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Asymmetric synthesis of *meso*- and (2*R*,4*R*)-2,4-diaminoglutaric acids

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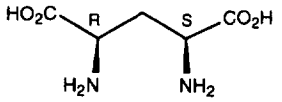
Abstract: In order to synthesize *meso*- and (2*R*,4*R*)-2,4-diaminoglutaric acids, a synthetic route has been developed starting from Garner's aldehyde and where the key steps are the asymmetric hydrogenations of (*E*)- and (*Z*)-(*R*)-3-*tert*-butoxycarbonyl-2,2-dimethyl-4-[2′-(benzamido)-2′-(methoxycarbonyl)ethenyl]-1,3-oxazolidine, under heterogeneous conditions, followed by oxidation and further hydrolysis. A model is proposed to explain the stereochemical outcome of the asymmetric hydrogenation. © 1997 Elsevier Science Ltd. All rights reserved.

The synthesis of the modified peptides based on the substitution of natural α-amino acids by non-standard residues in order to control flexibility and to determine conformations or to change the bio-availability and the inhibitory activity of the peptide has attracted significant attention over the last few years.[1] In particular, the incorporation of α-amino acids with functional groups that can act as receptor ligands is of great interest. In this case and as a part of our research program on the asymmetric synthesis of new α-amino acids, we have been interested in the synthesis of enantiomerically pure bis(α-amino acids).[2] In this context, we have recently reported, in a preliminary communication,[3] the synthesis of the *meso*-2,4-diaminoglutaric acid **1** (Figure 1) starting from Garner's aldehyde by a new methodology that involves the asymmetric hydrogenation of readily available (*Z*)-(*R*)-3-*tert*-butoxycarbonyl-2,2-dimethyl-4-[2′-(benzamido)-2′-(methoxycarbonyl)ethenyl]-1,3-oxazolidine **3**, followed by oxidation of the resulting protected hydrogenated products **4** and **5**, purification of the major ester derivative, and further hydrolysis. In this article we would like to complete this strategy in order to synthesize both, the *meso* and the optically active bis(α-amino acids) **1** and **2** (Figure 1).

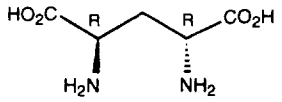
Synthesis of bis(α-amino acids)

The key step in the synthesis of *meso*-2,4-diaminoglutaric acid was the asymmetric hydrogenation of the olefin **3**, which occurred under heterogeneous conditions in the presence of palladium–carbon as a catalyst and 2-propanol as a solvent to give a diastereofacial selectivity **4**/**5**=94/6.[3] The *Z* configuration



1

meso-2,4-diaminoglutaric acid



2

(2R,4R)-2,4-diaminoglutaric acid

Figure 1.

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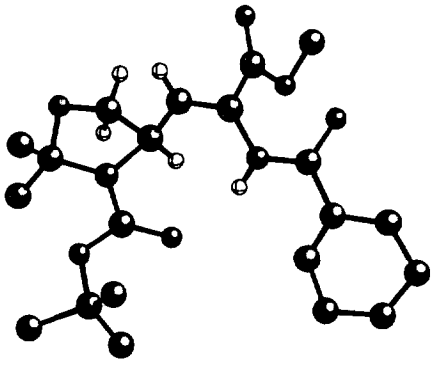
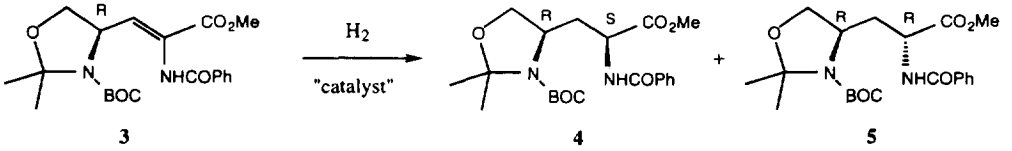


Figure 2.

of the olefin **3**, previously established by NOE difference ^{1}H-NMR experiments, was now confirmed by X-ray analysis[4] (Figure 2).

In order to invert the selectivity of the hydrogenation to obtain preferentially the stereoisomer **5** we have assayed the hydrogenation under homogeneous conditions. This reaction proceeded only with a moderate rate under these conditions, indeed it was necessary to increase the hydrogen pressure to 50–55 atmospheres and the temperature to 55°C and, even under these conditions, when $(Ph_3P)_3RuCl_2$ or $(Ph_3P)_3RhCl$ showed no reactivity. Moreover, we have examined the double asymmetric induction using homogeneous chiral catalysts and when the asymmetric reaction was carried out using (*S*)-(BINAP)(COD)$RhClO_4$, (*S*)-(BINAP)-*p*-cymene$RuCl_2$, (*S*)-(BINAP)$RuCl_2$, (*R*)-(BINAP)$RuCl_2$ as the chiral catalysts,[5] the most significant feature was that high levels of diastereoselectivity **4/5** (92/8 and 88/12 respectively) were obtained when chiral catalysts of (*S*)-(BINAP)–Ru or (*S*)-(BINAP)–Rh were used at 55°C and 50 atmospheres of pressure. All attempts to afford preferentially the opposite isomer obtained in the heterogeneous hydrogenation were unsuccessful and the highest percentage of compound **5** was achieved using (*R*)-(BINAP)$RuCl_2$ (91% after 168 h with a diastereoselectivity **4/5**=70/30 in the same conditions as described above) (Scheme 1).

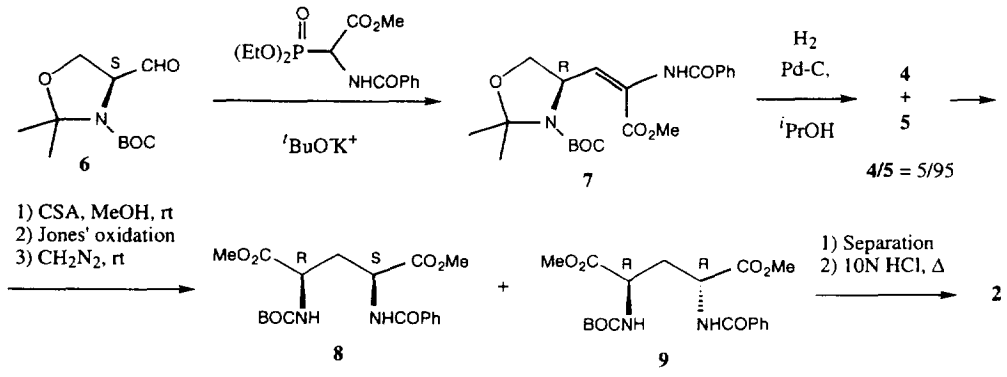


3 4 5

Scheme 1.

As the homogeneous hydrogenation of (*Z*)-olefin **3** was unsuccessful for obtaining the optically active (2*R*,4*R*)-2,4-diaminoglutaric acid as the major products, we decided to synthesize the other geometric isomer of olefin, (*E*)-**7**, starting from Garner's aldehyde **6** by a similar procedure to that described for (*Z*)-olefin **3**. The photochemical bromination of methyl N-benzoylglycinate followed by the Arbuzov reaction with triethyl phosphite gave the methyl 2-benzamido-2-(diethoxyphosphoryl)-acetate,[6] which was treated with potassium *tert*-butoxide and reacted with the Garner's aldehyde **6** under Wadsworth–Horner–Emmons olefination conditions[7] to obtain, with a 87% yield, a mixture of (*Z*)- and (*E*)-olefins **3** and **7** in a ratio of 40/60. From this mixture, by purification using silica gel column chromatography, (*E*)-olefin **7** was synthesised with a 52% yield (Scheme 2).

Several authors have observed partially racemisation during reactions with Garner's aldehyde.[8] Because of this, we have determined the enantiomeric purity of (*E*)-olefin **7** by means of ^{1}H-NMR,



Scheme 2.

using an europium(III) chelate as a chiral shift reagent and the (*R*)–(*E*)-olefin.[9] We have observed a 18% of racemisation in (*R*)–(*E*)-olefin **7** corresponding to (*S*)–(*E*)-olefin.

(*E*)-Olefin **7** was hydrogenated under the same heterogeneous conditions as (*Z*)-olefin **3** in the presence of palladium–carbon as a catalyst and using 2-propanol as a solvent at room temperature and atmospheric pressure to afford the mixture of hydrogenation products **4/5** in a ratio of 5/95. Following the same synthetic route as described in synthesizing the *meso*-2,4-diaminoglutaric acid **1**, starting from the mixture of products **4** and **5** arising from the hydrogenation of olefin **7**, we obtained the major diastereoisomer dimethyl ester of (2*R*,4*R*)-2,4-diaminoglutaric acid **9** using a protocol, which is described that occurs without epimerization.[10] This protocol consists in the partial deprotection of the aminoalcohols with camphorsulphonic acid, further oxidation by treatment with Jones' reagent, esterification with an excess of diazomethane and purification by a column chromatography (Scheme 2).

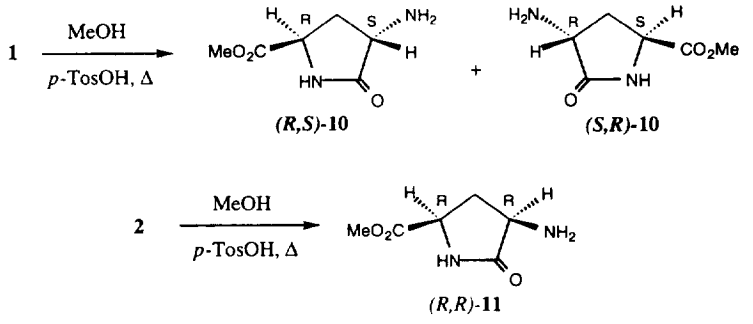
Diesters **8** and **9** were separated and their enantiomeric purity was again checked by means of ^{1}H-NMR, using an europium(III) chelate as a chiral shift reagent.[9] We have observed a 91% of enantiomeric purity in compound (*R*,*S*)-**8** and a 75% in compound (*R*,*R*)-**9**. In spite of racemisation and due to the lack of references in the literature about enantiomerically pure 2,4-diaminoglutaric acids, since they are very unstable (cyclization occurred to provide their γ-lactam derivatives), we have decided to carry out the hydrolysis of compound **9** in aqueous 10 N HCl at 110°C for 18 h. In this way, the optically active hydrochloride derivative of (2*R*,4*R*)-2,4-diaminoglutaric acid **2**, accompanied by a 7% of the corresponding γ-lactams as side products[11] was obtained (Scheme 2).

In order to determine the partial epimerization in the hydrolysis reaction, the mixture of optically active bis(α-amino acids) **2** was quantitatively converted into the corresponding (2*R*,4*R*)-γ-lactam methyl ester derivative **11** by treatment with *p*-toluenesulfonic acid in methanol, at reflux, for 24 h. In that way, a 11% of epimerization was observed in the ^{1}H-NMR spectra corresponding to (2*R*,4*S*)- and (2*S*,4*R*)-γ-lactam methyl ester derivatives **10**. The same feature was observed in the hydrolysis of compound **8** to obtain *meso*-bis(α-amino acid) **1** (9% of epimerization) (Scheme 3).

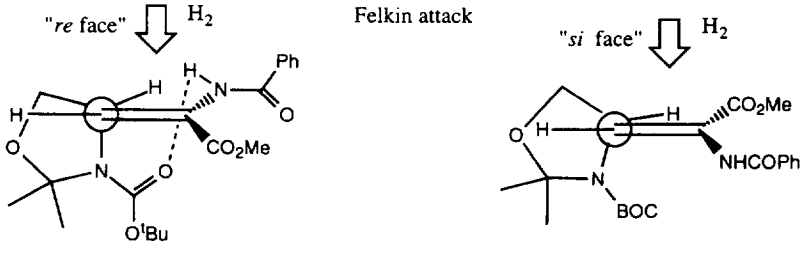
Stereochemical outcome of the asymmetric hydrogenation

The major and minor products obtained in the heterogeneous hydrogenation of chiral olefin **3** were those predicted by Felkin rules and, in order to rationalise the stereochemical course of hydrogenation reaction, we have made several theoretical studies. AM1 semi-empirical calculations[12] were carried out to evaluate the lowest energy conformers of olefin **3**.

The minimum value of heat of formation corresponded to the structure drawn in Figure 3 and agreed with the structure shown in solid state (see X-ray in Figure 2). This conformer is stabilised by an intramolecular hydrogen bonding between the carbonylic oxygen atom of *tert*-butoxycarbonyl group



Scheme 3.



ΔH_f = -194.0 kcal/mol (AM1)

ΔH_f = -189.4 kcal/mol (AM1)

Figure 3.

(BOC) and the hydrogen linked to the nitrogen atom of the benzamido group (interatomic distance O, H: 2.06 Å). The large shift (10.38 ppm) associated with NH proton accounts for the hydrogen bonding.[13] Moreover, the chemical shift remains unaffected when the solution is diluted[14] and this interatomic distance in the solid state is also in agreement (2.10 Å). This conformation places the CH–N bond perpendicular to the face of the double bond (H–C=C) and, in this situation, the N-BOC group probably shields the *si* face of the double bond in such a way that forces the addition of hydrogen to the *re* face of the olefin, so the reaction proceeds by an Felkin-type transition state[15] to give predominantly the stereoisomer **4** of *R,S* configuration.

The stereochemical outcome of hydrogen addition to olefin **3** in heterogeneous conditions could be explained by this model and the dihedral angle of 148.9 degrees (AM1) between the allylic and vinylic hydrogen atoms, achieved in the calculated conformation, is in excellent agreement with that estimated by applying the Karplus type of equation, especially developed by Garbish[16] for Csp^2–sp^3 rotamer (J=9.0 Hz, dihedral angle 147.5 degrees), and with that observed in the solid state (162.1 degrees).

The stereochemical course of the hydrogenation in the case of olefin **7**, was once again as predicted by Felkin rules and could be explained by the same model as described in olefin **3**, in spite of the lowest energy conformer of olefin **7**, as shown in Figure 3, obtained by AM1 semi-empirical calculations it is not stabilised by an intramolecular hydrogen bonding (interatomic distance O, H 4.78 Å and δ(NHCOPh=8.27 ppm)). This conformation places the N-BOC group shielding the *re* face of the double bond, so that the addition of hydrogen proceeds by the opposite face to afford principally the stereoisomer **5** of *R,R* configuration.

Apparently, although in the hydrogenation of olefin **3** it seems that one reason for the high asymmetric induction is the formation of the intramolecular hydrogen bonding, this one does not play

an important role because the hydrogenation of olefin **7** occurs with excellent asymmetric induction and there is not hydrogen bonding.

In summary, we have synthesised two bis(α-amino acids) using a methodology different from the most currently used asymmetric dialkylation of chiral glycine equivalents developed by Schollkopf and Seebach.[17] In this procedure, the chiral auxiliary, olefins' moiety coming from Garner's aldehyde, contributes a chiral centre to the bis(α-amino acid) and the other chiral centre was created by asymmetric hydrogenation of the didehydroamino acid derivatives **3** and **7**. The enantiomer of (2*R*,4*R*)-2,4-diaminoglutaric acid **2** could be obtained using this strategy but starting from the enantiomer of (*Z*)-olefin **3**, which is available from the enantiomer of Garner's aldehyde. Further works in order to carry out the asymmetric synthesis of other families of bis(α-amino acids) are in progress.

Experimental section

Solvents were purified according to standard procedures. Analytical TLC was performed by using Polychrom SI F_{254} plates. Column chromatography was performed by using Silica gel 60 (230–400 mesh). ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker ARX-300. Deuterated chloroform was used as a solvent with tetramethylsilane as the internal standard and deuterated water or methanol with tetramethylsilane as the external standard using a coaxial microtube (the chemical shifts are reported in ppm on the δ scale, coupling constants in Hz). Melting points were determined on a Büchi 530 and are uncorrected. Microanalyses were carried out on a Perkin–Elmer 240-C analyser and were in good agreement with the calculated values. Optical rotations were measured in 1 and 0.5 dm cells of 1 and 3.4 mL capacity, respectively. HPLC analysis were performed using a Liquid Chromatograph HP 1090M.

*(Z)-(*R*)-3-*tert*-Butoxycarbonyl-2,2-dimethyl-4-[2′-(benzamido)-2′-(methoxycarbonyl)ethenyl]-1,3-oxazolidine 3*

A 1 M solution of potassium *tert*-butoxide in THF (2 mL) was added dropwise, at −78°C, to a solution of methyl 2-benzamido-2-(diethoxyphosphoryl)-acetate[7] (658 mg, 2.0 mmol) in CH_2Cl_2 (10 mL). The solution was stirred at −78°C for 15 min and then a solution of Garner's aldehyde **6** (458 mg, 2.0 mmol) in CH_2Cl_2 (5 mL) was added. The cooling bath was removed and the mixture was allowed to warm to room temperature with stirring for 6 h. The reaction mixture was concentrated and the residue dissolved in ethyl acetate (20 mL), extracted with water (3×10 mL), dried over anhydrous $MgSO_4$, filtered and evaporated. The resulting mixture of *Z* and *E* isomers in a ratio 7:1 (determined by ^{1}H-NMR) was purified by crystallization in ethyl ether to yield 523 mg of compound **3** as a white solid. (65%). Mp: 140–1°C; $[\alpha]^{25}_D$ (c=1.31, $CHCl_3$)=+1.04. Anal. Calcd. for $C_{21}H_{28}N_2O_6$: C: 62.35, H: 6.98, N: 6.93. Found: C: 62.45, H: 7.05, N: 7.01. ^{1}H-NMR ($CDCl_3$): δ=1.48–1.60 (m, 15H, 5Me); 3.82 (s, 3H, COOMe); 3.90 (d, 1H, J_{5a-5b}=9.0, H_{5a}); 4.05 (dd, 1H, J_{5b-5a}=9.0, J_{5b-4}=5.3, H_{5b}); 4.65 (dd, 1H, $J_{4-1'}$=9.0, J_{4-5b}=5.3, H_4); 6.24 (d, 1H, $J_{1'-4}$=9.0, $H_{1'}$); 7.41–7.59 (m, 3H, Arom.); 8.03–8.06 (m, 2H, Arom.); 10.38 (brs, 1H, NHCOPh). ^{13}C-NMR ($CDCl_3$): δ=24.2, 27.6, 28.2, 28.5, 29.7 (5Me); 52.6 (CHN); 54.1 (COO*Me*); 67.5 (CH_2O); 81.8 (*C*Me$_3$); 93.8 (*C*Me$_2$); 127.8, 128.0, 128.5, 132.1 (Arom.); 131.4 (*C*H=C); 132.9 (CH=*C*); 153.3 (NCOO); 165.0 (Ph*C*ONH); 165.9 (*C*OOMe).

Heterogeneous hydrogenation. General procedure

A solution of compound **3** (100 mg, 0.25 mmol) in ^{i}PrOH (6 mL) was hydrogenated at room temperature for 8 h with 10% palladium–carbon (10 mg) as a catalyst. Removal of the catalyst and the solvent gave a residue of hydrogenated products **4** and **5** which was analyzed by ^{1}H-NMR and HPLC.

Homogeneous hydrogenation. General procedure

A degassed solution of compound **3** (100 mg, 0.25 mmol) in ^{i}PrOH (6 mL) was treated with the corresponding chiral catalyst (5.10^{-3} mmol) and the homogeneous mixture was degassed. The solution was transferred under a positive pressure of argon *via* cannula into a hydrogenation vessel that was filled, vented and refilled with a hydrogen atmosphere several times. The solution was then

stirred for the appropriate time, temperature and hydrogen pressure. The solvent was then evaporated and the residue analyzed by ^{1}H-NMR and HPLC.

*(R)-3-*tert*-Butoxycarbonyl-2,2-dimethyl-4-[(S)-2′-(benzamido)-2′-(methoxycarbonyl)ethyl]-1,3-oxazolidine* ***4***

(^{1}H-NMR data extracted from the mixture **4/5**=94/6) ^{1}H-NMR ($CDCl_3$): δ=1.38–1.60 (m, 15H, 5Me); 2.13 (m, 1H, $H_{1'a}$); 2.30 (m, 1H, $H_{1'b}$); 3.73 (s, 3H, COOMe); 3.82 (m, 1H, H_{5a}); 3.92–4.10 (m, 2H, H_{5b}+H_4); 4.75–4.84 (m, 1H, $H_{2'}$); 7.42–7.51 (m, 3H, Arom.); 7.82 (brs, 1H, NHCOPh); 7.95–8.00 (m, 2H, Arom.).

meso-*2,4-Diaminoglutaric acid* ***1***

The mixture of hydrogenated compounds **4** and **5** (150 mg, 0.37 mmol) obtained from the heterogeneous hydrogenation was dissolved in MeOH (15 mL) and treated with camphorsulphonic acid (10 mg). The solution was stirred at room temperature for 20 h and the solvent was removed under reduced pressure to give the corresponding alcohol derivatives, which were again dissolved, without purification, in acetone (5 mL) and an excess of Jones' reagent[8] was added dropwise with stirring, at 0°C, until complete conversion of starting material to the corresponding carboxylic acids. The excess of Jones' reagent was destroyed with 2-propanol. The mixture was then extracted with ethyl acetate several times. The combined extracts were washed with water, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residual oil was dissolved in ethyl ether and treated with an excess of diazomethane in an ethereal solution, at room temperature (monitored by TLC). The solvent was evaporated and the major methyl ester derivative **8** was purified by silica gel column chromatography eluting with hexane–ethyl acetate (3:2), yielding 97 mg of compound **8** (67%) as an oil; $[\alpha]^{25}_D$ (c=5.87, $CHCl_3$)=+23.47 (with a 91% of enantiomeric purity).[9] Anal. Calcd. for $C_{19}H_{26}N_2O_6$: C: 60.29, H: 6.93, N: 7.41. Found: C: 60.36, H: 7.05, N: 7.45. ^{1}H-NMR ($CDCl_3$): δ=1.48 (s, 9H, 3Me); 2.28–2.40 (m, 1H, CH_aH$_b$); 2.49 (d′t′, 1H, *J*=14.1 *J*=5.4, *J*=5.4, CH$_a$$H_b$); 3.68 (s, 3H, COOMe); 3.77 (s, 3H, COOMe); 4.57 (d′t′, 1H, *J*=9, *J*=9, *J*=5.4, CH); 5.11 (d′t′, 1H, *J*=8.1, *J*=5.4, *J*=5.4, CH); 5.36 (brd, 1H, *J*=9.0, NHBOC); 7.43–7.51 (m, 3H, Arom.); 7.53 (brd, 1H, *J*=5.4, NHCOPh); 7.93–7.97 (m, 2H, Arom.). ^{13}C-NMR ($CDCl_3$): δ=28.3, 29.7 (3Me); 34.7 (CH_2); 49.3 (*C*HNHBOC); 50.0 (*C*HNHCOPh); 52.7 (2COO*Me*); 80.8 (CMe_3); 127.3, 128.6, 131.9, 133.4 (Arom.); 155.8 (NCOO); 167.0 (Ph*C*ONH); 172.2 (*C*OOMe); 172.5 (*C*OOMe).

Compound **8** (96 mg, 0.25 mmol) was hydrolysed by heating under reflux for 18 h with aqueous 10 N HCl (25 mL). After extraction with CH_2Cl_2 (3×15 mL) the aqueous layer was evaporated *in vacuo* to afford 49 mg (84%) of a mixture of the hydrochloride derivative of *meso*-2,4-diaminoglutaric acid **1** and the products corresponding to γ-lactams in a ratio 92:8; $[\alpha]^{25}_D$ (c=5.83, H_2O)=0 (with a 9% of epimerization). Anal. Calcd. for $C_5H_{12}N_2O_4Cl_2$: C: 25.64, H: 5.17, N: 11.97. Found: C: 25.77, H: 5.09, N: 12.05. ^{1}H-NMR (D_2O): δ=2.12–2.23 (m, 1H, CH_aH$_b$); 2.39–2.50 (m, 1H, CH$_a$$H_b$); 4.10 (t, 1H, *J*=6.3, 2CH). ^{13}C-NMR (D_2O): δ=29.8 (CH_2); 49.5 (CH); 170.3 (COO).

*(E)-(R)-3-*tert*-Butoxycarbonyl-2,2-dimethyl-4-[2′-(benzamido)-2′-(methoxycarbonyl)ethenyl]-1,3-oxazolidine* ***7***

In a similar way to that described for olefin **3**, starting from Garner's aldehyde **6** and methyl 2-benzamido-2-(diethoxyphosphoryl)-acetate, but warming at room temperature when the Garner's aldehyde **6** was added, olefin **7** was obtained in 52% yield as a white solid. Mp: 110–1°C; $[\alpha]^{25}_D$ (c=2.90, $CHCl_3$)=−12.84 (with a 82% of enantiomeric purity).[9] Anal. Calcd. for $C_{21}H_{28}N_2O_6$: C: 62.35, H: 6.98, N: 6.93. Found: C: 62.39, H: 6.87, N: 7.00. ^{1}H-NMR ($CDCl_3$): δ=1.38–1.69 (m, 15H, 5Me); 3.90 (m, 4H, COOMe+H_{5a}); 4.26 (dd, 1H, J_{5b-5a}=8.4, J_{5b4}=6.6, H_{5b}); 5.29 (m, 1H, H_4); 7.40–7.58 (m, 4H, Arom.+$H_{1'}$); 7.72–7.87 (m, 2H, Arom.); 8.24 (s, 1H, NHCOPh). ^{13}C-NMR ($CDCl_3$): δ=24.1, 25.1, 26.3, 27.2, 28.4 (5Me); 52.9 (COO*Me*); 55.7, 56.3 (CHN); 69.0, 69.5 (CH_2O); 79.9, 80.5 (CMe_3); 94.0, 94.4 (CMe_2); 126.9, 128.8, 131.9, 132.0 (Arom.); 132.4 (*C*H=C); 133.6 (CH=*C*); 152.4 (NCOO); 164.0, 164.2 (Ph*C*ONH); 165.6, 165.7 (*C*OOMe).[18]

*(*R*)-3-*tert*-Butoxycarbonyl-2,2-dimethyl-4-[(*R*)-2′-(benzamido)-2′-(methoxycarbonyl)ethyl]-1,3-oxazolidine 5*

In a similar way to that described for the heterogeneous hydrogenation of (*Z*)-olefin **3**, (*E*)-olefin **7** was hydrogenated to give a mixture of compounds **4** and **5**. (^{1}H-NMR data extracted from the mixture **4/5**=5/95) ^{1}H-NMR ($CDCl_3$): δ=1.38–1.67(m, 15H, 5Me); 2.24 (m, 1H, $H_{1'a}$); 2.35 (m, 1H, $H_{1'b}$); 3.65–3.87 (m, 4H, COOMe+H_4); 3.97 (d, 1H, *J*=8.7, *J*=5.4, H_{5a}); 4.10 (m, 1H, H_{5b}); 4.51 (m, 1H, $H_{2'}$); 7.38–7.55 (m, 3H, Arom.); 7.90–8.08 (m, 2H, Arom.); 8.42 (brs, 1H, NHCOPh).

*(2*R*,4*R*)-2,4-Diaminoglutaric acid 2*

In a similar way to that described for **1**, starting from the mixture of hydrogenated compounds **4** and **5** (300 mg, 0.74 mmol) obtained from the heterogeneous hydrogenation of olefin **7**, methyl ester derivative **9** was obtained in 70% from **5** as an oil; $[\alpha]^{25}_D$ (c=3.93, $CHCl_3$)=−4.77 (with a 75% of enantiomeric purity).[9] Anal. Calcd. for $C_{19}H_{26}N_2O_6$: C: 60.29, H: 6.93, N: 7.41. Found: C: 60.37, H: 7.10, N: 7.52. ^{1}H-NMR ($CDCl_3$): δ=1.43 (s, 9H, 3Me); 2.30–2.58 (m, 2H, CH_2); 3.67 (s, 3H, COOMe); 3.80 (s, 3H, COOMe); 4.29–4.41 (m, 1H, CH); 4.62–4.75 (m, 1H, CH); 5.43 (brd, 1H, *J*=6.3, NHBOC); 7.35 (brd, 1H, *J*=5.2, NHCOPh); 7.41–7.52 (m, 3H, Arom.); 7.95–7.98 (m, 2H, Arom.). ^{13}C-NMR ($CDCl_3$): δ=28.3 (3Me); 34.4 (CH_2); 50.4 (*C*HNHBOC); 50.7 (*C*HNHCOPh); 52.7 (COO*Me*); 52.8 (COO*Me*); 80.4 (CMe_3); 127.2, 128.6, 131.9, 133.4 (Arom.); 155.5 (NCOO); 167.1 (Ph*C*ONH); 172.1 (*C*OOMe); 172.5 (*C*OOMe).

Compound **9** (104 mg, 0.27 mmol) was hydrolysed in the same way as described above to afford 55 mg (88%) of a mixture of the hydrochloride derivative of (2*R*,4*R*)-2,4-diaminoglutaric acid **2** and the product corresponding to γ-lactam in a ratio 93:7; $[\alpha]^{25}_D$ (c=4.17, H_2O)=−5.26 (with a 11% of epimerization). Anal. Calcd. for $C_5H_{12}N_2O_4Cl_2$: C: 25.64, H: 5.17, N: 11.97. Found: C: 26.74, H: 5.06, N: 12.09. ^{1}H-NMR (D_2O): δ=2.42 (t, 2H, *J*=6.6, CH_2); 4.28 (t, 2H, *J*=6.6, 2CH). ^{13}C-NMR (D_2O): δ=30.5 (CH_2); 50.6 (CH); 171.1 (COO).

Determination of the partially epimerization in the hydrolysis reactions

Bis(α-amino acid) 1

p-Toluenesulfonic acid (5 mg) and the mixture of hydrochloride derivative of *meso*-2,4-diaminoglutaric acid **1** and the corresponding γ-lactams (49 mg) were dissolved in methanol (20 mL) and heated under reflux for 24 h. Evaporation of the solvent gave a mixture of γ-lactams in a ratio 1/0.28, which was analysed by NMR experiments. The major compound corresponded to the methyl *rac*-4-aminoazolidin-5-one-2-carboxylate **10**. ^{1}H-NMR (CD_3OD): δ=1.54–1.73(m, 1H, H_{3a}); 1.91(br dd, 1H, *J*=12.9, *J*=8.7, H_{3b}); 2.96(s, 3H, COOMe); 3.28(br t, 1H, *J*=9.3, H_4); 3.54(br d, 1H, *J*=9.3, H_2). ^{13}C-NMR (CD_3OD): δ=30.8(C_3); 50.2(C_4); 53.3(C_2); 54.0(COO*Me*); 173.3, 173.5(*C*OOMe, CONH).

Bis(α-amino acid) 2

p-Toluenesulfonic acid (5 mg) and the mixture of hydrochloride derivative of (2*R*,4*R*)-2,4-diaminoglutaric acid **2** and the corresponding γ-lactam (55 mg) were dissolved in methanol (20 mL) and heated under reflux for 24 h. Evaporation of the solvent gave a mixture of γ-lactams in a ratio 1/0.21, which was analysed by NMR experiments. The major compound corresponded to methyl *cis*-4-aminoazolidin-5-one-2-carboxylate **11**. ^{1}H-NMR (CD_3OD): δ=1.28 (ddd, 1H, *J*=13.2, *J*=9.3, *J*=9.0, H_{3a}); 2.10 (ddd, 1H, *J*=13.2, *J*=9.3, *J*=7.2, H_{3b}); 2.93 (s, 3H, COOMe); 3.30 (br t, 1H, *J*=9.3, H_4); 3.55 (dd, 1H, *J*=9.0, *J*=7.2, H_2). ^{13}C-NMR (CD_3OD): δ=30.6 (C_3); 51.2 (C_4); 53.1 (C_2); 53.7 (COO*Me*); 172.2, 172.6 (*C*OOMe, CONH).

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