Preparation and Assignment of Configuration of 
1-Benzoyl-(25)-tert-butyl-3-methyl-perhydropyrimidin-4-one. 
Useful Starting Material for the Enantioselective Synthesis of 
α-Substituted β-Amino Acids

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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 (S)-α-methyl-β-alanine, allowing the assignment of the (S) configuration in (+)-1.

Introduction.

β-Amino acids, although less abundant than their α-analogs, 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.

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. 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), 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).
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.\textsuperscript{5}

**Results.**

(\textit{s})-Asparagine was condensed with pivalaldehyde according to the procedure described by Konopeński, et al.\textsuperscript{6} Benzoylation of the amine nitrogen of 2 (C\textsubscript{6}H\textsubscript{5}COCl, NaHCO\textsubscript{3}) yielded 3 as an amorphous solid in 98\% yield from asparagine. Treatment of 3 under oxidative decarboxylation conditions [Pb(OAc)\textsubscript{4}, catalytic Cu(OAc)\textsubscript{2}]\textsuperscript{6,7} afforded enone 4 in 60\% yield. Finally, \textit{N}-methylation of 4 under basic conditions proceeded in 55\% yield, and catalytic hydrogenation yielded (+)-1 in 98\%. The overall yield of (+)-1 from (\textit{s})-asparagine was a remarkable 32\% (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. 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 (S). Therefore, the absolute configuration of (+)-1 must be (S).

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.

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