Tetrahedron: Asymmetry Vol. 3, No. 6, pp. 723-726, 1992
Printed in Great Britain

0957-4166/92 $5.00+.00

Preparation and Assignment of Configuration of 1-Benzoyl-(2*S*)-*tert*-butyl-3-methyl-perhydropyrimidin-4-one. Useful Starting Material for the Enantioselective Synthesis of α-Substituted β-Amino Acids[1]

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(*Received* 12 *May* 1992)

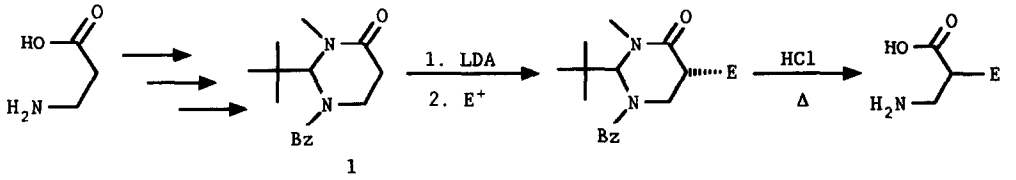
Abstract.

(S)-Asparagine, an inexpensive β-amino acid was converted into the title heterocycle (+)-**1** in very good overall yield. The highly selective *trans* methylation of (+)-**1**-Li, and the hydrolysis of the resulting adduct afforded (*R*)-α-methyl-β-alanine, allowing the assignment of the (*S*) configuration in (+)-**1**.

Introduction.

β-Amino acids, although less abundant than their α-analogues, are also present in peptides and, in free form, they show interesting pharmacological effects. Furthermore, β-amino acids can be cyclized to β-lactams, which are potentially biologically active substances of current interest. For these reasons, the synthesis of enantiomerically pure β-amino acids is receiving growing attention.[1-3]

In this respect, β-alanine was recently converted into racemic 2-*tert*-butylperhydropyrimidinone, *rac*-**1**, which was alkylated with high diastereoselectivity via its corresponding enolate.[3] The high stereoselectivity for the reaction of **1**-Li with electrophiles was ascribed to steric hindrance generated by an axial disposition of the *tert*-butyl group at C(2),[3,4] which directs addition from the enolate face opposite to this group. The hydrolysis of the resulting adducts affords the expected α-substituted β-amino acids in good yield (Scheme 1).[3]

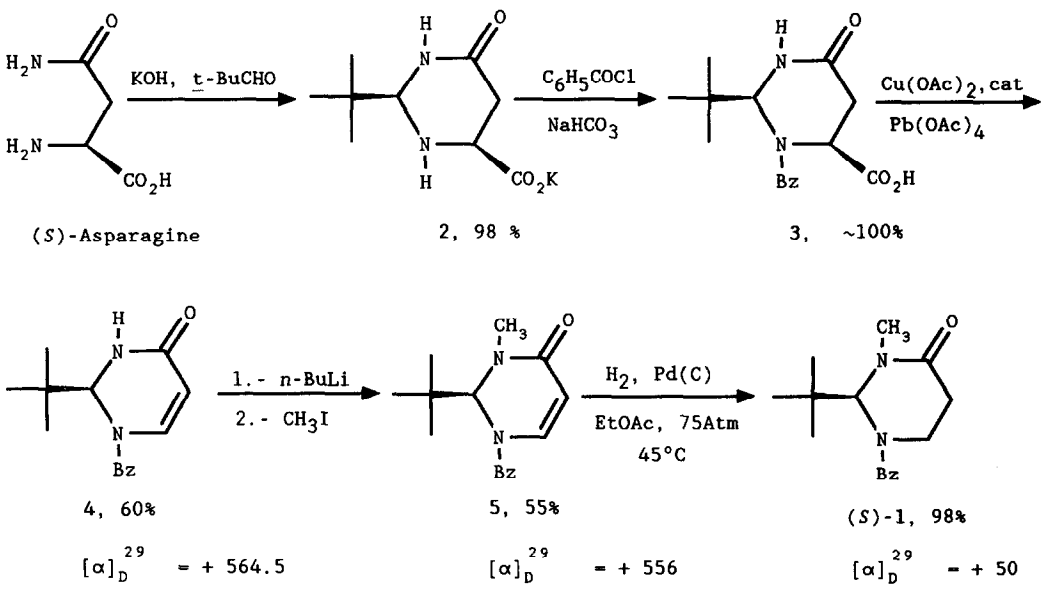


Scheme 1

While these results paved the road for the development of a new asymmetric synthesis of β-amino acids, a method was required for the efficient preparation of enantiomerically pure starting pyrimidinone **1**.[5]

Results.

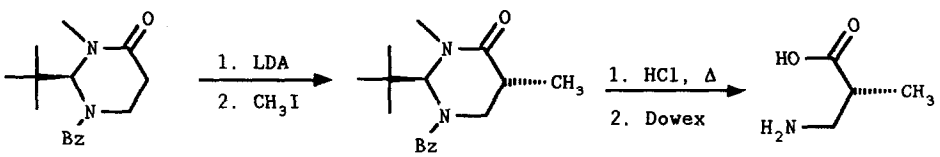
(*S*)-Asparagine was condensed with pivalaldehyde according to the procedure described by Konopelski, et al.[6] Benzoylation of the amine nitrogen of **2** (C_6H_5COCl, $NaHCO_3$) yielded **3** as an amorphous solid in 98% yield from asparagine. Treatment of **3** under oxidative decarboxylation conditions [$Pb(OAc)_4$, catalytic $Cu(OAc)_2$][6-8] afforded enone **4** in 60% yield. Finally, *N*-methylation of **4** under basic conditions proceeded in 55% yield, and catalytic hydrogenation yielded (+)-**1** in 98%. The overall yield of (+)-**1** from (**S**)-asparagine was a remarkable 32% (Scheme 2).



Scheme 2

Assignment of Configuration.

It is well-established that the addition of **1**-Li to electrophiles takes place from the enolate face opposite to the *tert*-butyl group.[3] Therefore, when **6**, the product of methylation of (+)-**1**, was hydrolyzed to (-)-α-methyl β-alanine, (-)-**7**, the configuration of this amino acid could be assigned as (*R*).[9] Therefore, the absolute configuration of (+)-**1** must be (*S*). (Scheme 3).



(+)-1 $[\alpha]_D^{29}$ = + 50 (+)-6 $[\alpha]_D^{29}$ = + 37 (-)-7 $[\alpha]_D^{29}$ = -12

Scheme 3

Summary.

An efficient method for the preparation of enantiomerically pure pyrimidinone (*S*)-**1** is now available. This chiral *N,N*-acetal is a useful precursor for the enantioselective preparation of α-substituted β-amino acids. The absolute configuration of (*S*)-(+)-**1** was assigned by chemical correlation with (-)-α-methyl-β-alanine.

Acknowledgments.

We are indebted to Prof. D. Seebach and Dr. B. Lamatsch for useful comments, and to the Commission of the European Communities (grant No. CI1*.0558-ME-JR) for financial support.

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