Regioselective Lipase-Catalysed Amidation of *N*-Blocked L- and D-Aspartic Acid Diesters[‡]

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The amidation of *N*-protected aspartic acid diesters catalysed by *Candida antarctica* lipase B described in this paper takes place in a regioselective way. It may, if the amino function is protected by a suitable protecting group, be a synthetically useful method for regioselective preparation of both aspartic monoamides. The L derivatives react preferentially through the α-position, while the D series substrates display β-selectivity. Because of the short length of the side chain of aspartic acid, the nature of the protecting group and its interaction with the active site determine not only the reaction rate but also the selectivity and synthetic usefulness of the reaction.

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Introduction

Dicarboxylic amino acids are suitable as cheap chiral building blocks for the fine chemicals industry, although they present the negative corollary that, in many cases, initial selective functionalization of one of the two carboxylic groups[1] is required. Normally, when classical chemical methods are used, this regioselective functionalization is a difficult and tedious task involving some protecting and deprotecting steps that considerably affect the final yield of the process. The use of enzymes is an attractive alternative, and lipases in particular have proved to be efficient catalysts for selective acylation reactions on a wide range of substrates.[2]

We have previously reported several studies on the regioselective enzymatic amidation of dicarboxylic amino acid esters with *Candida antarctica* lipase B (CAL) as catalyst. When L-glutamic acid derivatives were used as substrates[3,4] the reactions proceeded in a fast and totally α-regioselective manner, independently of the *N*-blocking group (bulky groups slowed down or could even block the reaction, but the regioselectivity remained unchanged). On the other hand, the reaction rates of the D series analogues[5] were significantly lower and γ-regioselective, but with the γ/α ratio related to the nature of the *N*-blocking group. An increase in the length of the side chain of the substrate (derivatives of α-aminoadipic and α-aminopimelic acids)[6] changed the regioselectivity towards the ω position, whatever the enantiomer or *N*-blocking group used.

In continuation of this line of research, we wanted to study the effect on this reaction of a decrease, by one methylene group, in the length of the side chain of some glutamic derivatives that we have already studied. Here we report our results for the CAL-catalysed amidation of *N*-protected aspartic acid diesters in an anhydrous organic solvent, in terms both of the relationship between regioselectivity and the enantiomer employed as substrate and of the influence of the *N*-blocking group on the degree of this regioselectivity.

Enzymatic reactions of aspartic acid derivatives are less common than those of other amino acids. There are some few reported examples of hydrolysis, alcoholysis and acylation reactions catalysed by esterases,[7] proteases,[8] lipases[9] and acylase.[10] Amidations, catalysed by proteases and normally associated with the synthesis of the sweetener aspartame, are very scarce.[11] As far as we know, only one lipase-catalysed amidation of aspartic acid derivatives has previously been described.[12]

The aim of this study was the development of a regioselective, clean and easy method through which to obtain L- and D-aspartic monoamide derivatives, potentially useful chiral synthons. In the general context of our research, we also tried to obtain a deeper understanding of the interaction of dicarboxylic amino acid substrates with the active site of CAL. As an application, these results are already being successfully applied to the synthesis of compounds with potential activity for the treatment of Alzheimer's disease.[13]

Results and Discussion

On the basis of the results cited above and for comparative purposes, we synthesised different *N*-blocked derivatives

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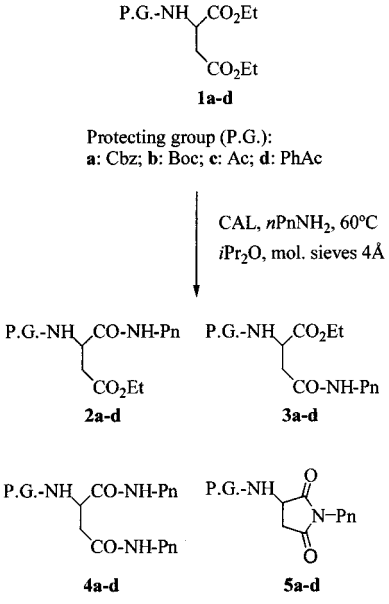
of L- and D-aspartic acid diethyl esters: the benzyloxycarbonyl (*N*-Cbz, **1a**) and *tert*-butyloxycarbonyl (*N*-Boc, **1b**) carbamates and the acetyl (*N*-Ac, **1c**) and phenylacetyl (*N*-PhAc, **1d**) amides, for use as substrates in CAL-catalysed amidation with pentylamine. The reactions were initially performed on an analytical scale in 2-mL screw-cap vials, shaken at 60 °C, containing CAL and 4 Å molecular sieves suspended in an anhydrous diisopropyl ether solution of the corresponding enantiopure substrate **1**−**4a**, pentylamine and either *N*-methylacetanilide or *N*-methylbutyranilide as internal standards.[4] Control reactions without enzyme did not display any conversion.

As a general rule, substrates of the L series preferentially yielded the α-monoamides, while those of the D series showed β-regioselectivity. In contrast with the behaviour of glutamic, α-aminoadipic and α-aminopimelic acid derivatives, in which only monoamides were formed, up to four different possible amidation products were in some cases obtained: the α- (**2a**−**d**) and β-monoamides (**3a**−**d**), the diamides (**4a**−**d**) and the aminosuccinimides (**5a**−**d**) (Scheme 1).



Scheme 1. Possible products of the CAL-catalysed amidation of **1a**−**d** with pentylamine

Regioselectivity in the L Series

Amidation of compounds L-**1a**−**d** yielded the α-monoamides as the main product in all cases (Table 1). However, while the L-glutamic derivatives had displayed absolute α-regioselectivity, the L-aspartic analogues provided mixtures of products. This is probably due to the more similar distances of the two ester groups to the stereogenic centre, as this difference is only of one methylene link. The primary sequence and crystal structure of *Candida antarctica* lipase B has already been described.[14] The same authors also determined[15] that, while the nucleophile active side pocket is a narrow tunnel with a well-defined shape, the acyl side is more spacious and its steric requirements are less strict, in general displaying a lower selectivity than that seen for nucleophile moieties.

The reaction behaviour of L-**1a** showed good α-regioselectivity, with a 10:1 ratio of **2a** to the imide **5a** at 70% conversion. Cyclization of aspartic derivatives to aminosuccinimide derivatives is a well-known reaction,[12] both from α-amido-β-ester and from β-amido-α-ester starting materials, favoured by the presence of a base.[16] β-Monoamide L-**3a** was not detected either at analytical or at preparative scales, probably due to instantaneous cyclization to afford **5a** in the reaction medium. To confirm this point, α-monoamide L-**2a** was isolated from a preparative scale reaction and incubated under the same experimental conditions. After 24 h, L-**2a** had been converted exclusively into the diamide L-**4a**, indicating that the aminosuccinimide had definitely been formed by spontaneous cyclization of L-**3a** (Scheme 2).

The rest of the reactions proceeded with lower regioselectivities (see Table 1). Monoamides L-**2c** and L-**3c** were detected (HPLC) in the reaction medium, but they easily underwent cyclization during the isolation and purification process (see Exp. Sect.). Significant amounts of the diamides L-**4b** and L-**4c** were also detected. Amidation of *N*-PhAc derivative L-**1d** yielded a mixture of α- and β-monoamides with a poor α/β regioselective ratio of 3.4:1.

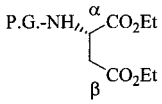
In agreement with the results observed for L-glutamic acid analogues, *N*-carbamate derivatives reacted significantly more rapidly than *N*-amides, supporting the existence of an influence of electronic effects on reactivity. The synthetic usefulness of the reaction as a regioselective α-amidation method is limited to the Cbz derivative L-**1a**, probably due to the spontaneous cyclization of the β-monoamide L-**3a**, which prevents the amidation of its α-position to form the diamide.

Regioselectivity in the D Series

Amides D-**1c** and D-**1d** underwent rapid and completely regioselective reactions, without any formation either of imide or of diamide detected in the reaction medium (Table 2), in an efficient route to the β-monoamide derivatives of D-aspartic acid. In contrast with homologous D-glutamic acid derivatives,[6] the reactions in the case of the carbamates D-**1a** and D-**1b** were much slower than those of the amides and not regioselective at all. Aminosuccinimide D-**5a** was again spontaneously formed in the reaction medium − from the undetected β-monoamide D-**3a** − and only traces of diamide D-**4a** were found.

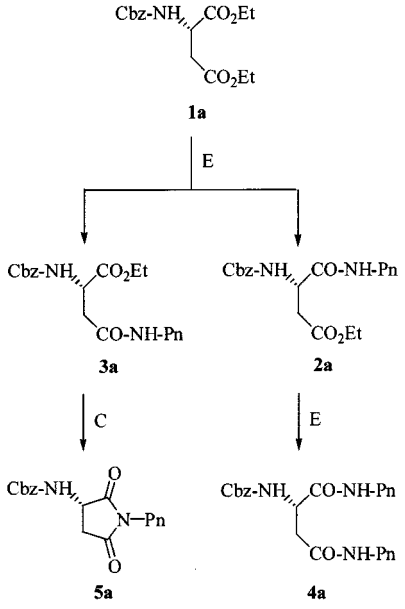
In our previous studies of the effect of the *N*-protecting group in the amidation of L-glutamic derivatives, we reported[4] that although carbamates and amides share some chemical similarities, the oxygen atom of the carbamates was able to interact with the polar region around the catalytic triad of the enzyme and thus favoured α-substitution. The amidation of D-glutamic acid always displayed γ-regioselectivity, low with *N*-carbamates and high with *N*-amides, but a reduction in the length of the side chain by one methylene group enhances the β-regioselectivity of the amides D-**1c** and D-**1d** and lowers that of the carbamates.

Table 1. Amidation of L-**1a**−**d**



Substrate	P.G.	Time [min]	Conversion[a] [%]	α-Amide **2a**−**d** [%]	β-Amide **3a**−**d** [%]	Diamide **4a**−**d** [%]	Imide **5a**−**d** [%]
L-**1a**	Cbz	60	77	70	−	traces	7[b]
L-**1b**	Boc	90	88	57	16	15	traces
L-**1c**	Ac	90	69	34	9	23	3
L-**1d**	PhAc	90	66	51	15	−	−

[a] Analytical scale, HPLC data with internal standard. [b] Formed by spontaneous cyclization of **3a**.



Scheme 2. Amidation reaction of L-**1a**; E: enzymatic reaction (CAL, $PnNH_2$, *i*Pr2O, 60 °C and 4 Å molecular sieves), C: chemical reaction, same experimental conditions but without enzyme

ive site is the configuration **I**, represented in a highly simplified way in Figure 1, which would yield α-substitution for the L-aspartic series. It may be assumed that **I** is favoured both by the steric preferences of the active site and, in the case of *N*-carbamates, by the electronic interactions. The equivalent configuration for D-analogues **II** would produce β-substitution, and this can be expected to be more important than in D-glutamic derivatives because of the shorter distance between the stereogenic centre and the β-ester group in the aspartic analogues. When α-directing electronic interactions do not exist (*N*-amides), conformation **II** increases its relative significance, and β-monoamides are the only products obtained.

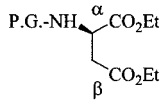
Structural Assignment

The structural assignment of all compounds was made by ^1H and ^{13}C NMR techniques, two-dimensional NMR experiments being necessary on some occasions.

Monoamides

The site of amidation was assigned by comparing the ^{13}C NMR spectra of the initial esters and the corresponding amides, as previously described.[4−6] Larger chemical shift differences in C-β than in C-α mean β-substitution, while larger chemical shift differences in C-α than in C-β mean substitution in the α-position. The chemical shift differences

Table 2. Amidation of D-**1a**−**d**



Substrate[a]	P.G.	Time [h]	Conversion [%]	α-Amide **2a**−**d** [%]	β-Amide **3a**−**d** [%]	Diamide **4a**−**d** [%]	Imide **5a**−**d** [%]
D-**1a**	Cbz	4	70	25	−	traces	45[b]
D-**1b**	Boc	4	30	12	18	traces	−
D-**1c**	Ac	4	87	−	87	−	−
D-**1d**	PhAc	4	92	−	92	−	−

[a] Analytical scale, HPLC data with internal standard. [b] Formed by spontaneous cyclization of **3a**.

This can be explained on the basis of the results obtained for L-glutamic and L-aspartic derivatives: the substrate's preferred way of approaching the catalytic serine in the act-

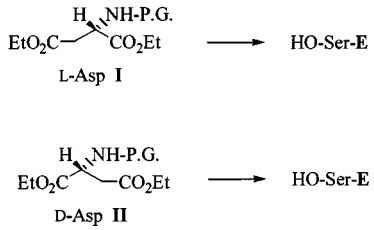
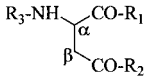


Figure 1. Representative L- and D-aspartic acid derivative configurations approaching the catalytic serine in the enzyme to produce α- (**I**) and β-substitution (**II**)

between the diesters and the final monoamides were larger in C-β than in the corresponding C-α, confirming the β-amidation (Table 3). Substitution of the β-ester group by an amide induces deshielding of the carbon atom in this position, its resonance appearing at lower field. Because of its proximity to the stereogenic centre when the amidation takes place in the α-position, C-β is shielded, introducing a difference between the ester and the α-monoamide in their C-β chemical shifts. This effect was not observed in the α-monoamides of glutamic acid,[4] in which the side chain ester group is separated from the stereogenic centre by two methylene groups, and therefore not affected by it.

Table 3. Differences in ^{13}C NMR chemical shifts between the monoamides and the corresponding diethyl esters of *N*-block-aspartic acid



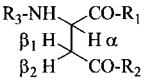
Compd.	R^1	R^2	R^3	$\Delta\delta$ [a] [b] α-C	$\Delta\delta$ [a] β-C
L-**2a**	NHPn	OEt	Cbz	−0.54	0.52
D-**2a**	NHPn	OEt	Cbz	−0.60	0.48
L-**2b**	NHPn	OEt	Boc	−0.65	0.62
L-**3b**	OEt	NHPn	Boc	−0.61	−1.34
D-**2b**	NHPn	OEt	Boc	−0.60	0.71
D-**3b**	OEt	NHPn	Boc	−0.59	−1.23
D-**3c**	OEt	NHPn	Ac	−0.72	−1.01
L-**2d**	NHPn	OEt	PhAc	−0.65	0.43
L-**3d**	OEt	NHPn	PhAc	−0.76	−1.29
D-**3d**	OEt	NHPn	PhAc	−0.80	−1.18

$\Delta\delta = \delta(\text{diester}) - \delta(\text{amide})$.

As a result of the proximity of the stereogenic centre, the protons in the β-position are diastereotopic. When the α-monoamide is formed, one of the protons is more strongly deshielded than the other, producing an effective increase in the separation of these two signals. On the other hand, when the β-monoamide is formed, the chemical environment of these diastereotopic protons is affected in the same way and both protons are equally deshielded, keeping the distance between them similar to that in the diester.

Table 4 shows the differences in the chemical shifts of the two β protons of the diesters and of the two monoamides. Through these values it is possible to assign positions of amidation solely from the ^1H NMR spectra of the initial diester and of the final monoamide.

Table 4. Differences in ^1H NMR chemical shifts between the two β-protons of the monoamides and the corresponding diesters of *N*-block-aspartic acid



Compd.[a]	R^1	R^2	R^3	H-α	H-β_1	H-β_2	$\Delta\delta$[b]
L-**1a**	OEt	OEt	Cbz	4.59	3.01	2.80	0.20
L-**2a**	NHPn	OEt	Cbz	4.50	2.98	2.64	0.34
D-**1a**	OEt	OEt	Cbz	4.60	3.00	2.80	0.20
D-**2a**	NHPn	OEt	Cbz	4.48	2.99	2.62	0.37
L-**1b**	OEt	OEt	Boc	4.47	2.91	2.72	0.19
L-**2b**	NHPn	OEt	Boc	4.41	2.92	2.61	0.30
L-**3b**	OEt	NHPn	Boc	4.43	2.84	2.65	0.19
D-**1b**	OEt	OEt	Boc	4.49	2.93	2.74	0.19
D-**2b**	NHPn	OEt	Boc	4.39	2.91	2.59	0.32
D-**3b**	OEt	NHPn	Boc	4.39	2.80	2.61	0.18
D-**1c**	OEt	OEt	Ac	4.79	2.98	2.79	0.19
D-**3c**	OEt	NHPn	Ac	4.71	2.87	2.67	0.20
L-**1d**	OEt	OEt	PhAc	4.74	2.91	2.71	0.19
L-**2d**	NHPn	OEt	PhAc	4.75	2.86	2.57	0.28
L-**3d**	OEt	NHPn	PhAc	4.72	2.84	2.66	0.18
D-**1d**	OEt	OEt	PhAc	4.78	2.95	2.76	0.19
D-**2d**	OEt	NHPn	PhAc	4.66	2.80	2.62	0.18

[a] 300 MHz, $CDCl_3$. [b] $\Delta\delta = \delta(\text{H-}\beta_1) - \delta(\text{H-}\beta_2)$.

Diamides

The structures of the diamides were assigned by their ^1H and ^{13}C NMR spectra. Signals corresponding to two pentyl groups appeared, together with two NH groups. The signals of both ethyl groups had disappeared.

Imides

The structure of the imide L-**5a** was assigned from its ^1H and ^{13}C NMR spectra and by an HMBC (heteronuclear multiple bond correlation) experiment. In the ^1H and ^{13}C NMR spectra, signals corresponding to one pentylamine chain were observed. The signals from the two ethyl groups had disappeared and no signals from NH groups were present. The HMBC experiment showed the correlation of the two carbonyl groups in the α- and β-positions with the CH_2 of the pentylamine directly bonded to the nitrogen atom. These results were only compatible with the cyclic structure of the imide, and so this compound was assigned as the imide L-**5a**. The rest of the imides were assigned in the same way, although HMBC was not necessary.

Conclusions

In this work we present a study of the CAL-catalysed regioselective amidation of different derivatives of aspartic acid. The regioselectivity of the process appeared to be de-

termined by the enantiomer used as substrate: as a general rule, L-aspartic acid derivatives [configuration (*S*)] preferentially undergo α-substitution and, although the reaction can afford mixtures of both α- and β-monoamides, diamide and aminosuccinimide, amidation of *N*-Cbz derivative L-**1a** is a useful synthetic method to produce L-aspartic α-monoamide derivatives in regioselective fashion. The products obtained in the amidation of D-aspartic acid derivatives [configuration (*R*)] depend dramatically on the *N*-protecting group used: while *N*-carbamates afforded low reaction rates and no selectivity, *N*-amides regioselectively produce β-monoamides in high yields and with short reaction times.

Experimental Section

General: Analytical HPLC was performed with a Beckman chromatograph connected to a UV detector with a Waters DeltaPak C_{18}-5μ (3.9 × 15 mm) column and acetonitrile/water containing 0.05% of trifluoroacetic acid as mobile phase, at a flow rate of 1 mL/min. Wavelength and mobile phase composition are specified in each case. All compounds were characterised by NMR spectroscopic techniques. Spectra were recorded in deuterated chloroform with tetramethylsilane as internal reference, with Varian XL-300 or Varian Inova-400 spectrometers. Elemental analyses were performed with a Perkin−Elmer 240C apparatus. Chromatographic separations were carried out on Merck silica gel columns (230−240 mesh ASTM) by the flash chromatography technique. Preparative thin layer chromatography and circular chromatography were performed with Merck 60 PF_{254} silica gel. The eluents are specified in each case. Optical rotations were measured with a Perkin−Elmer 241 MC polarimeter, in 1-dm cells with a sodium vapour lamp (λ = 589 nm) at 20 °C. Diisopropyl ether was distilled from sodium wire and stored over 4 Å molecular sieves. Pentylamine was distilled from, and stored over KOH pellets. All other chemicals were obtained from commercial sources and used without further purification. Novozym 435 is a Novo Nordisk immobilised preparation of CAL-B and was used as received. It is commercially available from Boehringer as Chirozyme L-2. The abbreviation used for pentyl is Pn.

Synthesis of Substrates. − *N*-Block-Asp(OEt)OEt 1a−d: Enantiopure substrates were synthesised from commercial D- or L-aspartic acid, by methods previously reported by us.[4,5] Both enantiomers of the corresponding derivative were purified in the same way and showed similar spectroscopic data. Details are given for the L enantiomer.

***N*-Cbz-L-Asp(OEt)OEt (L-1a):** Purification was by silica gel column chromatography (hexane/EtOAc, 8:1). Colourless solid (25%), m.p. 42 °C. $[\alpha]_D^{20}$ = +21.5 (*c* = 1, $CHCl_3$). ^{1}H NMR: δ = 7.33 (m, 5 H, Ar Cbz), 5.74 (d, 1 H, α-NH), 5.10 (s, 2 H, CH_2 Cbz), 4.59 (m, 1 H, CH-α), 4.19 (q, 2 H, CH_2 Et), 4.11 (q, 2 H, CH_2 Et), 3.01 (dd, 1 H, CH_2-β_1), 2.80 (dd, 1 H, CH_2-β_2), 1.24 (t, 3 H, CH_3 Et), 1.22 (t, 3 H, CH_3 Et). ^{13}C NMR: δ = 170.7, 170.6 (CO-α, CO-γ), 155.9 (CO-Cbz), 136.2, 128.5, 128.1 128.0 (Ar, Cbz), 67.0 (CH_2 Cbz), 61.8, 61.0 (CH_2 Et), 50.5 (C-α), 36.7 (C-β), 14.1, 14.0 (CH_3 Et). $C_{16}H_{21}NO_6$ (323): calcd. C 59.43, H 6.54, N 4.33; found C 59.60, H 6.70, N 4.35.

***N*-Cbz-D-Asp(OEt)OEt (D-1a):** Colourless solid (31%); m.p. 41−42 °C. $[\alpha]_D^{20}$ = −21.6 (*c* = 1, $CHCl_3$). $C_{16}H_{21}NO_6$ (323): calcd. C 59.43, H 6.54, N 4.33; found C 59.70, H 6.80, N 4.48.

***N*-Boc-L-Asp(OEt)OEt (L-1b):** Purification was by silica gel column chromatography (hexane/EtOAc, 9:1). Colourless syrup (62%). $[\alpha]_D^{20}$ = +23.1 (*c* = 1, $CHCl_3$). ^{1}H NMR: δ = 5.44 (d, 1 H, α-NH), 4.47 (m, 1 H, CH-α), 4.13 (q, 2 H, CH_2 Et), 4.07 (q, 2 H, CH_2 Et), 2.91 (dd, 1 H, CH_2-β_1), 2.72 (dd, 1 H, CH_2-β_2), 1.19 (t, 3 H, CH_3 Et), 1.18 (t, 3 H, CH_3 Et), 1.37 (s, 9 H, CH_3 Boc). ^{13}C NMR: δ = 170.9, 170.8 (CO-α, CO-γ), 155.3 (CO-Boc), 79.9 (C Boc), 61.6, 60.8 (CH_2 Et), 50.0 (C-α), 36.8 (C-β), 28.2 (CH_3, Boc), 14.0, 13.9 (CH_3 Et). $C_{13}H_{23}NO_6$ (289): C 53.98, H 7.96, N 4.84; found C 54.22, H 7.74, N 5.02.

***N*-Boc-D-Asp(OEt)OEt (D-1b):** Colourless syrup (54%). $[\alpha]_D^{20}$ = −22.2 (*c* = 1, $CHCl_3$). $C_{13}H_{23}NO_6$ (289): C 53.98 , H 7.96, N 4.84; found C 53.83, H 8.12, N 5.01.

***N*-Ac-L-Asp(OEt)OEt (L-1c):** Purification was by silica gel column chromatography (hexane/EtOAc, 6:1). Colourless syrup (40%). $[\alpha]_D^{20}$ = +50.8 (*c* = 1, $CHCl_3$). ^{1}H NMR: δ = 6.62 (d, 1 H, α-NH), 4.75 (m, 1 H, CH-α), 4.13 (q, 2 H, CH_2 Et), 4.05 (q, 2 H, CH_2 Et), 2.92 (dd, 1 H, CH_2-β_1), 2.74 (dd, 1 H, CH_2-β_2), 1.95 (s, 3 H, CH_3 Ac) 1.18 (t, 3 H, CH_3 Et), 1.17 (t, 3 H, CH_3 Et). ^{13}C NMR: δ = 170.9, 170.6 (CO-α, CO-γ), 169.7 (CO-Ac), 61.6, 60.8 (CH_2 Et), 48.4 (C-α), 36.2 (C-β), 22.9 (CH_3 Ac), 13.9, 13.9 (CH_3 Et). $C_{10}H_{17}NO_5$ (231): C 51.94, H 7.41, N 6.06; found C 52.00, H 7.72, N 6.15.

***N*-Ac-D-Asp(OEt)OEt (D-1c):** Colourless syrup (81%). $[\alpha]_D^{20}$ = −52.4 (*c* = 1, $CHCl_3$).$C_{10}H_{17}NO_5$ (231): calcd. C 51.94, H 7.41; N 6.06; found C 51.88, H 7.62, N 6.31.

***N*-PhAc-L-Asp(OEt)OEt (L-1d):** Purification was by silica gel column chromatography (hexane/EtOAc, 5:1). Colourless needles (35%); m.p. 53 °C. $[\alpha]_D^{20}$ = +39.5 (*c* = 1, $CHCl_3$). ^{1}H NMR: δ = 7.23 (m, 5 H, Ar PhAc), 6.42 (d, 1 H, α-NH), 4.74 (m, 1 H, CH-α), 4.09 (q, 2 H, CH_2 Et), 3.98 (q, 2 H, CH_2 Et), 3.53 (s, 2 H, CH_2 PhAc), 2.91 (dd, 1 H, CH_2-β_1), 2.71 (dd, 1 H, CH_2-β_2), 1.15 (t, 3 H, CH_3 Et), 1.10 (t, 3 H, CH_3 Et). ^{13}C NMR: δ = 170.6, 170.6 (CO-α, CO-γ), 170.4 (CO-PhAc), 134.4, 129.2, 128.8, 127.2 (Ar, PhAc), 61.7, 60.8 (CH_2 Et), 48.6 (C-α), 43.4 (CH_2−Ph PhAc), 36.1(C-β), 13.9, 13.9 (CH_3 Et). $C_{16}H_{21}NO_5$ (307): C 62.53, H 6.89, N 4.56; found C 62.62, H 7.15, N 4.50.

***N*-PhAc-D-Asp(OEt)OEt (D-1d):** Colourless needles (37%); m.p. 53 °C. $[\alpha]_D^{20}$ = −38.6 (*c* = 1, $CHCl_3$). $C_{16}H_{21}NO_5$ (307): C 62.53, H 6.89, N 4.56; found C 62.71, H 7.10, N 4.68.

Enzymatic Reactions. − General Procedure: The general experimental conditions were: CAL and powdered molecular sieves (4 Å, 50 mg/mL each) were added to a diisopropyl ether solution containing the corresponding substrate **1a−d** (20 mM) and pentylamine (50 mM) and the resulting suspension was incubated at 60 °C in an orbital shaker at 250 r.p.m. The reactions were initially performed in 2-mL screw cap vials on a 1-mL scale. As internal references,[4] *N*-methylacetanilide (8 mM) (**1a**) or *N*-methylbutyranilide (5 mM) (**1b−d**), were added to the reaction medium. Aliquots (20 μL) were periodically withdrawn, concentrated, redissolved in acetonitrile, centrifuged and analysed by HPLC (conditions specified for each case). Parallel blank reactions without enzyme were also carried out, and showed no changes over the reaction time. Preparative scale reactions were accomplished under the same experimental conditions as described above, starting from 100 mg of substrate unless otherwise specified and without internal references. After conclusion, the enzyme and molecular sieves were filtered off, and washed with acetonitrile, methanol and dichloromethane to extract all products. The organic solvent was evaporated and the final products were purified by preparative TLC or column chromato-

graphy. Details of each reaction are given. The L and D enantiomers of the same derivative were purified in the same way, unless specified otherwise. They showed similar spectroscopic data (details are given for the L enantiomer). Proportions of imide higher than would have been expected from the analytical data were obtained at preparative scale, owing to cyclization of the unstable monoamides during the purification process.

Amidation of *N*-Cbz-L-Asp(OEt)OEt (L-1a)

Analytical Scale: HPLC conditions: H_2O/AcN, 65:35, λ = 215 nm.

Preparative Scale: After a reaction time of 90 min, the reaction mixture was purified by preparative TLC, with hexane/chloroform/methanol (1:1:0.1) as eluent. The product with the higher R_f value corresponded to the α-monoamide L-**2a** and the second one was identified as L-**5a**. The β-monoamide was not detected at any time.

***N*-Cbz-L-Asp(OEt)NHPn (L-2a):** Colourless solid (37 mg, 33%); m.p. 65 °C. $[\alpha]_D^{20}$ = +18.3 (*c* = 1, $CHCl_3$). ^{1}H NMR: δ = 7.32 (m, 5 H, Ar Cbz), 6.47 (d, 1 H, α-NH), 6.01 (s, 1 H, NH-Pn), 5.09 (s, 2 H, CH_2 Cbz), 4.50 (m, 1 H, CH-α), 4.10 (q, 2 H, CH_2 Et), 3.18 (m, 2 H, *CH*$_2$-NH), 2.98 (m, 2 H, CH_2-β$_1$), 2.64 (m, 2 H, CH_2-β$_2$), 1.21 (t, 3 H, CH_3 Et), 0.85 (t, 3 H, CH_3 Pn). ^{13}C NMR: δ = 171.9, 170.0 (CO-α, CO-β), 156.0 (CO-Cbz), 136.0, 128.5, 128.3, 128.1 (Ar Cbz), 67.2 (CH_2 Cbz), 61.0 (CH_2 Et), 51.0 (C-α), 39.6 (NH−CH_2), 36.2 (C-β), 29.0, 28.9, 22.2 (CH_2-Pn), 14.0 (CH_3 Et), 13.9 (CH_3 Pn). $C_{19}H_{28}N_2O_5$ (364): C 62.64, H 7.69, N 7.57; found C 62.61, H 7.74, N 7.68.

3-(Benzyloxycarboxamido)-*N*-pentylsuccinimide (5a): Colourless solid (12 mg, 12%); m.p. 69−71 °C. $[\alpha]_D^{20} \approx 0$ (*c* = 1, $CHCl_3$). ^{1}H NMR: δ = 7.32 (m, 5 H, Ar Cbz), 5.49 (d, 1 H, α-NH), 5.08 (s, 2 H, CH_2 Cbz), 4.28 (m, 1 H, CH-α), 3.50 (m, 2 H, CH_2−N), 3.06 (m, 2 H, CH_2-β$_1$), 2.71 (m, 2 H, CH_2-β$_2$), 0.86 (t, 3 H, CH_3 Pn). ^{13}C NMR: δ = 175.5, 174.1 (CO-α, CO-β), 155.7 (CO-Cbz), 136.0, 128.6, 128.4, 128.2 (Ar Cbz), 67.5 (CH_2 Cbz), 50.2 (C-α), 39.2 (N−CH_2), 35.9 (C-β), 28.8, 27.2, 22.2 (CH_2-Pn), 13.9 (CH_3 Pn). $C_{17}H_{22}N_2O_4$ (318): C 64.15, H 6.96, N 8.80; found C 64.40, H 7.30, N 8.61. A second reaction was stopped after 10 h and the products were purified by silica gel column chromatography, eluting first with hexane/EtOAc (4:1) and then EtOAc. The diamide L-**4a** and a mixture of the α-monoamide L-**2a** and the imide L-**5a** were isolated.

***N*-Cbz-L-Asp(NHPn)NHPn (L-4a):** Colourless solid (67 mg, 53%); m.p. 178−180 °C. $[\alpha]_D^{20}$ = +5.0 (*c* = 1, MeOH/$CHCl_3$, 1:1). ^{1}H NMR: δ = 7.33 (m, 5 H, Ar Cbz), 6.97 (s, 1 H, NH-Pn), 6.96 (s, 1 H, NH-Pn), 6.54 (d, 1 H, α-NH), 5.10 (s, 2 H, CH_2 Cbz), 4.45 (m, 1 H, CH-α), 3.18 (m, 4 H, *CH*$_2$-NH), 2.83 (m, 2 H, CH_2-β$_1$), 2.49 (m, 2 H, CH_2-β$_2$), 0.86 (t, 6 H, CH_3 Pn). ^{13}C NMR: δ = 170.4, 170.4 (CO-α, CO-β), 156.0 (CO-Cbz), 136.2, 128.6, 128.2, 128.0 (Ar Cbz), 67.1 (CH_2 Cbz), 51.8 (C-α), 39.7 (NH−CH_2), 38.1 (C-β), 29.1, 29.0, 22.3 (CH_2-Pn), 13.9 (CH_3 Pn). $C_{22}H_{35}N_3O_4$ (405): C 65.16, H 8.70, N 10.36; found C 65.03, H 8.82, N 10.21.

Amidation of *N*-Cbz-D-Asp(OEt)OEt (D-1a): By the same procedure as used with L-**1a**, β-monoamide D-**1a** and imide D-**5a** were obtained after a reaction time of 5 h. The diamide D-**4a** was obtained in a second reaction, stopped after 14 h.

***N*-Cbz-D-Asp(OEt)NHPn (D-2a):** Colourless solid (21 mg, 19%); m.p. 65−67 °C. $[\alpha]_D^{20}$ = −15.8 (*c* = 1, $CHCl_3$). $C_{19}H_{28}N_2O_5$ (364): C 62.64, H 7.69, N 7.57; found C 62.51, H 8.23, N 7.18.

3-(Benzyloxycarboxamido)-*N*-pentylsuccinimide (5a): Colourless solid (35 mg, 35%); m.p. 68−71 °C. $[\alpha]_D^{20}$ = −2.7 (*c* = 1, $CHCl_3$). $C_{17}H_{22}N_2O_4$ (318): C 64.15, H 6.96, N 8.80; found C 63.91, H 6.92, N 8.48.

***N*-Cbz-D-Asp(NHPn)NHPn (D-4a):** Colourless solid (29 mg, 23%); m.p. 176−178 °C. $[\alpha]_D^{20}$ = −6.3 (*c* = 1, $CHCl_3$/MeOH, 1:1). $C_{22}H_{35}N_3O_4$ (405): C 65.16, H 8.70, N 10.36; found C 65.49, H 8.92, N 10.01.

Amidation of *N*-Boc-L-Asp(OEt)OEt (L-1b)

Analytical Scale: Two different HPLC analysis were carried out, with λ = 240 nm, H_2O/AcN (75:25) to monitor the β-amide and the imide, and H_2O/AcN (65:35) to separate the diamide.

Preparative Scale: The reaction, starting from 150 mg L-**1b**, was stopped after 1.5 h. The products were isolated from the reaction mixture by means of a silica gel column (hexane/EtOAc, 4:1, changing progressively to EtOAc, 100%). The order of elution of the products was: L-**2b**, L-**5b**, L-**3b** and L-**4b**.

***N*-Boc-L-Asp(OEt)NHPn (L-2b):** Colourless solid (33 mg, 19%); m.p. 60−61 °C. $[\alpha]_D^{20}$ = +8.3 (*c* = 2, $CHCl_3$). ^{1}H NMR: δ = 6.51 (d, 1 H, α-NH), 5.69 (s, 1H NH-Pn), 4.41 (m, 1 H, CH-α), 4.10 (q, 2 H, CH_2 Et), 3.18 (m, 2 H, *CH*$_2$-NH), 2.92 (m, 1 H, CH_2-β$_1$), 2.61 (m, 1 H, CH_2-β$_2$), 1.40 (s, 9 H, CH_3 Boc), 1.21 (t, 3 H, CH_3 Et), 0.83 (t, 3 H, CH_3 Pn). ^{13}C NMR: δ = 172.0, 170.5 (CO-α, CO-β), 155.5 (CO-Boc), 80.3 (C Boc), 60.9 (CH_2 Et), 50.6 (C-α), 39.5 (NH−CH_2), 36.2 (C-β), 29.1, 28.9, 22.2 (CH_2-Pn), 28.2 [$(CH_3)_3$ Boc], 14.0 (CH_3 Et), 13.9 (CH_3 Pn). $C_{16}H_{30}N_2O_5$ (330): C 58.16, H 9.15, N 8.48; found C 58.45, H 9.16, N 8.72.

***N*-Boc-L-Asp(NHPn)OEt (L-3b):** Colourless solid (12 mg, 7%); m.p. 60−62 °C. $[\alpha]_D^{20}$ = +16.8 (*c* = 1, $CHCl_3$). ^{1}H NMR: δ = 6.72 (d, 1 H, α-NH), 5.65 (s, 1 H NH-Pn), 4.43 (m, 1 H, CH-α), 4.18 (q, 2 H, CH_2 Et), 3.19 (m, 2 H, *CH*$_2$-NH), 2.84 (m, 1 H, CH_2-β$_1$), 2.65 (m, 1 H, CH_2-β$_2$), 1.41 (s, 9 H, CH_3 Boc), 1.24 (t, 3 H, CH_3 Et), 0.86 (t, 3 H, CH_3 Pn). ^{13}C NMR: δ = 171.4, 169.6 (CO-α, CO-β), 155.7 (CO-Boc), 79.9 (C Boc), 61.6 (CH_2 Et), 50.6 (C-α), 39.5 (NH−CH_2), 38.1 (C-β), 29.2, 29.0, 22.3 (CH_2-Pn), 28.3 [$(CH_3)_3$ Boc], 14.0 (CH_3 Et), 13.9 (CH_3 Pn). $C_{16}H_{30}N_2O_5$ (330): C 58.16, H 9.15, N 8.48; found C 57.87, H 9.54, N 7.99.

***N*-Boc-L-Asp(NHPn)NHPn (L-4b):** Colourless solid (29 mg, 15%); m.p. 137−138 °C. $[\alpha]_D^{20}$ = +17.1 (*c* = 3, $CHCl_3$). ^{1}H NMR: δ = 6.98 (s, 1 H, NH-Pn), 6.52 (s, 1 H, NH-Pn), 6.29 (d, 1 H, α-NH), 4.36 (m, 1 H, CH-α), 3.13 (m, 4 H, *CH*$_2$-NH), 2.76 (m, 1 H, CH_2-β$_1$), 2.47 (m, 1 H, CH_2-β$_2$), 1.39 (s, 9 H, CH_3 Boc), 0.83 (t, 3 H, CH_3 Pn). ^{13}C NMR: δ = 171.2, 170.9 (CO-α, CO-β), 155.7 (CO-Boc), 80.0 (C Boc), 51.5 (C-α), 39.5 (NH−CH_2), 37.8 (C-β), 29.0, 28.9, 22.2 (CH_2-Pn), 28.2 [$(CH_3)_3$ Boc), 13.9 (CH_3 Pn). $C_{19}H_{37}N_3O_4$ (371): C 61.42, H 10.04, N 11.31; found C 61.57, H 10.71, N 11.65.

3-(*tert*-Butoxycarboxamido)-*N*-pentylsuccinimide (5b): Traces. Identified by HPLC by correlation of its retention time with that of D-**5a**.

Amidation of *N*-Boc-D-Asp(OEt)OEt (D-2b)

Preparative Scale: The reaction was stopped after 5.5 h. Aminosuccinimide D-**5b** had not been detected in the analytical scale reaction, but was isolated from the preparative reaction, probably originating during the purification process from cyclization of D-**2b** and **3b**. Initial product (50 mg, 50%) was recovered and the two monoamides D-**2b** and D-**3b**, diamide D-**4b** and aminosuccinimide D-**5b** were obtained.

***N*-Boc-D-Asp(OEt)NHPn (D-2b):** Colourless solid (17 mg, 15%); m.p. 58−59 °C. $[\alpha]_D^{20} = -6.8$ (c = 1, $CHCl_3$). $C_{16}H_{30}N_2O_5$ (330): C 58.16, H 9.15, N 8.48; found C 58.24, H 9.52, N 8.11.

***N*-Boc-D-Asp(NHPn)OEt (D-3b):** Colourless solid (15 mg, 13%); m.p. 63−64 °C. $[\alpha]_D^{20} = -18.3$ (c = 1, $CHCl_3$). $C_{16}H_{30}N_2O_5$ (330): C 58.16, H 9.15, N 8.48; found C 58.55, H 9.08, N 8.29.

***N*-Boc-D-Asp(NHPn)NHPn (D-4b):** Colourless solid. Traces. Identified by correlation of its HPLC retention time with that of its homologous L-**4b**.

3-(*tert*-Butoxycarboxamido)-*N*-pentylsuccinimide 5b: Colourless solid (5 mg, 5%); m.p. 77−79 °C. $[\alpha]_D^{20} = -0.9$ (c = 0.1, $CHCl_3$). ^{1}H NMR: δ = 5.19 (d, 1 H, α-NH), 4.43 (m, 1 H, CH-α), 4.18 (c, 2 H, CH_2 Et), 3.46 (m, 2 H, CH_2−N), 3.00 (m, 1 H, CH_2-β_1), 2.70 (m, 1 H, CH_2-β_2), 1.37 (s, 9 H, CH_3 Boc), 0.81 (t, 3 H, CH_3 Pn). ^{13}C NMR: δ = 175.9, 174.4 (CO-α, CO-β), 155.5 (CO-Boc), 78.7 (C Boc), 50.2 (C-α), 39.1 (NH−CH_2), 36.2 (C-β), 28.9, 27.2, 22.2 (CH_2-Pn), 28.2 [(CH_3)$_3$ Boc], 13.9 (CH_3 Pn). $C_{14}H_{24}N_2O_4$ (284): C 59.13, H 8.51, N 9.85; found C 59.04, H 8.72, N 9.62.

Amidation of *N*-Ac-L-Asp(OEt)OEt (L-1c)

Analytical Scale: HPLC conditions: H_2O/AcN (85:25) (0−10 min), (60:40) (11−40 min), λ = 200 nm.

Preparative Scale: The reaction, starting from 150 mg, was stopped after 2 h. The products were purified through a silica gel column (hexane/EtOAc, 1:1, and then EtOAc/methanol, 40:1), affording the initial product (31 mg, 21%), diamide L-**4c** and imide L-**5c**. Although detected in the analytical scale reaction, monoamides L-**2c** and L-**3c** could not be isolated.

***N*-Ac-L-Asp(NHPn)NHPn (L-4c):** Colourless solid (39 mg, 19%); m.p. 188−190 °C. $[\alpha]_D^{20} \approx 0$ (c = 1, $CHCl_3$). ^{1}H NMR: δ = 7.66 (d, 1 H, α-NH), 7.42 (s, 1H NH-Pn), 6.77 (s, 1H NH-Pn), 4.69 (m, 1 H, CH-α), 3.13 (m, 4 H, *CH_2*-NH), 2.72 (m, 1 H, CH_2-β_1), 2.46 (m, 1 H, CH_2-β_2), 1.95 (s, 3 H, CH_3 Ac), 0.82 (t, 3 H, CH_3 Pn), 0.81 (t, 3 H, CH_3 Pn). ^{13}C NMR: δ = 171.0, 170.9 (CO-α, CO-β), 170.4 (CO-Ac), 50.3 (C-α), 39.6 (NH−CH_2), 37.8 (C-β), 29.0, 28.9, 22.3 (CH_2-Pn), 23.1 (CH_3 Ac), 13.9, 13.8 (CH_3 Pn). $C_{16}H_{31}N_3O_3$ (313): C 61.31, H 9.96, N 13.40; found C 61.50, H 10.21, N 12.98.

3-(Acetamido)-*N*-pentylsuccinimide (5c): Colourless solid (72 mg, 49%); m.p. 121−122 °C. $[\alpha]_D^{20} \approx 0$ (c = 1, $CHCl_3$). ^{1}H NMR: δ = 6.58 (d, 1 H, α-NH), 4.26 (m, 1 H, CH-α), 3.45 (m, 2 H, CH_2−N), 3.00 (m, 1 H, CH_2-β_1), 2.69 (m, 1 H, CH_2-β_2), 1.97 (s, 3 H, CH_3 Ac), 0.82 (t, 3 H, CH_3 Pn). ^{13}C NMR: δ = 175.8, 174.4 (CO-α, CO-β), 170.8 (CO-Ac), 49.5 (C-α), 39.1 (N−CH_2), 35.6 (C-β), 28.8, 27.1, 22.1 (CH_2-Pn), 22.5 (CH_3 Ac), 13.8 (CH_3 Pn). $C_{11}H_{18}N_2O_3$ (226): C 58.39, H 8.02, N 12.38; found C 58.63, H 8.40, N 12.10.

Amidation of *N*-Ac-D-Asp(OEt)OEt (D-1c)

Preparative Scale: The reaction, starting from 150 mg of D-**1c**, was stopped after 4 h. The enzyme and molecular sieves were washed only with acetonitrile. After evaporation of the solvent, the product was recrystallised from diisopropyl ether/acetonitrile, affording pure β-monoamide D-**3c**.

***N*-Ac-D-Asp(NHPn)OEt (D-3c):** Colourless solid (101 mg, 57%); m.p. 97−98 °C. $[\alpha]_D^{20} = -45.9$ (c = 4, $CHCl_3$). ^{1}H NMR: δ = 6.86 (d, 1 H, α-NH), 5.85 (s, 1H NH-Pn), 4.71 (m, 1 H, CH-α), 4.18 (q, 2 H, CH_2 Et), 3.17 (m, 2 H, *CH_2*-NH), 2.87 (m, 1 H, CH_2-β_1), 2.67 (m, 1 H, CH_2-β_2), 1.99 (s, 3 H, CH_3 Ac) 1.23 (t, 3 H, CH_3 Et), 0.85 (t, 3 H, CH_3 Pn). ^{13}C NMR: δ = 171.1, 170.1 (CO-α, CO-β), 169.7 (CO-Ac), 61.5 (CH_2 Et), 49.2 (C-α), 39.3 (NH−CH_2), 37.2 (C-β), 29.0, 28.8, 22.1 (CH_2-Pn), 22.9 (CH_3 Ac), 13.9 (CH_3 Et), 13.8 (CH_3 Pn). $C_{13}H_{24}N_2O_4$ (272): C 57.33, H 8.88, N 10.29; found C 57.61, H 9.02, N 10.59.

Amidation of *N*-PhAc-L-Asp(OEt)OEt (L-1d)

Analytical Scale: HPLC conditions: H_2O/AcN (67:32), λ = 215 nm.

Preparative Scale: The reaction, starting from 150 mg of L-**1d**, was stopped after 2.5 h. The products were purified through a silica gel column (hexane/EtOAc, 4:1, progressively changing the proportion to pure EtOAc). In this case, both α- and β-monoamides L-**2c** and L-**3c** and imide L-**5c** (not detected by HPLC under the analytical conditions), but not diamide L-**4c**, were isolated.

***N*-PhAc-L-Asp(OEt)NHPn (L-2d):** Colourless solid (38 mg, 22%); m.p. 120−122 °C. $[\alpha]_D^{20} = -7.0$ (c = 1, $CHCl_3$). ^{1}H NMR: δ = 7.27 (m, 5 H, Ar PhAc), 6.92 (d, 1 H, α-NH), 6.55 (s, 1 H, NH-Pn), 4.75 (m, 1 H, CH-α), 4.09 (q, 2 H, CH_2 Et), 3.56 (s, 2 H, CH_2 PhAc), 3.13 (m, 2 H, *CH_2*-NH), 2.86 (m, 1 H, CH_2-β_1), 2.57 (m, 1 H, CH_2-β_2), 1.21 (t, 3 H, CH_3 Et), 0.86 (t, 3 H, CH_3 Pn). ^{13}C NMR: δ = 171.8, 171.1 (CO-α, CO-β), 169.9 (CO-PhAc), 134.4, 129.0, 128.9, 127.3 (Ar PhAc), 61.0 (CH_2 Et), 49.2 (C-α), 43.5 (CH_2 PhAc), 39.5 (NH−CH_2), 35.7 (C-β), 28.9, 28.8, 22.1 (CH_2-Pn), 14.0 (CH_3 Et), 13.9 (CH_3 Pn). $C_{19}H_{28}N_2O_4$ (348): C 65.49, H 8.10, N 8.04; found C 65.44, H 8.41, N 8.35.

***N*-PhAc-L-Asp(NHPn)OEt (L-3d):** Colourless solid (26 mg, 15%); m.p. 120−121 °C. $[\alpha]_D^{20} = +32.3$ (c = 1, $CHCl_3$). ^{1}H NMR: δ = 7.27 (m, 5 H, Ar PhAc), 6.83 (d, 1 H, α-NH), 5.71 (s, 1 H, NH-Pn), 4.72 (m, 1 H, CH-α), 4.16 (q, 2 H, CH_2 Et), 3.56 (s, 2 H, CH_2 PhAc), 3.14 (m, 2 H, *CH_2*−NH), 2.84 (m, 1 H, CH_2-β_1), 2.66 (m, 1 H, CH_2-β_2), 1.22 (t, 3 H, CH_3 Et), 0.89 (t, 3 H, CH_3 Pn). ^{13}C NMR: δ = 170.8, 170.8 (CO-α, CO-β), 169.5 (CO-PhAc), 134.6, 129.2, 128.8, 127.2 (Ar PhAc), 61.7 (CH_2 Et), 49.3 (C-α), 43.4 (CH_2 PhAc), 39.5 (NH−CH_2), 37.4 (C-β), 28.9, 28.8, 22.2 (CH_2-Pn), 14.0 (CH_3 Pn), 13.9 (CH_3 Et). $C_{19}H_{28}N_2O_4$ (348): C 65.49, H 8.10, N 8.04; found C 65.42, H 7.93, N 8.13.

3-(Phenylacetamido)-*N*-pentylsuccinimide (5d): Colourless solid (10 mg, 7%); m.p. 77−78 °C. $[\alpha]_D^{20} = +2.8$ (c = 1, $CHCl_3$). ^{1}H NMR: δ = 7.29 (m, 5 H, Ar PhAc), 6.10 (d, 1 H, α-NH), 4.24 (m, 1 H, CH-α), 3.61 (s, 2 H, CH_2 PhAc), 3.49 (m, 2 H, CH_2−N), 3.01 (m, 1 H, CH_2-β_1), 2.69 (m, 1 H, CH_2-β_2), 0.86 (t, 3 H, CH_3 Pn). ^{13}C NMR: δ = 175.4, 174.2 (CO-α, CO-β), 171.6 (CO-PhAc), 133.9, 129.4, 129.1, 127.6 (Ar PhAc), 49.7 (C-α), 43.1 (CH_2 PhAc), 39.2 (N−CH_2), 35.6 (C-β), 28.9, 27.1, 22.1 (CH_2-Pn), 13.9 (CH_3 Pn). $C_{17}H_{22}N_2O_3$ (302): C 67.53, H 7.33, N 9.26; found C 67.79, H 7.41, N 9.38.

Amidation of *N*-PhAc-D-Asp(OEt)OEt (D-1d)

Preparative Scale: The reaction was stopped after 8 h. β-Monoamide D-**3d** and the imide D-**5d**, as a by-product formed during the purification process, were isolated.

***N*-PhAc-D-Asp(NHPn)OEt (D-3d):** Colourless solid (33 mg, 29%); m.p. 122−123 °C. $[\alpha]_D^{20} = -33.8$ (c = 1, $CHCl_3$). $C_{19}H_{28}N_2O_4$ (348): C 65.49, H 8.10, N 8.04; found C 65.35, H 8.50, N 7.98.

3-(Phenylacetamido)-*N*-pentylsuccinimide (5d): White solid (12 mg, 12%); m.p. 79−80 °C. $[\alpha]_D^{20} = -4.5$ (c = 1, $CHCl_3$). $C_{17}H_{22}N_2O_3$ (302): C 67.53, H 7.33, N 9.26; found C 67.44, H 7.60, N 8.98.

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