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The Synthesis and Conformation of Dihydroxy-cyclo(D-Pro-L-Pro-D-Pro-L-Pro)

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The first synthesis of a derivative of cyclo(D-Pro-L-Pro-D-Pro-L-Pro) is reported. The convergent route to the molecule is amenable to the synthesis of gram quantities of the desired compound. The cyclization of the linear tetramer was found to give specifically one conformation of the 12 member macrocycle. The structural assignment, by 2D NMR, of the favored conformation is also reported.

We are interested in using stable, well organized peptide structures as ligands for transition metals. We recently reported the synthesis of a helical peptide phosphine ligand.[1] Besides helices, peptides offer other interesting structures. Blout and others reported that cyclic proline containing peptides often possess stable structures.[2-6] In 1989 Mästle, Weber, Thewalt and Rothe reported the synthesis and properties of an interesting proline tetramer, cyclo(D-Pro-L-Pro-D-Pro-L-Pro) (figure 1).[7] For molecules of this type to be useful as transition metal ligands, routes to functionalized derivatives must be developed. This paper reports the synthesis and interesting conformational preference of the dihydroxy derivative of cyclo(D-Pro-L-Pro-D-Pro-L-Pro).

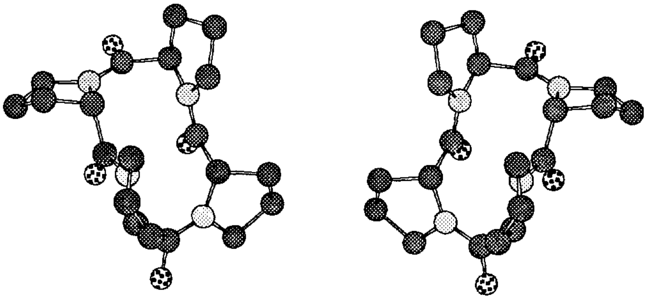
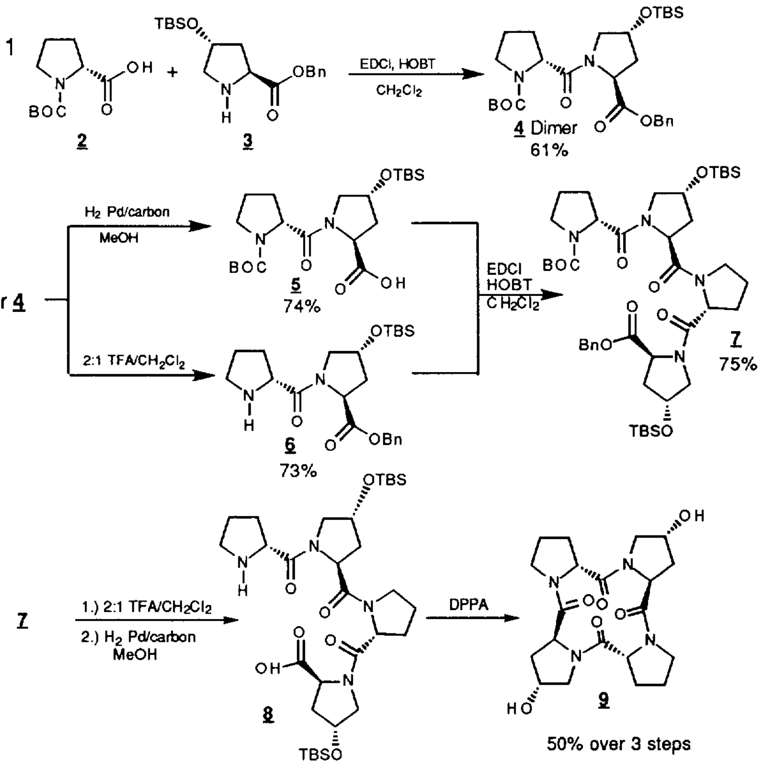


Figure 1: Cycloenantiomers of Cyclo(D-Pro-L-Pro-D-Pro-L-Pro)

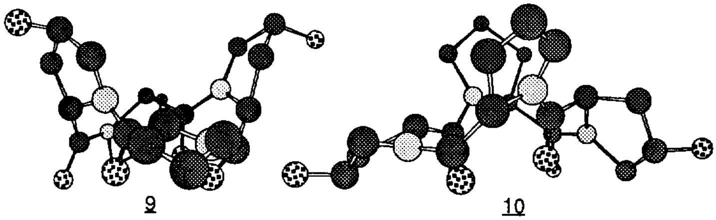
The single crystal x-ray structure of cyclo(D-Pro-L-Pro-D-Pro-L-Pro) indicates that it exists in two conformations. In each conformation, two proline rings opposite each other are parallel and approximately perpendicular to the plane of the macrocycle. The other two rings are parallel to the pseudo plane of the macrocycle (figure 1). The amide bonds in these macrocycles are cis, trans, cis, trans. The two conformations differ from each other in that the proline rings exchange their relative orientations, the prolines perpendicular to the plane of the macrocycle become parallel to it and the parallel rings become perpendicular. This is accomplished by the trans amide bonds isomerizing to cis and the cis to trans. These two conformations are nonsuperimposable mirror images of each other and consequently are cycloenantiomers.[8] The other interesting feature is that the four amide carbonyls are all on the same face of the molecule. This makes one face of the molecule hydrophobic and the other hydrophilic. Upon isomerization the four carbonyls move up through the center of the molecule to be positioned on the other face of the macrocycle, exchanging the hydrophobic and hydrophilic faces of the molecule.

Scheme 1



The original synthesis, by Mästle et al, was by solid phase peptide synthesis and cyclization of the linear tetramer after cleavage from the resin.[7] Rather than take a linear solid phase approach to the desired molecule we have designed a convergent solution phase route. Coupling of protected D-proline **2** with protected trans-4-hydroxy-L-proline **3** proceeds in high yield to give the key dimer[9] **4** necessary for the synthesis of the cyclic tetramer. Reaction of half of the dimer with hydrogen under catalysis by palladium on carbon gives free acid **5**. Reaction of the other half of the dimer with trifluoroacetic acid gives free amine **6**. The acyclic tetramer **7** is synthesized by coupling **5** and **6** with EDCl and HOBT. Deprotection of the two ends of the tetramer yields **8** ready for cyclization. The conditions reported by Mästle were used for the cyclization, slow addition of tetramer **8** to a solution of DPPA.

The product of the cyclization is readily characterized by ^{13}C NMR. Upon cyclization the number of ^{13}C resonances decreases by half, clearly indicating the product cyclized to give the symmetrical tetramer. The ^{13}C spectra contains ten carbon resonances while the mass of the molecule indicates a molecular formula of $C_{20}H_{28}N_4O_6$.



9 10

Figure 2: The Two Possible Conformations of Cyclo Dihydroxy D-Pro-L-Pro-D-Pro-L-Pro

Substitution of the two L-prolines with trans-4-hydroxy-L-proline renders the two conformations of this molecule diastereomeric rather than enantiomeric (figure 2). It is interesting that only one of the two possible conformations is obtained from our synthetic sequence. We have observed NOEs from the α-proton of the D-proline to the methylene protons (figure 3) of the two L-hydroxy prolines. This, along with the absence of such an NOE from the α-proton of L-hydroxyproline (figure 3), indicates that the conformation obtained is **9** where the proline rings with the OHs attached are up out of the pseudo plane of the macrocyclic ring.[10]

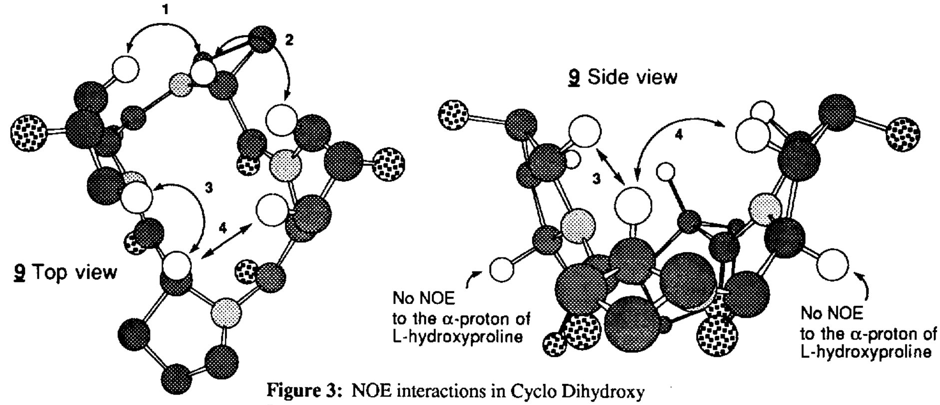


Figure 3: NOE interactions in Cyclo Dihydroxy D-Pro-L-Pro-D-Pro-L-Pro: **1**, D-ProCα-3CH L-hydroxyproline; **2**, D-ProCα-5CH L-hydroxyproline; **3**, D-ProCα-5CH L-hydroxyproline; **4**, D-ProCα-3CH L-hydroxyproline;

In their work Mästle et al found that cyclo(D-Pro-L-Pro-D-Pro-L-Pro) **1** isomerizes at 45°C in DMF and 80°C in H_2O^7. We have not been able to isomerize the dihydroxy derivative of this molecule **9**. Mästle et al speculate that isomerization takes place by the carbonyls passing through the center of the ring. If this is true it is difficult to appreciate how positioning two hydroxyls on the L-proline rings inhibit this process. Further work with other derivatives of these molecules may help elucidate the isomerization mechanism.

We are currently investigating routes for the derivatization of the hydroxyprolines by both attachment through ether linkages and substitution at the hydroxyl bearing carbons. Conversion of the alcohols to other functionalities that can bind transition metals into these highly ordered molecules is currently under way.

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(10) *The two other structures with all trans or all cis amide bonds are ruled out by the NOE data.*

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