**Diastereoselective alkylation of cyclo-β-dipeptides *en route* to enantiopure β-amino acids***

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**Abstract:** The cyclization of various β-amino acids with PhP(O)Cl₂ affords cyclo-β-dipeptides, whose boat conformation is probably responsible for the high diastereoselectivity observed in the alkylation reactions of their lithium enolate derivatives.

**Keywords:** β-amino acids; β-peptides; diastereoselective reactions; enantioselective; pyrimidinones.

**INTRODUCTION**

Although less abundant in Nature than their α-analogs, several β-amino acids exhibit interesting pharmacological activity on their own, or can be found in important natural products. Furthermore, these compounds can serve as building blocks in peptide chemistry; indeed, the structure and conformation of α-peptides tend to be unique [1]. A number of derivatives of β-amino acids are currently being tested in clinical studies owing to their potential in medicinal chemistry [2].

As a consequence of the above, the synthesis of enantiopure β-amino acids has emerged as an important and challenging synthetic endeavor. Indeed, whereas only 5 pertinent literature entries on this subject appear registered prior to 1980, and 11 for the period 1980–1990, more than 500 reports have appeared during 1991–2004 [3]. The present report summarizes our recent work in the area of enantioselective synthesis of α-substituted β-amino acids, as disclosed in the 15th International Conference on Organic Synthesis on 5 August 2004.

**1-BENZOYL-2-(S)-TERT-BUTYL-3-METHYLPERPYRIDIN-4-ONE**

Among the various methods available for the preparation of enantioenriched α-amino acids, those employing chiral glycine derivatives have been particularly successful. Scheme 1 illustrates the conversion of glycine, an achiral α-amino acid, into 1,3-imidazolidin-4-one 1—a chiral derivative. Treatment with lithium diisopropylamide (LDA) generates the corresponding enolate, whose diastereotopic faces are differentiated by an approaching electrophile. In particular, steric hindrance by the bulky tert-butyl group leads to highly diastereoselective trans-electrophilic addition, and hydrolysis to the formation of enantiopure α-substituted α-amino acids [4].

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It can be appreciated in Scheme 1 that diastereoselectivity in the alkylation step (1 → trans-2) is the result of 1,3-stereoinduction [5]. Thus, extension of the methodology to the chiral pyrimidinone 3 derived from β-alanine may not be as efficient a process, owing to the fact that 1,4-stereoinduction in this case could be anticipated to be lower (Scheme 2).

Scheme 2 Is chiral pyrimidinone 3 useful for the enantioselective preparation of α-substituted β-amino acids?

Luckily, and as a consequence of allylic A\textsuperscript{1,3} strain in heterocycle 3, the bulky tert-butyl group adopts an axial orientation in the six-membered ring, and in this conformation the corresponding enolate reacts with alkyl halides to give the trans-products 4 with high diastereoselectivity and good yields [6].

Hydrolysis of the alkylated pyrimidinones (2S,5R)-4 was achieved by acid hydrolysis (6 N HCl, 90–100 °C) followed by purification on an ion-exchange column, to afford α-alkylated β-amino acids of (R) configuration (eq. 1) [6].

A convenient protocol for the preparation of the enantiomeric α-alkylated β-amino acids of (S)-configuration involves epimerization of trans-(2S,5R)-4 derivatives into the cis-(2S,5S)-4 diastereomers, followed by hydrolysis (Scheme 3) [6].
Pyrimidinone (S)-3 is also a useful starting material for the preparation of α,α-disubstituted β-amino acids [7]. Recently, owing to the high price of pivalaldehyde, we have substituted this aldehyde with isobutyraldehyde in the synthesis of pyrimidinone (R)-6, which proved to be a convenient substrate for the enantioselective synthesis of α-substituted α,β-diaminopropionic acids (Scheme 4) [8].

SYNTHESIS OF CYCLO-β-DIPEPTIDES FROM β-AMINO ACIDS

The cyclization of β-amino acids by means of activating agents is one of the most useful approaches for the construction of β-lactams; however, we found that when PhP(O)Cl₂ (in Et₂N) is employed as the activating agent, reaction of the derived “active ester” affords varying amounts of cyclo-β-dipeptides, depending on reaction conditions (solvent, temperature, and concentration), as well as on the substitution pattern in the starting β-amino acid (Scheme 5) [9]. Although ordinary ¹H and ¹³C NMR spectra, and even EI (70 eV) mass spectra may be unsuitable for distinction between β-lactams 7 and cyclo-β-dipeptides 8, characteristic infrared bands allow easy differentiation [10]. In particular, whereas β-lactams 7 present carbonyl stretch absorptions around 1730–1750 cm⁻¹, cyclo-β-dipeptides 8 exhibit C=O values close to 1640 cm⁻¹ (Scheme 5).
DIASTERESELECTIVITY OF THE DOUBLE ALKYULATION OF CYCLO-(N-BENZYL-β-ALANINE-N-BENZYL-β-ALANINE)

The double alkylation of cyclo-β-dipeptide 8a (R = H) was achieved by treatment with 2 equiv of LDA in THF and at –78 °C, followed by the addition of 2 equiv of the electrophile. As summarized in Table 1, the diastereoselectivity of the reaction was excellent, and a single diastereomeric product is observed in most cases (Table 1).

Suitable crystals of dialkylated derivatives 8b–8d were obtained by recrystallization, and X-ray crystallographic analysis provided the solid-state conformations and structures presented in Fig. 1. It is appreciated that the relative configuration in these compounds is like (R,R or S,S) [11], in slightly distorted boat conformations where the substituents occupy pseudoequatorial orientations (Fig. 1).
The nearly exclusive formation of the \( \text{cis (like)} \) diastereomeric products \( 8b-\text{e} \) may be interpreted as a consequence of the boat conformation of dienolate \( 8a\text{-Li}_2 \), where the approach of the electrophile is restricted to the outer faces owing to steric hindrance encountered upon approach to the inner faces (Fig. 2).

![Fig. 1 Molecular structure and solid-state conformation of cyclo-\( \beta \)-dipeptides \( 8b \) and \( 8c \).](image)

![Fig. 2 Suggested boat conformation in dienolate \( 8a\text{-Li}_2 \), where electrophilic approach on the outer faces leads to formation of the \( \text{cis (like)} \) dialkylated products (racemic).](image)

**DIASTEREOSELECTIVE ALKYLATION OF (\( \pm \))-CYCLO-(\( N \)-BENZYL-\( \beta \)-ALANINE-\( N \)-BENZYL-\( \beta^2 \)-HOMOPHENYLALANINE)**

An interesting question is whether products \( 8b-\text{e} \) are the result of highly diastereoselective alkylation of monosubstituted intermediates \( 9 \); that is, it is possible that 1,5-stereoinduction is highly effective in alkylation reactions of eight-membered cyclo-\( \beta \)-dipeptides \( 9 \) (eq. 2).

![Fig. 2 Suggested boat conformation in dienolate \( 8a\text{-Li}_2 \), where electrophilic approach on the outer faces leads to formation of the \( \text{cis (like)} \) dialkylated products (racemic).](image)

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{N}
\end{align*}
\]

**In the event, alkylation of benzylated cyclo-\( \beta \)-dipeptide (\( \pm \))\( 9 \) (\( R = \text{PhCH}_2 \)) both in the absence or presence of salt (LiCl) or cosolvent (HMPA) additives proceeded with good to excellent diastereoselectivity. Best results are observed in the methylation reaction of (\( \pm \))\( 9 \) in the presence of 6 equiv of LiCl (entry 2 in Table 2), and in the benzylation reaction of the same substrate in the presence of 6 equiv of HMPA cosolvent (entry 4 in Table 2).**

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**Table 2** Diastereoselective alkylation of racemic cyclo-((N-benzyl-β-alanine-N-benzyl-β²-homophenylalanine) (±)-9.

<table>
<thead>
<tr>
<th>Entry</th>
<th>RX</th>
<th>Additive</th>
<th>Equiv.</th>
<th>Yield (%)</th>
<th>dr (l:u)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃I</td>
<td>—</td>
<td>—</td>
<td>70</td>
<td>4:1</td>
</tr>
<tr>
<td>2</td>
<td>CH₃I</td>
<td>LiCl</td>
<td>6</td>
<td>55</td>
<td>9:1</td>
</tr>
<tr>
<td>3</td>
<td>PhCH₂Br</td>
<td>—</td>
<td>—</td>
<td>39</td>
<td>&gt;49:1</td>
</tr>
<tr>
<td>4</td>
<td>PhCH₂Br</td>
<td>HMPA</td>
<td>6</td>
<td>50</td>
<td>&gt;49:1</td>
</tr>
</tbody>
</table>

Molecular modeling (PM3) of enolate intermediate 9-Li indicates that steric hindrance prevents addition of the electrophile on the Si face of the enolate (Fig. 3). As inferred from this analysis, addition of the electrophile to the Re face of enolate 9-Li should afford the cis (like) dialkylated product, as experimentally observed.

**Fig. 3** Lowest energy conformation of enolate 9-Li showing the preferential approach of an electrophile on the Re face (PM3 level).

### DIASTEREOSELECTIVE ALKYLATION OF ENANTIOPURE (S)-CYCLO-(N-BENZYL-β-ALANINE-N-BENZYL-β²-HOMOPHENYLALANINE)

As anticipated, the alkylation of enantiomerically pure cyclo-β-dipeptide (S)-9 proceeded with similar diastereoselectivity to give enantiopure dialkylated derivatives of like relative configuration, whose acid hydrolysis should provide enantiopure α-substituted β-amino acids (Scheme 6).

**Scheme 6** Diastereoselective alkylation of (S)-9 en route to enantiopure α-substituted β-amino acids.
REFERENCES