Selective Catalytic Hydrogenation of γ-Amino α,β-Unsaturated Esters in the Presence of Hydrogenable Protecting Groups

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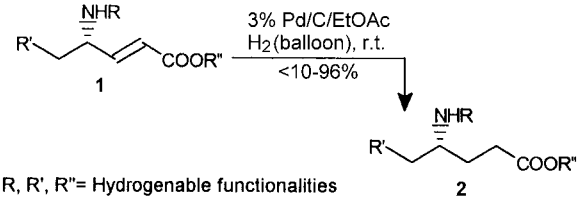
Abstract: The chemoselective catalytic hydrogenation of substituted γ-amino α,β-unsaturated esters bearing benzyl ether, benzyl ester functionalities and *N*-Cbz protecting groups by 3% Pd/C in EtOAc was investigated. The results revealed a good selectivity for substrates with benzyl ethers and benzyl esters in the side chain and for α,β-unsaturated benzyl esters. Moderate selectivity was observed for substrates with *N*-Cbz protecting group.

Key words: chemoselective hydrogenation, 3% Pd/C, γ-amino α,β-unsaturated esters, protected γ-amino acids

γ-Amino acids possess various biological activities, especially as enzyme inhibitors; for instance γ-aminoadipic acid is able to bind the Glu and Asp receptors,[1] whilst 4-amino-5-hydroxypentanoic acid is an inhibitor of enzymes involved in the neurotransmission mechanism.[2] Few general methods are described in literature[3] to obtain enantiomerically pure γ-amino acids, most of them starting from α-amino acids. A simple synthetic strategy to prepare these compounds is based on a Wittig homologation of a suitable α-amino aldehyde, followed by reduction to the saturated ester. Although a number of methods[4] are available for the reduction of α,β-unsaturated esters, the hydrogenation with heterogeneous catalyst is the method which combines mild conditions with high yields. However, this synthetic approach seems to be precluded by the presence of other reducible functionalities, e.g. by the presence of protecting groups labile under hydrogenation conditions. While several catalytic systems are available for the hydrogenation of alkenes, selective reduction in the presence of other hydrogenable groups has not been fully addressed. During the course of synthetic studies,[5] we searched for a method to hydrogenate some substituted γ-amino α,β-unsaturated esters in the presence of benzyl ether, benzyl ester functionalities and *N*-benzyloxycarbonyl protecting groups. A review of the literature revealed that only few examples of selective reduction of alkenes in the presence of a benzyl ether are reported. These methods involve the use of 5% Rh/Al_2O_3[6] or 5% Pd/C in the presence of 5% butylamine or ammonia,[7] as well as the Lindlar catalyst in MeOH.[8]

We wish to report here the results obtained by the use of 3% Pd/C in EtOAc for the selective catalytic hydrogenation of substituted γ-amino α,β-unsaturated esters in the presence of the above hydrogenable protecting groups (Scheme). All the starting *trans*-α,β-unsaturated esters were synthesized in 60−70% yields by a one-pot reduction/Wittig−Horner reaction from the *N*-protected α-amino acid esters with the proper lithium trialkylphosphonoacetate according to Knaus et al.[9]



Scheme

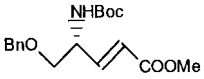
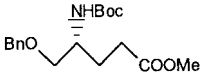
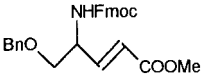
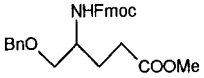
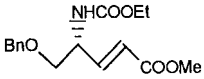
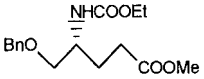
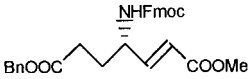
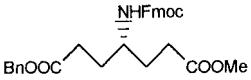
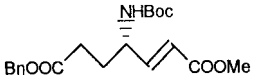
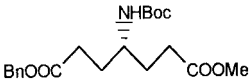
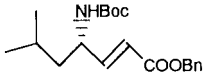
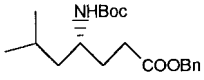
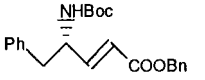
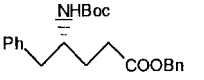
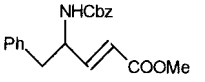
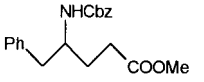
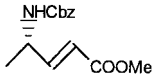
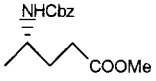
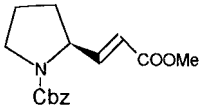
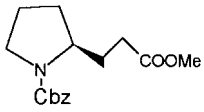
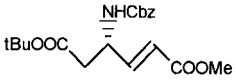
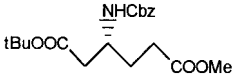
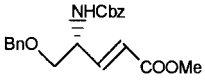
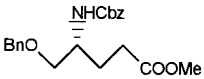
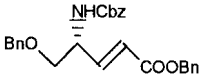
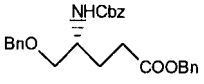
Each substrate was treated under the same conditions; namely it was dissolved in freshly dried[10] EtOAc (0.2 M) containing a catalytic amount (5% by wt) of commercial 3% Pd/C. The reaction mixture was stirred under an atmospheric pressure of H_2 until TLC[11] indicated the disappearance of the γ-amino α,β-unsaturated ester. Reactions were complete usually within 1 hour, but some experiments were allowed to stand for 16 hours to evaluate the selectivity by time.

The results, summarized in the Table, indicate that under the above reaction conditions α,β-unsaturated esters can be selectively reduced in the presence of benzyl ether, benzyl ester functionalities and, in a less selective way, also in the presence of *N*-benzyloxycarbonyl protecting group.

Initially, experiments were run with γ-amino α,β-unsaturated esters possessing a benzyl ether in the side chain **1a−c**; clean reduction occurred within 1 hour and the saturated esters **2a−c** were obtained in high yields (~ 95%) without any effect on the ether function.

When the reaction was allowed to stand for 16 hours (entry **1a**) the reduction product **2a** was obtained in 90% yield, confirming the good selectivity towards the benzyl ether protecting group. A control of the optical purity[12] for **2a** gave an ee value of 95%. Good yields (90−93%) were also obtained for the catalytic reduction of γ-amino α,β-unsaturated esters carrying a benzyl ester in the side chain (compounds **1d**, **1e**); moreover the selectivity was confirmed when the compound **1d** was allowed to stand for 16 hours and the saturated product **2d** was obtained in 82% yield. Notably, α,β-unsaturated benzyl esters **1f** and

Table Selective Reduction of Substituted γ-Amino α,β-Unsaturated Esters in the Presence of Benzyl Ether, Benzyl Ester and N-Cbz Functionalities.

Entry	Substrate **1**	Product **2**	Time	Yield (%)
a			50 min 16 h	94 90
b			1 h	96
c			1 h	95
d			1 h 16 h	90 82
e			1 h	93
f			1 h 16 h	95 83
g			1 h	92
h			45 min 3 h	60 <10
i			40 min	62
j			40 min	60
k			45 min	64
l			40 min	72
m			45 min	76

1g were also selectively reduced in 92 and 95% yield, respectively, without any modification of the benzyl ester function. The reaction conditions were again so mild to inhibit the hydrogenolysis of the benzyl ester in **1f** even if the reaction was allowed for 16 hours, and the saturated compound **2f** was obtained in 83% yield. To our knowledge, this is the first example of selective catalytic hydrogenation under heterogeneous conditions of α,β-unsaturated benzyl esters to the saturated compounds. A control of the enantiomeric excess for the compound **2g**[12] gave a value of 96%. By contrast the selectivity was moderate when a benzyloxycarbonyl group was present as protecting group for an amine function (compounds **1h−k**).

Within the time required for the reduction of the α,β-unsaturated esters the saturated products were obtained in yields ranging from 60−64%. The byproduct was the corresponding 2-pyrrolidinone, formed by the loss of the Cbz group and cyclization. The stability of Cbz under these conditions was time dependent as shown by the substrate **1h** where the Cbz was almost entirely removed within 3 hours.

Additional studies were performed on substrates with two or three hydrogenable protecting groups. The substrate **1l** was thus reduced in 72% yield to the saturated product **2l**, whereas the compound **1m**, carrying all the protecting groups studied up to now, was hydrogenated in 30 minutes in 76% yield. These results, together with those obtained for **1h−k**, indicate that, in the case of γ-amino α,β-unsaturated esters carrying a *N*-Cbz protecting group, the yields of saturated products are variable and substrate depending.

In summary we have shown that the combination of catalytic amount (5% by wt) of commercial 3% Pd/C in EtOAc is the system of choice for the selective hydrogenation of substituted γ-amino α,β-unsaturated esters when a benzyl ether or benzyl ester functionality is present in the molecule. A lower selectivity was instead observed when a *N*-benzyloxycarbonyl group was present. Following the above results, we believe that the present method should find broad application in organic synthesis.

Melting points were determined in open capillaries using a Büchi apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were run on a Varian Gemini 300 spectrometer at 300 and 75 MHz, respectively, in $CDCl_3$. Chemical shifts (δ scale) are relative to TMS as internal reference. The ^{1}H and ^{13}C NMR data of compound **2j** were collected at T = 60 °C, since at r.t. double signals, due to the restricted rotation of the N−CO bond, were observed. Optical rotations were determined on a Perkin Elmer 243 polarimeter at 23 °C (concentration g/100 mL). TLC was performed on Merck silica gel 60 F_{254} glass plates. Compounds **2a−m** gave C, H, N analysis ±0.3%.

Selective Catalytic Hydrogenation of γ-Amino α,β-Unsaturated Esters; General Procedure

A mixture of the appropriate α,β-unsaturated ester (1 mmol), 3% Pd/C (5% by weight, Aldrich) in freshly distilled EtOAc (5 mL) was subjected to two N_2/H_2 cycles and then stirred under a H_2 filled ballon. After the proper time (Table) the reaction mixture was diluted with an equal amount of EtOAc and filtered through a paid of Celite. The solvent was removed under reduced pressure and the residue was passed through a short silica gel column (50% EtOAc/hexane) to give the corresponding hydrogenated compound.

(*R*)-Methyl 5-Benzyloxy 4-[(tert-butoxycarbonyl)amino]pentanoate (2a)

mp 45−46°C; $[\alpha]_D$ +19.98 (c = 2.12, $CHCl_3$)

^{1}H NMR: δ = 7.40−7.25 (5 H, m, C_6H_5), 4.77 (1 H, br d , *J* = 9.0 Hz, NH), 4.53, 4.49 (1 H each, d, *J* = 12.0 Hz, OC*H*$_2$C$_6$H$_5$), 3.78 (1 H, m, Σ *J* = 31.0 Hz, CHN), 3.67 (3 H, s, OCH_3), 3.47 (2 H, d, *J* = 4.0 Hz, CH_2O), 2.38 (2 H, t, *J* = 7.5 Hz, CH_2CO), 1.94 (1 H, dtd, *J* = 14.0, 7.5, 5.5 Hz, C*H*$_A$H$_B$), 1.86 (1 H, dq, *J* = 14.0, 7.5 Hz, CH$_A$*H*$_B$), 1.43 (9 H, s, 3 CH_3).

^{13}C NMR: δ = 173.89 (s, COO), 155.59 (s, CON), 138.03, 128.39, 127.69, 127.58 (s, 2 d, d, 2 d, C_6H_5), 79.28 (s, quat C), 73.20 (t, OC$H_2C_6H_5$), 72.11 (t, CH_2O), 51.61 (q, OCH_3), 49.91 (d, CHN), 30.81 (t, *C*H_2CO), 28.36 (q, 3 CH_3), 27.55 (t, CH_2).

(*R,S*)-Methyl 5-Benzyloxy-4-[(fluorenylmethoxycarbonyl)amino]pentanoate (2b)

mp 99−100 °C

^{1}H NMR: δ = 7.76 (2 H, br d, *J* = 7.5 Hz, Fmoc), 7.59 (2 H, br d, *J* = 7.5 Hz, Fmoc), 7.40 (2 H, br t, *J* = 7.5Hz, Fmoc), 7.35−7.25 (5 H, m, C_6H_5), 7.31 (2H, br t, *J* = 7.5 Hz, Fmoc), 5.07 (1 H, br d, *J* = 9.0 Hz, NH), 4.53, 4.49 (1 H each, d, *J* = 12.0 Hz, OC*H*$_2$C$_6$H$_5$), 4.42 (2 H, d, *J* = 7.0 Hz, CH_2), 4.21 (1 H, t, *J* = 7.0 Hz, CH), 3.85 (1 H, m, Σ *J* = 32 Hz, CHN), 3.66 (3H, s, OCH_3), 3.49 (2H, d, *J* = 4.0 Hz, CH_2O), 2.38 (2H, t, *J* = 7.5 Hz, CH_2CO), 1.96, 1.89 (1H each, dq, *J* = 14.0, 7.5 Hz, CH_2).

^{13}C NMR: δ = 173.78 (s, COO), 156.10 (s, CON), 143.93, 143.89, 141,29 (s, s, 2 s, Fmoc), 137.89, 128.42, 127.75, 127.64 (s, 2 d, d, 2 d, C_6H_5), 127.01, 125.02, 119.83, 103.32 (d each, Fmoc), 73.25 (t, OC$H_2C_6H_5$), 71.82 (t, CH_2O), 66.59 (t, CO_2CH_2), 51.62 (q, OCH_3), 50.61 (d, CHN), 47.28 (d, CH), 30.72 (t, *C*H_2CO), 27.31 (t, CH_2).

(*R*)-Methyl 5-Benzyloxy-4-[(ethoxycarbonyl)amino]pentanoate (2c)

oil; $[\alpha]_D$ +10.5 (c = 2.2, $CHCl_3$)

^{1}H NMR: δ = 7.40−7.25 (5 H, m, C_6H_5), 4.94 (1 H, br d , *J* = 8.5 Hz, NH), 4.53, 4.49 (1 H each, d, *J* = 12.0 Hz, OC*H*$_2$C$_6$H$_5$), 4.09 (2 H, q, *J* = 7.0 Hz, OC*H*$_2$CH$_3$), 3.83 (1 H, m, Σ *J* = 31.0 Hz, CHN), 3.49 (2 H, d, *J* = 4.0 Hz, CH_2O), 2.39 (2 H, t, *J* = 7.5 Hz, CH_2CO), 1.94 (1 H, dtd, *J* = 14.0, 7.5, 5.5 Hz, C*H*$_A$H$_B$), 1.86 (1 H, dq, *J* = 14.0, 7.5 Hz, CH$_A$*H*$_B$), 1.23 (3 H, t, *J* = 7.0 Hz, CH_3).

^{13}C NMR: δ =173.83 (s, COO), 156.34 (s, CON), 137.83, 128.39, 127.71, 127.58 (s, 2 d, d, 2 d, C_6H_5), 73.23 (t, OC$H_2C_6H_5$), 71.95 (t, CH_2O), 60.78 (t, OCH_2CH$_3$), 51.62 (q, OCH_3), 50.38 (d, CHN), 30.74 (t, *C*H_2CO), 27.45 (t, CH_2), 14.57 (q, CH_3).

(*R*)-Methyl 4-[(Fluorenylmethoxycarbonyl)amino]-6-benzyloxycarbonylhexanoate (2d)

mp 123−124 °C; $[\alpha]_D$ +11.9 (c = 0.53, $CHCl_3$)

^{1}H NMR: δ = 7.74 (2 H, br d , *J* = 7.5 Hz, Fmoc), 7.56 (2 H, br d, *J* = 7.5 Hz, Fmoc), 7.38 (2 H, br t, *J* = 7.5 Hz, Fmoc), 7.33 (5 H, br s, C_6H_5), 7.29 (2 H, br t, *J* = 7.5 Hz, Fmoc), 5.09 (2 H, s, OCH_2), 4.61 (1 H, d, *J* = 9.0 Hz, NH), 4.40 (2 H, d, *J* = 6.5 Hz, CH_2, Fmoc), 4.17 (1 H, t, *J* = 6.5 Hz, CH, Fmoc), 3.66 (1 H, m, Σ *J* = 37.0 Hz, CHN), 3.64 (3 H, s, OCH_3), 2.40, 2.34 (2 H each, br t, *J* = 7.5 Hz, 2 C*H*$_2$CO), 1.88, 1.86, 1.74, 1.68 (1 H each, m, 2 CH_2).

^{13}C NMR: δ =173.80 (s, COO), 156.16 (s, CON), 143.87, 141.34 (s each, Fmoc), 135.93, 128.57, 128.26 (s, 2 d, 3 d, C_6H_5), 127.69, 127.06, 124.99, 119.96 (d each, Fmoc), 66.43 (t, OCH_2), 51.72 (q, OCH_3), 50.87 (d, CHN), 47.36 (d, CH, Fmoc), 30.91, 30.66 (t each, 2 *C*H_2CO), 30.49, 29.71 (t each, 2 CH_2).

(*R*)-Methyl 4-[tert-Butoxycarbonyl)amino]-6-benzyloxycarbonylhexanoate (2e)

mp 38−39 °C; $[\alpha]_D$ −4.06 (c = 2.44, $CHCl_3$)

^{1}H NMR: δ = 7.36 (5 H, br s, C_6H_5), 5.12 (2 H, s, OCH_2), 4.31 (1 H, d, *J* = 9.5 Hz, NH), 3.67 (3 H, s, OCH_3), 3.60 (1 H, dp, *J* = 9.5, 4.5Hz, CHN), 2.44, 2.38 (2 H each, t, *J* = 7.5 Hz, 2 C*H*$_2$CO), 1.87, 1.85 (1 H each, dtd, *J* = 14.0, 7.5, 4.5 Hz, CH_2), 1.78, 1.76 (1 H each, m, CH_2), 1.42 (9 H, s, 3 CH_3).

^{13}C NMR: δ =173.87, 173.18 (s each, 2 COO), 155.67 (s, CON), 135.93, 128.59, 128.25 (s, 2 d, 3 d, C_6H_5), 79.33 (s, quat C), 66.39 (t, OCH_2), 51.71 (q, OCH_3), 50.11 (d, CHN), 31.00, 30.73 (t, 3 t, 2 CH_2CO, 2 CH_2), 28.38 (q, 3 CH_3).

(*R*)-Benzyl 6-Methyl-4-[(tert-butoxycarbonyl)amino]heptanoate (2f)

mp 71−72 °C; $[\alpha]_D$ −7.13 (c = 2, $CHCl_3$)

^{1}H NMR: δ = 7.35 (5 H, s, C_6H_5), 5.12 (2 H, s, OCH_2), 4.31 (1 H, br d , *J* = 9.0 Hz, NH), 3.68 (1 H, m, Σ *J* = 37.0 Hz, CHN), 2.44 (2 H, br t, *J* = 7.5 Hz, CH_2CO), 1.85 (1 H, dq, *J* = 13.0, 7.5 C*H*$_A$H$_B$CO), 1.67 (1 H, m, CH$_A$*H*$_B$CH$_2$CO), 1.59 (1 H, m, CH), 0.91, 0.90 (3 H each, d, *J* = 6.5 Hz, 2 CH_3).

^{13}C NMR: δ = 173.47 (s, COO), 155.61 (s, CON), 135.96, 128.52, 128.19 (s, 2 d, 3 d, C_6H_5), 79.40 (s, quat C), 66.27 (t, OCH_2), 48.42 (d, CHN), 45.12 (t, *C*H$_2$CH), 31.11, 30.97 (t each, *C*H$_2$CO, CH_2), 28.36 (q, 3 CH_3), 24.92, 23.01 (q each, 2 CH_3), 22.21 (d, CH).

(*R*)-Benzyl 5-Phenyl-4-[(tert-butoxycarbonyl)amino]pentanoate (2g)

mp 93−94 °C; $[\alpha]_D$ +7.58 (c = 2.42, $CHCl_3$)

^{1}H NMR: δ = 7.34 (5 H, br s, $OCH_2C_6H_5$), 7.27, 7.21, 7.16 (2 H d, 1 H t, 2 H br d, *J* = 8.0 Hz, $CH_2C_6H_5$), 5.10 (2 H, s, OCH_2), 4.37 (1 H, d, *J* = 9.0 Hz, NH), 3.84 (1 H, m, Σ *J* = 37.0 Hz, CHN), 2.81, 2.74 (1 H each, dd, *J* = 13.0, 7.0 Hz, C*H*$_2$C$_6$H$_5$), 2.46 (1 H, ddd, *J* = 16.0, 9.0, 7.0 Hz, C*H*$_A$HBCO), 2.40 (1 H, dt, *J* = 16.0, 7.5 Hz, CH$_A$*H*$_B$CO), 1.88 (1 H, dddd, *J* = 14.0, 9.0, 7.0, 4.0 Hz, C*H*$_C$H$_D$), 1.62 (1 H, ddt, *J* = 14.0, 10.5, 7.5 Hz CH$_C$*H*$_D$), 1.39 (9 H, s, 3 CH_3).

^{13}C NMR: δ = 173.29 (s, COO), 155.46 (s, CON), 137.79, 129.43, 128.40, 126.42 (s, 2 d, 2 d, d, $CH_2C_6H_5$), 135.90, 128.55, 128.20 (s, 2 d, 3 d, $OCH_2C_6H_5$), 79.22 (s, quat C), 66.33 (t, OCH_2), 51.38 (d, CHN), 41.75 (t, *C*H$_2$C$_6$H$_5$), 31.17 (t, *C*H$_2$CO), 29.29 (t, CH_2), 28.35 (q, 3 CH_3).

(*R,S*)-Methyl 5-Phenyl-4-[(benzyloxycarbonyl)amino]pentanoate (2h):

mp 61−62 °C

^{1}H NMR: δ = 7.30−7.14 (5 H, m, $OCH_2C_6H_5$), 7.26, 7.24, 7.16 (2 H d, 1 H t, 2 H br d, *J* = 7.5 Hz, C_6H_5), 5.07 (2 H, s, OCH_2), 4.65 (1 H, d, *J* = 9.0 Hz, NH), 3.91 (1 H, m, Σ *J* = 36.0Hz, CHN), 3.62 (3 H, s, OCH_3), 2.85, 2.76 (1 H each, dd, *J* = 14.0, 7.0 Hz, C*H*$_2$C$_6$H$_5$), 2.37 (2 H, t, *J* = 7.5 Hz, CH_2CO), 1.88 (1 H, dtd, *J* = 14.0, 7.5, 4.0 Hz, C*H*$_A$H$_B$), 1.65 (1H, dq, *J* = 14.0, 7.5 Hz, CH$_A$*H*$_B$).

^{13}C NMR: δ = 173.91 (s, COO), 155.94 (s, CON), 137.46, 129.40, 128.48, 126.55 (s, 2 d, 2 d, d, $CH_2C_6H_5$), 135.92, 128.48, 128.06, 127.96 (s, 2 d, d, 2 d, C_6H_5), 66.56 (t, OCH_2), 52.11 (d, CHN), 51.67 (q, OCH_3), 41.59 (t, *C*H$_2$C$_6$H$_5$), 30.87 (t, *C*H$_2$CO), 29.21 (t, CH_2).

(*S*)-Methyl 4[(Benzyloxycarbonyl)amino]pentanoate (2i):

mp 47−48 °C; $[\alpha]_D$ +8.44 (c = 1.95, $CHCl_3$)

^{1}H NMR: δ = 7.40−7.25 (5 H, m, C_6H_5), 5.08 (2 H, s, OCH_2), 4.65 (1 H, d, *J* = 8.5 Hz, NH), 3.76 (1 H, m, Σ*J* = 43Hz, CHN), 3.65 (3 H, s, OCH_3), 2.38 (2 H, t, *J* = 7.5 Hz, CH_2CO); 1.82 (1 H, dtd, *J* = 14.0, 7.5, 5.0 Hz, C*H*$_A$H$_B$), 1.72 (1 H, q, *J* = 14.0, 7.5 Hz, CH$_A$*H*$_B$), 1.17 (3 H, d, *J* = 6.5 Hz, m, CH_3).

^{13}C NMR: δ = 173.86 (s, COO), 155.82 (s, CON), 136.55, 128.49, 128.05 (s, 2 d, 3 d, C_6H_5), 66.56 (t, OCH_2), 51.64 (q, OCH_3), 46.92 (d, CHN), 31.95 (t, CH_2CO), 30.80 (t, CH_2), 21.30 (q, CH_3).

(*S*)-1-(Benzyloxycarbonyl)-2-(2-methoxycarbonyl)ethyl pyrrolidine (2j)

oil; $[\alpha]_D$ −37.8 (c = 1.83, $CHCl_3$)

^{1}H NMR (60 °C): δ = 7.40−7.25 (5 H, m, C_6H_5), 5.12 (2 H, s, OCH_2), 3.91 (1 H, m, Σ*J* = 23.5 Hz, CHN), 3.62 (3 H, s, OCH_3), 3.47 (1 H, br dt, *J* = 11.0, 7.5 Hz, C*H*$_A$CH$_B$N), 3.36 (1 H, ddd, *J* = 11.0, 7.0, 5.0 Hz, CH$_A$C*H*$_B$N), 2.32 (2 H, t, *J* = 7.5 Hz, CH_2CO), 1.96, 1.68 (1 H each, m, CH_2), 1.88, 1.62 (1 H each, m, CH_2), 1.83 (1 H, ddd, *J* = 14.0 Hz, C*H*$_C$H$_D$), 1.74 (1 H, ddd, *J* = 14.0, 7.5, 6.0 Hz, CH$_C$*H*$_D$).

^{13}C NMR (60 °C): δ = 173.42 (s, COO), 155.03 (s, CON), 137.06, 128.31, 127.75, 127.72 (s, 2 d, d, 2 d, C_6H_5), 66.61, (t, OCH_2), 56.95 (br d, CHN), 51.24 (q, OCH_3), 30.92 (t, *C*H$_2$CO), 30.38 (br t, CH_2), 29.69 (t, CH_2), 23.36 (br t, CH_2).

(*R*)-Methyl 4-[(Benzyloxycarbonyl)amino]-5-tert-butoxycarbonylpentanoate (2k)

mp 55−56 °C; $[\alpha]_D$ 15.21 (c = 2.11, $CHCl_3$).

^{1}H NMR: δ = 7.35 (5 H, m, $OCH_2C_6H_5$), 5.08 (2 H, s, OCH_2), 3.98 (1 H, dtt, *J* = 9.5, 7.5, 5.5 Hz, CHN), 3.65 (3 H, s, OCH_3), 2.50, 2.43 (1 H each, dd, *J* = 16.0, 5.5 Hz, CH_2CO), 2.40 (2 H, t, *J* = 7.5 Hz, C*H*$_2$COOCH$_3$), 1.43 (9 H, s, 3 CH_3).

^{13}C NMR: δ = 173.61 (s, *C*O$_2$CH$_3$), 170.56 (s, *C*O$_2$C$_4$H$_9$-*t*), 155.87 (s, CON), 136.51, 128.48, 128.05, 128.02 (s, 2 d, 2 d, d, C_6H_5), 81.27 (s, quat C), 66.65 (t, OCH_2), 51.66 (q, OCH_3), 48.01 (d, CHN), 40.37 (t, CH_2CO), 30.84 (t, CH_2CO), 29.55 (t, CH_2), 28.04 (q, 3 CH_3).

(*R*)-Methyl 5-Benzyloxy-4-[(benzyloxycarbonyl)amino]pentanoate (2l)

mp 53−54 °C; $[\alpha]_D$ +16.25 (c = 3.95, $CHCl_3$)

^{1}H NMR: δ = 7.45−7.30 (5 H, m, $CO_2CH_2C_6H_5$), 7.41 (5 H, br s, C_6H_5), 5.16 (2 H, s, CO_2CH_2), 5.12 (1 H, br d , *J* = 9.0 Hz, NH), 4.58, 4.54 (1 H each, d, *J* = 12.0 Hz, OCH_2), 3.92 (1 H, m, Σ*J* = 31.0 Hz, CHN), 3.71 (3 H, s, OCH_3), 3.55 (2 H, d, *J* = 4.0 Hz, CH_2O), 2.45 (2 H, t, *J* = 7.5 Hz, CH_2CO), 2.01, 1.93 (1 H each, dq, *J* = 14.0, 7.0 Hz, CH_2).

^{13}C NMR: δ = 173.76 (s, COO), 156.07 (s, CON), 137.88, 128.39, 127.71, 127.57 (s, 2 d, d, 2 d, $CH_2OCH_2C_6H_5$), 136.49, 128.48, 128.05, 128.02 (s, 2 d, 2 d, d, C_6H_5), 73.23 (t, $CH_2OCH_2C_6H_5$), 71.82 (t, *C*H$_2$OCH$_2$C$_6$H$_5$), 66.67 (t, OCH_2), 51.60 (q, OCH_3), 50.58 (d, CHN), 30.71 (t, CH_2CO), 27.41 (t, CH_2).

(*R*)-Benzyl 5-benzyloxy-4-[(benzyloxycarbonyl)amino]pentanoate (2m)

mp 69−70 °C; $[\alpha]_D$ +17.76 (c =1.69, $CHCl_3$)

^{1}H NMR: δ = 7.36−7.23 (5 H, m, $CH_2OCH_2C_6H_5$), 7.33 (10 H, br s, 2 C_6H_5), 5.09, 5.07 (2 H each, s, 2 CO_2CH_2), 5.06 (1 H, br d , *J* = 9.0 Hz, NH), 4.50, 4.46 (1 H each, d, *J* = 12.0 Hz, OCH_2), 3.86 (1 H, dtt, *J* = 9.0, 7.0, 4.0 Hz, CHN), 3.48 (1 H, d, *J* = 4.0 Hz, CH_2O), 2.43 (2 H, t, *J* = 7.5 Hz, CH_2CO), 1.97, 1.87 (1 H each, dq, *J* = 14.0, 7.0 Hz, CH_2).

^{13}C NMR: δ = 173.11 (s, COO), 156.05 (s, CON), 137.87, 136.46, 128.48, 128.49, 127.71, 127.57 (s, s, 2 d, 2 d, 2 d, 4 d, 2 $CO_2CH_2C_6H_5$), 135.90, 128.51, 128.05, 128.02 (s, 2 d, 2 d, d, C_6H_5), 73.20 (t, $CH_2OCH_2C_6H_5$), 71.82 (t, *C*H$_2$OCH$_2$C$_6$H$_5$), 66.67, 66.29 (t each, 2 OCH_2), 50.53 (d, CHN), 30.94 (t, CH_2CO), 27.36 (t, CH_2).

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(10) The solvent was dried prior the use according to: Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, Pergamon Press: Oxford, 1988. Commercial EtOAc gave lower selectivity.

(11) TLC plates were run twice in EtOAc/hexane (4:6) and the saturated product was identified by negative reaction with an alkaline solution (0.1 M) of $KMnO_4$.

(12) The enantiomeric excess of **2a** and **2g** was obtained by integrating the relevant peaks in ^{1}H NMR spectrum in the presence of 0.15 equiv and 0.21 equiv of $Eu(hfc)_3$, respectively.

(13) No attempts have been made so far to scale-up the method.

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