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AMINO ACID DERIVATIVES THAT STABILIZE SECONDARY STRUCTURES OF POLYPEPTIDES-- I. SYNTHESIS OF LL-3-AMINO-2-PIPERIDONE-6-CARBOXYLIC ACID (LL-Acp), A NOVEL RETA-TURN-FORMING AMINO ACID

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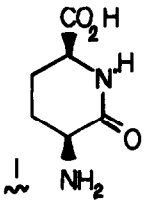
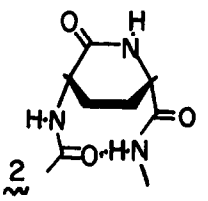
Abstract: A six-step synthesis is reported of LL-3-amino-2-piperidone-6-carboxylic acid from L-homoserine lactone and the mono-t-butyl ester of N-benzyloxycarbonylaminomalonic acid. Evidence of chiral integrity is discussed.

The β-turn is one of the simplest elements of protein conformation, and is intimately involved in protein folding and activity.[1] The availability of unnatural amino acids that strongly stabilize turns when incorporated into polypeptides could be very valuable means of preparing protease-resistant analogs of hormones and other turn-bearing proteins. In this communication we report a synthesis of LL-3-amino-2-piperidone-6-carboxylic acid, (LL-Acp), 1, and in the accompanying paper we provide evidence for its turn-forming capacity.



1



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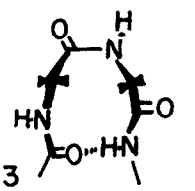
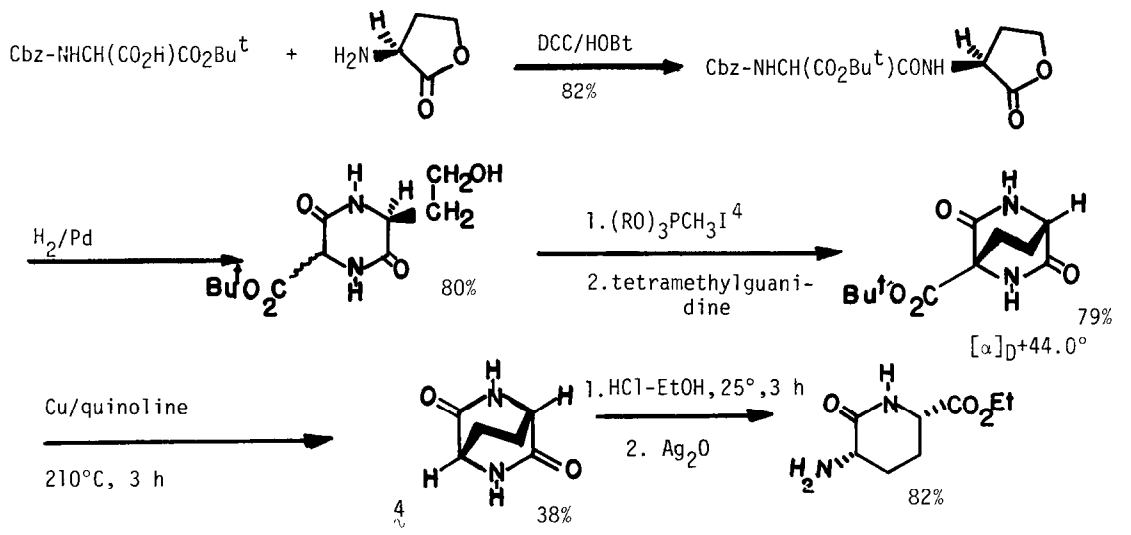


3

From models, a species RCO-Acp-NHR' is expected to adopt the intramolecularly hydrogen-bonded conformation 2, which is that seen in the rare β-turn 3, observed for a few cyclic peptides containing N-alkylamino acids.[2] Whereas a simple turn conformation such as 3 contains four single bonds about which rotation can occur, species RCO-Acp-NHR' have only two such bonds, and the resulting conformational restraint should favor turn-formation. Although racemic 1 has been reported,[3] there are no literature syntheses of single enantiomers of this species. The synthesis of Scheme I[3] has proved satisfactory in our hands and has provided multigram quantities of 1, despite the low yield observed for the penultimate step, for which alternatives have proved still less satisfactory. Extensive racemization can attend this step unless the quinoline used as solvent is scrupulously dried by distillation from zinc dust.

Scheme I



$[\alpha]_D$+44.1°(c 0.3,CH_3OH) $[\alpha]_D$+1.4° (CH_3OH)

Two results established the optical purity of 1 prepared by Scheme I. A partially racemic sample of H-Acp-OEt was obtained from 4 with $[\alpha]_D$+18°, which is 41% of the rotation of 4 obtained with carefully dried solvent. Acylation with Boc-L-Phe-OH (DCC) gave a diastereomeric mixture which was resolved by HPLC into two peaks of relative area 0.68:0.32, which may be compared with a L:D ratio of 0.71:0.29 which is obtained from the observed rotations of 4. Examination of Boc-L-Phe-Acp-OEt prepared from 4 with a rotation of +44.1° were shown by HPLC analysis to contain 95% of the LL-Acp isomer.

The lactam function of 1 is reasonably stable to most of the conditions employed in routine peptide synthesis, including Tfa-CH_2Cl_2 treatment (1:1), and ester saponification. However, it is quite labile to aqueous or alcoholic acids, and partial lactam cleavage can be detected during the conditions used in Scheme I to open the diketopiperazine 4. Appropriate precautions are therefore required during acidic manipulation of derivatives of 1.

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References

1. Smith, J. and Pease, L., CRC Crit. Rev. in Bioch., 1980, 8, 315.
2. Karle, I. "Peptides: Chemistry, Structure, and Biology", R. Walter and J. Meienhofer, eds., Ann Arbor Science Publishers, 1975, pp.68-69.
3. Newman, H., J. Het Chem., 1974, 11, 449-451. CbzNHCH(CO_2H)CO_2Bu^t; mp 90-97°C, was prepared in four steps in overall yield of 36% from diethyl aminomalonate; L-homoserine lactone HCl was prepared by acid-catalyzed cyclization of L-homoserine. Satisfactory elemental analyses were obtained for the products of Scheme 1.
4. Verheyden, J.P.H., and Moffat, J.G., J. Org. Chem., 1970, 35, 2319.

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