Pergamon

Tetrahedron Letters, Vol. 38, No. 18, pp. 3143-3146, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00563-7

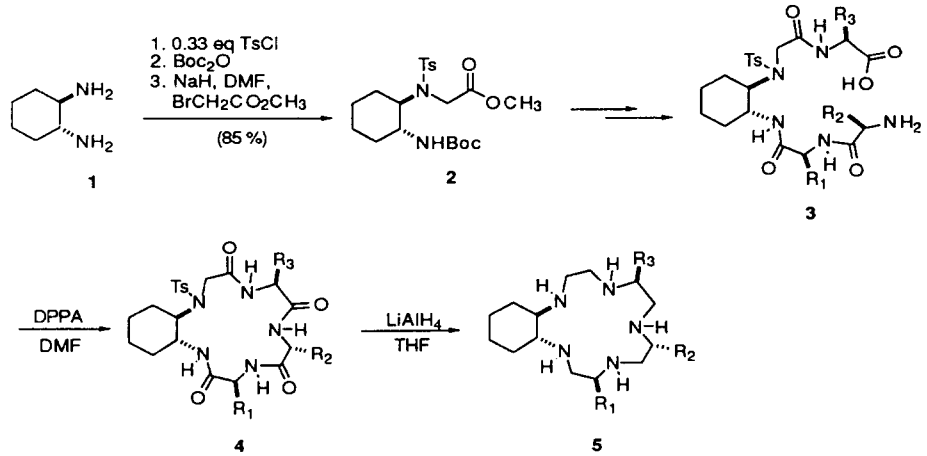
Pseudopeptide Synthesis of a Pentaazamacrocycle Containing Two *trans*-Fused Cyclohexane Rings.

William L, Neumann,* Gary W. Franklin, Kirby R. Sample, Karl W. Aston,
Randy H. Weiss, Dennis P. Riley and Nigam Rath†

Monsanto Corporate Research, 800 N. Lindbergh, St. Louis, Missouri 63167
and The University of Missouri, St. Louis, Missouri 63121†

Abstract: The synthesis of a bis-cyclohexyl-fused pentaazamacrocycle via head-to-tail pseudopeptide cyclization chemistry is described. The bis-cyclohexyl-fused cyclic pseudopeptide 11 displays intramolecular hydrogen bonding which has been characterized by variable temperature NMR spectroscopy and X-Ray Crystallography.

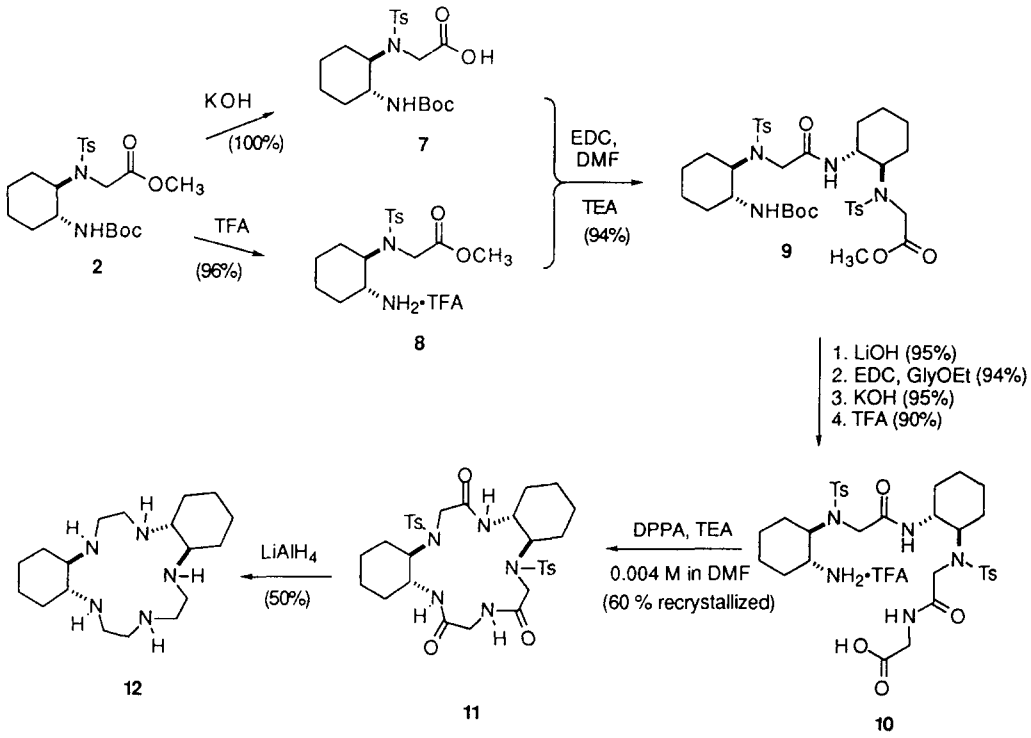
We have recently reported the synthesis of functionalized pentaazamacrocycles containing a fused cyclohexane group for conformational control.[1] This methodology involves the elaboration of readily available (1*R*, 2*R*)-diaminocyclohexane **1** into a pseudodipeptide **2** which is then incorporated into a larger peptide by standard methods (Scheme 1). As the central "residue" of a pseudopentapeptide **3**, the *trans*-diaminocyclohexane group serves to preorganize the N- and C-termini for cyclization affording excellent macrocyclization yields (60 - 90 %). Thus, the same conformational control element that preorganizes the final macrocyclic ligand system for metal



Scheme 1

chelation also drives the synthesis by preorganizing the peptide-like macrocyclization step. A series of cyclic pseudopeptides were prepared and reduced to the corresponding pentaazamacrocycles **5** with lithium aluminum hydride.

In other work from these laboratories, Lennon[2] has reported the facile synthesis of bis-cyclohexyl-fused pentaazamacrocycles via a bis(chloroacetamide) cycloalkylation approach. As our work using head-to-tail peptide and pseudo-peptide segments for the construction of polyazamacrocycles developed, we became interested in appling this chemistry to bis-cyclohexyl-fused targets as well. The versatility of peptide chemistry[3] and side-chain substitution combined with the ability to build-in peptide registry secondary structural features[4] which can enhance macrocyclization chemistry made this a desirable alternative. We now report that the pseudopeptide chemistry (Scheme 1) has also been performed in an iterative sense for the preparation of the further rigidified bis-cyclohexyl macrocycle **12** (Scheme 2). Pseudodipeptide **2**



Scheme 2

was split into two fractions; half of the material was saponified to **7** and the other half was deprotected at the N-terminus to afford TFA salt **8**. Peptide coupling of **7** and **8** afforded compound **9**. This material was further elaborated to **10** by saponifiction and peptide coupling with glycine ethyl ester followed by another saponification and TFA-mediated cleavage of the N-terminal Boc group. Compound **10** was cyclized using DPPA as the coupling agent in either ACN or DMF to afford product **11** in 60% yield (recrystallized). Lithium aluminum hydride reduction afforded the analytically pure ligand system **12** in 50% yield after recrystallization from ACN.[5] It is noteworthy that this synthesis requires no chromatographies and has been carried out on 50 to 100g scale.

Crystallographic analysis of **11** shows a rigid intramolecular hydrogen bond between carbonyl oxygen O(1) and amide N(4)H with a distance of 1.987 Å (Figure 1).[6a] With the diaminocyclohexane group occupying a "loop-residue" position, this hydrogen bonded ring resembles a 10-membered β-turn structure.[4] This hydrogen bond is retained in solution as determined by variable temperature NMR spectroscopy.[7] The temperature coefficient, $\Delta\delta/\Delta t$, for

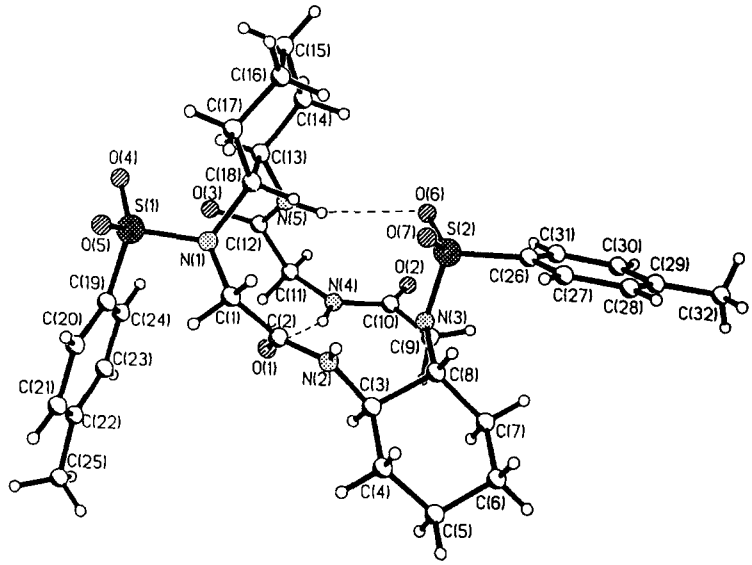


Figure 1. Perspective plot for 11.

amide NH(4) was zero over a 55 °C temperature range in DMSO-d_6, indicating complete shielding from the strongly hydrogen bonding solvent. In addition, another solvent shielded proton was identified by variable temperature NMR. In this case the amide N(5)H displays a temperature coefficient, $\Delta\delta/\Delta t$ = 1.2, a value which is characteristic of hydrogen bonded amide NH's in more flexable systems.[7b,c] The crystal structure of **11** also indicates a close contact of 2.353 Å between amide N(5)H and sulfonamide oxygen O(6) which is consistent with the solvent shielding observed for this proton in the variable temperature NMR experiment.

In summary, the chemistry outlined in Schemes 1 and 2 defines new peptide-like syntheses of conformationally-tailored pentaazacyclopentadecane ligand systems for metal chelation. Detailed analysis of intramolecular hydrogen bonding as a sensitive indicator of the preorganization of cyclization substrates and synthetic extentions to more functionalized macrocycles will be the subject of further studies.

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(*Received in USA* 10 *January* 1997; *revised* 17 *March* 1997; *accepted* 18 *March* 1997)