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TETRAHEDRON: *ASYMMETRY*

First asymmetric synthesis of (*R*)-(–)-α-phenyl δ-amino valeric acid

Monique Calmes,* Françoise Escale, Emmanuelle Juan, Marc Rolland and Jean Martinez

Laboratoire des Aminoacides, Peptides et Protéines, UMR-CNRS 5810-Universités Montpellier I et II, UM II, Place E. Bataillon, 34095 Montpellier cedex 5, France

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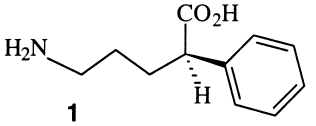
Abstract

An efficient synthesis of the (*R*)-(–)-α-phenyl δ-amino valeric acid **1** is described starting from commercially available compounds. The key intermediate in this synthesis is the corresponding totally protected prochiral ketene.

1. Introduction

δ-Amino acids and their derivatives are an important group of compounds particularly in the development of the corresponding functionalized δ-lactams[1,2] and new peptidomimetics.[3] Moreover, the anticonvulsant effects of 3-mono- or 3-di-substituted δ-lactams have recently been described[2] and underline the special interest of the stereoselective synthesis of their α-substituted δ-amino acid precursors.

We have recently developed a convenient and effective deracemization reaction[4] involving prochiral ketenes, which is well adapted to the synthesis of optically active α-phenyl substituted carboxylic acids. We decided to examine this method for the asymmetric preparation of the α-phenyl δ-amino valeric acid **1**. To our knowledge, only the racemic α-phenyl δ-amino valeric acid has been described previously and used for the preparation of a new semisynthetic penicillin analogue[5] or more recently as a new potential $GABA_B$ receptor antagonist.[6]



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* Corresponding author. Fax: 04 67 14 48 66; e-mail: monique@ampir1.univ-montp2.fr

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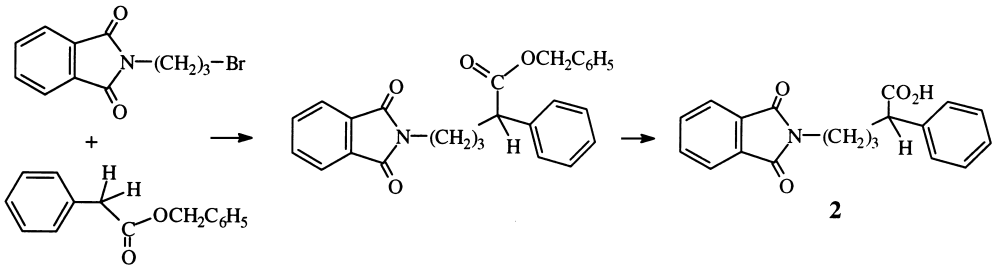
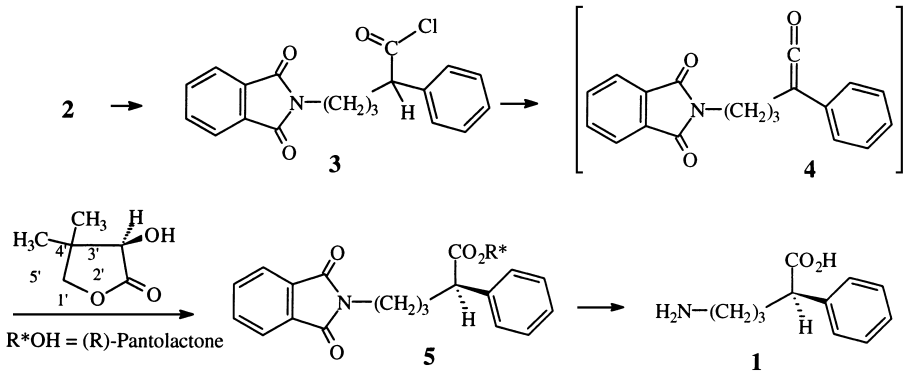
2. Results and discussion

The synthesis was performed through the asymmetric transformation of the racemic mixture of the *N*-phthalyl δ-amino acid derivative **2** by stereoselective addition of a chiral alcohol to the corresponding prochiral ketene **4** (Scheme 2). The (*R*)-pantolactone, a very efficient commercially available auxiliary,[4,7] was used as the chiral alcohol. The phthalimido group, which totally protects the amine function, avoids the NH addition to the intermediate ketene and has the advantage of being easily introduced and removed.

The racemic *N*-phthalyl δ-amino acid derivative **2** was easily obtained by alkylation by *N*-bromopropylphthalimide of the phenylacetic acid benzyl ester prepared from the cheap commercially available corresponding acid (Scheme 1). This reaction was achieved in good yield (80% after purification) by using lithium diisopropylamide as base and DMPU as co-solvent at low temperature. Under these conditions we never observed dehydrobromination of the electrophile with formation of *N*-allyl phthalimide, as described previously when using diethyl phenylmalonate as the starting compound.[6,8]



Scheme 1. Synthesis of racemic *N*-phthalyl α-phenyl δ-amino valeric acid **2**



Scheme 2. Stereoselective synthesis of (*R*)-(–)-α-phenyl δ-amino valeric acid **1**

After cleavage of the benzyl ester by hydrogenolysis, the corresponding acid chloride **3** was quantitatively obtained by treatment with oxalyl chloride at room temperature (Scheme 2). The ketene **4** was next formed in situ by treatment of **3** with triethylamine (1.1 equivalents) for 1 h at room temperature. The subsequent addition of (*R*)-pantolactone (1.1 equivalents) at the same temperature afforded the *N*-phthalyl pantolactonyl ester **5** in high chemical yield (78%) and with a high diastereoisomeric excess (94%).[9] Although the reaction was not totally diastereoselective,

the enantiomerically pure **5** can be obtained by simple recrystallization from ether giving colorless plates which were subjected to X-ray crystallographic analysis[10] (Fig. 1). The absolute configuration of the newly generated stereogenic center was determined to be (*R*) by using the (*R*)-pantolactonyl moiety as internal reference.

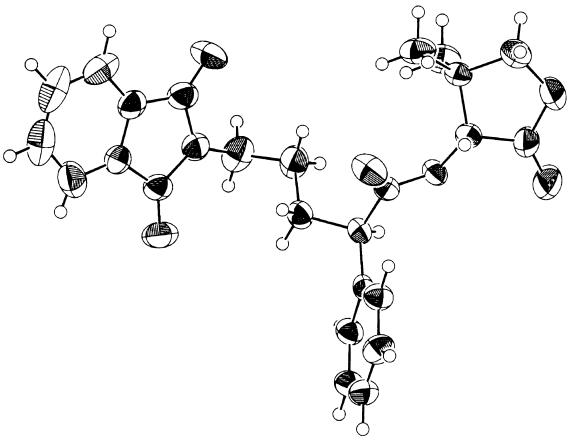


Figure 1. ORTEP drawing of the ester (α*R*,3′*R*)

Hydrolysis[4] under acidic conditions of the diastereomerically pure (α*R*,3′*R*) *N*-phthalyl pantolactonyl ester followed by propylene oxide treatment afforded the corresponding free (*R*)-α-phenyl δ-amino valeric acid **1**.[11]

3. Conclusion

We have described the first asymmetric synthesis of the (*R*)-α-phenyl δ-amino valeric acid via stereoselective addition of the (*R*)-pantolactone to the corresponding *N*-phthalyl ketene which took place with high stereoselectivity at room temperature.

References

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9. The diastereoisomeric excess (de) of **5** was determined for the crude product from the ^{1}H NMR spectrum ($CDCl_3$) by integration of the 3′-C*H* signal of the pantolactonyl moiety of the mixture of diastereoisomers.
10. (αR,3′*R*)-**5** has the following physical data: mp 86°C; $[\alpha]_D = -13$ (c = 2 in CH_2Cl_2); [FAB$^+$/GT] [M+H$^+$] 436; ^{1}H NMR ($CDCl_3$): $\delta = 1.04$ (s, 3H, 4′-CH_3); 1.12 (s, 3H, 4′-CH_3); 1.68–2.26 (m, 4H, CHCH_2CH_2CH_2N); 3.74 (t, $J_1 = J_2 = 6.8$ Hz, 2H, CH_2N); 3.78 (t, $J_1 = J_2 = 7.6$ Hz, 1H, C*H*COO); 3.98 (d, J = 9.1 Hz, 1H, 5′-HC*H*); 4.04 (d, J = 9.1 Hz, 1H, 5′-HC*H*); 5.32 (s, 1H, 3′-C*H*); 7.33 (m, 5H, *H*-phenyl); 7.72 (m, 2H, *H*-phthalyl); 7.85 (m, 2H, *H*-phthalyl). The diffraction data were collected on an Enraf–Nonius KappaCCD automatic diffractometer using graphite-monochromated Mo-Kα radiation and the ϕ-scan technique up to $\theta = 25.41$. Crystal data of **5**: molecular formula $C_{25}H_{25}NO_6$, molecular weight = 435, orthorhombic, space group P $2_12_12_1$, cell constants: $a = 5.9045(2)$ Å, $b = 11.4802(7)$ Å, $c = 32.836(2)$ Å, $\alpha,\beta,\gamma = 90.0°$, $V = 2225.8(2)$ Å^3, $Z = 4$, $Dc = 1.299$ mg m^{-3}, $T = 298$ K, final $Rw = 0.089$. Details of crystal structure determination have been deposited at the Cambridge Crystallographic Data Centre (deposition number CCDC138846).
11. (*R*)-**1**, 97% de determined by HPLC analysis after derivatization with Marfey's reagent,[12] has the following physical data: mp 240°C (dec.); $[\alpha]_D = -87$ (c = 2 in 1N HCl); ^{1}H NMR (D_2O+Na): $\delta = 1.25$ (m, 2H, CH_2CH_2N); 1.59 (m, 1H, HC*H*CH_2CHCOO); 1.87 (m, 1H, HC*H*CH_2CHCOO); 2.46 (t, $J_1 = J_2 = 7.1$ Hz, 2H, CH_2N); 3.32 (t, $J_1 = J_2 = 7.4$ Hz, 1H, C*H*COO); 4.72 (s, 1H, 3′-C*H*); 7.20 (m, 5H, *H*-phenyl).
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