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An alternative route to the proline derivative (2*S*,5*R*)-5-ethoxycarbonylmethyl-pyrrolidine-2-carboxylic acid from protected glutamic acid☆

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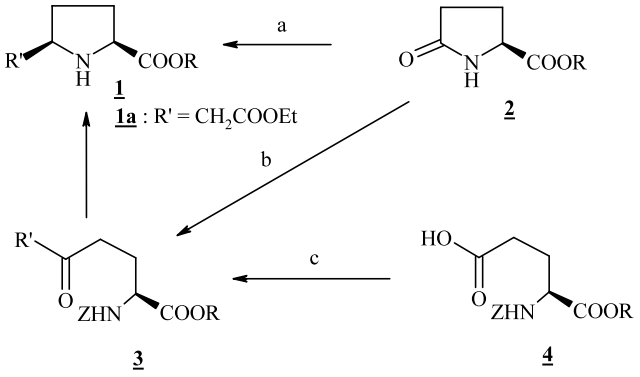
Abstract—The synthesis of (2*S*,5*R*)-5-ethoxycarbonylmethyl-pyrrolidine-2-carboxylic acid was achieved in two steps, with an overall yield of 53%. This synthesis used Cbz-Glu-OBzl as the starting material and led to the titled compound with a d.e.>96%.

Proline derivatives have been extensively studied, especially for their structural properties when incorporated into peptides.

The asymmetric synthesis of 5-substituted prolines of the general formula **1** (Scheme 1) has been described in many reports, generally starting from pyroglutamic acid **2**. The latter can be either partially reduced with Dibal-H, condensed via a Wittig–Horner reaction then reduced (pathway a), or opened with a strong nucleophile, generally a carbanion, and further reduced (pathway b). For instance, a 5-methylproline was recently prepared from pyroglutamic acid via this reductive amination process, after ring-opening with an α-lithiated sulphone.[1]



Scheme 1. Syntheses of 5-substituted prolines **1**. a: partial reduction and Wittig–Horner condensation; b: ring opening then reduction; c: acid conversion then reduction.

We report herein the synthesis of a proline substituted on the 5-position by an ethoxycarbonylmethyl group, both substituents in positions 2 and 5 being in the relative *cis* configuration. Both diastereoisomers of the title compound were previously synthesized, using different synthesis pathways involving several more steps.

Concerning the titled compound **1a** (R′ = CH_2COOEt), the isomer bearing the relative *trans* configuration was published in several reports, from pyroglutamic acid **2**.[2a–c] This compound is a useful precursor in the synthesis of carbapenam antibiotics[3] and was also described[4a] as an intermediate in the synthesis of anatoxin-a. As far as the *cis* isomer is concerned, its preparation was described in several steps, either from pyroglutamic acid or its thio-derivative,[4a,b] or by asymmetrisation via an enzymatic process.[4c] Another synthesis of the racemic *cis* isomer used the catalytic reduction of the pyrrole precursor.[4d] All these syntheses proved to be efficient but mostly proceeded in approximately 5 steps.

In this paper we describe an alternative route to an example of 5-substituted proline, starting directly from protected glutamic acid **4** (pathway c).

Compound **1a** encompasses two asymmetric carbons. We took (L)-glutamic acid as starting material, thus

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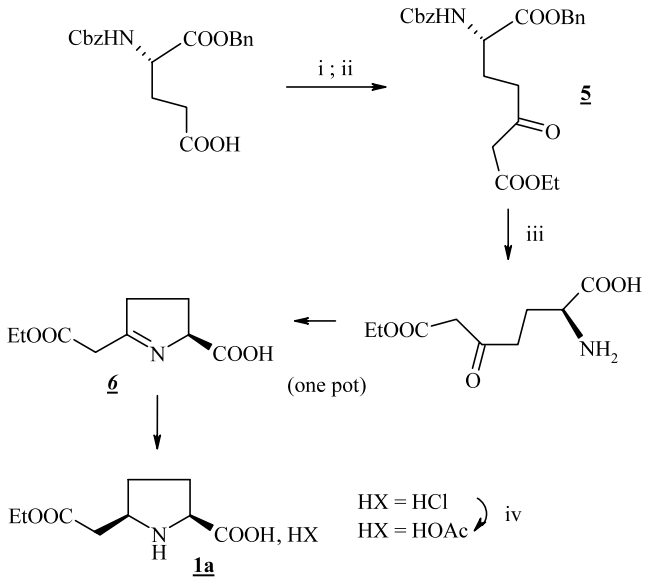

Scheme 2. Preparation of (2*S*,5*R*)-5-ethoxycarbonylmethylpyrrolidine-2-carboxylic acid. *Reagents and conditions*: i: carbonyldiimidazole, THF, 2 h; ii: $(EtOOCCH_2COO)_2Mg$, rt, overnight, 62% overall; iii: 1 atm H_2, Pd/C, CH_3COOH, 85%; iv: H_2O, HCl (1 equiv.), evaporation.

having already the C2 chiral carbon. As cyclisation of the nitrogen with the carbon of the side-chain carboxylic acid was required, we first transformed this group into a more reactive β-ketoester.

This transformation was achieved owing to the efficient method described by Masamune,[5] which is well documented even in the case of amino acids.[6] Starting from commercially available Cbz-Glu-OBn (Z-Glu-OBzl, Bachem), we first activated the side-chain carboxylic acid by treatment with carbonyl diimidazole. The resulting species was subsequently subjected to condensation with the magnesium salt of monoethyl malonic acid, prepared from the commercial potassium salt, via acidification at low temperature and treatment with magnesium ethoxide. Pure β-ketoester **5** was obtained with a 62% yield after column chromatography on silica-gel. Interestingly, the elongation of glutamic acid side-chain with two carbons at the same time is also postulated in the biosynthesis of these compounds, wherein acetate is the source of carbon.[4b] As depicted in Scheme 2, the latter compound was subsequently deprotected by means of hydrogenolysis in the presence of 10% palladium on activated charcoal in glacial acetic acid, this solvent being chosen in order to favor the further cyclisation step. The amine obtained was not isolated but immediately led to a nucleophilic attack onto the ketone, providing the intermediate imine **6** (not isolated) which was further reduced in situ during the process. After evaporation of the solvent, the residue was taken-up in water and one equivalent of HCl and evaporated, in order to obtain the hydrochloride salt **1a** instead of the acetate. This one-pot synthesis proceeded smoothly with a 85% yield, ^1H NMR and HPLC showing a 98:2 ratio for both *cis*:*trans* diastereoisomers obtained. The stereoselectivity of the reduction was consistent with that stated in the literature[1] and can be easily explained by the hydrogenation of the less-hindered face of the cyclic imine.

The absolute (2*S*) configuration was postulated according to the configuration of the starting glutamic acid. Assignment of the relative configuration was achieved by means of NOESY and TOCSY experiments, a complete ^1H and ^{13}C assignment being listed in Table 1.

NOEs were observed between Hd and He/e′, Hc′, Hb′ and Ha, confirming the *trans* configuration of this compound. Moreover, no NOE appeared between Hd and Hc, nor Hb.

Conclusion

This synthesis provides a very short route to an example of 5-substituted proline, starting from cheap protected glutamic acid, (L) and (D) enantiomers being commercially available. This constitutes an alternative synthesis which does not require strong nucleophiles for the ring opening of pyroglutamic acid. The high yield and the diastereoisomeric excess obtained for the reduction step makes it a method of choice for the preparation of both enantiomers of these compounds.

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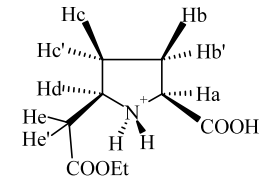
Table 1. NMR assignment of compound **1a**

	^1H NMR (d-6 DMSO, 400 MHz) : Ha : 4.27 (t, *J=7.4 Hz*) ; Hb : 2.0-2.1 (m) ; Hb' : 2.2-2.3 (m) ; Hc : 1.56-1.64 (m); Hc' : 2.1-2.2 (m); Hd : 3.76 (m, *J=7.4 Hz*) ; He and He' : 2.88 (dd, *J=16.8 and 7.2 Hz*) and 2.76 (dd, *J=16.8 and 6.8 Hz*); NH_2^+ : 8.56 and 10.3 ; CH_2 (Et) : 4.05 (t, *J=7.2 Hz*); CH_3 (Et) : 1.16 (t, *J=7.2 Hz*) ^{13}C NMR : COOH and COOEt : 170.2 and 170.0 ; Ca : 59.0 ; Cb : 26.5 ; Cc : 28.5 ; Cd : 55.6 ; Ce : 35.8 ; CH_2 (Et) : 60.6 ; CH_3 (Et) : 14.0

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