene diamine units), 2.30 (dd, *J* = 11.3, 10.0 Hz, 1 H, NC*H*(CH$_3$)CH$_2$N), 2.08 (apparent t, *J* = 10.7 Hz, 1 H, NC*H*(CH$_3$)CH$_2$N), 1.82 (bs, 5 H, N*H*), 1.00 (d, *J* = 6.3 Hz, 3 H, NHCH(C*H*$_3$)CH$_2$NH), 0.99 (d, *J* = 6.0 Hz, 3 H, NHCH(C*H*$_3$)CH$_2$NH); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 56.1 (d, NCH(CH$_3$)CH$_2$N), 54.8 (d, NCH(CH$_3$)CH$_2$N), the following shifts are for NCH$_2$CH$_2$N of ethylene diamine units; 54.2 (t), 54.0 (t), 48.9 (t), 48.7 (t), 48.5 (t), 48.4 (t), 48.3 (t), 46.7 (t); 18.9 (q, NHCH(*C*H$_3$)CH$_2$NH), 18.8 (q, NHCH(*C*H$_3$)CH$_2$NH). MS (HRFAB) *m/z* 244.2516 (M+H)$^+$; 244.2501 calcd for $C_{12}H_{29}N_5$ (M+H)$^+$. Anal calcd. for $C_{12}H_{29}N_5$: C, 59.22; H, 12.01; N, 28.77. Found: C, 58.76; H, 11.96; N, 28.46 (* Methylene chloride appears to be the best solvent for extractive recovery of the reduction product from the concentrated (aqueous sodium sulfate-quenched) reaction mixture. However, prolonged exposure of these polyamine systems to chlorinated hydrocarbon solvents can result in alkylation side-products which lower yields and complicate recrystallizations. In these cases ethyl ether, BHT-free THF or dioxane may be substituted).
10. For procedures representative of the transfer-hydrogenation conditions used see: Bieg, T; Szeja, W. *Synthesis* **1985**, 76.

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