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Stereospecific Synthesis of (2*R*,3*S*)-3-Amino-2-Piperidineacetic Acid Derivatives for Use as Conformational Constraint in Peptides

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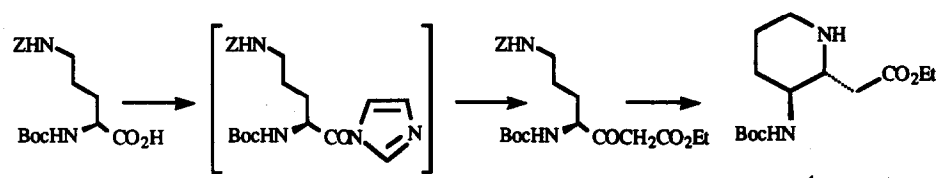
Abstract.—Catalytic hydrogenation at 40°C of the β-ketoester, obtained from Boc-Orn (Z)-OH and ethyl lithioacetate, provides exclusively ethyl (2*R*,3*S*)-3-*tert*-butyloxycarbonylamino-2-piperidineacetic acid which when suitably protected, can be used for peptide synthesis.

Conformational restriction is a strategy widely used for enhancing ligand-receptor interactions. Thus, reduction of conformational mobility of acyclic amino acid derivatives by incorporation of piperazine and piperidine rings has led to more potent ligands for the *N*-methyl-D-aspartate (NMDA) receptor.[1,2] In the field of bioactive peptides, the optimization of peptide-receptor binding, via insertion of conformationally constrained amino acids into the peptide sequence, provides a foundation for the design of peptidemimics.[3,4] Therefore, methods giving access to conformationally restricted non-proteinogenic amino acids in enantiomerically pure forms, from easily available starting materials, can prove to be of a great value.

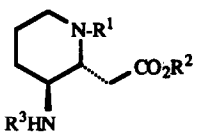
Based on the known ability of ornithyl derivatives to intramolecular cyclizations,[5] we reported an easy procedure for the preparation of 8-amino-3-oxoindolizidine-2-carboxylic acid with high degree of stereocontrol at C-8 and C-8a.[6] On this basis, we now report a readily accesible method for the stereospecific synthesis of *trans*-3-amino-2-piperidineacetic acid derivatives with defined chirality from the β-keto ester **3** obtained in 80% yield by condensation of Boc-Orn(Z)-OH (**1**) with the lithium enolate of ethyl acetate in THF, using 1,1-dicarbonyldiimidazole as activating agent.[7] Catalytic hydrogenation of compound **3** in EtOH[8] for 6 h at 40°C and 40 psi of pressure, using 10% Pd-C as catalyst, gave the (2*R*,3*S*)-3-amino-2-piperidineacetic acid **4** in 90% yield, as the only reaction product.



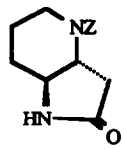
1 **2** **3** **4**

A (10:1) mixture of the *trans*-piperidine derivative **4** and its *cis*-diastereomer was obtained in 75% total yield, when the hydrogenation was achieved at 10°C for 4 days.[9] The $J_{2,3}$ values in the ^1H NMR spectra of these compounds allowed us to assign the *R* configuration for C-2 of the piperidine derivative **4** ($J_{2,3}$=10.4 Hz) and the *S* configuration for its diastereomer ($J_{2,3}$=2.0 Hz). The enantiomeric purity of these compounds was evidenced from the ^1H NMR spectrum and HPLC chromatogram of the *N*-(*R*)-2-methoxy-2-phenyl-trifluoromethylacetyl (*N*-MTPA)[10] derivative **7**. This derivative was prepared by protection of the piperidine nitrogen of **4** with the Z group

to give the fully protected analogue **5**, Boc deblocking with TFA and subsequent acylation of the resulting 3-aminopiperidine **6** with (+)MTPA in CH_2Cl_2 using BOP reagent[11] as coupling agent in the presence of Et_3N (69% yield from **4**).[9] The formation of the N^3-acylated compound **7** also demonstrated the possibility of using the 3-NH_2 group for incorporation into peptides, since no γ-lactamization of the 3-amino-2-acetate substituted piperidine **6** was observed at r.t. in the presence of Et_3N. Compound **6** was found to cyclize quantitatively to lactame **8** in refluxing xylene for 5 h in the presence of this base. Acylation and alkylation of the piperidine nitrogen was also achieved by standard procedures. Thus, coupling of Z-Ala-OH with compound **4** by the DCC/HOBt method gave compound **9** in 53% yield while alkylation with benzylbromide in CH_3CN, using Et_3N as base, led to the *N*-benzyl analogue **10** in 66% yield. Finally, saponification of the fully protected derivative **5** provided the free carboxylic acid **11**.[9]



No	R^1	R^2	R^3
5	Z	Et	Boc
6	Z	Et	H
7	Z	Et	MTPA
9	Z-Ala	Et	Boc
10	CH_2Ph	Et	Boc
11	Z	H	Boc



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In conclusion, the method here described for the stereospecific synthesis of *trans*-3-amino-2-piperidineacetic acid derivatives proceeds without affecting the chirality of the starting ornithine. These conformationally restricted basic amino acids with defined absolute configuration can be selectively protected for use in peptide synthesis. The application of this method to the preparation of 2,3-disubstituted piperidine analogues bearing side chains on the acetic acid moiety is in progress.

REFERENCES AND NOTES

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