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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 $PhP(O)Cl_2$ 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-METHYLPERHYDROPYRIMIDIN-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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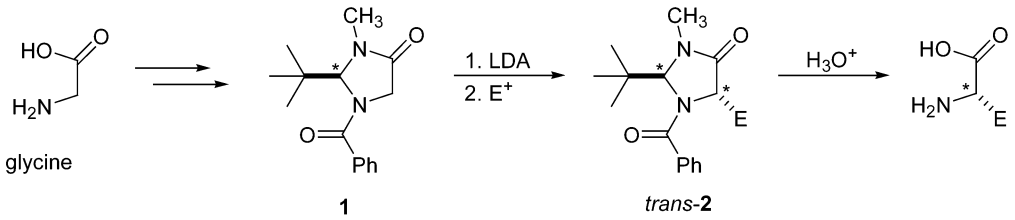
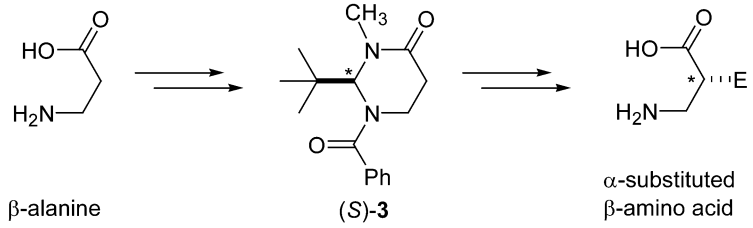


Scheme 1 Use of chiral glycine enolates for the preparation of enantiomerically pure α-substituted β-amino acids [4].

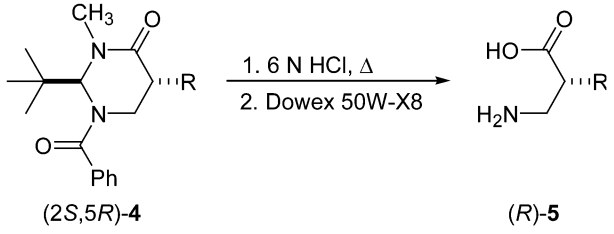
It can be appreciated in Scheme 1 that diastereoselectivity in the alkylation step (**1** → *trans*-**2**) is the result of 1,3-stereoinduction [5]. Thus, extension of the methodology to the chiral pyrimidinone **3** derived from β-alanine may not be as efficient a process, owing to the fact that 1,4-stereoinduction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

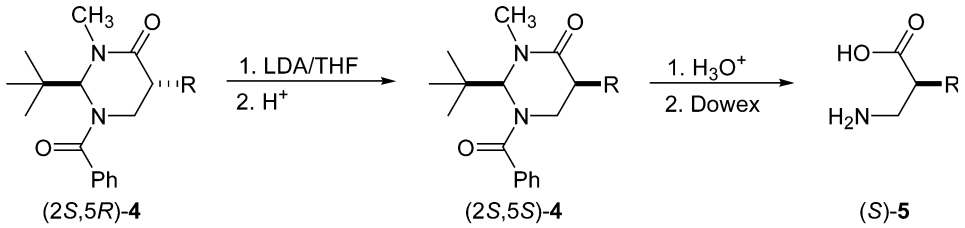
Luckily, and as a consequence of allylic $A^{1,3}$ strain in heterocycle **3**, the bulky *tert*-butyl group adopts an axial orientation in the six-membered ring, and in this conformation the corresponding enolate reacts with alkyl halides to give the *trans*-products **4** with high diastereoselectivity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

Hydrolysis of the alkylated pyrimidinones (2*S*,5*R*)-**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].



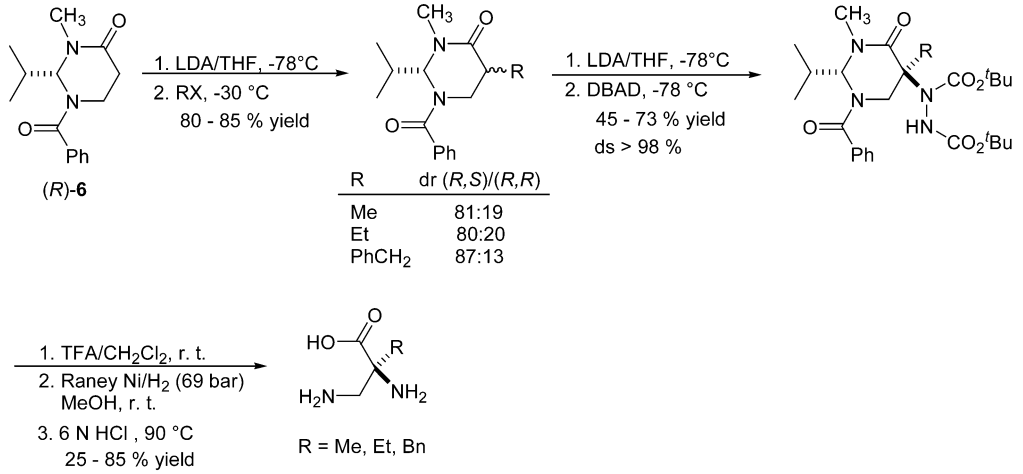
(1)

A convenient protocol for the preparation of the enantiomeric α-alkylated β-amino acids of (*S*)-configuration involves epimerization of *trans*-(2*S*,5*R*)-**4** derivatives into the *cis*-(2*S*,5*S*)-**4** diastereomers, followed by hydrolysis (Scheme 3) [6].



Scheme 3 Epimerization of *trans*-disubstituted pyrimidinones (2*S*,5*R*)-**4** into *cis*-diastereoisomers (2*S*,5*S*)-**4** in the preparation of α-alkylated β-amino acids (*S*)-**5** [6].

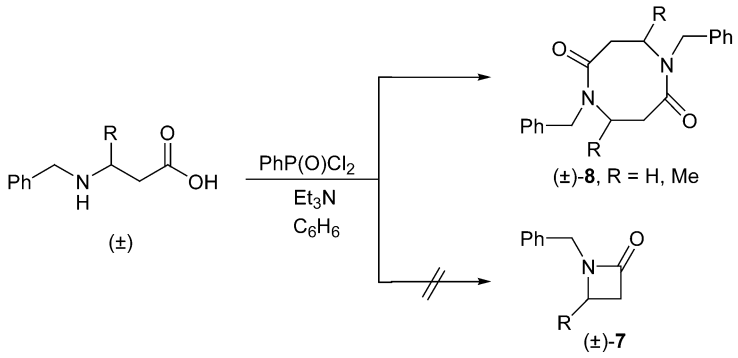
Pyrimidinone (*S*)-**3** is also a useful starting material for the preparation of α,α-disubstituted β-amino acids [7]. Recently, owing to the high price of pivalaldehyde, we have substituted this aldehyde with isobutyraldehyde in the synthesis of pyrimidinone (*R*)-**6**, which proved to be a convenient substrate for the enantioselective synthesis of α-substituted α,β-diaminopropionic acids (Scheme 4) [8].



Scheme 4 Enantioselective synthesis of α-substituted α,β-diaminopropionic acids [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 $PhP(O)Cl_2$ (in Et_3N) 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 ^{13}C 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).

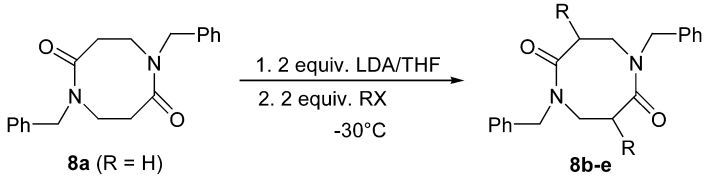


Scheme 5 Synthesis of cyclo-β-dipeptides from β-amino acids [9].

DIASTEREOSELECTIVITY OF THE DOUBLE ALKYLATION 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).

Table 1 Diastereoselectivity of dienolate **8a**-Li_2 alkylations.



Product	RX	Yield (%)	ds (%)	$\upsilon_{C=O}$ (cm^{-1})
8b	CH_3I	75	>98[a]	1638
8c	$PhCH_2Br$	63	>98[a]	1642
8d	CH_2=CH–CH_2Br	60	98	1634
8e	CH_3CH_2I	23	>98[a]	1634

[a]A single diastereomeric product is observed by ^1H NMR spectroscopy.

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).

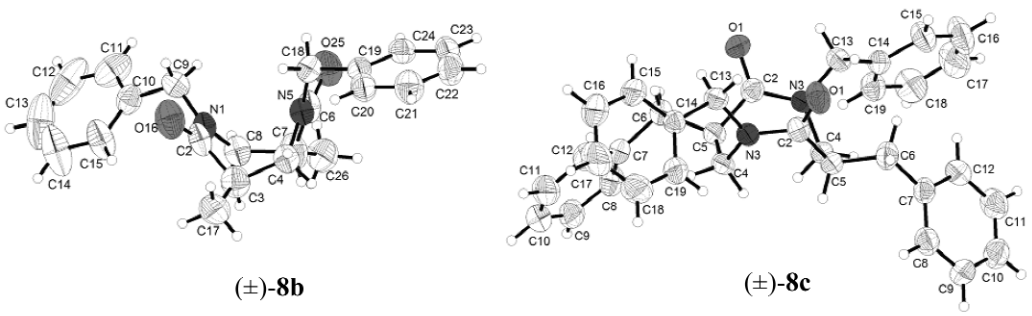


Fig. 1 Molecular structure and solid-state conformation of cyclo-β-dipeptides **8b** and **8c**.

The nearly exclusive formation of the *cis* (*like*) diastereomeric products **8b–e** may be interpreted as a consequence of the boat conformation of dienolate **8a**-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).

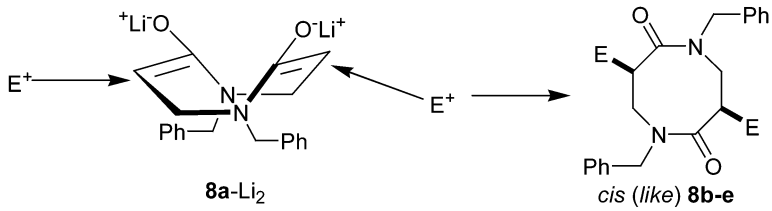
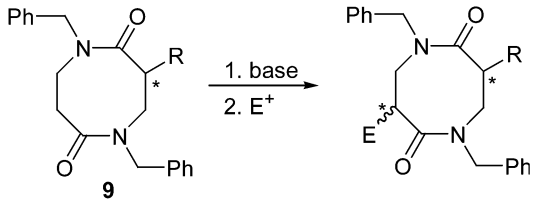


Fig. 2 Suggested boat conformation in dienolate **8a**-Li_2, where electrophilic approach on the outer faces leads to formation of the *cis* (*like*) dialkylated products (racemic).

DIASTEREOSELECTIVE ALKYLATION OF (±)-CYCLO-(*N*-BENZYL-β-ALANINE-*N*-BENZYL-β^2-HOMOPHENYLALANINE)

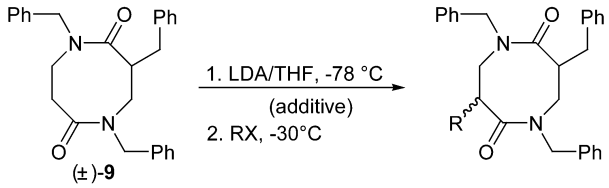
An interesting question is whether products **8b–e** are the result of highly diastereoselective alkylation of monosubstituted intermediates **9**; that is, it is possible that 1,5-stereoinduction is highly effective in alkylation reactions of eight-membered cyclo-β-dipeptides **9** (eq. 2).



(2)

In the event, alkylation of benzylated cyclo-β-dipeptide (±)-**9** (R = $PhCH_2$) 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 (±)-**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).

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



Entry	RX	Additive	Equiv.	Yield (%)	dr (*l*:*u*)
1	CH_3I	—	—	70	4:1
2	CH_3I	LiCl	6	55	9:1
3	$PhCH_2Br$	—	—	39	>49:1
4	$PhCH_2Br$	HMPA	6	50	>49:1

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 eletrophile to the *Re* face of enolate **9**-Li should afford the *cis* (*like*) dialkylated product, as experimentally observed.

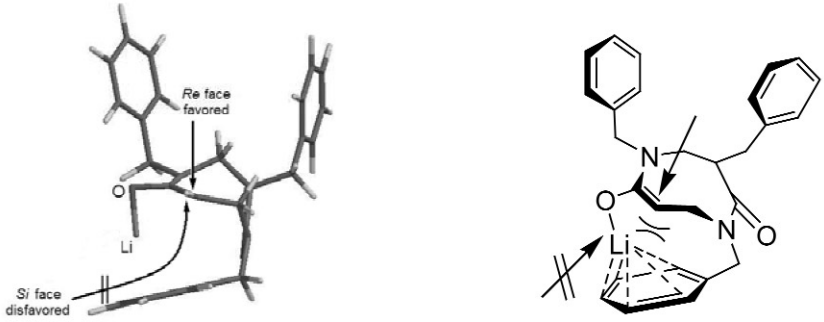
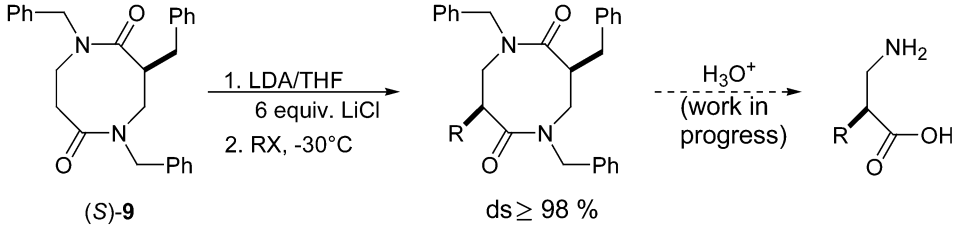


Fig. 3 Lowest energy conformation of enolate **9**-Li showing the preferential approach of an electrophile on the *Re* face (PM3 level).

DIASTEREOSELECTIVE ALKYLATION OF ENANTIOPURE (*S*)-CYCLO-(*N*-BENZYL-β-ALANINE-*N*-BENZYL-β^2-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.

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