Synthesis of *meso*-2,4-Diaminoglutaric Acid.

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Abstract: In order to synthesise *meso*-2,4-diaminoglutaric acid a synthetic route has been developed, starting from Garner's aldehyde, in which the key step is the hydrogenation of *(Z)-(R)*-3-*tert*-butoxycarbonyl-2,2-dimethyl-4-[2'-(benzamido)-2'-(methoxycarbonyl)ethenyl]-1,3-oxazolidine, followed by oxidation and further hydrolysis. Copyright © 1996 Elsevier Science Ltd

The incorporation of synthetic amino acids into peptides and proteins has attracted significant attention during the last few years since it was recognised that it constitutes a powerful approach for generating peptides with altered physical properties and biological activity.[1] In particular, the incorporation of α-amino acids with functional groups that can act as receptor ligands is of great interest. In this area, and as a part of our research programme concerning the asymmetric synthesis of novel α-amino acids, we have been interested in the synthesis of enantiomerically pure bis(α-amino acids).[2] The most common methodology used to synthesise this class of compound is based on the asymmetric alkylations of chiral glycine equivalents, such as the chiral reagents developed by Schöllkopf and Seebach.[3] In this context, it was decided to prepare *meso*-2,4-diaminoglutaric acid because relatively little is known about its synthesis.[4] Herein a new methodology, starting from Garner's aldehyde **1** (easily available from L-serine[5]), is described as an efficient procedure for the synthesis of 2,4-diaminoglutaric acids. The key step in this route is the hydrogenation of the didehydroamino acid derivative **2**. The major hydrogenated product can be then oxidized and converted into the required bis(α-amino acid) **3** (Scheme 1).
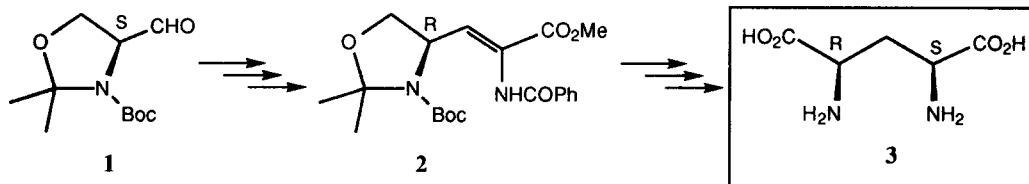
Scheme 1

Olefin **2** was synthesised, under Wadsworth-Horner-Emmons olefination conditions,[6] by condensation of aldehyde **1** with the potassium salt of methyl 2-benzamido-2-(dimethoxyphosphoryl)acetate, which was obtained according to the procedure described in the literature,[7] involving photochemical bromination of methyl *N*-benzoylglycinate followed by the Arbuzov reaction with trimethyl phosphite. The olefination product was isolated in 77% yield after purification by crystallisation from diethyl ether and, as expected under these conditions, the *(Z)* isomer was major product formed. The *(E)* isomer was detected (13%) by ^{1}H-NMR in the reaction mixture before purification.[8] The double bond geometry could not be unequivocally assigned from the *vicinal* C,H coupling constants between the vinylic proton and the carbonyl carbon of the methyl ester group attached to the double bond [*J* of the *(E)* isomer < *J* of the *(Z)* isomer][9] due to its complexity. Nevertheless, the *(Z)* configuration of olefin **2** was established by NOE ^{1}H-NMR experiments.[10] The relevant NOE enhancements observed in the aromatic and NH protons when the CH₃ protons of the *tert*-butoxycarbonyl group (BOC) were presaturated, and also in the vinylic proton when the CH₃ protons of the methoxycarbonyl group were irradiated, confirmed the stereochemical assignment (Figure 1).
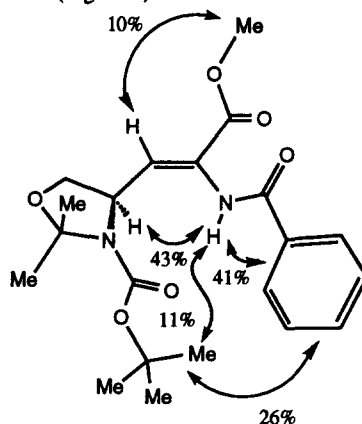

Figure 1

The hydrogenation of olefin **2** under heterogeneous conditions in the presence of palladium-carbon as a catalyst using either ethyl acetate or dichloromethane as the solvent proved unsuccessful. However, a good yield was obtained when methanol was used as the solvent, but side products were formed in addition to the hydrogenation products **4** and **5** because the 1,3-oxazolidine heterocycle was opened to give the corresponding *tert*-butoxycarbonylamino alcohol derivative due to the action of methanol as a nucleophile. To avoid this problem, 2-propanol was used instead of methanol and, after 8 h at atmospheric pressure at room temperature, the reaction proceeded with quantitative yield without affecting the 1,3-oxazolidine heterocycle (Scheme 2).
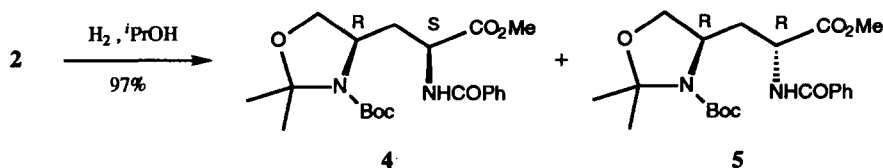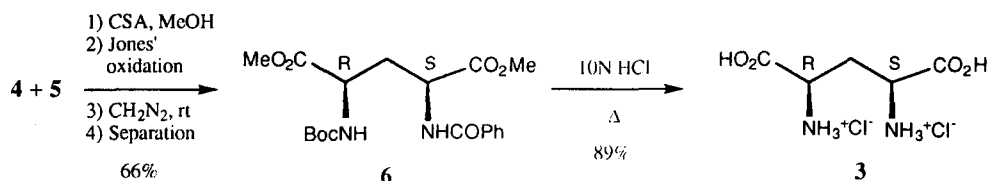

Scheme 2

Nitrogen inversion in the oxazolidine ring causes considerable line broadening and duplication of signals in the ^{1}H-NMR spectra and so this technique could only be used to determine the yield of the hydrogenation reaction. The diastereofacial selectivity (**4/5**) could, however, be determined by HPLC analysis[11] (**4/5** = 94/6).

The major product obtained in the heterogeneous hydrogenation of the chiral olefin **2** was that which corresponds to the addition of hydrogen on the *re* face of the olefin, so the reaction predominantly gave the stereoisomer **4** of *(R,S)* configuration.[12]

The unexpected high selectivity obtained in the asymmetric hydrogenation reaction under heterogeneous conditions opens the way to the synthesis of the *meso*-bis(α-amino acid) **3**. The mixture of hydrogenation products was treated at 0 °C with Jones' reagent[13] which led to partial deprotection of the amino alcohol and oxidation of the hydroxy group to give the carboxylic acid. Jones' oxidation was selected in order to avoid racemization of the stereogenic centres present in this kind of system as described by Beaulieu.[14] The mixture of carboxylic acid derivatives was converted into the corresponding methyl esters by the addition of excess diazomethane as an ether solution at room temperature. The major diastereoisomer, the dimethyl ester of *(2R,4S)*-2,4-diaminoglutaric acid **6**, was obtained by purification of the crude mixture of diastereoisomeric esters by column chromatography. Compound **6** was subsequently hydrolysed in aqueous 4N HCl at 90 °C to give the desired hydrochloride derivative of *meso*-2,4-diaminoglutaric acid **3**,[15] along with a side product (in 17% yield), corresponding to the formation of the two possible γ-lactams as observed in γ-substituted glutamic acids.[16] In order to minimise the formation of cyclization products, the hydrolysis reaction was carried out under more acidic conditions[17] using aqueous 10N HCl at 110 °C for 18 h. Under these conditions the γ-lactams were formed in only 8% yield (Scheme 3).

Scheme 3

In summary, a bis(α-amino acid) has been synthesised by a synthetic route other than the commonly used asymmetric dialkylation of chiral glycine equivalents. The starting material for this synthesis is Garner's aldehyde, which contributes one chiral centre to the bis(α-amino acid). The other chiral centre in the product is created by asymmetric hydrogenation of the didehydroamino acid derivative **2**. Further studies are in progress in order to carry out the asymmetric synthesis of optically active *(2R,4R)*-2,4-diaminoglutaric acid and other families of bis(α-amino acids).

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8. The *(Z)/(E)* ratio was determined by integration of the ^{1}H-NMR signals corresponding to the allylic protons: *(Z)*: δ 4.65(m, 1H); *(E)*: δ 5.25(m, 1H).

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11. Diastereofacial selectivity was determined by HPLC using a 40:60 hexane:*tert*-butylmethyl ether mixture as the mobile phase and a flow rate of 2.0 mL/min. Retention times: **4** = 13.70 min, **5** = 11.30 min, **2** = 7.26 min.

12. Further studies are in progress in order to explain the stereochemical outcome of the hydrogenation reaction.

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15. Spectroscopic data for the hydrochloride derivative of compound **3** recorded on a Bruker ARX 300MHz: ^{1}H-NMR(D_2O): δ= 2.30–2.43(m, 1H, C$\underline{H}_aH_b$); 2.53–2.64(m, 1H, CH$_a\underline{H}_b$); 4.27(t, 1H, *J*=6.3, 2CH). ^{13}C-NMR(D_2O): δ= 29.8(CH_2); 49.5(CH); 170.3(COO).

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