Amino Acids (1994) 7: 79–81

Amino
Acids

Asymmetric synthesis of α-substituted β-amino acids using a β-alanine derivative with two chiral handles

M. Akssira[1], M. Boumzebra[1], H. Kasmi[1], M. L. Roumestant[2], and Ph. Viallefont[2]

[1] Laboratoire de Chimie Organique, Université Abdelmalek Essaadi Faculté des Sciences, Tétouan, Maroc
[2] URA 468-Université Montpellier II, Montpellier, France

Accepted October 9, 1993

Summary. Enantiomerically pure α-substituted β-amino acids have been synthesized, the key step being the diastereoselective alkylation of a β-alanine derivative with two chiral handles (1S,2R,5S)-menthyl N-[(1S,2S,5S)-2-hydroxypinan-3-ylidene] β-alaninate.

Keywords: Amino acids – β-Amino acid – Asymmetric synthesis – Schiff base – 2-Hydroxypinan-3-one – Menthol

Introduction

Chemical methods for the production of enantiomerically pure α-amino acids have been the focus of much research activity in recent years (Williams, 1989). Conversely, there are relatively few methods for the synthesis of their chiral β-analogues (El Marini et al., 1992; Konopelski et al., 1991; Juaristi et al., 1992), although there is considerable interest in these compounds as components of peptides and natural products (Drey, 1985) and as precursors to β-lactams which are substances of current interest.

Encouraged by the enormous potential of non racemic Schiff base derivative of glycine and 2-hydroxypinan-3-one as precursors of optically active α-amino acids (Boumzebra et al., 1988; Tabcheh et al., 1991), we decided to explore the usefulness of the chiral β-alanine enolate as a starting material for the preparation of (R) or (S) β-amino acids.

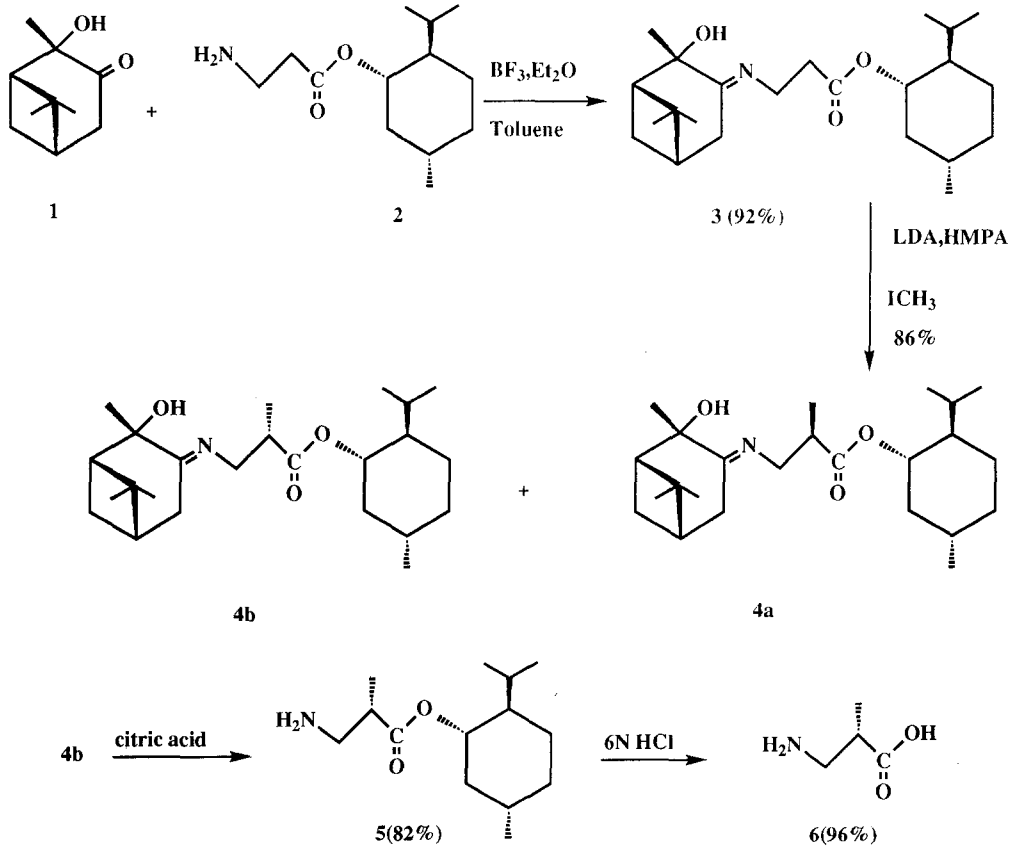
Results

The alkylation in THF of the Schiff base **3** prepared from (1S, 2S, 5S) 2-hydroxypinan-3-one **1** and (1S, 2R, 5S) menthyl β-alaninate **2** with methyl iodide using LDA as base failed; the desired product was obtained in 15% yield, the

remainder being the starting product. However after addition of HMPA (5 equivalents), **4** was obtained in 86% yield, as a mixture of two diastereoisomers (**4a/4b**: 8/92) easily separated by column chromatography using ether/hexane (3/2) as eluent. Hydrolysis of **4b** by 15% citric acid in THF gave rise to the methylated compound **5** which appeared as a single diastereoisomer as detected in the ^{1}HNMR spectrum.

The ester group was removed with 6N HCl followed by treatment with methyl oxirane thus affording (+) α-methyl β-alanine **6**. The configuration of this amino acid could be assigned as (S) (Balenovic and Bregant, 1959; Juaristi et al., 1992) and therefore, the configuration of **4b** must be (S). However when (−) menthyl ester was used instead of (+) menthyl ester and alkylation was carried out under the same conditions, the methylated compound was obtained in 91% yield, but the diastereoisomeric excess was very poor. This result is not suprising because it is known that the diastereoselectivity in double asymmetric induction depends on both auxiliaries: "Concept of matched and mismatched pair" (Masamune et al., 1985).

In summary, Schiff base **3** appeared to be a versatile intermediate for the enantioselective preparation of α-substituted β-amino acids.



References

Balenovic K, Bregant N (1959) Absolute configuration of α-methyl β-alanine. Tetrahedron 5: 44–46

Boumzebra M, Elachqar A, Roumestant ML, Viallefont Ph (1988) 2-Hydroxy-3-pinanone as chiral auxiliary in the asymmetric synthesis of α-amino acids. Tetrahedron 44: 5319–5332

Drey CNC (1985) Chemistry and biochemistry of amino acids. In: Barrett GC (ed) Chemistry and biochemistry of the amino acids. Chapman and Hall, London, p 25

El Marini A, Roumestant ML, Viallefont Ph, Razafindramboa D, Bonato M, Follet M (1992) Synthesis of enantiomerically pure β and γ-amino acids from aspartic and glutamic acid derivatives. Synthesis: 1104–1108 and references cited

Juaristi E, Escalante J, Lamatsch D (1992) Enantioselective synthesis of β-amino acids. Preparation of the like stereoisomers of 2-methyl and 2-benzyl-3-aminobutanoic acid. J Org Chem 57: 2396–2398 (Juaristi E, Quintana D (1992) Preparation and assignment of configuration of 1-benzoyl-(2S)-tert-butyl-3-methyl-perhydropyrimidine-4-one. Useful starting material for the enantioselective synthesis of α-substituted β-amino acids. Tetrahedron Asymmetry 3: 323–327)

Konopelski JP, Chi SK, Negrete GR (1991) Self reproduction of chirality. Asymmetric synthesis of β-aryl-β-amino acids from enantiomerically pure dihydropyrimidinones. J Org Chem 56: 1355–1357

Masamune S, Choy W, Peterson JS, Sija LR (1985) Double asymmetric synthesis and a new strategy for stereochemical control in organic synthesis. Angew Chem Int Ed Engl 24: 1–76

Tabcheh M, El Achqar A, Pappalardo L, Roumestant ML, Viallefont Ph (1991) Alkylation and protonation of chiral Schiff bases: diastereoselectivity as a function of the nature of reactants. Tetrahedron 26: 4611–4618 and references cited

Williams RM (1989) Synthesis of optically active α-amino acids. In: Baldwin JE (ed) Synthesis of optically active α-amino acids. Pergamon Press, Oxford

Authors' address: Dr. M. L. Roumestant, URA 468, CNRS – Université Montpellier II, F-34095 Montpellier Cedex 5, France.