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Exceptional Stereoselectivity in the Synthesis of 1,3,4-Trisubstituted 4-Carboxy β-Lactam Derivatives from Amino Acids

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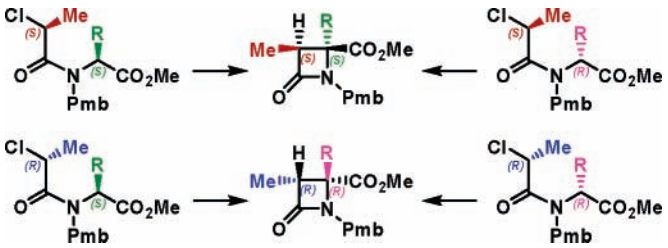
ABSTRACT



The base-promoted cyclization of optically pure *N*-(*p*-methoxybenzyl)-*N*-(2-chloro)propionyl amino acid derivatives resulted in a diastereo- and enantioselective approach to valuable 1,3,4,4-tetrasubstituted β-lactams. The stereochemical outcome of the reaction is exclusively governed by the configuration of the *N*-(2-chloro)propionyl moiety.

The azetidin-2-one (β-lactam) ring is widely recognized as a key structural motif in several families of antibiotics.[1] In addition to this, differently substituted monocyclic β-lactams function as mechanism-based inhibitors of serine proteases, such as tryptase,[2] human leukocyte elastase,[3] human cytomegalovirus and HIV proteases,[4] and prostate specific antigen.[5] Additionally, the 1,3,4-trisubstituted 2-azetidinone derivative Ezetimibe has recently been commercialized as an effective acyl-CoA cholesterol acyltransferase inhibitor for lowering cholesterol levels.[6]

Apart from their significance in medicinal chemistry, enantiopure β-lactams also serve as versatile chiral intermediates in organic synthesis (β-lactam synthon methodology)[7] and as useful building blocks to induce reverse turn secondary structures in peptides.[8]

This triple biomedical, synthetic, and structural interest has stimulated considerable research efforts toward the enantioselective synthesis of β-lactams.[9] The stereocontrolled Staudinger reaction (ketene−imine cycloaddition), which relies on the use of chiral auxiliaries, and the Gilman−

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Speeter reaction (enolate−imine condensation), using an enantiomerically pure ester or imine component, are among the most extensively used methodologies to achieve this goal.[10,11] In addition, several examples of the direct catalytic enantioselective synthesis of β-lactams have lately been reported.[12]

In this context, we have described that the base-promoted cyclization of *N*-benzyl-*N*-chloroacetyl amino acid derivatives **I** affords the corresponding 3-unsubstituted 4-alkyl-4-alkoxycarbonyl-2-azetidinones **II** (Figure 1).[13] Of particular

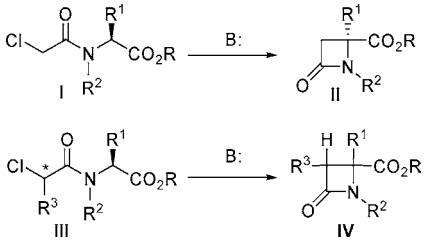

Figure 1. 1,3,4-Tri- and 1,3,4,4-tetrasubstituted β-lactams from amino acid derivatives.

interest in this synthesis is the modest enantioselectivity observed during the β-lactam ring formation (ee up to 58%), constituting novel examples of asymmetry due to the memory of chirality.[14]

Considering that the 1,3,4-substitution pattern is frequently observed among the bioactive monocyclic 2-azetidinones, the development of stereoselective routes to related 1,3,4,4-tetrasubstituted analogues could be of value to medicinal chemistry programs. To this purpose, we decided to investigate the cyclization of enantiomerically pure *N*-benzyl-*N*-chloroalkanoyl amino acid derivatives **III** (Figure 1). We were interested in answering two main questions: (a) could the 1,3,4,4-tetrasubstituted β-lactams **IV** be obtained by a procedure similar to that described for the 1,4,4-trisubstituted analogues **II** and (b) will the additional stereogenic center in **III** have any influence on the memory of the chirality process? The modulation of the memory of chirality by an extra stereogenic center at the amino acid side chain has been previously examined,[15] but there are no reports on the possible modulation due to the chirality of the alkylating agent.

This piece of work deals with our initial attempts to shed light on the above indicated points through the cyclization of different optically pure *N*-(*p*-methoxybenzyl)-*N*-(2-chloro)propionyl amino acid derivatives (**III**, $R^3 = CH_3$).

Because the Phe derivatives **I** (R^1 = Bzl) were stereoselectively converted into the corresponding β-lactams **II**, due to the memory of chirality,[14c] Phe was selected as an appropriate initial model to investigate the **III** to **IV** transformation. To explore the stereochemical outcome of the cyclization reaction, the four possible diastereoisomeric intermediates were needed. Using Pmb-L-Phe-OMe (**1a**) as a starting amino acid derivative, intermediates **3a** and **3b** were prepared by acylation with racemic 2-chloropropionyl chloride (**2ab**), followed by separation of the diastereoisomers in a flash column (Scheme 1). The absolute configuration of these *N*-chloropropionyl Phe derivatives was assigned by unequivocal synthesis of isomer **3a** by coupling **1a** with enantiomerically pure 2(*S*)-chloropropionic acid (**4a**) in the presence of BOP. This coupling reaction evolved with lower yield than the acylation with the acyl chloride, and some unwanted racemization of the 2(*S*)-chloropropionic acid was observed. Due to this fact and to the ease of the chromatographic separation, the racemic 2-chloropropionyl chloride (**2ab**) was also used for the synthesis of diastereoisomeric intermediates **3c** and **3d** from H-Pmb-D-Phe-OMe (**1b**).

The base-promoted cyclization of each diastereoisomer of **3** resulted in a unique 3,4-*cis* β-lactam, indicating the high degree of diastereoselectivity in this reaction (Scheme 1). Moreover, regardless of the α-configuration, 2′*S*-intermediates **3a** and **3c** afforded the same 3*S*,4*S* 2-azetidinone, **5a** (64%, ee >98%).[16] The same cyclization reaction with derivatives **3b** and **3d**, both with a 2′*R* configuration, resulted in the 3*R*,4*R* β-lactam **5b** (66%), the enantiomer of **5a**. These results pointed out the exquisite enantiocontrol of this transformation, with the construction of the quaternary stereogenic center fully directed by the configuration of the 2-chloropropionyl substituent and completely independent of the configuration of the starting amino acid. Therefore, it can be concluded that the asymmetry due to the memory of chirality is not relevant at all in this case. A similar 2,3-*cis* selectivity was observed in a related intramolecular alkylation leading to azetidine-derived amino acids.[17,18]

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(16) The *S*,*S*/*R*,*R* ratio was measured by chiral HPLC. Column: Chiralpack ID (0.46 × 15 cm). Eluent: EtOH/hexane 5:95. Flow rate: 1 mL/min. t_R: **5a** = 10.81 min. t_R: **5b** = 9.75 min.

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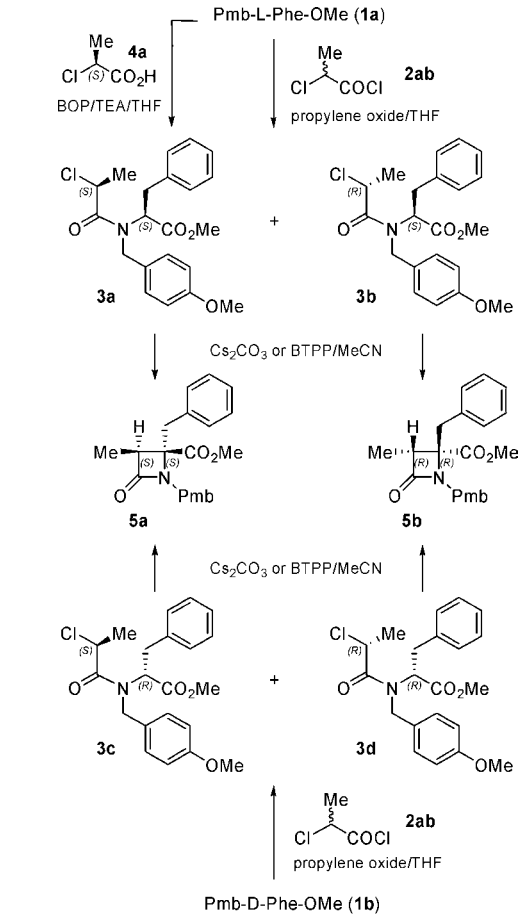
Scheme 1. Synthesis of 1,3,4,4-Tetrasubstituted β-Lactams from Phe Derivatives



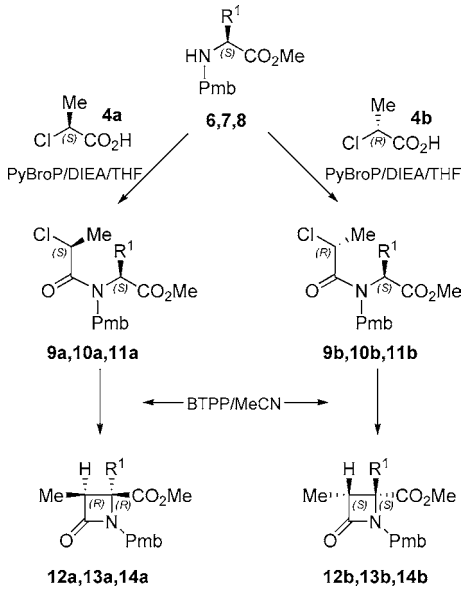
To further evaluate the scope of this reaction, we explored the synthesis of β-lactams from different amino acids, namely, Ala, Lys, and Glu (Scheme 2). Due to inefficient chromatographic separation, the enantiopure 2-chloropropionyl derivatives **9a**−**11a** and **9b**−**11b** were prepared by coupling of the corresponding *N*-Pmb amino acid derivative with 2(*S*)- and 2(*R*)-chloropropionic acid, respectively. PyBroP/DIEA was used to minimize as much as possible the racemization of the starting chloropropionic acid.[19,20] Again, only one β-lactam (**12**−**14**, 60−70% yield) was obtained from each *N*-chloropropionyl precursor, demonstrating the versatility and usefulness of the developed procedure to synthesize enantiomerically pure tetrasubstituted 2-azetidinones.

The assignment of the absolute configuration of the highly substituted β-lactams described here was performed in two steps. First, the *trans*-relationship between the alkyl substituents at 3,4 positions was determined by NOE experiments. Although a weak NOE (0.5%) between the 3-CH_3 protons and one of the 4-CH_2 protons in compound **5a** could suggest

(19) Full details of the coupling agents and bases used for the optimization of the synthesis of **9a** are indicated in the Supporting Information.

(20) Diastereoisomeric excess values: **9a** (96%), **9b** (92%), **10a** (83%), **10b** (81%), **11a** (98%), and **11b** (98%). Measured by HPLC.

Scheme 2. Synthesis of 1,3,4,4-Tetrasubstituted β-Lactams from Different Amino Acids

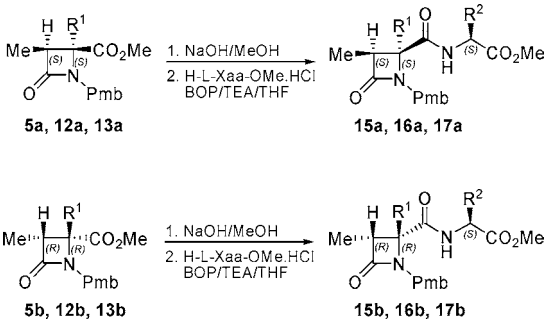


a *cis* disposition between these groups, the final *trans* spatial arrangement was confirmed after transformation of **5a** into **18a** (Figure 2). Thus, in **18a**, there is a strong NOE (2.5%) between the 3-CH_3 protons and one proton of the 4-hydroxymethyl group, resulting from the reduction of the methyl ester in **5a**, while keeping the above-mentioned weak NOE (0.3%) between Me and Bzl groups. In a similar way, a 3.5−9% NOE value between H-3 and 4-CH_3 or 4-CH_2 protons in compounds **12**−**14** is indicative of the placement of these protons in the same face of the four-membered ring.

In the second step, the configuration at the C4 position of the β-lactam was indirectly assigned through the synthesis of dipeptide derivatives **15a**−**17a** and **15b**−**17b**, having L-Ala-OMe or L-Phe-OMe C-terminal residues.[21] In each pair of diastereoisomers, the dipeptide with high retention time in HPLC and a more shielded chemical shift of the β-H aliphatic side chain protons was assigned as the heterochiral dipeptide, namely, **15b**−**17b** (Table 1).[22]

These stereochemical results could be explained through the formation of enolate intermediates in which the approach

Scheme 3. Synthesis of β-Lactam-Derived Dipeptides



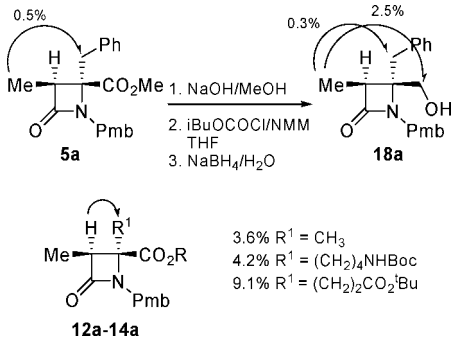


Figure 2. NOE experiments.

of the alkylating agent is dictated by the configuration of the 2-chloropropionyl moiety. As shown in Figure 3, the formation of the *trans*-3*R*,4*S* β-lactam is hindered by the existence of close contacts between the 2′-methyl group and the amino acid side chain, destabilizing the precursor pro-*R*,*S* enolate.

In summary, we have developed a highly stereoselective synthesis of tetrasubstituted β-lactams from simple amino acid derivatives. The stereochemical control of the cyclization to the four-membered ring is fully dictated by the configuration of the 2-chloropropionyl group in the linear precursors. In fact, the presence of the propionyl chiral center totally abolished the asymmetric induction by memory of chirality observed in the cyclization of the corresponding acetyl

Table 1. Chemical Shifts and Retention Times Used for Configurational Assignments

compd	R^1	R^2	δ β-H[a] (ppm)	t_R HPLC (min)
15a	CH_2Ph	CH_3	0.84	13.34[b]
15b	CH_2Ph	CH_3	0.71	15.02[b]
16a	CH_3	CH_2Ph	1.46	13.20[c]
16b	CH_3	CH_2Ph	1.37	15.25[c]
17a	$(CH_2)_4NHBoc$	CH_2Ph	1.85	7.89[d]
17b	$(CH_2)_4NHBoc$	CH_2Ph	1.72	8.35[d]

[a] β-H of the aliphatic residue. [b] 40:60 MeCN/H_2O (0.05% TFA), Novapak. [c] 35:65, Novapak. [d] 45:55, Deltapak.

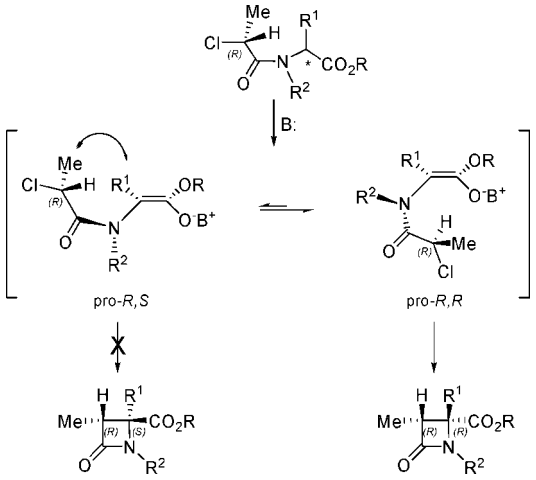


Figure 3. *Z*-Enolates from 2(*R*)-chloropropionyl amino acid derivatives.

analogues. In addition to the exceptional diastereo- and enantiocontrol, the process tolerates a wide variety of substituents, is short and mild, and is operationally simple. Given the usefulness of β-lactams in organic and medicinal chemistry, we believe that the procedure presented herein may be of great applicability in these fields.

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Supporting Information Available: Experimental details and analytical and spectroscopic data for compounds **3**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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